State of Vermont
Green Mountain Care Board

Docket No. GMCB-010-15con

In re: Application of ACTD, LLC
For Green Mountain Surgery Center (GMSC)

In Response to CON Condition #10

Evidence-Based Studies Supporting Procedures/Surgeries to be Offered at GMSC

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Patient Preference and Adherence

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REVIEW

Carpal tunnel surgery: patient preferences and predictors for satisfaction

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Abstract: Carpal tunnel syndrome is a debilitating disease of the upper extremity affecting patient function and quality of life. Surgical interventions have been developed that effectively treat this disease. However, there remains a subset of patients who are not fully satisfied with their outcome. Extensive investigation has been undertaken to analyze preoperative factors predictive of higher patient satisfaction. This review summarizes the role of unique patient characteristics and patient psychology, worker's compensation, patient demographics, certain clinical features, and patient preferences and expectations regarding patient satisfaction following carpal tunnel surgery. Understanding the complex nature of patient satisfaction will enable surgeons to indicate patients for surgical intervention better, provide appropriate preoperative counseling, and manage expectations postoperatively.

Keywords: outcome, workers' compensation, biopsychosocial, patient demographics

Introduction

The incidence of carpal tunnel syndrome is 3.5 cases per 1000 person-years, making it the most common compressive neuropathy of the upper extremity.[1] Carpal tunnel syndrome affects the median nerve distribution, producing a constellation of symptoms that includes numbness, tingling, and pain, as well as functional deficits that include muscular atrophy and weakness. Carpal tunnel surgery (with release of the entrapped median nerve) is an effective treatment for patients with carpal tunnel syndrome recalcitrant to conservative measures. Open and endoscopic methods achieve good or excellent outcomes in approximately 70%–90% of patients.[2] A tremendous amount of research has been dedicated to identifying clinical variables that may predict the success and failure of surgical treatment.

While patient satisfaction is a critical component in determining success following carpal tunnel surgery, it remains poorly understood. An effective evaluation of patient satisfaction should extend beyond the variables traditionally included in the surgical literature, and should explore the psychosocial aspects of the patient and their decision-making process; demographic contributions such as age, gender, and workers' compensation; and patient expectations and desired outcomes following the surgical outcome.

Preoperative discussion about patient expectations allows the surgeon to counsel the patient on appropriate postoperative expectations, while also giving the surgeon a framework to best judge success in each patient. Many factors influence patient satisfaction, and each patient has an individual set of priorities that contribute to their ultimate level of satisfaction.

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The patient and patient psychology

Each patient has a very personal understanding of the disease process, view of the physician-patient relationship, and level of confidence in the available treatment options. The biopsychosocial model of health care attempts to reconcile the traditional decision-making strategies of medicine with the subjective, individualized outlook of each patient.[3] Outcomes research in carpal tunnel surgery has highlighted the complex nature of predicting and obtaining successful outcomes,[4] and application of the biopsychosocial model may be beneficial by improving outcomes.

Patients are taking an increasingly active role in their health care and decision making. The wide availability of medical information through the Internet and other sources has led to a more informed patient base that may have a greater understanding of the risks, benefits, and outcomes of surgery.[5–8] Traditionally, three fundamental approaches to clinical decision-making have been emphasized: paternalistic, shared, and consumerist.[9] The evolution of patient-centered care has moved decision making from the paternalistic approach towards a more shared or consumerist approach. Gong et al demonstrated that over three-quarters of patients with carpal tunnel syndrome preferred to share decision making with their physicians.[10] Moreover, recent literature has shown greater patient satisfaction when shared decision making is employed.[11] Establishing a relationship with patients and involving them in the decision-making process can help increase patient satisfaction.

Understanding and adapting to patient psychology is an essential aspect of the doctor–patient relationship. An individual psychological response accompanies every illness and influences the way the patient perceives and responds to the diagnosis. For example, a patient's mental status may affect the severity of symptoms, both pre- and postoperatively, and may lower his or her satisfaction after surgical intervention.[12] Several factors may contribute to this finding, including delayed presentation for care, inability to comply with postoperative instructions, and a wholly pessimistic outlook. More specifically, depression has been associated with dissatisfaction.[13] While poor coping skills could inherently undermine a patient's response to the treatment of any medical condition, this has been specifically investigated following carpal tunnel release.[14]

Perceived disability is also important to understanding patient satisfaction. Kelley-Moore et al defines perceived disability as "a patient's subjective assessment of their own health and functional status."[15] Perceived disability is highly individualized and depends on how a patient internalizes feedback from loved ones and physicians, the availability of emotional and physical support a patient encounters in times of major need, and the ability of the patient to fulfill certain social roles.[16] Ultimately, the way a patient views his or her level of disability has a profound effect on his or her expectations of and response to treatment.

Treatment strategies that incorporate the biopsychosocial model acknowledge the characteristics inherent to the patient. These strategies consider the patient's view of the disease process; the stability of his or her mental state regarding understanding the risks, benefits, and expectations of surgery; and ultimately, the patient's postoperative ability to cope with postsurgical pain, hand therapy, and overall outcome.

Workers' compensation

Over 10% of orthopedic services in the United States are paid for by workers' compensation.[17] Injuries to the upper extremity are the most common type of all workplace-associated injuries, with carpal tunnel representing approximately 3% of cases and requiring a median of 27 days off from work.[17] The association between workers' compensation and treatment outcomes in carpal tunnel syndrome is complex. Workers' compensation claimants utilize a greater share of the available surgical and physiotherapy treatments,[18] yet data suggest that they fare worse than patients without third-party compensation incentives.[18] Indeed, workers' compensation claims have been linked to more severe symptoms, decreased satisfaction, prolonged long-term disability, and worse objective outcomes.[12,19] For example, workers with an attorney involved in their cases described more severe symptoms and lower satisfaction with treatment when compared to patients with no attorney involved in their cases.[19] Fewer patients with workers' compensation claims return to their previous jobs, with a majority attributing their inability to work to symptoms of carpal tunnel syndrome.[20] Workers' compensation patients generate a higher physician workload, and therefore a higher cost of health care, in the form of more-frequent office visits, documentation, and phone calls, and the performance of more diagnostic studies.[21] Overall, patient satisfaction appears to be lower in this subset of patients.[22]

The concept of moral hazard refers to the change that occurs in a patient's behavior when that individual is no longer responsible for the costs of his or her actions.[23] Day et al describe moral hazard as "a change in a person's behavior when that individual no longer bears the cost of his or her actions."[23] This concept has been explored in relation to workers' compensation claims as a possible explanation for poor outcomes.[23,24] Workers' compensation benefits vary

by state, but typically involve health care cost coverage, paid medical leave from work, and other employee financial benefits. When patients have an outside agency playing such a large role in their care, it is argued that patients are encouraged to be in, and remain in, the sick role.[23] Multiple references in the literature highlight the fact that as workers' compensation benefits become more generous, the frequency and severity of claims increase.[25–28] Furthermore, one study found that a 10% increase in workers' compensation benefits led to an up to 11% increase in the number of workers' compensation claims.[29] These phenomena may be partially explained by moral hazard as patients are offered incentives to utilize a greater share of the health care system. This becomes particularly important in diagnoses that are heavily reliant on subjective data from patients, such as those with carpal tunnel syndrome. This clearly represents a barrier for the surgeon in interpreting a patient's severity of disease, response to treatment, and long-term prognosis.

Another hypothesis to explain poor outcomes in workers' compensation patients is secondary gain.[30,31] Secondary gain is defined as the benefit obtained indirectly from organic or professed illness.[32] Strong consideration must be given to secondary gain, especially in clinical studies that rely on subjective patient-rated questionnaires as determinants of outcome. This may be explained by the potential reporting bias generated by ulterior motives. However, it should also be noted that the effect of workers' compensation must be viewed within the context of the relevant health care system. Patient preferences and decisions may differ, for example, in a heavily privatized system (such as in the United States) compared to a single-payer system. The implications of workers' compensation cases and medical–legal disputes over a physician's management of a patient cannot be overlooked. Pressure from attorneys may drive physicians to more aggressively utilize resources to avoid unnecessary scrutiny and possible litigation. The physician should be aware of these inherent biases while striving to provide the best care for patients with carpal tunnel syndrome.

Patient demographics

Like many other procedures, outcomes after carpal tunnel surgery can be influenced by age, gender, race, socioeconomic status, and education level.[33–36] Previous investigations have not yielded a consensus on the effects of age or gender on satisfaction after carpal tunnel surgery. However, a recent investigation with long-term follow-up has shown substantial satisfaction after carpal tunnel release in elderly patients, with a satisfaction rate of 85% at the 5-year follow-up.[37] Moreover, Ettema et al compared nonoperative to surgical treatment of carpal tunnel syndrome in patients over 70 years of age and showed increased satisfaction after surgical management.[36] The appropriate approach to the elderly patient, therefore, may be similar to that for younger patients: identify and indicate the appropriate surgical candidates.

Gender-based disparities in outcomes are becoming increasingly apparent within the field of orthopedic surgery.[38] While patient gender has been accounted for in most studies regarding carpal tunnel surgery, these studies have not demonstrated any substantial influence of gender on outcomes after carpal tunnel surgery.[13,19,34] However, Hansen and Larsen demonstrated that women have higher satisfaction than men after carpal tunnel surgery.[39] While there is no clear consensus on the influence of gender on outcomes after carpal tunnel treatment, gender-based differences in a patient's general outlook on disease and expectations for treatment may exist, and further investigation is warranted.

Clinical features predictive of higher satisfaction

An understanding of the effect of the disease process on quality of life is helpful in guiding treatment choices. Patient satisfaction is rooted in the physician's ability to understand the patient's functional impairment and to tailor treatment appropriately.[37] When evaluating the patient with carpal tunnel syndrome, the physician should identify factors that have previously been associated with poorer outcomes. Turner reviewed the literature over the past 20 years for predictors of poor outcome and found that patients with diabetes mellitus, thoracic outlet syndrome, double-crush phenomena (where a peripheral nerve is compressed in two separate locations), a history of alcohol abuse, and a history of tobacco use have a worse prognosis.[40] Furthermore, worse outcomes were also observed in patients with normal preoperative nerve conduction studies, in those with signs of abductor pollicis brevis muscle wasting, and in workers' compensation cases involving preoperative litigation.[40]

Predictors for higher satisfaction after carpal tunnel treatment can also be solicited from clinical evaluation. Gong et al found that clinical predictors of higher satisfaction were nocturnal pain and the absence of cold intolerance.[41] In addition, patients who were not experiencing any subjective weakness had high rates of satisfaction. In general, patients with symptoms indicative of early carpal tunnel syndrome without resultant muscle weakness have greater satisfaction and more predictable outcomes from their surgery. Once median nerve compression has progressed to clinically

evident muscle atrophy (in carpal tunnel syndrome), the goal of carpal tunnel release is to halt the further progression of disease. In these cases, patient satisfaction is more difficult to predict and may be related to the patient's return to a premorbid level of muscle function.

Patient preferences for outcomes, expectations, and satisfaction

Increasing attention is being given to patient preferences and expectations throughout the musculoskeletal literature. As discussed previously, patients with carpal tunnel syndrome often complain of a combination of numbness, night pain, pain, functional limitation, or weakness. Detailed evaluation of patients who undergo surgery reveals differences in their prevailing symptoms and preferences. Bessette et al found that the most important reason for choosing surgery was night pain and numbness in nearly 60% of patients; however, 17% chose functional improvement.[12] Night pain and numbness are symptoms that quickly and reliably improve with surgery, whereas functional improvement is less predictable and can take much longer. Despite these considerations, preference for grip strength was the only statistically significant variable associated with satisfaction; specifically, preference for grip strength was associated with lower satisfaction. Kadzielski et al also looked at preoperative expectations and found no significant correlation with patient satisfaction.[42] After multivariable analysis, Kadzielski et al found that simply the fulfillment of expectations explained most of the variance in postoperative satisfaction.

The individual context of each patient's expectations and preferences is important to understanding their influence on outcomes. As discussed previously, the patient's mental health status and coping skills may influence the patient's overall perception of the disease process, perceived disability, and subsequent treatment outcomes. Workers' compensation status and education level are intimately linked with an expressed interest in returning to work. Certainly, the health care system in which a patient receives care may result in unique differences in expectations and levels of satisfaction. One aspect of patient expectations not considered in the current literature is the nature and extent of the discussion that the surgeon has with each patient prior to surgery. Not all surgeons present treatment options in a similar fashion, and each patient may respond differently to a given preoperative discussion. There is a clear need for a preoperative questionnaire or survey for evaluating and measuring patients' preoperative expectations and postoperative fulfillment.

It is important for physicians not only to understand the patient's perceptions, but also to delve deeper to understand the patient's rationale for their views. Patients may have an uninformed or distorted view of the risks, benefits, and potential complications of surgery. Both under- and over-emphasizing the perceived risks is common, but patients are particularly prone to misconstrue negative outcomes.[43] Developing a rapport with each patient and understanding his or her fears, concerns, and perception of treatment options cannot be overstated, and if done properly, can optimize the patient's satisfaction with treatment.

Conclusion

In the appropriately selected patient, carpal tunnel surgery has the potential for excellent outcomes with high levels of patient satisfaction. In a certain subset of patients, however, a reliable outcome cannot be predicted. Many variables have been studied to explain this, including baseline mental health status, workers' compensation, certain demographic data, and patient expectations. Despite extensive investigation, there remains an incomplete understanding of this information, and further study is warranted.

Patient-reported measures of health status are crucial to the evaluation, indication, treatment, and ultimate outcome of carpal tunnel surgery.[19] The evolution of care for patients with carpal tunnel syndrome must involve a closer examination of the patient that extends beyond surgical treatment of the disease. Physicians should work to accurately identify patients who are at greatest risk for poor outcomes and use preoperative education and counseling to establish appropriate, customized expectations for treatment. An evaluation of patients through an individualized, patient-centered approach will enable the most complete assessment and treatment of patients with carpal tunnel syndrome.

Disclosure

The authors report no conflicts of interest in this work.

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The Safety of Hand and Upper-Extremity Surgical Procedures at a Freestanding Ambulatory Surgery Center: A Review of 28,737 Cases

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Abstract

Background: More procedures are being completed on an outpatient basis at freestanding ambulatory surgery centers. The purpose of our study was to determine the safety and rate of adverse events in outpatient hand and upper-extremity surgical procedures.

Methods: A retrospective review of cases at a single, freestanding ambulatory surgery center over an eleven-year period was performed. In our analysis, 28,737 cases were performed and were included. Adverse events were defined as serious complications causing harm to a patient or leading to additional treatment. Using state-reportable adverse events criteria as a guideline, we divided the adverse events into seven categories: infection requiring intravenous antibiotics or return to the operating room, postoperative transfer to a hospital, wrong-site surgical procedure, retention of a foreign object, postoperative symptomatic thromboembolism, medication error, and bleeding complications. These adverse events were then analyzed to determine if they led to additional laboratory testing, hospital admission, return to the operating room, emergency department visits, or physical or mental permanent disability.

Results: There were fifty-eight reported adverse events, for an overall rate of 0.20%. There were no deaths. There were fourteen infections, eighteen postoperative transfers to a hospital, twenty-one hospital admissions after discharge, one medication error, and four postoperative hematomas. There were no cases of wrong-site surgical procedures or retained foreign bodies.

Conclusions: Our study shows that, with a selected patient population, a very low adverse event rate (0.20%) can be achieved. Our review showing few adverse events, no deaths, and no wrong-site surgical procedures supports our view that hand and upper-extremity surgical procedures can be completed safely in the outpatient setting at a freestanding ambulatory surgery center.

Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Advances in medicine have allowed surgeons to perform procedures that were once reserved solely for hospital operating rooms in outpatient surgery centers. Outpatient surgical procedures give patients and physicians an option for safe, cost-effective surgical care offering improved patient comfort and increased efficiency 1. The current U.S. Medicare fee schedule indicates that hospital outpatient surgical facilities are paid 81% more than ambulatory surgery centers for the same service. The U.S. Centers for Disease Control and Prevention (CDC) performed a survey in 2006 and found that 62% of all procedures were performed in an outpatient setting and 43% of the outpatient surgical procedures were performed in a freestanding ambulatory surgery center 2. A freestanding ambulatory surgical center is defined as a facility independent from a hospital. The number has grown dramatically; in 1983, there were 239 ambulatory surgery centers in the U.S., and in 2008 there were more than 5000 such centers 2,3. In 2007, on the basis of Medicare claims, approximately 7% of all procedures performed at ambulatory surgery centers were orthopaedic in nature; and from 2000 to 2007, there was a 77% growth in orthopaedic procedures performed at ambulatory surgery centers because of a shift of service from an inpatient to an outpatient setting 3.

The U.S. Healthcare Cost Utilization Project (HCUP) states that the State Ambulatory Surgery and Services Databases (SASD) include data from hospital-owned ambulatory surgery facilities; however, patient safety data in hand and upper-extremity surgical procedures are not available for freestanding surgery centers. Despite the rapid growth in the number of outpatient surgical procedures being performed, to our knowledge, there remains a paucity of literature on the subject. As the number of procedures performed on an outpatient basis continues to grow, it becomes important that we continue to examine and to monitor the safety of outpatient surgical procedures. In 2010, the U.S. Agency for Healthcare Research and Quality (AHRQ) initiated a safety program for ambulatory surgical procedures with this concern in mind 4.

There is literature on risk factors for adverse outcomes in ambulatory surgery centers 5-7; however, to our knowledge, no specific literature exists on the safety of outpatient hand and upper-extremity surgical procedures. The purpose of this study was to determine the rate of adverse events affecting outpatients undergoing hand and other upper-extremity surgical procedures at a freestanding ambulatory surgery center. We hypothesized that, with the selected patient population, a very low rate of adverse events could be achieved.

Materials and Methods

After obtaining institutional review board approval, a retrospective review of cases performed by five board-certified hand and upper-extremity surgeons at a single, freestanding ambulatory surgery center over an eleven-year period (2001 to 2012) was performed. Upper-extremity surgical procedures predominate at this facility; however, other surgical procedures are also performed, such as ophthalmologic; oculoplastic; urologic; ear, nose and throat (ENT); foot and ankle; and pain management surgical procedures. The surgery center is not affiliated with any particular hospital. The five contributing hand surgeons have partial ownership of the ambulatory surgery center, and the surgeons have an academic affiliation with the University of Pittsburgh and train orthopaedic and plastic surgery residents and hand surgery fellows. There are two board-certified anesthesiologists who perform regional and general anesthesia and supervise nurse anesthetists. They are permitted to provide medical direction in up to four operating rooms simultaneously, consistent with guidelines from the Centers for Medicare & Medicaid Services (CMS).

Depending on the patient's medical condition, preoperative clearance by the patient's primary care physician or cardiologist is obtained, and the anesthesiologists confirm the patient's appropriateness for the surgery center. Patients with severe lung disease, latex allergy, active infection (methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, or Clostridium difficile), quadriplegia, or an American Society of Anesthesiologists physical status (ASA PS) classification of 4 are not allowed to have their procedure performed at the facility. Patients with morbid obesity or other medical problems (such as chronic kidney disease or cardiac disease) are reviewed by the anesthesiologists on a case-by-case basis.

All of the 28,737 procedures that were performed were included in our analysis. Of these cases, 8% were shoulder procedures and the remaining cases were hand, wrist, or elbow procedures; 95% of the cases were elective in nature, and 5% were related to trauma. Procedures canceled in the preoperative holding area prior to the administration of anesthesia, by either the surgeon or the anesthesiologist, were not counted in our adverse event analysis. Adverse events were defined as serious complications causing harm to a patient or leading to additional treatment. Using state-reportable adverse events criteria as a guideline, we divided these into seven main categories: acute infection (defined as requiring formal irrigation and debridement in the operating room or inpatient admission for intravenous antibiotics), postoperative transfer to a hospital, wrong-site surgical procedure, retention of a foreign object, postoperative symptomatic thromboembolism, medication error, and bleeding complications. Infections that only required oral antibiotics were considered minor and not major adverse events. These minor infections were also not consistently reported, and therefore we did not include them in our analysis. Medication sensitivities that did not result in hospital admission were not included in our analysis, as these were considered minor occurrences. These adverse events were then analyzed and were categorized to determine if they led to additional laboratory testing, hospital admission, return to the operating room, emergency department visits, permanent physical disability, or permanent mental impairment. We identified adverse events by reviewing occurrence reports, which are collected from every office at a minimum of thirty days from the day of the surgical procedure. All of these adverse events were additionally reported to the state.

Results

Cancelled Cases

From the 28,838 cases scheduled, there were 101 cases (0.35%) that were cancelled by either the surgeon or the anesthesiologist in the preoperative holding area prior to the administration of anesthesia. Of these cases, 16% were cancelled because either the patient or the surgeon believed that the surgical procedure no longer needed to be performed, 15% were cancelled because of a protocol breach (e.g., the patient had coffee the morning of the surgical procedure), 17% were cancelled because of the presence of a skin lesion at the surgical site (e.g., burn or rash), and 52% were cancelled for medical optimization reasons (44% of these for hypertension, 30% for cardiac arrhythmias or electrocardiogram abnormalities, 8% for elevated blood glucose, 10% for respiratory reasons, and 8% for fevers).

Adverse Events

Of the 28,737 cases, 24% of the patients were classified as ASA 1, 43% were ASA 2, and 33% were ASA 3. There were a total of fifty-eight occurrence reports for the 28,737 cases, for a reported adverse event rate of 0.20%. The majority of the adverse events (fifty-four of fifty-eight) occurred in patients with ASA scores of 1 and 2. Four of the fifty-eight adverse events occurred in four different patients with an ASA score of 3, for a total adverse event rate of 0.04% in cases where the patient was classified as ASA 3. Figure 1 summarizes the adverse events.

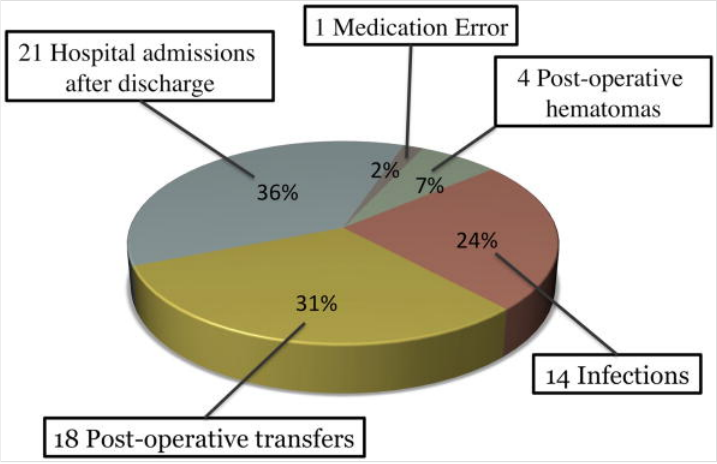

Fig. 1. Pie chart showing a total of fifty-eight adverse events of 28,737 cases performed. Adverse events were defined as serious complications causing harm to a patient or leading to additional treatment.

Infection

There were fourteen patients with major infections, for a rate of 0.05%. Of these fourteen, eleven patients required return to the operating suite for irrigation and debridement, and three patients required inpatient admission for intravenous antibiotic administration. Open shoulder surgical procedures accounted for five of the eleven cases requiring irrigation and debridement. The other six cases were for soft-tissue procedures in the hand or wrist. All infections were successfully treated with some combination of intravenous antibiotics and debridement.

Bleeding Complications

Four patients (0.01%) had to be taken back to the operating room for complications related to bleeding. Two of these patients had had nerve block anesthesia and the other two had had local anesthesia. Two patients were taken back immediately after the surgical procedure from the post-anesthesia care unit because of saturated dressings or hematoma formation, and two patients presented to the office with hematomas requiring surgical evacuation. Three of the cases were open shoulder cases (one rotator cuff repair, one labral repair, and one soft-tissue biopsy), and the other case was a wrist arthrodesis. None of the patients sustained any long-term morbidity.

Postoperative Symptomatic Thromboembolism

There was one case of postoperative pulmonary embolism, for a rate of 0.003%. This patient presented to an emergency room ten days after an open rotator cuff repair and acromioplasty, reporting chest pain and shortness of breath. A review of the case did not identify an underlying predisposition or cause of the pulmonary embolism, and the patient made a full recovery (this patient is counted in the postoperative transfer to hospital subcategory).

Retention of a Foreign Object

There were no cases reported of retained foreign objects. A standard count is performed by the circulating nurse and technician prior to closure.

Medication Error

There was one medication error, for a total rate of 0.003% (one of 28,737 patients). This patient was inadvertently given intravenous cefazolin despite a penicillin allergy; Benadryl (diphenhydramine) was given and no adverse reaction occurred. There were another fifty-eight patients who reported a sensitivity to the medication prescribed to them, such as a skin rash, pruritis, or gastrointestinal upset. Nine of the fifty-eight patients went to their local emergency room for symptoms related to medication sensitivity, and two were admitted for electrolyte imbalance due to prolonged nausea and vomiting (these two patients are counted in the postoperative transfer to hospital subcategory). There were no long-term morbidities reported.

Wrong-Site Surgical Procedure

There were no cases of wrong-site surgical procedure reported among the 28,737 procedures performed. In the case of upper-extremity surgical procedures, the approximate incision is marked by the attending surgeon in the preoperative holding area and is confirmed with the patient. In the operating room prior to incision, the surgeon also performs a surgical time-out.

Postoperative Transfer or Admission to a Hospital

Seventeen patients were transferred to a hospital immediately postoperatively, and one patient was transferred prior to the surgical procedure but after an axillary block had been administered, leading to a total transfer rate of 0.06% (eighteen of 28,737). In all of the cases in which the patient was transferred postoperatively, the abnormality was detected in the operating room or in the post-anesthesia care unit, and the procedure was safely completed in all cases. Of the seventeen patients, six were transferred for cardiac abnormalities (irregular rhythms and chest pain); two were transferred for uncontrolled hypertension; three were transferred for respiratory issues, with one patient requiring emergency intubation in the post-anesthesia care unit secondary to low oxygen saturation (this patient was extubated prior to transfer); three were transferred for pain control (two had incomplete blocks, and one had an open reduction and internal fixation of a clavicle fracture done under general anesthesia); two were transferred because of excessive drowsiness, with subsequent negative work-ups at the hospital for any pathological cause; and one was transferred after sustaining a generalized seizure in the post-anesthesia care unit and was stabilized prior to transfer. One patient sustained symptoms of a transient ischemic attack after an axillary nerve block was placed but prior to starting the scheduled surgical procedure. There were no deaths in this subgroup of patients.

Twenty-one patients were admitted to the hospital in the immediate postoperative period (within seven days of the surgical procedure) but after discharge from our ambulatory surgery center, for a rate of 0.07%. Six of the twenty-one patients were admitted for pain control after the regional anesthesia had worn off. Two patients had myocardial infarctions; one required a cardiac stent, and the other required a permanent pacemaker. Both patients had undergone soft-tissue hand procedures and had shown no evidence of cardiac abnormalities during or immediately after the surgical procedure. One patient had a pulmonary embolism. Two of the twenty-one patients were admitted for decreased oxygen saturation. Subsequent testing was unable to determine a cause, and both patients were discharged after short observational stays. One patient had an acute compartment syndrome after revision open reduction and internal fixation for nonunion of both-bone forearm fractures necessitating emergency fasciotomy on the first postoperative day, but the patient did not have any long-term sequelae. Of the twenty-one patients, three were admitted for postoperative nausea, and two were admitted for intravenous antibiotics.

One patient was admitted to the intensive care unit after developing diabetic ketoacidosis after a carpal tunnel release. Postoperative blood glucose just prior to discharge from the surgery center had been 93 mg/dL. Another patient was found unresponsive by his son on postoperative day 1 and had sustained a cerebral hemorrhage; the exact etiology was not clear. He unfortunately did have some permanent deficits. One patient was admitted for postoperative confusion, and one patient was admitted for postoperative constipation.

Combining both patients transferred to the hospital directly from the ambulatory surgery center and those admitted within the immediate postoperative period, the rate of admission to a hospital after upper-extremity surgery at our ambulatory surgery center was 0.14% (thirty-nine of 28,737).

Discussion

Outpatient surgical procedures performed at ambulatory surgery centers can offer certain advantages over those performed in a hospital-based setting. Ambulatory surgery centers often specialize in certain procedures. This specialization leads to increased volume for these specific procedures and leads to improved patient outcomes 8,9. By performing more of the same procedure, these centers become more efficient as staff become more familiar with their routines 10. Hair et al. showed, in an analysis of the 2006 National Survey of Ambulatory Surgery public data, that surgical procedures performed in freestanding ambulatory surgery centers took a mean of 39% less total time than those performed in hospital-based ambulatory surgery centers 11. With greater specialization and efficiency, coordination and communication among staff are also improved, potentially leading to fewer adverse events 12. Grisel and Arjmand analyzed the quality of four common pediatric ENT procedures performed at an ambulatory surgery center compared with a hospital-based facility. Of 211 cases at the hospital-based facility, there were nine unexpected events, whereas, at the ambulatory surgery center, there were no unexpected events in 275 cases 13. Martín-Ferrero et al. reported on their experience of 10,032 patients undergoing an outpatient orthopaedic surgical procedure (upper and lower extremity) in an ambulatory surgery center located in Spain 14. They had an unplanned overnight admission rate of 0.14%, a readmission rate of 0.11% within thirty days, an emergency room visit rate of 1.21%, and no deaths in their series. The rate of unexpected events in our study is lower, perhaps because we only included upper-extremity procedures.

In our freestanding outpatient surgery center, hand and upper-extremity surgical procedures are the predominant surgery performed. There have been five hand and upper-extremity surgeons operating at the facility during the eleven-year time period studied, and four of the surgeons are very involved in the education of surgical fellows and residents at the surgery center. There is a low turnover rate among the operating room staff, with most being there for more than five consecutive years, and thus they are very familiar with the surgical routines of the surgeons. They also take pride in their work, are efficient (the mean turnover time is thirteen minutes), and make sure that the patients have a safe surgical experience.

We report no wrong-site upper-extremity surgical procedures after 28,737 cases despite hand surgical procedure being high-risk 15,16. At this facility, the attending physician always marks the surgical incision site in the preoperative holding area with the patient awake. Further, we strictly adhere to our surgical checklist and time-out, allowing all members of the operative team to agree on the procedure and surgical site before incision. Checklists have been shown to be effective in reducing complications in multiple health-care settings 17. In addition, there is less staff handover during and after cases, as the majority of cases performed are less than one hour long. This also has been shown to reduce complications 18.

In the current study, we did not examine the associations between the occurrence of infection and deliverance of preoperative antibiotics or patient comorbidities. However, in a prior study performed at the surgery center, it was found that the rate of surgical site infections was not associated with the use of preoperative antibiotics but was associated with smoking status, diabetes mellitus, and longer operative time 19.

This study did raise the question of whether some procedures should be performed in the hospital with a planned admission. Of the 28,737 cases performed in the ambulatory surgery center, only nine patients were admitted to a hospital for postoperative pain control. Pain management after extensive surgery involving bone work can be difficult. However, the great majority of such cases did not result in postoperative admissions for pain control, and therefore admitting all of these patients is believed to be unnecessary and a waste of health-care dollars. We also had one case of acute compartment syndrome after a forearm nonunion surgical procedure. This patient had been discharged home with a regional block in effect. Although the risk of compartment syndrome after this procedure is quite low, consideration should be given to performing this procedure in the hospital setting with a planned admission.

Selection bias of patients treated at a freestanding outpatient surgery center exists. Healthy patients are allowed to undergo procedures at a freestanding surgery center, whereas sicker and more complex patients are often treated at facilities attached to a hospital. This selection process exists for the safety of patients 20. Our review showing few complications (0.20%) and no deaths supports our view that hand and upper-extremity surgical procedures can be completed safely in the outpatient setting at a freestanding surgery center with careful patient selection, coordinated care, and strict adherence to patient safety protocols.

Investigation performed at the Hand & UpperEx Center, Wexford, Pennsylvania

Disclosure: There was no external funding source. The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article.

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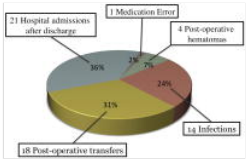

Fig. 1

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ORIGINAL ARTICLE

Long-term patient reported outcomes of elbow, wrist and hand surgery for rheumatoid arthritis

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Abstract

Aim: A retrospective questionnaire survey was conducted to investigate the long-term outcomes of elbow, wrist and hand surgery for rheumatoid arthritis (RA).

Methods: One hundred and thirteen RA patients underwent primary elective elbow, wrist or hand surgery at our hospital between January 2002 and December 2003. To evaluate the outcomes at 10 years after surgery, the patient-reported outcomes were assessed using an original questionnaire that inquired about the site of treatment; the modified Stanford Health Assessment Questionnaire (mHAQ) was also used.

Results: Responses were obtained from 67 patients (98 sites). In the 10 years after surgery, the Disease Activity Score of 28 joint – erythrocyte sedimentation rate (4) and the modified Health Assessment Questionnaire scores of the patients showed significant improvement. Nearly 85% of patients were satisfied with the outcome at the surgical site. The most frequent reason for perceived improvement was 'pain relief' (all surgical sites). An 'improved appearance' was frequently reported after finger surgery and 'increased power' was frequently reported after wrist and thumb surgeries. With regard to elbow surgery, 30% of the patients were satisfied with the increase in motion and power. In contrast, approximately 20% of patients complained of decreased power around the surgical site after elbow and thumb surgeries.

Conclusions: Our original patient-reported outcome assessment tool revealed that elbow, wrist and hand surgery provided long-lasting benefits in RA patients. While the efficacy differed in some of the surgical sites, pain relief was the most favorable effect. Altered medical therapy may also have impacted the patient-perceived outcomes of surgery at 10 years.

Key words: patient reported outcome, questionnaire, rheumatoid arthritis, surgery, upper extremity.

INTRODUCTION

A patient's assessment of the effects of surgery for rheumatoid arthritis (RA) is useful in clinical practice as it offers a patient-friendly method of assessing the effects of surgery. Various surgical procedures are available for the treatment of the elbow, wrist and hand in RA patients. Several patient-reported outcome measures can be used to assess RA disease activity.[1] However, few studies have assessed the efficacy of surgical intervention based on patient-reported outcomes.[2] Previous studies have assessed postoperative outcomes based on objective clinical and radiological measures.

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Several reports have investigated the long-term postoperative outcomes for elbow,[3–5] wrist[6–9] and hand[10,11] surgery for RA with a minimum follow-up period of 10 years. However, with the exception of pain, most of these reports only mention objective outcomes and did not describe subjective outcomes. Thus, in the present study, a retrospective questionnaire survey was conducted to assess the changes in subjective findings, and to investigate the differences in the long-term effects of surgery for RA according to the site of the procedure.

METHODS

Patients

One-hundred and thirteen RA patients underwent primary elective surgery of the elbow, wrist, thumb or fingers at our hospital between January 2002 and December 2003. Each patient was diagnosed with RA according to the 1987 revised American College of Rheumatology (ACR) criteria for RA.[12]

After the exclusion of 25 patients who were deceased or unable to reply because they were staying in a nursing home or due to severe dementia, our original questionnaire sheet was mailed to 88 RA patients. This questionnaire was used to assess the patient-reported outcomes of upper extremity surgery.

Questionnaire (original)

Our original questionnaire was created based on the satisfaction questionnaire described by Riches *et al.*[2] It was composed of seven questions that each included 3–6 possible answers, as follows:

Q1: 'Do you remember the type of surgery that you received 10 years previously?'
1: Remember very well. 2: Remember well. 3: Remember partially. 4: Slightly remember. 5: Do not remember.
Q2: 'What is the present condition of the surgically treated site in comparison to the preoperative condition?'
1: Much better. 2: Better. 3: Unchanged. 4: Worse. 5: Much worse.
Q3: 'What improvement(s) have you noticed in comparison to the preoperative condition?' (Multiple answers were allowed)
1: Pain relief. 2: Improved appearance. 3: Increase in power. 4: Easy to grasp. 5: Increase in motion. 6: Other.
Q4: 'What aspect(s) do you consider to have declined in comparison to the preoperative condition?' (Multiple answers were allowed)
1: Increased or unchanged pain. 2: Worsened or unchanged appearance. 3: Decrease in power. 4: Difficulty in grasping. 5: Decrease in motion. 6: Other.
Q5: 'How is the usability of the hand at the surgically treated site in comparison to before surgery?'
1: Good. 2: Relatively good. 3: Neither good nor poor. 4: Relatively poor. 5: Poor.
Q6: 'Are you satisfied with the results of the surgical treatment?'
1: Highly satisfied. 2: Satisfied. 3: Neither satisfied nor dissatisfied. 4: Somewhat dissatisfied. 5: Dissatisfied.
Q7: 'Would you recommend the same surgery for patients such as yourself?'
1: Yes. 2: Uncertain. 3: No.

The patient background information and the answers to the questionnaire were carefully reviewed. The background information from just before surgery was compared with that at 10 years after surgery.

Statistical analysis

The overall cohort was divided into subgroups according to the site of surgical treatment and the results of the subgroups were compared. The mean and standard deviation (SD) values were determined for each group. All of the statistical analyses were performed using the IBM SPSS Statistics 21 software program (IBM, Armonk, NY, USA). The paired *t*-test was used for parametric data and the Wilcoxon signed-rank test was used for nonparametric data. *P*-values of <0.05 were considered to indicate statistical significance.

Ethics

This study was approved by the Institutional Review Board of our hospital.

RESULTS

Among the 88 patients (77.8%) to whom the questionnaire was sent, three were deceased and 18 were unable to reply; thus responses were obtained from 67 patients (98 sites), which represented 59.3% of the original cohort (Fig. 1). After excluding the patients who indicated that they were unable to recall (or only slightly able to recall) the surgery in Q1, 63 patients (93 sites) remained. The responses to the subsequent questions (Q2 to Q7) were analyzed for these patients.

Surgery was performed to treat structural joint damage due to RA, which caused disability in the patient's daily life due to functional loss. The sites of surgery

included the elbow (n = 20), wrist (n = 42), thumb (n = 15) and finger (n = 16) (Table 1). The common procedures were: total elbow arthroplasty (n = 13); wrist synovectomy and the Darrach procedure (n = 31); radiolunate arthrodesis (n = 17); the Sauvé-Kapandji operation (n = 6); extensor tendon reconstruction (n = 38); arthroplasty at the metacarpophalangeal (MP) joint of the thumb (Swanson) (n = 8); and arthroplasty at the MP joint of the fingers (Swanson) (n = 26). The sites of additional surgical procedures that were performed during the 10-year period (after the primary surgery) included the elbow (n = 2), wrist (n = 11), thumb (n = 5) and finger (n = 2). The additional procedures performed for the lower extremities included total hip arthroplasty (n = 1), total knee arthroplasty (n = 4) and forefoot reconstruction (n = 6).

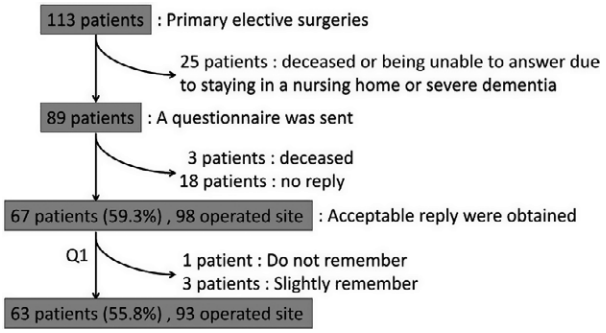

Figure 1 Chart showing the target patients who were sent our original questionnaires and their response rates

Background characteristics of the study population

At surgery, the mean age (range) of the 63 patients was 57.5 (21–78) years, the male/female ratio was 14/53

Table 1 Surgical site and procedures

Surgical site	Procedures	Primary surgery		Additional surgery	
		n (joints)		n (joints)	
Elbow	Synovectomy	5	20	1	2
	TEA	13		1	
	Bursectomy	1		0	
	Ulnar neurolysis for	1		0	
Wrist	Synovectomy and Darrach procedure	31	42	3	11
	Radio lunate arthrodesis	17		2	
	Total wrist arthrodesis	5		1	
	Clayton's tendon transfer	5		2	
	Capitate head replacement	2		1	
	Sauvé-Kapandji operation	6		0	
	Reconstruction of the extensor tendon	38‡		2‡	
	Reconstruction of the flexor tendon	3‡		3‡	
	Neurolysis (carpal tunnel syndrome)	1		1	
Thumb	Arthroplasty at the CMJ (suspensionplasty)	3	15†	2	5†
	Synovectomy at the MPJ	2		1	
	Arthroplasty at the MPJ (Swanson)	8		2	
	Arthrodesis at the MPJ	2		0	
	Arthrodesis at the IPJ	4		1	
Finger	Synovectomy at the MPJ	2	16†	0	2†
	Arthroplasty at the MPJ (Swanson)	26		0	
	Synovectomy at the PIPJ	4		1	
	Flexor tenosynovectomy	6‡		0	
	Fusion at the DIP joint	1		1	
Hip	THA			1	11
Knee	TKA			4	
Foot	Forefoot reconstruction			6	

†Number of hands. ‡Number of digits. BHA, bipolar hip arthroplasty; CM, carpometacarpal; IP, interphalangeal; MP, metacarpophalangeal; PIP, proximal interphalangeal; TEA, total elbow arthroplasty; THA, total hip arthroplasty; TKA, total knee arthroplasty.

Table 2 Patient background

	At the time of surgery	10 years after surgery	
Age, years, mean (range)	57.5 (21–78)	68.1 (31–89)	
Gender, male/female	14/53	14/53	
Disease duration, years, mean (range)	12.3 (0.6–39)	22.5 (11–50)	
PSL usage, %	54.4	54.4	
MTX usage, %	23.5	52.9	
Other csDMARDs usage, %	89.7	70.6	
bDMARDs usage, %	0	19.1	
DAS28-ESR(4)	4.51	2.89	$P < 0.001$*
mHAQ	0.73	0.6	$P = 0.045$*
mHAQ of upper extremity function (items 1, 3, 5 and 7)	0.86	0.64	$P = 0.016$*

*Significant difference by Wilcoxon signed-rank test. bDMARDs, biological disease-modifying anti-rheumatic-drugs; csDMARDs, conventional synthetic disease-modifying anti-rheumatic-drugs; DAS28-ESR(4), Disease Activity Score of 28 joints – erythrocyte sedimentation rate (4); mHAQ, modified Stanford Health Assessment Questionnaire; MTX, methotrexate; PSL, prednisolone.

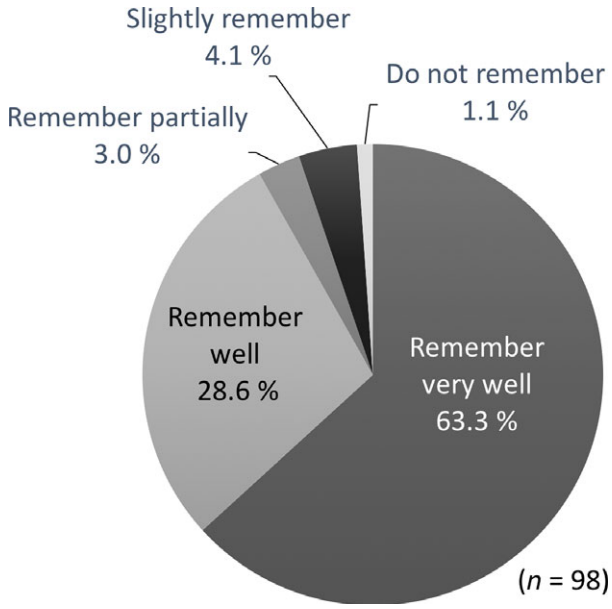

Figure 2 Response to Question 1: 'Do you remember the type of surgery that you received 10 years previously?'

and the mean disease duration (range) was 12.3 (0.6–39) years (Table 2). The drugs administered just before surgery included prednisolone (PSL) (54.4%), methotrexate (MTX) (23.5%), and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) other than MTX (89.7%). No biological DMARDs (bDMARDs) were used at the time of surgery. The mean Disease Activity Score of 28 joints – erythrocyte sedimentation rate (4) (DAS28-ESR[4])[13] was 4.51, the mean modified Stanford Health Assessment Questionnaire (mHAQ) score[14] was 0.73.

At 10 years after surgery, the drugs administered to the patients included PSL (54.4%), MTX (52.9%), csDMARDs other than MTX (70.6%) and bDMARDs (19.1%). In comparison to the distribution just before surgery, a similar number of patients were treated with PSL, the number of patients treated with MTX had increased, and bDMARDs were newly used by approximately 20% of the patients. The mean DAS28-ESR(4) value decreased significantly from 4.51 (moderate disease activity [MDA]) to 2.89 (low disease activity [LDA]) ($P < 0.001$). Thus, a large number of patients shifted from MDA to LDA. The disease activity decreased in all of the surgical site subgroups ($P < 0.001$). In the whole cohort, the mean mHAQ score decreased significantly from 0.73 to 0.60 ($P = 0.045$); there were no significant changes in the comparisons among the surgical site subgroups. The mean item scores that were mainly associated with the upper extremity function (items 1, 3, 5 and 7) decreased significantly from 0.86 to 0.64 ($P = 0.016$). At 10 years after surgery, a significant improvement was noted in items 3 ('Lift a full cup or glass to your mouth'; $P = 0.004$) and 8 ('Get in and out of a bus, car, train, or airplane'; $P = 0.042$).

There were no superficial or deep wound infections at the surgical sites in this study group.

Patient-reported clinical outcomes

A1: Most patients indicated they remembered the type of surgery they received 'Well' (28.6%) or 'Very well' (63.3%) (Fig. 2).

A2: Over 85% of the patients answered 'Much better' (35.9%) or 'Better' (50.0%). Among the surgical site subgroups, finger surgery was associated with the

Table 3 Response to Question 2: 'What is the present condition at the surgically treated site in comparison to the preoperative condition?'

	Elbow (n = 20)	Wrist (n = 41)	Thumb (n = 15)	Finger (n = 16)	Total (n = 92)
Much better	8	15	5	5	33 (35.9%)
Better	9	20	7	10	46 (50.0%)
Unchanged	0	0	0	0	0 (0%)
Worse	2	4	1	0	7 (7.6%)
Much worse	1	2	2	1	6 (6.5%)
Much better and Better	85.0%	85.4%	80.0%	93.8%	79 (85.9%)

Table 4 Response to Questions 3 and 4

	Elbow (n = 20)	Wrist (n = 42)	Thumb (n = 15)	Finger (n = 16)	Total (n = 93)
Pain relief, %	75.0	73.8	46.7	50.0	65.6
Improved appearance, %	20.0	7.1	33.3	50.0	21.5
Increase in power, %	30.0	42.9	33.3	37.5	37.6
Easy to grasp, %	15.0	23.8	26.7	31.3	23.7
Increase in motion, %	39.0	26.2	13.3	12.5	22.6
Others, %	0.0	0.0	0.0	12.5	2.2
Increased or unchanged pain, %	5.0	6.7	6.3	0.0	5.4
Worsened or unchanged appearance, %	10.0	0.0	0.0	0.0	2.2
Decrease in power, %	20.0	8.9	18.8	12.5	14.0
Difficult to grasp, %	0.0	2.2	12.5	12.5	5.4
Decrease in motion, %	10.0	17.8	12.5	12.5	15.1
Others, %	0.0	0.0	6.3	0.0	1.1

Table 5 Response to Question 5: 'How is the usability of the hand at the surgically treated site in comparison to before surgery?'

	Elbow (n = 20)	Wrist (n = 41)	Thumb (n = 15)	Finger (n = 16)	Total (n = 91)
Good	7	18	5	5	35 (38.5%)
Relatively good	9	19	8	10	46 (50.5%)
Neither good nor poor	1	3	1	0	5 (5.5%)
Relatively poor	0	1	0	0	1 (1.1%)
Poor	2	0	1	1	4 (4.4%)
Good or Relatively good	84.2%	90.2%	86.6%	93.8%	81 (89.0%)

highest percentage of favorable responses (93.8%) (Table 3).

A3: The most frequent reason for improvement was 'Pain relief' at all surgical sites. More than 70% of the patients who received elbow and wrist surgery indicated they were satisfied with their level of pain relief. An 'Improved appearance' was frequently noted after finger surgery and 'Increased power' was frequently noted after wrist and finger surgeries. Thirty percent of the patients who received elbow surgery indicated they were satisfied with their increased motion and power (Table 4).

A4: Approximately 20% of the patients who underwent elbow and thumb surgeries complained of a decrease in power around the surgical site, while 18% of the patients who underwent wrist surgery complained of a decrease in motion (i.e., flexion and extension). These patients had undergone radiolunate arthrodesis or total wrist arthrodesis (Table 4).

A5: Overall, 38.5% of the patients answered 'Good usability' and 50.5% answered 'Relatively good usability'. Regarding the outcomes of surgery in the surgical site subgroups, finger joint surgery was associated with highest percentage of favorable outcomes (93.8%) (Table 5).

A6: Overall, 36.2% of the patients were highly satisfied and 48.4% were satisfied. The level of satisfaction with the surgery was highest in the following order:

Table 6 Response to Question 6: 'Are you satisfied with the results of the surgical treatment?'

	Elbow (n = 19)	Wrist (n = 41)	Thumb (n = 15)	Finger (n = 16)	Total (n = 91)
Highly satisfied	6	16	5	6	33 (36.2%)
Satisfied	8	20	7	9	44 (48.4%)
Neither satisfied nor dissatisfied	0	0	2	1	3 (3.3%)
Somewhat dissatisfied	3	5	1	0	9 (9.9%)
Dissatisfied	2	0	0	0	2 (2.2%)
Highly satisfied or Satisfied	73.7%	87.1%	80.0%	93.8%	77 (84.6%)

Table 7 Response to Question 7: 'Would you recommend the same surgery for patients such as yourself?'

	Elbow (n = 19)	Wrist (n = 40)	Thumb (n = 15)	Finger (n = 16)	Total (n = 90)
Yes	12	29	8	8	57 (63.3%)
Uncertain	4	10	7	8	29 (32.2%)
No	3	1	0	0	4 (4.5%)

finger (93.8%), wrist (87.1%), thumb (80.0%) and elbow (73.7%) (Table 6).

A7: More than 60% of the patients would recommend the same surgery (63.3%). This was lower than the rate of satisfaction. The number of patients who answered 'Uncertain' was 32.2%, while 4.5% answered 'No' (Table 7).

The number of respondents to each questionnaire is indicated by the 'n' number at the top-right of the table. The numbers of missing responses for each question were as follows: Q1, Q3, Q4 (n = 0, 0%), Q2 (n = 1, 1.1%), Q5 and Q6 (n = 2, 2.2%) and Q7 (n = 3, 3.2%).

DISCUSSION

To date, several patient-reported outcome instruments, such as the mHAQ, have been used to assess physical function and quality of life (QoL) of RA patients.[14] These instruments deal with the general status of the patients, but they are not sufficient for assessing the status of surgically treated patients because the responses do not directly reflect the status of the surgical site. Thus, we created an original questionnaire about the surgical site and the degree of patient satisfaction based on the study by Riches *et al.*[2] The questionnaire asked about the present condition, improvements, aspects of decline, usability, satisfaction and whether they recommended that other patients undergo the same treatment. In addition, each question had a practical rating system that was directly connected to the surgical effect.

Several studies have investigated the long-term outcomes of elbow, wrist and hand surgery in patients with RA. Although the surgical outcomes after a minimum follow-up period of 10 years have been reported for total elbow arthroplasty,[3–5] radiocarpal arthrodesis,[6] total wrist arthroplasty,[7,8] wrist synovectomy and the Darrach procedure,[9] and metacarpophalangeal joint arthroplasty,[10,11] most of these studies investigated the postoperative changes in the objective findings other than pain. Riches *et al.*[15] evaluated the usefulness of surgical treatment of the hand and wrist in RA patients using a validated modified score for the assessment and quantification of chronic rheumatoid effects of the hand (M-SACRAH) and the original satisfaction was assessed with a questionnaire, with a 3-year postoperative follow-up period.[2] Among the studies that investigated the patient-reported outcomes, our study, which had a follow-up period of 10 years (using similar questionnaires), had the longest follow-up period.

It has been reported that a favorable subjective outcome after rheumatoid upper extremity surgery can be anticipated if disease activity is well-controlled.[16] The favorable responses to our questionnaire might reflect that the disease activity was suppressed by advanced pharmacotherapy during this 10-year period. Ishikawa *et al.*[17] reported that the postoperative serum C-reactive protein level affected the level of postoperative pain. Thus, there seems to be a relationship between the intensity of inflammation and the patient's satisfaction with a pain-free condition at the site of surgery. Some previous reports demonstrated that surgical intervention, especially synovectomy and arthroplasty, enhances

the amelioration of systemic disease activity as well as joint function.[18–23] In this study, the elbow, wrist and hand surgeries might have enhanced the amelioration of the disease activity to some extent.

Our results showed a significant improvement in the DAS28-ESR(4) and the mHAQ scores at 10 years after surgery. It is generally said that lower extremity surgery might contribute to the improvement of disease activity and the mHAQ score. However, a relatively small number of patients in our cohort underwent lower extremity surgery, and the items of the mHAQ that reflected the upper limb function showed greater improvement. This indicated that the disease activity, physical function and QoL of the patients improved after elbow, wrist and hand surgery and that—on the whole—the effect was maintained for 10 years. Durmus *et al.*[24] investigated the relationship between patient-reported outcome instruments and disease activity, and concluded that the HAQ could determine disease activity in RA patients better than other patient-reported outcome measures. Surgical intervention was recommended to some patients in whom clinical remission or LDA was considered to be difficult to maintain with pharmacotherapy due to structural joint damage, and who did not show a low mHAQ score (i.e., ≤0.5 or functional remission). In this study, surgical intervention seemed to be associated with a favorable response to our questionnaire as well as improved mHAQ and DAS28 scores.

In the present study, 84.6% of the patients answered that they were satisfied with the surgically treated site at 10 years after surgery, and 63.3% of the patients indicated that they recommended the same surgery. The difference in the two rates was based on the patients' opinions about the changes in their situation and differences in their background characteristics. On the whole, it appeared that patients were satisfied with their surgery, and that their satisfaction levels remained high for 10 years.

The present study is associated with several limitations, which should be considered when interpreting the results. First, there was some bias when assessing the patient-reported outcomes. The responses were not available for all of the surgically treated patients at 10 years after surgery. Thus, the 46 patients (40%) who were excluded from the analysis might have had worse background factors and a lower satisfaction level. Second, 20 patients (30% of the responders) received additional elbow or hand surgery in the 10 years after the primary surgery. No cases required revision surgery at the primary site. Third, several different surgical procedures were sometimes performed at one surgical site. Fourth, no non-surgical control group was established in this study. Withholding surgery from a disabled patient might pose ethical problems. Finally, the favorable outcomes in the present study might have also been associated with pharmacotherapy. It is difficult to clearly determine the extent to which surgery or pharmacotherapy contributed to these outcomes.

Long-lasting benefits were confirmed in RA patients who underwent upper extremity surgery. If no severe comorbidities were observed and the disease activity could be controlled, then a favorable effect could be maintained at the surgically treated site throughout the 10-year study period. The combination of pharmacotherapy and surgery for disabled patients with damaged joints was important for improving the QoL and maintaining high-level QoL in RA patients.

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None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest in association with the present study.

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Surgical versus non-surgical treatment for carpal tunnel syndrome (Review)

Verdugo RJ, Salinas RA, Castillo JL, Cea G

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[Intervention Review]

Surgical versus non-surgical treatment for carpal tunnel syndrome

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ABSTRACT

Background

Carpal tunnel syndrome results from entrapment of the median nerve in the wrist. Common symptoms are tingling, numbness, and pain in the hand that may radiate to the forearm or shoulder. Most symptomatic cases are treated non-surgically.

Objectives

The objective is to compare the efficacy of surgical treatment of carpal tunnel syndrome with non-surgical treatment.

Search methods

We searched the Cochrane Neuromuscular Disease Group Trials Register (January 2008), MEDLINE (January 1966 to January 2008), EMBASE (January 1980 to January 2008) and LILACS (January 1982 to January 2008). We checked bibliographies in papers and contacted authors for information about other published or unpublished studies.

Selection criteria

We included all randomised and quasi-randomised controlled trials comparing any surgical and any non-surgical therapies.

Data collection and analysis

Two authors independently assessed the eligibility of the trials.

Main results

In this update we found four randomised controlled trials involving 317 participants in total. Three of them including 295 participants, 148 allocated to surgery and 147 to non-surgical treatment reported information on our primary outcome (improvement at three months of follow-up). The pooled estimate favoured surgery (RR 1.23, 95% CI 1.04 to 1.46). Two trials including 245 participants described outcome at six month follow-up, also favouring surgery (RR 1.19, 95% CI 1.02 to 1.39).

Two trials reported clinical improvement at one year follow-up. They included 198 patients favouring surgery (RR 1.27, 95% CI 1.05 to 1.53). The only trial describing changes in neurophysiological parameters in both groups also favoured surgery (RR 1.44, 95% CI 1.05 to 1.97). Two trials described need for surgery during follow-up, including 198 patients. The pooled estimate for this outcome

indicates that a significant proportion of people treated medically will require surgery while the risk of re-operation in surgically treated people is low (RR 0.04 favouring surgery, 95% CI 0.01 to 0.17). Complications of surgery and medical treatment were described by two trials with 226 participants. Although the incidence of complications was high in both groups, they were significantly more common in the surgical arm (RR 1.38, 95% CI 1.08 to 1.76).

Authors' conclusions

Surgical treatment of carpal tunnel syndrome relieves symptoms significantly better than splinting. Further research is needed to discover whether this conclusion applies to people with mild symptoms and whether surgical treatment is better than steroid injection.

PLAIN LANGUAGE SUMMARY

Surgical versus non-surgical treatment for carpal tunnel syndrome

Carpal tunnel syndrome is caused by compression of the median nerve which goes through the carpal tunnel in the wrist. It causes tingling, numbness and pain, mostly in the hand. Treatment is controversial. This review aimed to compare surgical decompression with non-surgical treatments such as splinting or corticosteroid injections. Four trials were found and included, while three are awaiting assessment. The results suggest that surgical treatment is probably better than splinting but it is unclear whether it is better than steroid injection. Further research is needed for those with mild symptoms.

BACKGROUND

Carpal tunnel syndrome (CTS) is the clinical condition resulting from entrapment of the median nerve where it passes under the transverse carpal ligament in the wrist. This region is a closed space within which pressure may rise. Thickening of tendon sheaths or encroachment by other structures leads to a sustained rise in pressure within the canal. This pressure is further increased by flexion or extension of the wrist (Dawson 1999). Carpal tunnel syndrome has been accepted as the most common entrapment neuropathy (Stewart 1993; Martyn 1997). Cross-sectional studies in the Netherlands suggest a prevalence of 9.2% in the female and 0.6% in the male population (de Krom 1992). It has an important economic impact, affecting active people and may occur as a work-related disorder (Rossignol 1997) leading to compensation claims (Leigh 1998).

The most common symptoms are tingling, numbness and pain within the median nerve distribution (particularly the thumb, index and middle fingers) worsening at night. Pain may radiate proximally to the forearm or shoulder. On examination, there may be weakness and atrophy of the thenar muscles associated with sensory loss in the affected fingers.

In spite of the public health importance of CTS, there are no universally accepted diagnostic clinical and laboratory criteria. However, it is agreed that certain electrophysiological abnormalities support the diagnosis. The most frequently used parameters are distal motor and sensory latencies as well as the sensory conduction velocity across the carpal tunnel (Stevens 1997). Other techniques such as a comparison between the distal sensory or motor latencies stimulating the ulnar and median nerve (Felsenthal 1977) or the radial and median nerves (Carroll 1987) have been used. The 'inching technique' (Kimura 1979) allows a precise localisation of the site of entrapment, but its clinical relevance is under debate (Geiringer 1998). There is no universally accepted therapy for CTS (Rosenbaum 1993) although clinical guidelines have been suggested (AAN 1993). For symptomatic patients a range of treatment is offered varying widely around the world, within individual countries, and even hospitals. Most patients are treated non surgically (Miller 1994).

This is an update of a systematic review aiming at discovering whether the evidence supports the assumed therapeutic benefit of surgery over non-surgical treatment. Due to the lack of agreement regarding the criteria for diagnosis of CTS, all studies of symptomatic patients including a control group were to be considered regardless of the diagnostic criteria applied. Subgroup analysis of those trials using the American Academy of Neurology practice parameter for the diagnosis of CTS (AAN 1993) were to be performed if data had been available. Non-surgical therapies such as wrist splints, modification of activities, non-steroidal anti-inflammatory drugs, diuretics and steroid injection into the carpal tunnel (AAN 1993), were to be considered as valid comparisons with the surgical group. Because there is no universally accepted surgical

technique for the treatment of this condition, all procedures such as open or endoscopic section of transverse carpal ligament, with or without neurolysis were to be included. The comparison of the therapeutic effect of different surgical techniques is the subject of a parallel systematic review (Scholten 2007).

OBJECTIVES

The objective of this review is to compare the efficacy of surgical treatment of CTS with non-surgical treatment in improving clinical outcome.

METHODS

Criteria for considering studies for this review

Types of studies

We intended to include all published and unpublished studies in any language, attempting to compare surgical treatment with either non-surgical or no treatment in a randomised way, irrespective of the quality of randomisation and blindness of the design.

Types of participants

All participants diagnosed with CTS were included irrespective of the diagnostic criteria used, aetiology of the syndrome, associated pathology, gender and age.

Types of interventions

All surgical techniques were included and all non-surgical treatments were considered.

Types of outcome measures

Primary outcomes

The primary outcome measure was relevant clinical improvement after three months of follow-up. The improvement was considered relevant if it implied significant relief of pain and paraesthesiae, by at least 50% of the baseline level (Verdugo 1994), or improvement of hypoaesthesia or muscle weakness resulting in improvement in quality of life and functional status.

Secondary outcomes

1. Improvement of neurophysiological parameters.
2. Clinical improvement reported by authors without including its relevance to the functional status of the participant, for example better performance with the two point discrimination test.
3. Clinical improvement at less than three months of follow-up.
4. Clinical improvement at one year of follow-up.
5. Complications of surgery including formation of a painful neuroma of the palmar cutaneous branch of the median nerve, tender or hypertrophic scar, section of the motor branch, subluxation ('bow stringing') of flexor tendons, wound infection and reflex sympathetic dystrophy.
6. Need for surgery during follow-up in participants treated medically or secondary surgery in those treated surgically.
7. Complications of medical treatments, particularly steroid injections. These include among others damage to the median nerve, chemical synovitis, infection and digital flexor tendon rupture.
8. Return to work at three months or less of follow-up.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Neuromuscular Disease Group Trials Register for randomised trials using 'median nerve entrapment', 'carpal tunnel syndrome' and 'entrapment neuropathy' as the search terms. We originally searched MEDLINE and EMBASE and the LILACS database. LILACS is a specialised database, supported by the Pan-American Health Organisation, aiming to collect all biomedical literature published in Latin America.
We updated the search of the Cochrane Neuromuscular Disease Group Trials Register (January 2008), MEDLINE (January 1966 to January 2008), EMBASE (January 1980 to January 2008) and LILACS (January 1982 to January 2008), which revealed two further relevant trials.

For full search strategies for each of the databases listed above, see Appendix 1,Appendix 2 and Appendix 3.

Searching other resources

We checked the bibliographies in relevant papers and contacted the authors to obtain information about other published or unpublished studies.

Data collection and analysis

A search was conducted to identify new trials not included previously, to update this review. The abstracts were read by two authors independently (RS and RV). Any disagreement about inclusion of a study would have been discussed with a third author (JGC) and a consensus reached. Data were extracted independently by three authors (RV, RS and JGC) using a structured sheet. Any disagreement would have been discussed by the complete group of authors to reach a consensus. Statistical analysis was performed using the Review Manager (RevMan) software developed by the Cochrane Collaboration. Both proportional and absolute risk reductions were calculated for each outcome. Heterogeneity between trial results was tested with a standard Chi squared test. The main analysis was based on consideration of all included trials. Trials with good allocation concealment would also have been analysed separately (Schulz 1995). We also planned a priori sensitivity analyses based on:

1. gender and
2. diagnostic criteria (trials using the diagnostic criteria proposed by the AAN (AAN 1993) and those which did not).

RESULTS

Description of studies

We found four randomised controlled trials (Garland 1964; Gerritsen 2002; Ly Pen 2005; Hui 2005). One of them (Garland 1964) included 22 women diagnosed with CTS based on clinical evaluation and distal motor latency of the median nerve greater than 4.5 milliseconds, although the distance between distal stimulating and recording sites was not given. Participants were allocated to one of two groups by a secretary, using 'a previously prepared random list'. One group had open section of the anterior carpal ligament; the other had splinting 'of the hand, wrist and arm for one month'. Eleven participants were allocated to each arm. One participant allocated to the surgical arm refused surgery, but was included by us in the originally allocated group. The other 11 participants underwent splinting. Both groups of participants 'were reviewed clinically and electromyographically at regular intervals for up to one year,' and outcomes were given for the end of this period of follow-up. Another study (Gerritsen 2002) included 143 women and 33 men out of 326 participants examined for eligibility. The diagnosis of CTS was based on clinical evaluation and electrophysiological findings (decreased sensory conduction velocity in the median nerve or an increased median-ulnar distal sensory latency difference). Participants were allocated to overnight splinting of the wrist for at least six weeks, or open surgical release of the carpal tunnel ligament, using a block randomisation method stratified by centre. The sequence was generated using random number tables. Eighty-seven participants were allocated to surgery and 89 to splinting. Fourteen participants allocated to surgery and 13 participants allocated to splinting did not receive the treatment as assigned. Both groups of participants were evaluated by a physiotherapist at baseline and at three, six and twelve months after randomisation. Clinical improvement was evaluated using a six-point ordinal scale. Two further primary outcomes were considered: number of nights that the participant awoke due to the symptoms during the past week and the severity of the main complaint. A third study (Ly Pen 2005) included 93 women and 8 men. This study considered wrists, rather than patients, as the unit of randomisation. Patients with bilateral CTS were included, undergoing separate randomisation for each wrist. They thus report that 163 out of 217 "wrists" eligible for randomisation, were included. In the published paper they report a subgroup analysis of outcome in 69 patients with either unilateral CTS or in the most symptomatic wrist in patients with bilateral CTS. These are the patients included in our statistical analysis. Patients were 18 years old or older. Inclusion criteria were symptoms of CTS of at least three months, unresponsive to a course of at least two weeks of nonsteroidal anti-inflammatory drugs and splinting. They were enrolled only if clinical and electrophysiological features of CTS were present (distal motor latency in the median nerve above 4.2 msec or a decrease in the sensory conduction velocity at the carpal tunnel below 44 m/sec.). Patients were allocated to open surgery or steroid injection beneath the transverse carpal ligament from the ulnar side of the wrist. For the subgroup of patients included in our meta-analysis, the authors reported a 70% improvement in nocturnal paraesthesias at three, six and twelve months. They reported that "results for 20% and 50% improvement in the three domains were similar". The fourth study (Hui 2005) included 48 women and 2 men out of 63 patients examined for eligibility. Patients with newly diagnosed CTS of more than three months but less than one year of duration were enrolled if clinical and electrophysiological features of CTS were present. The electrophysiological criteria were: median-ulnar palmar sensory latency difference greater than 0.5 msec. or distal motor latency (DML) greater than 4.0 msec. Severe CTS with thenar atrophy or unobtainable DML were excluded. Patients were randomly allocated by a computer-generated code to surgical decompression of the carpal tunnel (by one experienced neurosurgeon), under local anaesthesia or steroid injection. The primary outcome considered was improvement in symptoms as measured by the global symptom score (GSS) 20 weeks after intervention. GSS rates symptoms on a scale of 0 (no symptoms) to 10 (severe) in five categories: pain, numbness, paraesthesia, weakness/clumsiness, and nocturnal awakening (Hui 2005). They considered as secondary outcomes, electrophysiological measures (DML and sensory nerve conduction velocity) and grip strength measurements using a dynamometer.

Risk of bias in included studies

The four included studies stated that participants were allocated randomly, although in one of them (Garland 1964) it is not clear how the randomisation sequence was generated, or if it was properly concealed. The fact that the 22 participants turned out to be distributed in even sets of eleven, raises doubts about the quality of the randomisation and allocation concealment but we do not have evidence to support this suspicion. No losses to follow-up were reported. The other three studies (Gerritsen 2002; Hui 2005; Ly Pen 2005) had adequate allocation concealment since the allocated treatment was included in a coded and sealed opaque envelope. In the surgical arm of one of them (Gerritsen 2002) there were nine participants (10.3 %) not included in the analysis at three months of follow-up and 14 (16 %) at one year. In the non-surgical arm three participants (3.3 %) were not included in the analysis at three months and six (6.6%) at twelve months. In the third study (Ly Pen 2005) there were no losses to follow-up at three months, which is the time of our primary outcome, while they reported in the surgical group one "wrist" loss at six months and four additional "wrists" at twelve months of follow-up. In the injection wrist group they reported two "wrists" lost to follow-up at twelve months. The authors of the fourth study (Hui 2005) reported no losses to follow up.

Two of the four studies were not blinded (Garland 1964; Ly Pen 2005). Two of them (Gerritsen 2002; Hui 2005) attempted to hide the scar from the evaluators with a plaster.

See Table 1.

Effects of interventions

The analyses included all events regardless of the compliance of the participants with the treatment to which they were allocated.

Primary outcome

Three trials (Gerritsen 2002; Ly Pen 2005; Hui 2005) considered relevant clinical improvement after three months. In one of them (Gerritsen 2002) treatment success was defined as completely recovered or much improved using the ordinal scale mentioned above. Out of 87 participants allocated to surgery, 62 (71%) were in these categories at three months. Out of 89 participants allocated to splinting, 46 (51.6%) qualified for treatment success. The confidence interval favoured the surgical group (relative risk (RR) 1.38, 95% confidence interval (CI) 1.08 to 1.75). In the second trial (Ly Pen 2005), out of 33 patients allocated to injection, 29 (87.9%) had 70% improvement in nocturnal paraesthesiae while out of 36 patients allocated to surgery 21 (58.3%) obtained the same result, at three months (RR 0.66, 95% CI 0.49 to 0.90). A third trial (Hui 2005) reported clinical improvement publishing averages at baseline, 6 and 20 weeks after intervention. At 20 weeks they published an improvement in the GSS from 25.2 to 16.6 in the injection group, and from 28.6 to 4.3 in the surgical group. The corresponding author sent us the raw data showing that in the injection group 11 out 25 patients improved by at least 50% in the GSS while in the surgical group 24 out of 25 improved by 50% or more at 20 weeks (RR 2.18, 95% CI 1.39 to 3.42). The meta-analysis gave a pooled estimate of RR 1.23, CI 1.04 to 1.46 favouring surgery (see Analysis 01.01).

Two trials (Gerritsen 2002, Ly Pen 2005) also considered clinical improvement at six months. In the first (Gerritsen 2002) seventy-two participants (82.7%) from the surgical group showed significant clinical improvement while 57 participants (64%) in the non-surgical group did so. The CI favoured the surgical group (RR 1.29, 95% CI 1.08 to 1.55). In the second (Ly Pen 2005) 24 patients (72.7%) in the injection group and 25 (69.4%) in the surgical group achieved a 70% response in nocturnal paraesthesiae (RR 0.95, 95% CI 0.71 to 1.29). The pooled estimate from all three trials was RR 1.19, 95% CI 1.02 to 1.39, again favouring surgery (see Analysis 01.02).

Secondary outcome

(1) Clinical improvement at one year of follow-up

In one trial (Garland 1964) all the patients operated upon in the trial were completely relieved of symptoms for at least one year,' while only two participants allocated to the non-surgical group 'were relieved temporarily'. Although for these two participants an exact time period was not given, we considered them as being relieved of symptoms for at least one year. The result favoured the surgical group (RR 5.00, 95% CI 1.41 to 17.76). The other trial (Gerritsen 2002) reported significant improvement at one year in 67 out of 87 patients (77%) in the surgical group, and 60 out of 89 (67.4%) in the non-surgical group, favouring surgery (RR 1.14, 95% CI 0.95 to 1.37). The pooled estimate favoured surgery (RR 1.27, 95% CI 1.05 to 1.53) (see Analysis 02.01). A third trial (Ly Pen 2005) reported a non significant difference favouring surgery, in nocturnal paraesthesiae, at 12-month follow-up (63.6% of wrists in the injection group and 69.4% in the surgery group achieved a 70% response).

(2) Clinical improvement reported by authors without including its relevance to the functional status of the participant

One trial (Hui 2005) reported improvement in grip strength at 20-week as measured by a trained occupational therapist using a JAMAR hydraulic hand dynamometer. The results favoured the non-surgical group without reaching statistical significance (RR 0.71, 95% CI 0.43 to 1.15) (see Analysis 02.02).

(3) Improvement of neurophysiological parameters

One trial (Garland 1964) described complete reversal of the neurophysiological abnormalities in all operated participants but this

outcome was not described in the non-operated participants, preventing the comparison between the two groups. A second trial (Gerritsen 2002) reported improvement in distal sensory latency in the median nerve, median-ulnar distal sensory latency difference, and distal motor latency in the distal nerve in both treatments groups. However, only average figures were given, preventing us from calculating the differences in risks between both groups. A third trial (Hui 2005) reported improvement in DML and sensory nerve conduction after both interventions greater in the surgical group. In the surgical group 23 out of 25 patients showed improvement in amplitude of sensory potential while 16 out of 25 in the injection group did so (RR 1.44, 95% CI 1.05 to 1.97) (see Analysis 02.06).

(4) Need for surgery during follow-up in participants treated medically or secondary surgery in those treated surgically

In one trial (Garland 1964) among the 11 participants treated medically, eight underwent surgery during follow-up. Apparently no operated participant required re-operation, although no information was given regarding secondary surgeries. The result favoured the surgical group (RR 0.06, 95% CI 0.00 to 0.91). In other series (Gerritsen 2002) one out of 87 participants in the surgical group underwent re-operation and 35 out of 89 participants in the splinting group underwent surgery (RR 0.03, 95% CI 0.00 to 0.21). The pooled estimate indicated that a significant proportion of medically treated people required surgery while the risk of re-operation in the surgically treated people is low: RR 0.04, 95% CI 0.01 to 0.17 (see Analysis 02.03). The other two trials (Ly Pen 2005; Hui 2005) did not report need for surgery in the injection group or need for a second surgery in the surgical group.

(5) Clinical improvement at less than three months of follow-up

One trial (Gerritsen 2002) reported relevant clinical improvement at one month of follow-up. Twenty-three out of 87 participants (26.4%) assigned to undergo surgery, and 37 out of 89 participants in the non-surgical group (41.5%) showed significant improvement. This outcome favoured non-surgical treatment (RR 0.64, 95% CI 0.41 to 0.98) (see Analysis 02.04).

(6) Complications of surgery and medical treatment

Secondary outcomes (5) and (6), as stated in the methods, were merged for the purpose of this analysis. One of the trials (Gerritsen 2002) reported adverse effects during the follow-up period. Adverse effects include painful or hypertrophic scar; wound haematoma and infection; stiffness, swelling or discomfort of the wrist and reflex sympathetic dystrophy. Fifty-eight out of 87 participants (56.6%) allocated to surgery and 46 out of 89 participants (51.7%) in the non-surgical group had at least one adverse effect. The authors did not describe major complications such as damage to a nerve and a significant proportion of complications in the group assigned to splinting were attributed to surgery needed during the follow-up. Another series (Hui 2005) reported no major surgical complications; there were two wound haematomas and nine cases of mild to moderate wound pain in the surgical group while in the injection group there were one case of cellulitis and four cases of pain at the injection site. The pooled results favoured non-surgical treatment (RR 1.38, 95% CI 1.08 to 1.76) (see Analysis 02.05).

DISCUSSION

In this update, we included four randomised controlled trials comparing surgical and non-surgical therapies in people diagnosed as suffering carpal tunnel syndrome. These trials indicate that there is a better response from people undergoing surgical treatment compared with splinting (Garland 1964; Gerritsen 2002) but it is unclear whether there is a better response from surgical treatment compared with steroid injection (Ly Pen 2005; Hui 2005). The difference is statistically significant. Detection bias could not be ruled out because of the lack of blinding of the outcome assessment in two trials (Garland 1964; Ly Pen 2005) while the other two (Gerritsen 2002; Hui 2005) attempted to hide the scar with a plaster. In one of the trials (Garland 1964) it is not clear if selection bias was avoided due to the lack of information about the randomisation procedure. Apparently there was a high level of heterogeneity among the participants admitted to this trial, judging from the period of time of symptoms, ranging from one month to twenty years. As there is no information on the baseline clinical and electrophysiological status of the two groups, we cannot be sure that the risk of both groups was similar in this trial. The other three trials had adequate allocation concealment (Gerritsen 2002; Hui 2005; Ly Pen 2005). Significant improvement after three months, defined as the primary outcome in this review, was reported by three trials (Gerritsen 2002; Hui 2005; Ly Pen 2005) favouring surgery with a RR of 1.23 (95% CI 1.04 to 1.46). However, significant statistical heterogeneity exists among the included trials (test for heterogeneity $Chi^2 = 22.96$, $df = 2$ $p < 0.0001$, $I^2 = 91.3\%$), that may be explained by clinical diversity among trials. Two of these trials favoured surgery (Gerritsen 2002; Hui 2005) and one favoured steroid injection (Ly Pen 2005). A possible cause for the heterogeneity is the fact that in the trial that reported a better outcome for non surgical treatment (Ly Pen 2005), only the subgroup with unilateral STC was included in our analysis. Furthermore this trial considered as inclusion criteria non-respondent patients to medical treatment including splinting. In these trials the participants allocated to surgical and non-surgical groups showed no significant differences in relevant features.

The pooled number of participants included in these trials was adequate to detect differences in improvements between both arms.

At the time of collecting data for the primary outcome analysis the losses were 6.08% (9 out of 148 participants) in the surgical group and 2.04% (3 out of 147 participants) in the non-surgical group. A sensitivity analysis assuming that all participants lost to follow-up in the surgical group did not improve and all participants lost in the splinting group improved, did not change the significance of the primary outcome analysis, although the lower limit of the 95% confidence interval for the RR was 1.01. Both treatment groups had a good success rate in two trials (Gerritsen 2002; Ly Pen 2005) although it should be noted that a large number of patients allocated to splinting in one trial (Gerritsen 2002) underwent surgery during follow-up and the other trial (Ly Pen 2005) did not report need for surgery during follow up in the injection group. A third trial (Hui 2005) reported good recovery rate in the surgical group but only 44% of patients improving with steroid injection. Even though a subgroup analysis was not specified for different non-surgical treatments, it should be noted that when surgery is compared with steroid injection, the combined results do not clearly favour one intervention over the other, at least for a short-term outcome such as three months symptomatic response.

Only two trials reported adverse effects during the follow up period (Gerritsen 2002; Hui 2005) and these were common in both groups, although a significant number of adverse events reported in the non-surgical group was caused by surgery during follow-up. This pooled estimate was based on the intention-to-treat analysis which was confounded by the fact that many participants in the non surgical group had received surgery before the one year follow-up visit. Most adverse effects in the non surgical group were reported by one trial (Gerritsen 2002). The frequency of adverse events must be considered by the treating physician when advising on the choice of surgical or non-surgical therapies.

There is insufficient information in the paper reporting better outcome in the splinting group at one month of follow-up (Gerritsen 2002) to draw any meaningful conclusion. The results after one year of follow-up could be analysed including only two trials (Garland 1964; Gerritsen 2002). Both of them suggest that choosing surgery improves the chance of a good outcome. One of them (Garland 1964) shows a statistically significant improvement while the other does not (Gerritsen 2002). The pooled results show an overall better outcome for surgery by about 14%, but it should be noted that the statistical heterogeneity between trials is significant. This heterogeneity may be explained by the clinical and methodological diversity existing among trials. The inclusion of more severely affected patients may explain the better results in the surgical group in one of the trials (Garland 1964). In the earlier trial (Garland 1964) the neurophysiological criterion used was a distal motor latency of the median nerve greater than 4.5 msecs, while in the other trial (Gerritsen 2002) electrophysiological criteria included decreased sensory conduction velocity in the median nerve or an increase median to ulnar sensory latency. These different criteria might have resulted in the inclusion of patients with a lesser degree of severity in the Gerritsen trial (Gerritsen 2002). A further possible reason for the significant heterogeneity between the trials may reside in the high proportion of patients allocated to splinting that ended up undergoing surgery within one year of follow-up in one of the trials (Gerritsen 2002). Furthermore, the trial whose outcomes at one year were not included in the analysis due to the way in which the results were presented (Ly Pen 2005), reported no significant difference between surgical and non-surgical treatments at one year of follow up.

Although the better results in the surgical group are statistically significant, the lower limit of the CI is close to the non significant threshold. The high incidence of adverse events indicates the need to identify subgroups of participants who would be most likely to benefit from surgery. Therefore there is still a need for well designed clinical trials addressing the question of the efficacy of surgery in CTS. These studies should consider age, occupation, duration of symptoms and severity of the entrapment, among others, as criteria to identify subgroups in advance.

AUTHORS' CONCLUSIONS

Implications for practice

Surgical treatment seems to be better than non-surgical treatment for relieving symptoms of carpal tunnel syndrome. The superiority of surgery over splinting seems evident, but this not so clear with steroid injection.

Implications for research

There is a need for further research to assess the effect of operation on functional outcome and in subgroups such as those with mild symptoms. Further studies are also necessary comparing surgery with steroid injection.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Garland 1964

Methods	R = random sequence administered by secretary. Not known if the allocation was properly concealed. No blinding
Participants	22 women. CTS diagnosed based on clinical evaluation and distal motor latency > 4.5 msec
Interventions	Surgical intervention by open section of the anterior carpal ligament versus splinting for one month
Outcomes	Complete relief of symptoms and reversal of neurophysiological parameters
Notes	UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Gerritsen 2002

Methods	R = block randomisation using coded and sealed opaque envelopes. Sequence generated using random number tables
Participants	176 Dutch literate adult patients, diagnosed based on clinical evaluation and electrophysiology
Interventions	Overnight splinting inmobilising the wrist in neutral position for at least six weeks versus standard open section of the carpal ligament
Outcomes	Primary outcomes: (1) Relevant clinical improvement. (2) Number of nights that the patient woke due to the symptoms in a week. (3) Severity of the main complaint during the past week. Secondary outcomes: (1) Symptom severity and functional status scales. (2) Overall severity of CTS complaints scored by physiotherapist. (3) Neurophysiological parameters after 12 months. (4) Severity of pain, paraesthesia, and hypoesthesia both at night and during the day. All primary and two secondary outcomes were measured at 3, 6 and 12 months after randomisation
Notes	Attempts were made to undertake a blind evaluation. The trial took place in the Netherlands

Gerritsen 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Hui 2005

Methods	R = random computer-generated code. A research assistant not involved in the management of cases prepared and coded opaque envelopes containing the treatment allocation.
Participants	48 women and 2 men, with more than 3 months and less than one year duration of symptoms, diagnosed clinically and electhrophysiologically
Interventions	Surgical decompression under local anaesthesia or steroid injection
Outcomes	Primary outcome: Improvement in symptoms as measured by the global symptom score (GSS) 20 weeks after intervention. Secondary outcomes: (1) Electrophysiological measures (DML and sensory nerve conduction velocity) (2) grip strength measurements using a dynamometer.
Notes	Hong Kong, China

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Ly Pen 2005

Methods	R = random sequence generated by computer in blocks of 6 cases. Sealed envelopes containing the treatment assignments were provided by our biostatistics unit.
Participants	93 women and 8 men, 18 years old or older with symptoms of at least 3 months, unresponsive to a course of at least 2 weeks of nonsteroidal anti-inflammatory drugs and splinting. Clinically and electrophysiologically confirmed
Interventions	Open surgery or steroid injection beneath the transverse carpal ligament from the ulnar side of the wrist

Ly Pen 2005 (*Continued*)

Outcomes	Primary outcome: percentage of wrists reaching at least a 20% reduction in the VAS score for nocturnal paraesthesias at 3 months of follow up. Secondary outcomes: percentages of wrists with a 20% reduction in the VAS score for nocturnal paraesthesias at 6 and 12 months, a 20% response for pain and functional impairment, as well as a 50% and a 70% response in nocturnal paraesthesias, pain, and functional impairment.
Notes	Wrists rather than patients were used as the units for randomisation. Bilateral CTS were excluded from our analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Sparapani 2006	Not randomised, as informed by the correponding author in a personal communication

Characteristics of studies awaiting assessment *[ordered by study ID]*

Elwakil 2007

Methods	Not known
Participants	Not known
Interventions	Not known
Outcomes	Not known
Notes	Not known

Ucan 2006

Methods	Not known
Participants	Not known
Interventions	Not known
Outcomes	Not known
Notes	Not known

DATA AND ANALYSES

Comparison 1. Surgical versus non-surgical treatment - primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in clinical symptoms at three months	3	295	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [1.04, 1.46]
2 Improvement in clinical symptoms at six months	2	245	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.02, 1.39]

Comparison 2. Surgical versus non-surgical treatment - secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical improvement at one year of follow-up	2	198	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.05, 1.53]
2 Clinical improvement without including its relevance	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.43, 1.15]
2.1 Improvement in grip strength	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.43, 1.15]
3 Need for surgery or secondary surgery during follow-up	2	198	Risk Ratio (M-H, Fixed, 95% CI)	0.04 [0.01, 0.17]
4 Clinical improvement at less than three months	1	176	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.41, 0.98]
5 Complications of surgery and medical treatment	2	226	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.08, 1.76]
6 Improvement in neurophysiological parameters	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.05, 1.97]
6.1 Change in amplitude of sensory potential	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.05, 1.97]

ADDITIONAL TABLES

Table 1. Methodological quality of included studies

Study	Alloc. concealment	Diagnostic criteria	Baseline differences	Patient blinding	Observer blinding
Garland 1964	unclear	adequate	not reported	not attempted	not attempted
Gerritsen 2002	adequate	adequate	adequate	not attempted	inadequate

Table 1. Methodological quality of included studies (*Continued*)

Hui 2005	adequate	adequate	adequate	not attempted	inadequate
Ly-Pen 2005	adequate	adequate	adequate	not attempted	not attempted

WHAT'S NEW

Last assessed as up-to-date: 24 January 2008.

Date	Event	Description
16 August 2016	Review declared as stable	This review is not longer being updated. See Published notes.

HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 2, 2002

Date	Event	Description
14 May 2008	New search has been performed	The review was updated to incorporate two new trials in January 2008
14 May 2008	New citation required and conclusions have changed	The review was updated to incorporate two new trials in January 2008 resulting in a revision to the review conclusions
13 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Two authors (RS and RV) read the papers independently and agreed on inclusion. The data were extracted independently by three reviewers (RV, RS and JGC) using a structured sheet. The papers were discussed by three reviewers to clarify the statistical method used and the number of patients originally allocated to the different treatments. The review was written by all four reviewers.

DECLARATIONS OF INTEREST

None declared.

NOTES

This Cochrane systematic review is no longer being updated. New reviews of surgical interventions for carpal tunnel syndrome, which include comparisons with nonsurgical interventions, will replace this review. Endoscopic release for carpal tunnel syndrome was published in 2014 (Vasiliadis 2014a). Open release for carpal tunnel syndrome is a published protocol (Vasiliadis 2014b). A further review of Mini-open release for carpal tunnel syndrome is planned.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [therapeutic use]; Carpal Tunnel Syndrome [*surgery; therapy]; Randomized Controlled Trials as Topic; Splints

MeSH check words

Humans

GYNECOLOGY

Cost-effectiveness of treatments for heavy menstrual bleeding

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BACKGROUND: Heavy menstrual bleeding affects up to one third of women in the United States, resulting in a reduced quality of life and significant cost to the health care system. Multiple treatment options exist, offering different potential for symptom control at highly variable initial costs, but the relative value of these treatment options is unknown.

OBJECTIVE: The objective of the study was to evaluate the relative cost-effectiveness of 4 treatment options for heavy menstrual bleeding: hysterectomy, resectoscopic endometrial ablation, nonresectoscopic endometrial ablation, and the levonorgestrel-releasing intrauterine system.

STUDY DESIGN: We formulated a decision tree evaluating private payer costs and quality-adjusted life years over a 5 year time horizon for premenopausal women with heavy menstrual bleeding and no suspected malignancy. For each treatment option, we used probabilities derived from literature review to estimate frequencies of minor complications, major complications, and treatment failure resulting in the need for additional treatments. Treatments were compared in terms of total average costs, quality-adjusted life years, and incremental cost-effectiveness ratios. Probabilistic sensitivity analysis was conducted to understand the range of possible outcomes if model inputs were varied.

RESULTS: The levonorgestrel-releasing intrauterine system had superior quality-of-life outcomes to hysterectomy with lower costs. In a probabilistic sensitivity analysis, levonorgestrel-releasing intrauterine system was cost-effective compared with hysterectomy in the majority of scenarios (90%). Both resectoscopic and nonresectoscopic endometrial ablation were associated with reduced costs compared with hysterectomy but resulted in a lower average quality of life. According to standard willingness-to-pay thresholds, resectoscopic endometrial ablation was considered cost effective compared with hysterectomy in 44% of scenarios, and nonresectoscopic endometrial ablation was considered cost effective compared with hysterectomy in 53% of scenarios.

CONCLUSION: Comparing all trade-offs associated with 4 possible treatments of heavy menstrual bleeding, the levonorgestrel-releasing intrauterine system was superior to both hysterectomy and endometrial ablation in terms of cost and quality of life. Hysterectomy is associated with a superior quality of life and fewer complications than either type of ablation but at a higher cost. For women who are unwilling or unable to choose the levonorgestrel-releasing intrauterine system as a first-course treatment for heavy menstrual bleeding, consideration of cost, procedure-specific complications, and patient preferences can guide the decision between hysterectomy and ablation.

Key words: abnormal uterine bleeding, cost-effectiveness, endometrial ablation, heavy menstrual bleeding, hysterectomy, levonorgestrel-releasing intrauterine device, management, menorrhagia, treatment

In the United States, more than $1 billion is spent every year for the treatment of heavy menstrual bleeding, and more than $12 billion is incurred in indirect costs through lost productivity.[1,2] Heavy menstrual bleeding is estimated to account for one third of all gynecology visits and represents a significant burden for more than 10 million women.[2-4]

Multiple treatment options exist for women whose symptoms cannot be controlled with more conservative methods such as oral contraceptives, each offering different combinations of symptom control, complication risk, and cost. As health systems and policies continue to emphasize value-based treatment decisions, it is important to give physicians and patients the tools to understand the health and economic trade-offs associated with each of these options.

For heavy menstrual bleeding, hysterectomy offers complete symptom control, but it is expensive, invasive, and irreversible and requires considerable recovery time.[5,6] Procedure alternatives to hysterectomy include resectoscopic endometrial ablation, nonresectoscopic endometrial ablation, and the levonorgestrel intrauterine system (LNG-IUS).[7,8] Hysterectomy alternatives are less invasive and offer reduced initial cost. However, additional procedures may be required if symptoms are not successfully controlled, resulting in additional expense and potential complications.

Previous studies have demonstrated the risks and benefits of each treatment in isolation or in limited combinations,[9-12] but there has yet to be a head-to-head comparison of cost effectiveness for these 4 options in the context of the US health care system. Decision analytic models are a technique to incorporate information from multiple clinical trials and observational studies to simulate a head-to-head comparison of treatment options. Information from these simulated comparisons can provide important insight for women and their physicians as they consider treatment options.

We created a cost-effectiveness model to understand the cost and quality trade-offs associated with hysterectomy,

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resectoscopic ablation, nonresectoscopic ablation, and LNG-IUS for the treatment of heavy menstrual bleeding over a 5 year time period.

Materials and Methods

Women in our hypothetical cohort of 100,000 premenopausal women could undergo 1 of 4 possible treatments for heavy menstrual bleeding of benign etiology: hysterectomy, resectoscopic endometrial ablation, nonresectoscopic endometrial ablation, or LNG-IUS.

A rigorous review of existing literature was conducted to understand treatment-related complications, outcomes, and costs. PubMed key word searches were performed using combinations of search terms including menorrhagia, heavy menstrual bleeding, abnormal uterine bleeding, levonorgestrel intrauterine device, Mirena (Bayer, Whippany, NJ) hysterectomy, endometrial ablation, cost-benefit analysis, cost-effectiveness, and quality-adjusted life-years.

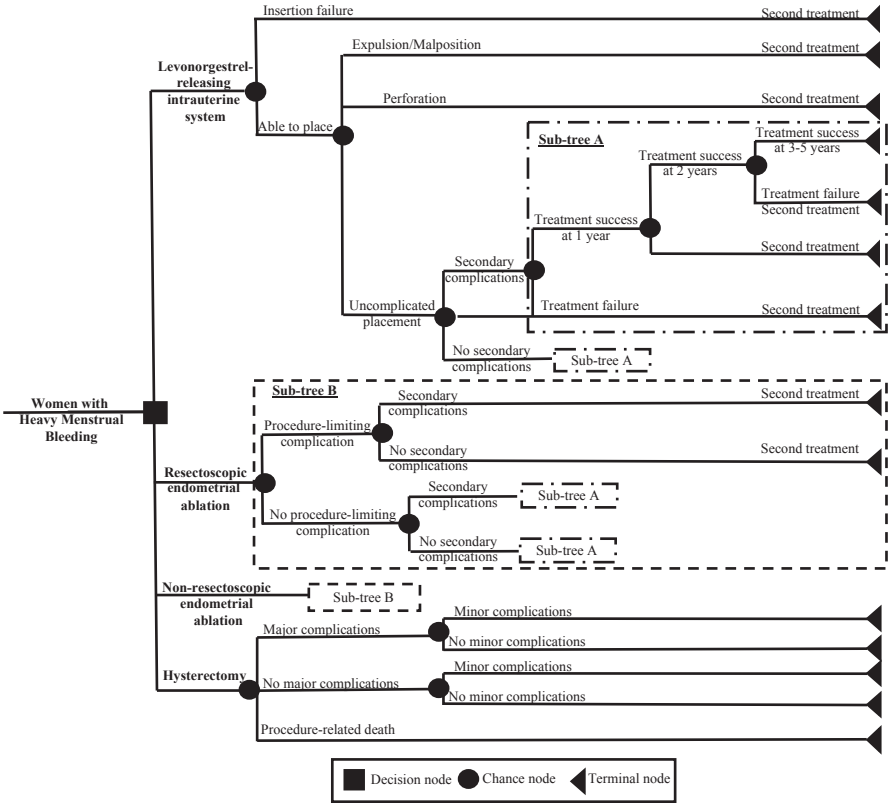
Studies were initially identified from abstract review and then independently evaluated by 3 authors for inclusion (J.C.S., M.L., V.E.). Studies were required to be available in English and compare 2 or more treatment modalities for women with heavy menstrual bleeding or abnormal uterine bleeding. Although articles were initially required to be published in the last 10 years, for several rare outcomes, more recent data were not available, and this time frame was expanded to the last 15 years.

Preference was given to randomized controlled trials or meta-analyses, but for outcomes with no such evidence available, the highest-quality evidence was used (US Preventive Services Task Force Quality of Evidence for Individual Studies II-2 and II-3). Disagreement over study eligibility, base-case estimates, transition probabilities, and utilities was resolved by consensus among all authors and then subsequently arbitrated by 2 independent clinical experts.

A simplified version of our decision tree model is shown in Figure 1. We followed up women in our hypothetical cohort through each treatment option over 5 years as they experienced treatment complications and outcomes based on probabilities derived from the literature (Supplemental Table). For non-hysterectomy options, we provided an evidence-based probability that the treatment failed to control symptoms, and thus, a second treatment was offered, either hysterectomy or endometrial ablation, as derived from previous observational studies.[13,14] If secondary treatments also failed, we assumed that women did not undergo a third treatment option. Robust data on outcomes beyond 5 years were not available for women undergoing LNG-IUS, and therefore, a 5 year time horizon was used.

Probabilities for hysterectomy were calculated as an average of complications and outcomes from abdominal, laparoscopic, robotic-assisted, and vaginal hysterectomy methods, weighted by frequency of use.[10] Endometrial ablation was categorized as either resectoscopic (methods that required hysteroscopic

FIGURE 1
Decision tree



A hypothetical cohort of premenopausal women seeking treatment for heavy menstrual bleeding select between LNG-IUS, resectoscopic endometrial ablation, nonresectoscopic endometrial ablation, or hysterectomy. Women move through the tree from left to right. Patients undergoing LNG-IUS first experience either successful placement or placement failure. After successful placement, patients may experience expulsion or malposition requiring removal, uterine perforation, or uncomplicated placement, which may be followed by secondary complications. Patients undergoing either resectoscopic or nonresectoscopic endometrial ablation may first encounter procedure-limiting complications, potentially followed by secondary complications either during or following the ablation. Following either type of endometrial ablation or LNG-IUS, patients experience adequate control of symptoms or initiate a second treatment after 1, 2, or 3—5 years. Women undergoing hysterectomy may experience major complications, minor complications, or procedure-related death.

LNG-IUS, levonorgestrel-releasing intrauterine system.

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visualization) or nonresectoscopic (methods that do not require hysteroscopic visualization, including global radiofrequency ablation, cryotherapy, thermal balloon ablation, and microwave ablation).

Costs for each procedure were derived from 2 previous studies conducted using a private insurance claims database[2,15] and adjusted for inflation using the Consumer Price Index medical expenditure category to 2015 US dollars.[16] Procedure costs were reported for each treatment, including a weighted average across ablation techniques and across hysterectomy type (vaginal, laparoscopic, robotic assisted, or abdominal) by frequency of use.

Data for costs associated with individual complications were not available, so the average cost of procedure-specific complications for each treatment group was used (Table 1). Using the probabilities for complications and treatment failure, we determined the average total cost for each treatment option over 5 years from a private payer perspective, including the initial procedure, any secondary procedures, and all complications.

To understand quality-of-life improvements offered by each treatment, utility estimates for uncontrolled bleeding and for convalescence, complications, and fully recovered states within each treatment type were also estimated from the literature (Table 2). Consistent with previous studies,[2,9] recovery was estimated to span 1 month for resectoscopic ablation, nonresectoscopic ablation, and LNG-IUS. Recovery was weighted for hysterectomy, assuming a 1 month recovery time for laparoscopic, robotic-assisted, and vaginal methods and 3 months of recovery for abdominal hysterectomy.

Quality-of-life information was not available for individual complications, so one procedure-specific complication utility based on published values was used for each treatment.[2,9,13,14] This utility was assumed to represent the average quality of life decrement for all complications within each treatment type.

Complications were grouped by duration to represent a decreased utility for 1 month, 3 months, or 12 months.[2,13] Total quality-adjusted life years (QALYs) experienced for each treatment were determined by adding utility values for each 1 month time period in the 5 years following each treatment.

Costs and utility values were discounted at 3% to account for time preferences, according to standard practice.[17] Although cost-effectiveness results in the US setting are traditionally presented by comparing each choice with the next best alternative, we compared each treatment option with hysterectomy as the definitive and irreversible treatment for heavy menstrual bleeding, a more useful comparator group for clinical decision making.

The incremental change in cost was divided by the incremental improvement in quality of life for each treatment relative to hysterectomy to calculate the incremental cost-effectiveness ratio (ICER). A traditional willingness-to-pay threshold of $50,000/QALY gained was used to evaluate cost-effectiveness.

To assess a range of possible outcome values, we performed probabilistic sensitivity analysis. Each model parameter was assigned a distribution based on the range of values observed in the literature, and all parameters were varied simultaneously with 5000 iterations of possible input values, generating an equal number of possible cost and quality outputs.

Cost variables were modeled using a gamma distribution, which restricts values to be nonnegative and can represent the usually right-skewed nature of cost data[17,18] (Table 1). Probabilities were modeled with a beta distribution, which restricts probabilities between 0 and 1. This is generally described by the number of times a given event occurred (α) and number of times and the event did not occur (β) (Supplemental Table 1). Utility values were modeled

TABLE 1
Cost parameters

Treatment	Event	Cost, mean (SD)[a]	Source
Hysterectomy (weighted)	Procedure	$13,020 (8446)	Bonafede et al[15]
	Complication	$1796 (3054)	Bonafede et al[15]
Resectoscopic ablation	Procedure	$6289 (4327)	Bonafede et al[15]
	Complication	$1824 (2593)	Bonafede et al[15]
Nonresectoscopic ablation	Procedure	$6289 (4327)	Bonafede et al[15]
	Complication	$1824 (2593)	Bonafede et al[15]
LNG-IUS	Procedure	$1550 (905)	Miller et al[2]
	Complication	$1615 (847)	Miller et al[2]

All costs are converted to 2015 US dollars.

LNG-IUS, levonorgestrel intrauterine system.

[a] For probabilistic sensitivity analysis, costs are varied using a gamma distribution, which is defined by mean and SD.

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TABLE 2
Utility parameters

Treatment modality	State	Utility estimate	Utility Range[a]	Source
Hysterectomy	Postprocedure recovery (weighted)	0.81	0.74–0.85	Clegg et al,[13] Roberts et al,[14] Miller et al,[2] Sculpher[12]
	Complication	0.51	0.49–0.55	Clegg et al,[13] Roberts et al,[14] Miller et al,[2] Sculpher[12]
	Well: symptoms controlled	0.87	0.84–0.93	Clegg et al,[13] Roberts et al,[14] Miller et al[2]
Resectoscopic endometrial ablation	Postprocedure recovery (1 mo)	0.81	0.76–0.85	Clegg et al,[13] Roberts et al,[14] Miller et al,[2] Sculpher[12]
	Complication	0.59	0.50–0.78	Clegg et al,[13] Roberts et al,[14] Miller et al[2]
	Well: symptoms controlled	0.86	0.82–0.90	Clegg et al,[13] Roberts et al,[14] Miller et al,[2] Sculpher[12]
Nonresectoscopic endometrial ablation	Postprocedure recovery (1 mo)	0.81	0.76–0.85	Clegg et al,[13] Roberts et al,[14] Miller et al[2]
	Complication	0.59	0.50–0.78	Clegg et al,[13] Roberts et al,[14] Miller et al[2]
	Well: symptoms controlled	0.87	0.84–0.90	Clegg et al,[13] Roberts et al,[14] Miller et al[2]
Levonorgestrel-releasing intrauterine system	Postprocedure recovery (1 mo)	0.87	0.80–0.90	Clegg et al,[13] Roberts et al,[14] Miller et al[2]
	Complication	0.64	0.58–0.78	Clegg et al,[13] Roberts et al,[14] Miller et al,[2] Sculpher[12]
	Well: symptoms controlled	0.89	0.84–0.93	Clegg et al[13]
	Abnormal uterine bleeding	0.60	0.50–0.76	Clegg et al,[13] Roberts et al,[14] Miller et al,[2] Sculpher et al[12]

[a] For probabilistic sensitivity analysis, costs are varied using a triangle distribution, which is defined by an upper and lower bound and has a peak at the base-case utility value.

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with a triangle distribution describing the expected maximum, minimum, and modal value (Table 2).

Using this method, we also identified the most influential individual parameters in our model by those whose changes were associated with the largest changes in ICER estimates.

The model was constructed using Excel 2016 (Microsoft, Redmond, WA), and sensitivity analysis was performed using Crystal Ball (Oracle, Redwood Shores, CA). This study was determined to be exempt from review by the Institutional Review Board at the University of North Carolina because it involved analysis of existing published data.

Results

Quality of life was fairly high for all options, with average QALYs of 3.96, 3.99, 4.04, and 4.07 over a 5 year time period for resectoscopic ablation,

TABLE 3
Base-case cost-effectiveness of 3 alternatives to hysterectomy

Variables	Average cost	Average QALY	Incremental cost	Incremental QALY	ICER
Hysterectomy	$13,574	4.04	Reference	Reference	Reference
Resectoscopic ablation	$9615	3.96	−$3959	−0.08	$49,428
Nonresectoscopic ablation	$9557	3.99	−$4017	−0.05	$87,619
LNG-IUS	$4509	4.07	−$9065	0.03	Dominates

Incremental cost and quality are presented relative to hysterectomy.

ICER, incremental cost-effectiveness ratio; *LNG-IUS*, levonorgestrel intrauterine system; *QALY*, quality-adjusted life-year.

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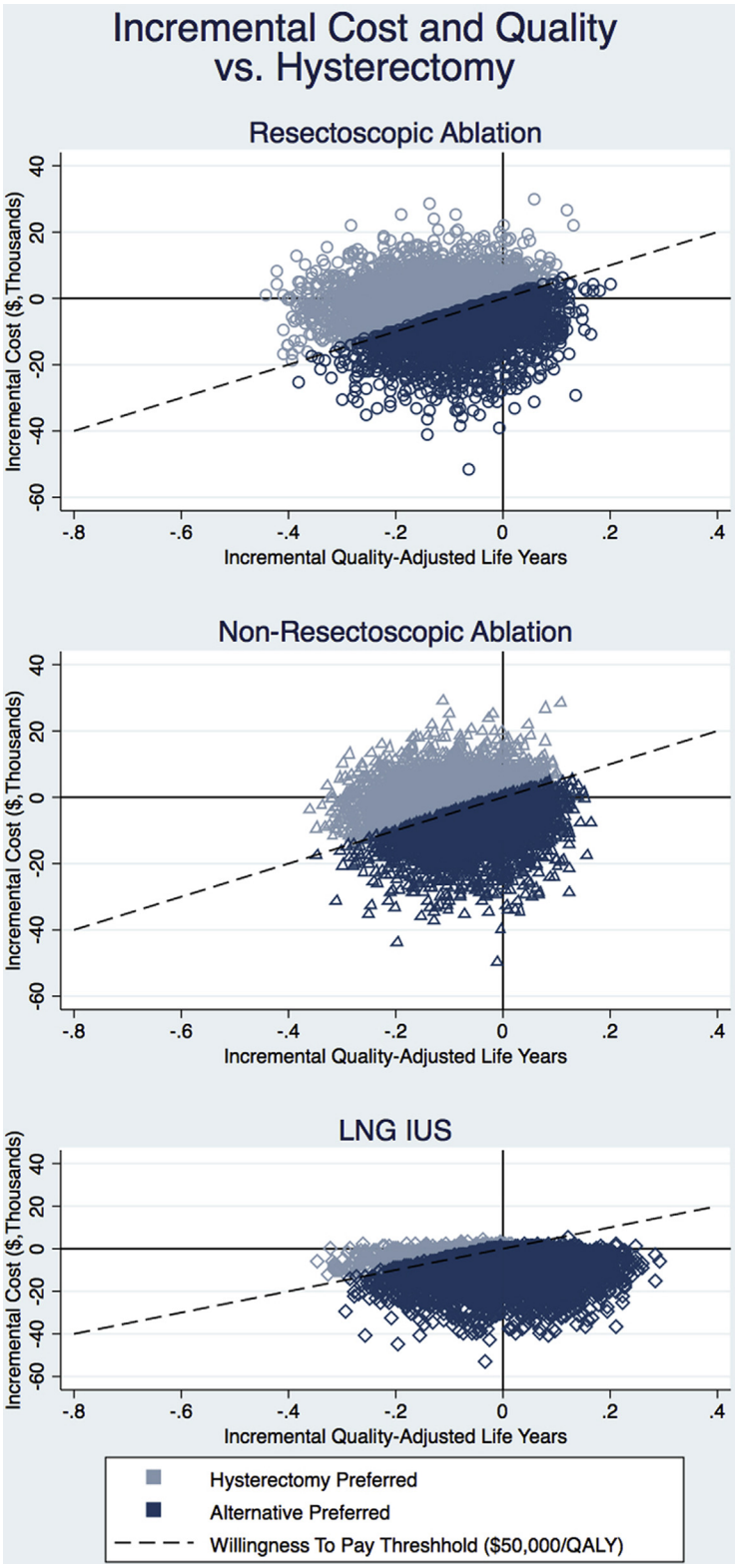
FIGURE 2
Incremental cost and QALY of treatment options compared with hysterectomy



Incremental changes in cost are represented on the y-axis, in which positive values represent increased cost compared with hysterectomy. Incremental changes in quality of life are on the x-axis, in which positive values represented improve quality compared with hysterectomy. Values below the willingness-to-pay line of $50,000/QALY indicate the comparator is considered cost effective relative to hysterectomy.

QALY, quality-adjusted life-year.

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nonresectoscopic ablation, hysterectomy, and LNG-IUS, respectively. However, estimated costs and complications for each treatment alternative were markedly different between treatment options.

In our base-case scenario, LNG-IUS was superior to all alternatives in both cost and quality, making it the dominant strategy compared with hysterectomy, resectoscopic endometrial ablation, and nonresectoscopic endometrial ablation (ie, LNG-IUS cost less and resulted in higher QALYs compared with each alternative). The 5 year cost of women undergoing LNG-IUS was $4500, about half the cost of endometrial ablation ($9500) and about one third the cost of hysterectomy ($13,500) (Table 3).

Compared with hysterectomy, both types of endometrial ablation were approximately $4000 less expensive, but both resulted in slightly lower total QALYs: a loss of 0.05 for nonresectoscopic ablation and 0.08 for resectoscopic ablation over 5 years. The ICER, a ratio of increased cost to improved quality, indicates that hysterectomy costs an additional $88,000 per QALY gained when compared with nonresectoscopic ablation and $49,000 per QALY gained when compared with resectoscopic ablation.

The base-case results reflect the best available evidence from our literature review. To further understand how estimates are affected by changes in input parameters based on the range of values in the published literature, we conducted a probabilistic sensitivity analysis. LNG-IUS was the preferred treatment in 90% of 5000 simulations, compared with hysterectomy, which was favored in 10% of 5000 simulations (Figure 2).

While nonresectoscopic endometrial ablation was cost effective relative to

hysterectomy in our base-case scenario, both types of ablation were sensitive to changes in input parameters during sensitivity analysis. Nonresectoscopic ablation was cost effective compared with hysterectomy in 53% of simulations, while resectoscopic ablation was cost effective compared with hysterectomy in 44% of simulations.

Using the range of inputs and outputs from our sensitivity analysis, we find that in the comparison of hysterectomy and LNG-IUS, the parameters with the most influence on ICER estimates are the utility values for women after recovery from each procedure. When comparing hysterectomy and nonresectoscopic ablation, the most influential parameters are the initial procedure costs associated with each, followed by utility estimates.

Comment

Our analysis finds strong evidence in favor of LNG-IUS as a cost-saving, dominant alternative to hysterectomy for women with heavy menstrual bleeding. LNG-IUS as a first-line treatment offers both improved quality and reduced cost in our base-case scenario. When looking over a range of possible values, we found that LNG-IUS was cost effective compared with hysterectomy in the large majority of scenarios (90%), suggesting this conclusion is robust to changes in our model assumptions.

If LNG-IUS is removed from consideration for reasons of either patient preference or clinical indication; our findings suggest decisions between hysterectomy and ablation are more complex. Hysterectomy results in better quality of life in the majority of simulations but is cost effective in just more than half of the simulations compared with either resectoscopic or nonresectoscopic ablation. Therefore, consideration of cost, procedure-specific complications and patient preferences may guide the decision between hysterectomy and endometrial ablation.

No previous studies have examined the cost-effectiveness of all 4 of these options in the context of the US health care setting, but our findings are consistent with several studies from non-US settings.[5,13,19] Where our findings deviate from previous quality or cost-effectiveness studies,[2,14,15] differences result from our inclusion of a wider range of surgical and postsurgical complications, particularly for endometrial ablation, and use of multiple sources to estimate utilities for each treatment option.

Our model compares QALYs and costs for the first 5 years after treatment because data for follow-up times beyond 5 years are limited. Additionally, data on out-of-pocket cost for each treatment, time missed from work, and other indirect costs are not available, and, therefore, only the private payer perspective is reported. Lastly, because the majority of included trials excluded women with large fibroids, polyps, or other uterine pathologies, we are unable to extend the results of this work to these groups. Future work could consider the comparative outcomes when the data regarding longer-term results, indirect costs, or other uterine pathologies are available.

The combination of 4 methods of hysterectomy as a weighted average between abdominal, vaginal, robotic-assisted, and laparoscopic methods allows consideration of hysterectomy as a single alternative and enables the use of higher-quality data for procedure cost and utility.

With an increasing proportion of hysterectomies using a minimally invasive approach and same-day discharge,[20-22] we may be underestimating the cost-effectiveness of present-day hysterectomy. However, in a sensitivity analysis, even changes of hysterectomy complication rates and costs to the most extreme values (highest or lowest) were not enough to alter our base-case evaluation of LNG-IUS as cost effective compared with hysterectomy nor our conclusions that hysterectomy is superior to nonresectoscopic ablation in quality of life and complication rates.

The cost-effectiveness of hysterectomy relative to ablation was sensitive to assumptions about procedure costs, and all comparisons were sensitive to changes in the utility estimates for women after successful symptom control within each treatment. In the future, high-quality research regarding patient-reported quality of life after treatment could help to reduce decision uncertainty, particularly comparing hysterectomy and endometrial ablation. Information on outcomes beyond 5 years would also help to examine whether conclusions of cost-effectiveness are different if considered over 10 or even 20 years.

Lastly, information is limited on the risk of endometrial cancer after ablation, although the risk appears to be reduced after LNG-IUS.[23] Implications regarding cancer prevention should be considered in terms of both cost and quality of life and would be particularly relevant for understanding treatment options for patients at high risk of endometrial cancer.

The comparative cost-effectiveness of endometrial ablation and hysterectomy highlights important trade-offs for patients and providers to consider when selecting between treatment options, such as the need for future procedures or the potential for rare, but serious, complications. For women with heavy menstrual bleeding, LNG-IUS offers the best outcomes at the least cost, saving an average of $9000 compared with hysterectomy, and adding the equivalent of 2 quality-adjusted weeks of life over 5 years.

When LNG-IUS is not an option, hysterectomy offers better outcomes, increasing quality-adjusted life years by 0.05 (about 2 weeks) over 5 years compared with nonresectoscopic endometrial ablation or by 0.08 (3.5 weeks) over 5 years compared with resectoscopic ablation but at a cost approximately $4000 higher than either of these methods.

In summary, comparing all trade-offs associated with 4 possible treatments of heavy menstrual bleeding, LNG-IUS was superior to both hysterectomy and endometrial ablation in terms of cost and quality of life. If LNG-IUS is not a reasonable treatment option because of preferences or clinical indication, hysterectomy is associated with superior quality of life and fewer complications than either type of ablation but at a higher cost. ■

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SUPPLEMENTAL TABLE 1
Transition probabilities

Treatment modality	Condition	Probability	Distribution[a]	Source
Hysterectomy	Major complication (12 mo utility state)[b]	0.0818	8; 992	Matteson et al[6] Siedhoff et al[22] Clarke-Pearson et al[24]
	1 mo complication (1 mo utility state)[c]	0.2159	21; 979	Siedhoff et al[22] Johnson et al[25] Aarts et al[20]
	3 mo complication (3 mo utility state)[d]	0.0108	10; 990	Matteson et al[6] Aarts et al[20]
	Procedure-related death	0.0003	3; 9997	Siedhoff et al[22] Wingo et al[26]
Resectoscopic endometrial ablation	Equipment failure	0.0063	1; 186	Bhattacharya et al[5] Lethaby et al[11]
	Procedure-limiting complication[e]	0.0317	54; 1646	Bhattacharya et al[5] Lethaby et al[11]
	Secondary complication (1 mo utility state)[f]	0.0317	40; 1580	Bhattacharya et al[5] Lethaby et al[11]
	Secondary complication (3 mo utility state)[g]	0.3975	80; 120	Bhattacharya et al[5] Lethaby et al[11]
	Procedure converted to hysterectomy	0.0100	17; 1680	Bhattacharya et al[5] Lethaby et al[11]
	5 y failure rate	0.2500	70; 210	Bhattacharya et al[5] Lethaby et al[11]
	Second treatment: repeat resectoscopic ablation	0.4000	Not varied	Clegg et al[13] Roberts et al[14]
	Second treatment: hysterectomy	0.6000	Not varied	Clegg et al[13] Roberts et al[14]
Non-resectoscopic endometrial ablation	Equipment failure	0.1010	20; 177	Bhattacharya et al[5] Lethaby et al[11]
	Procedure-limiting complication[e]	0.0027	3; 1463	Bhattacharya et al[5] Lethaby et al[11]
	Secondary complication (1 mo utility state)[f]	0.0154	224; 1237	Bhattacharya et al[5] Lethaby et al[11]
	Secondary complication (3 mo utility state)[g]	0.4672	190; 218	Bhattacharya et al[5] Lethaby et al[11]
	Procedure converted to hysterectomy	0.0006	1; 1624	Bhattacharya et al[5] Lethaby et al[11]
	5 y failure rate	0.2500	76; 291	Bhattacharya et al[5] Lethaby et al[11]
	Second treatment: resectoscopic ablation	0.4000	Not varied	Clegg et al[13] Roberts et al[14]
	Second treatment: hysterectomy	0.6000	Not varied	Clegg et al[13] Roberts et al[14]
Levonorgestrel-releasing intrauterine system	Insertion failure	0.0054	2; 370	Bhattacharya et al[5] Brown et al[18] Majoribanks et al[27]
	Expulsion/malposition	0.0420	16; 360	Bhattacharya et al[5] Majoribanks et al[27]

Spencer et al. Management of heavy menstrual bleeding. Am J Obstet Gynecol 2017. *(continued)*

SUPPLEMENTAL TABLE 1
Transition probabilities *(continued)*

Treatment modality	Condition	Probability	Distribution[a]	Source
	Uterine perforation	0.0010	1; 1118	American College of Obstetrics and Gynecology[8]
	Infection (1 mo utility state)	0.0420	10; 90	Bhattacharya et al[5]
	Dysmenorrhea (3 month utility state)	0.1010	5; 114	Meyer et al[28] Bhattacharya et al[5]
	5 y failure rate	0.2200	26; 104	Bhattacharya et al[5] Brown et al[18] Majoribanks et al[27]
	Treatment following expulsion, malposition, perforation: repeat LNG-IUS	0.3333	Not varied	Assumption
	Treatment following expulsion, malposition, perforation: resectoscopic ablation	0.2367	Not varied	Bhattacharya et al[5]
	Treatment following expulsion, malposition, perforation: hysterectomy	0.4300	Not varied	Bhattacharya et al[5]
	Treatment following removal: resectoscopic ablation	0.3550	Not varied	Bhattacharya et al[5]
	Treatment following removal: hysterectomy	0.6450	Not varied	Bhattacharya et al[5]

LNG-IUS, Levonorgestrel-releasing intrauterine system

[a] Beta distribution reflecting a continuous probability range based on published data, represented as the number of times the event occurred and the number of times the event did not occur; [b] Major complication (12 month utility state): venous thromboembolism, hernia, need for additional surgery; [c] One month complication (1 month utility state): blood transfusion, infection, vaginal cuff dehiscence, urinary tract injury, unspecified fever; [d] Three month complication (3 month utility state): bowel injury, readmission; [e] Procedure-limiting complication: fluid overload, uterine perforation; [f] Secondary complication (1 month utility state): urinary tract infection, cervical laceration, anesthesia complications; [g] Secondary complication (3 month utility state): uterine cramping, visceral damage, hematometra, dysmenorrhea.

Spencer et al. Management of heavy menstrual bleeding. Am J Obstet Gynecol 2017.

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REVIEW

Minimally invasive hysterectomy for benign indications: an update

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ABSTRACT

Hysterectomy is one of the most commonly performed surgeries worldwide. Indication for hysterectomy is most often benign, which includes conditions such as prolapse, abnormal uterine bleeding, fibroids and pelvic pain. A broad range of surgical approaches exists for hysterectomy, ranging from open to minimally invasive techniques. Under this minimally invasive umbrella, the following techniques are included: vaginal hysterectomy, laparoscopic hysterectomy, and variations of those two techniques, such as laparoscopic-assisted vaginal hysterectomy, robotic-assisted hysterectomy, laparo-endoscopic single-site laparoscopic hysterectomy, mini-laparoscopic hysterectomy, and natural orifice transluminal endoscopic surgery hysterectomy. As hysterectomy is being performed increasingly *via* a minimally invasive route, it is important that gynecologists are familiar with the established as well as emerging techniques for minimally invasive hysterectomy (MIH). Surgical planning is a complex process, which requires an in depth and informed conversation between a patient and her physician. Patient preferences, surgeon skill and indication for surgery all should be taken into consideration when determining the most appropriate surgical approach. This article will review the different routes of MIH. Perioperative considerations will be discussed, as will the advantages and disadvantages of each minimally invasive approach.

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Key words: Hysterectomy - Laparoscopy - Minimally invasive surgical procedures - Robotics.

Hysterectomy is one of the most commonly performed surgeries worldwide with over 600,000 performed annually.[1] Indication for hysterectomy is most often benign, which includes conditions such as prolapse, abnormal uterine bleeding, fibroids and pelvic pain. A broad range of surgical approaches exists for hysterectomy, ranging from open to minimally invasive techniques. Under this minimally invasive umbrella, the following techniques are included: vaginal hysterectomy (VH), laparoscopic hysterectomy (LH), and variations of those two techniques, such as laparoscopic-assisted vaginal hysterectomy (LAVH), robotic-assisted hysterectomy (RH), laparo-endoscopic single-site laparoscopic hysterectomy (LESS), mini-laparoscopic hysterectomy (MLH), and natural orifice transluminal endoscopic surgery (NOTES) hysterectomy.

History

Reports of the first vaginal hysterectomies originate from early second century AD. While a number of unsuccessful attempts at performing vaginal and abdominal hysterectomies ensued in the centuries to follow, with the advent of improved anesthesia, antibiotics and surgi-

cal techniques, the first elective and successful VH was in 1813 by Conrad Lagenbeck. 50 years later, Charles Clay successfully performed the first elective AH.[2]

Not until the late 20th century was a significant surgical advancement introduced to the gynecologist's armamentarium. In 1989, Harry Reich performed the first LAVH, and then in 1993, he successfully performed a total LH.[2] Although initially invented to advance medical care in the battlefield, robotic technology became implemented in other surgical arenas. While the first RH was performed in the late 1990s, the US Food and Drug Administration officially approved the use of robotics in gynecologic surgery in 2005.[3]

Trends

Despite a broad range of minimally invasive techniques and data that support a minimally invasive approach over AH, a large proportion of hysterectomies in the early 2000's was still being performed *via* an open approach. In 2003, the most common route of hysterectomy was abdominal hysterectomy with a rate of over 60%. The second most common was vaginal with a rate ranging from 20% to 30% of cases, followed by laparoscopic at 12%.[1, 4]

Interestingly, the number of cases performed vaginally decreased over the past few decades. The rate of VH was 24% in 1990, 22% in 2003,[1] and 19% by 2010. According to a recent multicenter study by Lim *et al.*, which relied on data from the Premiere Perspective database, the rate of VH has continued to drop to a rate of 15% in 2013.[5] Lim *et al.* also noted a decline in AH rates to 22% in 2013.

While the rates of VH have steadily declined, an inverse response has been seen in LH. The drop in rates of VH corresponds temporally to the introduction of the robotic technology to the field of gynecology, though it is difficult to draw a causal relationship between the two events.[6] Less than 1% of hysterectomies were performed laparoscopically in 1990. By 2010, 25% of hysterectomies were performed laparoscopically. A more surprising trend is that nearly one fifth of those laparoscopic cases in 2010 were robotic-assisted.[6-8] According to the study by Lim *et al.*, by 2013, the rate of laparoscopic hysterectomies rose to 32%.[5] They also reported an equal number of cases being performed robotically as laparoscopically, reflecting a rapid adoption of this new technology.[3]

As the rates of VH are on the decline and LH and RH are on the rise in the US, other countries have seen different trends in hysterectomy. For instance, in Sweden, the rate of VH increased from 4% in the late 1980s to 29% in the early 2000's, while the rates of LH and LAVH remained stable during the 1987-2003 time frame at approximately 1-3%.[9] A study in Denmark reported similar trends in VH.[10] AH demonstrated a decline in both studies.

As hysterectomy is being performed increasingly *via* a minimally invasive route, it is important that gynecologists are familiar with the established as well as emerging techniques for minimally invasive hysterectomy (MIH). This article will review the different routes of MIH. Perioperative considerations will be discussed, as will the advantages and disadvantages of each minimally invasive approach.

Minimally invasive hysterectomy techniques

Vaginal hysterectomy

The entire procedure is performed through the natural orifice of the vagina. Ligation of pedicles can be accomplished either by traditional suture ligation or using a vessel sealing device. The patient is positioned in high lithotomy with either Allen or candy cane stirrups. Trendelenburg can be employed to assist with visualization during the procedure.

Advantages of a vaginal approach are fewer blood transfusions, less febrile morbidity and less risk of injury to the ureter. These benefits must be weighed against the higher risk for bleeding complications and bladder injury.[11]

Laparoscopic hysterectomy

The entire procedure is performed through small abdominal incisions. The peritoneal cavity is insufflated with carbon dioxide, and

laparoscopic instruments are introduced into the peritoneal cavity through the abdominal incisions *via* trocars. Monopolar and bipolar cautery, as well as sharp and blunt dissection, can be used to perform the surgery. The vaginal cuff can be closed laparoscopically using a barbed or non-barbed suture; however, some surgeons prefer to close the cuff vaginally for a number of reasons. First, laparoscopic closure of the cuff can be technically challenging, and some surgeons feel more comfortable performing cuff-closure *via* a vaginal approach. Second, some surgeons believe that a vaginal closure decreases the risk of cuff dehiscence and subsequent evisceration. Lastly, a vaginal approach to cuff closure facilitates performing a concomitant vaginal vault suspension by vaginal route if clinically indicated.

An advantage of the laparoscopic approach over a strictly vaginal approach is the improved visualization of the intra-abdominal cavity, which allows for added dexterity in performing additional procedures such as adnexal surgery, excision of endometriosis, and ureterolysis.

Laparo-endoscopic single-site hysterectomy and mini-laparoscopic hysterectomy

LESS is one of the newer approaches to hysterectomy, and the risks and benefits of this approach are currently being examined. The procedure has been described as being performed using a single, large umbilical port through which multiple laparoscopic instruments are introduced. Despite its argued improved cosmetic result, this approach introduces significant technical challenges as multiple ports are placed in close proximity, limiting the ability to triangulate the laparoscopic instruments.[12] While data is limited, there does not appear to be an increased risk of complications, such as umbilical hernia, when comparing outcomes between conventional laparoscopy and LESS.[13, 14]

MLH approach refers to a laparoscopic approach where the incisions do not exceed 3 to 5 mm.[15] The goal of MLH is to improve cosmetic outcomes associated with conventional laparoscopic and LESS hysterectomy and to decrease incisional trauma associated with surgeries that require larger abdominal incisions. Both MLH and single-site MLH have been described in the literature. In the original MLH technique, the hysterectomy is performed using the same steps as the conventional TLH with the exception of the use of the mini-laparoscopic instruments, which are more delicate than conventional laparoscopic instruments. The single-site MLH technique described in the literature involves two 3-mm trocars inserted through the umbilicus.[15]

Vaginal manipulation of the uterus and cervix is critical to execute this type of MIH. The vaginal cuff is closed *via* a vaginal approach due to fact that the mini-laparoscopic instruments are not well suited for intra or extracorporeal suturing of the vaginal cuff. Technical challenges of performing MLH and LESS have made this option of hysterectomy less accessible than other approaches.

Laparoscopic-assisted vaginal hysterectomy

Both single-port and multi-port approaches to LAVH have been described. With both approaches, it is common for the surgeon to ligate the infundibulopelvic or utero-ovarian pedicles laparoscopically; however, depending on the skillset of the surgeon and the complexity of the case, any portion of the hysterectomy can be performed laparoscopically or vaginally. Usually, the hysterectomy is considered laparoscopically assisted if at least one major pedicle is ligated laparoscopically. An advantage of this approach is the improved access to and visualization of the adnexa and in turn allows for adhesiolysis to be performed intra-abdominally.

Robotic-assisted laparoscopic hysterectomy

The procedure is similar to LH; however, rather than using traditional laparoscopic instruments, robotic instruments are introduced *via* robotic trocars attached to the robotic platform once insufflation is achieved. Adhesiolysis may be required to place additional trocars

safely. The primary surgeon, then, manipulates these instruments at the robotic console. A bedside assistant is often employed. This assistant often holds a traditional laparoscopic instrument and assists with improving visualization or providing counter traction in order to facilitate performing certain steps of the procedure.

Advantages of robotic technology have been cited as the three-dimensional optics, improved ergonomics and dexterity of motion with seven degrees of freedom and wristed instrumentation. The improved dexterity can be helpful in technically challenging cases due to significant adhesive disease, requirement of extensive retroperitoneal dissection, suture labor, or a large, bulky uterus.[12] Also, the use of a fourth robotic arm can replace the need for an assistant if skilled assistants are not available to the surgeon.

Natural orifice transluminal endoscopic surgery

NOTES is an emerging field in minimally invasive surgery and has been recently applied to hysterectomy. NOTES can be performed *via* a variety of approaches, including through the stomach, esophagus, bladder, and rectum, but the majority of cases have been performed transvaginally.[16] When performing vaginal NOTES, a trocar is introduced into the peritoneal cavity *via* the vaginal canal. Once insufflation is achieved, laparoscopic instruments can be introduced into the peritoneal cavity solely through the vagina as in "pure" vaginal NOTES procedures. When laparoscopic instruments are introduced into the peritoneal cavity *via* a combination of both vaginal and transabdominal ports, the procedure is referred to as a "hybrid" NOTES procedure.

In 2012, Su *et al.* reported the first NOTES hysterectomy.[17] The first portion of the procedure proceeds as though one were performing a standard VH. After a posterior colpotomy is performed, the uterosacral ligaments and cardinal ligaments are clamped and divided with a biopolar vessel sealer. A wound retractor and surgical gloves are fashioned to create a vaginal port through which the laparoscopic instruments were introduced. The intraperitoneal cavity is then insufflated, the endoscope is introduced. The remaining steps of the hysterectomy are performed using transvaginally introduced laparoscopic instruments. The advantage of the NOTES hysterectomy, according to the authors, is that it overcomes challenges faced by conventional VH when large uteri are encountered, especially in accessing the uterine vessels. More recently in 2015, Baekelandt published a case series in which he described a new approach to vaginal NOTES hysterectomy, in which the entire surgery is performed through a NOTES port.[18] Baekelandt concluded from his experience that NOTES hysterectomy actually increased the number of cases that were attempted *via* a vaginal approach by decreasing "the percentage of total laparoscopic hysterectomies in favor of the less invasive NOTES approach."[18]

While transvaginal NOTES hysterectomy represents one of the most recently introduced innovations in gynecologic surgery, it remains technically challenging. Further investigation, innovation, and training are required before this route will be adopted by mainstream gynecologic practitioners.

Preoperative considerations

Decision regarding surgical approach

The decision to proceed with a definitive surgery to treat benign gynecologic disease is a personal one and requires in-depth discussions between provider and patient. Just which type of approach to employ is equally personal, and all clinical factors — both patient and surgeon — should be considered when formulating a surgical plan.

Indication for surgery

One of the most important considerations for a surgeon when choosing a surgical approach is the indication for surgery. If the hysterectomy is being performed in the setting of prolapse, then the vaginal approach is preferred. If the patient has an extensive history of pain, then an argument exists for performing all or a portion

of the procedure laparoscopically in order to assess for and excise endometriosis if present. Also, the presence of endometriosis may distort the pelvic anatomy and, thus, a laparoscopic view of the pelvic structures can be beneficial.

Even in the setting of large uteri, vaginal hysterectomy has been shown to be safe.[19] Patient factors that could increase the technical difficulty of performing a VH should be assessed such as vaginal parity and pubic arch. Increased gluteal or thigh adiposity can limit access to the vaginal cavity, making VH technically challenging. Other factors to consider are the mobility, size and descent of the uterus.

Adhesive disease

The presence of adhesive disease is an important consideration in determining the surgical plan for hysterectomy. The vaginal approach may be challenging in the presence of significant intra-abdominal adhesions. Newer application of established technologies, such as NOTES approach though the vaginal orifice to remove adnexa in the setting of significant adhesive disease or other challenging pathology, can provide surgeons with more tools to allow for a fully vaginal approach.[20] History of prior cesarean section has been associated with a higher rate of complications in the setting of VH.[21] However, skilled vaginal surgeons can safely perform VH even in patients with a history of prior cesarean sections.[21, 22]

Comorbidities

Any patient comorbidity that would limit the patient's ability to tolerate long periods of Trendelenburg should be considered when planning a laparoscopic or robotic approach. Patients with pulmonary disease, in particular COPD, restrictive lung disease, and pulmonary hypertension, may not tolerate Trendelenburg positioning and insufflation of the peritoneal cavity.[12] Other considerations are patients with ocular disease such as glaucoma given the fact that intraocular pressure increases substantially due to the patient positioning.[23] Of note, there is a risk of corneal abrasion whenever a patient undergoes anesthesia and both operative and anesthesia teams must be conscientious about minimizing patients' risk of acquiring such a complication.

Obesity may pose technical challenges in terms of accessing the surgical field. Increased abdominal obesity not only can pose a challenge to ventilation during a procedure that requires steep Trendelenburg due to the weight of the abdominal wall, but also can make trocar placement challenging and may require the use of long trocars in order for appropriate placement and manipulation of instruments through a thick abdominal wall. Some surgeons prefer the use of the robot in significantly obese patients to conventional laparoscopy due to the argument that the technical challenges of manipulating hand-held instruments can be overcome by the robot. Interestingly, obesity does not incur a specific increase in morbidity following laparoscopic and robotic hysterectomy.[24-26]

Cancer screening

In preparation for MIH, all patients should undergo appropriate cancer screening with a pap smear, if not up to date, and endometrial sampling, if necessary depending on the clinical indication for surgery. Other cancer screening, such as mammography and colonoscopy, should also be considered for age appropriate patients. If surgery is being performed for fibroids, then surgeons could consider obtaining MRI imaging of the pelvis to help discern whether the mass has components suggestive of leiomyosarcoma (LMS), although no effective preoperative screening test or imaging has been able to consistently distinguish LMS from benign fibroids.[27]

When encountered with a large uterus, the surgeon may have to perform morcellation in order to remove the specimen from the abdominal cavity. In minimally invasive surgery, this can be achieved *via* a vaginal approach or through a mini-laparotomy either through an umbilical or suprapubic incision. Surgeons must speak with their patients in depth regarding the possible need for morcellation in the setting of a bulky uterus and the implications

of performing morcellation in the setting of an occult malignancy, specifically LMS. Notably, due to concerns regarding microscopic dissemination of occult cancer, the FDA placed a moratorium on power morcellation in 2014. In response, the American Association of Gynecologic Laparoscopists (AAGL) published a practice report which reviewed the current literature surrounding occult malignancy and concluded that "*the risk of occult malignancy seems to be extremely low, in particular in women of reproductive age*." AAGL set forth practice guidelines for the use of morcellation in surgery for benign indication, in particular fibroid uteri, which include: 1) appropriate evaluation of the myometrium, cervix and endometrium; 2) performing laparotomy and deferring morcellation if there is any suspicion for a malignant or pre-malignant condition exists; 3) morcellation should be avoided when planning surgery for postmenopausal women given the elevated risk of occult malignancy in this population; and 4) the decision whether or not to morcellate should be a patient-centered decision which includes a thorough discussion of the risks and benefits of morcellation.[28]

Of note, any form of morcellation, whether it be vaginal, hand-assisted, or contained, is associated with the risk of disseminating occult disease. There have been measures, such as retrieval pouches, which surgeons have employed and are intended to theoretically reduce the risk of dissemination of malignancy; however, the AAGL clearly states that "*the use of morcellation within specimen retrieval pouches for containment of benign or malignant uterine tissue requires substantial skill and experience, and the use of specimen retrieval pouches should be investigated further in a controlled setting for safety and outcomes*."[29]

Intraoperative management

Positioning

In laparoscopic surgery, the patient is placed in low lithotomy, and steep Trendelenburg is often employed in order to improve visualization and exposure during the case. Arms are also tucked at the patient's side. Care should be taken to ensure that the patient's hands, wrists and elbows are properly protected to avoid pressure ulcers and nerve injury. Similarly, careful positioning of the legs in Yellofins® stirrups (Allen, Acton, MA, USA) with padding of the patient's legs at the pressure points is an important step to protect the patient from injury. Attention to patient positioning at the start of the procedure is of great importance and is arguably as important as the technical execution of the surgery, as the risk of nerve injury for a patient under general anesthesia increases with each hour that the patient is in lithotomy position.[29, 30]

Different approaches are employed to ensure that the patient is secured on the operating table and that the patient's position is not compromised while in Trendelenburg. Use of a bean bag designed for securing and padding the patient in Trendelenburg position, slip resistant padding such as egg crate, and the use of chest straps or taping of the chest with appropriate padding can be helpful in securing the patient to the operating room table in a safe manner. The use of shoulder braces has been shown to be associated with an increased rate of brachial plexus injuries and should be avoided.[30]

Advantages and disadvantages

Rate of complications

A 2015 Cochrane Database Review, which analyzed 27 randomized controlled trials, evaluated the different surgical approaches to hysterectomy for benign disease. The study was unable to definitively comment on the safety of the different approaches to hysterectomy given the overall low rate of complications reported.[31] However, VH was superior to LH in terms of bleeding, and LH had more urinary tract injuries than AH. VH was identified as the best approach to hysterectomy when possible, due to the fact that patients who underwent VH had a faster return to baseline and shortest time in the hospital.

A 2014 Cochrane Database Review examining robotic surgery in gynecology was unable to assert a conclusive stance on the difference between the rates of complications between LH and RH, both intraoperative and postoperative, due to limitations of the current published data.[3] Regarding the newer laparoscopic approaches, a 2016 systematic review that examined LESS *versus* conventional laparoscopic approaches to hysterectomy was unable to find any difference in the rate of perioperative complications.[32]

Operative time

Conflicting data exist on the most time efficient approach to hysterectomy. A study by Shah *et al.*, which examined over 36,000 MIH, found that the vaginal route for hysterectomy was shorter than other routes (TLH or LAVH) regardless of patient body mass index or uterine size.[33] As for RH *versus* LH, a number of studies have noted longer operative times for the robotic compared to the conventional laparoscopic approach.[34, 35] Paraiso *et al.*, and Sarlos *et al.*, published RCTs comparing LH and RH, both of which found that operating time was significantly longer in the RH arm, a findings supported by a 2014 Cochrane review. The systematic review described longer operating time in the RH arm compared with LH arm (42 minutes longer) based on moderate quality evidence.[3] The RH arm was found to have a shorter hospital stay of approximately 7 hours; however, this conclusion was based on low-quality evidence.

In contrast, a few recent studies have noted a similar operative time for LH and RH. A systematic review and meta-analysis published by Albright *et al.* in 2016 compared LH and RH for benign disease and found no difference between total operating time (defined in minutes, as skin-to-skin time from incision to closure, including docking time for the robot) between the two approaches.[36] Lonnerfors *et al.* published a RCT in 2015 comparing VH, LH and RH and did not find a significant different between operating time of LH and RH. The mean operating time for LH was 145 minutes *versus* 147 minutes for RH.[37] Interestingly, the mean operating time of VH was 71 minutes less than for LH or RH. When comparing LESS to LH, LESS procedures required significantly longer operative time to complete than the conventional approach.[32]

Cost

Identifying the safest yet most cost-effective route of hysterectomy is very important given the growing costs associated with healthcare, particularly in the US. The 2015 RCT published by Lonnerfors *et al.* compared the hospital costs incurred by VH, LH and RH and concluded that VH is the most cost-effective approach with a cost of US$ 4579 per surgery compared with US$ 7059 for LH. When comparing RH with LH, the cost of the two different approaches was comparable if the use of the robot had been well established at the given institution (US$ 7059 *vs*. US$ 7016). If the robotic equipment had been newly acquired, then the additional cost to perform RH *vs*. LH was US$ 1607 more than a traditional laparoscopic approach; however, this study reported a lower rate of complications and blood loss in the robotic arm.[37]

Other studies have shown that RH is more expensive without significant clinical benefit to the patient in terms of improved perioperative outcomes.[6, 8] Rosero found a US$ 2489 increase in cost to execute an RH compared to LH. This cost difference is reflected in a number of differences between the set up and execution of the two approaches. First, the robot itself is a very expensive device, costing anywhere from 1 to 2.5 million dollars for each robot system.[35] These systems also require contracts with the robotic device company for scheduled maintenance, which also incur a cost. The instruments, which are used in robotic surgery, are limited use, meaning after 10 uses, whether the instrument is still functional, the robot will not recognize the instrument, and a new instrument must be introduced. The amount of time required to set up for the robot is longer, and as a result, time in the operating room is longer, which in turn increases cost of

the procedure. An argument, therefore, exists that since both VH and LH do not depend on the technology of a robot, they are more cost effective approaches.

Expert consensus

Given the range of surgical approaches for hysterectomy for benign indications and multiple advantages and disadvantages to each, identifying the superior approach in a given clinical situation is of the utmost importance. A Cochrane systematic review published in 2015, which compared various clinical outcomes amongst AH, VH, LH and RH concluded that VH is "*the most effective and safe surgery for hysterectomy in women with benign gynecological disease."*[27] When VH is not feasible, however, other routes must be considered. The review found a number of advantages of LH over AH in the metrics of recovery, infectious complications and febrile episodes. The review also concluded that at the time that the review was conducted there was very limited evidence to support RH or LESS over LH.

Given this body of data, professional groups such as AAGL and the American Congress of Obstetricians and Gynecologists (ACOG) have published position statements in support of VH as the preferred method of hysterectomy,[36] and when the vaginal approach is not feasible, then a laparoscopic approach is preferred over AH.[37-41]

Conclusions

A wide array of choices for MIH exist for women, who decide to undergo surgical management for benign gynecologic conditions. According to expert consensus, VH is the preferred approach for MIH; however, when a vaginal approach is deemed unsafe for the patient due to comorbidities or pathology, then LH should be considered as the first alternative.[27] Other minimally invasive approaches such as RH or LESS should not be considered as first line alternative to VH as these approaches have not been shown to decrease operative time, blood loss, and length of stay.[12]

In conclusion, surgical planning is a complex process, which requires an in depth and informed conversation between a patient and her physician. Patient preferences, surgeon skill and indication for surgery all should be taken into consideration when determining the most appropriate surgical approach. Given the lack of evidence showing the benefit of RH, LESS or MLH over other more established approaches, further studies should be performed to further scrutinize clinical outcomes prior to widespread adoption of these newer techniques. Until such studies are performed, gynecologists should practice according to the current guidelines.

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Endometriosis: Where are We and Where are We Going?

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Abstract

Endometriosis currently affects ~5.5 million reproductive-aged women in the U.S. with symptoms such as painful periods (dysmenorrhea), chronic pelvic pain, pain with intercourse (dyspareunia), and infertility. It is defined as the presence of endometrial tissue outside the uterine cavity and is found predominately attached to sites within the peritoneal cavity. Diagnosis for endometriosis is solely made through surgery as no consistent biomarkers for disease diagnosis exist. There is no cure for endometriosis and treatments only target symptoms and not the underlying mechanism(s) of disease. The nature of individual predisposing factors or inherent defects in the endometrium, immune system, and/or peritoneal cavity of women with endometriosis remains unclear. The literature over the last 5 years (2010-2015) has advanced our critical knowledge related to hormones, hormone receptors, immune dysregulation, hormonal treatments, and the transformation of endometriosis to ovarian cancer. In this review, we cover the aforementioned topics with the goal of providing the reader an overview and related references for further study to highlight the progress made in endometriosis research, while concluding with critical areas of endometriosis research that are urgently needed.

Introduction

Endometriosis is an estrogen-dependent gynecological condition characterized by the presence and growth of ectopic endometrial tissue, often associated with inflammation, severe and chronic pain, and infertility (Hickey *et al.* 2014). Lesions identified during laparoscopy are categorized as superficial peritoneal lesions, endometriomas, or deep infiltrating nodules, with high degree of individual variability in lesion color, size, and morphology. Histopathological analysis requires the presence of at least two features for a

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diagnosis of endometriosis, the features being endometrial epithelium, endometrial glands, endometrial stroma, and hemosiderin-filled macrophages (Hsu *et al.* 2010). Retrograde menstruation, in which uterine epithelial and stromal cells are disseminated and implanted into the peritoneal cavity via the fallopian tubes, is the most accepted mechanism for the pathogenesis of endometriosis (Sampson 1927b, Ahn *et al.* 2015a). Greater than 90% of women undergo retrograde menstruation; however, the prevalence of endometriosis in the general population is 6-10% (Sampson 1927a, Syrop & Halme 1987). Such a discrepancy between these two values suggests women who develop endometriosis are likely to have other genetic, biochemical, and pathophysiological factors contributing to development of the disease (Ahn *et al.* 2015a).

The goal of this review is to provide a broad overview of the advancements in endometriosis research over the last 5 years (2010-2015). First, we delve into animal models often used in endometriosis research. After which, we cover critical areas of endometriosis study, including basic and clinical research, and the transformation of endometriosis into ovarian cancer. Within basic research, we focus on angiogenesis, cytokine/chemokine expression, and hormones and their receptors, and the significance they may play in the pathogenesis of endometriosis. This review is a synopsis of important findings for researchers to quickly find relevant sources of interest to his/her studies.

Animal Research Models

The use of animal models in the study of endometriosis allows for the control of numerous variables related to pathogenesis and disease progression, including angiogenesis, inflammation, and hormonal response. Non-human primate and rodent models are the most common animal models used, while the chicken chorioallantoic membrane model has limited use.

Non-human Primate Models

Non-human primates (baboons and rhesus macaques) are often used to study pathogenesis, progression, and treatment of endometriosis. While primates can spontaneously develop endometriosis at a low prevalence (D'hooghe *et al.* 1996, Zondervan *et al.* 2004, King *et al.* 2015), techniques have been developed to increase disease incidence. Cervical occlusion to promote retrograde menstruation (Scott *et al.* 1953, D'Hooghe *et al.* 1994) and a homologous model, in which endometrial tissue is excised from a donor primate and surgically transplanted or injected into a recipient primate, are used (Te Linde & Scott 1950, D'Hooghe *et al.* 1995, Sillem *et al.* 1996). Primate models, including advantages and disadvantages, have been previously described (Tirado-Gonzalez *et al.* 2010, Grummer 2012, King *et al.* 2015).

Rodent Models

Rodents are often used in endometriosis research due to quick generation time, ability for genetic manipulation, and relatively low cost, especially in comparison to non-human primate models. Rodent models of endometriosis are divided into two main groups: heterologous or homologous/autologous models. Heterologous models use human tissue

transplanted into immunocompromised mice, while homologous models involve transferring endometrial tissue from one animal to a syngeneic animal (Tirado-Gonzalez *et al.* 2010, King *et al.* 2015).

Heterologous models involve the transfer of human endometrial tissue into an immunocompromised rodent, such as athymic nude, severe combined immunodeficient (SCID), or Rag2γ(c) mice, to prevent the rodent immune system from attacking the foreign tissue (Zamah *et al.* 1984, Aoki *et al.* 1994, Greenberg & Slayden 2004). Once human tissue is collected, it is disseminated via intraperitoneal or subcutaneous injection into the immunocompromised rodent. Heterologous rodent models with associated advantages and disadvantages have been described (Tirado-Gonzalez *et al.* 2010, Bruner-Tran *et al.* 2012, Grummer 2012, King *et al.* 2015).

Several homologous rodent models are utilized in endometriosis research, and the generation of these models involves several important considerations regarding the reproductive status of the donor and recipient, transplantation method, and potential genetic manipulation (King *et al.* 2015). Often, the recipient rodents are ovariectomized and treated with estrogens to promote lesion growth (Cummings & Metcalf 1995, Somigliana *et al.* 1999, Styer *et al.* 2008, Burns *et al.* 2012). Critically valuable for the study of endometriosis is that the homologous model maintains an intact immune system. A large difference between homologous models is the method of transplantation and tissue dissemination. Various models exist for the development of ectopic lesions, including: 1) suturing uterine tissue into the peritoneal wall or intestinal mesentery, 2) injecting minced uterine tissue intraperitoneally to disperse freely and attach at sites within the peritoneal cavity, 3) using entire uterine tissue or endometrial tissue, and 4) using minced “menstruated” tissue for intraperitoneal injection (Vernon & Wilson 1985, Somigliana *et al.* 1999, Burns *et al.* 2012, Greaves *et al.* 2014). For models used to study endometriosis, it is critically important to remember the definition of and requirements for an endometriotic lesion. Discouragingly, some models inherently do not fulfill these criteria and are suboptimal for the study of endometriosis, ultimately occluding comprehensive comparison and interpretation of data in the scientific literature.

Chicken Chorioallantoic Membrane Model

The chicken chorioallantoic membrane (CAM) assay is used to study molecular processes involved in adhesion, invasion, and angiogenesis of developing endometriotic lesions. This assay involves culturing human endometrial tissue on the CAM of fertilized chicken embryos (Maas *et al.* 2001). The CAM has a dense microvasculature, useful for examining angiogenesis and for experimentation with anti-angiogenic agents (Nap *et al.* 2005). This method has been used to study the impact of matrix metalloproteinase (MMP) expression and activity on adhesion and invasion (Nap *et al.* 2004, Juhasz-Boss *et al.* 2010). However, it is not suited for studying immunological or inflammatory aspects of lesion development or for potential effects of systemic treatments.

Pathogenesis and Progression of Endometriosis

Animal models and human samples are paramount in the study of pathogenesis and progression of endometriosis. They allow for in-depth analysis of factors involved in this disease, including inflammation, angiogenesis, cytokine/chemokine expression, and endocrine alterations such as steroid and steroid receptor expression. These components also form a complex, interacting system greatly impacting the development of endometriosis. While we understand that several other factors are involved in the pathogenesis and progression of this disease, including genetics and epigenetics, and significant advances in these components have been made, covering them in depth is beyond the scope of this review. For researchers interested in these topics, an elegant and comprehensive review by Bulun *et al.* (2015) recently addresses the molecular biology, genetics, and epigenetics of endometriosis and covers 25 years of research (1990-2015).

Inflammation - Angiogenesis

Angiogenesis is the formation of new blood vessels, and subsequently, is a key process to form functional blood vessels to ectopic menstrual tissue for the establishment/maintenance of endometriotic lesions. Theorized is that women with endometriosis respond to retrograde menstrual tissue as a “wound” that must be healed and not as “self” that must be removed (Herington *et al.* 2011). Examining key players involved in angiogenesis, both in women with endometriosis and in animal models, similarities between angiogenesis in endometriotic lesions and angiogenesis in wound healing exist. A variety of growth factors and genes related to angiogenesis have been studied in endometriosis.

The VEGF protein family is well known for roles in angiogenesis, vasculogenesis, and lymphangiogenesis. Human peritoneal fluid (PF) from women with endometriosis show inconsistent protein levels of VEGF, but this may be due to sample size, dilution of PF, or true variability among women. For example, some studies show increased VEGF levels in the PF (Bourlev *et al.* 2010, Xu *et al.* 2013, Szubert *et al.* 2014); however, other studies show no increase in VEGF levels in women with endometriosis compared to healthy women (Barcz *et al.* 2012, Bersinger *et al.* 2012, Rathore *et al.* 2014). Interestingly, more consistency is found in animal models of endometriosis, most likely because of controlled onset of experimental conditions. A variety of rodent models of endometriosis show VEGF levels increase in endometriosis-like lesions (Machado *et al.* 2010, Ricci *et al.* 2011, Kumar *et al.* 2014, Lu *et al.* 2014a, Machado *et al.* 2014, Zhao *et al.* 2015). Data are inconsistent when attempting to target VEGF in the mouse to treat endometriosis (Xu *et al.* 2011, Novella-Maestre *et al.* 2012, Virani *et al.* 2013, Kumar *et al.* 2014); however, the data suggest VEGF drives angiogenesis in endometriosis. Furthermore, these results from human and animal models demonstrate challenges of clearly deciphering VEGF as an appropriate marker for endometriosis.

Other angiogenic factors play important roles in the adhesion and maintenance of endometriosis lesions, including hypoxia factors (ie. HIF1A), MMPs (ie. MMP9), and microRNAs (miRNA). As mentioned, the peritoneal microenvironment of women with endometriosis is often different from healthy women. In a heterologous mouse model, hypoxic conditions promote angiogenesis and proliferation of endometriosis demonstrated

by larger lesions, higher levels of VEGF, HIF1A, Ki67, and PECAM1 (Lu *et al.* 2014b). Concomitantly, the same group shows lesion location affects adhesion and angiogenesis when comparing intraperitoneal versus subcutaneous endometriotic tissue injection (Lu *et al.* 2014a), suggesting the microenvironment of the peritoneal cavity plays a crucial role in lesion adhesion and angiogenesis. MMPs are proteases required for reorganizing existing blood vessels during budding angiogenesis (Page-McCaw *et al.* 2007). Recently, the role of MMPs in endometriosis were not studied in-depth; but MMPs play a known role in endometriosis (Machado *et al.* 2010). For example, *Mmp9*$^{-/-}$ uterine tissue does not grow in a mouse suture endometriosis model (Han *et al.* 2012); however, this model does not account for actual tissue attachment. An emerging field in endometriosis is the function of miRNA in angiogenesis. Primary eutopic and ectopic endometrial stromal cells exposed to PF from women with endometriosis have downregulated miRNAs known to regulate VEGF expression compared to cells exposed to PF from control women (Braza-Boils *et al.* 2013, Braza-Boils *et al.* 2014, Braza-Boils *et al.* 2015). Future in-depth analysis of the interplay between inflammation and angiogenesis in the early stages of endometriosis development is needed to determine which molecules could potentially be targeted therapeutically.

Inflammation - Cytokine and Chemokine Expression

Cytokines and chemokines are emerging as key players in endometriosis pathobiology. Cytokines are a broad group of secreted proteins important in cell signaling, while chemokines are a family of cytokines important in inducing chemotaxis in nearby cells. A complete overview of chemokines and cytokines in endometriosis is too exhaustive; however, these proteins are altered in PF, ectopic lesions, eutopic endometrium, and serum. To demonstrate the growing role of cytokine research in the study of endometriosis, Table 1 lists cytokines and chemokines that appear in > two endometriosis research papers between 2010-2015. Additional to the dysregulation of cytokines/chemokines, altered levels of a large number of cytokines/chemokines are found in cyst fluid removed from endometriomas/chocolate cysts (Chen *et al.* 2013b). Before the interplay and implications of chemokines and cytokines can be elucidated in endometriosis, large scale controlled human studies or meta-analyses will need to be conducted to fully encompass cytokine dysregulation. Most likely, with the signaling complexity of the immune system and endometriosis as a disease, a single chemokine/cytokine will not diagnose disease, but instead, a disease profile of altered cytokines may be used to establish disease diagnosis. Furthermore, as nicely outlined in Fassbender et al., international standardized methods for BioBanking endometriosis samples needs to be implemented (Fassbender *et al.* 2013).

Hormones and Hormone Receptors

Endometriosis is intimately associated with steroid metabolism and associated pathways, corresponding to the paramount roles estrogen receptors (ESRs) and progesterone receptors (PGRs) play in uterine biology. Both human and animal model studies show endometriosis is estrogen (E2) dependent and is regulated through the ESRs alpha and beta (*ESR1* and *ESR2*) (Burns *et al.* 2012, Pellegrini *et al.* 2012, Wu *et al.* 2012, Han *et al.* 2015, Zhao *et al.* 2015). An increased ratio of *ESR2* to *ESR1* mRNA is observed in endometriomas compared with endometriosis implants and eutopic endometrium (Bukulmez *et al.* 2008). Knockout studies in mice show lesion attachment, size, and proliferation are closely associated with

the presence or absence of *Esr1* and *Esr2* (Burns *et al.* 2012). The Bulun Laboratory have focused efforts on ESR2 and demonstrate ESR2 expression is highly increased in endometriotic tissue due to hypomethylation of the promoter region (Dyson *et al.* 2014). They also identify RAS-like estrogen-regulated growth inhibitor (RERG) as a key enzymatic target of estradiol signaling through ESR2. This enzyme regulates numerous factors involved in the progression of endometriosis, including cell proliferation and apoptotic resistance (Monsivais *et al.* 2014). Additionally, they have nicely detailed multiple studies on the role of ESR2 in endometriosis in a comprehensive review (Bulun *et al.* 2012). Use of estrogen receptor ligands, inhibitors, and agonists also support the role of ESRs in endometriosis (Colette *et al.* 2011, Kulak *et al.* 2011, Han *et al.* 2012, Chen *et al.* 2014, Naqvi *et al.* 2014, Palmer *et al.* 2015, Zhao *et al.* 2015). Specifically, selective estrogen receptor modulators (SERMs) are synthetic molecules which bind to ESRs and act either as antagonists or agonists. Two compounds, chloroindazole (CLI) and oxabicycloheptene sulfonate (OBHS), have strong ER-dependent anti-inflammatory effects on endometriosis lesions *in vivo* in a suture mouse model of endometriosis and *in vitro,* with primary human endometriotic stromal cells (Zhao *et al.* 2015). Their data suggests that both CLI and OBHS inhibit the establishment of new lesions and reduce the size of already established lesions; however, important next studies using these inhibitors will be to examine lesion attachment without a suture endometriosis model, as suturing alone creates an unnecessary inflammatory response similar to any reaction towards a foreign body, (Carr *et al.* 2009) and, in some respects, negates the use of homologous tissue.

Progesterone (P4) and its receptor isoforms, PGR-A and –B, also have established roles in endometriosis. The endometrium of women with endometriosis demonstrates an attenuated response to P4 because PGR responsive genes are not suppressed in the eutopic endometrium of women with endometriosis compared to healthy women in the early secretory phase of the menstrual cycle, suggesting the presence of a progesterone resistance phenotype in these women (Burney *et al.* 2007). A more recent study to discriminate between the PGR isoforms finds elevated levels of PGR-A in endometriosis lesions and eutopic endometrium from women with endometriosis and shows a PGR-A-dominant state, regardless of menstrual phase (Bedaiwy *et al.* 2015). While the data is from a small cohort of women, their findings suggest a PGR-A-dominant menstrual efflux in the peritoneal cavity may mirror the growth and invasive properties known about cancers overexpressing PGR-A.

Aromatase is the enzyme responsible for the aromatization of androgens into estrogens. Aromatase protein level is increased in vaginal septum lesions and decreased in intestinal lesions in women with endometriosis (Goncalves *et al.* 2015). Ovarian endometriomas express higher levels of aromatase and peroxisome proliferator-activated receptor gamma co-activator 1 alpha (PPARGC1A) than associated ectopic lesions and eutopic endometrium (Suganuma *et al.* 2014). Activation of peroxisome proliferator-activated receptor gamma (PPARG) inhibits the growth and survival of human endometriotic cells by suppressing E2 biosynthesis and prostaglandin E2 (PGE2) signaling (Lebovic *et al.* 2013). The use of AIs for the treatment of endometriosis is becoming more common and is discussed below.

The last 5 years have expanded our knowledge of hormones, hormone receptors (HRs), and associated co-regulators. These studies are important for integrating dysregulation found in

ectopic lesions, but also have allowed for the design of more targeted areas to be studied. More in-depth studies with targeted HR uterine knockouts, co-regulator knockouts, and/or with the recently synthesized SERMS will lead to greater understanding of the role of HR in disease. The results of these future experiments will allow for even more targeted experiments and hopefully development and use of more targeted therapeutic paradigms.

Interactions between Inflammation and the Endocrine System

Cross-talk between the immune/inflammatory and endocrine systems can significantly impact pathogenesis and progression of endometriosis. The sex hormone receptors can markedly alter the immune response in ectopic tissue. Both *ESR1* and *ESR2* have distinct roles in regulating the immune response, as discovered through the use of multiple animal models. Signaling of E2 through ESR1 appears to have both an anti- and pro-inflammatory role, as observed by increased mitogenesis and decreased *IFNG*, *TNF*, and *IL12* transcript expression (Burns *et al.* 2012). Overexpression of *ESR2* activates the inflammasome and modulates TNF-induced apoptosis, as observed with increases in IL1B and cleaved caspase-1 levels and decreases in cleaved caspase-8 levels in ectopic lesions (Han *et al.* 2015).

Hormones themselves also directly alter the immune system. Monocyte chemotactic factor-1 (MCP1/CCL2) is an example of a chemokine significantly affected by sex hormones. In human endometrial endothelial cells from women with endometriosis, both E2 and P4 increase *MCP1* mRNA and protein expression; this effect is not observed in cells from healthy women (Luk *et al.* 2010). After treating monocytes with control peritoneal fluid (cPF) or endometriotic peritoneal fluid (ePF), the addition of E2 to the culture suppresses MCP1 release from cPF-treated monocytes. However, E2 does not suppress MCP1 release from ePF-treated monocytes (Lee *et al.* 2012). E2 promotes a pro-inflammatory environment by increasing secretion of IL6 and TNF from peritoneal macrophages from women with endometriosis compared to control women. This effect is further enhanced by co-treatment with lipopolysaccharide (Khan *et al.* 2015). Other chemokines, CXCR4 and CXCL12, are downregulated by sex hormones in human epithelial endometrial cells and human endometrial stromal cells respectively (Ruiz *et al.* 2010). All of these findings provide evidence that the immune environment and its response to sex hormones is altered in women with endometriosis; however, a definitive mechanism for these differences is largely unknown and is a major area that future research needs to address.

A third aspect to the endocrine-immune crosstalk involves aromatase expression. Macrophage migration inhibitory factor (MIF) increases aromatase mRNA and protein expression in ectopic endometrial stromal cells via posttranscriptional stabilization (Veillat *et al.* 2012). Interestingly though, E2 treatment in the same cells increases *MIF* mRNA and protein expression, suggesting a positive feedback loop between the endocrine and immune systems in women with endometriosis (Veillat *et al.* 2012). Potential for a continuous positive feedback loop between these systems is an area for further exploration to understand the dynamic and altered environment in women with endometriosis.

Clinical Symptoms and Diagnosis of Endometriosis

Endometriosis is often characterized by pelvic pain that manifests in a variety of ways; most commonly, patients present with dysmenorrhea, noncyclical pelvic pain, and dyspareunia, but other common symptoms are dyschezia, dysuria, and infertility (Fritz MA 2011, Practice Committee of the American Society for Reproductive 2014). Definitive diagnosis of endometriosis is by visualization or excision of lesions via laparoscopy. The American Society for Reproductive Medicine (ASRM) grading system for endometriosis guides surgeons in determining the severity of disease (1997) and was created to help predict pregnancy with fertility treatment. The grading system does not correlate with pain level, and has limited reproducibility to predict pregnancy; however; it remains the best objective way to communicate disease severity between physicians and surgeons.

Accuracy of visual diagnosis increases with disease severity (Fernando *et al.* 2013). While the European Society of Human Reproduction and Embryology (ESHRE) requirements suggest surgical diagnosis by visualization alone is appropriate, ASRM stresses that biopsies be taken when diagnosis is unclear (Fernando *et al.* 2013). Importantly, poor correlation exists between clinical symptoms and disease burden (Dunselman *et al.* 2014, Practice Committee of the American Society for Reproductive 2014). Diagnosing endometriosis by pelvic pain alone is not sufficient, as pelvic pain is also a symptom of many other diseases, including pelvic adhesions, adenomyosis, and gastrointestinal urologic disorders (Bulun 2009, Practice Committee of the American Society for Reproductive 2014). This vast differential diagnosis for pelvic pain can complicate the diagnosis of endometriosis.

Treatments

Several different treatment modalities, including medical, surgical, and alternative, exist for endometriosis. First-line medical management includes options that have a favorable safety and cost profile, are well tolerated by the patient, and are effective in treatment (Zito *et al.* 2014). If medical therapy fails, surgical therapy to remove endometriotic lesions and endometriomas is performed. Finally, alternative therapies are being used to supplement conventional treatments.

Medical Therapy

Combined oral contraceptive pills (OCPs), which include ethinyl estradiol (EE) and various progestins, are used to treat endometriosis, particularly in women not trying to conceive (Practice Committee of the American Society for Reproductive 2014, Zito *et al.* 2014). Historically, OCPs have been first-line therapy, but most studies are decades old and the pills contained higher doses of EE. Based on a more recent randomized control trial (RCT) in 100 patients, low dose OCPs decrease pain more significantly than placebo on the Visual Analog Scale (VAS) (Harada *et al.* 2008). Continuous OCPs decrease recurrence rates of dysmenorrhea after surgical therapy when compared to cyclic OCPs (Muzii *et al.* 2015, Zorbas *et al.* 2015). Of the progestins, the 19-nortestosterone derivatives are less androgenic and offer better side effect profiles (Angioni *et al.* 2014). In a RCT, dienogest significantly decreases endometriosis-related pain similar to gonadotropin releasing hormone agonists (GnRHa), both as initial and post-operative therapy, without the negative side effect profile

of GnRHa (Angioni *et al.* 2014, Andres Mde *et al.* 2015, Granese *et al.* 2015, Strowitzki *et al.* 2015). Levonorgestrel, delivered through an intrauterine system after conservative surgery, significantly decreases dysmenorrhea, dyspareunia, and non-cyclic pelvic pain compared to expectant management in a RCT of 55 patients (Tanmahasamut *et al.* 2012, Imai *et al.* 2014).

Several therapies aim to create a hypoestrogenic state in women with endometriosis. Examples of these treatments include GnRHa, GnRH antagonists (GnRH-ant), synthetic androgens, and AIs. GnRHa therapy downregulates gonadotropin receptors and desensitizes the body to gonadotropins. It decreases pain and endometriotic nodules in comparison to placebo (Leone Roberti Maggiore *et al.* 2014, Brown & Farquhar 2015). A multi-center RCT comparing GnRHa to OCPs as post-surgical therapy reports both groups increase quality of life scores (Granese *et al.* 2015). Although GnRHa is proven effective, a severe side effect is decreased bone mineral density (BMD); therefore, estrogens or progestins are given for bone protection (Leone Roberti Maggiore *et al.* 2014, Zito *et al.* 2014). In contrast, GnRH-ant inhibit gonadotropin receptors. Elagolix improves dysmenorrhea and dyspareunia compared to placebo in a phase 2 RCT (Ezzati & Carr 2015, Munoz-Hernando *et al.* 2015) and, comparing BMD profiles of elagolix with depot medroxyprogesterone acetate, both minimally impact BMD (Carr *et al.* 2014, Ezzati & Carr 2015).

Danazol, a synthetic androgen, inhibits the luteinizing hormone (LH) surge; however, it also increases free testosterone, causing undesired side effects including hirsutism, deepening of voice, weight gain, and acne. Danazol effectively decreases pelvic pain compared to placebo, and is as effective as other hormonal therapies, but the numerous side effects limit use (Practice Committee of the American Society for Reproductive 2014, Zito *et al.* 2014). AIs are currently a second line treatment in women refractory to first line treatments (Abu Hashim 2014). AIs such as letrozole decrease estrogen stimulation of endometriosis and, when used in combination with GnRHa, improve pelvic pain more than GnRHa alone. Additionally, letrozole with norethindrone acetate add-back has improved endometriosis symptoms, and high dose aromatase inhibition reduces ovarian endometrioma size (Agarwal *et al.* 2015). In contrast, a small RCT investigating post-surgical endometriosis pain comparing OCPs alone and in combination with letrozole reports similar pain scores, suggesting no benefit with letrozole addition (Almassinokiani *et al.* 2014).

Surgical Therapy

Surgical therapy for endometriosis is typically necessary for intractable pelvic pain despite medical therapy. Several different surgical techniques are performed (Table 2), including excision/removal of endometriosis, uterosacral nerve ablation, presacral neurectomy, and hysterectomy with bilateral salpingo-oophorectomy (BSO) (Daniels *et al.* 2010, Healey *et al.* 2014, Posadzka *et al.* 2015), and some techniques provide better symptomatic control than others. For symptom improvement and preventing disease recurrence, endometrioma removal is superior to drainage (Duffy *et al.* 2014, Practice Committee of the American Society for Reproductive 2014). Hysterectomy without BSO is less effective because of continued hormonal stimulation of microscopic endometriotic lesions. Hysterectomy with BSO leads to surgical menopause, which negatively impacts bone and cardiac health.

Extreme surgical management is reserved for patients who fail conservative management (Duffy *et al.* 2014, Practice Committee of the American Society for Reproductive 2014).

Alternative Therapy

Given that endometriosis is such a difficult disease to treat, alternative therapies are welcomed in addition to conventional therapy. Comparing Chinese medicine (CM) to GnRHa as post-surgical treatment for endometriosis found no differences in recurrence rates on follow-up (Weng *et al.* 2015). In contrast, Chinese herbal enemas decrease dysmenorrhea comparable to danazol (Kong *et al.* 2014), and CM and herbal enema combination is superior to danazol in decreasing pain symptoms (Flower *et al.* 2012). An acupuncture study in addition to conventional medical therapy significantly decreases pelvic pain by 5 to 6 points on the 10-point VAS (Rubi-Klein *et al.* 2010). Pelvic physical therapy includes internal manual treatment to stretch pelvic floor muscles, myofascial release, biofeedback, and trigger point release. In those with myofascial chronic pelvic pain, 63% report significant pain improvement after at least 6 sessions (Bedaiwy *et al.* 2013). Exercise can provide pain relief, based on questionnaire studies composed of 50-2730 women with endometriosis and 400-4000 control women; however, other survey studies correlate exercise with increased pelvic pain. Unfortunately, not all of these studies are controlled and all are from self-reporting (Bonocher *et al.* 2014). Large prospective cohort or case-control studies demonstrate increased risk of endometriosis with diets high in trans-fatty acids and decreased risk with diets containing high levels of long-chain omega 3 fatty acids (Hansen & Knudsen 2013). More high quality studies are needed in these areas and importantly, a positive publication selection bias likely exists with alternative therapies, exaggerating true effectiveness (Kong *et al.* 2014).

Association between Endometriosis and Cancer

The potential association between endometriosis and cancer has been theorized for decades. This association is based upon observational case-control and cohort studies that propose malignant transformation occurs within endometriotic lesions, giving rise to cancer. Our molecular-genetic understanding of both endometriosis and ovarian cancer continues to rapidly evolve; yet, a definitive mechanism for malignant transformation remains elusive.

Risk and Prognosis

The 10% prevalence of endometriosis and an even higher prevalence for women with infertility or chronic pelvic pain, makes the establishment of an absolute “cause-and-effect” relationship problematic. Lifetime risk of developing ovarian cancer in the general population is ~1.4%, with a median age of onset in the early 60s (Schorge *et al.* 2010). Epithelial ovarian cancer is no longer seen as a single disease, but rather a constellation of multiple diseases based upon histologic subtypes and unique molecular signatures (Galic *et al.* 2013). The risk of ovarian cancer increases for women who incur fewer pregnancies and/or suffer from infertility. The possibility of confounding when assessing associative risk between these two entities must be considered because infertility is related to both conditions.

Nonetheless, a number of epidemiologic and clinical features lead investigators to propose an association between endometriosis and cancer. The establishment of an association was reported 90 years ago (Sampson 1925) and was refined in 1953, proposing that benign endometriosis should be observed in close anatomic proximity to the arising endometriosis-associated cancer (Scott 1953). Chief among the observations are that both entities produce tissues that can metastasize, invade, and destroy normal surrounding tissues. Furthermore, cancers often are identified in endometriotic lesions or in tissues that are contiguous with endometriosis, and there are often findings of candidate precursor lesions exhibiting histologic atypia in these surrounding tissues (Wei *et al.* 2011). Finally, endometriosis in younger women, which persists into older age, creates a long window for malignant transformation.

Several retrospective studies initially document the increased rate of endometriosis in women with ovarian cancer. A Swedish study containing over 20,000 patients that cross-matched inpatient endometriosis diagnosis and any cancer diagnosis (Brinton *et al.* 1997) found a small increased risk of any cancer, but the risks were not confirmed upon longer-term follow up (Brinton *et al.* 1997). The risk of ovarian cancer, however, is significantly increased in both the initial and long-term analyses. In patients with a history of prolonged endometriosis, the statistical risk for the development of ovarian cancer is even higher.

A linkage analysis of over 99,000 women from Denmark shows an endometriosis-related increase in ovarian cancer occurs in two histologic subtypes, clear cell and endometrioid (summarized in Table 3) (Brinton *et al.* 2005). Recent evidence also suggests a correlation between endometriosis and high-grade serous histologic type ovarian cancer (Lee *et al.* 2016). A large case-control study confirms an approximate 3-fold increased risk of clear cell or endometrioid ovarian cancer in association with endometriosis (Rossing *et al.* 2008). Malignant transformation risk to ovarian cancer from ovarian endometriosis is reportedly 0.2-2.5% (Gadducci *et al.* 2014). Recent studies also show the association between endometriosis and different forms of ovarian cancer: serous, mucinous, clear-cell, and endometrioid, with the predominant cell types being clear cell and endometrioid (Table 4).

A meta-analysis conducted by Kim *et al.* (2014) evaluates the risk and prognosis of ovarian cancer in ~445,000 women with or without endometriosis. Based on 35 studies, women with endometriosis are significantly at risk of developing ovarian cancer; however, stage is more likely to be early and low-grade, suggesting the cancer is slow growing and less invasive. Endometrioid and clear cell are common in women with endometriosis, with the serous subtype occurring less frequently and the mucinous subtype displaying no differences between control women and women with endometriosis (Kim *et al.* 2014). Endometriosis does not affect prognosis, and overall survival in women with endometriosis-associated ovarian cancer (EAOC) and in women with non-EAOC are similar when accounting for histology, disease status, assessment of endometriosis, and potential confounding factors. Unfortunately, the effect of endometriosis on a successful debulking surgery is not analyzed (Kim *et al.* 2014), so it is unknown if there is a benefit in survival in women with EAOC.

Proposed Mechanisms of Malignant Transformation

Complex hormonal, genetic, and immunologic interactions must be considered when assessing the interplay between endometriosis in the development of epithelial primary peritoneal or ovarian carcinomas. Chronic inflammation, autocrine and paracrine effects, hormonal interactions, and micro-environmental alterations caused by endometriosis in the pelvic region could be relevant mechanisms for malignant transformation. Aberrant immune function, stimulated by estrogens, may create a positive feed-forward loop, enhancing growth and invasiveness of endometriosis and promoting malignant transformation (Ness 2003). Zanetta et al. report a role for a hyper-estrogenic state in stimulating endometriosis and promoting malignant transformation (Zanetta *et al.* 2000).

A permissive microenvironment and accumulation of genetic mutations is suggested to cause malignant change of endometriosis (Wei *et al.* 2011). Distinct molecular events may occur in early stages of tumorigenesis of endometriosis-associated carcinoma. Recent studies focus on genetic alterations such as phosphatase and tensin homolog (*PTEN*), tumor protein p53 (*TP53*), and B-cell lymphoma (*BCL*) gene mutations that lead to malignant changes of endometriosis (Nezhat *et al.* 2008, Munksgaard & Blaakaer 2012, Lai *et al.* 2013, McConechy *et al.* 2014). An interplay of genetics and oxidative stress, with decreased expression of interleukin 1 receptor type 2 (*IL1R2*), is a common signature between endometrioid ovarian cancer and endometriosis (Kobayashi *et al.* 2009, Keita *et al.* 2010, Keita *et al.* 2011). IL1 ligands are expressed by all endometriosis-associated ovarian cancer subtypes and endometrial cells. A decrease in IL1R1 levels, a protector against the tumorigenic effects of IL1, occurs in endometrioid carcinoma (Keita *et al.* 2010, Keita *et al.* 2011).

Multiple tumor-associated somatic mutations, detected by examining single gene or by whole genome sequencing, have revealed a signature of mutations. Mutations in catenin beta 1 (*CTNNB1*) are seen in 60% of ovarian endometrioid carcinomas (Matsumoto *et al.* 2015). Mutations in AT Rich Interactive Domain 1A (*ARID1A*) and phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*) appear most consistently in clear cell ovarian carcinomas (Gadducci *et al.* 2014, Anglesio *et al.* 2015, Matsumoto *et al.* 2015). Mutations in *ARID1A*, involved in chromatin remodeling, are present in both clear cell (15-75%) and endometrioid carcinomas (30-55%) (Wiegand *et al.* 2010, Gadducci *et al.* 2014). Associated with malignant transformation, mutations in *ARID1A* lead to the loss of its product, BAF250a, which correlates strongly with ovarian clear-cell carcinoma and endometrioid carcinoma subtypes, as well as with high-grade endometrial carcinomas (Wiegand *et al.* 2010, Wiegand *et al.* 2011, Ayhan *et al.* 2012, Lowery *et al.* 2012, Samartzis *et al.* 2012, Chene *et al.* 2015). *ARID1A* mutations and BAF250a loss are also observed in tumors and contiguous atypical endometriosis, but not in distant endometriotic lesions. The loss of *ARID1A* expression usually coexists with PI3K-Akt pathway activation and/or zinc finger protein 217 (ZNF217) amplification in ovarian clear cell cancers and may indicate an early event in the malignant transformation of endometriosis into the various histotypes of ovarian cancer (Ayhan *et al.* 2012, Huang *et al.* 2014).

Loss of *PTEN* is observed in clear cell-associated endometriosis and cancers, including a significant increase in expression levels of X-ray repair cross-complementing protein 5

(XRCC5), patched 2 (PTCH2), elongation factor 1-alpha 2 (EEF1A2) and protein phosphatase 1 regulatory subunit 14B (PPP1R14B). However, these changes are not observed in benign endometriosis (Worley *et al.* 2015). *PTEN* loss is proposed as an early and permissive event in endometriosis development, while loss of *ESR1* and polycomb-mediated transcriptional factor cause ultimate malignant transformation (Worley *et al.* 2015).

Future research will clarify the likely complex interaction between genetic alterations, estrogen exposure, inflammatory cytokines, and the immunologic microenvironment in the transformation of endometriosis to endometrioid and clear cell ovarian and primary peritoneal cancers. Treatment of these cancers will hopefully improve with use of targeted and immunologic therapies that address underlying causes of malignant transformation.

Concluding Remarks: Where are we going?

While the studies reviewed from the last 5 years demonstrate a deeper understanding of endometriosis as dysregulations pertain to hormones, hormone receptors, immune function, and transformation to ovarian cancer, endometriosis still remains mysterious from many facets. Critically needed for this enigmatic disease are mechanistic understandings of disease initiation and perturbation that will hopefully lead to the development of non-invasive disease diagnosis and the development of treatments that do not negate hormonal cyclicity or have other undesired side effect profiles and decrease the need for surgical extirpation. To allow for this to happen, the following areas of need are identified:

- Establish clear limits to animal models and clarify what the model may and may not reveal
- Establish international standards for collection of patient information and samples as outlined by (Fassbender *et al.* 2013)
- Establish disease profile through clearer understanding of cytokines and the potential association with autoimmune disorders
- Characterization of interplay between the hormonal milieu and immune system
- Focus on lifetime exposures, acute and chronic, to endocrine disrupting chemicals that may interfere with uterine development, immune system regulation, and ultimately endometriosis development
- Full recognition that this disease is truly multifaceted with pain, psychology, infertility, immunity, etc.
- Transformation of endometriosis to ovarian cancer through characterization of the lag between endometriosis found on the ovary to an ovarian cancer diagnosis
- Determine if age, parity, weight, hormonal regulators (oral contraceptives) contribute to transformation to cancer diagnosis

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Table 1
Cytokine or Chemokine Alterations in Endometriosis

Cytokine/chemokine	Model	Results	Reference
CCL2 (MCP-1)	hPF	+, ++, +++	(Mier-Cabrera *et al.* 2011, Margari *et al.* 2013), (Tao *et al.* 2011),(Bersinger *et al.* 2012)
CCL5 (RANTES)	hPF	NS, +, ++	(Bersinger *et al.* 2012, Margari *et al.* 2013), (Mier-Cabrera *et al.* 2011),(Beste *et al.* 2014)
	hEctopic	qualitative +, ++	(Wang *et al.* 2010),(Yang *et al.* 2013)
CCL11 (Eotaxin)	hPF	++, +	(Bersinger *et al.* 2012), (Mier-Cabrera *et al.* 2011)
CXCL1 (GROa)	hPF	Nearing	(Bersinger *et al.* 2012)
CXCL8 (IL8)	hPF	NS,+, ++	(Velasco *et al.* 2010, Bersinger *et al.* 2012), (Mier-Cabrera *et al.* 2011, Beste *et al.* 2014), (Milewski *et al.* 2011, Malhotra *et al.* 2012)
	hSerum	++	(Carmona *et al.* 2012)
	hEESCs	++	(Delbandi *et al.* 2013)
	hPF mRNA Cells	NS	(Yeo *et al.* 2013)
CXCL10 (IP-10)	hLesion	NS trend –	(Bellelis *et al.* 2013)
	hPF	++	(Bersinger *et al.* 2012)
CXCL12 (SDF1)	hEctopic	+	(Bellelis *et al.* 2013)
	hPF	+	(Leconte *et al.* 2014)
IL1B	hPF	+, +++	(Mier-Cabrera *et al.* 2011, Beste *et al.* 2014), (Sikora *et al.* 2012)
	hEctopic	+	(Chen *et al.* 2013)
	hPF cells	NS	(Yeo *et al.* 2013)
IL4	hPF	NS, ++	(Mier-Cabrera *et al.* 2011, Wickiewicz *et al.* 2013), (Beste *et al.* 2014)
IL6	hPF	NS, +, ++, +++	(Rathore *et al.* 2014), (Mier-Cabrera *et al.* 2011, Khan *et al.* 2015), (Velasco *et al.* 2010, Kang *et al.* 2014), (Milewski *et al.* 2011, Bersinger *et al.* 2012, Podgaec *et al.* 2012, Wickiewicz *et al.* 2013)
	hSerum	+, ++, +++	(Kinugasa *et al.* 2011), (Carmona *et al.* 2012), (Elgafor El Sharkwy 2013)
	hEESC	++	(Delbandi *et al.* 2013)
	hPF mRNA Cells	NS	(Yeo *et al.* 2013)
	hSerum/PF	NS/NS	(Andreoli *et al.* 2011)
IL10	hPF	NS, +	(Bersinger *et al.* 2012, Podgaec *et al.* 2012), (Mier-Cabrera *et al.* 2011, Wickiewicz *et al.* 2013)
	hPF mRNA Cells	NS	(Yeo *et al.* 2013)
	hSerum/PF	NS/NS	(Andreoli *et al.* 2011)
IL12	hPF	NS	(Mier-Cabrera *et al.* 2011)
	hPF mRNA Cells	NS	(Yeo *et al.* 2013)
IL17A	hEndo, Serum	**/+	(Ahn *et al.* 2015)
	hSerum/PF	NS/NS	(Andreoli *et al.* 2011)
	hPF	NS	(Podgaec *et al.* 2012)
	hFF/Serum	+++/+++	(Sabbaghi *et al.* 2014)
IL18	hPF	+, ---	(Bersinger *et al.* 2012), (Sikora *et al.* 2012)
IL22	hEctopic	**	(Guo *et al.* 2013)
	hSerum	--	(Santulli *et al.* 2013)
IFNG	hPF	NS, +	(Wickiewicz *et al.* 2013),(Mier-Cabrera *et al.* 2011)

Cytokine/chemokine	Model	Results	Reference
MIF	hPF mRNA Cells	NS	(Yeo *et al.* 2013)
	hPF	*++*	(Beste *et al.* 2014)
	hEctopic	*++*	(Lin *et al.* 2010)
TGFB	hPF	*+++*	(Podgaec *et al.* 2012)
	mKO w/human	- size	(Hull *et al.* 2012)
TNFA	hPF	NS, *+*, *++*	(Tao *et al.* 2011, Wickiewicz *et al.* 2013),(Mier-Cabrera *et al.* 2011, Beste *et al.* 2014, Young *et al.* 2014a, Young *et al.* 2014b), (Khan *et al.* 2015)
	hEctopic cd56^{+}	*+*	(Chen *et al.* 2013)
	pfNKcell	*+*	(Funamizu *et al.* 2014)
	bEctopic	NS	(Ilad *et al.* 2010)
	hPF mRNA Cells	NS	(Yeo *et al.* 2013)

Increased levels:

$^{+}$= p<0.05,

$^{++}$= p<0.01,

$^{+++}$= p<0.001,

**= qualitative IHC,

Decreased levels: - = p<0.05; NS = non-significant

h=human, b=baboon, Ectopic=ectopic endometriosis lesion, PF=peritoneal fluid, FF=follicular fluid, EESC=ectopic endometrial stromal cells

Table 2
Endometriosis Surgical Treatments and Associated Efficacy

Surgical Treatment	Surgical Technique	Compared Treatment	Efficacy
Laparoscopic Ablation	Ablate, or apply heat, to lesion	CO_2 laser vs. electric cautery	Decreased pain with ablation (NRS 3) vs. CO_2 laser (NRS) (Posadzka *et al.* 2015)
		Diagnostic Laparoscopy	Decreased overall pain OR 5.63 (Duffy *et al.* 2014)
Laparoscopic Excision	Remove lesion with scissor or laser	Ablation	No difference in overall pain, dyspareunia, or dyschezia at 1 year (Bulun 2009, Duffy *et al.* 2014)
			Excision decreased dyspareunia (VAS 3.2) vs. ablation (VAS 6.0) at 5 years (Healey *et al.* 2014)
			Ablation required more medical treatment (31%) vs. excision (20%) (Healey *et al.* 2014)
Conservative Laparoscopy	Ablate or excise lesions, restore anatomy, adhesiolysis	Diagnostic Laparoscopy	Decreased overall pain OR 6.58 (Duffy *et al.* 2014)
Laparoscopic Uterosacral Nerve Ablation	Ablate nerve fibers responsible for pain pathway	Conservative Laparoscopy	No difference in pain level (Daniels *et al.* 2010)
Endometrioma Removal	Separate cyst wall from ovary and excise cyst	Cyst drainage	Decreased recurrence of cyst (Dunselman *et al.* 2014)
			Decreased recurrence of dysmenorrhea (OR 0.15) (Brown & Farquhar 2015)
Presacral Neurectomy	Disrupts sympathetic innervation of uterus at level of superior hypogastric plexus	Conservative Laparoscopy	1 RCT: decrease midline dysmenorrheal (Practice Committee of the American Society for Reproductive 2014) (Dunselman *et al.* 2014)
			1 RCT: no additional benefit (Practice Committee of the American Society for Reproductive 2014)
Hysterectomy + BSO	Debulking to place in surgical menopause	Hysterectomy without BSO	Improved symptoms (Practice Committee of the American Society for Reproductive 2014)(Dunselman *et al.* 2014)(Duffy *et al.* 2014)

BSO = bilateral salpingo-oophorectomy, VAS = Visual Analog Scale, NRS = Numeric Rating Scale, OR = Odds Ratio

Table 3

Summary of Risks Associated with Endometriosis and Cancer from Registry Studies by Brinton et. al. (Brinton *et al.* 1997, Brinton *et al.* 2005)

Population	Risk	SIR* or RR	95% CI
History of endometriosis admission (HEA)	Any cancer	1.2*	1.1-1.3*
HEA	Ovarian Cancer	1.9*	1.3-2.8*
HEA & Prolonged endometriosis	Ovarian cancer	4.2*	2.0-7.7*
HEA	Endometrial cancer	1.1*	0.6-1.9*
HEA Long term F/U	Any cancer		
HEA Long term F/U	Ovarian Cancer	1.43*	1.19-1.71*
Long term F/U & Prolonged endometriosis	Ovarian Cancer	2.23*	1.36-3.44*
HEA Denmark cohort	Clear cell Ovarian Cancer	3.37	1.24-9.14
HEA Denmark cohort	Endometrioid Ovarian Cancer	2.53	1.19-5.38

HEA-History of endometriosis admission, SIR- Standardized incidence ratio, RR-Relative Risk, CI – Confidence interval, F/U- Follow up

Table 4
Ovarian Cancer Types Arising from Endometriosis Transformation

Population (# Patients EAOC/Total in Study)	Ovarian Cancer Type in EAOC	Age (Mean ± SD) years	Reference
Quebec, BC (41/2854)	Serous 19.51% Mucinous NR Clear-Cell 21.9% Endometrioid 24.4%	OC 53.9 ± 11.4 EAOC 48.3 ± 10.8	(Aris 2010)
Belegrade, Serbia (23/210)	Serous 3.5% Mucinous NR Clear-Cell 36.8% Endometrioid 31.6%	NR	(Dzatic-Smiljkovic *et al.* 2011)
Michigan, USA (42/184)	Serous 55% Mucinous 10% Clear-Cell 21% Endometrioid 14%	OC 59 EAOC 52	(Kumar *et al.* 2011)
Athens, Greece (17)	Serous 5.9% Mucinous NRClear-Cell 58.8% Endometrioid 35.3%	EAOC 58 (27-76)	(Kondi-Pafiti *et al.* 2012)
Ovarian Cancer Association Consortium (738/7911)	Serous 7.1% Mucinous 6.0% Clear-Cell 20.2% Endometrioid 13.9%	OC 56.1 EAOC 56.3	(Pearce *et al.* 2012)
Ankara, Turkey (45/1086)	Serous 13.3% Mucinous 8.9% Clear-Cell 37.8% Endometrioid 33.3%	EAOC 55 (35-77)	(Boyraz *et al.* 2013)
Massachusetts, USA (67/134)	Serous 0% Mucinous NR Clear-Cell 38.8% Endometrioid 61.2%	OC 56.6 EAOC 51.7	(Davis *et al.* 2014)
Milano, Italy (27/73)	Serous NR Mucinous NRClear-Cell 76.1%Endometrioid NR	OC 58.4 ± 11.2 EAOC 51.4 ±10	(Scarfone *et al.* 2014)
San Juan, Puerto Rico (20/192)	Serous 2.2% Mucinous 2.7% Clear-Cell 23% Endometrioid 50%	OC 56.1 ± 14.9 EAOC 48.8 ± 11.6	(Acien *et al.* 2015)
Shiraz, Iran (28/110)	Serous 14.5% Mucinous 0% Clear-Cell 14.5% Endometrioid 39%	OC 50.18 ± 12.8 EAOC 49.93 ±9.36	(Akbarzadeh-Jahromi *et al.* 2015)

OC=Ovarian Cancer, EAOC=Endometriosis Associated Ovarian Cancer, NR=not reported

EXHIBIT #2

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Cost-Effectiveness of Retinal Detachment Repair

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Abstract

Objective—To evaluate costs and treatment benefits of rhegmatogenous retinal detachment (RD) repair.

Design—A Markov model of cost-effectiveness and utility.

Participants—There were no participants.

Methods—Published clinical trials (index studies) of pneumatic retinopexy (PR), scleral buckling (SB), pars plana vitrectomy (PPV) and laser prophylaxis were used to quantitate surgical management and visual benefits. Markov analysis, with data from the Center of Medicare and Medicaid Services (CMS), was used to calculate adjusted costs of primary repair by each modality in a hospital-based and ambulatory surgery center (ASC) setting.

Main Outcome Measures—Lines of visual acuity (VA) saved, cost of therapy, adjusted cost of therapy, cost per line saved, cost per line-year saved, cost per quality-adjusted life years (QALY) saved.

Results—In the facility, hospital surgery setting, weighted cost for PR ranged from $3,726 to $5,901 depending on estimated success rate of primary repair. Weighted cost for SB was $6,770, for PPV was $7,940 and for laser prophylaxis was $1,955. The dollars per line saved ranged from $217 to $1,346 depending on the procedure. Dollars per line-year saved ranged from $11 to $67. Dollars per QALY saved ranged from $362 to $2,243.

In the non-facility, ASC surgery setting, weighted cost for PR ranged from $1,961 to $3,565 depending on the success rate of primary repair. The weighted costs for SB, PPV and laser prophylaxis were $4,873, $5,793 and $1,255, respectively. Dollars per line saved ranged from

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$139 to $982. The dollars per line-year saved ranged from $7–$49 and the dollars per QALY saved ranged from $232 to $1,637.

Conclusions—Treatment and prevention of RD is extremely cost-effective when compared to other treatment of other retinal diseases regardless of treatment modality. RD treatment costs did not vary widely, suggesting providers can tailor patient treatments solely on the basis of optimizing anticipated results since there were not overriding differences in financial impact.

Introduction

Rhegmatogenous retinal detachment (RD), the most common type of retinal detachment, has long been the defining target of surgical retinal efforts.[1] In 2009, the Medicare database reported a total of 21,762 RD repair procedures.[2] Untreated, retinal detachment usually leads to substantial, frequently severe, permanent vision loss, that might be accompanied by painful hypotony and phthisis. Many highly successful treatment options constitute the standard armamentarium including scleral buckling (SB), vitrectomy (PPV), and pneumatic retinopexy (PR). Many clinical trials and series comparing these methods of retinal detachment repair have shown comparable success rates, but have enumerated factors that are helpful in choosing the most suitable technique for certain subsets of patients.[3–19]

Few studies comparing cost-effectiveness of retinal reattachment surgery to other ophthalmologic or general medical treatments, or among techniques have been published.[14,19,20] Generally, cost considerations have not been a factor in clinical decision-making in choosing retinal reattachment treatments. Previous studies have outlined similar cost analyses for age-related macular degeneration (AMD),[20] diabetic macular edema (DME)[21] and retinal vein occlusion (RVO),[22] but treatment of RD has never been subjected to such an analysis of various treatment options.

The purpose of the current report is to calculate parameters of cost-effectiveness using a Markov decision-tree analysis for the main methods of RD repair: PR, SB and PPV.

Methods

Representative index studies were identified to ascertain representative anatomic success rates for each treatment modality of RD repair including PR,[8,14–19] SB,[4–8,10–13] PPV with or without SB[4–12] and laser prophylaxis of RD.[23] Based on these studies our models assumed 60%, 75%, or 90% success for PR, 85% success for SB, and 90% success for PPV with or without SB. Medicare fee data for 2013 were acquired from the Centers for Medicare and Medicaid Services (CMS) to ascertain the allowable cost (in United States dollars) associated with each procedure, study or office visit.[24–28] The costs were calculated for both facility (hospital-based with surgery performed in a hospital operating room) practice in the geographic area of Miami, FL, and also for a non-facility (i.e. office based clinical services with surgery performance in an ambulatory surgery center (ASC)) in the same geographic area to demonstrate the range of potential reimbursement. The purpose in this dichotomy was to calculate the range of maximum and minimum possible incident costs for the various procedures. The permutations of a practice utilizing facility-based clinic visits with ASC-based surgery, and non-facility-based clinic visits and hospital based surgery would fall in

between these limits. PR and laser prophylaxis costs were calculated as if done in an office, without the use of an operating room or anesthesiologist in both models. It should be noted, the differential of professional fees of facility versus non-facility costs is only relevant for clinical visits, not for surgical and treatment procedures.

The dollars per relative value unit (RVU) used (conversion factor) was $34.023 since that was the established rate for most of 2013.[25] The cost for a given provider service is an equation that considers work (w) RVUs (professional fees), practice expense (pe) RVUs, and malpractice (mp) RVUs, each of which are subject to geographic modifiers that adjust for costs and relative malpractice risk.[25]

A Markov analysis[29] was performed to generate a cost for each procedure based on the anatomic success rates of index studies, but also for three different hypothetical success rates for PR. Four hypothetical treatment groups were modeled and analyzed (Figure 1) for each of the two different practice setting permutations described above.

The first model was treatment with PR (in an office, without hospital or anesthesia fees); failures were treated by PPV with or without SB (costs are the same), and any subsequent re-operations treated with PPV. The second model was treatment with SB; failures were treated by PPV, and subsequent failures treated with PPV. The third model was treatment with primary PPV; failures were treated by PPV with or without SB, and subsequent failures were treated with PPV. For contrast, a final model was treatment of laser prophylaxis (also assumed to be done in an office without operating room or anesthesia fees) for a retinal break (assuming 95% success), with failures treated initially with SB, and subsequent failures treated with PPV to provide a sense of the cost of prophylactic therapy as well.

All phakic PPV patients were assumed to also require cataract surgery (phacoemulsification with intraocular lens implantation). The incidence of patients who were phakic was assumed to be 70% for all groups, a frequency of previous RD treatment cohort studies.[7,17]

The current procedural terminology (CPT) codes used for the procedures were as follows: 67110 for PR, 67107 for SB, 67108 for PPV, 67112 for PPV in cases of re-operation, and 67145 for laser demarcation of retinal breaks (Table 1). In addition to the costs of the RD repair procedure, the cost for associated cataract surgery (CE) (CPT code 66984), and one level 4 new patient visit (CPT code 99204) and three level 3 follow up visits (CPT code 99213) were added to the total cost to represent one year of continued treatment. In any instance, if the scenario called for PPV following a previous PPV (i.e. 67112), the −78 modifier was applied so that only 70% of the total reimbursement fee was applied for that procedure. If the PPV followed a SB, or if the SB followed PR or laser for a retinal break, the −58 modifier was used so the more complex procedure was calculated at 100% of the Medicare allowable. The reimbursement schedules for procedures are based on the CMS terminology for procedures done in hospital or in an ASC, but only CE, SB, and PPV were ever modeled to be performed in an operating suite setting. PR and laser prophylaxis of RD were modeled as performed in the clinic setting regardless of practice setting permutation. The setting of CE was considered to be the same as the setting of RD repair, thus the

calculations for facility-based RD repair includes CE under hospital-based billing, and the calculations for non-facility-based RD repair includes CE in an ASC.

Anesthesia professional fees (when applicable) were calculated based on the sum of base units and time units, multiplied by the conversion factor 25.52.[28] CPT code 00145, anesthesia for vitreoretinal surgery is weighed as 6 base units. One time unit is 15 minutes and an estimated one hour was applied for vitreoretinal cases. Thus, the anesthesia professional fee for vitreoretinal cases was calculated as $255. In cataract surgery, CPT code 00142 is weighed as 4 base units, and the cases were estimated to use 2 time units, for a total of $153 in anesthesia professional fees.

We assumed that an untreated retinal detachment results in 20/400, but that a successful repair preserves 20/25 for a macular sparing RD and 20/80 for a macula off RD. We also assumed that 70% of RDs are macular involving and 30% are macular sparing. We purposely chose the highest number reported for macular involving rates, and also chose what are probably better natural history assumptions, so that, if anything, our model for all procedures errs on the side of being less cost-effective. Patients undergoing reoperations were assumed to retain 20/400, thus representing a failure to yield any better vision compared to natural history. Based on this calculation, a retinal detachment repair was calculated to save 5.9 lines of vision, likely an underestimate. Furthermore, we assumed that the visual acuity (VA) results were the same regardless of the technique.[17] An average age of 62 years old was used based on previous literature.[7] Years of life expectancy were derived from actuarial tables of the Social Security Administration.[30] Quality-adjusted life year (QALY) data were adapted from previously published articles; a conversion of 0.03 QALYs per line-year of vision saved was applied.[31]

Calculations and analysis were performed using Microsoft Excel (Microsoft Corporation, Seattle, WA) software.

Results

The tabulated facility, professional fee, and anesthesia costs for each individual procedure are listed in Table 1. A summary of the adjusted results is presented in Table 2 for facility, hospital surgery and Table 3 for non-facility, ASC surgery.

Primary Retinal Detachment Repair with Pneumatic Retinopexy

The groups with primary PR treatment were evaluated at 60%, 75%, and 90% success rates for initial procedure. These rates were chosen because previously reported studies have a wide range of success. Studies have reported a range from 60–65% primary success,[3,8,16–18] 75% primary success,[15,19] and even higher rates, up to 90–95%.[14]

For a patient in a facility-based setting, when PR was assigned a 75% success rate, and subsequent surgery with PPV given a 90% success rate, the Markov analysis yielded a weighted cost of $3,691 (carrying it for the possibility of three procedures). Since 99% of patients would have successful RD repair after the three procedures, the model was never carried to a fourth intervention. If cataract surgery is factored in as described in the methods,

the cost for these procedures was $4,155. When one level 4 new patient visit and three level 3 follow-up office visits were added to the cost, the total was $4,814. The dollars per line saved was $816, and the dollars per line-year saved was $41. The dollars per QALY saved calculation, as described above, was $1,360.

If a more favorable success rate for PR of 90% is assigned in the facility setting, as described for certain subgroups in the literature,[14] then the weighted cost in the Markov analysis was $2,882 after three procedures, with a 99.9% reattachment rate. When cataract development was factored in, the cost was $3,068. With clinic visits factored into the calculation, the total was $3,726. The dollars per line of vision saved was $632, and the dollars per line-year saved was $32. The cost per QALY saved was calculated as $1,053. Similarly, if a 60% PR success rate is presumed, the model yields an imputed cost of $5,901, a cost/line of $1,000, a cost/line-year of $50, and a QALY cost of $1,667.

In a non-facility setting, if a 75% success for PR is assigned, then the Markov analysis with subsequent PPV for primary failures yielded a weighted cost of $2,011. When cataract surgery is factored into this cost, then the weighted cost was $2,343. Inclusion of a level 4 new patient visit and three level 3 follow-up visits generated a weighted cost of $2,763. The cost per line was $468. The dollars per line-year saved was $23 and the dollars per QALY saved was $780.

When a 60% or 90% success for PR was assigned in a non-facility setting, the weighted cost with subsequent PPV for primary failures was $2,615 / $1,408. Factoring in cataract surgery, the cost was $3,145 / $1,540. With included office visits, the cost was $3,565 / $1,961 and the cost per line was $604 / $322. The dollars per line-year was $30 / $17, and the dollars per QALY saved was $1,007 / $554.

Primary Retinal Detachment Repair with Scleral Buckling

The modeled cost of a patient in a facility setting initially undergoing SB surgery for RD in a hospital operating room with 80% primary success rate, and subsequent PPV for failures and another PPV for additional failures was $5,740 using the Markov analysis. The overall re-attachment rate was 99.8% after the three procedures. If the cataract rate as described in the methods was used, the cost was $6,112. Factoring in a level 4 new patient visit and three level 3 follow-up visits led to a cost of $6,770. The cost per line saved was $1,147 and the dollars per line-year saved was $57. When dollars per QALY saved were calculated, the total was $1,912.

This same evaluation in a non-facility setting, ASC surgery, with SB as the initial procedure and PPV for subsequent failures, yielded a weighted cost of $4,188 carrying out for three procedures. When cataract surgery is included in this weighted total, the cost was $4,453. The addition of clinic visits as described above generated a cost of $4,873. The cost per line was $826. Cost per line-year saved was $41 and the cost per QALY was $1,377.

Primary Retinal Detachment Repair with Vitrectomy

A primary PPV without scleral buckling was assumed in this model to have a 90% success rate. For facility cases performed in a hospital operating room, the Markov analysis

demonstrated a modeled cost of $5,425 in this setting, with a PPV with or without SB as the second and third procedures for failed RD repair. When cataract development was factored in, the cost was $7,282. Including one level 4 new patient visit and three level 3 follow-up visits, the cost was $7,940. Cost per line was calculated to be $1,346 and the dollars per line-year saved were $67. Dollars per QALY saved were $2,243.

Primary PPV in the non-facility setting, operated in an ASC operating room, with the same success rate as described above, demonstrated a weighted cost of $4,048. Inclusion of cataract surgery yielded a cost of $5,373, and inclusion of clinical visits yielded a cost of $5,793. The cost per line was $982, the cost per line-year was $49 and the cost per QALY was $1,637.

Laser Prophylaxis for Symptomatic Retinal Breaks

Laser prophylaxis for a retinal break was assumed to have a 95% success rate in preventing retinal detachment as detailed in prior studies.[23] For the patients that developed retinal detachment, scleral buckling was selected as the first procedure with an 80% success rate, and pars plana vitrectomy selected as a second procedure with a 90% success rate in this scenario. The modeled cost for facility patients after Markov analysis was $1,278. When cataract development for the vitrectomy patients was factored in, this cost was $1,296. Inclusion of one level 4 new patient and three level 3 follow-up visits led to a cost of $1,955. The number of lines saved in this scenario was considered to be 9 lines, as the group of patients with retinal breaks have better baseline vision than those with retinal detachment, and a higher rate of treatment success. Cost per line of vision was $217. The cost per line-year saved was $11 and the dollars per QALY saved was $362.

The same algorithm was applied for patients in a non-facility setting. The weighted cost was $822 for the laser and RD repair in failed laser cases. Inclusion of cataract surgery led to a cost of $835. The inclusion of one level 4 new patient and three level 3 follow-up visits totaled $1,255. The cost per line saved was $139, the cost per line-year saved was $7 and the cost per QALY was $232.

Discussion

The analysis presented demonstrates that when factoring in clinical visits and subsequent cataract surgery (which have not been included in other cost-consideration studies), the costs for repair of primary rhegmatogenous RD range from $2,763 to $7,940 depending on the treatment modality (PR, SBP, or PPV) practice and surgical setting. The PR cost could be even lower if a 90% success rate is modeled- a relatively high rate, but one that might be applicable in certain patient subsets.[14] Correspondingly, the dollars per QALY saved ranged from $554 to $2,243. Although these ranges are moderately broad, these costs are much lower than for other therapeutic interventions within ophthalmology and other fields of medicine, and well under what has been offered as the acceptable cost of a QALY ($50,000 to $100,000).[31] For contrast, the cost per QALY of treatment of *H. pylori* is roughly $1,830, and the cost per QALY in of treatment of systemic arterial hypertension with beta blockers is $7,389.[31] The cost / QALY of the treatment of hyperlipidemia is $77,800, much higher than that of RD treatment.[31] In comparison to other retinal treatments, a previous analysis

the QALY value of these interventions compared favorably to pan retinal photocoagulation (PRP) for diabetic retinopathy ($700), and prophylaxis of retinal breaks was even more cost-effective ($232–$362).[20] Recent analyses of costs associated with one year of pharmacologic therapy macular edema from RVO yielded a range of dollars per QALY saved from $824 for intravitreal bevacizumab to $25,566 for intravitreal ranibizumab.[20–22]

Several limitations are present in this report. A number of assumptions are made in the modeling the treatment of the patients including the average age, lens status, visual results, and fees for operating room anesthesia. The data presented are based on a Miami, Florida-based practice, and costs will vary depending on a given practice setting and type, or with different treatment algorithms. The conclusions were based on a "worst case scenario" regarding costs- highest setting, highest geographic area, and associated costs. Even with this intended bias, the cost-effectiveness was favorable. When the same costs were evaluated for lowest cost geographic areas, the cost parameters were reduced by 10% or less (Tables 4 and 5, available at http://aaojournal.org). While these figures do not apply directly in other countries where the reimbursement schedules are different and healthcare is distributed differently, the high level of cost-effectiveness of RD repair relative to other medical and ophthalmologic interventions is likely to be valid regardless of surgical approach or reimbursement region.

Our model further erred on the side of undervaluing RD repair by underestimating its VA value. Our assumptions that all re-operations were visual failures and led to no lines of saved vision and our assumption that the natural history or untreated or failed treatment was for 20/400 VA are almost certainly pessimistic and would lead to higher calculated cost values. Furthermore, we assumed a 70% macular involving rate, which is higher than the 50% range reported by some,[17,19] and would result in a better value of lines saved and, hence, higher calculated cost values. If we incorporated some of these more favorable assumptions, the lines of vision saved might reasonably be doubled. Hence, the costs per lines of vision saved and QALY values halved, further distinguishing retinal reattachment treatments as extremely cost-effective. Moreover, rhegmatogenous RD may progress to a bilateral condition in 25–40% of patients,[33] further amplifying the benefit of treatment and prevention.

While this study demonstrates PR to be less costly than surgery, not all cases can be equally managed, and in some hands the success rates are not as high as assumed. While others have reported lower costs for PR (albeit without including reoperations, clinical visit costs, or actualized cataract costs), this sort of comparison was not the primary purpose of the current study design.

This study demonstrates the unequivocally high level of cost-effectiveness of retinal detachment repair regardless of technique used. That the cost-effectiveness for the different methods of RD repair (PR, SB, PPV) are reasonably comparable frees the surgeon of significant financial constraint considerations, allowing them to tailor the repair method that they feel is most appropriate for a given patient's pathology and situation. The results of this study suggest that repair of RD may be undervalued when compared to pharmacologic treatments for other chronic retinal illnesses, and even for surgical treatment for other

subacute problems. Similar Markov analyses may facilitate evaluation of costs for other retinal diseases or pathologies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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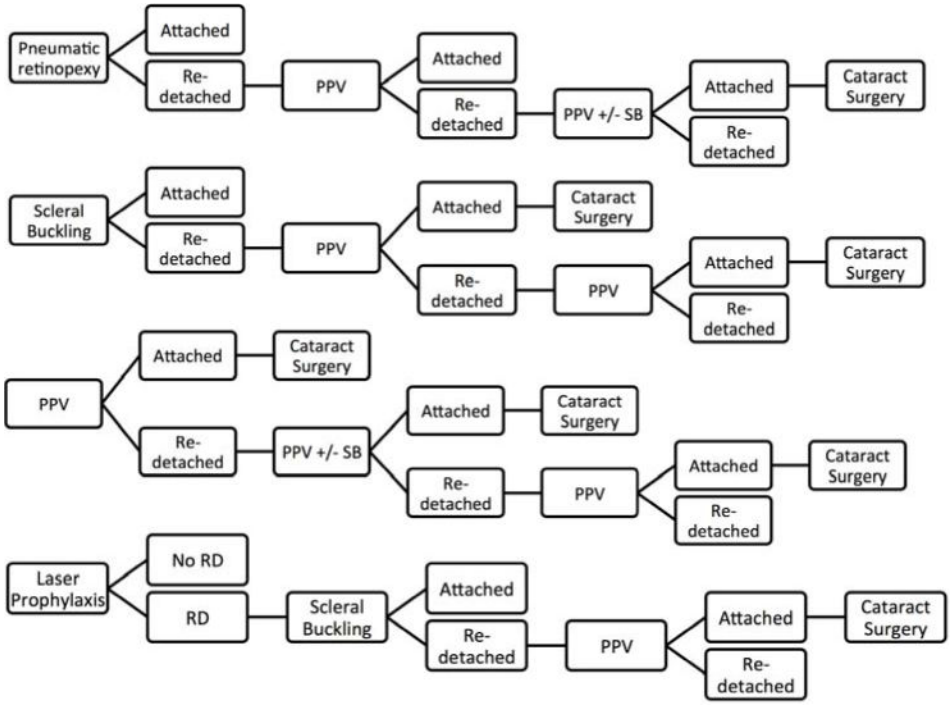

Figure 1. Decision Model Used in Markov Analysis

PPV = pars plana vitrectomy, SB = scleral buckling. RD = retinal detachment. Phakic patients (assumed to be 70% of total cohort) were expected to require cataract surgery after PPV

Table 1

Medicare Allowable Costs for Retinal Detachment Repair and Associated Treatments

	Facility, Hospital Operating Room Surgery					Non-Facility, ASC Surgery			
Procedure	**CPT Code**	**Professional**	**Non-technical**	**Anesthesia**	**Total**	**Professional**	**Nontechnical**	**Anesthesia**	**Total**
PR	67110	$901	$1,442	–	$2,343	$1,005	$0	–	$1,005
SB	67107	$1,493	$2,914	$255	$4,662	$1,493	$1,635	$255	$3,383
PPV	67108	$1,892	$2,914	$255	$5,061	$1,892	$1,635	$255	$3,782
PPV +/– SB	67112	$1,563	$2,914	$255	$4,732	$1,563	$1,635	$255	$3,453
Laser prophylaxis of RD	67145	$583	$411	–	$994	$615	$0	–	$615
Cataract surgery	66984	$769	$1,730	$153	$2,652	$769	$971	$153	$1,893
Level 4 new patient visit	99204	$145	$128	–	$273	$183	$0	–	$183
Level 3 follow up visit	99213	$55	$74	–	$128	$79	$0	–	$79

All amounts are in United States dollars. ASC = ambulatory surgery center, CPT = current procedural terminology, PR = pneumatic retinopexy, SB = scleral buckle, PPV = pars plana vitrectomy, RD = retinal detachment.

Table 2

Weighted Costs of Retinal Detachment Repair with Dollars per Line Saved, Dollars per Line-Year Saved and Dollars per QALY for Facility, Hospital Operating Room Surgery

Initial Procedure	Weighted Cost	Weighted Cost with CE/IOL	With Clinic Visits	Lines Saved	Dollars per Line Saved	Mean Life Expectancy (Years)	Dollars per Line-Year Saved	Dollars per QALY
PR 60%	$4,500	$5,243	$5,901	5.9	$1,000	20	$50	$1,667
PR 75%	$3,691	$4,155	$4,814	5.9	$816	20	$41	$1,360
PR 90%	$2,882	$3,068	$3,726	5.9	$632	20	$32	$1,053
SB	$5,740	$6,112	$6,770	5.9	$1,147	20	$57	$1,912
PPV	$5,425	$7,282	$7,940	5.9	$1,346	20	$67	$2,243
Laser prophylaxis	$1,278	$1,296	$1,955	9	$217	20	$11	$362

All amounts are in United States dollars. QALY = quality adjusted life years, CE/IOL = phacoemulsification of cataract with intraocular lens, PR = pneumatic retinopexy, 60% = primary procedure success rate of 60%, 75% = primary procedure success rate of 75%, 90% = primary procedure success rate of 90%, SB – scleral buckling, PPV = pars plana vitrectomy

Table 3

Weighted Costs of Retinal Detachment Repair with Dollars per Line Saved, Dollars per Line-Year Saved and Dollars per QALY for Non-facility, ASC Surgery

Initial Procedure	Weighted Cost	Weighted Cost with CE/IOL	With Clinic Visits	Lines Saved	Dollars per Line Saved	Mean Life Expectancy (Years)	Dollars per Line-Year Saved	Dollars per QALY
PR 60%	$2,615	$3,145	$3,565	5.9	$604	20	$30	$1,007
PR 75%	$2,011	$2,343	$2,763	5.9	$468	20	$23	$780
PR 90%	$1,408	$1,540	$1,961	5.9	$322	20	$17	$554
SB	$4,188	$4,453	$4,873	5.9	$826	20	$41	$1,377
PPV	$4,048	$5,373	$5,793	5.9	$982	20	$49	$1,637
Laser prophylaxis	$822	$835	$1,255	9	$139	20	$7	$232

All amounts are in United States dollars. ASC = ambulatory surgical center, QALY = quality adjusted life years, CE/IOL = phacoemulsification of cataract with intraocular lens, PR = pneumatic retinopexy, 60% = primary procedure success rate of 60%, 90% = primary procedure success rate of 90%, SB – scleral buckling, PPV = pars plana vitrectomy

COMBINED OR SEQUENTIAL SURGERY FOR MANAGEMENT OF RHEGMATOGENOUS RETINAL DETACHMENT WITH MACULAR HOLES

ANIL J. SINGH, FRCS, FRCOPHTH

Purpose: To describe the anatomical success and visual outcome in patients with rhegmatogenous retinal detachment and coexisting macular holes using two different management strategies.

Methods: Nonrandomized, prospective interventional case series where patients either had combined surgery, i.e., vitrectomy, internal limiting membrane peel, retinopexy to the peripheral breaks, and gas tamponade; or sequential, i.e., vitrectomy, retinopexy to the peripheral breaks, and gas tamponade with macular hole surgery if indicated, as a secondary procedure.

Results: Five patients (Group 1) had combined surgery and 7 (Group 2) had sequential treatment. All retinas were reattached irrespective of surgical approach. In Group 1, best-corrected visual acuity improved in all patients from 1.8/60 to 9.2/60 Snellen (P = 0.06). In Group 2, there was improvement in best-corrected visual acuity in all patients from 3.3/60 to 12.9/60 Snellen (P = 0.05). After comparison of the logarithm of the minimum angle of resolution, postoperative best-corrected visual acuity improvement was not significantly different between both groups (P = 0.68).

Conclusion: The results of this study suggest that good anatomic and visual outcome can be achieved using either approach. Visual acuity improved in all patients from both groups. In sequential surgery some of the macular holes may close spontaneously. However, combined surgery offers the clinical and cost benefit of a single procedure.

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The management of patients with macular hole retinal detachment has been previously described with several proposed treatment strategies. These studies have focused on patients with the characteristic ocular syndrome of high myopia with posterior staphyloma, chorioretinal atrophy, and no peripheral retinal breaks.[1–8]

This study describes a different cohort of patients in which a macular off rhegmatogenous retinal detachment with peripheral retinal breaks coexists with a macular hole. This has much less frequently been described in the literature.[9]

Surgery to repair rhegmatogenous retinal detachment now achieves high rates of anatomical success and for vitrectomy and gas procedures can be as much as 80% to 94%.[10–12] Macular hole surgery can also attain high rates of anatomical hole closure, with recent published results of 90% to 100%.[13–16]

We undertook this study to examine the rate of retinal reattachment, macular hole closure, and visual outcome in patients with rhegmatogenous retinal detachment and coexisting macular holes by two different management strategies.

Methods

All patients with rhegmatogenous retinal detachment presenting to 1 surgeon at the Birmingham and Midland Eye Centre from November 2006 to February 2008 were recorded on a computerized database. In the cohort of patients with macular off rhegmatogenous retinal detachment, 12 had coexisting macular holes in addition to peripheral retinal breaks. The macular hole was noted preoperatively in 10 patients

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and intraoperatively in 2. Data were studied prospectively. The following were collected: age, gender, preoperative best-corrected visual acuity (BCVA), duration of symptoms, refractive status, grade of retinal detachment, size of macular hole, location and number of peripheral breaks, presence of proliferative vitreoretinopathy, preoperative lens status, surgical management, rate of retinal reattachment and macular hole closure, final lens status, and postoperative BCVA.

There were no patients in this study with the characteristic ocular syndrome of high myopia with posterior staphyloma, chorioretinal atrophy, and macular hole retinal detachment. The study conformed to the tenets of the Declaration of Helsinki and informed consent was obtained from all patients.

Preoperative examination included slit-lamp biomicroscopy with a wide-angle fundus lens and binocular indirect ophthalmoscopy with peripheral scleral indentation. In all patients, peripheral retinal breaks were seen preoperatively.

In 10 patients, the macular hole was seen preoperatively. In the other two patients, the macular was obscured by retinal folds but became apparent intraoperatively during vitrectomy. No patients were known to have macular holes preoperatively.

Patients were not randomized, but informed consent was obtained after discussion of the risks and benefits of having combined surgery, i.e., vitrectomy, internal limiting membrane (ILM) peel, retinopexy to the peripheral breaks, and gas tamponade, versus sequential surgery, i.e., vitrectomy, retinopexy to the peripheral breaks, and gas tamponade with macular hole surgery, if indicated, as a secondary procedure.

In the 10 patients in whom the macular hole was seen preoperatively, 5 agreed to have combined surgery and the remaining 5 chose sequential surgery. In the patients in whom the macular hole was not seen preoperatively, no macular hole surgery was performed during the primary retinal detachment repair.

Surgery was performed using a standard 3-port pars plana 20-gauge vitrectomy technique with a wide-angle noncontact viewing system.

In the combined surgery group, after vitrectomy, peripheral breaks were identified and marked with endodiathermy. Trypan blue 0.16% (Membrane Blue; DORC International, Rotterdam, The Netherlands) was then used for 3 minutes under air to stain the posterior retina. The ILM was peeled with fine intraocular forceps under perfluorocarbon liquid. The ILM peel was complete in all cases. On average the area of ILM peel was approximately 1.5 disk diameters in size, centered on the fovea. Fluid–air exchange was performed via a peripheral break, and cryopexy under air was used to treat all peripheral breaks as per standard practice in our institution. Gas tamponade with either 20% SF_6 or 12% C_3F_8 was used at the discretion of the surgeon, and all patients were postured face down for 1 week. No patients had silicone oil tamponade.

In the sequential surgery group, after vitrectomy, peripheral breaks were marked with endodiathermy. After fluid–air exchange, the breaks were treated with cryopexy as is our standard practice. This was followed by gas tamponade with either 20% SF_6 or 12% C_3F_8. Posture was determined by the position of the retinal breaks. In all patients, there was 80% to 90% gas fill on the first postoperative day.

If the retina remained flat after the initial surgery, the status of the macular hole was determined. Where the macular hole was open, patients were offered macular hole surgery consisting of ILM peel and gas tamponade. The ILM was stained with 0.16% trypan blue under air and peeled under balanced salt solution infusion with micro forceps. For phakic patients, phacoemulsification and posterior chamber lens implantation were performed at the time of ILM peeling if there was significant lens opacity obscuring a clear view of the macular.

In all patients, the post-ILM peel macula status was determined by ophthalmoscopy and optical coherence tomography examination. Minimum follow-up was 4 months in all patients.

Statistical Analysis

Visual acuity was measured using Snellen charts and converted to equivalent notation for statistical analysis. Calculations were based on the Minitab statistical software program. Average data are expressed as a mean with the standard deviation (SD). The Wilcoxon signed-rank test for nonparametric data was used to analyze change between preoperative and postoperative BCVA. For data with continuous variables, the Mann–Whitney U test was used. $P < 0.05$ was considered significant.

Results

There were 12 patients who fulfilled the study criteria. Four were women. Average age was 69 years. The refractive errors were as follows: 1 patient was a low hyperope, 5 were emmetropes, and the remaining 6 all had less than 4 D of myopia. No patient had high myopia of greater than 6 D.

Five patients had combined surgery (Group 1) and 7 had sequential surgery (Group 2). All retinas were reattached at 3 months postsurgery in both groups.

Table 1. Group 1, Combined Surgery

Age (years)	Gender	Preoperative Lens Status	Preoperative VA	Final Retinal Status	Final Lens Status	Postoperative Macular Hole Status	Postoperative VA	Follow-Up Period (months)
87	F	Pseudophakic	1/60	Flat	Pseudophakic	Closed	6/36	4
81	M	Pseudophakic	1/60	Flat	Pseudophakic	Closed	6/36	4
61	M	Phakic	3/60	Flat	Phakic	Closed	6/36	6
72	F	Phakic	2/60	Flat	Pseudophakic	Closed	6/60	6
74	M	Pseudophakic	2/60	Flat	Pseudophakic	Closed	6/36	4

VA, visual acuity; F, female; M, male.

In Group 1, there were 2 women, and the average age was 75 years. Mean BCVA improved in all 5 patients from 1.8/60 (SD, 0.9/60; range, 1/60–3/60) to 9.2/60 (SD, 1.8/60; range, 6/60–6/36). This difference did not reach statistical significance ($P = 0.06$; Table 1).

In Group 2, there were 2 women, and the average age was 65 years. Mean BCVA improved in all 7 patients from 3.3/60 (SD, 3/60; range, 2/60–6/36) to 12.9/60 (SD, 10.2/60; range, 3/60–6/12). This difference was also not statistically significant ($P = 0.05$). In this group, spontaneous closure of the macular hole occurred in 2 patients (Table 2).

Statistical comparison of logarithm of the minimum angle of resolution postoperative BCVA improvement in both groups was done using the Mann–Whitney U test. There was no significant difference between both groups of patients ($P = 0.68$). There were no significant postoperative complications during the follow-up period.

Discussion

Patients with rhegmatogenous retinal detachment from peripheral breaks and coexisting macular holes essentially present two management problems. The first is successful anatomical retinal reattachment, but success should also be judged in the context of improved visual function after treatment.

The second is management of the macular hole. Successful anatomical retinal reattachment can occur in the presence of an open macular hole.[4,9,17] However, in such a case, the resulting visual acuity would be very limited, and any treatment should have the ultimate aim of improving visual function.

Modern surgical techniques can achieve rates of macular hole closure of more than 90%. In the presence of a detached retina, macular hole surgery is technically demanding and potentially time consuming. It is feasible though, using dye to stain the ILM and then peel ILM under perfluorocarbon liquid. One should, however, note that the ILM behaves differently under perfluorocarbon liquid and appears to have greater elastic recoil compared with peeling under balanced salt solution. Peeling the ILM under perfluorocarbon liquid also eliminates the need for bimanual counter pressure and facilitated atraumatic and complete peeling in all cases in this study.[3,18,19] In this technique, there are risks of serious complications including macular trauma, creation of paramacular breaks, and photic toxicity, all of which have implications on long-term macular function should they occur.

Table 2. Group 2, Sequential Surgery

Age (years)	Gender	Preoperative Lens Status	Preoperative VA	Final Retinal Status	Final Lens Status	Postoperative Macular Hole Status	Postoperative VA	Follow-Up Period (months)
59	M	Phakic	2/60	Flat	Phakic	Open, patient declined further surgery	3/60	4
64	M	Pseudophakic	2/60	Flat	Pseudophakic	Closed	3/60	4
76	M	Phakic	3/60	Flat	Pseudophakic	Closed, spontaneous closure	6/12	6
63	M	Phakic	2/60	Flat	Phakic	Closed	6/18	4
57	M	Pseudophakic	2/60	Flat	Pseudophakic	Closed, spontaneous closure	6/24	6
58	F	Pseudophakic	2/60	Flat	Pseudophakic	Closed	4/60	4
62	F	Phakic	6/36	Flat	Pseudophakic	Closed	6/24	8

VA, visual acuity; F, female; M, male.

The advantages of combined surgery are that both the retinal detachment and macular hole are treated in the same operation, avoiding two admissions to the operating room. From this perspective of reducing surgical burden on the patient, combined surgery would be superior. Any improvement in vision is also noticed sooner because both the retinal detachment and macular hole are treated at the same time.

Sequential treatment is less likely to cause macular trauma because the ILM peeling takes place in reattached as opposed to detached retina. It, however, means that one has to wait for the retina to successfully reattach before attempting the ILM peel. In this series, we waited for complete absorption of all intraocular gas before subsequent surgery to be certain that the retina was reattached without any intraocular tamponade. Whether this delay has any deleterious effect on visual function is difficult to determine because of the small sample size and nonrandomization in this study. From previous macular hole studies, it would seem reasonable that unless the hole is left untreated for more than 6 months, visual improvement after surgery may not be compromised.[13–16] However, during the time between the initial surgery and any subsequent procedure to close the macular hole, the holes can increase in size. This could possibly lead to a less favorable visual outcome in using a sequential approach. We did not observe enlargement of the macular holes before ILM peeling was performed in this study but our sample size is small (n = 4).

An advantage of sequential surgery is that in a proportion of patients the macular hole can undergo spontaneous closure avoiding further surgery. In this series, this occurred in 2 of 7 patients (29%). This is similar to the closure rate of 31% (5 of 16 patients) in a previous study where ILM peeling was not performed as part of the primary retinal detachment repair.[9] In these 2 patients, BCVA improved from preoperatively 3/60 and 2/60 to postoperatively 6/12 and 6/24, respectively. It was interesting to note that in the patients where the hole closed spontaneously, the clinical impression was that the hole appeared smaller than those that remained opened, but the dimensions of a macular hole can be difficult to judge in detached retina.

All retinas were reattached irrespective of surgical approach. Best-corrected visual acuity improved in all patients from both groups. Group 1 patients had final mean postoperative BCVA of 9.2/60. The mean postoperative BCVA was somewhat better in Group 2, 12.9/60. These patients were younger (Group 1, 75 years; Group 2, 65 years) and had better baseline preoperative BCVA than Group 1 patients (Group 1, 1.8/60; Group 2, 3.3/60), and these may have been contributory factors. This difference was not, however, statistically significant. A larger sample size may have revealed a difference, but the incidence of rhegmatogenous retinal detachment with coexisting macular holes is low, and it would be difficult to have any large-scale studies to determine the best course of treatment. In this study, good anatomic and visual outcome was achieved with both combined and sequential surgery. However, with such small numbers in the study, the potential for variability is high. Consequently, no firm conclusions could be drawn from the statistical analyses. The limitations of this study are the small sample size, nonrandomization, and lack of age-matched controls. However, given the rarity of this form of retinal detachment it would be difficult to identify suitable controls.

Summary

In sequential surgery some macular holes may close from vitrectomy and gas tamponade alone without the need for ILM peeling in a subsequent operation. This has to be weighed against the delay in performing macular hole surgery where the hole remains open after the primary repair of the retinal detachment with subsequent less favorable visual outcome.

Combined surgery offers the clinical and cost benefit of a single procedure with less surgical burden on the patient in minimizing admissions to the operating room by having only one surgical procedure. It also allows more rapid visual rehabilitation and reduces the duration of time when the patient remains visually disadvantaged.

Key words: macular hole, rhegmatogenous retinal detachment, visual outcome.

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Retinal Surgery in Ambulatory Surgery Centers versus Hospital Outpatient Departments

After the January 2008 landmark regulations passed by the Centers for Medicare and Medicaid Services (CMS) approving ambulatory surgery center (ASC) reimbursement for essentially all ophthalmic surgical procedures, there has been a substantial movement of surgery cases from hospital outpatient department (HOPDs) to ASCs.[1] In 2015, an American Society of Retina Specialists survey showed that approximately 50% of retina specialists perform most surgical procedures in an ASC.[2] The benefits ascribed to using ASCs compared with HOPDs include a smaller environment dedicated to eye surgery and a highly trained staff that facilitates the surgeon's efficiency.[3] Criticisms of ASCs are that they cannot take on more complicated cases, such as those involving intraocular gases, silicone oils, or perfluoron; diabetic traction retinal detachments; or emergencies. There is also concern for patient safety. Reports of case selection complexity and patient safety in ASCs versus HOPDs are limited.

We performed a retrospective analysis of these issues in our large, single-specialty retinal referral practice, which performs >1500 vitrectomies a year in a major metropolitan center with a geographically and socioeconomically diverse population. The Sterling Institutional Review Board ruled that approval was not required for this study. We reviewed all of our surgeries done over a 5-year period (July 1, 2010, to June 30, 2015). Cases were routinely scheduled at the ASC, unless directed to the HOPD by the surgeon, medical preoperative review, anesthesiologist review, or insurance contracting. Access to equipment, materials, and anesthesia (general vs. local) were identical at both the ASCs and HOPDs. We categorized the cases by Current Procedural Terminology (CPT) codes and used the 10 most common CPT codes for analysis: pars plana vitrectomy (PPV) and internal limiting membrane peel (67042), PPV for retinal detachment repair (67108), PPV for complex retinal detachment (67113), PPV (67036), PPV and panretinal photocoagulation (67040), PPV and membrane peel (67041), scleral buckle for retinal detachment repair (67107), PPV and removal of intraocular lens posterior segment (67121), PPV and focal endolaser (67039), and PPV with aqueous shunt to extraocular equatorial plate reservoir (66180).

We reviewed incident reports, broadly defined as any happening not consistent with the routine operation of the ASC or HOPD as defined in the institutions' procedure manuals. This includes hospital admissions or emergency department visits within 24 hours of surgery. Cases were classified into 2 categories, elective and emergent. Emergent cases were identified as those with retinal detachment CPT codes (67107, 67108, 67113). The elective cases were those assigned the remaining CPT codes. We also reviewed the reasons that cases were scheduled at the HOPD over the ASC for the most recent 18 months (January 1, 2014, to June 30, 2015), the only period of time for which these specific data were available to us.

Categorical data for case distributions were summarized by counts and percentages. Relative frequencies of procedures were compared using the chi-square test of contingency table data or Fisher's exact test. Rates of medical incidents were calculated along with 95% confidence intervals (CIs) using the modified Wald method. Proportions of incidents were compared using Fisher's exact test for all procedures combined, as well for subgroupings, elective and emergent.

Over 5 years, there were 5737 ASC cases and 213 HOPD cases. For the 10 most common retinal surgery CPT codes, ASC cases numbered 5683; HOPD, 190. There was a significant difference ($P < 0.001$) in the relative frequencies of procedures at ASCs versus HOPDs for all 10 of the most common retinal surgery CPT codes (Table 1).

The rate of incident reports was 7 in 5737 procedures (0.12%) (95% CI, 0.05%–0.26%) at ASCs and 0 in 213 procedures (0%) (95% CI, 0.00%–2.13%) at HOPDs. Of the 7 ASC incidents, 4 patients were transferred to emergency departments (3 for cardiac concerns, 1 for neurologic changes) and sent home from the emergency departments. The remaining 3 patient incidents did not require transfer and included 1 retrobulbar block of wrong eye, 1 unresponsive patient after retrobulbar block, and 1 macular trauma due to startle reflex during membrane peeling. There were no long-term medical or ocular sequelae for any patient. For all procedures aggregated, as well as for each subgrouping, elective and emergent, the 95% CIs of ASCs and hospitals overlapped. Examining these data with Fisher's exact test, there were no differences in incident reports, either for all procedures combined ($P = 0.21$) or for the subgroupings ($P > 0.99$ for each subgroup).

There were 43 surgeries performed at the HOPDs in the 18 months for which scheduling data were available. The reasons for scheduling at an HOPD were as follows: 30 scheduling conflicts, 6 insurance requirements, 5 pediatric cases, and 2 medical indications (severe developmental disability and pregnancy).

In this study, there was significantly more utilization of the ASCs over the HOPDs for the 10 most common categories of retinal surgery cases that were studied, with no apparent difference in the rate of medical incidents. It seems that surgery at ASCs is similar in safety compared with HOPDs. It is also performed at a lower cost. Medicare currently pays 78% more to HOPDs than to ASCs for the same procedures.[4] Applying that ratio to this study, CMS saved >$7 million dollars as a result of the surgeries being done in ASCs. Furthermore, the Office of the Inspector General determined that CMS could have saved approximately $15 billion if the HOPDs were paid at ASC rates for 2012 through 2015.[5]

This study is limited by its retrospective nature and data collection from a single retinal surgery practice with specific geographic characteristics. Also, the study did not report any eye-specific outcomes between surgeries in ASCs versus HOPDs, such as ocular complications, reoperation rates, or visual outcomes, because these measures were beyond the scope of the review. In addition, the rarity of medical incidents associated with retinal surgery makes statistical analysis of safety very difficult. However, our study suggests that shifting virtually all

Table 1. Relative Frequencies of Procedures (Ambulatory Surgery Center vs. Hospital Outpatient Department) for the 10 Most Common Retinal Surgery Current Procedural Terminology Codes

Procedure (CPT Code)	Total (no.)	Surgeries in an ASC		Surgeries in an HOPD	
		No.	%	No.	%
PPV + internal limiting membrane peel (67042)	1918	1907	99.43	11	0.57
PPV + retinal detachment repair (67108)	1346	1266	94.06	80	5.94
PPV, complex retinal detachment (67113)	920	876	95.22	44	4.78
PPV (67036)	778	757	97.30	21	2.70
PPV + panretinal photocoagulation (67040)	519	510	98.27	9	1.73
PPV + membrane peel (67041)	157	153	97.45	4	2.55
Scleral buckle, retinal detachment repair (67107)	100	86	86.00	14	14.00
Removal intraocular lens posterior segment (67121)	68	62	91.18	6	8.82
PPV + focal endolaser (67039)	35	34	97.14	1	2.86
Aqueous shunt to extraocular equatorial plate reservoir (66180)	32	32	100	0	0
Total	5873	5683	96.76	190	3.24

ASC = ambulatory surgery center; CPT = Current Procedural Terminology; HOPD = hospital outpatient department; PPV = pars plana vitrectomy. All $P < 0.001$.

retinal surgeries to ASCs seems to be possible and is more cost effective, although rare systemic medical conditions may require HOPD settings.

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Abbreviations and Acronyms:
ASC = ambulatory surgery center; **CI** = confidence interval; **CMS** = Centers for Medicare and Medicaid Services; **CPT** = Current Procedural Terminology; **HOPD** = hospital outpatient department; **PPV** = pars plana vitrectomy.

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Endoscleral Patch Graft: A Novel Closure for Complex Pars Plana Scleral Defects

External scleral patch grafts have been used in the management of scleral necrosis for conditions such as scleritis or after glaucoma or pterygium surgery.[1–4] We present a novel technique for repairing a large defect in necrotic sclera with a scleral patch graft secured internally rather than externally.

A 27-year-old man was referred to Mayo Clinic after experiencing thermal burns to both eyes approximately 2 months before. On presentation, he had complete necrosis of all 4 eyelids and large bilateral corneal perforations that were treated with corneoscleral grafts. At the time of surgery, extensive necrosis and softening of the corneal and anterior scleral tissue of the left eye were noted. A portion of the intraocular contents had been expulsed, and a retinal detachment was present. A 14-mm corneoscleral graft procedure was performed on the left eye, with plans to address the retinal detachment at a later time. One week later, the patient underwent a retina reattachment procedure via a 3-port 23-gauge pars plana vitrectomy using valved cannulas and visualized through a temporary keratoprosthesis. When the superotemporal cannula was removed, the underlying sclerotomy

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CLINICAL STUDY

Patient-reported benefit from oculoplastic surgery

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Abstract

Purpose **It is vital that surgeons undertaking oculoplastic procedures are able to show that the surgery they perform is of benefit to their patients. Not only is this fundamental to patient-centred medicine but it is also important in demonstrating cost effectiveness. There are several ways in which benefit can be measured, including clinical scales, functional ability scales, and global quality-of-life scales. The Glasgow benefit inventory (GBI) is an example of a patient-reported, questionnaire-based, post-interventional quality-of-life scale that can be used to compare a range of different treatments for a variety of conditions.**

Methods **A cross-sectional study was undertaken using the GBI to score patient benefit from four commonly performed oculoplastic procedures. It was completed for 66 entropion repairs, 50 ptosis repairs, 41 ectropion repairs, and 41 external dacryocystorhinostomies (DCR). The GBI generates a scale from −100 (maximal detriment) through zero (no change) to +100 (maximal benefit).**

Results **The total GBI scores of patients undergoing surgery for entropion, ptosis, ectropion, and external DCR were: +25.25 (95% CI 20.00–30.50, $P<0.001$), +24.89 (95% CI 20.04–29.73, $P<0.001$), +17.68 (95% CI 9.46–25.91, $P<0.001$), and +32.25 (95% CI 21.47–43.03, $P<0.001$), respectively, demonstrating a statistically significant benefit from all procedures.**

Conclusion **Patients derived significant quality-of-life benefits from the four most commonly performed oculoplastic procedures.**

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Keywords: Glasgow benefit inventory; entropion; ectropion; ptosis; dacryocystorhinostomy

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Introduction

Health service providers around the world are increasingly called upon to justify the allocation of finite resources to an ever expanding number of health technologies (medicines, procedures, and health-promotion interventions). This leads to rigorous examination of cost effectiveness, a role undertaken for the National Health Service (NHS) in England and Wales by the National Institute for Health and Clinical Excellence (NICE). The unit of effectiveness used by NICE is the 'quality-adjusted life year' (QALY) (http://www.nice.org.uk/media/68D/29/The_guidelines_manual_2009_-_Chapter_7_Assessing_cost _effectiveness.pdf). QALYs are an overall measure of health outcome that weigh the life expectancy of a patient against an estimate of their health-related quality-of-life (HRQL). Typically NICE considers a health technology costing below £20 000 per QALY to be 'cost-effective'. To date, the only oculoplastic procedure to have been the subject of a NICE appraisal is endoscopic dacryocystorhinostomy (DCR), which was approved (http://www.nice.org.uk/nicemedia/live/11027/30616/30616.pdf).

The majority of health-care provision by the NHS in England is, at present, the responsibility of regional commissioning bodies known as primary care trusts (PCTs) who purchase primary and secondary care on behalf of their patients. Collectively, PCTs spend around 80% of the NHS budget. In commissioning services PCTs typically follow the advice published by NICE, but outside these guidelines are free to make local judgements about funding priorities. As with NICE, these are cost-effectiveness decisions, and in the field of oculoplastic surgery it is increasingly common for PCTs to set rigid clinical criteria before agreeing to fund treatment. Examples include a demonstrable visual field defect with ptosis or dermatochalasis, or chronicity and discomfort with meibomian cysts. Many PCTs are implementing lists of 'low priority

procedures' that they will not fund, and which increasingly include oculoplastic procedures.

The use of rigid criteria in the allocation of health resources is controversial. While it reflects a desire to place simple, consistent conditions on funding decisions, it can be at odds with the ethos of patient-centred medicine. As clinicians it is vital that we can demonstrate a genuine benefit to our patients, both ethically and financially, yet patient benefit can be difficult to measure. The clinician's perception of success may differ from that of the patient, and patients themselves can vary from one to another given apparently similar functional outcomes from surgery.[1] The height of the lid after ptosis surgery, for example, may be a surgeon's measure of success, but previous studies have shown a surprising mismatch between objective clinical assessment and subjective benefit.[2] Furthermore, it is the patients who report the greatest subjective preoperative functional impairment who derive the greatest quality-of-life improvements from surgery, rather than those with the greatest clinical impairment.[3]

Measuring patient benefit from medical interventions has been the subject of extensive research. The various scoring systems that have been developed tend to fall into one or more of three broad categories: clinical scales, activities of daily living/functional ability scales, and global quality-of-life scales. Clinical scales typically rely on objective, physical outcome measures, whereas the functional and quality-of-life scales typically rely on subjective patient-reported responses obtained using questionnaires. Over 800 examples of such questionnaire-based tools can now be found on the Mapi Institute 'Quality of Life Instruments Database' (http://www.mapi-institute.com). In devising this study, we examined the strengths and weaknesses of some of the most widely used quality-of-life questionnaires, including the Sickness Impact Factor[4], the Nottingham Health Profile[5], the Euroqol[6], the Medical Outcomes Short-Form 36 (SF-36)[7], and the Glasgow Benefit Inventory (GBI)[8].

Of these, we concluded that the GBI was the most suitable for our study. The GBI was initially developed for otorhinolaryngological interventions, and the original paper was used to compare patient benefit from cochlear implant, middle ear surgery (for hearing and for infection), rhinoplasty, and tonsillectomy. However, a major strength of the GBI is its ability to compare a range of different treatments for a variety of conditions, and across diverse demographic and cultural groups. It also benefits from being post-interventional quick and easy to administer by telephone or post, focused on change (rather than taking preoperative and postoperative measures and subtracting one from the other), and its use has been validated for oculoplastic procedures (DCR[9–13] and botulinum toxin for blepharospasm[14]).

In this study, we have used the GBI to assess patient benefit from four commonly performed oculoplastic operations: ptosis repair, entropion repair, ectropion repair, and DCR. Although not normally life- or vision-threatening, the symptoms associated with ptosis, entropion, ectropion, and nasolacrimal obstruction are often distressing to patients with a major adverse impact to HRQL. The visual disability associated with epiphora, for example, is often underestimated. One study comparing 14 measures of vision-dependent activities of daily living (VF-14) in patients with epiphora and those awaiting second eye cataract surgery found that those with epiphora performed worse in 12 out of 14 tasks.[15] The study recorded moderate to major difficulty in reading in 48% of patients with epiphora compared with 26% in those patients with cataract.

To date, the oculoplastic procedure most widely investigated for its quality-of-life benefits is DCR. Four studies have been published in peer-reviewed journals reporting GBI outcomes for DCR. Although these all take slightly different approaches, the results for external DCR range from $+18.5$ [9] to $+23.2$,[10] and for endonasal DCR from $+16.8$ [10] to $+52.0$.[11] Elsewhere in the literature, satisfaction with botulinum toxin is reported as $+29.2$ for blepharospasm,[14] and $+38.0$ for spasmodic dysphonia,[16] and with otorhinolaryngological surgery at $+20.0$ for rhinoplasty,[17] $+11.3$ for septoplasty,[18] and $+23.0$ for functional endoscopic sinus surgery.[19]

Materials and methods

The GBI consists of 18 questions with responses scored on a five-point Likert scale, from a large deterioration through to a large improvement in health status. The questions assess the patient's general perception of well-being, with psychological, social, and physical subscales. Post hoc analysis converts the results of the questionnaire to a score from -100 (maximal detriment) through zero (no change) to $+100$ (maximal benefit). A full list of the GBI questions is provided in Figure 1.

The questionnaire was completed during a telephone interview conducted by a member of the study team, a process that typically took 5–10 min. Subjects were identified from the theatre log at Maidstone hospital, using consecutive patients under the care of a single consultant oculoplastic surgeon (CAJ) who underwent surgery between April 2008 and April 2010. Verbal consent was obtained before proceeding with the questionnaire, and the study was conducted in accordance with the ethical standards of the Declaration of Helsinki. The study was approved by the Ethics Committee of Maidstone Hospital NHS Trust.

For each question patients are asked to score the answer on a 5 point Likert scale:

1 Much worse
2 A little or somewhat worse
3 No change
4 A little or somewhat better
5 Much better

Question	Total Score	General Subscale	Social Subscale	Physical Subscale
1. Have the results of your operation affected the things you can do?	*	*		
2. Have the results of your operation made your overall life better or worse?	*	*		
3. Since your operation have you felt more or less optimistic about the future?	*	*		
4. Since your operation do you have more or less self-confidence?	*	*		
5. Since your operation do you feel better or worse about yourself?	*	*		
6. Since your operation have you found it easier or harder to deal with company?	*	*		
7. Since your operation do you feel more or less confident about job opportunities?	*	*		
8. Since your operation do you feel more or less embarrassed when with a group of people?	*	*		
9. Since your operation do you feel more or less self-conscious?	*	*		
10. Since your operation are you more or less inconvenienced by your (specific) problem?	*	*		
11. Since your operation have you been able to participate in more or fewer social situations?	*	*		
12. Since your operation have you been more or less inclined to withdraw from social situations?	*	*		
13. Since your operation do you feel you have more or less support from your friends?	*		*	
14. Since your operation do you feel you have more or less support from your family?	*		*	
15. Since your operation are there more or fewer people who really care about you?	*		*	
16. Since your operation have you been to your doctor, or any reason, more or less often?	*			*
17. Since your operation have you had to take more or less medicine, for any reason?	*			*
18. Since your operation have you been more or less inconvenienced by your other health problems?	*			*

Figure 1 GBI Likert scale and questions.

Suitable patients were selected for four commonly performed oculoplastic procedures: entropion repair, ptosis repair, ectropion repair, and external DCR. The number of appropriate subjects was 79, 63, 50, and 50, respectively, of which the GBI questionnaire was successfully completed for 66, 50, 41, and 41, respectively (representing a completion rate of 85, 79, 82, and 82%). The mean age (with ranges) of patients undergoing surgery was 78.4 (53–94), 64.0 (20–89), 75.6 (56–100), and 67.4 (20–90) years old, respectively, and the proportion of men was 62, 52, 63, and 27%. The majority of cases where the questionnaire was not completed related to incorrect contact details and an inability to reach the patient by telephone.

Results

The total GBI scores of patients undergoing surgery for entropion, ptosis, ectropion, and external DCR were +25.25 (95% CI 20.00–30.50, $P<0.001$), +24.89 (95% CI 20.04–29.73, $P<0.001$), +17.68 (95% CI 9.46–25.91, $P<0.001$), and +32.25 (95% CI 21.47–43.03, $P<0.001$), respectively, demonstrating a statistically significant benefit from all procedures (Table 1). Confidence intervals were calculated using a Student's *t*-distribution, Instat 3 biostatistics (GraphPad, La Jolla, CA, USA).

Subscale analysis groups responses to certain questions to give further information about the nature of the benefit the patient derived. These subscales are general impact (psychological benefit to self), physical impact (overall physical health), and social impact (support from others). The mean scores for entropion, ptosis, ectropion, and external DCR using the general subscale were +31.12, +38.58, +21.85, and +37.80, respectively, using the physical subscale were +17.43, −7.67, +4.47 and +15.85, respectively, and using the social subscale were +9.09, +2.47, +14.23 and +26.42, respectively (Table 2).

Table 1 Total GBI scores

	Entropion	*Ptosis*	*Ectopion*	*External DCR*
Sample size	66	50	41	41
Mean score	25.25	24.89	17.68	32.25
Median score	30.56	25.00	5.56	38.89
Standard deviation	21.35	17.05	26.06	34.16
Minimum score	−25.00	−22.22	−16.67	−55.56
Maximum score	72.22	66.67	100.00	100.00
Lower 95% CI	20.00	20.04	9.46	21.47
Upper 95% CI	30.50	29.73	25.91	43.03

Table 2 GBI subscale scores

	Entropion	*Ptosis*	*Ectopion*	*External DCR*
General impact	31.12	38.58	21.85	37.80
Physical impact	17.43	−7.67	4.47	15.85
Social impact	9.09	2.47	14.23	26.42

Discussion

Patients report levels of satisfaction with these four common oculoplastic procedures that compare favourably with other treatments that have been studied using the GBI. Our results show slightly higher levels of patient benefit from external DCR compared with

previous reports in the literature (+32.25 compared with +18.5[9] and +23.2[10]).

Within the overall GBI score, the scores achieved on the general, physical, and social subscales demonstrate some important differences between the four procedures. While the general score, reflecting overall psychological benefit, is reasonably consistent, the social and physical scores are more variable.

The social subscale records support received from family and friends, and suggests a large benefit from external DCR, more modest improvements from correction of ectropion and entropion, and relatively little benefit from ptosis repair. This may reflect the fact that chronically watering eyes are more socially stigmatising than eyelid malposition, with some patients reporting that they were thought of as being emotionally labile as they were seen to be 'crying all the time'. Similarly, patients suffering with the red, crusty lids and recurrent conjunctivitis of ectropion and entropion felt they were perceived as having poor personal hygiene. Improved watering and healthy-looking eyes may in turn have improved a patients' perception of their interaction with family and friends by making them feel less self-conscious. The social subscale of the GBI specifically reflects the patients' perception of how others respond to them, whereas the general subscale reflects the way that the patients themselves interact with others. Overall, the quality of social interaction will be a combination of these factors, and on this measure ptosis patients reported much more positive results, feeling both less self-conscious about how others saw them, and more self-confident about themselves.

One of the potential weaknesses of the GBI score is that a negative score may not indicate a genuinely adverse outcome from the surgery. On the social and general subscales, for example, much relies on the personality of individual patients, with those who did not find the condition adversely affecting them socially or psychologically before surgery tending to report less significant improvements after. But perhaps more importantly two out of three questions on the physical subscale ask about additional treatment or additional health problems for any reason since their surgery, and which could give a negative score even when completely unrelated to the lid/lacrimal surgery. Together, these factors probably account for the negative minimum scores we have demonstrated in all procedures, and for the negative mean score for physical health following ptosis surgery. It is our impression that these negative scores do not tend to reflect individually poor outcome in terms of postoperative complications of failed surgery.

Analysing the mean, median, and SD for the four procedures demonstrates some interesting patterns (Table 1, Figure 2). Benefit from ectropion surgery appears to be skewed by a small group of patients with a particularly negative experience (large positive skew), and entropion and DCR by a larger group of patients with more positive experiences (small negative skew). Outcome from ptosis surgery is quite consistent (small SD), and from DCR quite variable (large SD).

Although the GBI offers a straightforward, flexible tool for measuring patient benefit, questionnaires like these suffer from some inherent limitations. Subjective responses offer no measure of consistency and may be influenced by factors such as the style of interviewer, the time of day, or concurrent activities. There is also the suspicion that responses may owe as much to the personality of the respondent as to the effect of the procedure. It is expected, however, that such biases would be equally represented in all groups allowing a valid comparison.

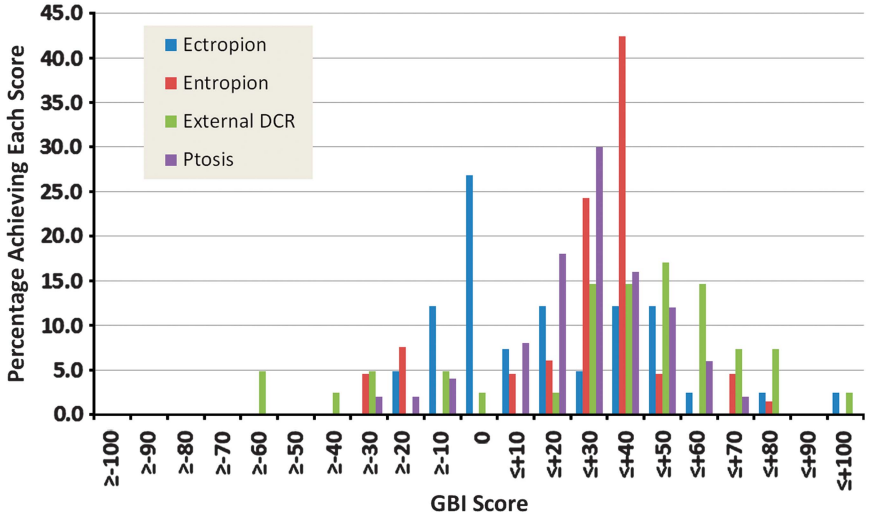

Figure 2 Graph comparing total GBI scores for different procedures.

As medical practitioners, we aim to improve the quality of our patients' lives. A significant body of evidence points to the mismatch between objective clinical impairment and subjective HRQL.[2] In patient-centred medicine, and with non-lifesaving interventions, high-quality data to demonstrate patient benefit are essential. Our study using the GBI shows significant improvements in quality-of-life from the four oculoplastic procedures we have examined, and subjective benefit to the patient should be an important consideration when appraising the value of a given intervention. We believe that greater use of patient benefit questionnaires such as GBI could contribute positively to decision making when PCTs commission services for their patients. Furthermore, patient benefit questionnaires offer a potentially useful measure of performance that could be used to compare outcomes from surgery against recognised standards in clinical audit.

In the NHS in England 2009–2010, the volume of surgery undertaken of the four procedures we have examined was as follows: entropion repair 5449, ptosis repair 5445, ectropion repair 5741, and DCR 4380 (http://www.hesonline.nhs.uk/Ease/servlet/AttachmentRetriever?site_id=1937&file_name=d:/e fmfiles/1937/Accessing/DataTables/Annual inpatient release2010/MainOp4_0910.xls&short_ name=MainOp4_0910.xls&u_id=8920). Almost all of these procedures were performed as day cases, and with the exception of DCR almost exclusively under local anaesthesia. As such, they are relatively low-cost interventions that we have shown bring genuine benefits physically, socially, and psychologically to our patients. Our results show that this group of conditions should not be considered purely within the realms of cosmetic surgery, and we hope that this study can contribute to well-informed commissioning of oculoplastic procedures in the future.

Summary

What was known before

- The Glasgow benefit inventory is a questionnaire-based, post-interventional quality-of-life scale that measures patient benefit from medical interventions. It has been validated for oculoplastic procedures, but until now has only been used in dacrocystorhinostomy and botulinum toxin for blepharospasm.

What this study adds

- We applied this tool to four commonly performed oculoplastic procedures: entropion repair, ectropion repair, ptosis repair, and external dacrocystorhinostomy. We show significant patient-reported quality-of-life improvements from these interventions. Our results confirm that these procedures are of benefit to our patients, and enable us to quantify the improvements. This gives a benchmark for future audit, and may be of value as we are increasingly called upon to justify the cost effectiveness of oculoplastic interventions.

Conflict of interest

The authors declare no conflict of interest.

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driving at night. In general, patients with latent strabismus, macular disease, or optic nerve disease make poor candidates for monovision, unless they have previously done well with optical correction.

Presbyopia-correcting IOLs can be classified as multifocal, with near and distance elements in the optic of the lens, or accommodative, whereby the lens changes position or shape within the eye.

Multifocal IOLs achieve their effect by dividing incoming light into two or more focal points and can be classified as refractive or diffractive.[606] A Cochrane systematic review concluded that multifocal IOLs were effective at improving near vision when compared with monofocal IOLs and that unaided distance visual acuity was similar in the two groups.[607] Optical effects of multifocal IOLs may include reduced contrast sensitivity, halos around point sources of light, multiple images, and glare.[608] Whether the improvement in near unaided acuity outweighs the optical side effects of multifocal IOLs will vary among patients, with important factors being the motivation to achieve eyeglass independence and adaptation over time.[609] Patient selection and counseling are particularly important with these IOLs. There may be a symptomatic reduction in the quality of distance vision, particularly if other ocular pathology is present, such as macular pathology or latent strabismus. Therefore, the candidacy of patients with amblyopia or abnormalities of the cornea, optic disc (such as glaucoma), and macula for a multifocal IOL must be carefully considered.[600] *(III, insufficient quality, discretionary recommendation)*

Multifocal toric IOLs are currently also available to correct astigmatism concurrently while providing a range of vision. When compared with multifocal IOLs with limbal relaxing incisions, they were found to be more predictable and to have good rotational stability.[610,611]

Multifocal IOLs are available with a lower add for near vision that can help minimize issues of halo and glare.[612,613]

In an attempt to mimic human accommodation, accommodative (with or without a toric component) presbyopia-correcting IOLs are designed to change position or shape in the eye with accommodative effort. These IOLs have demonstrated varied accommodative potential without the loss of contrast sensitivity inherent in multifocal IOLs.[614-617] A modified monovision technique with the nondominant eye corrected for -0.50 D or -0.75 D is used by some surgeons to improve uncorrected near vision.

Outcomes

Multiple large studies on cataract surgery, including a current Cochrane review, have repeatedly demonstrated favorable outcomes.[618] The 1994 ASCRS National Cataract Database reported that at 3 months postoperatively 86% of all patients had a 20/40 or better BCVA, 57% of patients had 20/25 or better postoperative BCVA, and 75% of patients were within ±1.0 D of target spherical equivalent.[619] With 5788 responses, the mean visual function index score at 3 months postoperatively was 70% compared with 55% preoperatively. (The score is based on a scale of 0 to 100, with 0 indicating inability to perform any of the activities.) The 1999 European Cataract Outcome Study reported that 89% of patients achieved a postoperative visual acuity of 0.5 D or more (20/40 or better), the average induced astigmatism was 0.59 D, and 86% of patients had an induced astigmatism within ±1.0 D.[620] This study was conducted in 14 countries with up to 40 participating surgeons during the years 1995 to 1999, and it collected operative and follow-up information on a total of 8646 patients, including 3033 patients in 1999.

The American Academy of Ophthalmology National Eyecare Outcomes Network (NEON) database (n=7626) also found similar rates of success, with an improvement in visual acuity in 92% of patients and improvement in VF-14 in over 90% of patients.[621] Best-corrected visual acuity of 20/40 or better was achieved by 89% of all NEON patients and by 96% of NEON patients who lacked preoperative ocular comorbid conditions.[621] Seventy-eight percent of patients were within ±1.0 D of target spherical equivalent. Ninety-five percent of patients reported being satisfied with the results of their surgery. Patients

who were dissatisfied with the results of their surgery were slightly older and more likely to have an accompanying ocular comorbidity. More recently, a large multicenter study in the United Kingdom showed results from cataract surgery of 20/40 or better in 95% of eyes with no ocular comorbidity.[622] Several recent papers on clinical outcomes with FLACS report results similar to standard ultrasonic phacoemulsification but with a higher incidence of subconjunctival hemorrhage.[623]

In studies of phacoemulsification cataract surgery performed by ophthalmology residents, the reported range of patients with postoperative BCVA of 20/40 or better was 80% to 91%.[624-629] If eyes with ocular comorbidities are excluded, the reported range of patients with postoperative BCVA of 20/40 or better was 86% to 98%.[627-630] Good predictive results have also been achieved with toric IOLs in resident phacoemulsification cases.[631]

The Cataract Patient Outcomes Research Team (PORT) study identified independent predictors of greater improvement after surgery: younger age (under 65), less comorbidity, higher cataract symptom score, and worse VF-14 (measure of visual function) score.[147] In several studies, preoperative Snellen visual acuity was found to be unrelated to the likelihood of improvement in symptoms or self-reported visual function after cataract surgery.[147,150,632] In another study, a prospectively validated model found that predictors of improvement included younger age, a poorer preoperative visual function as measured by the ADVS, and absence of diabetes.[632] However, even patients with diabetes and age-related macular degeneration (AMD) showed significant improvements after cataract surgery, albeit at a lower magnitude than patients without these conditions.[633-637] Although these studies have shown greater benefits in younger patients, the improvement in quality of life for those 75 and older is still functionally and statistically significant.

Another study used a validated visual function questionnaire and a variety of psychophysical methods to assess visual improvement in patients with symptomatic cataracts but with preoperative Snellen acuity better than or equal to 20/50.[638] Even in eyes with 20/20 or better preoperative Snellen acuity, cataract surgery improved patients' self-reported visual impairment.[150] Neither the preoperative best corrected high-contrast Snellen distance acuity nor change in Snellen acuity predicted the observed improvement in visual function as reflected in the pre- and postoperative questionnaire scores. The strongest preoperative indicators for improved visual function were glare disability tested at low and medium spatial frequencies and the visual function questionnaire score. This suggests that in patients with symptomatic nonadvanced cataract, Snellen visual acuity in isolation does not accurately predict who will benefit from surgery.

Complications of Cataract Surgery

Although numerous complications can occur intraoperatively or postoperatively with cataract surgery, those resulting in permanent loss of vision are rare. Major complications are potentially sight-threatening and include infectious endophthalmitis, TASS, intraoperative suprachoroidal hemorrhage, CME, retinal detachment, persistent corneal edema, IOL dislocation, ptosis, corneal decompensation, diplopia, and blindness.

The Cataract PORT reviewed the incidence of cataract complications from studies published prior to 1992 and with an overall phacoemulsification/manual ECCE case mix of 2:1.[639] Six subsequent studies of adverse perioperative outcomes from cataract surgery are summarized in Table 2. In one of these studies, Greenberg et al[640] reviewed the incidence of complications from cataract surgeries performed at the U.S. Veterans Health Administration system from 2005 to 2007. The most common ocular complications were posterior capsular tear, anterior vitrectomy, or both during surgery (3.5%), and PCO after surgery (4.2%). The rate of CME was 3% and the rate of retained lens fragments was 2%.

Stein et al[641] stratified Medicare beneficiaries who underwent cataract surgery into three cohorts: those who had their first cataract surgery in 1994–1995 (n=57,780), 1999–2000 (n=73,064), or 2005–2006 (n=90,750). The overall rate of severe complications in the 1-year postoperative period was 0.5%; severe complications were defined as endophthalmitis (0.16%), suprachoroidal hemorrhage (0.06%), and retinal detachment (0.26%). The

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Measuring patient-based outcomes in a plastic surgery service: breast reduction surgical patients

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SUMMARY. On admission for breast reduction surgery, 110 patients completed a preoperative assessment pack containing: 1) Personal and demographic questions; 2) Condition-specific questions including physical symptoms and areas of life affected by their condition; 3) The SF-36 Health Survey Questionnaire; and 4) The Rosenberg Self-esteem Scale. At 3 months and again at 6 months after surgery, these same patients were sent postal follow-up packs containing the SF-36 and Rosenberg questionnaires and postoperative condition-specific questions requesting information on complications, relief of physical symptoms, scarring, pain and opinion of the aesthetic result. The response rate was 82% (90 patients) at 3 months and 76% (84 patients) at 6 months. The results of the data collected indicate that breast reduction surgery confers very substantial benefit to patients in terms of greatly improved physical and psychological health and well-being.

For any medical intervention, the purpose of collecting patient outcome information must be to inform clinical practice and to identify benefit (or lack of it) to patients. The consideration of benefit to patients is obviously central to the problems encountered in the cost-effective allocation of resources available for health care. Without valid, reliable and sensitive measures of patient outcome, health care may come to be provided on the basis of cost alone. Few studies have addressed the consideration of how to incorporate outcome measures that are of importance to the patients themselves alongside clinical assessments, probably because of the difficulties involved in establishing appropriate measures for use within a particular clinical setting. However, it is becoming increasingly accepted that the patient's own perspective must be taken into account when assessing the effectiveness of health care, and this is particularly so for some areas of the Plastic Surgery Service where there is a significant psychosocial component to the evaluation of the results of the procedures.

The aim of this study was to attempt to assess the outcome of plastic surgery procedures using a variety of patient self-assessment instruments on a pre-treatment and post-treatment basis. Four groups of patients were chosen to reflect the range of the Service at the Regional Plastic Surgery Centre at Salisbury District Hospital. This paper presents the findings for patients undergoing breast reduction surgery.

Patients and methods

Assessment pack

On admission to the ward, before their operation, patients received:

1. A letter explaining the purpose of the study, stressing the importance of participation and thanking the patients for taking part;
2. Personal and demographic questions to allow calculation of body mass index, and standard occupational classification (Office of Population Censuses and Surveys);
3. Condition-specific questions (Table 1);
4. The SF-36 Health Survey Questionnaire,[1] a 36-item scale encompassing eight dimensions of health: physical function; physical role; emotional role; social function; mental health; energy; pain; and health perception.
5. The Rosenberg Self-esteem Scale, a short 10-item scale measuring self-concept.[2]

At 3 and 6 months after surgery, all patients who had completed the admission pack received a follow-up pack containing a reply-paid envelope, the SF-36 and Rosenberg questionnaires and postoperative condition questions requesting information on many areas including complications, pain and scarring, and the patient's opinion of the result of the operation. (Follow-up pack available on request from the authors.)

All data were collected and processed by an independent research analyst and were not seen by medical staff involved in patient-care.

Patients

The assessment pack was completed on admission to the ward before surgery by all 110 female breast reduction patients (age range 15–68 years, mean 35 years, median 33 years), admitted over a 9-month period in 1995. No patients refused to participate. However, not every patient answered every question. Patients referred to all consultant plastic surgeons in the plastic surgery unit were included in the study. At 3 months and again at 6 months after surgery these same patients were sent, by post, the follow-up pack. The response rate was 82% (90 patients) at 3 months, and 76% (84 patients) at 6 months. Again, not every question in

Table 1 Condition-specific questions

ABOUT YOUR CONDITION

What bra size do you wear? .....
What bra size would you like to wear? .....

Do you consider your breasts to be the wrong shape	Yes	No
Do you consider your breasts to be symmetrical (that is, of approximately equal sizes)	Yes	No
Do you currently have any of the following problems? (please tick)	Yes	No
Back pain	( )	( )
Breast pain	( )	( )
Neck pain	( )	( )
Skin rash beneath breasts	( )	( )
Discomfort due to rubbing of bra straps	( )	( )
Discomfort when taking part in sport/exercise	( )	( )
Finding clothes which fit properly	( )	( )
Comments or looks from others which you find offensive or embarrassing	( )	( )
A tendency to stoop rather than stand straight	( )	( )
Difficulty in finding a comfortable sleeping position	( )	( )

Are there any other problems which you are currently experiencing? Please describe them briefly.
.....
.....
.....

How long have you wanted this operation? .....

Was there any event in particular which prompted you to visit your G.P. to ask about having the operation? .....
.....
.....

Do you consider that the plastic surgeon to whom you were referred has satisfactorily answered your questions, and adequately explained the operation procedure and what to expect afterwards?	Yes	No

If you wish, list what you consider to be the most important areas or activities in your life affected by your condition.

the pack was answered. Overall, 95 patients returned at least one follow-up questionnaire pack. The 6-month follow-up acted as a reminder to non-respondents. Six patients were lost to follow-up from military service families who had left the area.

Because of the many variables involved in the management of admission of patients from the waiting lists of several consultant surgeons, we did not find it feasible to carry out the study on a matched group of patients who were awaiting but not called for surgery.

Results

Physical parameters and symptoms

For the 110 preoperative patients (mean height = 5 ft 5 in; mean weight = 11 st 1 lb; median weight = 11 st 0 lb) body mass index was calculated as: 20–24.9 (normal), 43 patients; 25–29.9 (overweight), 48 patients; 30–40 (obese), 17 patients; > 40 (severely obese), 2 patients.

Mean underbreast chest size reported on admission was 36.6 in (standard deviation 3.0) and 94% of patients (103) fell within the range of cup-sizes D/DD –H/HH. After operation, 98% of responders (88 patients) fell within the range B/BB–D/DD. Seventy-three per cent of preoperative patients (80) considered their breasts to be the wrong shape, and 44% (48) considered them to be asymmetrical.

The length of time patients had wanted to have the operation (not time on the waiting list) ranged from 1 year or less (19 patients) to 28 years, with many patients responding 'many years' (63 patients).

Ninety-seven per cent of patients (107) completing the admission pack considered that their surgeon had satisfactorily explained the procedure and what to expect afterwards.

The data shown in Table 2 were obtained after analysis of patients' responses to the request for the main reason or event which prompted them to visit their General Practitioner about the operation. The responses were sorted into the broad categories shown.

Table 2 Main reason given by patients for requesting breast reduction surgery

Reason	*Patients n = 105 (%)*
Pain or discomfort (back, neck, breast, etc.)	25 (24)
Advised by health professional (doctor, physio, chiropractor, etc.)	13 (12)
Informed of NHS availability by friend, or magazine/newspaper article	12 (11)
Family complete, or finished breast-feeding	11 (10)
Rashes or excessive breast weight	6 (6)
Knew other recipients, or advised by family	7 (7)
Clothes/underwear fit, and availability	8 (8)
Infections/breast lumps	3 (3)
Depression due to body-image	4 (4)
New relationships/sexual factors	2 (2)
No specific reason given	14 (13)

The extent to which patients suffer physical problems as a result of their condition and the reported relief of physical symptoms at 3 months after surgery is shown in Figure 1. At the 6-month follow-up, the pattern of reported relief of symptoms was almost identical, with a small reduction in the number of patients reporting breast pain from 36% to 30% of responders.

By 3 months after surgery, 93% of responders (84 patients) had returned to their normal activities. The rates of minor complications (mainly wound infections) and re-admission for major adverse events are shown in Table 3. Patients' expectations and opinions of scarring, and overall satisfaction with the result of the surgical procedure are shown in Tables 4 and 5. Overall, in the light of their experiences, 98% of responders (88 patients) would choose to have the procedure again and 98% would recommend it to a friend.

Table 3 Complications/readmission rates

	3 months n = 89 (%)	*6 months n = 84 (%)*
Minor complications (mainly minor wound infection, undissolved stitches, etc.)	33 (37)	4 (5)
Readmission (mastectomy for abnormal histology; revision of abnormal scarring)	3 (3)	3 (4)
Further operation required (as readmission)	3 (3)	3 (4)

Table 4 Scarring

	3 months n = 89 (%)	*6 months n = 83 (%)*
Expectation:		
Scarring much worse than expected	4 (4)	5 (6)
Worse than expected	16 (18)	13 (16)
As expected	50 (56)	40 (48)
Better than expected	19 (21)	25 (30)
Scar pain:		
Very painful	4 (4)	2 (2)
Quite painful	7 (8)	6 (8)
Occasional pain	56 (63)	44 (53)
No pain	22 (25)	31 (37)

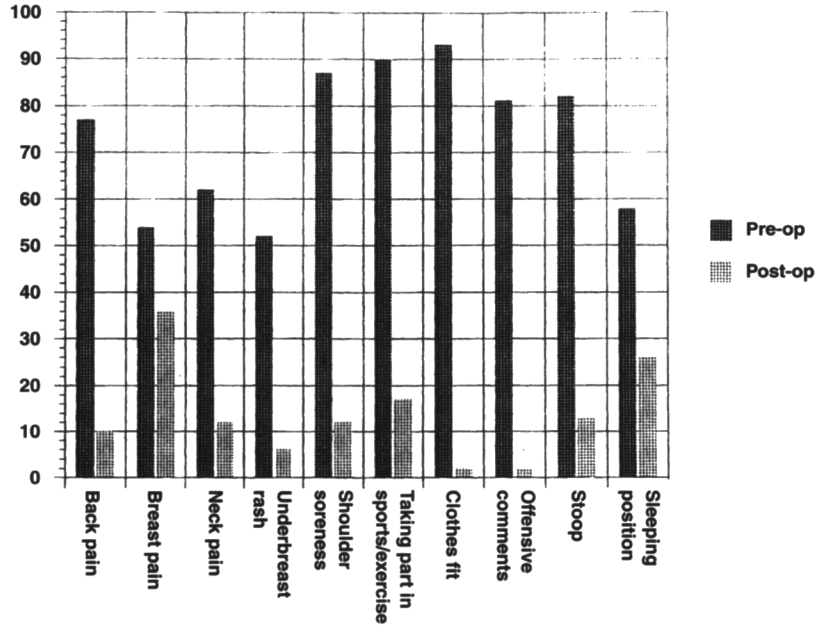

Fig. 1

Figure 1—Percentage of patients at 3 months after surgery answering 'yes' to the question 'Do you currently have any of the following problems?'

Table 5 Satisfaction with outcome/effect on life

A) **Patient expectations concerning cup-size vs. surgical outcome achieved**	*n = 89 (%)*	
Larger than patient-stated preference	27 (30)	
Similar to stated preference	58 (65)	
Smaller than stated preference	4 (5)	
B) **Post-op satisfaction with size**		
Too small	0	
About right*	85 (95)*	
Still too large	4 (5)	
Much too large	0	
* 25 patients with larger than expected size were, nevertheless, satisfied with their result		
C) **Overall result**	*3 months*	*6 months*
Excellent	46	42
Very good	32	28
Good	9	10
Fair	1	2
Poor	0	1
D) **Effect on life**		
Very pleased	65	57
Pleased	19	22
Neither pleased nor displeased	2	2
Disappointed	2	2
Very disappointed	0	0

Health-status assessments

SF-36. Scores for each of the eight dimensions of health measured by the SF-36 questionnaire range from 0 to 100,[1] where higher scores indicate better health. Table 6 shows the mean scores for the preoperative and postoperative (3 month) states. Statistical analysis was carried out using CSS:Statistica (StatSoft). Tests for significance of differences in means between the preoperative and postoperative data were performed using either dependent *t* tests or the Wilcoxon matched pairs signed rank test as appropriate. Change-effect size, which is a measure of the magnitude of a change, is defined as the mean difference between the pre- and postoperative scores, divided by the standard deviation of the baseline score.[3] It can be seen from Table 6 that significant or highly significant improvements exist between preoperative and postoperative states for general health, physical function, social function, pain, mental health, and energy. Furthermore, the change-effect size shows moderate change on four of the dimensions. No significant change in emotional or physical role limitation was found.

At 6 months after surgery, the significant or highly significant improvements were maintained for all dimensions of the scale, with the exception of general health, which was found not to differ significantly from the preoperative score at this stage.

In order to compare SF-36 scores for our patient sample with those of the general female population of comparable age range, normative data has been taken from the large community study for the SF-36 in the Oxford Health Region.[4] Since the size of the normal subject sample is very large, it is likely that it provides a comparable measure for other regions within the country. Comparison of sample-means for our study group with the estimated population-means (females aged 18–45 years) was performed using the one sample *t* test which allows direct comparison of a sample mean with an estimated population mean if standard deviations are known. Table 7 shows that, before treatment, physical function, physical-role limitation, social function, pain, mental health, and energy were all significantly below normative values, whilst general health and emotional-role were comparable with normal. At 3 months after surgery, physical function, physical-role limitation and social function had improved to normal levels, whilst mental health, energy, general health and emotional-role limitation were significantly above normative values. Only postoperative pain scores remained below those of the general female population, probably due to the continuing existence of occasional pain due to scarring at this stage. At 6 months, scores on all dimensions were comparable with normative values, except for mental health and energy which remained significantly above normal.

Table 6 SF-36 questionnaire scores

	No. of subjects	*Physical function*	*Social function*	*Physical role*	*Emotional role*	*Mental health*	*Pain*	*Energy*	*General health*
Mean pre-op score (SD)	88	77.33 (21.62)	75.13 (24.82)	75.60 (31.38)	79.05 (34.48)	66.18 (19.27)	66.25 (26.88)	54.38 (19.80)	74.15 (19.22)
Mean post-op score: 3 months	88	91.48 (13.63)	88.02 (18.76)	83.13 (33.95)	87.48 (27.51)	75.47 (16.42)	73.95 (22.49)	63.35 (18.93)	79.63 (18.41)
Mean change (95% confidence interval)		14.15 (11.20, 17.10)	12.89 (6.76, 19.00)	7.53 (–1.81, 16.70)	8.43 (–0.53, 17.40)	9.29 (4.76, 13.80)	7.70 (1.34, 14.10)	8.97 (4.41, 13.60)	5.48 (2.68, 8.82)
Significance of difference in means†		****	***	ns	ns	***	*	***	***
Change-effect size‡		0.66	0.52	0.24	0.24	0.48	0.29	0.45	0.28

† Dependent *t* test or Wilcoxon signed rank test. ****$P < 0.0001$; *** $P < 0.001$; * $P < 0.05$. ‡ Change-effect size: mean change in score between baseline and follow-up divided by standard deviation of baseline: 0.2–0.5 small/moderate; 0.5–0.8 moderate/large; > 0.8 large. ns: not significant.

Table 7 Comparison of patients' SF-36 scores with normative data

	No. of subjects	*Physical function*	*Social function*	*Physical role*	*Emotional role*	*Mental health*	*Pain*	*Energy*	*General health*
Normative values*	1299	90.80 (15.30)	86.50 (19.70)	86.50 (28.90)	79.90 (33.50)	71.10 (16.80)	81.10 (21.30)	58.80 (19.60)	74.50 (19.70)
Pre-op mean score	110	76.02 (21.55)	73.72 (25.47)	76.90 (33.91)	80.88 (33.33)	67.41 (18.25)	64.92 (26.44)	55.69 (18.62)	74.08 (19.52)
Pre-op deviation from normal		−14.78 ***	−12.78 ***	−9.60 **	0.98 ns	−3.70 *	−16.18 ***	−3.11 *	−0.42 ns
3 mth post-op mean score	88	91.48 (13.71)	87.01 (21.00)	82.75 (33.95)	87.66 (27.50)	75.46 (16.51)	73.95 (22.62)	63.35 (18.93)	79.63 (18.52)
Post-op deviation from normal (3 mth)		0.68 ns	0.51 ns	3.75 ns	7.76 *	4.36 *	−7.15 **	4.55 *	5.13 *
Post-op deviation from normal (6 mth)	83	0.86 ns	1.20 ns	0.82 ns	1.35 ns	4.25 *	−2.94 ns	5.96 *	2.31 ns

* Normative values are for females averaged over ages 18–45 years. Values are means (SD). *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$ (2-sided test). ns = not significant.

Table 8 Rosenberg Self-esteem Scale

	No. of subjects	*Mean score*
Pre-op score (SD)	88	29.11 (4.84)
Post-op score (SD)	88	31.76 (4.87)
Mean change (95% confidence interval)	2.65 (1.70–3.60)	
Dependent *t* test for difference in means	$P < 0.0001$	
Change-effect size	0.55	

Rosenberg Self-esteem Scale. Scores for this short scale range from 10 to 40, where higher scores indicate higher self-esteem. Pre- and postoperative scores, mean changes with confidence intervals and paired *t* tests for significance of difference in means are shown in Table 8. Improvement in self-esteem after treatment, at both follow-up periods, was highly significant ($P < 0.0001$) with a moderate change-effect size.

Discussion

In the face of limitations on resources available for health care, some health authorities in the United Kingdom have excluded or restricted certain procedures from their service contracts, on the basis that they may lead only to limited health gain.[5] One such surgical procedure which has faced exclusion is breast reduction, which may have been considered to be entirely 'cosmetic' and of limited benefit in terms of health improvement.[6] Since a reasonably large number of patients are referred each year to the plastic surgery unit at Salisbury District Hospital for National Health Service breast reduction surgery, we have therefore chosen this procedure to try to assess patient-based changes in physical and psychological health and well-being as a result of surgery.

In terms of the preoperative psychological status of the patients admitted for this operation, the data obtained indicate that the patient group studied were not unduly preoccupied with problems of self-image or aesthetic considerations. Only 4 patients cited dissatisfaction or depression due to their body image as their main reason for requesting referral, with a further 8 citing lack of availability or high cost of clothing and underwear. Furthermore, over a third of the patients indicated that they had been advised to request the procedure by a health professional or that they suffered physical pain or discomfort (Table 2). Although many of the patients were overweight or obese, these patients did not have unrealistic preoperative expectations regarding the outcome in terms of their breast size and appearance, and the vast majority of responders considered the overall result excellent or very good (Table 5). Figure 1 shows the effectiveness of the procedure, and hence the benefit to patients, in providing relief from physical and other problems.

With regard to postoperative problems reported, the rate of minor complications at 3 months appears to be high at 37% of responders (33 patients) (Table 3). These were mainly soreness, minor infections, or undissolved stitches treated by Health Visitors or General Practitioners. Five per cent of responders at 6 months (4 patients) were still reporting minor problems. Three patients required re-admission and further surgery, one of which was for mastectomy following the finding of malignant changes on histology. Table 4 shows that, at 6 months, scarring was worse, or much worse, than expected in 22% of patients (18 patients), although pain in the scarred area was only reported to be a problem in 8 patients by the 6-month follow-up. The preoperative counselling of patients by surgeons

with regard to scarring may have room for improvement, although patients' perceptions on admission were that the information provided was good.

Any patient reporting specific postoperative problems in the space provided for comments on the questionnaire was referred to their consultant plastic surgeon and further medical consultation or appointment was offered, if appropriate. The vast majority of responders were pleased or very pleased with the effect the operation had on their everyday lives (Table 5) and individually many commented that they were delighted with the result and the standard of care they had received. Only two patients expressed some disappointment with the outcome, both due to problems with unsightly scarring.

For assessment of general health status, the SF-36 questionnaire was chosen because it has been widely used in a variety of patient groups in the UK and USA,[7] and normative data on a large number of subjects are available.[4] The disadvantages of the instrument are that it generates eight separate scores for each patient at each time point and it is time-consuming to score manually in the absence of an expensive automated scanning system. The SF-36 questionnaire proved sensitive to change in the study group of breast reduction patients, who showed significant or highly significant improvement in six of the eight dimensions of health from the preoperative to the 3-month postoperative state (Table 6). However, although the patients perceived their general health to be improved at the time of the 3-month follow-up, the perceived improvement was not maintained at 6 months after surgery, when general health was comparable to preoperative levels. Since mean general health score before treatment was found not to differ from female population means (Table 7), it is likely that the perceived improvement at the shorter follow-up time period may be ascribed to psychosocial factors rather than a real improvement in this dimension of health.

Overall, comparison with female population means of the same age range (Table 7) showed breast reduction patients to score significantly below normative values on six dimensions of health, whereas 6 months after surgery scores had improved to normal levels (or above, in the case of mental health and energy). In addition, self-esteem was found to be greatly improved at both the 3-month and 6-month follow-up periods.

The SF-36 questionnaire and the Rosenberg Self-esteem Scale have recently been employed to assess health status in patients who have undergone plastic surgery procedures in the Oxford Health Region,[8,9] where change in health status from before to 6 months after surgery was measured in 58 breast reduction patients. The results from the Oxford study show that these patients underwent moderate to large improvements for all dimensions of the SF-36, with large improvements in self-esteem. The results of our study are in broad agreement with those of Klassen and colleagues. However, we failed to find an improvement in the two role-limitation dimensions and in general health perception at 6 months after surgery, even though our measurement of change is based on a larger number of post-treatment responders (83/110) than that of the Oxford study (58/128) at 6 months follow-up. In this respect, it should be noted that scores for emotional-role limitation and general health perception in our patient sample, before surgery, appear to be comparable with those of the normal female population of the same age range. In contrast, regression analysis with adjustment for the effects of age for the Oxford breast reduction patients, before surgery, indicated significantly lower scores than those of the general population on all eight dimensions.

The use of a valid patient-based assessment pack provides a method of assessment of outcome of health care interventions which is a true reflection of the patients' views on the care they have received and which is independent of clinical opinion. A recently published study[10] on assessment of outcomes in total hip replacement surgery has used similar methodology of a disease-specific questionnaire and the SF-36 health-status instrument to assess change before and after surgery. This study found that the questionnaires employed offered a valid and practical means of monitoring outcomes for this orthopaedic procedure.

In our study, patient compliance in providing the information required was excellent. Ninety-five patients returned at least one of the follow-up questionnaires and, taking into account non-responders from Armed Services backgrounds who had left the UK, 101 of the 110 patients on whom preoperative information was obtained were accounted for after treatment. The information gained from the use of condition-specific questions in addition to established health-status instruments indicates that substantial benefit in terms of improvement in physical health and psychological well-being were gained in patients as a result of breast reduction surgery. If provision of health care is to be based on demonstrable need and evidence of health gain by patients, then the results of this study indicate that breast reduction surgery meets these criteria.

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Review

A journey through liposuction and liposculture: Review

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ABSTRACT

Introduction: Nowadays, liposuction is the most frequently performed aesthetic surgery procedure in Western Countries. This technique has had rapid development since the 1970s, when it was experimented for the first time by A. and G. Fischer. It is currently widely used in clinical practice for many different situations in aesthetic, reconstructive and functional fields.

Materials and methods: This review aims to describe the historical evolution of liposuction by analyzing the transformation of the method in function of the introduction of innovative ideas or instruments. We have also focused on reporting the major clinical applications of this surgical technique, applicable to almost the entire body surface. We finally analyzed the complications, both major and minor, associated with this surgical technique.

Results: Liposuction is mainly used to correct deep and superficial fat accumulations and remodel the body contour. It has become an essential complementary technique to enhance the aesthetic result of many other aesthetic procedures such as reduction mammoplasty, abdominoplasty, brachioplasty, thigh lift and post bariatric body contouring. However, it can be largely used for the treatment of innumerable pathologies in reconstructive surgery such as lipomas, lipedema, lipodystrophies, pneudogynecomastia and gynecomastia, macromastia e gigantomastia, lymphedema and many others. The complication rate is very low, especially when compared with conventional excisional surgery and the major, complications are generally associated with improper performance of the technique and poor patient management before and after surgery.

Conclusion: Liposuction is a safe, simple and effective method of body contouring. It has enormous potential for its application in ablative and reconstructive surgery, far from the most common aesthetic processes with a very low complication rate.

1. History

Liposuction is a very common cosmetic procedure: a safe, simple and effective method of body contouring. The first attempt to remodel the body silhouette dates back to 1921, when Dr. Charles Dujarrier wanted to improve the shape of the ankles and knees to a dancer patient. He removed a large part of skin and soft tissue, with a broad subcutaneous dissection and long skin incision. The result was tragic because of an excessive removal of tissue and suture too tight and live. This caused necrosis and amputation [1,2].

After that, many other attempts are followed with less tragic results, with *en bloc* resection of both fat and skin to recontour outer thigh adiposity. Several complications such as hematoma, long-term seroma, necrosis, infections, and many post-operative body deformities burdened this technique [3,4].

In 1972, the German physician Schrudde published a new less invasive technique to remove subcutaneous fat, using a uterine curette in a "sharp" technique of subcutaneous surgery. Several other surgeons used this technique through the mid 1970's: Kesserling and Meyer [5], in 1976, used a large, double blade cutting curette connected to a low-power aspirator to suck the fat, previously separated from the deep plane by scissors. This "sharp" technique restricts its use only to poorly vascular regions to limit the complications, which are already high [6,7].

In 1975, Arpad and Giorgio Fischer [8], father and son cosmetic surgeons, developed the modern technique of liposuction. They was the first to introduce blunt hollow cannula attached to a suction source and the criss-cross suctioning technique from multiple incision sites. This "blunt" method allowed obtaining better and more predictable aesthetic results with much less complications. The Fischer applied their method only to outer thigh adiposity [9].

Illouz and Fournier, two Parisian surgeons, modified and popularized the Fischer's technique. In 1977, Illouz [10] developed modified equipment for performing liposuction and extended technique to the

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whole body. He introduced blunt cannulas of smaller diameter to reduce the section of nerves, lymphatic vessels and blood vessels. He used three different size of blunt-tipped cannulas depending on the area to be aspirated: the larger (10 mm) for the flanks, hips and buttocks, the middle one for knees, ankles, abdomen and the smaller for the face.

To make the technique less traumatic and reduce hemorrhagic risk, he gradually developed the “wet technique”, based on the injection of saline solution and hyaluronidase into the fat performing a hydrodissection before the liposuction procedure.

The hydrotomy allowed preserving the neurovascular bundles, the enlargement of the deep adipose layer that needs to be aspirated. This make easer for the surgeon preserving the superficial flap and removing only the deep layer [11].

Fournier, who also worked in Paris, was initially a supporter of the “dry technique”, in which no fluid was injected before the procedure, considering it more precise and accurate. However, experience has led it to abandon this approach in favor of local lidocaine infiltration and eventually the tumescent technique, recognizing the bleeding advantages.

He has also strongly supported the need for taped compression to support and shape the suctioned tissue, during the post-operative period.

However, the greatest merit of Fournier was to travel the world teaching others this technique and inspiring those [12].

Lawrence Field, a Californian based dermatological surgeon, visited and studied this evolving technique in 1977. He was probably the first American to visit France and learn the new technique of liposuction from the Italian and French pioneers [13,14].

After that, in the early 1980s, many other surgeons traveled to France to study this procedure. The blunt cannula technique came to be the accepted liposurgical method in this country and around the world, and in 1982, the American Society of Lipo-Suction was formed to bring surgeons from both the United States and foreign countries into one group to establish a teaching program [15,16].

Furthermore, by 1984, liposuction training was available in some dermatology and plastic surgery residency program [17,18].

Throughout this period, liposuction surgery was mostly performed under general anesthesia.

Dermatologists were very interested in performing the process in local anesthesia. Therefore, they started to combine a slight preoperative sedation with local lidocaine infiltration. However, the possible applications were limited by the maximum recommended local anesthetic dosage to few cases with small areas to be treated.

In 1987 Jeffrey Klein, a Californian dermatologist, first reported on the use of large volumes of very dilute anesthesia which allowed liposuction to be performed in larger volumes completely under local anesthesia without the need of sedation or general anesthesia. Klein invented a recipe consisting of 0.05% lidocaine, 1:1,000,000 epinephrine, and 10 mL sodium bicarbonate per liter of saline, which could be infused into tissue prior to liposuction [19].Klein also demonstrated that the same dosage of lidocaine diluted in a large volume of fluid allowed obtaining a good degree of anesthesia even on large areas, without evidence of systemic toxicity.

Moreover, the presence of epinephrine produced an important vasoconstriction which greatly reduces bleeding during the procedure, which was a major liposuction problem prior to Klein's development [20,21].

Lillis demonstrated that the Klein's tumescent technique offered significant reduction in blood loss, even in suction case of over 3L. He verified, also, that Klein's work demonstrating minimal plasma absorption of lidocaine when low concentration solutions were infused [22,23].

Furthermore, performing liposuction without general anesthesia offered other different advantages like reduction of hospitalization, costs and risks of anesthesia.

The main disadvantage of this method is that infiltration of the anesthetic takes a significant length of time. In addition, the cannulas used to extract the fat need to be somewhat finer in diameter to be tolerated by the patient and hence the time to remove a given volume of fat is lengthened compared with general anesthesia [24].

Liposuction was born as a suction technique by means a vacuum pump [25]. However, the Brazilian Luiz Toledo, in 1988 [26], experienced the use of disposable syringes of different gauges and size for aspiration of adipose tissue. The main advantage was a wider freedom of movement for the operator during the procedure, making surgery simpler and easier. In addition, the syringes allow you to know precisely the amount of local anesthetic that has been infiltrated before the procedure and the exact amount of fat removed from each area, all data which are just approximate with the use of the lipoaspirator. Toledo also proposed creating a patient's body map to ensure symmetry as much as possible. A nurse marked exactly the amount of injected local anesthetic and fat tissue removed from each body area to improve as much as possible the aesthetic result and symmetry [27].

The main advantage of syringe liposuction is, therefore, the precision and accuracy in measurement of adipose harvested volumes, in addition to the possibility of injecting fat. The vacuum-pump assisted liposuction makes the surgical procedure more comfortable and less tiring for the surgeon, especially in case of large amounts of fat to be removed. Therefore, the vacuum pump assisted liposuction was usually chosen for major lipoplasty procedures, in which quantity of fat to be removed is a priority over the topographic, symmetric, precise distribution of fat harvest [28].

Ultrasonic liposuction was introduced by Zocchi, in Italy, in 1992 [29] as an alternative to conventional blunt cannula suction. Zocchi credits Scuderi for the original concept of lipo-exeresis [30].

This technique is based on the application of ultrasounds to the fatty tissue to be aspirated, resulting in both thermal effects and mechanical effects to the surrounding adipocytes. These mechanical oscillations pass through the cannula that emits the waves from its tip. The thermal effects play a role in fat dissolution and must be dissipated by tissue infiltration [31,32].

In this way, Zucchi tried to make aspiration easier and to preserve the neurovascular structures, which can be destroyed by the cannulas.

Zocchi detailed what he believed were the advantages of Ultrasonic technique over traditional liposuction: a more selective destruction of the undesired tissue while preserving surrounding higher-density structures; elimination of the “fluid part” of the adipose tissue (fatty acids), leaving the adipocyte wall and intercellular substance to create a smooth skin surface; skin contraction secondary to stimulation of the dermis by ultrasonic energy; correction of cellulite; once the fat is dissolved with ultrasound, the procedure requires less physical exertion on the part of the surgeon [29,33].

Ultrasonic liposuction was embraced initially in South American and Europe and then largely rejected after experience with skin sloughs, burns, and seromas [34].

Laser-lipolysis began to spread after the publication of the studies about the interaction between laser and adipose tissue, conducted by Apfelberg [35] and Apfelberg et al. [36,37] in 1992.

Laser-assisted liposuction represents a relatively recent advancement in the treatment of lipodystrophies and irregularities of adipose tissue. The laser beam is directly propagated to adipose tissue with which it keeps a direct contact. The action of the laser causes the rupture of the adipocyte membrane and consequent release of oily content into the extracellular fluid. Complications and results of laser-assisted liposuction are similar to those obtained with the majority of liposuction techniques. In addition to the cytolitic effects on adipocytes, the laser can cause neoformations and remodeling of the collagen and reorganization of the reticular dermis. It is particularly indicated for localized areas of lipodystrophy in the body or face [2,38].

Table 1
Summary of the main functional and therapeutic indications.

Main indications of liposuction procedure	
Lipoma and Multiple lipomatosis	Muscocutaneous or fasciocutaneous flaps management
Lipedema and Lipodystrophy syndromes	Scar revision
Insulin-induced lipodystrophy	Genital area and Sexual dysfunction
Hiv-associated cervicodorsal lipodystrophy	Tracheostomy, Colostomy, and Urostomy management
Gynecomastia, Macromastia and Gigantomastia	Axillary hyperhidrosis
Postbariatric body contouring	Aesthetic body contouring

2. Indications

Liposuction is the most performed aesthetic surgery in the world. It is mainly used to correct deep and superficial fat accumulations and remodel the body contour. It has become an essential complementary technique to enhance the aesthetic result of many other aesthetic procedures such as cervicoplasty, reduction or augmentation mammoplasty, abdominoplasty, brachioplasty thigh lift and postbariatric body contouring.

It now seems to have enormous potential for its application in ablative and reconstructive surgery, far from the most common aesthetic processes [39] (Table 1).

One of the first non-cosmetic clinical applications of liposuction was the aspiration of a large lipoma without leaving a visible scar [10].

Lipomas are the most common benign tumor of soft tissues and have very variable dimensions. Simple surgical excision remains the main and most effective treatment, however, removal of large or multiple lesions may be problematic and result in significant objectionable scars [40].

However, the removal of bulky lipomas or multiple lipomas through liposuction has been described in the literature [40–42]. The disadvantage of this technique lies in the frequent incomplete resection and at a high recurrence rate associated with it [41].

The small liposuction incision can also be located in a less visible area than the area affected by the lipoma, so you can choose the less visible region where to position the scar. Furthermore, in the case of multiple lipomatosis, it is possible to remove more injuries with a single incision, the healing of the small incision is rapid, and there is a minimal postoperative discomfort [43].

Liposuction can also be a useful solution for the treatment of the multiple-lipoma syndromes and familiar multiple lipomatosis associated with some genetic pathology [44,45].

Lipedema is characterized by bilateral symmetrical and localized subcutaneous fat deposits of the buttocks and lower limbs. It causes significant physical disability, fatigability, pain, difficulty in wearing shoes and boots [46].

Diet and exercise, even if performed correctly, are not enough to reduce the disproportion between the upper and lower body. Indeed, sometimes, they make the anesthetic dispensation more noticeable, as the patient slides only in the upper body of the body [47,48]. Skin and subcutaneous excision significantly improve the size and shape of the limbs; however, it may be associated with severe complications. Suction-assisted lipectomy may be a good surgical option given the diffuse nature of lipedema adipose hypertrophy and it may be combined with limited skin and subcutaneous tissue excision in cases of persistent redundant skin [9,48].

In these patients, liposuction provides good aesthetic results, improving the proportion between the upper and lower body and, also, it reduces painful symptoms, especially at the lower limb articulations, ensuring better mobility [50].

Lipodystrophies represent a group of rare diseases characterized by selective body fat loss with altered body fat amount and/or repartition that can be either generalized or partial. Lipodystrophies are usually associated with insulin resistance, type 2 diabetes, dyslipidemia, liver steatosis, polycystic ovaries, acanthosis nigricans, and cardiovascular complications [46,50].

Treatment of lipodystrophies is difficult. Lifestyle is generally very helpful in controlling the disease but not enough. Aesthetic surgery is essential to improve the body contouring, especially in areas where there has been loss of adipose tissue [51]. The only therapeutic options for controlling the metabolic disorder are insulin sensitizers, insulin, and lipid-lowering drugs. Autologous adipose tissue transplantation or implantation of dermal fillers can improve facial appearance and excess adipose tissue from the chin, buffalo hump, and vulvar region can be surgically excised or removed by liposuction [46,52].

In addition, hypertrophic insulin lipodystrophy may benefit from suction-associated lipectomy. It occurs frequently in the sites of multiple insulin injections in diabetic patients causing functional and aesthetic disorders including pain, reduction of treatment efficiency, hematoma and edema [53,54].

Cervicodorsal lipodystrophy is another secondary lipodystrophy in which liposuction is needed to achieve satisfactory results. It is a side effect of some drugs including the corticosteroids (Cushing's syndrome) and human immunodeficiency virus (HIV) medications [55,56].

Liposuction subcutaneous mastectomy is the initial surgical approach of choice for pneudogynecomastia and gynecomastia. In pseudogynecomastia, there is an increased development of the fatty component in the male breast region. In true gynecomastia, however, there is an increase in volume of the male breast gland with a dense fibrous and vascular stroma, which makes suction more difficult. The gynecomastia liposuction treatment is usually associated to a resection under direct vision of the glandular tissue through a periareolar or transareolar incision. After that, compression dressing and limited activity are necessary for several days to minimize bruising and hematoma formation allowing the skin to adhere to the chest in a favorable position [57–59].

In female macromastia and gigantomastia, there is an important increase in breast fat component. Bulky and heavy breasts often cause significant symptoms such as neck and back pain, dermatitis and skin irritations. Liposuction combined with traditional resection mammoplasty allows volume reduction before excision and refining the results after the reconstruction with an easier surgical procedure and better aesthetic results [60–62].

Lymphedema is a condition with a wide range of etiologies; the most common cause is the removal of one or more lymph nodes stations for neoplastic disease. Consists in the accumulation of lymphatic fluid in the dermis and subcutaneous tissues, due to a blockage of the lymphatic flow. Chronically accumulated lymphatic fluid causes cutaneous dermal thickening, hypercellularity, and progressive fibrosis. Secondary to restricted lipid transport from limited lymph flow, lipids accumulate in adipocytes and macrophages, resulting in increased adipose tissue [49,63–65].

In chronic lymphedema, the increase in volume of the area is mainly due to the accumulation of adipose tissue and not fluid. For this reason, conservative therapies and lymphatic flow regeneration are not effective at this stage. Before it is necessary to surgically remove the bulky subcutaneous tissues. Traditional surgical excision, however, causes unacceptable complications and scar and often the result is unsatisfactory, liposuction provides good aesthetic and functional long-term results with a minimum complications rate [66–68].

It is important to emphasize that liposuction alone cannot eliminate the tendency to accumulate fluids and fat tissue, therefore it must always be associated with conservative therapies and lymphatic flow regeneration [64,66–68].

Muscocutaneous or fasciocutaneous flaps are widely used successfully for the reconstruction of a wide variety of defects. In many cases, the flaps are set up to a greater extent than necessary, in the sense of

having enough tissue for the recoating, resulting in unsatisfactory aesthetic results.

Surgical review in a second time is needed to remodel the flap, especially at certain body areas such as the ankles, knees, feet and breast, to obtain a better aesthetic result and to improve the functionality of that area. Liposuction allows thinning the subcutaneous tissue usually without the risk of flap necrosis and reduces the number of revision procedures required to achieve optimal aesthetic and functional result [69,70].

Other less common clinical applications include axillary hyperhidrosis [71–73], revision of surgical scars [74–76], sexual dysfunctions and genital area (e.g. the “buried” penis in fatty men) [77,78].

Liposuction is also used to facilitate tracheostomy, colostomy and urostomy in great obese patients, in which the stoma could be occluded by excessive fatty tissue surrounding [79–81].

3. Surgical technique

Before the surgery it is important preparing for surgery by marking. Areas to be suctioned are typically marked with a circle in a topographic pattern. Zones of adherence and areas to avoid are marked with hash marks [82].

Areas that can be suctioned effectively include the face, chin, neck, anterior and posterior axillary areas, arms, breasts, abdomen, waist, hips, buttocks, thighs, knees and ankles.

The current options for anesthesia are dry, wet, superwet, and tumescent. The essential differences between these techniques focus on the amount of infiltrating solution injected into the tissues and the resultant blood loss as a percentage of aspirated fluid. The dry technique involves no infused fluid and results in approximately 25–40 percent blood loss of the volume removed. Blood loss has been estimated to represent approximately 1 percent of the liposuction aspirate volume for both tumescent and superwet techniques [83,84].

Klein's tumescent technique has been gradually embraced by all medical specialties [4], because of the advantages including especially bleeding reduction [20,21].

With awake tumescent liposuction, the patient is able to drink normally the night before and the day of surgery, eliminating the need to replace deficits after important bleeding, avoiding the risks of postoperative overhydration or underhydration [85].

The Klein's solution, consisting of 0.05% lidocaine, 1:1.000.000 epinephrine, and 10 mL sodium bicarbonate per liter of saline, is infused into tissue prior to liposuction [19] by blunt multi-hole cannulas (Figs. 1–2). This helps avoid damage to the surrounding tissues, and this means less postoperative edema and ecchymoses [39]. Tissue blanching and moderate tension are considered clinical endpoints of infiltrate [84].

Small incisions are performed in different places depending on the area to be treated, but always designed to hide the small surgical scar [16].

For example, the chin and neck can be approached through a small incision placed in the submental crease, posterior lobular crease, or in the nasal vestibule. These incisions are limited to 5–10 mm and are made within relaxed skin tension lines. They are well hidden and allow excellent access to the cervicofacial region [39].

Fig. 1. Suction cannula collected to vacuum pomp.

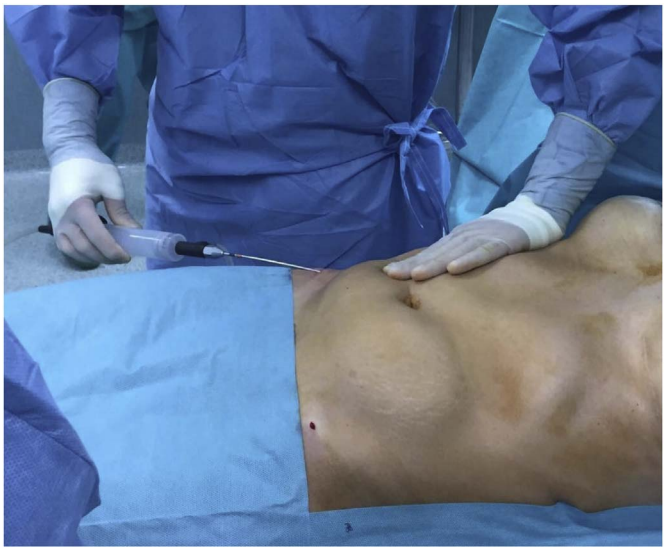

Fig. 2. Klein's solution infiltration.

An abdominal procedure could be approached through three or four incisions. Two incisions are suprapubic, at the lower abdominal fold and another incision is placed over the umbilicus. Other incisions can be placed under the breast or through an existing scar. Of course, different situations require different incisions [16,39].

The cannula is inserted with the opening away from the skin, and the adipose tissue is broken loose from the fibrous stroma with multiple crisscross movements. These movements create tunnels in the subcutaneous flap of the area [16] (Figs. 3 and 4).

The deep and/or intermediate fat layer should be suctioned primarily [86], but in rare cases, superficial or subdermal liposuction may be appropriate [85–87].

Anatomical “zones of adherence,” present in both men and women, are important to identify preoperatively. These are areas with relatively dense fibrous attachments running to the underlying deep fascia where they help define the natural shape and curve of the body. These areas are not to be suctioned because of the high potential for contour deformities [85–88].

For the body 2–4.6-mm cannulas with lengths from 15 to 45 cm are used according to the areas to be treated. For the face and other delicate work 10-ml syringes and cannula gauges between 1 and 3 mm are

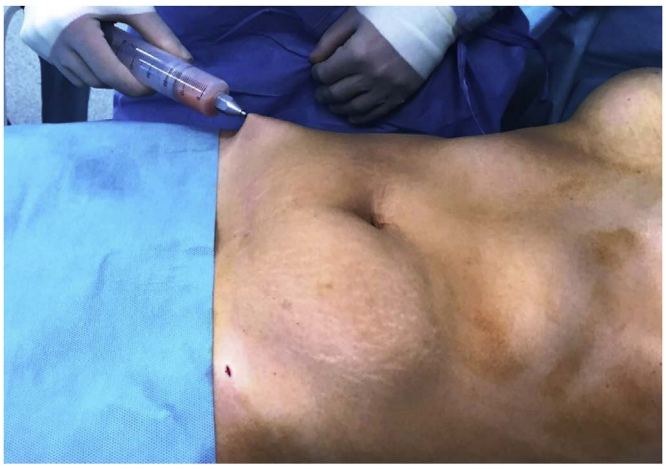

Fig. 3. Harvesting abdominal fat.

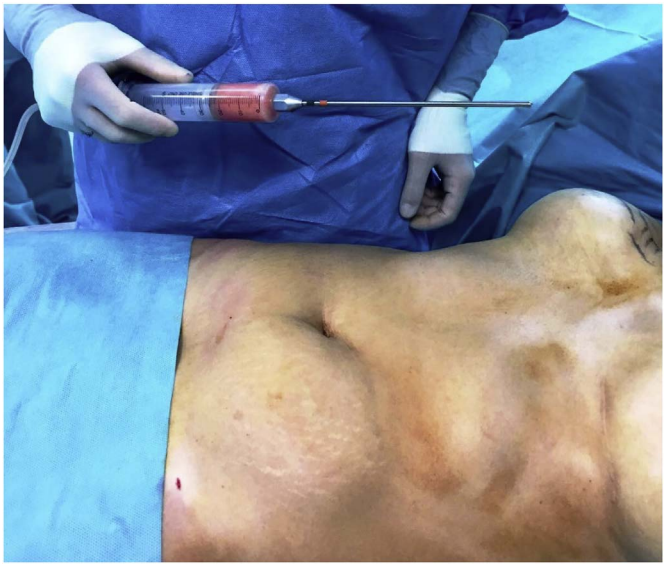

Fig. 4. Harvesting fat collected in the syringe. This allows to precisely knowing the exact quantity of adipose tissue aspirated. In this picture is possible to note the different between the right abdomen, in which the liposuction has already been performed, and the left abdomen.

preferred [39].

The dominant hand directs the cannula, with the other hand used as a guide for this blind procedure [16].

Liposuction is generally performed by two methods: the syringe method and the power pump method. Small volume procedures or procedures primarily for harvesting fat can be performed with syringe liposuction. The syringe technique used blunt-tip suction cannulas connected to a syringe. Drawing back the syringe plunger generates the negative pressures needed to remove fat during liposuction and replaces the electric vacuum pump and connecting tubing traditionally used for this procedure [26,27,89,90].

Following extraction, the multiple tunnels created by the cannula form a “honeycomb” inside the suctioned area that allows the skin to adhere to its new profile following surgery. Pressure bandages occlude the tunnels by collapsing the remaining fat into the spaces of the honeycomb [12].

4. Complications

With appropriate patient selection and minimally traumatic techniques, many complications can be avoided.

True complications that are possible include contour defects, permanent skin color changes, infection, emboli, hematomas, or seromas.

The presence of ecchymosis depends on the localization and size of the treated area, the length of the procedure and individual factors. Edema is very common and generally persists for several weeks, in some venous areas such as ankles and calves may persist for six months or a year [2].

Hyperesthesia and dysesthesia are common sequelae of the procedure, which will gradually improve in three to six months after surgery. Hyperpigmentation is relatively infrequent condition and when it shows up it diminishes gradually, and in more serious cases, it responds well to treatment with topical agents [2].

Overly aggressive liposuction can lead to seromas. The collection of serous fluid in a treated area may lead to extensive breaking of the fibrous tissue network, leading to the formation of a single cavity [91].

Infection is extremely uncommon (< 1 percent incidence). This may be because of a combination of sterile technique, small incisions, and the antibacterial effects of lidocaine [92].

The most common postoperative complication is contour irregularities, with an incidence of 2.7% [93].

Using small cannulas, not performing superficial liposuction, turning the suction off when exiting incisions, crisscrossing areas, constantly analyzing areas (visual and tactile), and proper positioning can all help reduce the chance of contour irregularities. Autologous fat transfer at the time of surgery or 6 months postoperatively can be used to help correct deformities [85].

Grazer and De Jong [94] reported a fatality rate of 19.1 per 100,000 liposuction procedures. The most frequent potentially lethal complications associated with liposuction are pulmonary embolism, fat embolism, sepsis, necrotizing fasciitis, and perforation of abdominal organs. The most frequent cause of death was deep venous thrombosis (DVT) associated with pulmonary embolism (23.1%). The risk of DVT is associated with blood flow stasis, trauma and possible hypercoagulation status. Intermittent compression devices for legs, early mobilization and the use of low molecular weight heparins can reduce the risk.

Abdominal and bowel perforations are reported as the second commonest lethal event (14.6%). To reduce the risk of perforation, the cannula tip has always to be accompanied by the palm, in particular in obese patients, in whom it is difficult to visualize the cannula, and the position should be hyperextension of the abdomen and severe abdominal pain should always suggest the occurrence of a possible perforation, which may require a laparotomy [2,93,94].

In 10% of cases, the death was caused by the use of local anesthesia, sedation and other medications.

Bleeding, formerly the most relevant cause of death due to lipoaspiration, represents just a 4.6% of lethal events [95].

Major risk factors for the development of severe complications are multiple procedures, poor standards of sterility, excessive infiltration and intoxication from lidocaine or adrenaline, excessive removal of adipose tissue with volume depletion in the third space, permissive postoperative discharge, and selection of unfit patients [92].

Furthermore, when tumescent infiltration of large volumes of dilute lidocaine and epinephrine are combined with intravenous fluid replacement and general anesthesia, there are significantly increased risks of fluid overload, pulmonary edema, and drug interaction [96].

5. Conclusions

After more than 40 years of being born, liposuction is currently one of the most accomplished aesthetic interventions around the world.

Surgical technique is simple and has a very low complication rate. However, if you want to get good aesthetic results and want to avoid the greatest possible complications you need a good technical study and a great experience (Figs. 5 and 6).

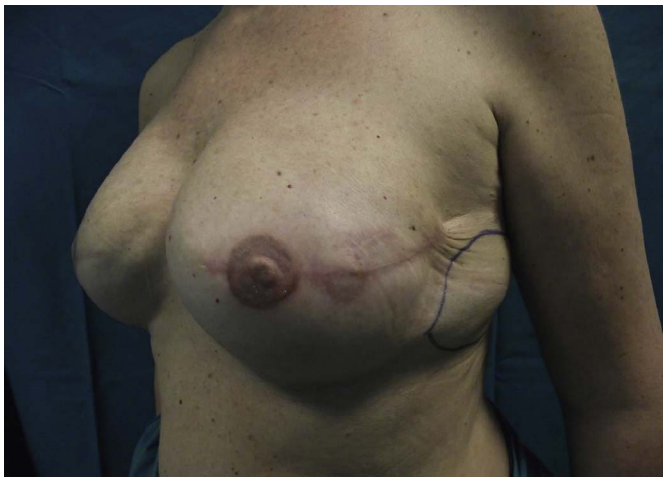

Fig. 5. Body remodeling of the left axillary pillar in a 53 years old patient, after oncologic breast reconstruction. Pictures before and after liposuction procedure.

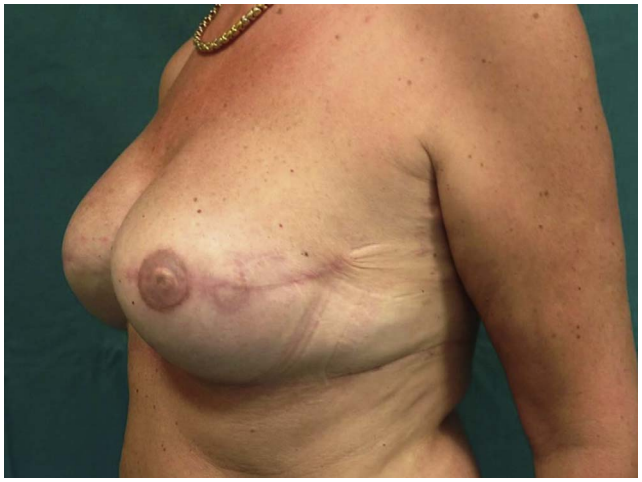

Fig. 6. Body remodeling of the left axillary pillar in a 53 years old patient, after oncologic breast reconstruction. Pictures before and after liposuction procedure.

Liposuction has many clinical applications both in the field of aesthetic surgery and in functional and reconstructive surgery.

Obesity, initially a clear criterion of exclusion, was no longer considered as such [2].

Liposculture is a great tool for redefining the body's profile in patients who undergo significant weight loss. However, in order to obtain satisfactory aesthetic results, it is always necessary to associate the excision surgery to remove the skin excess. The suction of adipose tissue allows having empty areas, making surgery easier, shorter and reducing possible complications [97–100].

A recent study reports the use of abdominal lipectomy as an adjunctive procedure to assist with long-term weight loss as part of the overall treatment of bariatric surgery patients [101].

In recent years, liposuction has become more important as a method for harvesting autologous fat and adipose-derived stem cells. Lipofilling is a widely used technique in several different clinical situations such as correction of asymmetry and defects in the body's profile, loss of volume, to improve retrograde or atrophic scars or regenerative medicine for the treatment of chronic wounds [102–112].

Recently, interest in adipose tissue has increased considerably. In last decades, numerous studies have demonstrated the wide differentiation and regenerative capacity of adipose-derived stem cells [113–118].

The harvesting technique is currently the traditional liposuction, carried out in small quantities and with the syringes method to limit the traumas on adipocytes. Adipose-derived stem cells have potentially very high clinical applications in various medical and surgical specialties, justifying the present and future significant efforts on new techniques for isolating, collecting and maximizing these stem cells [119–122].\\\\

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Author contribution

Edoardo Raposio: study design and data analysis.
Michele P. Grieco: management of clinical cases.
Elisa Bellini: data collection and writing the manuscript.

Conflicts of interest

None.

Guarantor

Prof. Edoardo Raposio is the Guarantor of the study.

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An Update on the Safety and Efficacy of Outpatient Plastic Surgery: A Review of 26,032 Consecutive Cases

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Background: Outpatient surgery offers many advantages, including cost-containment, privacy, and convenience. However, patient safety must take precedence over these benefits. Limited well-designed studies exist in the plastic surgery literature on patient safety in the outpatient setting, particularly those that identify risk factors for adverse outcomes.

Methods: A retrospective review was performed on 26,032 consecutive cases completed by board-certified plastic surgeons at an accredited outpatient surgical center between 1995 and 2017. All cases were reviewed for potential morbidity and mortality events, and variables were analyzed to determine potential risk factors for postoperative complications and inpatient admission.

Results: A total of 26,032 cases were performed over a 23-year period. There were a total of 203 complications (0.78 percent). Compared with the control population, the 12 patients (0.05 percent) that sustained venous thromboembolic events demonstrated higher body mass indexes ($p < 0.01$), greater lipoaspirate amounts ($p = 0.04$), longer operative times ($p < 0.01$), and were more likely to have undergone a combined procedure ($p < 0.01$). In addition, the 22 patients (0.08 percent) that were transferred to inpatient facilities demonstrated greater body mass index ($p < 0.01$) and longer operative times ($p = 0.01$).

Conclusions: Plastic surgery is safe to perform in an accredited outpatient facility for a majority of patients. According to the authors' data, postoperative monitoring in a nursing facility should be considered for the following high-risk patients: those with a body mass index greater than 30 kg/m^2, operative times greater than 4 hours, lipoaspirate volumes greater than 3 liters, and those undergoing combined procedures. (*Plast. Reconstr. Surg.* 141: 902, 2018.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Risk, III.

Over the past decade, the demand for cosmetic surgery has continued to rise and transition toward the outpatient setting. In 2015, 15.9 million cosmetic cases were performed, compared with 13.2 million in 2010.[1] Traditionally, these procedures are performed in one of three types of ambulatory surgery centers: hospital-based, free-standing, or office-based. In 2015, 91 percent of cosmetic cases were performed in a free-standing surgical facility or office-based setting, a 5 percent increase from the previous year.[1,2]

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The outpatient setting offers the advantages of cost-containment, privacy, and convenience to the physician and patient, and more efficient, consistent care by nurses and support staff. Despite these benefits, patient safety must take precedence. In

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addition, many medical malpractice claims occur with patients who elect to undergo ambulatory surgery and sustain adverse outcomes.[3]

Several studies have assessed patient safety in the outpatient setting, but they are limited by their design (i.e., large database queries, questionnaires), the population studied (i.e., non–plastic surgery patients), or their failure to identify specific risk factors for adverse outcomes.[4–12] As a result, regulators and state-licensing agencies lack the appropriate data to develop standardized policies that help determine the safest facility for a patient's procedure and postoperative care. In an attempt to develop general guidelines for patient safety, a task force from the American Society of Plastic Surgeons published *Pathways to Preventing Adverse Events in Ambulatory Surgery* in 2011.[3] They identified the following patients as high risk for ambulatory plastic surgery: those with a body mass index greater than 35 kg/m^2, age older than 60 years, and operative time greater than 6 hours; those undergoing liposuction with lipoaspirate greater than 5000 ml; those in whom large-volume liposuction is combined with other procedures (e.g., abdominoplasty); and those with a medical history of obstructive sleep apnea or other cardiopulmonary disease. However, many of these recommendations are based on data from other surgical specialties. The purpose of our study was to determine the safety of performing plastic surgery procedures in an accredited outpatient surgical center and to discern risk factors for adverse outcomes and inpatient admissions.

PATIENTS AND METHODS

A retrospective review was performed on 26,032 consecutive cases completed between the years of 1995 and 2017. All cases were performed by board-certified plastic surgeons at an American Association for Accreditation of Ambulatory Surgery Facilities–accredited outpatient surgical center, the Dallas Day Surgery Center. Multiple procedures were performed on some patients, but the overall number of cases (26,032) does not reflect multiple procedures. A majority of cases were cosmetic procedures, including rhytidectomy, brow lift, blepharoplasty, rhinoplasty, otoplasty, laser resurfacing, chemical peels, breast augmentation, mastopexy, liposuction, abdominoplasty, and gluteal fat augmentation. A small number of cases were reconstructive and hand/upper extremity related.

All cases were reviewed for potential mortality and morbidity events, including hematoma, seroma, infection, wound dehiscence, and venous thromboembolic events (either deep vein thrombosis or pulmonary embolism). The morbidity events measured included early postoperative complications (occurring within 48 hours after surgery) and those requiring return to the operating room. Variables were analyzed to determine potential risk factors for postoperative complications, including age, body mass index, operative time, lipoaspirate amount, and whether the procedure was a combined case.

Patients that required postoperative monitoring were transferred to a hotel adjacent to our surgical suites that is staffed full time by a registered nurse. The decision for postoperative monitoring was made (usually preoperatively) by the patient's plastic surgeon and anesthesiologist based on medical comorbidities, duration of case/anesthesia, large lipoaspirate amounts, and combined cases. Complications/events that prompted transfer to inpatient admission (from the postanesthesia care unit or hotel suite) included uncontrolled pain, hypovolemia, arrhythmia, altered mental status, respiratory failure, pneumothorax, and venous thromboembolism. The same variables listed above (i.e., age, body mass index, operative time, lipoaspirate amount, and multiple procedures) were then analyzed to determine potential risk factors for inpatient admission.

Statistical analysis was performed using the nonparametric Wilcoxon rank sum test for numeric variables and Fisher's exact test for categorical variables. A difference between the variables studied was considered statistically significant for values of $p < 0.05$. Given that all patient information was deidentified and retrospective, consent was not obtained from the patient population.

RESULTS

A total of 26,032 cases were performed over a 23-year period, most of which were cosmetic. The three most common procedures were those of the breast (33.6 percent) and face (25.4 percent) and liposuction (10.4 percent) (Table 1). Breast cases included augmentation, mastopexy, implant exchange, capsulotomy, and reduction; face cases included rhytidectomy, brow lift, neck lift, blepharoplasty, and genioplasty. Gluteal augmentation was performed predominantly with autologous fat placed in the superficial and intramuscular plane. A total of 18.2 percent were combined cases involving two or more procedures, with the most common being the combination of abdominoplasty and liposuction (5.8 percent of total cases). A large majority of patients were female (90.5 percent).

Table 1. Types of Procedures and Relative Percentages Based on Total Number of Cases (*n* = 26,032)

Type of Procedure	Percentage of Total Cases
Breast	33.6
Face	25.4
Liposuction	10.4
Rhinoplasty	10.1
Laser resurfacing/chemical peel	7.1
Liposuction and abdominoplasty	5.8
Abdominoplasty	4.0
Buttock augmentation	1.8
Otoplasty	1.0
Brachioplasty	0.4
Thighplasty	0.4

Table 2. Types of Complications Requiring Return to the Operating Room with Relative Percentages Based on Total Complications (*n* = 203)

Complication with Return to OR	Total	Percentage
Hematoma	166	81.8
Seroma	15	7.4
Infection	15	7.4
Wound dehiscence	7	3.4
Total	203	—

OR, operating room.

The overall complication rate was 0.98 percent, with a total of 203 complications (0.78 percent) requiring return to the operating room (Table 2). A majority of patients were returned to the operating room secondary to hematoma (81.8 percent). The infection rate requiring return to the operating room was 0.06 percent. There were two mortalities (mortality rate, 0.008 percent), with the causes of death being cardiac arrest and pulmonary embolism. Both patients were combined cases and were monitored postoperatively in our hotel suites where the event was first diagnosed. Details of these two mortalities are summarized in Table 3.

A total of 12 patients sustained venous thromboembolic events postoperatively (venous thromboembolism complication rate, 0.05 percent). All 12 patients had image-confirmed pulmonary emboli, one of which underwent venous duplex imaging that identified the source as a lower extremity deep vein thrombosis. A large majority of the venous thromboembolism patients underwent combined procedures (83.3 percent), compared to non–venous thromboembolism patients (18.2 percent; $p < 0.01$). Of these 12 patients, 91.7 percent underwent abdominoplasty and 75.0 percent underwent abdominoplasty combined with liposuction. Compared with the control population, venous thromboembolism patients demonstrated higher body mass indexes (mean, 30.1 kg/m^2 versus 24.9 kg/m^2; $p < 0.01$), greater lipoaspirate amounts (mean, 3075 ml versus 2223 ml; $p = 0.04$), and longer operative times (mean, 4.28 hours versus 3.15 hours; $p < 0.01$). In addition, a total of 22 patients were transferred to inpatient facilities (transfer to inpatient rate, 0.08 percent). See Table 4 for indications for transfer. Of these 22 patients, 45.5 percent underwent combined procedures, compared with 18.2 percent of controls ($p = 0.14$). Compared with the control population, those that were transferred to inpatient facilities demonstrated greater body mass indexes (mean, 29.7 kg/m^2 versus 24.9 kg/m^2; $p < 0.01$) and longer operative times (mean, 3.92 hours versus 3.15 hours; $p = 0.01$) (Tables 5 and 6).

DISCUSSION

With the number of outpatient plastic surgery cases steadily increasing, it is important to ensure proper patient safety and establish evidence-based guidelines to circumvent adverse outcomes. Currently, the plastic surgery literature lacks well-designed studies that accomplish these objectives. One of the first groups to evaluate patient safety in the plastic surgery population was Morello and colleagues in 1997. They performed a 5-year retrospective review of an American Association

Table 3. Summary of Two Mortalities in Our Series of 26,032 Consecutive Patients

Patient	Cause of Death	Procedure	Details
1	Pulmonary embolism	Combined abdominoplasty and liposuction	Patient admitted overnight in adjacent hotel suite. After developing respiratory distress and increasing oxygen demands, she was transferred to nearby inpatient hospital where CT scan confirmed pulmonary embolism. Patient progressed to respiratory failure requiring intubation. She developed respiratory complications and died 14 days postoperatively.
2	Cardiac arrest	Combined face and breast	Patient admitted overnight in adjacent hotel suite. On nursing rounds later that night, patient was found unresponsive. Despite multiple rounds of ACLS, patient died.

CT, computed tomographic; ACLS, advanced cardiac life support.

Table 4. Indications for Transfer to Inpatient Facility with Relative Percentages Based on Total Number of Transfers (*n* = 22)

Indication for Transfer	Percentage
VTE	36.4
Respiratory failure	18.2
Hematoma	18.2
Hypovolemia	9.1
Pneumothorax	0.5
Perforated bowel	0.5
Altered mental status	0.5
Arrhythmia	0.5

VTE, venous thromboembolism.

Table 5. Statistical Comparison of Control Population and Patients That Sustained Venous Thromboembolic Events*

Variable	Control Croup	VTE Group	*p*
Combined case, %	18.2	83.3	<0.01†
Age, yr	47.1	46.8	0.97
BMI, kg/m^2	24.9	30.1	<0.01†
Operative time, hr	3.15	4.28	<0.01†
Lipoaspirate amount, ml	2223	3075	0.04†

VTE, venous thromboembolism; BMI, body mass index.
*Mean values are given for each variable.
†Statistically significant ($p < 0.05$).

Table 6. Statistical Comparison of Control Population and Patients That Were Transferred from Our Surgical Center to an Inpatient Facility for Higher Level Care

Variable	Transfer Group	Nontransfer Group	*p*
Combined case, %	18.2	45.5	0.14
Age, yr	47.1	48.7	0.53
BMI, kg/m^2	24.9	29.7	<0.01*
Operative time, hr	3.15	3.92	0.01*
Lipoaspirate amount, ml	2223	2586	0.26

BMI, body mass index.
*Statistically significant ($p < 0.05$).

for Accreditation of Ambulatory Surgery Facilities questionnaire completed by 400,675 patients from 241 different accredited office-based surgical facilities.[6] They reported a 0.47 percent complication rate and a 0.0017 percent mortality rate, with no difference in risk compared to patients undergoing surgery in the hospital-based ambulatory surgical facility. In 2004, Keyes et al. conducted a 2-year retrospective review on 411,670 patients from 621 office-based surgical facilities with data collected from the Internet-Based Quality Assurance and Peer Review database.[8] They found a complication rate of 0.33 percent and, in a more recent study, a mortality rate of 0.002 percent.[9] Several other studies have shown similar outpatient complication rates ranging between 0.3 and 0.7 percent and a mortality rates less than 0.01 percent.[7,13,14]

Focusing on venous thromboembolic complications, reports have estimated the venous thromboembolism risk for plastic surgery patients in the outpatient setting to range from 0.001 to 2 percent, with higher rates among patients undergoing abdominoplasty, extensive body contouring, and combined procedures.[15–20] A recent study by Winocour and colleagues stands out from previous data in that it is one of the first that comprehensively analyzed risk factors for venous thromboembolism occurrence. They analyzed 129,007 patients identified from the CosmetAssure database that underwent cosmetic surgery over a 6-year period. They reported a 0.09 percent venous thromboembolism rate, and on multivariate logistic regression, they demonstrated the following significant risk factors for venous thromboembolism: body procedures, combined procedures, increased body mass index, and increased age.[12]

The validity and reliability of the studies discussed above are confined by a variety of limitations. Data from several of the studies are obtained from large database queries and questionnaires, which can lead to underreporting, thereby producing potentially unreliable and inconsistent results. In addition, some studies include non–plastic surgery patients in their analysis. Others have short time intervals of data collection, some as brief as 1 to 2 years. Most importantly, a majority of these studies fail to identify specific risk factors for adverse outcomes in the outpatient setting. Table 7 summarizes all previous pertinent studies.[4,6–8,11,12,21]

Better-quality data on patient safety and risk factors for adverse outcomes are necessary to guide plastic surgeons in selecting the appropriate surgical setting for each patient. In addition, these data would help our governing bodies (e.g., *American Society of Plastic Surgeons*, *American Society for Aesthetic Plastic Surgery*) and regulators/state-licensing agencies to develop standardized policies that would further optimize patient care. In an attempt to accomplish this task, the American Society of Plastic Surgeons convened a task force that published *Pathways to Preventing Adverse Events in Ambulatory Surgery* (chaired by Loren Schechter, M.D.) in 2011.[3] This was an update from the task force that published *Patient Safety in Office-Based Surgery Facilities* in 2002.[22] Dr. Schechter and other committee members identified the following as posing a high risk for those undergoing outpatient plastic surgery: body mass index greater than

Table 7. Summary of Relevant Studies in the Literature Pertaining to Safety, Complications, and Mortality in the Outpatient Setting

Reference	Summary	Complication and Mortality Rate	Limitations
Natof et al., 1980[4]	Prospective study of 13,433 patients at free-standing ambulatory surgical center	Complication rate, 0.78%; mortality rate, 0%; transfer to inpatient facility, 0.12%	Non–plastic surgery patients enrolled (general surgery, GU, ENT, OB/GYN); short follow-up (2 wk); does not identify risk factors for outpatient surgical safety
Morello et al., 1997[6]	5-yr retrospective review of 241 different accredited, office-based surgical facilities, 400,675 patients completed AAAASF questionnaire	Complication rate, 0.47%; mortality rate, 0.0017%	Questionnaire based; study time interval; does not identify risk factors for outpatient surgical safety
Hoefflin et al., 2001[7]	Retrospective review of 23,260 patients undergoing plastic surgery in office-based surgical facility over 18-yr period measuring anesthetic complications	No anesthetic complications or mortalities; 1 VTE	Measured anesthetic outcomes, no surgical outcomes; does not identify risk factors for outpatient surgical safety
Byrd et al., 2003[21]*	Single-center retrospective review of 5316 consecutive patients over 6-yr period at accredited office-based surgical facility	Complication rate, 0.7%; mortality rate, 0%; transfer to inpatient facility, 0.19%	Study time interval; population size; does not identify risk factors for outpatient surgical safety
Keyes et al., 2004[8]	Two-year retrospective review of 621 office-based surgical facilities, data from 411,670 patients in IBQAP database	Complication rate, 0.33%; mortality rate, 0.002%	Database query; study time interval; does not identify risk factors for outpatient surgical safety
Gupta et al., 2016[11]	Retrospective review of 129,007 patients from CosmetAssure database comparing safety of inpatient vs. ambulatory vs. office-based over 6-yr period	Office-based complication rate, 1.3%	Database query; study time interval; does not identify risk factors for outpatient surgical safety
Winocour et al., 2016[12]	Retrospective review of 129,007 patients from CosmetAssure database over 6-yr period analyzing rates of VTE and risk factors	VTE rate, 0.09%; risk factors include combined procedures, body procedures, increased BMI, and age	Database query; study time interval; only analyzes VTE risks
Our results	Single-center retrospective review of 26,032 consecutive patients at accredited office-based surgical facility; all board-certified plastic surgeons over 23-yr period.	Complication rate, 0.78%; VTE rate, 0.05%; mortality rate, 0.008%; risk factors for morbidity/mortality and inpatient admission include combined cases, high BMI, prolonged OR time, and large lipoaspirate amount	Single-center study

GU, urology; ENT, otolaryngology; OB/GYN, obstetrics/gynecology; AAAASF, American Association for Accreditation of Ambulatory Surgery Facilities; IBQAP, Internet-Based Quality Assurance and Peer Review; VTE, venous thromboembolism; BMI, body mass index; OR, operating room.
*Previous study from our group.

35, age older than 60 years, operative time longer than 6 hours, lipoaspirate greater than 5000 ml, combining large-volume liposuction with other procedures (particularly abdominoplasty), and a history of cardiopulmonary disease. Although they represent great progress, many of these recommendations are based on poorly designed studies and data from other surgical specialties.

Our study is an update of an article published from the Dallas Day Surgery Center in 2003.[23] Since then, 26,032 consecutive patients have been accrued over a 23-year period. Based on our low rates of complications (0.78 percent), mortality (0.008 percent), and transfer to an inpatient facility (0.08 percent), our study continues to support the judicious use of accredited outpatient surgical facilities by board-certified plastic surgeons in the management of plastic surgery patients. In our previous study, a model for optimal patient safety is provided (please refer to Byrd et al.[21]). This commences in the preoperative setting with a detailed history, physical examination, and diagnostic workup performed in conjunction with our anesthesia colleagues. A comprehensive medical workup is pursued particularly in patients with a history of obstructive sleep apnea, intrinsic lung disease, diabetes, hypertension, coronary artery disease, cerebrovascular disease, or venous thromboembolism. Perioperatively, measures are taken to maximize patient comfort and minimize infection and adverse events. In the preoperative area, sequential compression devices are applied. On entering the operating room, the

Table 8. Comparison of Our Recommendations to Previous Advisories Assessing Safety and Outcomes in the Outpatient Surgical Setting

Safety Advisory	Recommendations/Risk Factors
Iverson, 2002[22]	EBL >500 ml; lipoaspirate >5000 ml; combination surgery of liposuction and abdominoplasty; operative time >6 hr (procedures should be done by 3 PM)
Horton et al., 2007[14]	Combination procedures; lipoaspirate >5000 ml; age >60 yr; history of VTE
Haeck et al., 2009[23]	Age >60 yr; history of obesity, OSA, HTN, CAD, CVD, VTE
ASPS *Pathways to Preventing Adverse Events in Ambulatory Surgery*[3] (2011)	BMI >35 kg/m^2; age >60 yr; operative time >6 hr; lipoaspirate >5000 ml; combining large-volume liposuction with other procedures (particularly abdominoplasty); history of cardiopulmonary disease
Our recommendations (for postoperative monitoring in an adjacent hotel or traditional hospital setting)	BMI >30 kg/m^2; operative time >4 hr; lipoaspirate >3 liters; combined cases, especially abdominoplasty with liposuction

EBL, estimated blood loss; VTE, venous thromboembolism; OSA, obstructive sleep apnea; HTN, hypertension; CAD, coronary artery disease; CVD, cerebrovascular disease; ASPS, American Society of Plastic Surgeons; BMI, body mass index.

patient is warmed and appropriate antibiotics are administered. A majority of patients underwent general anesthesia, and all were continuously monitored for optimal control of vital signs. Documentation throughout all stages of care is paramount to safety. Postoperatively, in the postanesthesia care unit and if monitored in the adjacent skilled postoperative care facility/hotel suites, patients are cared for by well-trained, qualified nurses who are familiar with each surgeon's postoperative protocol. This enhances patient safety and satisfaction, as patients and families are educated in a consistent manner, all questions are answered appropriately, and surgeon-specific protocols are followed should any complication arise. This also guarantees early 1-hour postoperative ambulation for venous thromboembolism prophylaxis. It is important that each surgeon has staff privileges at a nearby hospital and is credentialed to perform any procedure being contemplated at the outpatient facility. It is not surprising that many office-based plastic surgery injuries arise from physicians practicing outside their medical training.[14]

A limitation to our study is that we specifically included early postoperative complications (occurring within 48 hours) and those requiring return to the operating room. This may have led to underreporting of *nonoperative* complications that occurred later in the postoperative period. Although it would be ideal to include all postoperative complications, this would be difficult in aesthetic surgery patients, who often travel from out of town and are treated by other providers. In addition, another limitation is that our study measured data from only a single institution.

Above all, our study identifies important risk factors for adverse outcomes, including postoperative complications, particularly venous thromboembolism, and transfer to an inpatient facility. Patients who sustained venous thromboembolism complications and inpatient admissions were more likely to have longer operating room times (4.28 and 3.92 hours, respectively, compared with an overall mean of 3.15 hours) and higher body mass indexes (30.1 and 29.7 kg/m^2, respectively, compared to an overall mean of 24.9 kg/m^2). In addition, patients that sustained venous thromboembolism had higher lipoaspirate amounts (3075 ml, compared to an overall mean of 2223 ml) and were 4.6 times more likely to undergo a combined procedure. Based on these data, we recommend the consideration of postoperative monitoring in a nursing facility for patients with the following high-risk conditions: body mass index greater than 30 kg/m^2, operative time greater than 4 hours, lipoaspirate greater than 3 liters, and combined cases, especially abdominoplasty combined with liposuction. Table 8 compares these recommendations to previous task forces aimed to improve patient safety and ameliorate poor outcomes in plastic surgery.[3,14,22,23]

CONCLUSIONS

This study provides the safety profile of an accredited office-based surgical facility staffed by board-certified plastic surgeons over a period that spans more than two decades. We conclude that for a majority of patients, the overall risk is very low for undergoing plastic surgery in the outpatient setting. However, certain precautions should be considered to optimize safety of all patients and reduce adverse outcomes.

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Research article

Satisfaction and quality of life in women who undergo breast surgery: A qualitative study

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Abstract

Background: In cosmetic and reconstructive breast surgery, measurement of patient-reported outcomes has become increasingly important to research efforts and clinical care. We aimed to describe how breast conditions and breast surgery impact on patient satisfaction and quality of life.

Methods: We conducted qualitative, in-depth interviews with 48 women who had undergone either breast reduction (n = 15), breast augmentation (n = 12), or breast reconstruction (n = 21) surgery in order to begin to build a theoretical understanding of patient satisfaction and quality of life in breast surgery patients. Interviews were audio-taped, transcribed verbatim and analyzed thematically.

Results: The patient interviews revealed that breast conditions and breast surgery impact women in the following six main areas: satisfaction with breasts; satisfaction with overall outcome; psychosocial well-being; sexual well-being; physical well-being; and satisfaction with the process of care. We used these six themes to form the basis of a conceptual framework of patient satisfaction and quality of life in women who undergo breast surgery.

Conclusion: Our conceptual framework establishes the main issues of concern for breast surgery patients. This new framework can be used to help develop local guidelines for future clinical assessment, management and measurement, establish the validity of the current management strategies, and develop evidence-based guidance for the development of new patient reported outcome measures for future outcomes research.

Background

In the United States, over 500,000 women undergo breast surgery procedures each year [1]. Understanding the wide reaching impact of cosmetic and reconstructive breast surgery has thus become increasingly important for clinical research endeavors and surgical quality improvement efforts [2]. Traditional surgical outcomes, centered on morbidity and mortality, remain important but are no longer sufficient on their own. Thus, patient's perceptions of the impact of disease and treatment are increasingly

being considered as integral to understanding health outcomes [3-7].

Breast conditions and their associated surgical interventions have a major impact on quality of life. In fact, in specialties such as breast surgery, it has been suggested that "quality of life must be the major if not the only end point" [4]. Despite this, relatively little is known about the extent to which quality of life is impacted in breast surgery populations. There are a number of reasons for this. First, there is a lack of detailed qualitative research, based on inductive research methods, and a paucity of quantitative research, using valid, reliable, and responsive instruments to measure patient-reported outcomes in cosmetic and reconstructive breast surgery [8]. Second, few researchers have tried to understand exactly what having breast conditions means to women, and what impact surgery then has on these perceptions. Third, breast conditions are varied and are associated with complex symptomologies spanning the continuum of impact from physical functioning through to social interaction. As such, women with different conditions may experience the impact of these conditions differently.

It is clear that a thorough evaluation of the impact of breast conditions and their surgical treatment is required. Therefore, in this study we have adopted a qualitative approach [5,9] that involves in-depth interviews with women who had undergone breast surgery (i.e., breast reconstruction, breast reduction, breast augmentation) in order to collect data about their personal experience of breast surgery. This descriptive data was used to develop a theoretical understanding of patient satisfaction and quality of life in breast surgery patients. In particular, we have used detailed analysis [10] to compare and contrast the experiences of these women in order to develop a conceptual framework [11-13] with the view to improving our understanding of the impact of breast conditions and their surgical interventions.

Methods

Participants

The sample was recruited from the patients of four plastic surgeons practicing in Vancouver, Canada. These surgeons identified a pool of 120 women who had undergone three forms of breast surgery (i.e., reconstruction, augmentation, reduction). A letter and consent form was sent to each woman from their plastic surgeon inviting her to participate in an in-depth semi-structured interview. Sixty-two women (51.7%) returned a signed consent. Table 1 shows sample characteristics for 48 women (from the 62) that formed the final study sample.

We obtained local institutional ethics review board approval for this study. Women were invited by mail to participate in an interview where they could tell the *story* of how their breast condition and subsequent surgery had impacted their life. A reminder letter and replacement consent form was sent to non-respondents approximately three weeks after the first mailing. A one-page topic list, developed from a literature review of breast surgery outcome instruments [8], was developed to guide the inter-

Table 1: Characteristics of the study sample

Characteristics	N	%
Operation type		
Reduction	15	31.3
Augmentation	12	25.0
Reconstruction	21	43.8
Type of reconstruction		
Implant	12	57.1
Tram	7	33.3
Unilateral implant and tram	2	9.5
Timing of reconstruction		
Delayed	9	42.9
Immediate	11	52.4
Unilateral immediate and delayed	1	4.8
Time since surgery		
< 12 months	8	16.7
12 to 24 months	30	62.5
> 24 months	10	20.8
Age	3	6.4
20 – 29	14	29.8
30 – 39	13	27.7
40 – 49	17	36.2
50 – 75		
Marital Status		
Married	21	43.8
Common-law	4	8.3
Divorced	5	10.4
Widowed	2	4.2
Single	16	33.3
Ethnicity		
Caucasian	42	87.5
Ethnic minority	6	12.5
Main Activity		
Working	33	70.2
Homemaker	5	10.6
Student	3	6.4
Retired	3	6.4
Unemployed	2	6.4

views (see Table 2). This topic list was revised throughout the course of the study, with the findings from earlier interviews influencing and shaping its content. Interviews were initiated by having the participant discuss the circumstances that led to her decision to have surgery. Participants were thereafter encouraged to tell their story as completely as possible in their own words. The researcher consulted the interview guide and asked questions only as necessary to ensure that all topics had been discussed. Interviews were conducted by a trained interviewer (JK) either in the patients' home or a preferred location. All interviews were audio-taped and transcribed verbatim by a professional transcription service.

Data analysis

Data collection and analysis took place concurrently. The iterative interaction between data collection and analysis is the essence of attaining reliability and validity [14] and makes it possible for researchers to pursue emerging avenues of inquiry in further depth [10]. Each transcript was read carefully in order to gain an overview of the main issues of importance to participants. Transcripts were then examined in detail in order to identify basic patterns and recurrent themes using line-by-line coding to examine, compare and begin to develop conceptual categories. Categories were developed inductively using the constant comparison method [10]. Comparing each item with the rest of the data to create analytical categories and then grouping categories together made it possible to identify key themes [10]. All coding was done by one team member (JK) with the study investigators (AP, AK, SC) meeting regularly to discuss the coding results. Interviews were conducted until no new themes were identified through the data analysis. To enhance the accuracy of the account of our research, after completing data analysis, as a form of member-checking [15], we took our ideas back to research participants for their confirmation, holding two focus groups with a total of six women in each group who had undergone breast surgery. Focus groups were led by a trained facilitator who asked participants to discuss the extent to which the important themes that we had identified through our analysis of the interview transcripts reflected their subjective experience.

Results

Our interview findings with 48 breast surgery patients indicate that breast surgery procedures can clearly affect a woman in multiple spheres of function and quality of life.

Table 2: Interview guide

Pre-operation process: timing; influence/opinion/perceptions of partner, friends, and/or family; reason for operation; motivation; type of operation chosen; information seeking; Internet; decision-making
Pre/post operation perceptions: feelings going into the operation; concerns about complications/surgery process; expectations for recovery process; pre-op expectations for results; immediate feelings after operation
Post-op symptoms: pain; itchiness; discomfort; mobility problems; fatigue; complications; capsular contracture; rippling; numbness; swelling; movement of the arm; tightness in abdominal area
Functional ability and role performance: work and normal activities; interference in social activities; interference in family function; ability to participate in sports/fitness/activities; change in level of comfort; energy and vitality
Aesthetic outcome: size; shape; appearance of scar; symmetry; cleavage; appearance of nipple/areola complex; difference in fit of clothing; change in style of clothing; ability to wear desired clothes and styles; body wholeness/harmony; proportionate; feel to touch; breast-self exams; natural
Psychological well-being and self-concept: changes in mood; changes in confidence level; emotional distress resulting from teasing, comments, or stares prior to or after operation; body image issues; feelings clothed and unclothed; self-consciousness; self-esteem; feelings of femininity; cancer worry; closure to emotions surrounding disease; feelings of normalcy
Relationships with friends and family: reactions of friends and family; difference in treatment or attitude; marital relationship; family relationships; strain of physical or emotional problems on relationships; avoidance behavior; more or less outgoing; feelings in a social setting; undressing in public places
Sexual life: satisfaction with sex life; partner's satisfaction; change in frequency of sex; feelings of sexual attractiveness; degree of sensation in breasts; undressing in front of partner
Surgical care: satisfaction with care; satisfaction with information provided; comfort with surgeon; confidence in surgeon; surgical setting; clinic; staff; follow-up care; information about scar healing; massaging
Expectations: fulfillment of expectations; willingness to repeat and/or recommend procedure; satisfaction with overall appearance; regrets; outcome better or worse than expected; process better or worse than expected

The analysis revealed the following six key themes that formed the basis of our conceptual framework of patient satisfaction and quality of life in breast surgery patients:

- Satisfaction with breasts
- Satisfaction with overall outcome
- Psychosocial well-being
- Sexual well-being
- Physical well-being
- Satisfaction with the process of care

Satisfaction with breasts

This theme relates to women's satisfaction with their breasts. Women in all three surgical groups described satisfaction, or lack thereof, with reference to breast size, shape, symmetry, cleavage, scars, positioning, how natural their breasts look and feel, and how their breasts fit in proportion to the rest of the body. A woman who underwent breast augmentation shared:

> I have really nice voluptuous rounded normal-sized perky breasts and I am sooo happy with them. Soo happy.

Comments that expressed some dissatisfaction were sometimes qualified by the recognition that although the outcome wasn't perfect, breast appearance was vastly improved by surgery. A reconstructive patient expressed:

> So shape-wise, I mean, you know, it's the best it can be given what we have to work with, let's put it that way, but it's not where I'd like it to be.

Women also talked about how their breasts look in bras and clothes. Women in all three surgical groups described how surgery made it possible for them to wear lower cut or tighter fitting tops, and that they now had much more choice in terms of the type of bras, lingerie and swimsuits they could wear. As several women, each in a different surgical group, described:

> Some things are much more fun to put on, and the stuff that I used to wear looks way better–I am sure they looked good before, too–but I just fill in a bit more, look a bit more busty in them (Augmentation).

> I can fit into regular-sized clothes now, which is a huge difference (Reduction).

> I mean, they're not real breasts, and they never will be, but I can go out in a T shirt or buy clothes and they look much better (Reconstruction).

For breast augmentation and reconstruction patients, issues related to the appearance of their implants were discussed, such as rippling and how hard or soft the implants felt to the touch. Specific to reduction and reconstruction patients were issues to do with nipple appearance. A reconstructive patient shared:

> I can wear T shirts and because of the nipples, actually, that has been an amazing thing for me, is that I have nipples that show through the T shirt. It just feels normalizing.

Another woman, who underwent breast reduction, stated:

> I have one nipple that is sort of misshapen compared to the other one. They aren't exactly the same.

Satisfaction with overall outcome

This theme relates to an overall sense of satisfaction with the outcome of surgery that women have after going through the process of breast surgery. Women who were satisfied with their surgery overall, expressed how they felt with comments such as:

> If I had to do it again, I would do it again (Augmentation).

> There is not one day that goes by that I am not so pleased that I did it. (Augmentation)

> The bottom line is I really am glad that I did this (Reconstruction).

> It just made me feel like I had my body back again (Reconstruction)

> I would highly recommend it to anybody who is thinking about it (Reduction).

> I am very happy and I don't have any regrets about having the surgery, no matter what. (Reduction)

Psychosocial well-being

This theme relates to the way that women described the effects of breast surgery on their psychosocial well-being. Women in the three groups talked about how, with surgery, they felt better about themselves in many ways. A common theme was to mention feeling less embarrassed, more confident in a social setting and about their body, and more self-assured.

A breast augmentation patient expressed:

> For me it's a confidence thing, to walk into a room and the way my clothes fit now, you know, it's just cause I feel like the rest of my body is proportionate, its how I look in my gym clothes...overall, it has been really, really good...I just feel so much more confident, my self esteem and everything.

A woman who underwent breast reconstruction surgery had the following to say with respect to her outcome:

> I have greater self-esteem having been through all this and again because I could come through it and go through the big surgery and come out whole with two breasts...I think that has helped a great deal.

Thirdly, a breast reduction patient shared:

> I'm not so embarrassed or trying to hide all the time. So in that way it's better.

Women also talked about feeling more attractive, feminine, good about themselves and normal or like other women. Breast surgery was also seen as a way to bring the body in line with what was perceived to be the "norm" for a woman's body. A number of women who underwent breast reduction, for instance, talked about feeling deformed, or not like other women before surgery. However, with surgery, as one woman expressed:

> I feel like a normal person instead of like a freak.

Another breast reduction patient expressed how she felt almost too feminine because of the size of her breasts and how people treated her because of her large breasts. She described feeling:

> ...almost too feminine when I had big breasts, and that's all people really saw me as.

Women who had undergone reconstruction surgery for breast cancer often expressed how reconstruction was a way to get back what was lost and to move on from the cancer experience. As one woman described:

> I think once I had this surgery...it was just closure. It's really like that part of my life didn't happen. It's not denial. I mean I still have to be vigilant and everything its just I got my life back, I really did.

Finally, a breast augmentation summed up her experience as follows:

> My confidence level, my self esteem, my self respect, my self worth, everything...it has affected everything. I am just so much more solid, grounded. I feel like I am a whole woman now.

Sexual well-being

This theme deals with the way that a woman's breast condition and surgery impacts on her sexual life. Negative feelings about ones breasts may interfere with how sexually attractive a woman feels as well as with her sexual functioning and sexual pleasure. With surgery, many women commented that they felt more sexually attractive both when they were clothed and unclothed, more confident sexually, and more satisfied with their sex life. As one breast reduction patient said:

> Yes it's better because when they were larger I didn't feel sexy.

And a breast augmentation patient said the following:

> What I find now is that I am sensual, which I didn't feel before.

Following surgery, some women expressed concern about changes in their nipple sensation and how this affected sexual pleasure. For instance, one woman shared:

> I do really miss my real nipples, because they were really an important part of my sexuality. They are an essential part, and they are something I enjoy.

Physical well-being

This theme mainly relates to issues surrounding chest and upper body symptoms and how these impact on physical function and participation in activities before and after breast surgery. This theme was discussed in much greater detail by breast reduction and reconstruction patients than augmentation patients.

Reconstruction and reduction patients described a range of chest and upper body symptoms such as arm, shoulder, neck, back and breast pain, as well as tenderness, pulling, discomfort. They also discussed ways in which their breast conditions caused activity limitations, such as difficulty lifting or moving their arms and difficulty doing vigorous activities such as running, playing sports, or exercising, as well as doing everyday household chores. A patient who underwent breast reduction stated:

> Putting things into the dishwasher and taking them out has become a totally different experience for me.

Preoperatively, women in the breast reduction group described having painful gouges or grooves in their shoulders from their bra straps, rashes under their breasts, and difficulty sleeping due to breast discomfort. Women in this group were often motivated for surgery due to these physical symptoms, as well as for activity limitations they experienced due to the size of their breasts. A breast reduction patient shared:

> Before, I didn't want to run anywhere. Even across the street if something happened I would not run. It was painful and embarrassing.

For women who had reconstructive surgery, pain and activity limitations were often reported and tended to be related to the type of reconstruction and extent of surgery. For example, a woman who underwent Transverse Rectus Myocutaneous Flap (TRAM) surgery described experiencing abdomen weakness. She expressed:

> There is sort of a bit of a discomfort there, and I don't feel that I have a lot of strength in my abdomen...the way I used to. So I am pretty cautious about what I am doing exercise-wise.

Another breast reconstruction patient described:

> This implant feels as if it is low and I get rib pain.

Satisfaction with the process of care

Patients in our interviews repeatedly reflected on their satisfaction with process of care issues. Satisfaction with the process of care was clearly an important area in patients overall assessment of the surgery and thus formed an important domain in our conceptual framework. This theme was, however, broad and we identified three main subthemes: satisfaction with preoperative information; satisfaction with the care provided by the plastic surgeon; and satisfaction with the office staff and other members of the medical team.

Satisfaction with information was discussed in terms of general issues applicable to all three surgical groups, such as how the surgery was to be done, healing and recovery time, possible complications that might occur, breast appearance, risks, and scarring. Information needs described by women in our sample were surgery-specific (e.g., differences in types and complications associated with implants were relevant to reconstruction and augmentation but not breast reduction patients).

Patients' relationship with their plastic surgeons was an important aspect of process of care. Women talked about the extent to which their surgeon made them feel comfortable, was caring and reassuring, answered all their questions, understood what they wanted, involved them in the decision-making and provided adequate follow-up. The physician-patient relationship was sometimes mentioned as important in terms of giving the patient confidence to go ahead with surgery. As one woman shared:

> My doctor was terrific and I trusted her and I had a lot of confidence in her and it didn't seem like there were an awful lot of things to worry about.

But another woman who underwent a reconstruction felt quite differently:

> I had these fears and I just did not feel comfortable discussing them with her.

How women were treated by the medical and office staff was important in terms of satisfaction with the overall experience of care. Women talked about the medical team and the office staff in terms of whether they were professional, treated them with respect, and was kind and friendly. As one patient described:

> And once I came home, the home care, I don't know what they called it, but the nurses would come round and they were just excellent. They were all lovely people. They were very positive and very encouraging.

Formation of the conceptual framework

Relationships between the six main themes described above, which were developed through our detailed coding process, form a coherent and comprehensible conceptual framework of patient satisfaction and quality of life in breast surgery patients. Our conceptual framework is shown in Figure 1.

Discussion and conclusion

Research that seeks to understand the experiences of any particular patient group needs to employ inductive, qualitative methods. Our goal was to understand issues related to patient satisfaction and quality of life in breast surgery patients and to develop a conceptual framework to better understand the wide reaching impact of breast conditions and the surgical interventions used to treat them.

The patient interviews revealed that breast conditions and breast surgery impact women in six main areas: satisfaction with breasts; satisfaction with overall outcome; psychosocial well-being; sexual well-being; physical well-being; and satisfaction with the process of care. These themes form the basis of a conceptual framework of patient satisfaction and quality of life in women undergoing breast surgery. Patient satisfaction with breast appearance was without doubt the key theme and is a salient factor in determining the success of breast surgery. How-

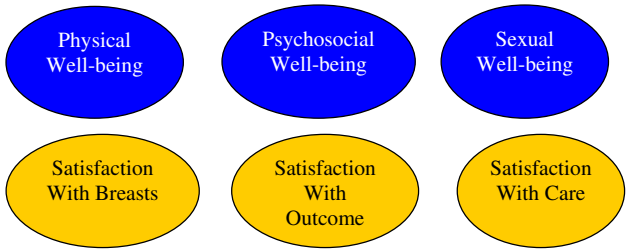

Figure 1
Conceptual model of patient satisfaction and quality of life in breast surgery patients.

ever, other themes were also identified that related to the broadened notion of quality of life, including concepts such as physical, psychological and sexual well-being. Recognition and examination of these themes confirms findings from existing research showing quality of life benefits following different forms of breast surgery [16-19].

While the six identified themes were common to women in all three groups, the specific issues for operative procedures that preserve or improve breast appearance varied in importance by surgical group. For example, while physical well-being was of only limited importance to breast augmentation patients (only a few reported pain and discomfort post-operatively), it was often the main motivation behind breast reduction surgery (patients reported substantial pain and activity limitations pre-operatively), and was often a problem for women following breast reconstruction. Similarly, while women in the three surgical groups all identified the six themes as being important to them, they expressed themselves differently. As an example, in terms of sexual well-being, an augmentation patient may describe 'feeling sexy' while a reconstruction patient may describe 'feeling normal'.

An important theme within our conceptual framework was that of satisfaction with the process of care. Patients discussed at length the extent to which they had received information about the operation, and their thoughts about their plastic surgeon and his/her medical team and office staff. A clearer understanding of aspects of the processes involved in breast surgery would be a useful addition for quality improvement studies. Using such information could help to determine whether, for example, women who are well informed preoperatively about the surgery (e.g., complications, healing and recovery time, expected results) and feel comfortable with their surgeon, may also report greater postoperative satisfaction and perceive better quality of life.

We are proposing that the six themes identified through patient interviews in this study can be used as the initial building blocks of a conceptual framework to help understand pre- and post-surgical satisfaction and quality of life in breast surgery patients. This new conceptual framework establishes the main issues of concern for breast surgery patients. With further development and input we envisage that this new framework can be used to help develop local guidelines for future clinical assessment, management and measurement, establish the validity of the current management strategies, and develop evidence-based guidance for the development of new patient reported outcome measures for future outcomes research.

We have already taken this work forward by using the conceptual framework to develop a new patient-reported outcome measure. The new measure, which we have named the BREAST-Q©, consists of three procedure-specific modules (Augmentation, Reconstruction and Reduction) with each module functioning independently [20]. The items for each module were developed directly from the interview data, and consisting only of items generated by patients who had undergone that procedure. Wherever possible, we maintained the exact wording used by patients for the generation of questionnaire items and ensured that all six themes identified as important to women were captured in each module.

We sought to incorporate patient input at each step in the development of the BREAST-Q©. Following the qualitative interviews, women were invited to be part of a focus group where we presented the conceptual framework and our draft questionnaires for their feedback. We also obtained feedback in later phases of our study using one-on-one cognitive debriefing interviews to obtain feedback on our preliminary questionnaires as well as our item-reduced questionnaires. Patient feedback was vital to refining the Breast-Q©.

Our team combined our qualitative findings with state-of-the art quantitative psychometric methods that included the use of modern psychometrics (i.e., Rasch analysis) to select the best items from the qualitative interviews for our scales. The use of Rasch analysis makes it possible to select a range of items for each scale that differ in terms of item difficulty such that they "map out" the construct that they propose to measure. The combination of extensive detailed qualitative research and modern psychometric methods make it possible to measure constructs, such as patient satisfaction, in a more clinically meaningful and scientifically robust way than has been done in the past in this patient group.

As described above, the new conceptual framework has value beyond the role it has played in the development of the BREAST-Q©. This framework establishes the main issues of concern for breast surgery patients and as such, will be an important resource for healthcare providers and

those involved in patient counseling. It may guide the development of patient education materials and facilitate shared-medical decision-making. As well, by conceptualizing patient-perceptions of breast surgery outcomes, it may inform advocacy efforts and future health-services research.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AK participated in the design of the study, data analysis and interpretation, manuscript writing and final approval of the manuscript. AP conceived and designed the study, participated in collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of the manuscript. AS participated in collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of the manuscript. JK participated in collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of the manuscript. SC participated in the design of the study, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of the manuscript.

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Ambulatory Laparoscopic Cholecystectomy Outcomes

J. M. Sherigar, G. W. Irwin, M. A. Rathore, A. Khan, K. Pillow, M. G. Brown

ABSTRACT

Background: Outpatient laparoscopic cholecystectomy is an established practice in the United States, but it is not well established in the United Kingdom, and evidence of experience is scarce. The aim of this study was to evaluate the effect of ambulatory laparoscopic cholecystectomy on postoperative morbidity and possible cost savings. We tried to elucidate possible predictors of unplanned admission and readmission rates after discharge.

Methods: This study was conducted in 2 phases. The first phase involved 112 patients and was a retrospective analysis from January 2002 to July 2003 (19 months). The second was a prospective study involving 86 patients from August 2003 to April 2005 (21 months). Consultants, associate specialists, or higher surgical trainees performed the surgeries in a dedicated outpatient procedure unit. The study ended 6 weeks after the operation.

Results: Hospital mortality was zero. Overall, 29 (15%) patients required unplanned admissions. Three (1.5%) patients required conversion to open cholecystectomy. Other causes included simple observations (7), wound pain (6), nausea and vomiting (6), suction drain (2), urinary retention (2), operation in the afternoon (2), and shoulder pain (1). Of the patients discharged, 7 (3.5%) required readmission after the initial discharge. Five of the 7 readmissions were wound related and treated conservatively. Two patients underwent laparotomy.

Conclusion: Ambulatory laparoscopic cholecystectomy appears to be safe, feasible, and cost-effective with a low conversion rate. The unplanned admission rate can be reduced by better training, criteria for discharge, and improvement in anesthesia. This will have implications for surgical training and healthcare resources.

Key Words: Ambulatory laparoscopic cholecystectomy, Training, Morbidity, Outcome.

INTRODUCTION

Ambulatory care settings worldwide have dramatically shifted the inpatient surgical services to outpatient settings. Laparoscopic cholecystectomy has been the procedure of choice for symptomatic cholelithiasis around the world. Postoperative recovery time and the length of hospitalization have decreased significantly since routine cholecystectomy changed from an open to a laparoscopic procedure.[1] Early positive results of ambulatory laparoscopic cholecystectomy, by Reddicke and Olsen in 1990,[1] fueled its further growth, and it is now well accepted as a safe, cost-effective procedure for symptomatic gallstone disease. Various studies have documented the safety, feasibility, cost-effectiveness, and patient acceptability of this operation as an out patient procedure.[1–9] Despite these results, it has only been practiced sporadically at centers in the UK and is not well established. Laparoscopic cholecystectomy has been routinely performed at this hospital, and patients have traditionally been admitted and discharged after an overnight stay. With the creation of a dedicated outpatient unit, ambulatory laparoscopic cholecystectomy (ALC) has been practiced since January 2002. The objective of this study was to evaluate postoperative morbidity and unplanned admissions, as well as readmissions following ambulatory laparoscopic cholecystectomy. We also tried to evaluate the cost savings of this procedure.

METHODS

From January 2002 to April 2005 (40 months), 253 patients underwent laparoscopic cholecystectomy in the Department of General Surgery. Fifty-five patients had their gallbladder removed as an inpatient, and 13 patients under-

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went bile duct exploration. ALC was offered to 198 of 253 well-motivated patients (79% day cases). The study was split into 2 phases **(Figure 1)**. The first phase was a retrospective analysis of 112 patients from January 2002 to July 2003 (19 months). All medical records were reviewed to document patient characteristics, perioperative details, unplanned admissions, and readmission rates. The second phase was a prospective study involving 86 patients from August 2003 to April 2005 (21 months). Data were collected prospectively for these patients.

All patients with symptomatic gallstone disease, with no evidence of CBD calculi and who met the selection criteria were offered ALC. Patients who had a common bile duct stone were initially offered an endoscopic retrograde cholangiopancreatography and booked for ambulatory laparoscopic cholecystectomy if considered suitable. Systematic preoperative liver function tests and hepatic ultrasonography were performed. All patients were assessed at a preoperative assessment clinic before the operation. A fully trained surgeon was responsible for confirming the indications and eligibility for outpatient surgery after discussion with the patient. Only patients belonging to ASA grade 1 & 2 were included in the initial study, and a few dedicated patients with ASA grade 3 (12 in all) were considered at a later stage of the study. Another criterion for inclusion was that a responsible adult would be present with the patient for a 24-hour period postoperatively. Patients who presented as an emergency with acute cholecystitis and underwent cholecystectomy on their initial admission were excluded from the study. Patients at significant risk of requiring conversion to an open operation, such as those with previous upper abdominal surgery, were also excluded.

All patients were scheduled for outpatient laparoscopic cholecystectomy in this hospital's purpose-built outpatient unit. Patients were admitted to the hospital on the morning of the operation, and every effort was made to accommodate them that morning, with the intention of discharging them in the evening. Consultants, associate specialists, and specialist registrars under supervision performed all surgeries. Preoperative cholangiography was not required in any of the patients. Surgery was performed with the patient under general anaesthesia and intubated.

Standard 4-port video-laparoscopic cholecystectomy was performed. Hasson's method of access was used for CO_2 insufflation. All patients received preoperatively a single dose of broad-spectrum antibiotic and infiltration of local anesthetic to the wound. The anesthetic technique used for these procedures depended on the anesthetist responsible for each surgical session. Induction was with propofol, and intubation was facilitated with rocuronium. Maintenance included N_2O/O_2 and an inhalational agent. Opiate and anti-emetic usage varied. All patients received either 8mg of ondansetron or 1mg of granisetron. Cyclimorphine was the most common opiate used, although pethidine was utilized in a significant number of cases. All patients received either diclofenac or parecoxib unless there was a contraindication to nonsteroidal anti-inflammatory drug use. At the conclusion of surgery, muscle relaxation was reversed using a neostigmine and glycopyrrolate combination. In recovery, IV analgesic continued with the intraoperative opiate as required. The patients were discharged before 8 p.m., with a responsible adult who could look after them for the first 24 hours, along with leaflets explaining the relevant postoperative advice and encouraging the patients to visit their own

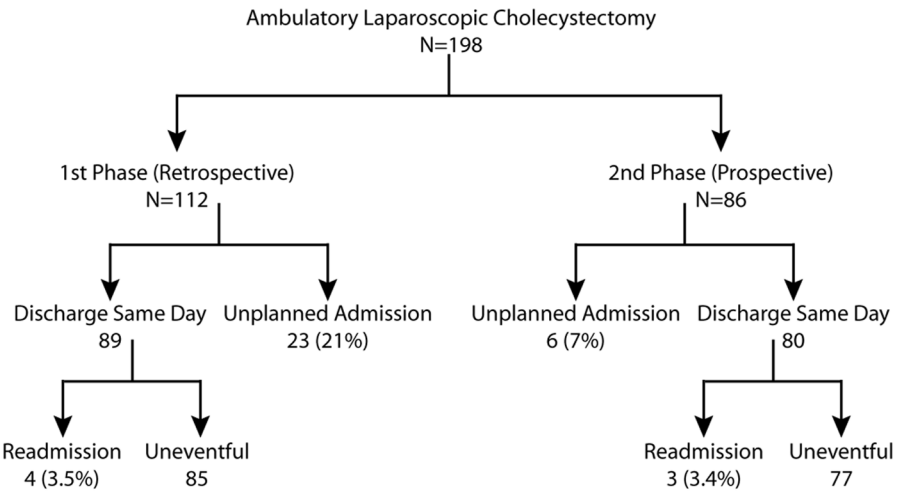

Figure 1. Flow chart of patients (Phases 1 and 2).

physician if they felt it were necessary. All patients were given a supply of a combination of codeine and paracetamol plus a nonsteroidal antiinflammatory drug for 48 hours. Patients who did not meet the discharge criteria, and those whose operation was converted to an open procedure, were admitted. The study ended 6 weeks after the surgery, with follow-up at the routine surgical clinic.

RESULTS

Of 253 patients, 198 (79% day cases) underwent ambulatory laparoscopic cholecystectomy during the 40-month study period. All of the 112 patients in the first phase of the study were either ASA grade I or II. There were 90 women (80%) and 22 men (20%) with a mean age of 45 years (range, 21 to 78). Thirty-six (32%) patients were over 55 years of age. Surgery was successfully performed in all the patients without any open conversions. However, 23 patients required unplanned admission for different reasons **(Table 1)**. Six patients insisted on an overnight stay and were discharged the next day. Persistent nausea and vomiting was the cause of admission in 5 patients. Other causes included wound pain,[5] urinary retention,[2] operation in the afternoon,[2] severe shoulder pain,[1] and 2 patients needed admission after the placement of a suction drain. Twelve (50%) of the 23 patients admitted were more than 55 years of age.

In total, 4 (3.4%) patients were readmitted after discharge. Three of these, with wound-related complaints, either hematoma, minor wound infection or wound pain, were treated conservatively. One patient, admitted 10 days after discharge with a massive lower GI bleed, was found at laparotomy, to have a cystic artery pseudoaneurysm eroding into the transverse colon. He recovered well after undergoing surgery.

Of the 86 patients in the second phase of the study, 72 (84%) were women and 14 (16%) were men 16 to 78 years of age (median, 48). Forty-three were >55 years of age. Twelve well-motivated patients with ASA class III were also considered in this phase of the study in addition to classes II and I. In 3 patients, the laparoscopic procedure was converted to open cholecystectomy due to difficult dissection, not being able to identify the proper anatomy, or abnormal anatomy. An unexpected admission was required for 6 (7%) patients, including 3 who had undergone conversion to an open procedure **(Table 2)**. One patient required admission for analgesia and another for continuous nausea. One of the patients had a history of sleep apnea due to obesity; it was thought it would be prudent to observe him as an inpatient.

Of the 3 patients readmitted after discharge, 2 were treated conservatively for wound-related problems. One patient developed a biliary leak from CBD injury and was admitted 7 days after discharge with biliary peritonitis. Laparotomy revealed a lateral laceration to the common bile duct, which was repaired with t-tube drainage.

DISCUSSION

Laparoscopic cholecystectomy has undergone a revolution since the advent of its being performed as an outpatient procedure. With continuing pressure on health service resources, there has also been a drive to reduce in-hospital stays and to increase the efficiency of procedures. The Audit Commission report[10] of 1990 encouraged

Table 1.
Unplanned Admission and Readmissions
(January 2002–July 2003)

	Number
Reason for Admission (median=1 d; N=23)	
Simple observation	6
Wound Pain	5
Nausea/Vomiting	5
Suction Drain	2
Urinary Retention	2
Operation in the afternoon	2
Severe shoulder pain	1
Reason for Readmission (N=4)	
Wound related	3
Leaking cystic artery pseudo-aneurysm	1

Table 2.
Unplanned Admission and Readmissions
(August 2003–April 2005)

	Number
Reason for Admission (median=1 d; N=6)	
Open conversion	3
Simple observation (obesity with sleep apnea)	1
Wound Pain	1
Nausea/Vomiting	1
Reason for Readmission (N=3)	
Wound related	2
Bile leak	1

the expansion of outpatient procedures, and laparoscopic cholecystectomy fulfills this niche and has been performed in several centers with success. With an increase in outpatient procedures, it is necessary to evaluate the conditions in which admission for overnight stays could be kept to a minimum, although realizing that the "holy grail" of no admissions is, realistically, unobtainable.

It is important to recognize the difference between studies that have evaluated outpatient cases, which relates to discharge on the same day of the procedure without requiring an inpatient bed, and other studies that include patients admitted overnight but discharged within 24 hours. In our study, we analyzed only those who were discharged on the same day of admission (before 8 pm). Whilst discharge the next day (within 24 hours) is admirable, and suggests good early mobilization, it still fails to satisfy the Audit Office criteria of true outpatient procedures.[10]

Unplanned admission after outpatient surgery is an indicator of quality assurance.[11] All discharged patients in our study were reviewed at 6 weeks. The unplanned admission rate, whilst initially high at 21%, fell to a much more respectable 7% (overall 15%) in comparison with that of other centers, which varied from 3% to 39%.[1,12–17] The causes of postoperative morbidity were similar in both phases **(Table 3)** except that 3 patients (1.5%) had to have their laparoscopic procedure converted to an open procedure in the second phase, and this did not occur in the first phase. Conversion rate is comparable to reported rates of 1.8% to 6.7%.[12–15]

Table 3.
Results From Phases 1 and 2 January 2002–April 2005 (N-198)

	Number
Reason for Admission (Median=1 d; range 1–3 d; N=29 [15%])	
Open conversion	3
Simple observation	7
Wound Pain	6
Nausea/Vomiting	6
Suction Drain	2
Operation in the afternoon	2
Urinary retention	2
Severe shoulder pain	1
Reason for Readmission (N=7 [3.5%])	
Wound related	5
Leaking cystic artery pseudo aneurysm	1
Bile leak	1

A drop in admission, from 21% to 7%, in the second phase is significant and needs to be analyzed further. Six patients were admitted for simple observation in the first phase. This was purely at the discretion of the patient; either they felt they were not fit enough to go home or there was low confidence amongst the nursing staff. This was evident in the second phase of the study when only one patient was admitted for observation as he had sleep apnea syndrome. Patients admitted for pain, nausea, or vomiting were also significantly reduced. Whilst there was not a universal anesthetic protocol, each patient received a preoperative opiate, NSAID, and antiemetic. We could not correlate the significant number of patients admitted with pain, nausea, and vomiting with any of the anesthetics or antiemetics used. Patients who were over the age of 55 years did not have a higher incidence of admission than those of a younger age group, contrary to the perception from the first phase of the study. Only 2 unplanned admission patients were aged above 55 years in the second phase, and both of them were ASA grade III. Previous reports emphasized the duration of procedure as one of the predictors of unplanned admission. In our study, the total operative time ranged from 16 minutes to 89 minutes (median, 35).

The readmission rate of 3.5% compares well with a range of 0% to 8% reported by other authors.[12–17] Admission would not have greatly changed the course of these patients, nor would it have prevented these complications from happening. However, biliary leak (7 days postop) would have been picked up earlier if the patient had been admitted. This patient and the patient with a pseudoaneurysm of the cystic artery (10 days postop) were readmitted a week after initial discharge. Even if they had been operated on as an inpatient, they could have been discharged before the complication became evident. A patient with massive gastrointestinal bleeding deteriorated fairly rapidly and collapsed after admission. There was no clinical evidence of an aortic aneurysm, the possibility of angio-enteric fistula having been considered. Esophagogastroscopy performed with the patient under anesthesia did not reveal any active upper gastrointestinal bleed. Emergency laparotomy was performed. At operation, the large clotted blood was noted at the gallbladder fossa, and some blood-stained fluid was present in the abdomen. The proximal transverse colon was adherent to a large mass of clotted blood in the gallbladder fossa. Following evacuation of the blood clot, there was brisk bleeding from the cystic artery stump proximal to the clips. The end

of the vessel was very necrotic. The vessel was undersewn. A hole was identified in the antimesenteric border of the colon where it had been adherent to the organized blood clot. There was no true pseudocapsule around the blood clot to indicate clearly the presence of an organized pseudoaneurysm, and the exact cause of the fistulation into the colon was unclear. Electrosurgical injury to the cystic artery stump was possible during surgery as it was a difficult laparoscopic cholecystectomy. It appeared that the clotted blood mass had eroded into the colon and was responsible for the gastrointestinal hemorrhage. The small defect was oversewn and recovery was uneventful. It is a known fact that most of the early complications after laparoscopic cholecystectomy occur within a week after surgery. We felt that early review, either by nurse-lead telephonic review or review in a surgical clinic, would pick up the complications earlier.

A further change that occurred between these 2 periods was the introduction of a checklist for use by the nursing staff. It was observed that, in the first period, the nursing staff were being asked to assess patients' fitness for discharge, having received no formal training, and fulfilling a role which, in this hospital, had been reserved for medically qualified staff. During the change, a major investment was made in educating nurses about their new role, and a checklist was drawn up to facilitate the nurses in this decision-making. Patients were discharged from the outpatient unit if they were tolerating oral fluids or a light diet, or both, with minimal nausea or vomiting, had passed urine, had adequate pain control and were ambulatory. A discharge letter was faxed to a referring general practitioner with operative details and recommended postoperative care. Consequently, this led to a marked reduction in the number of admissions for nausea and simple observations. Other studies have highlighted the effectiveness of a preoperative visit,[5] and our study again shows that, with stringent preoperative assessment, low numbers of unplanned admissions can be obtained.

The empowerment of the nurses yielded further rewards as the nurses decided to set up a team to allow follow-up of the patients. Up to August 2005, all the patients discharged were cared for by their own physician until their review in the routine general surgical clinic, 6 weeks after the operation. In September 2005, Telephone Nurse Interview Care Service (TONICS) was set up to review each case on Day 1 and then at 6 weeks following discharge. This proved to be an unqualified success, with only one person requesting a formal outpatient appointment, thereby freeing more of these appointments for new referrals or necessary reviews. It suggests that these patients do not require aggressive postoperative nursing care, after discharge, and that the availability of general practice or accident and emergency service may suffice instead of the costlier district nurse visit. Studies have shown that this is the case as long as a coherent and coordinated system of care is in place.[9] Indeed, it may even be that patients prefer a telephone call to a home visit.[18]

Training has become an important issue as the government strives to ensure that the National Health Service fulfils its service commitments, often to the detriment of training the next generation of medical staff. It is vital that trainees are exposed to all aspects of patient care so as to be fully aware of ambulatory surgery and its place in the surgeon's armory. It would seem wise, though, to limit involvement to more experienced trainees so as to have minimal impact on the service commitment and the admission rate. It is also possible that the collection of certain cases in one fixed service may, in fact, be beneficial to the trainee, as it would provide a definite area in which the trainee could focus and develop the practice, especially in the climate of the New Deal and European Working Time Directive.[3]

Much has been debated about the financial impetus in the move to further outpatient procedures. A cost analysis was undertaken in our trust, which showed that, while the actual operative costs were similar, the real saving came because it was cheaper to carry out the outpatient procedures in their totality compared with elective admissions, and both these mechanisms of laparoscopic cholecystectomy were markedly cheaper than emergency admission. The average cost of the elective inpatient laparoscopic cholecystectomy was £1793 compared with £1174 for outpatient cases (Finance Dept., Causeway Hospital-Year 2002/2003). This would be in keeping with other studies that showed that there was a potential reduction in costs of 11% to 25% per patient.[3]

CONCLUSION

Outpatient laparoscopic cholecystectomy is safe, feasible, and desirable in the majority of patients, with few changes to current practice, and has become established practice at our institution. For the admissions to be kept to a minimum, the procedures should be performed by experienced staff, patients should be given pre-emptive antiemetics, and analgesics, and experienced staff should be given the task of evaluating the discharge criteria. If this were established nationally, it would impact not only patient waiting times but also would result in significant cost savings.

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TOPIC HIGHLIGHT

Dr. Marco Scarpa, PhD, *Series Editor*

Health-related quality of life outcomes after cholecystectomy

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Abstract

Gallbladder diseases are very common in developed countries. Complicated gallstone disease represents the most frequent of biliary disorders for which surgery is regularly advocated. As regards, cholecystectomy represents a common abdominal surgical intervention; it can be performed as either an elective intervention or emergency surgery, in the case of gangrene, perforation, peritonitis or sepsis. Nowadays, the laparoscopic approach is preferred over open laparotomy. Globally, numerous cholecystectomies are performed daily; however, little evidence exists regarding assessment of post-surgical quality of life (QOL) following these interventions. To assess post-cholecystectomy QOL, in fact, documentation of high quality care has been subject to extended discussions, and the use of patient-reported outcome satisfaction for quality improvement has been advocated for several years. However, there has been little research published regarding QOL outcomes following cholecystectomy; in addition, much of the current literature lacks systematic data on patient-centered outcomes. Then, although several tools have been used to measure QOL after cholecystectomy, difficulty remains in selecting meaningful parameters in order to obtain reproducible data to reflect postoperative QOL. The aim of this study was to review the impact of surgery for gallbladder diseases on QOL. This review includes Medline searches of current literature on QOL following cholecystectomy. Most studies demonstrated that symptomatic patients profited more from surgery than patients receiving an elective intervention. Thus, the gain in QOL depends on the general conditions before surgery, and patients without symptoms profit less or may even have a reduction in QOL.

Key words: Gallbladder disease; Gallstones; Quality of life; Laparoscopy

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INTRODUCTION

Gallbladder diseases are very common in developed countries. They comprise a large spectrum of disorders caused by alterations in bile composition and biliary function, placing a substantial burden on inpatient and outpatient resources. Clinical manifestation of gall-

stone disease varies from attacks of intense biliary colic, prompting surgical intervention, to an absence of symptoms. Biliary colic is usually secondary to temporary obstruction of the cystic duct by a gallstone. When obstruction holds over, the gallbladder becomes inflamed and the patient may develop cholecystitis or other, potentially serious complications, such as cholangitis, gangrene, perforation, peritonitis, sepsis or pancreatitis. Complicated gallstone disease (e.g., symptomatic cholelithiasis) represents the most frequent of biliary disorders for which surgery is regularly advocated. In fact, patients with cholelithiasis account for about 10% to 15% of the total adult western population[1-4]; among them around 30% have surgery, and only 2% develop symptoms[4,5]. Today, cholecystectomy is a standard practice for cholelithiasis, and surgery for complicated gallstone diseases has a significant impact on quality of life (QOL) in developed countries[4]. QOL assessments are increasingly being recognized as an integral factor in surgical decision-making. However, considering the enormous number of cholecystectomies performed daily worldwide, surprisingly little data has been collected about QOL after biliary surgery. Laparoscopic cholecystectomy (LC) has become a very frequent surgical procedure, with over 500 000 operations annually in Western countries[5]. The laparoscopic technique, introduced in the 1990s, resulted in a significant reduction in the number of open cholecystectomies. As a consequence of this movement towards minimally invasive procedures, over the past 15 years the number of cholecystectomies increased, which may reflect a change in the threshold to perform surgery. This shift has also significantly impacted postoperative QOL. Today, estimates are that 86% of cholecystectomies are performed laparoscopically. This number continues to increase, especially in the treatment of acute cholecystitis and biliary colic; therefore, in recent years, the accumulating surgical experience and advances in technology have extended the indications for LC to include patients with complicated gallbladder disease[6,7]. On this basis, there is suggestive evidence that immediate postoperative health-related QOL (HRQOL) may be better after laparoscopic procedures. That being said, the introduction of LC has also increased the incidence of injuries to the biliary tree, along with an increasing number of serious vascular lesions[8-10]. In fact, 15%-20% of patients require conversion to open cholecystectomy for the safe completion of the procedure, countering the potential benefit of the laparoscopic approach[11].

To assess QOL, documentation of high quality care in cholecystectomy has been subject to extended discussions, and the use of patient-reported outcome satisfaction for quality improvement has been advocated for several years[12]. It would be ideal to consider the entire spectrum of gallbladder diseases that indicate surgery. Among them, for example, acalculous cholecystitis represents a controversial clinical indication for surgery, yet it accounts for 5%-20% of all cholecystectomies[13]. Furthermore, debate continues regarding the decision for elective surgery in patients following an acute episode of gallstone disease. Although several tools have been used to measure QOL after cholecystectomy, difficulty remains in selecting meaningful parameters in order to obtain reproducible data to reflect postoperative QOL. Classically, evaluations of surgical procedure outcomes have focused on perioperative complications, morbidity, recurrence rate, and long-term survival. However, much of the current literature lacks systematic data on patient-centered outcomes. Endpoints such as symptom resolution or duration of convalescence represent QOL measures that are at least as important as the classical outcomes. There has been little research done regarding QOL outcomes following cholecystectomy. Furthermore, laparoscopic surgery is usually perceived by patients as a routine procedure. Thus, the impact of LC on QOL, as well as the identification of predictors of subjective patients outcomes, remains undetermined in these patients[14].

Usually, the principal criterion guiding patients' acceptance of a treatment modality is their subjective condition prior to surgery. Additionally, those subjective reports become important criteria in a surgeon's decision-making process[15]. Thus, the aim of this review is to evaluate and summarize the published data on QOL after cholecystectomy in adults. A text word literature search was performed using the Medline databases. Although this was not a systematic review, the search terms used were as follows: gallstones, cholecystitis, surgery, gallbladder disease, and quality of life. The reference lists of identified articles were searched for further relevant publications. The databases were consulted from January 1993 to July 2010. The authors independently selected the studies, particularly those comparing different surgical approaches. Whenever there was discordance regarding study inclusion the authors negotiated an agreement.

GLOBAL QOL MEASURES FOR CHOLECYSTECTOMY: A LACK OF STANDARDIZED AND UNIVERSALLY VALIDATED INSTRUMENTS

HRQOL measures have been shown to be useful in predicting health care expenditure; different QOL indices exist and have been validated to determine the general subjective perceptions and expectations of individuals; in surgery in general, and in particular in the case of cholecystectomy, there is no clear, validated and standardized instrument for assessing QOL postoperatively. The development of well-validated and sensitive non-disease-specific questionnaires is useful for comparing different surgical approaches and techniques. Although specific, HRQOL instruments have been proposed for cholelithiasis and cholecystectomy, they have appeared

with only limited reproducibility, restricted psychometric aspects and with linguistic gaps when translated into different languages[16-18].

The most frequently used tool to assess QOL is the short form (SF)-36 questionnaire and the Gastrointestinal Quality-of-Life Index (GIQLI), each instrument having its own advantages and limitations. The generic SF-36 is a widely used instrument that allows comparison between different studies. However, it has a low discriminative ability and low specificity for identifying determinant changes related to a specific clinical factor. The GIQLI is an established tool for assessing QOL outcomes for patients with various gastrointestinal symptoms including domains of general health, but it is not specific for gallbladder disease.

Some studies used both SF-36 and GIQLI, combining a questionnaire for general well-being and another for more specific postoperative QOL. Quintana *et al*[19] used, for example, the SF-36 to validate the explicit appropriateness criteria in subjects after cholecystectomy. Their results indicated similar improvements in SF-36 QOL measures compared with GIQLI, indicating that both tools were adequate QOL measures and thus confirmed their validity. Recently Fledman *et al*[20] proposed a physical activity questionnaire (Community Health Activities Model Program for Seniors) as an indicator of postoperative recovery. Their aim was to specifically correlate physical activity caloric expenditure as an estimation of postoperative recovery after LC in older patients; evidence has been provided for the validity of this questionnaire as a measure of surgical recovery.

However, the most appropriate measures for identifying relevant changes in QOL after biliary surgery remain to be determined.

An important proposed concept of a questionnaire' s appropriateness is the accuracy of a measure over time in the same patient, assessing prospective changes in the patient's health status. In fact, a highly responsive QOL instrument has been considered able to detect significant treatment effects in a small sample size: an outstanding proposed tool is the "minimal clinically important difference" (MCID) that potentially can examine all significant differences at the individual patient level[21,22]. The MCID is one of the most effective and widely used methods of HRQOL assessment, and can be used to provide an indication of the minimal change that is of clinical relevance. An interesting work by Shi *et al*[23] aimed to estimate MCIDs for the GIQLI score of patients after cholecystectomy; they showed that this instrument can play a role in interpretation of scores and useful application in clinical practice. Thereafter, the same group clinically compared the responsiveness derived by the SF-36 and the GIQLI before and after cholecystectomy; correlation analyses revealed significant correlation between the SF-36 and GIQLI in the preoperative and 3-mo postoperative period[24].

In conclusion, there is an overall propensity to use both generic instruments, SF-36 and GIQLI, to assess the QOL after cholecystectomy; however in the case of limited time and resources, the GIQLI index may be used alone since it incorporates all domains of a QOL. The main issue is the choice of disease-specific outcome measures, adjusted for potential variables, that may act as confounders to identify the effective relevant changes after cholecystectomy.

IMPACT ON QOL OF LAPAROSCOPIC *VS* OPEN CHOLECYSTECTOMY

The literature offers positive and encouraging results in several reports comparing laparoscopic *vs* open surgery in the clinical setting. The development of the laparoscopic technique has drastically changed the protocols for treatment of gallstone disease and cholecystitis, and has been accompanied by evident clinical benefit for patients. Over the years since its introduction, reduced morbidity and mortality rates have confirmed LC as a safe and standard procedure in the treatment of some gallbladder diseases[25]. These results reinforce the feasibility of laparoscopy as a treatment modality for the biliary tract itself, and have provided reliable scientific material in support of an expanded role for laparoscopy in hepatobiliary surgery. Collected data seems to confirm a positive post-laparoscopic subjective satisfaction and perceived QOL[20,26]. Indeed, Harju *et al*[27] compared minilaparotomy with LC, demonstrating that the minilaparotomy procedure represents a good alternative to the LC procedure, when QOL is measured.

Although the rate of increase of QOL following LC is greater than that after open surgery, long-term overall QOL has proven to be only slightly better or show no difference when compared with open surgery. Therefore, the only significant long-term advantage of laparoscopic surgery, as compared with open surgery, seems to be the higher satisfaction rate regarding the cosmesis of the surgical scar. There remains no clear explanation regarding the similarity of this comparative data between the two surgical techniques; feasible hypotheses are that indications for LC might be more easily proposed than those for open surgery. This could impact patient selection as well as patient expectation regarding laparoscopy[28]. Furthermore, patients selected for open surgery more frequently have a lower perception of QOL and more co-morbidities than matched laparoscopic patients prior to surgical intervention. These factors likely influenced outcomes and potentially introduced bias in the above-mentioned studies.

ADULT PATIENTS WITH CHOLELITHIASIS: IMPACT OF QOL FOLLOWING LC

The use of objective outcome measures after surgical procedures, even though non-disease specific, is helpful

for laparoscopic surgery such as cholecystectomy. Quintana *et al*[29] aimed to determine clinical variables that predicted changes in HRQOL using both instruments, GIQLI and SF-36. Patients were grouped according to diagnosis (complicated symptomatic cholelithiasis, including acute cholecystitis, choledocholithiasis, pancreatitis or cholangitis; uncomplicated symptomatic cholelithiasis; asymptomatic cholelithiasis) and surgical risk categories; patients were asked to complete a questionnaire before and 3 mo after cholecystectomy. The study concluded that cholecystectomy is the suitable treatment especially for patients with symptomatic cholelithiasis and low surgical risk since they experienced the highest QOL gains; whereas patients with asymptomatic cholelithiasis or high surgical risk experienced least improvement. Conversely, Mentes *et al*[30] observed significant GIQLI score improvements in both symptomatic and asymptomatic gallstone groups. However, the gallstone-related QOL improvements were particularly marked in symptomatic patients, indicating that gallstone patients with lower baseline GIQLI scores are more likely to benefit from LC. Thus, LC seems to be the appropriate intervention for patients with symptomatic gallstone and low surgical risk.

Alternatively, Vetrhus *et al*[31] evaluated gallstone-related acute cholecystitis *vs* symptomatic but non-complicated disease. They used QOL and pain surveys to compare chronic gallbladder disease outcomes between conservative observational treatment and cholecystectomy. The patients in this study answered standardized questions at baseline (before surgery), and at 6, 12 and 60 mo post-cholecystectomy. The observation group (no intervention) had a higher rate (36% *vs* 19%) of gallstone-related events, but the difference was not significant. When patients were grouped according to randomization or actual operative outcome (+/- cholecystectomy), the authors did not find any significant differences in pain or QOL measurements. The authors concluded that conservative treatment in acute cholecystitis did not significantly increase the risk of subsequent gallstone events, and importantly this did not influence the QOL outcome and pain measurements. Thus, conservative (non-operative) treatment and observation of acute cholecystitis would be an acceptable option and should at least be considered in high risk patients[27].

Another longitudinal QOL study from Taiwan provided data using the SF-36 questionnaire and GIQLI scores[32]. The preoperative SF-36 scores from gallstone patients were significantly inferior to an age- and sex-matched control population; LC effectively reduced gastrointestinal symptoms, confirmed by the improvement in GIQLI total, physical well-being, mental well-being, gastrointestinal digestion, and defecation subscale scores. Yet, certain authors' evidence indicates that some patients did not regain full GIQLI scores after surgery, deducing that some residual gastrointestinal discomfort remained. Indeed, some investigators described a persistent decrement in many of the SF-36 health dimensions at 12 mo following surgery; thus they identified different markers to evaluate QOL outcomes after surgery; they found that QOL improvements can be partially predicted by the preoperative direct bilirubin level and by the placement of a drainage tube intra-operatively. This aspect confirms data indicating that patients with worse preoperative health conditions may have greater gains in QOL improvement following LC surgery; moreover, QOL measures should consider potential variables that may act as confounding events. In fact, although there is no doubt that cholelithiasis may decrease the QOL during its acute symptomatic phase, the postoperative course after cholecystectomy, independent of the operative technique, might be potentially altered by other factors (bloating, slow digestion, *etc*.) that were not sufficiently controlled or distinguished by researchers, and could determine cholecystectomy as an overused procedure.

Finan *et al*[33] designed a study to determine gastrointestinal symptoms and QOL after cholecystectomy for better measurement of the change in QOL after surgery. In this study, SF-36 was employed along with a symptom survey that was designed to include both classic symptoms of biliary disease as well as other benign gastrointestinal (GI) diseases. Their results showed that LC significantly improved GI symptoms as well as QOL in subjects with symptomatic gallstone disease; the quantitative evaluation of GI symptoms allowed for analysis of symptom improvement by including patient perceived severity and distress. These results permitted the development of clear indications for operative management, supporting the effectiveness of cholecystectomy for elective biliary disease. In conclusion, in adult patients operated for cholelithiasis, QOL improved most in patients with symptomatic disease and average surgical risk; particular attention must be paid in regard to appropriate selection of patients, especially in terms of discrimination between biliary disease-related symptoms and other GI disorders.

IMPACT ON QOL OF LC FOR ACALCULOUS CHOLECYSTITIS

One of the most controversial and frequent dilemmas for surgeons in clinical practice is recurrent acalculous biliary pain. Surgical treatment of this disease represents a controversial issue, especially considering the similarities between its clinical presentation and that of other GI conditions. Therefore, clinical resolution cannot be guaranteed with surgical interventions and there is significant risk for decreased QOL following this procedure. Planells Roig *et al*[13] evaluated the QOL in patients with chronic acalculous cholecystitis in comparison to a control group of patients who underwent cholecystectomy for chronic calculous cholecystitis. They concluded that the prevalence of associated gastrointestinal symptoms

was similar for both groups, and QOL was similarly affected by both chronic diseases. The limitation of this work was primarily a disparity between the numbers of subjects (34 patients with chronic acalculous cholecystitis *vs* 297 with chronic calculous cholecystitis); moreover, the study population was a highly selected, though heterogeneous group of patients. A comprehensive and reproducible preoperative investigation for proper diagnosis of biliary disease has constituted an essential prerequisite for the appropriate selection of patients for surgery, and the appropriate exclusion for other GI disorders. Thus, the frustration due to the lack of understanding this disease consequently implies an impact in terms of post-surgical QOL for these patients. An accurate clinical selection seems to remain the most important criterion for surgical and healthcare expenditures in primary hepatobiliary centers.

CHANGES IN QOL FOLLOWING IATROGENIC INJURIES AFTER CHOLECYSTECTOMY

Unfortunately, with the introduction of LC, an increase in potentially dangerous injuries to the biliary tree has been observed, along with an increasing number of serious vascular lesions. Nowadays iatrogenic bile duct-related injuries (BDI) occur in less than 0.3% of all cholecystectomy procedures[34]. BDI are not always identified immediately during the surgical procedure and sometimes appear only in the postoperative course, mostly between days 1 and 5[35]. The clinical manifestations start with early biliary obstruction, biliary abdominal collection or biliary peritonitis, whereas late presentations include obstructive jaundice and ascending cholangitis. On this basis the optimal management of complications often advocates interventional procedures such as percutaneous drain placement or, sometimes, second-look surgery. The literature includes numerous studies confirming satisfactory technical and clinical approaches, demonstrating acceptable clinical outcomes, even in tertiary hepatobiliary centers. However, data is lacking regarding QOL. Only poor documentation of high quality care after bile-duct injuries exists. Results vary significantly between studies, and most recorded true BDI rather than simple cystic duct leaks.

Hogan *et al*[36] has recently published an interesting study, which compared an iatrogenic BDI study group with an age- and sex-matched control group, which underwent uncomplicated cholecystectomy. The SF-36 form was administered to the patients at a median postoperative time of 12 years (range, 2 mo to 20 years). The authors finally concluded that QOL of the surviving patients following BDI seems to be favorable to that after uncomplicated LC. Other studies showed different results; in particular, Sarmiento *et al*[37] and Melton *et al*[40] showed favorable comparisons between BDI and a control group whereas Boerma *et al*[39] and Moore *et al*[38] found that the BDI group had lower QOL scores. However, Boerma's work has been criticized, although they had the largest series[37,39]: for example, patient enrollment included those with cystic duct as well as peripheral hepatic injuries (e.g., leakage, 30%), which technically do not represent BDI. Furthermore, different QOL instruments were used for measuring health-related impact, invalidating any potential comparison between groups. Sarmiento *et al*[37] assessed QOL with the SF-36 questionnaire with a minimum follow-up of 5 years; the QOL after surgical biliary reconstruction compared favorably with that of patients undergoing uneventful LC. Melton *et al*[40] assessed QOL of patients after surgical reconstruction of major bile duct injury from LC with a median follow-up of 59 mo. Although using different survey instruments, the conclusions of the studies are quite similar, and all found that major BDI should be managed surgically, which constitutes a definitive therapy (although more invasive), and is not punctuated by repetitive interventions; in fact, patients with BDI managed endoscopically often require repeat intervention resulting in a worse QOL. In any case, an equivalence of QOL in BDI and uncomplicated LC is quite surprising and points to a possible bias. Patients with the most severe BDI may die, thus QOL cannot be assessed. Moreover, the numbers of patients included were small and in general, the instruments employed were nonspecific.

CONCLUSION

Many studies in the literature lack systematic data regarding QOL outcomes after cholecystectomy. Reported works have conflicting data and sometimes several limitations (i.e., small sample size, single-institution experience), and thus may not be generalizable. A general agreement is that postoperative QOL depends on preoperative clinical status; moreover the first essential criterion for an improvement in subjective change in QOL is accurate preoperative diagnosis. In fact, appropriate patient selection for surgery represents the most important criteria guiding the patients' subjective feeling after cholecystectomy, independent of the selected surgical technique. On the other hand, an effective way to investigate the factors that may influence subjective QOL outcomes would be to measure the satisfaction rate pre- and post-surgery, and repeatedly after surgical treatment; a QOL assessment is generally suggested at 1 and 6 mo postoperatively. On this basis, symptomatic patients usually gain more QOL from a surgical intervention (open or laparoscopic) in terms of long-term well-being. Even though LC improves QOL faster than open surgery, long-term results are only slightly better or show no difference compared with those of open surgery; at the same time, these data should be considered as a mean, and might be limited by study design (e.g., small sample size, biased and confounding variables). The only certain and significant long-term advantage of laparoscopic surgery might be the higher satisfaction rate in regard to

scar cosmesis, in the absence of complications.

In conclusion, although sensitive and responsive instruments for the measurement of post-cholecystectomy QOL exist, more research is needed to identify modifications that could lead to significant improvements.

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Ambulatory Surgery for Breast Cancer Patients

Richard G. Margolese, MD, and Jean-Claude M. Lasry, PhD

Background: Less than two decades ago, early discharge of mastectomy patients was found to be possible while the drains were still in place, without noticeable consequences for patients. Most reported studies focused on surgical complication rates and found no significant evidence of it. The objective of the present study was to compare inpatient to same-day discharge surgery for breast cancer, on unselected patients.

Methods: All interviewed patients (n = 90) had routine level I and II axillary lymph node dissection under general anesthesia, combined with breast surgery for most of them. The outpatient group comprised 55 patients and the inpatient group 35. Psychological distress was assessed, as well as pain, anxiety, quality of life, emotional adjustment, recovery, social relations, stressful life events, and so on.

Results: The sociodemographic characteristics of both surgery groups was quite similar, except that time from surgery to interview was about 1 year longer for inpatients. Outpatients and hospitalized patients report similar levels of pain, fear, anxiety, health assessment, and quality of life. Ambulatory patients manifest a significantly better emotional adjustment and fewer psychological distress symptoms. Inpatients reported that it took an average of 27 days to feel that they had recovered from surgery, about 10 days longer than outpatients. Inpatient return to usual activities was also about 11 days later.

Conclusions: Same-day discharge patients are not at a disadvantage compared to hospitalized patients; i.e., they report faster recovery and better psychological adjustment. Outpatient surgery may thus foster patient emotional well-being better than routine hospitalization.

Key Words: Breast cancer—Psychological distress—Quality of life—Ambulatory care—Early discharge.

The increased use of outpatient surgery can be linked to the many changes in health services spurred by economic considerations. In the case of breast cancer, there has been some concern that this practice may have gone too far,[1] as reflected in President Clinton's remark, in his State of the Union address, about "drive-through mastectomies."[2] Some changes, however, may be worthwhile, regardless of cost factors.

Shortened hospital stay has progressed in a stepwise fashion. Studies have shown that discharging patients on the day after surgery, with the drain in place, reduced the number of days spent in the hospital and accelerated the return to work.[3] In a series of reports about early or same-day discharge, there were no differences in terms of deaths, serious complications, wound or drain site infections, range-of-motion problems, or rehospitalization rates.[4–10]

In a recent study, Warren et al.[11] analyzed Medicare data to provide population based information on mastectomies performed on elderly women as outpatient procedures. From 1986 to 1995, outpatient mastectomies increased in the United States, from 0% to 11%. Rehospitalizations for complications definitely related to surgery were not different from those after mastectomies involving inpatient hospitalization. Because their study was based on records only, the authors emphasized the need to assess patient satisfaction.

All the reviewed studies involved surgeon-selected or self-selected mastectomy patients, and in only two of them was surgery performed on an ambulatory basis, with discharge occurring on the same day as admission. Aside from anecdotal reports, most studies focused on

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surgical complication rates and found no evidence of problems. We therefore undertook a study on unselected patients, to compare ambulatory with inpatient surgery for breast cancer, focusing on patient personal experience. Our objective was to systematically assess, with a questionnaire, pain, anxiety, quality of life, emotional adjustment, distress symptoms, social relations, and recovery.

PATIENTS AND METHODS

Patients

The study comprises two groups of unselected consecutively treated patients who consented to answer a telephone questionnaire about their experience of having had breast cancer surgery either with overnight stay in the hospital (inpatient) or as day surgery (outpatient). In early 1995, one of us (R.M.), a surgeon treating breast cancer exclusively, made a switch in routine management of breast cancer patients. Until that time, all patients were admitted to a short-stay ward to spend one or two nights in the hospital after surgery. It was noted that most patients were up and doing well by the time of their evening meal and reported little or no analgesic use. Eventually, some patients were discharged on the same day and this seemed quite acceptable to the patients, so that it quickly became our standard method of patient management for breast cancer surgery. From April 1995 onward, all our subsequent patients were treated as outpatients without exception. As Fig. 1 shows, the transition period was very short; i.e., within 3 months, the procedure was switched from hospitalization to ambulatory care, so the two groups represent essentially unselected consecutive cases.

Surgical Considerations

Because breast removal is so uncommon in our practice, we selected axillary dissection as the operation to be surveyed, because it is the operation responsible for the major symptoms of breast cancer surgery. Breast surgery itself is a superficial operation, because muscle planes are not interrupted and postoperative pain is not a prominent feature. Mastectomy, in which flaps are created, denervates the chest wall and causes little or no discomfort, but axillary surgery, with its anatomical situation at

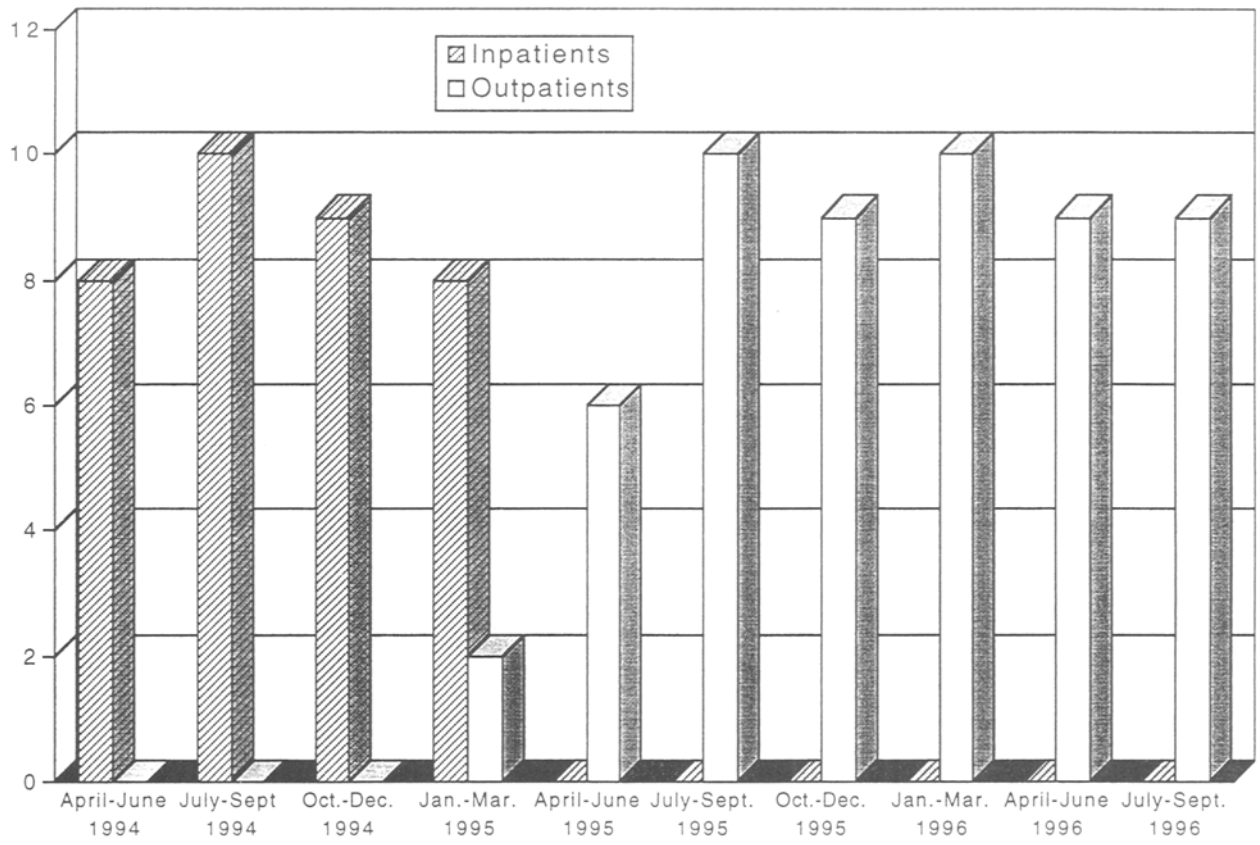

FIG. 1. Frequency and type of breast cancer surgery according to time (in trimester periods.)

a flexion joint and its drainage tube, usually causes discomfort with arm motion. All patients interviewed had routine level I and II axillary lymph node dissection while under general anesthesia, combined with breast surgery for most of them (80%). Patients who had simple breast surgery (lumpectomy) for benign or malignant disease were not included, because these were all done with the patient under local anesthesia and have been considered outpatient procedures for more than two decades.

On a master list of 121 patients, 90 (74%) agreed to be interviewed; of these, 9 had simultaneous total mastectomy (equivalent to modified radical mastectomy), 62 had simultaneous lumpectomy, and 19 had axillary surgery only, the lumpectomy having been done previously. Except for 7 patients (6%) who had died of breast cancer or other causes, only 5 (4%) patients refused to be interviewed, but 19 (16%) could not be reached for diverse reasons.

The outpatient group comprises 55 consecutive patients who underwent their surgical intervention from April 1995 to September 1996. For comparison purposes, we chose a similar sized group of consecutive patients admitted for surgery, going back approximately 1 year from that date (n = 45). The inpatient list was stopped in April 1994, to not have too long a time interval from surgery to answering the questionnaire. From April 1994 until March 1995, 45 patients were treated with overnight hospitalization; of these, 1 refused to participate, 5 died, and another 4 could not be located. The inpatient group thus included 35 patients who agreed to be interviewed, a percentage (78%) similar to that of the outpatient group (72%). These two blocks of patients represent all patients who underwent axillary node dissection and who agreed to participate in the study, in these two time periods.

Surgical Technique

For lumpectomy patients, the technique described in the NSABP (National Surgical Adjuvant Breast Project) Syllabus of Breast Conserving Surgery[12] was followed, except that all breast incisions are now made in a transverse fashion because they follow Langer's lines more closely and produce better cosmetic results than circumferential incisions. The surgical technique used for modified radical mastectomy patients is a transverse incision from near the parasternal border to the midaxillary line. The breast is removed from the edge of the clavicle down to the rectus fascia and a level I and II axillary node dissection was performed in continuity.

Standard technique for level I or level II axillary node dissection includes removing all the fibro-fatty tissue that reaches to the medial border of the pectoralis minor, which exposes and preserves the long thoracic nerve and the nerve to the latissimus dorsi as well as the axillary vein superiorly. All patients had closed suction drains that were generally removed on the fourth postoperative day, along with the clips used to close both incisions. An average of 9.5 lymph nodes were obtained per patient (9 in the day-surgery group and 10 in the inpatient group).

Instruments

Because the study was performed via the telephone, the questionnaire had to be brief enough not to deter respondents. The questionnaire included a standardized scale of psychiatric symptoms, standard questions about health satisfaction, pain, social relations and stressful life events, as well as basic sociodemographic data. It was completed in an average of 15 to 20 minute. Details of the instruments can be found in the Appendix.

Surgical complications such as hematoma, seroma, or infection were not specifically assessed, because previous studies have documented these are not considered to be a function of where the patient spends the first postoperative night. Inpatients are usually sent home before any signs of infection become manifest, and it is common practice to send them home with the drainage apparatus in place. In the study of Warren et al.,[11] based on Medicare data, there was no difference in surgery-related emergency room admissions between admitted and ambulatory patients.

RESULTS

As can be seen in Table 1, sociodemographic characteristics are quite similar for the two patient groups. The outpatient group is slightly more educated (about a year and a half more; $P < .06$) and presents with higher occupational prestige scores. But, because both groups

TABLE 1. *Sociodemographic characteristics of the two groups of surgery patients*

Variables	Inpatients	Outpatients	*P*
Age, y	58.1	57.4	NS
Years since menopause	9.2	11.0	NS
Married, %	50.0	57.1	NS
Education, y	12.1	13.7	<.06
Occupation score	36.8	53.1	<.01
Presurgery Occupation score	45.2	50.8	NS
Time since surgery, mo	29.6	16.0	<.001
Life Events, mean number	0.8	0.9	NS
Life Events, weighted score	3.3	3.9	NS
Social Relations index	56.5	69.8	NS
n	35	55	

NS, not significant.

have similar presurgery occupational scores, they were thus occupationally similar to start with. Although work status before and after surgery is similar in both groups, there is a significant postsurgery drop in the percentage of patients working full or part time, in the two groups (McNemar test; $P < .02$). Of the 11 patients who were no longer employed at time of interview, 6 were inpatients and 5 were outpatients. Table 2 documents clinical features of the cancers, i.e., tumor size, number of lymph nodes, and proportion of mastectomies.

A significant difference appears in the time interval from surgery to interview ($P < .001$). Inpatients were interviewed an average of 30 months after their intervention, whereas the interval is 16 months for the outpatient group. This difference is because of the way the ambulatory surgery procedure was introduced in the clinic, as explained in the Patients and Methods section. Other sociodemographic variables such as country of birth, mother tongue, or number of children, not reported in this table, are also comparable in both groups. The number of life events that have affected both patient groups is not different, whether one considers simple occurrence of events or the sum score weighted by the amount of stress experienced in each item. The number of social relations as well as the satisfaction derived from these social relations are also equivalent in both patient groups. In summary, the inpatient and outpatient groups are quite similar, except that time from surgery to interview is about 1 year longer for the inpatient group.

As Table 3 shows, on the first day after surgery, the pain intensity is similar for both patient groups, ranging from mild to discomforting. For the first postoperative week, both inpatients and outpatients again recalled the pain to be similar. Questions about anxiety and fear experienced during the first day and during the first week yielded equivalent results for both groups. In a similar manner, spending the first night after surgery in the hospital or at home does not make any difference for breast cancer patients, in terms of their reported quality of life or in terms of their general health. Both groups of patients also worry about their health to the same degree, both more than before surgery.

TABLE 2. *Pathological characteristics of the two groups of surgery patients*

	Day surgery	Inpatient
Tumor size, cm	1.9	1.8
Specimen size, cm	7.0	7.0
Avg. no. of positive nodes	0.4	0.9
No. of nodes removed	9	10
Mastectomy patients	10%	10%

TABLE 3. *Comparisons of mental and physical health indices in the two surgery groups*

Health indices	No. of items	α	Inpatients	Outpatients	P
Pain on first day[a]	1	—	1.76	1.59	NS
Pain during first week[a]	1	—	2.27	2.07	NS
General Health index[b]	3	0.84	3.28	3.23	NS
Quality of Life index[b]	3	0.89	3.56	3.70	NS
Emotional Adjustment index[b]	3	0.88	3.46	3.89	<.05
Distress symptom scale	15	0.89	11.7	8.6	<.09

[a] Scale from 0 to 5 (0 = no pain; 1 = mild; 2 = discomforting; 3 = distressing; 4 = horrible; 5 = excruciating).
[b] Scale from 1 to 5 (the higher the score, the better the index).

Unexpected differences appear in favor of outpatients; i.e., they report a significantly better emotional adjustment ($P < .05$) than patients who spent their first postoperative night in the hospital. The outpatients also tend to express somewhat less psychological distress symptoms ($P < .09$). Although this difference is marginal, it is clear that ambulatory patients are not feeling worse than inpatients. A comparison of patients who were free of all symptoms at the time of the interview revealed a more clearly marked difference; outpatients were more likely to be completely asymptomatic ($P < .02$).

The patients who spent their first night in the hospital reported that it took an average of 27 days to feel that they had recovered from surgery, about 10 days more than the outpatient group (Table 4). The return to their usual activities took about a month and a half, a significantly longer period, by about 11 days, when compared with the ambulatory care patients ($P < .02$). These recovery intervals are validated because recovery from the stress of breast surgery took a much longer period of time, about 4 months (whether the patient was treated as inpatient or outpatient).

Each group of patients was asked whether they would have rather spent their first night after surgery under the other procedure. Although only 12% of the inpatient group would have preferred the day-surgery procedure, 41% of outpatients would have chosen to spend the first night after surgery in the hospital, mostly because they felt the hospital would provide a greater feeling of secu-

TABLE 4. *Mean number of days for three different recoveries, according to type of surgery*

Question	Inpatients	Outpatients	P^a
How many days was it before:			
. . .you recovered from surgery?	26.8	17.4	<.05
. . .you recovered from the stress of breast surgery?	119.1	127.8	NS
. . .you returned to usual activities?	46.4	35.1	<.02

[a] Based on the Mann-Whitney nonparametric test.

rity. Nevertheless, 6 of 10 women from the outpatient group would not change their surgical arrangement; i.e., they would still prefer to undergo surgery on an ambulatory basis.

DISCUSSION

This study is the first reported comparison of unselected mastectomy patients who underwent either outpatient or inpatient surgery. Other reports have concerned selected groups of patients, which could bias the findings. A randomized clinical trial would be best, but this survey of consecutively treated patients with no omissions presents a group that is reasonably generalizable to the general population. Tables 1 and 2 document the comparability of the two groups.

The surgical procedures are described briefly, to show that these were orthodox operations and not modified to make it more suitable for any imagined needs of outpatients. Anesthetic techniques are not documented mainly because so many different anesthetists with so many different variations of technique were involved. Although postoperative nausea and vomiting and pain are features that may be related to anesthesia technique, our patients reported very few of these complaints and Table 3 shows no significant difference in the reporting of pain on the operative day or the subsequent week.

The population surveyed represents all consenting patients operated on during two consecutive time periods, with almost no overlap in procedures. The two groups consist of consecutive patients before and after an abrupt change in management from inpatient to outpatient. Although a prospective randomized study is always ideal, it was not considered reasonable to ask patients to spend a night in the hospital when it had already been demonstrated in a general way that they would be comfortable at home. Therefore, we chose to study these patients and compare them with the most immediate group of inpatients, those in the year before the changeover. Others had already shown that surgical complication rates and management of drainage tubes were no different because of outpatient surgery, and there was no reason to redocument and report on those again. Therefore, because of the level of controversy, especially in the lay press, we elected to study the psychological and social adjustments of patients undergoing major outpatient breast cancer surgery.

The two surgery groups are very similar in terms of sociodemographic characteristics, life events, and social relations, with the main difference being the time interval from surgery to interview. The very consequence of the survey design favors the adjustment of hospitalized patients, as they have had about 1 more year to adjust to breast cancer surgery before answering the questionnaire. Notwithstanding this difference, the subjective parameters of pain, fear, and anxiety, and the perceived levels of general health and of quality of life affect both groups in a similar fashion.

Two main differences point to a clear advantage for outpatient surgery, i.e., recovery and psychological adjustment. Recovery from surgery, and the more concrete end point of a return to a normal life and the usual activities, including work, occur about a week and a half sooner for patients who were not hospitalized. Kambouris[9] noted, also, an earlier return to occupational activities for his early discharged patients, whereas Tarazi et al.[3] were more specific in terms of time-off gains. Patients who were discharged early returned to work 11 days sooner, a gain that is almost identical to the one found in our study.

Inpatients, who spent their first night after surgery in the hospital, report a worse emotional adjustment and more psychological symptoms at the time of the interview, despite that they had more time to adjust to surgery. Although Boman et al.[5] found no differences in levels of mental well-being and general health between early and late discharge mastectomy patients, Pedersen et al.[8] did show that, with regard to mental well-being, patients scored themselves better after discharge than when compared with preadmission.

Most patients in both groups prefer the procedure they have undergone rather than the alternate one, a congruence often reported in social psychology. Fear of the unknown and uncertainty about the other surgical procedure most likely facilitated this choice. Although this preference was stronger for the inpatient group, still three of five ambulatory patients would select the same procedure if they had to do it again. The same high level of satisfaction was found in other accelerated discharge studies.[3,4,8]

Our results demonstrate that same-day discharge patients are not at a disadvantage compared with hospitalized patients. On the contrary, their recovery is faster and their psychological adjustment is better. Although there is some reluctance to believe that ambulatory surgery can be comfortable and appropriate for breast cancer patients, our study indicates it is a useful approach that has clear psychological advantages for patients, regardless of cost-saving elements. The economic arguments are useful for health care planning, but early discharge appears

important from the perspective of patient well-being. Goodman and Mendez[6] have emphasized the psychological advantages of early discharge. It tends to bring together patients and their families, to "downgrade the seriousness of the operation" and, thus, to have a better mental attitude toward recovery. In a similar manner, McManus and colleagues[7] state that surgery is only the beginning of a long and involved treatment process, and the surgeon's goal should be to make the surgical part of breast cancer treatment as atraumatic as possible. We share their conclusions that outpatient surgery may foster patient emotional well-being better than routine hospitalization; i.e., by giving a sense of personal control, ambulatory surgery tends to avert maladaptive sick role behavior and thus contributes to a more rapid recovery.

APPENDIX

The Psychological Distress Scale, a shortened version of the Hopkins Symptom Distress Checklist, assesses nonspecific psychological distress or demoralization[13] and has been validated on a normal population.[14] The 29-item scale has been translated into French and reduced to 14 items after factor analysis, and validated in a province-wide health survey of more than 19,000 persons.[15,16] The final scale includes four factors, often cited as psychological sequellae of cancer, i.e., Depression, Anxiety, Cognitive Disturbance, and Anger. In our study, the internal reliability of the 14-item scale is very high and almost identical to the coefficients evidenced in the cited studies (α = .89).

The pain intensity question is the pivotal item of the McGill Pain Questionnaire[17]; it ranges from no pain (= 0) to excruciating (= 5). The General Health Index includes three questions; the Health Satisfaction item assesses the perception the respondent has of his/her state of health in general, and is found in most health surveys.[18] The second question, also very common, measures the perceived health status according to five categories, from Poor to Excellent.[19] The third question also measures the perceived health status but according to a 10-point rating scale. A reliability analysis recommended rejection of the fourth question, assessing worry about health. The internal reliability of the final General Health index is very high (α = .84), similar to the other psychological health indices, i.e., Quality of Life and Emotional Adjustment (α >.88). The format of these two indices is identical to that of the General Health index.

Since the seminal article of Holmes and Rahe,[20] stressful life events have not only been linked to psychological distress[21] or alterations in the immune function,[22] but appear also to be "strong indicators of the risk of psychological distress for breast cancer patients."[23] The eight life events recorded in the Quebec health surveys[16] were used in our study, with each item weighted by the stress experienced if the event occurred.

Social relations are routinely assessed when psychological functioning is appraised. Sarason et al.[24] factor-analyzed their Social Support Questionnaire and reduced it to six items, assessing the number of social relations available and the satisfaction with them. Based on the very high reliability of the six-item scale, we reduced it further to three items. The internal reliability of this very brief social relations scale is also excellent, i.e., .87 for number of social relations and .78 for satisfaction.

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Breast cancer surgery in an ambulatory setting

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ABSTRACT

Aim: To evaluate the feasibility and efficacy of outpatient surgery for early breast cancer in an Italian ambulatory setting and to assess its benefits.

Patients and methods: A review of 88 women treated for breast cancer from an outpatient facility was undertaken from July 2003 to December 2006. The patients were selected for ambulatory surgery according to specific social, environmental, physical and oncological criteria.

Results: Eighty-eight women underwent a total of 107 surgical interventions in an ambulatory setting. Sixty out of the eighty-eight patients (68%) received a one-day conclusive surgical treatment, and the remaining 28 patients were promptly treated in two phases. Among this latter group, 18 patients (68%) were treated only in an outpatient facility, whereas the other 10 patients require reintervention with hospitalization. There were no intraoperative complications. In the postoperative period, 14 complications were observed: 6 wound infections, 3 hematomas, 1 axillary seroma and 4 readmissions. The patients' readmissions were due to nausea and emesis in one case, disphnoea in another case, and only two readmissions were due to surgical complications (hematoma in both cases). Patients that were interviewed exhibited a high level of satisfaction from the treatments they received.

Discussion: This study confirms the feasibility, efficacy and safety of the outpatient setting regime, which is highly appreciated by women and is more cost effective than surgery in a hospital setting.

1. Introduction

Breast cancer is the most frequent malignant neoplasm in women. In Italy, one out of eleven women develops breast cancer in her life. Breast cancer surgery has radically changed over the last decades with mammography screening programs more readily available and the advent of conservative interventions, such as quadrantectomy and sentinel lymph node biopsy. Furthermore, conservative surgery has reduced both early and late postoperative complications, as well as psychological implications of the disease.

In the last decade, mostly in the USA and Western Europe, various clinical studies have been carried out to verify the feasibility, efficacy and complications of ambulatory quadrantectomies, axillary lymphoadenectomies, simple or radical modified mastectomies and sentinel lymph node biopsies (SLNB).[1–6] These reports have encountered favorable results, confirming the safety of the approach and an acceptable complication rate that is similar to an inpatient setting regime. Also, there has been an increasing consensus within the population for this approach.[7] Outpatient surgery represents a precious and safe alternative only when performed in a context in which the patient is accurately prepared preoperatively and strictly controlled postoperatively. Furthermore, breast cancer surgery, when it is superficial and does not imply any significant bleeding or electrolyte shifts,[8] represents a good choice for ambulatory surgery.

2. Materials and methods

From July 2003 to December 2006, 484 women underwent breast cancer surgery at the Department of Surgical Sciences, University of Insubria in Varese, Italy. Of these, 396 women were treated in the hospital and the remaining 88 patients were selected for ambulatory surgery.

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Selection criteria were as follows:

1) Social criteria of the patient: sufficient hygiene and the ability to match pre and postoperative prescriptions.
2) Social criteria of the environment: residing no more than 30 min from the hospital; possessing a telephone and having the support of a responsible caretaker at home.
3) Physical criteria of the patient: age under 75; absence of morbid obesity or pathologic thinness; absence of a history of addiction to alcohol, drug or tobacco; ASA 1 or 2.
4) Oncological criteria of the patient: conservative intervention without reconstruction; cT1cN0 with high probability of a negative sentinel lymph node.

A preliminary visit was scheduled, where the surgeon selected the patient for the one-day surgical procedure based on the previously mentioned inclusion criteria.

An informed consent was obtained from the patient and a detailed information sheet was then provided, which also included telephone numbers of the ward.

Preoperative exams (chest X-ray, electrocardiography, blood sample) and staging procedures (abdomen ultrasound and bone scintigraphy) were coordinated by nurses and performed in a prepared ambulatory setting.

The day before the surgical intervention the patient was invited to undergo a psychological counseling session to assess her expectations and the impact of her outpatient treatment.

The same day the patient was taken to the Department of Nuclear Medicine for sentinel lymph node (SLN) mapping with 99mTc radioisotope: the scintigraphic images were obtained 15 and 30 min after the injection. In case of nonpalpable breast lesions, the injection of 99mTc radioisotope followed radioguided occult lesion localization (ROLL) by stereotactic localization of the tumor.

On the day of the surgery the patient arrived after fasting for at least 6 h. The evening before she was advised to take a bath or shower after accurate self-epilation of the axilla.

Surgical intervention was performed following standard techniques.

Radioguided surgery was used both for quadrantectomies of nonpalpable lesions and for SLNBs. Postoperative observation was for at least 5 h, after which the patient was evaluated by both the surgeon and the anesthesiologist (Table 1).

The patient was discharged the evening of the same day, and should any complications arise the surgeon then promptly organized admission of the patient to the hospital.

The day after the surgery, the patient was invited to the Center to change the dressing and remove any eventual surgical drainage. Drains were removed if less than 40 ml had accumulated during the previous 24 h.

A second counseling session with the same psychologist took place one to two weeks later to assess the patient's feelings on the day of surgery, the immediate postoperative course, her satisfaction of the outpatient setting regime and the eventual matching of her preoperative expectations.

Charts of the patients were then reviewed retrospectively to assess operative procedures, completion times, operative duration and the time of discharge.

3. Results

From July 2003 to December 2006, 484 women underwent surgery for breast cancer at the Department of Surgical Sciences, University of Insubria in Varese, Italy. Of these, 396 (82%) were treated in the hospital and the average hospitalization of these patients was 5.4 days (range: 3–12 days). The remaining 88 women (18%) were treated as outpatients. The average age of these patients was 58 years (range: 32–74 years). Of these 88 women, a total of 107 surgical interventions were performed. Details of the surgical procedures are illustrated in Table 2.

All surgical interventions were performed under general anesthesia. The mean procedure time was 88 min, ranging from 40 to 180 min.

At the beginning of this study, axillary staging (SLN biopsy) was performed before definitive breast cancer surgery. Later, the decision was made to offer the woman the option of a potential definitive procedure as an outpatient. Hence, 44 cases of quadrantectomy and SLN biopsy were performed at the same time in an outpatient facility.

In 10 cases, the patients underwent quadrantectomy without SLNB due to the fact that the preoperative pathologic examination (performed on a microbiopsy with mammotome) showed carcinoma *in situ* (7 of ductal and 3 of lobular type). Of this group, in one case final pathology report showed carcinoma *in situ* with foci of microinvasion, necessitating SLNB to be performed as an additional staging procedure.

In total, 78 SLNBs were performed. Preoperative SLN identification rate was 100%. Only in 1 out of 78 SLNB the intraoperative identification of SLN failed, necessitating an axillary lymphoadenectomy and quadrantectomy to be performed at the same time. Among the successfully performed SLNBs, 57 cases had only one SLN and of the remaining 20 cases more SLNs were dissected: 2 SLNs in 14 cases and 3 SLNs in 6 cases.

All patients who underwent a quadrantectomy procedure were discharged with closed system suction drainage, which was considered simple for the patient to empty.

There were no intraoperative complications. In total, 14 postoperative complications were observed: 6 wound infections, 3 hematomas, 1 axillary seroma and 4 readmissions. The 4 readmissions were due to nausea and emesis in one case, dyspnoea in another, and only two readmissions were due to surgical complications (hematoma in both cases).

Seventy-three out of eighty-eight women (83%) had a final pathology report showing invasive mammary carcinoma (59 ductal, 6 lobular, 3 tubular, 2 ductal microinvasive, 1 ductal and lobular, 1 apocrine and 1 mucinous) and two cases of invasive

Table 1
Surgical discharge criteria for the patients.

Surgical discharge criteria for the patient		
1. Stable vital signs	Yes	No
2. Oriented to space and time	Yes	No
3. Able to consume water and food	Yes	No
4. Able to spontaneously pass urine	Yes	No
5. Surgical dressing clean and in order	Yes	No
6. Absence of bleeding signs	Yes	No
7. Absence of complication signs	Yes	No
8. Autonomous motility	Yes	No
9. Presence of a responsible caretaker	Yes	No

Table 2
Types of surgical interventions.

Type of surgical intervention	Number of surgical procedures
Quadrantectomy + SLNB	69
Quadrantectomy	16
Axillary lymphoadenectomy	10
SLNB	8
Excision of malignancy recurrence	2
Widening of margins	1
Quadrantectomy + axillary lymphoadenectomy	1

ductal carcinoma were local recurrences. *In situ* breast cancer was found in 15 out of 88 patients (17%): 12 were ductal and 3 were lobular carcinoma *in situ*.

With regard to the extent of the invasive tumors, two cases were staged as pTmic, 7 as pT1a, 25 as pT1b, 32 as pT1c and 7 as pT2.

In three out of eighty-three patients, the resection margins of the specimens were involved by carcinoma necessitating reintervention to achieve surgical clearance. In total, 4 surgical procedures were performed: 2 mastectomies and 2 widening of the margins. In particular, in one case the reintervention (widening of margins) was performed in an ambulatory setting, whereas in another case involving widening of the margins the reintervention was not sufficient due to the extensive involvement by ductal carcinoma *in situ* and a mastectomy was performed in a prompt second phase.

Among the subgroup of 69 patients who underwent breast cancer surgery and SLNB simultaneously (see Table 2), final pathology report showed metastatic SLN in 17 cases (25%). Of these, 10 had a subsequent complete axillary dissection again in an ambulatory setting and the pathology report showed that the SLN was the only metastatic axillary lymph node. In the remaining 52 women (75%), cancer was radically removed with only one surgical procedure.

Psychological postoperative evaluation of the outpatient setting regime was performed on 20 out of 88 women. Of these, 19 patients expressed a high level of satisfaction with the treatment, and in only one case did a woman expressed dissatisfaction because of readmission the day after the original intervention.

4. Discussion

Ambulatory surgery represents a new prospective in surgical treatment of breast cancer, which has been widely present in the Anglo-Saxon medical environment since the early 1990s, and has not been yet popular in the Italian setting.

Notwithstanding the feasibility, patients' satisfaction and lowering of costs, in Italy outpatient surgery has not yet produced a strong decrease in hospital admissions for breast cancer surgery.[9,10] This may be the result of the Italian culture and the "need of caring" of Italian patients, as well as the surgeon's input: to change the patient's setting from inpatient to outpatient cannot occur in Italy without the surgeon's influence at almost every juncture. The manner in which options for surgery are presented will often influence the patient's decision. The lack of enthusiasm of many Italian surgeons is the major reason why outpatient breast surgery is not performed.

Although the outpatient setting regime has largely been the product of economic concerns, there have been many reports in literature that corroborate the safety of early discharge and the feasibility of an outpatient process.

Breast cancer surgery is relatively simple, without major bleeding, fluid or electrolyte shifts or significant complications.[11] Furthermore, in the last decades a less invasive approach to breast cancer surgery has occurred with the development of conservative treatment such as quadrantectomies and SLNBs. These new and less invasive techniques allow some to perform surgery on early breast cancer cases in an outpatient setting.[12]

One of the most relevant elements of the outpatient regime is the beneficial quality of life for outpatients in comparison to inpatients. In our series, psychological counseling showed that the majority of the interviewed patients were satisfied with the surgical treatment received and would not stay longer in a hospital setting.[13]

The key to patient acceptance of the proposed outpatient regime is the manner in which the subject is presented.

In our series, 60 patients received final surgical treatment in a one day procedure and 28 patients were treated in two phases. Among this latter group, 18 patients were treated in an outpatient environment, and the other 10 underwent reintervention in an ordinary hospital regime. With the exception of wound infections, the rate of complications was low and minor, from which the women soon fully recovered.

5. Conclusion

In conclusion, the results of this study confirm the feasibility, efficacy and safety of the outpatient setting regime, and the satisfaction of treated women, corroborating previously published literature.[1–15]

Understanding the economic debate with regard to Health Care in Italy, the results derived from this study strongly suggest that Italian surgeons should initiate this proposed outpatient regime for early breast cancer. However, to achieve this challenging goal it is necessary to have dedicated space, enthusiastic personnel and an appropriate manner in which options for outpatient surgery are presented, all of which may influence the patient's decision.

Conflict of interest
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None.

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Single hospital visit day case laparoscopic hernia repair without prior outpatient consultation is safe and acceptable to patients

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Abstract
Background For some common conditions, pre-operative clinic visits are often of little value to the patient or surgeon with transfer to the waiting list being predictable. In response to local patient feedback, we introduced a single hospital visit laparoscopic hernia surgery pathway with focus on informed consent, patient-reported outcomes and post-operative interaction with primary care services.
Methods A single hospital visit service for elective hernia repairs was created. Patients were not excluded on age, BMI or co-morbidity. Following referral, patients were telephoned by a surgeon. If considered appropriate, a symptom assessment tool, procedure information and consent form were sent. All patients were operated without attending clinic or pre-operative assessment. Surgeon-led telephone follow-up was made at either 2 or 7 days post-operatively and patient satisfaction assessed at 3 months.
Results A total of 517 patients were referred for single-stop surgery between 2012 and 2015. Median age was 58 (range 20–92), 91 % were male, and mean BMI was 25.6 (17.4–52.0). No patient refused the single-visit pathway. Single-stop patients had higher knowledge questionnaire scores (mean 16 vs. 10, $p = 0.01$) than patients who had attended clinic. Nine (1.7 %) were requested to attend clinic to confirm diagnosis, and three (0.8 %) were cancelled by their surgeon on the operative day. A total of 393 hernia repairs (331 TEP, 63 open) were performed under general anaesthetic. 92 % were discharged on day zero. Telephone follow-up day two rather than seven decreased attendance to primary care services (25 % vs. 57 %, $p = 0.001$). At 3 months, 95 % were satisfied and symptom scores were reduced (median 5–0, $p < 0.0001$).
Conclusion Single-visit surgery appears to extend the patient benefits of laparoscopy by reducing hospital visits without compromising safety. Single hospital visit hernia surgery for unselected primary care referrals is possible and acceptable to patients.

Keywords Single visit · One stop · TEP · Day case · Hernia

For many common, routine general surgical conditions, pre-operative clinic assessment visits may be of little value to the patient or surgeon with transfer to the waiting list being predictable. Current resource limitations, waiting list considerations and patient satisfaction issues have resulted in the adaptation and streamlining of UK surgical treatment pathways. Waiting times, pooled lists, independent or private sector outsourcing [1] and European working time directive restrictions [2, 3] can also reduce continuity of care. Subsequently, it is increasingly common for the operating surgeon to have not met the patient or be familiar with their situation. This can be undesirable for all parties.

We serve a relatively elderly population covering a wide geographical area with poor transport links to our out of town hospital site. Patient feedback regularly stated difficulty accessing our services. We hypothesised that the benefits of laparoscopy would allow delivery of routine day case hernia surgery performed without prior hospital visit. Possible secondary benefits may include simplification of referral pathways and reduction in disruption to patients, outpatient clinic use and time to intervention.

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Publication of surgical outcomes is increasing but day case surgery and rapid discharge can mean that no outcome data are available to assess the effectiveness of our interventions and the impact upon the patient's symptoms. Post-operative outpatient review is discouraged by UK NHS tariff arrangements, meaning that we commonly have no post-operative knowledge about a day case patient unless they are re-referred or readmitted to the same hospital. Primary care interactions or failure of symptom resolution are not known to the surgical team. When closely followed, 33 % reported a suboptimal recovery at 2 months following day case surgery [4] and 36 % reported ongoing symptoms [5]. Therefore, a secondary aim of this study was to improve outcome data collection in this group.

We aimed to assess the delivery of laparoscopic single hospital visit day case hernia repair with focus on informed consent, interaction with primary care services and patient-reported outcomes and satisfaction.

Methods

A single-visit day surgery service for inguinal, umbilical and ventral hernia repairs was created at a single NHS trust alongside standard services and prospectively evaluated. This was approved by the local ethics committee and trust board. The service and all documentation were designed together with a local patient-led focus group. Following primary care referral using a proforma (Fig. 1), patients were telephoned at a prearranged time by a hernia surgeon. There were no exclusion criteria relating to the previous hernia repair, co-morbidity, body mass index or ASA score. Patients who lived alone were booked for an overnight post-operative stay.

After surgeon-led telephone triage, those considered appropriate for single-visit surgery with an unequivocal history of a hernia were posted information about the single-stop service, a validated condition specific symptom assessment tool [6] (Fig. 2), information about the proposed procedure and a consent form. As proof of receipt and reading, return of a knowledge questionnaire (Fig. 3) was required prior to allocation of an operating list. Knowledge scores were compared with patients who had gone through traditional pre-operative surgical clinics pathways.

On day-of-surgery arrival, patients were able to discuss their case with their surgeon and were examined and informed consent was confirmed. There were no restrictions on surgical or anaesthetic techniques in single-stop patients. Balloon dissection (Autosuture, Covidien, USA) and 3DMax^{TM} (Bard Inc. RI, USA) mesh were used in all total extraperitoneal repairs (TEP) with flat Prolene^{TM} (Ethicon, USA) mesh for open inguinal cases. Umbilical hernias were repaired with a sublay Ventralex^{TM} hernia patch (Bard Inc. RI, USA). All incisions were closed with a subcuticular absorbable suture.

Prearranged telephone follow-up with the surgeon was made at either 2 or 7 days post-operatively. At 3 months, a postal survey was sent with a repeat of the symptom assessment tool. All single-stop patients were invited to attend focus group meetings to offer feedback and refine the service further. Additional prospective data recorded were post-operative acute urinary retention, any post-operative visit to primary care services, number of nights stay, unplanned readmission, hernia recurrence and patient-reported time to return to normal activities.

Statistical analysis was performed using SPSS version 19.0 (IBM^{TM}). A p value of <0.05 was considered significant. Complications were graded by the Clavien–Dindo classification [7].

Results

Of 2462 hernia referrals to Salisbury NHS Foundation Trust, UK, between January 2012 and December 2015, 517 patients (21 %) were referred on the single-visit pathway. Median age was 58 (range 20–92), 473 (91 %) were male and mean cohort BMI was 25.6 (17.4–52.0). All patients were contacted successfully at the prearranged time. No patient refused the single-visit pathway. 92.6 % of referrals were transferred to day surgery waiting lists after telephone consultation with nine patients (1.7 %) requested to attend an outpatient clinic to confirm diagnosis. Mean pre-operative knowledge questionnaire score was 16 for single-stop patients and 10 for outpatient clinic patients ($p = 0.01$).

There were no day-of-surgery cancelations due to anaesthetist, co-morbidity or drug history concerns, and there were no patient "no-shows". Three incorrect diagnoses were identified on pre-operative examination resulting in cancellation (0.8 %; one saphena varix, one lipohypertrophy secondary to insulin injection and no evidence of hernia in one patient). A total of 393 (76 %) patients underwent general anaesthetic hernia repair without prior visit to the hospital, 86 (17 %) are awaiting operation, and 38 (7 %) were not listed for surgery (Fig. 4). 84 % of cases were performed laparoscopically with one conversion.

Overall, 92 % patients were discharged home on day zero. No patient stayed longer than one night post-operatively. Eight patients developed post-operative acute urinary retention (2 %). Telephone follow-up on day 2 resulted in fewer patients attending primary care services compared to those called on day 7 (25 vs. 57 %, $p < 0.001$). Twenty-nine (7.3 %) patients reported bruising (Clavien–Dindo grade I), and three (0.8 %) required

Fig. 1 Single-stop hernia surgery referral form including brief explanation of patient pathway

Single Stop Hernia Surgery in Salisbury

Salisbury NHS
NHS Foundation Trust

Hospital no.		NHS number	
Surname		Forenames	
Sex	M / F	Title	
Date of birth			
Address		Home tel. no.	
		Mobile no.	
		e-mail	

Referring GP		Date of GP consultation	
GP Practice			
Please agree a Single Stop phone appointment with patient Available Wednesdays 16:00 to 18:00		Date for appointment	
		Time	

Hernia	
Site of hernia	Inguinal / femoral / umbilical / epigastric / incisional
Side	Right / Left / bilateral / not applicable
Is the hernia recurrent?	Y / N
Patient keen to pursue an operative procedure?	Y / N
Do you assess as medically fit?	Y / N
Will patient require planned overnight stay?	Y / N
Please note – General surgical clinics remain available for referrals if diagnostic doubt, significant co-morbidities, complex case or for specialist assessment and discussion	

How the single stop service works
You fax or e-mail appointment to our office – 01722 425294 or SingleStop@nhs.net
You and the patient agree a telephone appointment time and enter in the box above
We telephone your patient to introduce the process and discuss case and day surgical repair
Where they is diagnostic uncertainty or patient wish – we will arrange surgical clinic review
Patient will receive an information pack by post
Consent form and questionnaire is returned to us and suitability for Single Stop confirmed
Operation date arranged and admission letter and MRSA test kit sent to patient – we will check result
Operation – this should be the only visit to hospital
We telephone patient within one week post-operation
Post-operative symptom survey posted at three months – to allow assessment of the efficacy of treatment

community treatment for surgical site infection (Clavien–Dindo grade II). One patient was readmitted and reoperated for small bowel obstruction secondary to an unrecognised peritoneal defect following unilateral TEP repair of a primary inguinal hernia (Clavien–Dindo grade IIIb).

A total of 229 (58 %) of patients returned their 3-month survey. The median patient-reported time to return to normal activity was 4 weeks (range 1–8). 95 % reported being satisfied or completely satisfied with the service, with 98 % stating the post-op follow-up telephone call to have been of value. Three-month post-operative symptom scores were reduced from a median of 5 (range 0–17, IQR 1–7) to 0 (0–5, IQR 1–1, $p < 0.001$) (Fig. 5). No patient developed a recurrent hernia within the 3-month follow-up period.

Discussion

Increasing use of minimally invasive procedures, post-operative enhanced recovery pathways and day surgery facilities [8] have improved time to discharge and return to normal activities [9]. However, comparatively little focus

We would be grateful if you would answer all the questions below and return it in the stamped addressed envelope enclosed. This will help us to understand if we have given you enough information regarding your hernia operation.

Please indicate with a tick how much you agree or disagree with each of the following statements.

Hernia	Strongly agree	Agree	Disagree	Strongly Disagree
1. A hernia is a bulge through the muscle layer of the abdominal wall				
2. The size and discomfort from a hernia can change during the day				
3. Hernias are painful, even at night				
4. Only rarely does a hernia becoming strangulated (blood supply to a				
5. Emergency hernia repair is more dangerous than planned surgery				
6. Small hernias causing no symptoms do not always need to be re-				
Operation	Strongly agree	Agree	Disagree	Strongly Disagree
7. Not all patients are suitable for laparoscopic (keyhole) repair				
8. Laparoscopic (key-hole) repair uses a long-term mesh placed in				
9. Laparoscopic repair is performed through a few small incisions.				
10. There is a higher chance of long-term pain after open repair than				
11. There is a higher chance of the hernia coming back after laparo-				
12. Laparoscopic repair surgery is more difficult than open repair, but				
After your operation	Strongly agree	Agree	Disagree	Strongly Disagree
13. It is normally possible to go home on the day of my operation				
14. I should be able to resume normal activity within two weeks				
15. I would expect to get back to normal more quickly after an open				
16. It is normal for the wounds to become increasingly red, hot and				
17. The stitches used will not normally need to be removed				
18. After I go home I should contact my GP if I have any concerns				

Fig. 2 Knowledge questionnaire designed with our patient focus group. Sent with operative information pack after telephone consultation. Return was required before an operation date was allocated. Questionnaire was *negatively marked*

has been made on the patient's pre-operative journey. In response to feedback that attending clinics was troublesome given local distances and transport links, we assessed the introduction of a single-visit surgery for laparoscopic hernia repairs. This method relies on appropriate patient selection and correct diagnosis in primary care. As only 1.7 % of referrals were requested to attend for pre-operative review, GP selection appears possible and acceptable to day theatre teams. It is noteworthy that once enrolled, no patient refused the single hospital visit pathway.

We present the largest cohort of single-stop surgical patients and show that a laparoscopic one-stop service can be expanded to meet the needs of unselected primary care referrals without compromising safety or efficacy. We highlight patients were not excluded due to co-morbidity, age or obesity and this is the first series containing multiple hernia types. One-stop series of open [10] and TEP inguinal hernia repairs [11, 12], laparoscopic cholecystectomies [13] and paediatric surgery [14, 15] have previously been reported confirming proof of principle. In contrast to these reports, our patients were seen and examined within the day surgery unit alone and had no contact with any pre-assessment service. Combined with the low 0.8 % day-of-surgery cancellation rate (none were cancelled by an anaesthetist), a single-stop service can be expected to reduce demand on outpatient and pre-assessment facilities. One patient required re-referral for management of their

We would be grateful if you would complete the questionnaire below and return it in the stamped addressed envelope enclosed. This survey is designed to help us to understand the results of hernia operations and to improve the treatment that we offer. We thank you in anticipation of your help.

Please estimate the sort of pain in your groin on the side of your hernia (or the more severe hernia) you have had in the last week *Please tick the box to the right of your answer*		
	No pain	
	Pain, but easily ignored	
	Pain, cannot be ignored, but does not interfere with everyday activities	
	Pain, cannot be ignored and interferes with daily activities	
	Pain, cannot be ignored, interferes with most activities	
	Pain, cannot be ignored and needs to rest in bed	

The following items are about activities you might do during a typical day. Please estimate to what extent pain in your groin on the side of your hernia (or the more severe hernia) limits these activities? *Please tick the box to the right of each of your answers*				
		Limited a lot	Limited a little	Not limited at all
	Getting up from a low chair			
	Sitting down for more than half an hour			
	Standing up for more than half an hour			
	Going up or down stairs			
	Driving a car			
	Ability to exercise and perform sports			

3. What type of symptoms do you have?	Always/Often	Sometimes	Never
Do you have a lump where you feel you have a hernia?			
Does this become more noticeable when you stand up?			
Does this become more uncomfortable when you stand up?			
Do you ever get discomfort from the hernia when sitting, or at night?			

Could you indicate the main reason that you are considering having your hernia repaired?		
	Because of pain or discomfort	
	Because the hernia will not heal itself and I might as well get on with it	
	Because of the risk of strangulation (bowel getting stuck in the hernia and losing its blood supply)	
	Because I don't like the appearance of the hernia	
	I would like my hernia repaired for another reason.	
	Which is -	

Fig. 3 Hernia symptom questionnaire. Adapted from Franneby et al. [6]. Included with pre-operative and three monthly postal packs

newly diagnosed symptomatic saphena varix showing single-stop surgery did not generate high levels of additional hospital activity.

We were initially concerned that single-visit surgery could negatively impact on patient understanding and risk invalidating informed consent. Postal information and pre-operative consenting resulted in a higher score on a patient designed knowledge questionnaire compared with those who had attended an outpatient clinic.

There was a reduction in the number of visits to primary care services when the patient was telephoned at 48 h post-surgery rather than 7 days. Feedback obtained through the

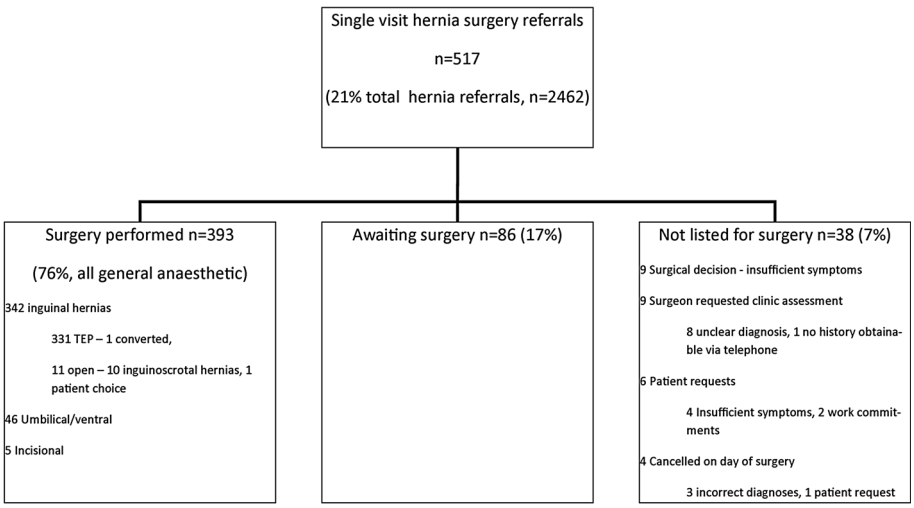

Fig. 4 Flow chart for patients referred to the single-stop pathway

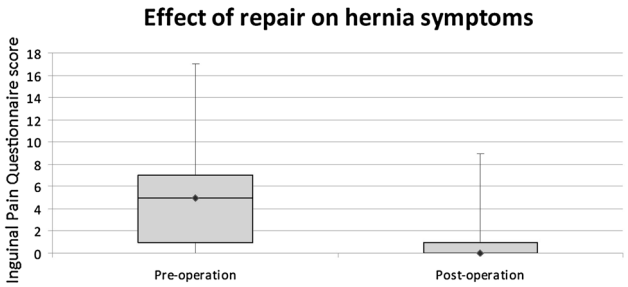

Fig. 5 *Box* and *whisker plot* showing hernia symptom score [6] pre- and 3 months post-operatively (median 5 and 0, $p < 0.001$)

patient-led focus groups stated that an early call was reassuring and allowed queries to be satisfactorily addressed. Embedded within this service is a method of routinely obtaining accurate outcome and satisfaction data. This is not generally available outside of prospective studies and allows us to confirm the efficacy of our laparoscopic interventions.

Caution is required when interpreting our study. Without comparable data from those undergoing hernia repairs via an outpatient consultation, we are unsure whether the high reported patient satisfaction is directly attributable to the fewer hospital visits. Additionally, whilst similar to attrition rates reported in postal questionnaire follow-up studies [16], 42 % of patients did not return their 3-month survey and their status is unknown. We cannot comment on satisfaction amongst our primary care colleagues but the high number of referrals (and high diagnostic accuracy) suggests single-stop surgery is acceptable. The timing of the post-operative phone call was not randomised but pragmatically delivered according to the surgeons' availability. Rationale for a randomised study on this issue appears clear.

Unanswered questions around single-visit surgical pathways remain. Avoiding the wait for clinic review may reduce the time until definitive surgical treatment benefiting the patient. Direct referral and coordination of pre-operative surgical and anaesthetic assessment reduced referral to surgery time by 60 % and number of hospital visits by 66 % in a pilot study [17]. A randomised controlled trial is currently recruiting to compare waiting times and costs in one-stop vs. clinic assessment routes [18]. The impact of single-visit surgical treatment pathways may result in a financial benefit to both primary and secondary care services. Our experience shows one-stop surgery can be expected to reduce outpatient and pre-operative assessment clinic visits without increasing day-of-surgery cancellation rates. Surgical staff may be freed to perform other duties; however, not all hernia patients will be suitable for one-stop services so the need for clinic provision continues.

Conclusion

Single-visit surgery appears to extend the patient benefits of laparoscopy by reducing hospital visits without compromising safety. Single hospital visit hernia surgery for unselected primary care referrals is possible and acceptable to patients.

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Compliance with ethical standards

Disclosures Carty NJ, Curtis NJ and Ranaboldo CJ have no conflicts of interest or financial ties to disclose.

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Open

Colonoscopy Reduces Colorectal Cancer Incidence and Mortality in Patients With Non-Malignant Findings: A Meta-Analysis

REVIEW

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OBJECTIVES: **Observational studies have shown that colonoscopy reduces colorectal cancer (CRC) incidence and mortality in the general population. We aimed to conduct a meta-analysis quantifying the magnitude of protection by colonoscopy, with screening and diagnostic indications, against CRC in patients with non-malignant findings and demonstrating the potentially more marked effect of screening over diagnostic colonoscopy.**

METHODS: **PubMed, EMBASE, and conference abstracts were searched through 30 April 2015. The primary outcomes were overall CRC incidence and mortality. Pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated using random-effect models.**

RESULTS: **Eleven observational studies with a total of 1,499,521 individuals were included. Pooled analysis showed that colonoscopy was associated with a 61% RR reduction in CRC incidence (RR: 0.39; 95% CI: 0.26–0.60; I^2=93.6%) and a 61% reduction in CRC mortality (RR: 0.39; 95% CI: 0.35–0.43; I^2=12.0%) in patients with non-malignant findings, although there was high heterogeneity for the outcome of CRC incidence. After excluding one outlier study, there was low heterogeneity for the outcome of incidence (I^2=44.7%). Subgroup analysis showed that the effect of screening colonoscopy was more prominent, corresponding to an 89% reduction in CRC incidence (RR: 0.11; 95% CI: 0.08–0.15), in comparison with settings involving diagnostic colonoscopy (RR: 0.51; 95% CI: 0.43–0.59; P<0.001).**

CONCLUSIONS: **On the basis of this meta-analysis of observational studies, CRC incidence and mortality in patients with non-malignant findings are significantly reduced after colonoscopy. The effect of screening colonoscopy on CRC incidence is more marked than diagnostic colonoscopy.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the fourth leading cause of cancer-related death throughout the world (1). By means of detection and subsequent resection of precancerous lesions and early-stage CRCs, screening is effective in reducing CRC incidence and mortality, which has already been demonstrated in trials with fecal occult blood test (2–6) and flexible sigmoidoscopy (7–11). Evidence for the effectiveness of colonoscopy screening in average-risk general population, however, is still limited as related large-scale randomized trials are still ongoing (12–15).

Since 2009, mounting evidence from observational studies has shown that colonoscopy screening is associated with reductions in both CRC incidence and mortality (16–19). However, colonoscopy screening programs have not been implemented in many European countries (20,21) and most of the Asia-Pacific region (22); even the colonoscopy screening rates in the United States and Germany, where screening programs were introduced early this

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century, were only 54% by 2013 (23) and ~20–30% by 2012 (24), respectively. A great number of studies from the real-world settings in which indications for colonoscopy included both screening and diagnostic also supported the protective effect of colonoscopy in the general population (25–29).

Two previous meta-analyses found significant reductions in CRC mortality (and incidence) after (screening) colonoscopy (30,31), but the generalizability of the findings in the general population is less than ideal due to the heterogeneity of the baseline population, as subjects with malignant findings were enrolled in some included studies but not in others. Ranging from negative findings, hyperplastic polyps, adenomas to serrated lesions, non-malignant findings at the index colonoscopy, which constitutes over 90% of the yield of colonoscopy in clinical practice (32,33), differ with malignant findings in the following aspects: non-malignant nature, mostly non-surgical treatment, longer surveillance interval, and better prognosis (34,35). We therefore aim to evaluate the magnitude of protection against CRC by colonoscopy, with screening and diagnostic indications, in patients with non-malignant findings and further determine the potentially more marked effect of screening over diagnostic colonoscopy in the magnitude of reductions in CRC incidence and mortality.

METHODS

Search strategy

The meta-analysis was performed according to MOOSE statement (MOOSE Checklist is available in **Supplementary Appendix A** online) (36). A comprehensive, computerized literature search was conducted in PubMed and EMBASE from the beginning of indexing for each database to 30 April 2015 by two reviewers (J.P. and L.X.) independently, with no restrictions in language. The search for relevant studies was performed using the following text words and corresponding Medical Subject Heading/Emtree terms: "colonoscopy or endoscopy" AND "colorectal, colon, rectum, or large bowel" AND "cancer, carcinoma, neoplasm, tumo(u)r, or adenocarcinoma" AND "relative risk(s), odds ratio(s), rate ratio(s), risk ratio(s), or hazard ratio(s)" AND "cohort, or case–control" (detailed search strategy is available in **Supplementary Appendix B**). Abstracts from Digestive Disease Week (DDW) and United European Gastroenterology Week (UEGW) were searched manually. In addition, we searched for additional studies in reference lists of identified articles.

Eligibility criteria

Three reviewers (J.P., L.X., and Y.-F.M.) independently evaluated all of the studies retrieved according to the eligibility criteria. Disagreements were resolved by consensus. Studies were included if they met all of the following criteria: (i) studies from which effect estimates assessing the effect of colonoscopy on CRC incidence and/or mortality in patients with non-malignant findings vs. no colonoscopy were extractable (patients with non-malignant findings were defined as a consecutive collection of both cases detected with non-malignant polyps and those with negative findings at the index colonoscopy; the index colonoscopy was defined as the initial colonoscopy performed during the study period for either screening or diagnostic purpose); (ii) all of the participants with and without the exposure to colonoscopy are from the same population source; (iii) all of the participants had no history of CRC; (iv) all (or the vast majority) of the participants had no history of inflammatory bowel disease and no family history of hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, or sporadic CRC; (v) effect estimates and the corresponding 95% confidence intervals (CIs) were adjusted for age at least; and (vi) studies with an observational design (prospective cohort, retrospective cohort, or case–control studies). For studies with multiple publications from the same population source, only data from the most recent publication was included.

Data extraction and quality assessment

Two reviewers (J.P. and L.X.) extracted the data independently, and disagreements were resolved by consensus. The following data were extracted from each study: first author, publication year, indications for index colonoscopy, study design, setting, study period, number of participants, age at baseline, sex, duration of follow-up, effect estimates with 95% CIs, and adjustments. For studies with several multivariable-adjusted estimates, we extracted those reflecting the greatest degree of control for potential confounders. The primary outcomes were overall CRC incidence and mortality; the secondary outcomes were CRC incidence and mortality according to indications for colonoscopy, site of cancer, sex, and study design. The study quality was assessed using the Newcastle–Ottawa Scale (37), and the studies awarded seven or more stars were considered of high quality.

Statistical analysis

The measure of effect of interest was the relative risk (RR). Odds ratio, rate ratio, risk ratio, or hazard ratio yielded similar estimates of RR (38). Study-specific RR estimates were combined using a random-effects model, which considers both within- and between-study variation (39). Statistical heterogeneity among studies was evaluated by I^2 and Q statistics (40). Studies with an I^2 of <25%, 25–50%, 50–75%, and >75% were considered to have no, low, moderate, and high heterogeneity, respectively. An I^2 of >50% indicated significant heterogeneity (41). Sensitivity analysis was performed to evaluate the robustness of results, in which pooled estimates were computed omitting one study in each turn (42). Subgroup analysis was performed by indications for colonoscopy, site of cancer, sex, and study design. We compared the pooled RR estimates from different subgroups with a test of interaction (43). Publication bias was evaluated by Begg's test and Egger's test (44,45). All statistical analyses were performed with Stata software, version 12.0 (Stata Corp, College Station, TX). $P<0.05$ was considered statistically significant.

RESULTS

Literature search

PubMed and EMBASE were searched for relevant studies. As shown in **Figure 1**, a total of 1,247 studies met our search strategy.

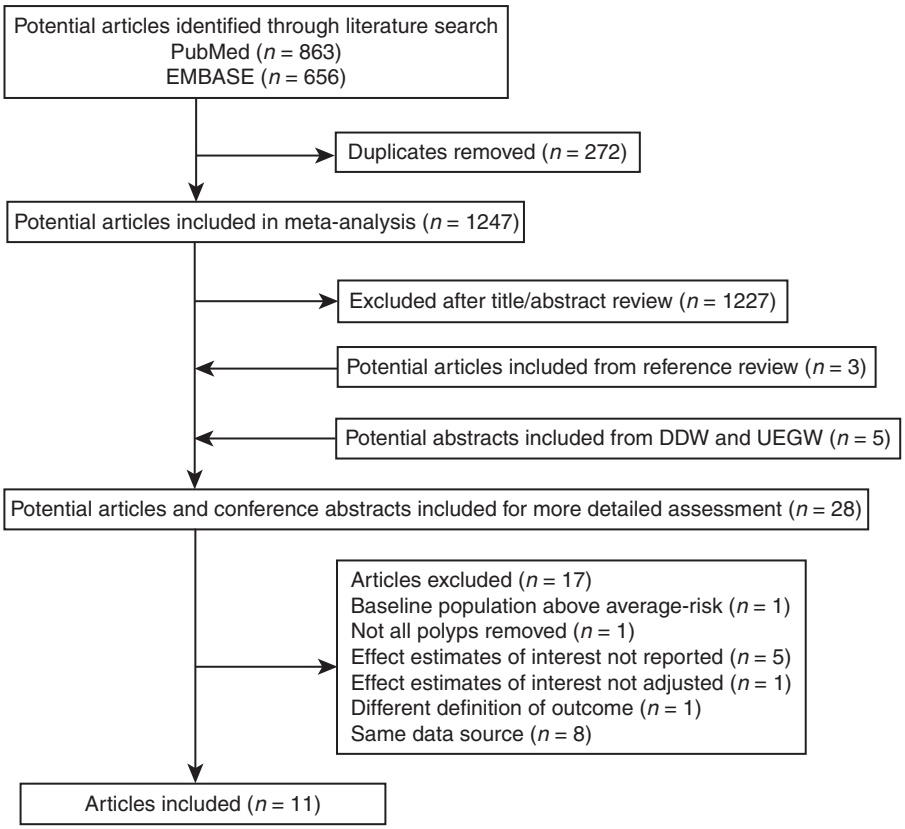

Figure 1. Flow diagram of literature search and study selection.

After title/abstract review, we excluded 1,227 studies; after including 3 studies from reference review and 5 abstracts from DDW and UEGW, 28 studies remained. Another 17 studies were further excluded for reasons listed as follows: baseline population above average risk (*n*=1) (46), not all polyps removed (*n*=1) (47), effect estimates of interest not reported (*n*=5) (17,48–51), effect estimates of interest not adjusted (*n*=1) (52), different definition of outcome (*n*=1) (53), and same data source (*n*=8) (25,27,54–59). Finally, 11 studies were included in the meta-analysis (18,19,28,29,60–66).

Study characteristics and quality assessment

Details of the 11 included studies are listed in **Table 1**. Of the 11 observational studies, 5 were cohort studies (18,60–63) (3 prospective (18,60,61) and 2 retrospective (62,63)) and 6 were case–control studies (19,28,29,64–66). A total of 1,499,521 individuals were included, in which 1 study enrolled over 1,000,000 individuals (62), 7 studies enrolled 10,000–100,000 individuals each (18,28,60,61,63–65), and the other 3 enrolled <10,000 individuals each (19,29,66). Duration of follow-up for cohort studies (or corresponding duration from exposure of colonoscopy to CRC occurrence/death for case–control studies) varied, with three studies of over 10 years (18,60,61), seven studies of 5–10 years (19,28,29,62–65), and one study of <5 years (66). Six studies reported CRC incidence only (19,29,61,63,64,66), four reported CRC mortality only (18,28,60,65), and one reported both CRC incidence and mortality (62). Indication(s) for index colonoscopy varied among studies, with screening in three studies (18,19,60), screening/diagnostic in five (28,29,61–63), and diagnostic in three (64–66). Eight studies were conducted in North America (18,28,29,60,62–65), and three in Europe (19,61,66). In each of the 11 studies, colonoscopy at baseline (combination of polypectomy with removal of all detected lesions and negative colonoscopy) was compared with no colonoscopy.

Effect estimate of the study by Brenner *et al.* (19) was extracted from authors' reply letter in which a widely accepted definition of screening exposure was adopted (67,68). One study by Müller and Sonnenberg (64) separately reported effect estimates for colon and rectal cancer, and we included the combined RR by pooling the two estimates using a random-effect model.

Strategies for excluding CRC cases to form the group of patients with non-malignant findings at the index colonoscopy varied among studies: two studies excluded CRC cases diagnosed at the index colonoscopy (64,65), four studies excluded CRC cases diagnosed at or within 6 months (exclusion window) of the index colonoscopy (28,29,63,66), one study used a longer exclusion window of 12 months (19), three studies used variable exclusion windows ranging from 0 to 24 or 36 months (18,60,61), and one study used a variable exclusion window ranging from 0 to 60 months (62).

Results for study quality assessment are also shown in **Table 1** (for details see **Supplementary Appendices C and D**). Six out of the 11 studies were awarded seven or more stars, indicating high study quality.

Table 1. Characteristics of included studies

Authors (reference)	Indications for the index colonoscopy	Study design	Setting	Study period	Number of participants[a]	Age at enrollment (years)[b]	Men (%)	Duration of follow-up[c]	Adjustments	Study quality[d]
Eldridge *et al.* (60)	Screening	Prospective cohort	NIH-AARP Study, USA	1995–2008	68,531 (22,780/45,751)	50–71[e]	62	11 years[f]	Age, sex, hormone replacement therapy, education, race, diabetes, family history of CRC, and healthy lifestyle score	6
Nishihara *et al.* (18)	Screening	Prospective cohort	Nurses' Health Study and Health Professionals Follow-up Study, USA	1988–2012	88,902 (NA/NA)	Men: 42–77[e] Women: 32–57[e]	35.7	1,841,586 person-years	Age, sex, calendar year of the questionnaire cycle, body mass index, smoking status, family history of CRC, status with respect to regular use of aspirin, physical activity level, red-meat intake, total caloric intake, alcohol intake, folate intake, calcium intake, multivitamin use, nonsteroidal antiinflammatory drug use, and cholesterol-lowering drug use	7
Brenner *et al.* (19)[g]	Screening	Case–control	Rhine-Neckar, Germany	1993–2010	4,800 (2,516/2,284)	70[h]	59	1–10 years[e]	Age, sex, county of residence, education, family history of CRC, smoking, body mass index, ever regular use of NSAIDs, ever use of hormone replacement therapy, and ever participation in a general health screening examination	7
Morois *et al.* (61)	Screening/ diagnostic	Prospective cohort	E3N Study, France	1990–2008	92,048 (37,459/54,589)	Colonoscopy group: 49.9±6.6 Control group: 48.8±6.6	0	15.4 years[h]	Age, physical activity, smoking status, family history of CRC, educational level, and body mass index	7
Jacob *et al.* (62)	Screening/ diagnostic	Retrospective cohort	Ontario, Canada	1996–2007	1,089,998 (86,837/1,003,161)	62[f]	45.1	Incidence: 7 years Mortality: 5 years	Age, sex, comorbidity as measured by the Adjusted Diagnostic Groups case-mix system, neighborhood income quintile, rural residence, and PCP characteristics (age, sex, and country of medical education)	9
Wang *et al.* (63)	Screening/ diagnostic	Retrospective cohort	SEER-Medicare, USA	1998–2005	53,676 (12,266/41,410)	Colonoscopy group: 73.1±3.8 Control group: 73.3±4.0	39.3	Colonoscopy group: 5 years[f] Control group: 5.3 years[f]	Age, sex, race, zip code, income and educational level, metropolitan county residence, endoscopist subspecialty, and SEER registry stratification	7
Baxter *et al.* (28)	Screening/ diagnostic	Case–control	SEER-Medicare, USA	1991–2007	37,099 (9,458/27,641)	Cases: 79.9 (70.0–89.9)[i] Controls: 79.8 (69.1–90.8)[i]	42.6	9.4 years[h]	Age, sex, race, SEER registry, individual comorbid conditions, socioeconomic status, and urban/rural status	6

Table 1 continued on following page

Table 1. Continued

Authors (reference)	Indications for the index colonoscopy	Study design	Setting	Study period	Number of participants[a]	Age at enrollment (years)[b]	Men (%)	Duration of follow-up[c]	Adjustments	Study quality[d]
Kahi *et al.* (29)	Screening/ diagnostic	Case–control	Veterans Affairs, USA	1997–2007	2,492 (623/1,869)	81.22±3.89	98.7	5.19 years[f]	Age, sex, race, NSAID use, and Charlson comorbidity index.	5
Müller and Sonnenberg (64)[j]	Diagnostic	Case–control	Veterans Affairs, USA	1981–1993	32,702 (16,351/16,351)	Cases (CC): 67.2±9.3 Cases (RC): 66.2±9.4 Controls: 57.0[f]	97.8	Cases (CC): 6.8 years[f] Cases (RC): 6.1 years[f] Controls: 7.1 years[f]	Age, sex, and race.	4
Müller and Sonnenberg (65)	Diagnostic	Case–control	Veterans Affairs, USA	1978–1992	20,889 (4,358/16,531)	Cases (CC): 69.1 (68.7–69.5)[k] Cases (RC): 68.3 (67.8–68.8)[k] Controls: 57.0 (57.0–57.1)[k]	97.7	Cases: 6.4 years[f] Controls: 8.3 years[f]	Age, sex, race, number of other colorectal procedures, procedures other than colorectal, length of coverage by the Department of Veterans Affairs, and presence of arthritis-related diseases.	4
Mulder *et al.* (66)	Diagnostic	Case–control	The Netherlands	1996–2005	8,384 (594/7,790)	Cases: 69.5±11.9 Controls: 69.3±11.9	51.7	2.8 years[h]	Age, sex, calendar time, duration of follow-up before the date of diagnosis (index date), and IBD.	7

CC, colon cancer; CRC, colorectal cancer; IBD, inflammatory bowel disease; NA, not available; NIH-AARP, National Institutes of Health American Association of Retired Persons; NSAID, nonsteroidal anti-inflammatory drug; RC, rectal cancer.

[a]Numbers in parentheses represented number of participants in colonoscopy/control group (cohort studies), or number of cases/controls (case–control studies).

[b]Values for age were presented as median (interquartile range) or mean±s.d. unless indicated otherwise.

[c]Duration of follow-up for cohort studies, and duration from the exposure of colonoscopy to CRC occurrence/death for case–control studies.

[d]Study quality was assessed based on the Newcastle–Ottawa Scale (range, 0–9 stars), details see **Supplementary Appendices C and D** online.

[e]Range.

[f]Mean.

[g]Effect estimate was extracted from authors' reply letter by Brenner *et al.* (68).

[h]Median.

[i]Median (range).

[j]Effect estimate was calculated by pooling the two separate estimates for colon and rectal cancer.

[k]Mean (95% CI).

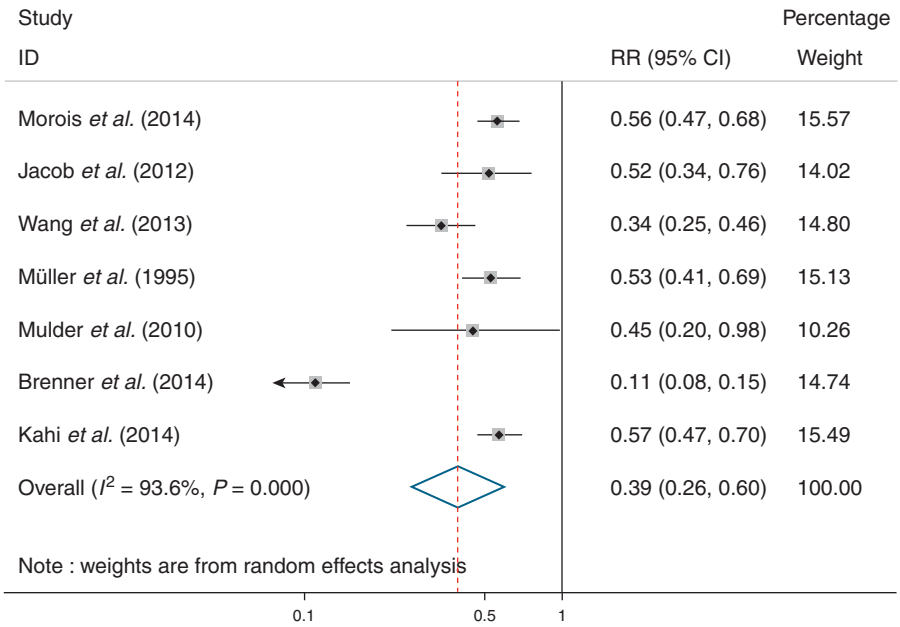

Figure 2. Forest plot of reduction in colorectal cancer incidence after colonoscopy in patients with non-malignant findings.

Primary outcomes

Seven studies were included for outcome of overall CRC incidence. Pooling by a random-effect model (**Figure 2**) yielded a pooled RR of 0.39 (95% CI: 0.26–0.60), corresponding to a 61% RR reduction in CRC incidence after colonoscopy in patients with non-malignant findings. There was evidence of high heterogeneity among studies (I^2=93.6%, P<0.001). Sensitivity analysis revealed that the study by Brenner *et al.* (19) substantially influenced pooled RR. After excluding this study, there was evidence of low heterogeneity (I^2=44.7%, P=0.11), and pooled RR was 0.51 (95% CI: 0.43–0.59). Funnel plot asymmetry test for publication bias was negative using both Begg's test (P=0.07) and Egger's test (P=0.43).

Five studies were included for outcome of overall CRC mortality. Pooling by a random-effect model (**Figure 3**) yielded a pooled RR of 0.39 (95% CI: 0.35–0.43), corresponding to a 61% RR reduction in CRC mortality after colonoscopy in patients with non-malignant findings. There was no evidence of heterogeneity among studies (I^2=12.0%, P=0.34). Sensitivity analysis further confirmed the robustness of our findings. Funnel plot asymmetry test for publication bias was negative using both Begg's test (P=0.22) and Egger's test (P=0.35).

Secondary outcomes

Subgroup analyses were conducted for the following secondary outcomes of CRC incidence (**Table 2**). As for indications, screening colonoscopy was associated with greater protection (RR: 0.11; 95% CI: 0.08–0.15) than screening/diagnostic and diagnostic colonoscopies (RR: 0.51; 95% CI: 0.43–0.59; $P_{interaction}$<0.001). As for site of cancer, colonoscopy was associated with a 28% non-statistically significant reduction in proximal CRC incidence (RR: 0.72; 95% CI: 0.50–1.03), whereas protection against distal CRC (RR: 0.32; 95% CI: 0.20–0.50) was much stronger ($P_{interaction}$=0.01). As for sex, results were similar for studies in men (RR: 0.55; 95% CI: 0.47–0.64) and women (RR: 0.56; 95% CI: 0.47–0.66; $P_{interaction}$=0.88). As for study design, results were also similar for cohort (RR: 0.47; 95% CI: 0.34–0.65) and case–control studies (RR: 0.35; 95% CI: 0.16–0.77; $P_{interaction}$=0.50).

Subgroup analyses were conducted for the following outcomes of CRC mortality (**Table 3**). As for indications, screening colonoscopy was associated with somewhat greater protection (RR: 0.36; 95% CI: 0.29–0.46) than screening/diagnostic and diagnostic colonoscopies (RR: 0.40; 95% CI: 0.32–0.49), but the difference between subgroups was not statistically significant ($P_{interaction}$=0.51). As for the site of cancer, colonoscopy was associated with less protection against proximal CRC mortality (RR: 0.57; 95% CI: 0.52–0.63) than distal CRC (RR: 0.18; 95% CI: 0.11–0.31; $P_{interaction}$<0.001). As for sex, colonoscopy provided a similar magnitude of protection for men (RR: 0.36; 95% CI: 0.32–0.40) and women (RR: 0.23; 95% CI: 0.10–0.54; $P_{interaction}$=0.30). As for study design, results were similar in the cohort (RR: 0.34; 95% CI: 0.26–0.45) and case–control studies (RR: 0.40; 95% CI: 0.37–0.43; $P_{interaction}$=0.26).

DISCUSSION

Overview

This meta-analysis shows that CRC incidence and mortality in patients with non-malignant findings were both 61% lower after colonoscopy. The protective effect was more prominent after screening colonoscopy, corresponding to an 89% reduction in CRC incidence.

Interpretations of study findings

Our study is the first meta-analysis to quantify the magnitude of protection against CRC that patients with non-malignant findings benefit from colonoscopy. When interpreting the study results, both the overall effect of colonoscopy and the individual

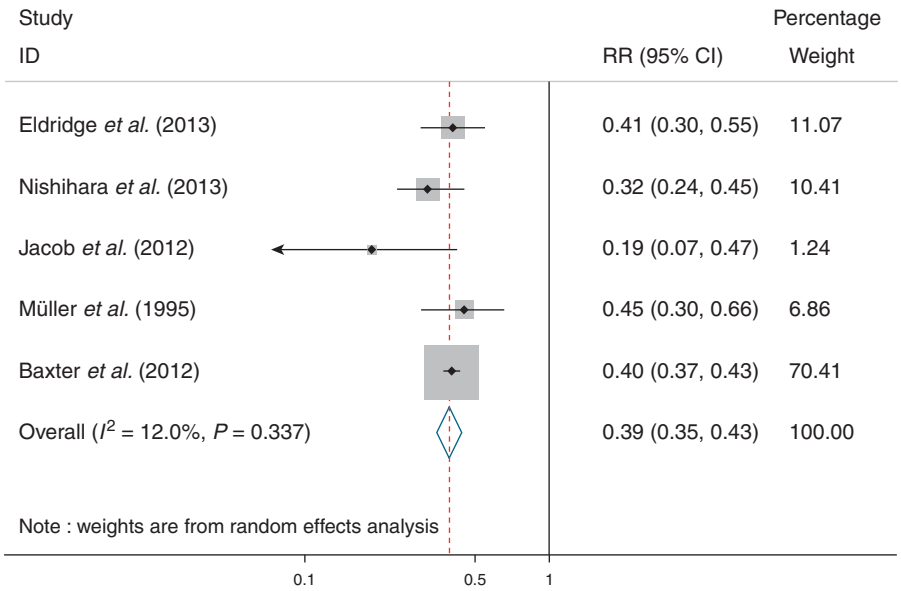

Figure 3. Forest plot of reduction in colorectal cancer mortality after colonoscopy in patients with non-malignant findings.

Table 2. Subgroup analyses for reduction in colorectal cancer incidence after colonoscopy in patients with non-malignant findings

Subgroups	Number of studies	Pooled RR (95% CI)	I^2 (%)	$P_{heterogeneity}$	$P_{interaction}$
Indications for colonoscopy					
Screening (19)	1	0.11 (0.08–0.15)	NA	NA	
Screening/diagnostic and diagnostic (29,61–64,66)	6	0.51 (0.43–0.59)	44.7	0.11	<0.001
Site of cancer					
Proximal CRC (29,61–63)	4	0.72 (0.50–1.03)	69.9	0.02	
Distal CRC (29,61–63)	4	0.32 (0.20–0.50)	75.7	0.01	0.01
Sex					
Men (29,62,64)	3	0.55 (0.47–0.64)	0.0	0.89	
Women (61,62)	2	0.56 (0.47–0.66)	0.0	0.82	0.88
Study design					
Cohort (61–63)	3	0.47 (0.34–0.65)	73.7	0.02	
Case–control (19,29,64,66)	4	0.35 (0.16–0.77)	96.3	<0.001	0.50

CI, confidence interval; CRC, colorectal cancer; NA, not available; RR, relative risk.

effect of screening colonoscopy derived from subgroup analysis are informative. As regular colonoscopy screening has not been implemented even in many developed countries (20,21), the primary outcome, which estimated the benefit derived from both screening and diagnostic colonoscopies, reflected the effect of regular colonoscopy in routine clinical practice. Subgroup analysis of screening colonoscopy provides data on the maximum cases of CRCs and CRC-related deaths that may be prevented in patients with non-malignant findings by population-based screening programs in standardized conditions, which is more important from a public health perspective.

There are several explanations for our findings. First, removal of all detected polyps (i.e., clearing colonoscopy) is the main modality responsible for the decreased CRC risk (69,70), while individuals with negative findings are inherently associated with lower risks of developing CRC even compared with postpolypectomy individuals (71). Second, interval CRCs could hardly be avoided because of factors such as missed lesions at the index colonoscopy, rapid growth of specific type of neoplasms, and incomplete resection of polyps (72). Therefore, both the aspects should be considered when interpreting the study findings.

In subgroup analysis, our study showed more prominent protection against CRC incidence by screening colonoscopy than

Table 3. Subgroup analyses for reduction in colorectal cancer mortality after colonoscopy in patients with non-malignant findings

Subgroups	Number of studies	Pooled RR (95% CI)	I^2 (%)	$P_{heterogeneity}$	$P_{interaction}$
Indications for colonoscopy					
Screening (18,60)	2	0.36 (0.29–0.46)	10.4	0.29	
Screening/diagnostic and diagnostic (28,62,65)	3	0.40 (0.32–0.49)	25.7	0.26	0.51
Site of cancer					
Proximal CRC (18,28,62)	3	0.57 (0.52–0.63)	0.0	0.66	
Distal CRC (18,28,62)	3	0.18 (0.11–0.31)	63.9	0.06	<0.001
Sex					
Men (18,28,62,65)	4	0.36 (0.32–0.40)	0.0	0.69	
Women (18,28,62)	3	0.23 (0.10–0.54)	93.5	<0.001	0.30
Study design					
Cohort (18,60,62)	3	0.34 (0.26–0.45)	28.1	0.25	
Case–control (28,65)	2	0.40 (0.37–0.43)	0.0	0.57	0.26

CI, confidence interval; CRC, colorectal cancer; RR, relative risk.

colonoscopy with indications of screening/diagnostic and diagnostic ($P_{interaction}$<0.001), and, similar tendency was observed for CRC mortality (RR: 0.36 (0.29–0.46) vs. 0.40 (0.32–0.49); $P_{interaction}$=0.51), as screening detects a different spectrum of findings (e.g., fewer polyps) compared with that diagnosed in the symptomatic population (35,73,74). Our results showed that colonoscopy was less effective in preventing proximal CRC incidence and mortality (both $P_{interaction}$<0.05) than distal CRC in patients with non-malignant findings, which might be explained by several factors concerning endoscopists, patients, and tumor biology: proximal serrated polyps could be easily missed by endoscopists because of flat or sessile appearance; patients' poor bowel preparation usually results in incomplete colonoscopy examination; differences in tumor biology exist between proximal and distal lesions of the colorectum (75,76).

Novelty of the study

Two previous meta-analyses are important studies on the effect of colonoscopy (30,31). Brenner *et al.* (30) found that screening colonoscopy is associated with 69 and 68% reductions in CRC incidence and mortality, respectively, and Elmunzer *et al.* (31) concluded that colonoscopy reduces CRC mortality by 57%. Novelty of our meta-analysis are threefold. First, in the two meta-analyses, patients with malignant findings were enrolled in some included studies but not in others. The significant heterogeneity of baseline population may strongly affect generalizability of their results in the general population. Therefore, we enrolled in our meta-analysis patients with non-malignant findings, a more homogeneous group constituting over 90% of the yield of colonoscopy in clinical practice (32,33) and featured with non-malignant nature, mostly non-surgical treatment, longer surveillance interval, and better prognosis compared with malignant findings (34,35). Second, the effect of screening colonoscopy and the effect of colonoscopy regardless of indication were separately reported in the two meta-analyses, without comparison, whereas our subgroup analysis found a more prominent effect of screening colonoscopy over screening/diagnostic and diagnostic colonoscopies on reducing CRC incidence. Third, with expanded colonoscopy indications (including both screening and diagnostic), study outcomes (including both incidence and mortality), and an updated inclusion of recent studies (18,29), our study (n=1,499,521) is responsible for a more robust conclusion with a larger sample size.

Study limitations

Our study has several limitations. First, in addition to excluding detected CRCs (CRCs diagnosed at or within 6 months of the index colonoscopy) to arrive at non-malignant findings at the index colonoscopy, five of the eleven included studies also excluded interval CRCs (CRCs diagnosed within 6 to 36 (or even 60) months of the index colonoscopy) (18,19,60–62). As interval CRCs certainly argue against the protective effect of colonoscopy (77,78), results of our study might be biased, causing overestimation of the magnitude of protection by colonoscopy. Therefore, study results should be interpreted with caution. Second, it should be noted that indications for colonoscopy according to original publications of some studies may not reflect real circumstances, e.g., studies by Nishihara *et al.* (18) and Eldridge *et al.* (60) initiated earlier than the nationwide introduction of screening colonoscopy. This may offer one of the explanations for the non-significant difference between the effect of screening vs. screening/diagnostic and diagnostic colonoscopy on CRC mortality. Third, statistical heterogeneity was significant for outcome of incidence. This might be explained by the differences in population enrolled, intervention strategy, and study designs. After excluding the study by Brenner *et al.* (19) (screening was the only indication for colonoscopy), statistical heterogeneity became non-significant.

Fourth, results of our study might be biased due to several other factors. Overestimation of the protective effect of colonoscopy might be caused by selection bias introduced by observational studies, e.g., participants in the colonoscopy (exposed) group tended to be more health-conscious (79), whereas underestimation of the

results might be caused by contamination of the control (unexposed) group, e.g., individuals with adenomas in this group may present with symptoms and therefore receive colonoscopy examination with polypectomy (80). Moreover, the initial age for screening in one study (18) is earlier than the guideline-recommended 50 years of age. In this sense, our results should be interpreted with caution, and randomized trials may better resolve this problem. Fifth, our study did not quantify individual CRC risk after either polypectomy or negative colonoscopy, as only one study by Nishihara *et al.* (18) reported effect estimates in subgroups of patients with polyps and those with negative findings.

CONCLUSIONS

In conclusion, findings from this meta-analysis of observational studies indicate that CRC incidence and mortality in patients with non-malignant findings are significantly reduced after colonoscopy, especially after screening colonoscopy. This provides additional evidence for the effectiveness of colonoscopy in the general population.

CONFLICT OF INTEREST

Guarantors of the article: Zhao-Shen Li, MD and Liang-Hao Hu, MD.

Specific author contributions: Jun Pan contributed to the study concept and design, data acquisition and interpretation, and drafting and final approval of the manuscript; Lei Xin and Yi-Fei Ma contributed to the data acquisition, data analysis and interpretation, and revision and final approval of the manuscript; and Zhao-Shen Li and Liang-Hao Hu contributed to the study concept and design, data analysis and interpretation, drafting and revision of the manuscript, and final approval of the manuscript.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Both screening and diagnostic colonoscopy have an important role in colorectal cancer (CRC) prevention.
- ✓ Negative findings, hyperplastic polyps, adenomas, and serrated lesions constitute over 90% of the yield of colonoscopy in clinical practice, which are non-malignant in nature and associated with better prognosis compared with malignant findings.
- ✓ There is no meta-analysis quantifying the effect of colonoscopy in patients with non-malignant findings and further demonstrating the potentially more marked effect of screening over diagnostic colonoscopy.

WHAT IS NEW HERE

- ✓ Colonoscopy, regardless of indication of screening or diagnostic, significantly reduced CRC incidence and mortality in patients with non-malignant findings.
- ✓ The protective effect was more prominent for screening colonoscopy compared with diagnostic one.
- ✓ Greater protection was seen against distal CRC than proximal CRC in patients with non-malignant findings.

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Review

Colonoscopy for Colorectal Cancer Screening

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Abstract

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States. Many, if not most, cases arise from premalignant lesions (adenomas) which may be identified and removed prior to becoming frankly malignant. For over a decade, colonoscopy has been the preferred modality for both CRC screening and prevention in the US. Early reports suggested that colonoscopic screening imparted a 90% risk reduction for colorectal cancer. Subsequent studies showed that estimate to be overly optimistic. While still an outstanding CRC screening and detection tool, colonoscopy has several important limitations. Some of these limitations relate to the mechanics of the procedure such as the risk of colonic perforation, bleeding, adverse consequences of sedation, and the inability to detect all colonic polyps. Other limitations reflect issues with patient perception regarding colonoscopy which, at least in part, drive patient non-adherence to recommended testing. This review examines the literature to address several important issues. First, we analyze the effect of colonoscopy on CRC incidence and mortality. Second, we consider the patient-based, periprocedural, and intraprocedural factors which may limit colonoscopy as a screening modality. Third, we explore new techniques and technologies which may enhance the efficacy of colonoscopy for adenoma detection. Finally, we discuss the short and long-term future of colonoscopy for CRC screening and the factors which may affect this future.

Key words: Colonoscopy, colon cancer, screening, adenocarcinoma

1. Introduction

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States (1). In 2008, the most recent year for which there are reliable statistics, 142,950 people were diagnosed with colorectal cancer and 52,857 people died from the disease. This is despite the fact that the incidence has dropped from 59.5 per 100000 people in 1975 to 44.7 per 100000 people in 2007 while mortality has decreased from 28.6 per 100000 people in 1976 to 16.7 per 100000 people in 2007.(2) Unfortunately, most early cancers are clinically silent making screening for frank malignancy as well as premalignant lesions an attractive option. While there are many potential screening modalities, the major clinical guidelines all recommend colonoscopy as the preferred test as it detects both cancers as well as precancerous lesions with high reliability. Moreover, the literature suggests a reduction in cancer incidence and mortality for those who undergo colorectal cancer screening via colonoscopy. From a population health standpoint, colonoscopy is also cost effective with cost-benefit analysis showing screening colonoscopy well within the acceptable rates of 20000$/year life saved. (3)

Screening colonoscopy is of potential benefit to patients in two ways. First and most commonly, it can detect and facilitate removal of precancerous polyps.

Several studies have shown that colonoscopy with polypectomy is effective at decreasing CRC (see section II). In addition, a negative colonoscopy, if of sufficient quality, has a high negative predictor value for CRC development which is some studies extends to 20 years. (4) Second, colonoscopy may detect cancers at an early stage where there is a higher chance for cure than in those discovered in a more advanced stage.

While a highly effective screening and prevention tool, colonoscopy is imperfect. Numerous studies have shown that there is a substantial, though variable, polyp miss rate even among expert examiners who know that they are being scrutinized. There are multiple factors which contribute to this miss rate, and it is likely that not all the reasons are yet known. This article will discuss the various factors – systemic, patient –based, and endoscopist-based, which play a role in adenoma detection. We will also discuss the current methods, both systemic and technical, of improving colonoscopy as a screening tool. Finally, we will discuss the future of colonoscopy for CRC screening.

2. Benefits of Colonoscopy for CRC Screening

In patients who do not have inflammatory bowel disease, most primary colorectal cancers are thought to derive from precancerous polyps. (5) The majority of these polyps arise over the course of a decade or more via a well described series of mutations. For years, our understanding of adenoma prevalence was that 25% of males and 15% of females will have adenomatous polyps by the time they reach age 50. Recent studies conducted in both academic and community practice settings suggest that the true rate may be higher. (6) Moreover, the vast majority of these polyps, and even early cancers, are asymptomatic. (5) Since colonoscopy allows for the detection and removal of these polyps prior to the progression to cancer, it would seem to be an ideal screening tool. Several critical questions needed to be answered, however, before colonoscopy could be considered a valid (and valuable) screening tool. For example, it has to be superior to other available screening modalities. In particular, it must be compared to flexible sigmoidoscopy (FS), a less invasive screening method which does not require sedation and which had been shown to reduce colorectal cancer incidence and mortality.(7) Several trials address the safety and efficacy of colonoscopy as a primary screening test in asymptomatic individuals. The first was the VA Cooperative Study-380 published by Lieberman and colleagues in 2000. (8) This cohort study examined 3196 subjects, 3121 of whom underwent a complete colonoscopy. While patients with adenomas in the distal colon were statistically more likely to have adenomas in the proximal colon than those without such lesions, 52 percent of those with advanced proximal neoplasia had no distal adenomas. Thus, advanced proximal lesions would have been missed in more than half the patients in an FS based screening program. One significant limitation of this study is the fact that nearly 97 percent of the subjects were male. To determine the efficacy of primary screening colonoscopy in asymptomatic woman, Schoenfeld and colleagues conducted the CONCeRN trial. (9) This prospective cohort study of 1463 women undergoing complete colonoscopy found that only 35% of women with proximal neoplasia would have had their lesions detected by flexible sigmoidoscopy. The authors concluded that colonoscopy may be the preferred CRC screening tool for women. From these studies, it is clear that colonoscopy detects more adenomas than flexible sigmoidoscopy. A more vital concern, perhaps, is the effect of adenoma removal (i.e. polypectomy) on colorectal cancer incidence and mortality.

Effect on Colon Cancer Incidence

There are reasonably good data to support a decrease in colorectal cancer in those undergoing colonoscopy with polypectomy. The first study to suggest this benefit was the National Polyp Study which was published in 1993. (10) While this study had some significant limitations, such the use of historical controls, its conclusion that colonoscopic polypectomy could prevent between seventy six and ninety percent of colorectal cancers. A similar study conducted in Italy by Citarda and colleagues showed a reduction in colon cancer incidence of sixty-six percent. (11) Again, this study was limited in that controls were not taken from a matched cohort, but rather a mathematical model was used to calculate the expected CRC incidence in a hypothetical group.

Effect on Colon Cancer Mortality

As for all outcomes of screening colonoscopy, the evidence for a reduction in CRC mortality is indirect. Nonetheless, the consistency of the data reassures us that a significant benefit is derived from colonoscopic screening, even if the magnitude of that benefit is not perfectly defined. Thus far, two primary study designs have been used to address the question: retrospective case-control studies and prospective cohort studies. While neither method has the strength of a randomized controlled trial, most study authors' have worked diligently to shore up the statistical limitations inherent in the studies' designs and these

studies represent the best available science on which clinicians must base patient care decisions. These studies are listed in table 1 below. (12-15)

In 2009, Baxter and colleagues published a population based, case-control study examining subjects who received a CRC diagnosis between 1996 and 2001 and who died of CRC by 2003. They matched each case 1:5 with a control. The authors noted an impressive 67% reduction in left sided colorectal cancer but none in right sided diseases. This study has several important limitations worth noting. The cecal intubation rate of 79-83% is substantially below the 95% rate which would be expected for screening examinations and 90% for all examinations. (16,17) While the authors rightly controlled for this by performing a sub-analysis on "complete" colonoscopies, the low rate of cecal intubation may reflect overall poor colonoscopic technique (including inspection for adenomas) which such adjustments will not mitigate. Additional support for this theory is found in the low polyp detection rate of 26% in case patients. Current standards dictate a 25% adenoma detection rate in men and a 15% adenoma detection rate in women. (18) Given that a number of the polyps detected in the study were likely hyperplastic, one would expect a total polyp detection rate (adenomas + hyperplastic) to be in the 30-40% range. Another limitation is the fact that not all of the colonoscopies included were performed for screening. Patients with symptomatic cancers which prompted the examination would be cases based on the design, but would have more likelihood of having advanced disease, and thus less chance of benefitting from the screening test. Despite these limits, the difference in right and left sided benefit in this study is impressive and should not be lightly dismissed.

Singh *et al.* found a similar disparity in the protective benefit of colonoscopy. In his retrospective cohort study, Singh used Manitoba's claims database to compare CRC mortality between patients who had colonoscopic CRC screening versus the standardized CRC mortality rate for the general population. In examining 54,803 subjects, he noted a 29% overall reduction in CRC mortality, all of which was derived from a decrement in left-sided cancer deaths. Interestingly, when the authors stratified the data according to the specialty of the endoscopists, gastroenterologist conferred a reduction in right sided CRC of 59%. This strongly suggests that the type of examiner (and by extension their training and experience) matter greatly in optimizing the performance characteristics of colonoscopy as a CRC screening tool.

Rabeneck and colleagues performed a cohort study on all adults 50-90 years old living in Ontario on 1 January 1993 in which they followed subjects for 14 years and stratified them by the "intensity of colonoscopy use" in their region. They performed multivariable analysis adjusting for age, gender, comorbidity, income, and residence (urban vs. rural). Rabeneck found that for every 1% Increase in the complete colonoscopy rate, the hazard rate of death decreased by 3%. While there are a number of limitations to this study, including an inability to attribute causality, the magnitude of the effect, the size of the sample study, and the biologic plausibility of the finding offer food for thought.

The most recent study to address the effect of screening colonoscopy on CRC mortality was from the National Polyp study. The authors examined 2602 patient who had had adenomas removed via colonoscopic polypectomy and then were followed for a mean of 15.8 years. Compared to historical controls, this group enjoyed a 53% reduction in CRC. While this study is limited by the fact that endoscopists were all in expert centers, the results are nonetheless compelling, particularly because they are in keeping with prior studies in showing a clear reduction in mortality in association with screening.

Table 1: Major trials addressing a reduction in CRC mortality.

Author	Year	Design	N	CRC Mortality Reduction
Baxter[12]	2009	Case-Control	10,292 (Case) 51,460 (Control)	67% - left sided 1% (NS) -right-sided
Singh [13]	2010	Cohort	54,803	29% overall 47% left-sided 0% right-sided
Rabeneck[14]	2010	Cohort	2,412,077	3% decrease/1% increase in colonoscopy
Zauber [15]	2012	Cohort	2602	53% overall

3. Limitations to Colonoscopy for CRC screening

Adherence to Screening

Despite the impressive statistics cited above, CRC remains the number two cause of cancer-related death among Americans, largely because only one in three eligible patients over 50 is screened. There are multiple barriers that diminish adherence to CRC screening. Overcoming these obstacles may yield further declines in CRC incidence and mortality.

Barriers to CRC screening include lack of health insurance limiting access to care, aversion to bowel preparations, and fear of invasive procedures. Psychosocial barriers identified as "parasexual" sensitivities affecting adherence include homophobia or prior sexual trauma, fatalism, negative prior experiences with testing, and financial skepticism about screening recommendations. (19) A recent telephone survey of 454 ethnically diverse adults ≥ 50 showed fear of embarrassment, fear of getting AIDs, fear of procedural pain, and older age were all positive markers of avoiding CRC screening. (20) Fear of cancer and medical mistrust were shown to be positive markers for willingness to undergo CRC screening. An effective, patient-centered approach to CRC screening which addresses the particular barriers found in a given patient population may overcome these hurdles

The psychology literature suggests that too much choice can in itself be a deterrent to action. (21) While each screening modality has its own strengths and weaknesses, the array of options may confuse patients and lead to screening inertia. What is lost in that confusion is that adherence to *any* CRC screening is superior to no screening at all. (22) A patient-centered approach focusing on their preference in the decision process is crucial for successful CRC screening. For example, when test sensitivity was rated highest among the patient's concerns, colonoscopy was the preferred test. (23-26) This data must be interpreted with caution, however, as a large percentage of patients in these studies were white males with previous exposure to colonoscopy potentially biasing their choice. Supporting this notion are other studies showing that when patients of different genders and ethnicity who were, screening-naïve patients were questioned, colonoscopy was not the preferred choice. (27-28) Inadomi and colleagues tested this patient-centered approach in a study of 1000 patients who were randomized into three arms, FOBT only, colonoscopy only, or a choice of either test. (29) Those offered either FOBT only or a choice of either test were twice as likely to undergo screening versus those only offered colonoscopy. This study showed variance along racial/ethnic and gender lines, but it did not support previous conclusions that offering a choice resulted in lower screening rates. One major difference was that patients were only given two options which implies that giving some options is beneficial for adherence compared to discussing all available options. Several studies support the notion that, among lower socioeconomic groups, the cost of the screening test exerts a major influence on test preference and screening adherence. (30-31) A British study with free CRC screening showed that higher cancer fatalism, lower socioeconomic status, and lower self-rated health were more of an influence to not undergo screening than cost. (32) Clearly, patient preference plays an important part in the adherence to CRC screening recommendations. Addressing patient-specific concerns, particularly at the primary care level, should enhance screening adherence.

Periprocedural Factors

A thorough colonoscopic purge is crucial to successful colonoscopic CRC screening. Unfortunately, up to 25% of all patients have an inadequate bowel preparation at the time of their examination. A significant amount of interest has been centered on the quality of the bowel preparation and its effect on one's ability to detect polyps <10 mm. A recent study by Sherer *et al.* in 2012 investigated ADR in 3638 subjects undergoing colonoscopy, separating them into poor and fair versus good and excellent bowel preps. (33) Only a poor prep led to a significant decline in ADR, suggesting that a patient with a fair prep could follow standard post-procedure guidelines. Another recent study, however, came to a very different conclusion. Chokshi and colleagues performed a retrospective chart review on 373 patients with inadequate bowel preps to see what was detected at their follow up colonoscopy. (34) The mean interval between colonoscopies was 340 days for low risk patients and 271 for high risk patients. On repeat examination, the per adenoma miss rate was 47.9 percent. Even more concerning is that in patients with no adenomas detected on index colonoscopy, 33.8% had an adenoma on repeat examination and 18% had advanced adenomas, placing them at high risk for subsequent malignancy if undetected.

Intraprocedural factors

The intraprocedural limitations of screening colonoscopy may be divided into three categories: endoscopist factors, equipment factors, and anatomic/physiologic factors. The recommendations on minimizing endoscopist-related factors focus on ad-

herence to an accepted group of quality indicators. (18) Ultimately, these indicators are designed to ensure adequate and careful visualization of the colonic mucosa which should lead to enhanced polyp detection, which seems to correlate with enhanced adenoma detection. (35) The indicators consist of a cecal intubation rate within accepted standards (including photo documentation of the cecum), a withdrawal time of ≥ 6 minutes, and documentation of the adequacy of bowel prep. Achieving these benchmarks should help endoscopists achieve adenoma detection rates (ADR's) of ≥25% for men and ≥15% for women in asymptomatic patients older than 50 undergoing routine screening. The American College of Gastroenterology Task Force recommends that all endoscopy centers employ these indicators as part of a continuous quality improvement process with the goal of reducing variation in sensitivity among endoscopists. (18)

Cecal intubation with photodocumentation and adequate withdrawal time are both markers of complete and careful examination of the entire colon. Complete colonoscopies with cecal intubation helps avoid excessive costs from repeat procedures and additional follow-up radiologic studies. Withdrawal times of ≥ 6 minutes have been suggested as quality indicator to meet benchmark adenoma detection rates. (36) However a recent study has questioned whether endoscopic interventions that target this and other quality indicators are successful. (37) This meta-analysis reviewed 7 studies and 10 abstracts which examined the effects of performance improvement measures on various outcomes. Only one study intervention led to any improvement in ADR -- using a combination of an audible timer to ensure adequate withdrawal time and training on enhanced inspection techniques. Thus, there is little current evidence that interventions targeting these quality indicators have any beneficial effect on polyp or adenoma detection rates. It may be that benchmarks such as the 6 minute withdrawal time are simply surrogate markers for a careful and attentive endoscopist. Thus, targeting the marker rather than the performance trait may not lead to improved performance.

The inability to identify and remove precancerous and early cancerous lesions of the colon is the main factor associated with a suboptimal reduction in CRC incidence and mortality, particularly within the right colon. The current evidence supporting our understanding of the colonoscopic miss rate was outlined by Rex et al. (18) Originally, the National Polyp Study showed a risk reduction of 76 to 90% for CRC in patients with adenomas. (10) Subsequent studies, however, using techniques like tandem colonoscopy/sigmoidoscopy and computed tomography (CT) colonography showed miss rates for large adenomas from 6 to 17% and up to 27% for diminutive polyps. (38-42) Additionally, and even more concerning, were two large studies showing miss rates for CRC in the 4-6% range.(43-45) One conclusion which came out of these studies was that miss rates were variable between gastroenterologists and non-gastroenterologists thus supporting operator performance as a key factor in the ability of colonoscopy to detect and prevent CRC.(40, 46) While ongoing process improvement efforts target enhancing the ADR among endoscopists, recent evidence suggests that the protective effect of colonoscopy is not the same for the proximal and distal colon. Multiple studies offer competing views on the protective effects of colonoscopy on CRC in the right versus left colon. (12, 47-49) Lakoff et al. showed no protective effect in the right colon until ~year 7 of the study which suggested that screening sigmoidoscopy would be just as beneficial as a colonoscopy with lower costs and less risk. (49) Several factors have been addressed as possible explanations for the lack of improvement in right-sided CRC such as poor prep, endoscopic technique, and different polyp characteristics. Based on several recent studies, ADR is highly operator dependent, and thus is, in theory, correctable. (13, 50-51).

Risks of Colonoscopy

Finally, as with any screening procedure where asymptomatic patients are examined for pre-malignant conditions, the risks of the procedure should not outweigh the benefit. Previous meta-analysis has shown an overall low rate of serious complications of 2.8 per 1000 procedures with 85% of those occurring in patients with polypectomy. (52) A more recent study in 2012 showed higher rates of serious adverse events of 4.7 per 1000 and 6.8 per 1000 for screening and follow-up colonoscopies, respectively. (53) The more serious complications in those select patients undergoing screening/surveillance colonoscopies included cardiopulmonary deterioration, bowel perforation, hemorrhage, infection, and post-polypectomy syndrome. The rate of cardiopulmonary complications in one review of the CORI database was 0.9% for all procedures but made up 67% of the unplanned events in the peri-procedural period. Perforation rates are typically less than 0.1%. (54, 55) Bleeding is almost always related to polypectomy with an overall risk of 0.1 to 0.6% and a post-polypectomy risk of 0.5 to 2.2% and can occur immediately or after 7-10 days. (56-60). Risk factors for post-polypectomy bleeding include polyp size,

histology, number removed, location in the right hemi-colon, and current anti-coagulation use. (56-58, 61-69) Aspirin use alone was not associated with higher bleeding rates but dual therapy with either aspirin or NSAIDs and clopidogrel was. (57-59, 67) Post-polypectomy syndrome is a full-thickness burn from electrocautery resulting in local peritonitis and occurs in the range of .003 to 0.1%. (70) Transient bacteremia has been reported in up to 4% of patients with a range of 0-25% however no definite causal relationship between colonoscopy and infection have been made. (60, 71) It is worth noting that other activities of daily living including eating, flossing one's teeth, and defecation are associated with similar bacteremia rates. Overall risk of death with or without polypectomy was reported as 0.03% in over 370,000 colonoscopies in one 2010 review and when only colonoscopy-specific mortality studies were examined it was reported at 0.007%. (55, 70, 72-80)

Enhanced Optics/Ancillary Equipment

It has become widely accepted that the ADR is the main target of effective CRC screening and that colonoscopy is the most effective screening test to accomplish that goal. What has yet to be decided is what endoscopic techniques, assist-devices, and image-enhancing options will allow us to more effectively perform these screening and surveillance procedures. What has also yet to be determined is whether the ADR is the best quality indicator for colonoscopy or is the absolute number of adenomas per patient a better marker of effective CRC screening. These various new techniques, devices, and scope optics are all designed to allow us a more careful and complete mucosal inspection of the colon with the goal of improving our ADR. Though it is unlikely that CRC can be completely eliminated, hopefully these areas of research will help optimize colonoscopic screening.

Device manufacturers have developed a number of advanced imaging systems (narrow-band imaging, FICE, iscan, etc.) designed to enhance the identification of colonic lesions. Unfortunately, studies to date have not shown any of these technologies to be superior to standard definition white light endoscopy (SD-WLE). This area of colonoscopy is rapidly evolving, and will be discussed in a separate publication in this issue.

Though originally studied in the hopes of decreasing discomfort during colonoscopy, and potentially reducing or eliminating the need for sedation, water immersion/water exchange colonoscopy has shown promise in increasing ADR as well. This technique involves the use of water instead of air for colonic distention during scope insertion. Though not the primary endpoint for the original trials, the authors showed an overall ADR of 26.8% vs. 34.9% for adenomas >9 mm using the air and water technique, respectively. (81) A larger study in 2011 confirmed these findings.(82) ADR with water immersion was 57.1 vs. 46.1% with standard technique. After controlling for various factors like age, BMI, and bowel prep, they showed an 81% higher chance of finding an adenoma with the water immersion technique. Importantly, they showed a benefit in the right colon specifically, with a right colonic ADR of 45.8% vs. 34.6%. Though these findings need to be confirmed in additional studies, this represents an area of promising research.

Given the recent trials showing a diminished benefit of colonoscopy in the prevention of right sided cancers, investigators have been interested in enhancing visualization of the posterior aspect of the colonics folds, where, based on CT colonography data, many of the missed polyps reside. Retroflexing the colonoscope in the proximal colon is one methods of achieving this end. Hewett *et al.* examined the safety and yield of retroflexion in the right colon after a standard forward-viewing examination. They showed a high technical success rate of 94.4% and with an enhancement in proximal colonic ADR to studies with tandem examinations. (83) The per-protocol adenoma miss rate was 9.8% and the intention-to-treat miss rate was 4.4%. This study was completed in high-volume academic centers with experienced endoscopists and has yet to be reproduced so whether their results are transferable to the general population is still a matter of debate.

Retroscope

The Third Eye© retroscope (TER) is a device specifically designed to evaluate the proximal side of folds, especially in the right colon. The TER is a disposable device which is inserted via the working channel of the colonoscope and which is designed to automatically retroflex once a certain distance beyond the scope tip. Three studies involving over 900 patients examined the TER in regard to both polyp and adenoma detection rates. (84-86)(See table 2.) All of the studies showed an increase in the PDR and ADR and the results were similar among the three groups with respect to the right colon. An interesting and unexpected finding was that a high number of additional polyps and adenomas detected on the left side with the third eye retroscope. The withdrawal times were not statistically different from the quality standard of ≥ 6 minutes and did improve with operator experience in one of the studies. (85) It remains to

be seen if these results are replicable in a community setting. Given the additional costs of the equipment, studies demonstrating an additional benefit in either detection or safety over simple retroflexion in the right colon are needed. The one study looking at retroflexion in the right colon mentioned earlier had an adenoma detection rate for missed lesions in the right colon of 9.8% which is similar to that in these studies.

Table 2. Increase in polyp and adenoma detection when using the Third Eye™ retroscope.

		Polyps			Adenomas		
		Entire Colon	Right Colon	Left Colon	Entire Colon	Right Colon	Left Colon
Author	**Standard Colo**						
Waye et al		257	133	124	136	87	49
DeMarco et al		182	80	102	100	58	42
Leufkens et al		160			107		
	TER						
Waye et al		34	22	12	15	13	2
DeMarco et al		27	12	15	16	7	9
Leufkens et al		34			15		
	%additional yield with TER						
Waye et al		**13.2**	16.5	9.7	**11.0**	14.9	4.1
DeMarco et al		**14.8**	15.0	14.7	**16.0**	12.1	21.4
Leufkens et al		**19.8**			**14.3**	13.0	32.7

Cap-assisted Colonoscopy

Finally, cap-assisted colonoscopy (CAC) is another technique which has been examined as an adjunct to improve ADR. For CAC, a clear transparent cap in inserted over the tip on the colonoscope which helps displace the colonic folds and thus, theoretically, may improve visualization and ADR. Initial studies were done to look at other quality indicators like cecal intubation rates and the proposed surrogate of ADR, polyp detection rates. In all, three studies looked at either adenoma detection or miss rates. The first, by Hewett *et al.* in 2010, showed a lower adenoma miss rate for cap-assisted colonoscopy of 21% versus 33% for conventional colonoscopy (CC). (87) The next two studies involving over 1700 patients showed mixed results with the larger of the two studies showing no difference in ADR overall, in advanced/flat/depressed morphology, or in proximal versus distal. The second study showed a significant difference of 13% higher number of patients with at least one adenomas, though the only difference was for polyps <5 mm. (88-89) These studies differed significantly in their patient demographics with one groups subjects consisting of >90% white males versus 50:50 male:female in the other study. The only significant statistical significant finding in both studies was a longer cecal intubation time of around 1 minute with questionable clinical impact. A recent meta-analysis of 16 randomized controlled trials including nearly 9,000 subjects found only a marginal benefit of CAC for polyp detection (RR 1.08) and cecal intubation time (-0.64 minutes) but not on total colonoscopy time.(90)Whether such marginal benefits are of clinical significance remains to be seen.

4. Conclusion

As outlined above, colonoscopy is a powerful, but imperfect, test for detecting and preventing, colorectal cancer. In 2012, colonoscopy remains the dominant CRC screening method in the United States. The data clearly support the conclusion that colonoscopy significantly reduces left-sided CRC incidence and mortality. The limited benefit for right sided CRC is of great interest to researchers and clinicians alike and is likely multifactorial. Given several studies which show that the type of endoscopists performing the examination has a significant effect on right-sided benefit, further efforts are needed to standardize training for all colonoscopists and to identify and institute adequate quality assurance measures which are not specialty specific. Whether the specialties can agree on certain minimum training standards which include competency (versus number) based assessments remains to be seen. One thing is certain -- colonoscopy performance must improve if we are to realize the full benefits of CRC screening, particularly in the right colon.

From a societal standpoint, redoubled efforts to

educate the public about the importance of colorectal screening are needed. Moreover, clinicians and public health personnel must work together to remove barriers to CRC screening. These efforts should be based on the specific culture and needs of the population in question. There is no "one size fits all solution."

To date, many modifications have been made to the basic colonoscope with the hopes of improving performance for CRC. These have, thus far, proven to be of marginal benefit. With the exception of the TER, ancillary devices have fared no better. Despite it's proven improvement in adenoma yield, the TER remains untested in a non-academic setting and the cost/benefit ratio of using this device for all who undergo colonoscopic CRC screening is yet unknown. For now, colonoscopists are better served by honing their technique than by investing in new equipment.

The future of colorectal screening in the United States will ultimately depend on numerous factors. These include cost, efficacy, acceptability, and insurance coverage of the various options. It may well be that some combination of tests, such as colonoscopy with interval fecal DNA testing, will provide the optimal risk/benefit ratio, provided that costs can be lowered in to an acceptable range. Whatever the future holds, colonoscopy will be the linchpin of CRC screening in the near term. High quality colonoscopy, with tracking of recognized performance improvement measures is paramount to maximizing its effectiveness.

Disclaimer

The views expressed in this manuscript are those of the authors and do not reflect the official policy of the Department of the Army, the Department of Defense.

Competing Interests

The authors have declared that no competing interest exists.

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Botulinum toxin in the management of chronic migraine: clinical evidence and experience

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Abstract: Chronic migraine (CM) is a severely disabling neurological condition characterized by episodes of pulsating unilateral or bilateral headache. The United States Food and Drug Administration (FDA) approved onabotulinumtoxinA (Botox®) for the prophylactic treatment of CM in 2010. It has been shown that onabotulinumtoxinA is effective in the reduction of headache frequency and severity in patients with CM. Treatment is well tolerated by the patients. This review reports on the history of botulinum neurotoxin (BoNT) in CM and presents the current clinical evidence for the use of onabotulinumtoxinA in the treatment of CM.

Keywords: Botox®, botulinum neurotoxin, chronic daily headache, chronic migraine, onabotulinumtoxinA

Introduction

Migraine is a common neurological disorder featuring recurrent attacks of headache. Typical migraine attacks last for 4–72 h and involve headaches of the following characteristics: pulsating quality, unilateral location, moderate or severe intensity and aggravation by routine physical activity. Attacks can be accompanied with nausea, vomiting, photophobia and phonophobia [Headache Classification Committee of the International Headache Society, 2013].

As stated by the International Headache Society (IHS) classification, migraine has two major subtypes: migraine without aura and migraine with aura. Aura symptoms are focal, neurological symptoms usually occurring prior to or sometimes during a migraine attack. They are fully reversible and last for 5–60 min. It is possible that patients suffer from migraine attacks both without and with aura.

More relevant to clinical practice is the distinction between episodic migraine (EM) and chronic migraine (CM). Although not mentioned in the IHS Classification, the term EM is quite common in scientific literature and among clinicians. It refers to patients, who suffer from migraine attacks, but miss the criteria for CM.

CM originally described a migraine headache present on at least 15 days per month for more than 3 months. According to the 2nd edition of the IHS classification, the diagnosis of CM could only be applied in patients without medication overuse [Headache Classification Subcommittee of the IHS, 2004]. Because only very few patients met these strict criteria, the IHS revised its definition for CM. The new definition was published in 2006 [Olesen *et al.* 2006] and finally incorporated in the 3rd edition of the International Classification of Headache disorders in 2013. According to the revised criteria CM is currently defined as a headache occurring on at least 15 days per month for more than 3 months, with typical features of migraine on at least 8 days per month. Medication overuse no longer excludes the diagnosis of CM [Headache Classification Committee of the IHS, 2013].

Epidemiology

A review of international studies on the epidemiology of CM presents a wide range of prevalence figures [Natoli *et al.* 2010]. Depending on the definition used and the population studied these numbers range from 0% [Rasmussen *et al.* 1991] to 5.1% [Queiroz *et al.* 2006]. More recent studies using the current IHS definition report a

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prevalence of 0.91% in the US population [Buse *et al.* 2012] and 0.5% in the German population [Katsarava *et al.* 2011]. Several studies in the general population and in patients with CM show that women are more likely to be affected by CM than men [Aurora *et al.* 2011; Blumenfeld *et al.* 2010; Diener *et al.* 2007]. Adjusted prevalence increases for both women and men from adolescence to midlife and declines after the fifth decade of life. In the population subgroup with the highest adjusted prevalence of CM (women between age 40–49) 1.89% are affected by CM [Buse *et al.* 2012].

In recent years, various studies investigated differences between episodic and chronic migraineurs. Compared with episodic migraineurs, patients with CM are at risk of a wide range of comorbid conditions such as asthma, chronic obstructive pulmonary disease, obesity, heart disease, stroke, depression and anxiety [Buse, 2010]. Due to the high frequency of migraine attacks, medication overuse is highly common among chronic migraineurs. Interventional studies in patients with CM found rates of 40.9% [Cernuda-Morollón *et al.* 2014] to 50.4% [Khalil *et al.* 2014] for medication overuse.

Socioeconomic status is reduced in patients with CM compared with those with less frequent headache. They have a lower annual income, are less likely to be employed part or full time and more likely to be occupationally disabled [Adams *et al.* 2015; Buse *et al.* 2010]. Patients with CM require more primary care visits, specialist visits, emergency room visits and are hospitalized more often. Unsurprisingly, CM has an enormous negative impact on quality of life [Blumenfeld *et al.* 2011; Wang *et al.* 2013].

Management and pharmacologic treatment

Diagnosis of CM is based on the patient's history (including a headache diary) and neurological examination. In some patients, cerebral magnetic resonance imaging and lumbar puncture might be necessary in order to rule out secondary causes for headaches [Diener *et al.* 2015].

The main goal in the treatment of CM is to reduce the impact of migraine on patients' lives. Therefore, it is necessary to keep migraine attacks as rare, short and as less-impairing as possible. Various nonpharmacological measures are useful to prevent migraine attacks: trigger avoidance (caffeine, alcohol, stress), dealing with risk factors (losing weight, modify response to stressors, getting sufficient sleep) [Schwedt, 2014].

Pharmacological treatment of CM is based on two pillars: abortive treatment of acute migraine attacks and prophylactic treatment. The substances most commonly used for the abortion of migraine attacks are nonsteroidal anti-inflammatory drugs (NSAIDs) and triptanes. There is good clinical evidence, that both substance groups are effective in the abortive treatment of acute migraine attacks. On the other hand, it has been shown, that both NSAIDs and triptanes may lead to medication overuse headaches. Therefore, the challenge is to restrict migraine-abortive substances to the least amount necessary. This observation highlights the special importance of prophylactic treatment in patients with CM. Generally, prophylactic medication can be given as soon as the diagnosis of CM is established. The choice of which substance is applied should be made with regard to the patient's comorbidities [Straube *et al.* 2012].

Because most clinical studies focused on EM, studies on prophylactic treatment of CM are scarce. The substances, which have been studied in patients with CM specifically, are: valproate [Yurekli *et al.* 2008], amitriptyline [Couch and Amitriptyline *versus* Placebo Study Group, 2011], gabapentin [Spira *et al.* 2003], topiramate [Diener *et al.* 2007; Silberstein *et al.* 2007; Silvestrini *et al.* 2003] and onabotulinumtoxinA. The latter one is the only substance approved by the United States Food and Drug Administration (FDA) for prophylactic treatment of CM. Guidelines of the American Academy of Neurology state that onabotulinumtoxinA is effective and should be offered to patients with CM [Simpson *et al.* 2016].

In the UK the National Institute for Health and Care Excellence (NICE) recommends onabotulinumtoxinA as a prophylactic treatment for CM in patients who did not respond to at least three prior pharmacologic prophylaxis therapies and whose condition is appropriately managed for medication overuse. According to NICE criteria, treatment with onabotulinumtoxinA should be stopped when patients do not respond to treatment adequately (defined as a reduction of monthly headache days of $<30\%$) or when the patient's condition changes to EM (defined as a

headache on <15 days per month in three consecutive months) [NICE, 2012].

Mode of action of botulinum neurotoxin

Botulinum neurotoxin (BoNT) is a protein complex produced by the Gram-positive, anaerobic bacterium *Clostridium botulinum*. There are at least seven different BoNT serotypes, of which only two are currently in clinical use: BoNT serotype A and BoNT serotype B [Bigalke, 2013].

After intramuscular or subcutaneous injection BoNT is internalized into peripheral motor neurons *via* SV2 binding protein [Mahrhold *et al.* 2006]. Once translocated into the cytosol, BoNT enzymatically cleaves the 25 kDa synaptosomal-associated protein (SNAP-25), a protein, which mediates the fusion of neurotransmitter-containing vesicles with the cell membrane. Through this mechanism, BoNT inhibits the release of neurotransmitters from presynaptic nerve endings [Rummel, 2015]. This effect has been best studied for the suppression of acetylcholine release at the neuromuscular junction. However, more recent studies show that BoNT also modifies the release of neurotransmitters, which are relevant in the transduction of pain such as substance P [Purkiss *et al.* 2000; Welch *et al.* 2000] or calcitonin gene-related peptide (GCRP) [Durham *et al.* 2004]. It is supposed that the inhibition of peripheral sensitization leads to an indirect inhibition of central sensitization and thus is a possible mechanism for the efficacy of BoNT in chronic pain [Aoki, 2003]. On the contrary, animal-model studies support the view, that there is a site for BoNT in the central nervous system, although the mechanisms of a central antinociceptive action of BoNT remain unclear [Matak and Lacković, 2014]. Research in this field is complicated by the absence of a widely accepted pathophysiological model for CM.

Clinical evidence

OnabotulinumtoxinA (Botox®)

The analgesic effects of BoNT were observed 30 years ago in patients with *Torticollis spasmodicus* [Tsui *et al.* 1986]. This observation was attributed to the myorelaxant effects of BoNT. The first evidence for an effect of BoNT on migraine was found in patients who were treated with BoNT for hyperfunctional lines of the face. The first open-label, nonrandomized study enrolled a total of 106 patients. Of these 106 patients, 77 patients were classified as true migraineurs according to IHS criteria and received prophylactic treatment with onabotulinumtoxinA (Botox®, Allergan Inc., Irvine, California, USA). Therapeutic benefit was measured by patients' self-reports. A total of 51% of the patients classified as having true migraine reported a complete response and 28%, a partial response [Binder *et al.* 2000].

The first placebo-controlled, double-blind study in migraine patients (2–8 migraine attacks per month) was carried out in the year 2000 with 123 patients. Participants were randomized into three groups and treated with either placebo, 25 or 75 mouse units (MU) onabotulinumtoxinA. The treatment with 25 MU onabotulinumtoxinA was found to be superior to placebo in the reduction of the number of monthly migraine attacks, whereas no differences could be identified between the 75 MU group and the placebo group [Silberstein *et al.* 2000].

In the following years, several subsequent studies failed to demonstrate positive effects on EM [Jackson *et al.* 2012] and tension headaches [Gaul *et al.* 2016]. For CM the results from controlled clinical trials were inconsistent.

In a placebo-controlled study conducted in 58 patients with chronic daily headache (CDH), onabotulinumtoxinA tended to improve the number of headache days in a 12-week period after injection, but missed the criteria for statistical significance [Ondo *et al.* 2004]. A multicentre study with 279 patients with CDH (three injection cycles) showed, that onabotulinumtoxinA increased the number of headache-free days in a 30-day period, but again differences between placebo and *verum* group were not statistically significant [Mathew *et al.* 2005]. A subgroup analysis of 228 patients without prophylactic medication at the date of study enrolment found a statistically significant difference in the number of headaches in a 30-day period. So the authors concluded that onabotulinumtoxinA was effective in the treatment of patients with CDH who do not receive other prophylactic medication [Dodick *et al.* 2005]. In another multicentre study 702 patients with CDH received three injection cycles with placebo or 75,175 or 225 MU onabotulinumtoxinA for 9 months. All groups responded to treatment, but the response was not superior to placebo [Silberstein *et al.* 2005]. In 2007, a small, but

double-blinded and placebo-controlled study with 32 participants failed to demonstrate a benefit for onabotulinumtoxinA in the prophylactic treatment of CM [Vo *et al.* 2007]. Freitag and colleagues treated 86 CM patients without medication overuse and found a statistically significant effect for onabotulinumtoxinA in the reduction of migraine episodes [Freitag *et al.* 2007]. An Italian double-blind study with 68 patients with CM found no difference between onabotulinumtoxinA and placebo in the reduction of headache days, but was able to show, that treatment with onabotulinumtoxinA reduced the consumption of acute pain medication [Sandrini *et al.* 2011].

The breakthrough of onabotulinumtoxinA in the treatment of CM came in 2010, when the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) study group published the results of the PREEMPT I and PREEMPT II trial, in which a total of 1384 Patients were enrolled into both trials (PREEMPT I: 679, PREEMPT II: 705). Both studies consisted of a 28-day baseline screening period, a 24-week double-blind, parallel-group, placebo-controlled phase (two injection cycles) and a 32-week open-label phase (three injection cycles). This pair of two multicentre randomized, placebo-controlled studies had an identical study design, but different endpoints.

In the PREEMPT I trial the primary endpoint reduction of migraine episodes was missed, but significant differences between the *verum* group and the placebo group were seen in the reduction of headache days and migraine days [Aurora *et al.* 2010]. The PREEMPT II trial confirmed the efficacy of onabotulinumtoxinA in the reduction of headache days as a primary endpoint [Diener *et al.* 2010].

Until now there were only two studies comparing onabotulinumtoxinA with other drugs effective in the prophylactic treatment of CM. Magalhães and colleagues showed, that onabotulinumtoxinA was as effective as amitriptyline in the prophylactic treatment of CM [Magalhães *et al.* 2010], Cady and colleagues compared onabotulinumtoxinA with topiramate and found similar efficacy for the prophylactic treatment of CM [Cady *et al.* 2011]. Taking all evidence into consideration a meta-analysis stated in 2012, that Botulinum toxin A compared with placebo was associated with a small-to-moderate benefit for CM and CDH [Jackson *et al.* 2012].

The positive results of the two PREEMPT trials led to the approval of onabotulinumtoxinA for the treatment of CM in September 2011 by the US FDA and subsequently many other registration authorities worldwide. After approval, various studies in real-life settings have been published on the use of onabotulinumtoxinA in CM. The results of these studies confirm the efficacy of onabotulinumtoxinA in CM [Cernuda-Morollón *et al.* 2014; Khalil *et al.* 2014; Negro *et al.* 2015; Russo *et al.* 2016].

Because medication overuse is a major problem in CM patients, a separate view on this subgroup of patients might be helpful. Pooled data of both PREEMPT studies reveal that onabotulinumtoxinA is effective in the reduction of headache days in CM patients with concomitant medication overuse [Silberstein *et al.* 2013]. In a prospective study no difference between CM patients with medication overuse and CM patients without medication overuse could be found in terms of efficacy of onabotulinumtoxinA [Ahmed *et al.* 2015]. There might be indications that in CM patients with concomitant medication overuse, treatment with 195 MU is superior to treatment with 155 MU in the reduction of headache days, migraine days and days with medication intake [Negro *et al.* 2015].

Beside its effects on headache frequency and severity treatment with onabotulinumtoxinA also improves quality of life in Patients with CM. In the PREEMPT studies patients treated with onabotulinumtoxinA had a significant higher quality of life throughout the double-blind phase [Lipton *et al.* 2011] and the open-label phase [Lipton *et al.* 2016].

Recently, a study from our centre confirmed these findings in a long-term real-life setting [Kollewe *et al.* 2016]. In this open-label study, 27 patients with CM received at least four injection cycles of onabotulinumtoxinA according to the PREEMPT injection paradigm. Monthly headache days, migraine days, days with nausea/vomiting and days with intake of pain medication were significantly reduced after the first treatment and this effect was stable throughout the entire study period. Furthermore, health-related quality of life and migraine-related quality of life improved after treatment with onabotulinumtoxinA. Patients were also screened for depression before the beginning of treatment and six weeks after every injection. Over the course of treatment patients had a significant decrease in depressive

symptoms. In contrast with most of the studies mentioned previously, patients with severe depression were allowed to participate in this study. Theoretically the improvement of depression might be caused by the additional antidepressive action of BoNT [Finzi and Rosenthal, 2014; Magid *et al.* 2014; Wollmer *et al.* 2012].

In all of these studies a certain number of patients did not respond to treatment with onabotulinumtoxinA. Up to 10% of patients might be concerned with treatment failure during long-term treatment [Cernuda-Morollón *et al.* 2014]. Currently the development of antibodies, an intrinsic worsening of migraine or an initial placebo effect are discussed as reasons for the development of resistance to treatment with onabotulinumtoxinA [Cernuda-Morollón *et al.* 2014].

In some studies, shorter duration of disease [Eross *et al.* 2005; Sandrini *et al.* 2011; Lee *et al.* 2016], predominantly unilateral location of pain, presence of scalp allodynia, and pericranial muscle tenderness [Mathew *et al.* 2007] and increased interictal calcitonin gene-related peptide (CGRP) levels [Cernuda-Morollón *et al.* 2014] for a favourable outcome were observed. In a Korean study patients were screened with transcranial Doppler sonography. Patients with a higher ratio of the mean blood flow velocity in the middle cerebral artery to that of ipsilateral internal carotid artery were more likely to respond to treatment with onabotulinumtoxinA [Lee *et al.* 2016]. However, reliable predictors and biomarkers for treatment response applicable in a real-world setting are lacking to date.

IncobotulinumtoxinA (Xeomin®) and abobotulinumtoxinA (Dysport®)

OnabotulinumtoxinA is the only BoNT preparation, which has been approved for the treatment of CM. Until now no prospective trials using other BoNT preparations in patients with CM have been published. There is only one retrospective case series of 21 CM patients treated with incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals GmbH, Frankfurt/M, Germany) [Kazerooni *et al.* 2015]. In this case series significant improvements in headache frequency and severity were observed under treatment with incobotulinumtoxinA.

AbobotulinumtoxinA (Dysport®, Beaufour Ipsen, Boulogne-Billancourt, France) has been investigated in patients with EM, but no significant effects on the frequency and severity of headache were found [Petri *et al.* 2009]. To the best of our knowledge to date no data are available for the use of abobotulinumtoxinA in patients with CM.

Doses and injection sites

The first studies with BoNT injections in headache and migraine used a variety of different dosages, concentrations and injection sites for BoNT. In 2010 the PREEMPT study group developed an injection paradigm based on various studies conducted in patients with EM, CM and tension-type headaches. The PREEMPT injection paradigm combines two different approaches for the injection of BoNT in migraine: fixed injections sites and follow the pain injection sites. Fifty MU of onabotulinumtoxinA are diluted with 2.0 ml of saline, yielding a concentration of 5 MU/0.1 ml. Each intramuscular injection site is injected with 5 MU onabotulinumtoxinA. The injection paradigm consists of 31 fixed sites in the following muscles: *mm. frontalis* 20 MU (four sites), *mm. corrugatores* 10 MU (two sites), *m. procerus* 5 MU (1 site), *mm. occipitalis* 30 MU (six sites), *mm. temporalis* 40 MU (eight sites), *mm. trapezii* 30 MU (in six sites), cervical paraspinal muscle group 20 MU (four sites). In these fixed sites a total dose of 155 MU onabotulinumtoxinA is applied. Additional 40 MU can be administered into temporalis (two sites), occipitalis (two sites) or trapezius muscles (four sites), receiving a maximum of 195 MU [Blumenfeld *et al.* 2010].

Little is known about the duration of analgesic effects of onabotulinumtoxinA. It is supposed, that it is similar to the duration of its myorelaxant effects. Therefore most studies used a fixed treatment interval of 12 weeks for onabotulinumtoxinA injections. Clinical experience in the use of BoNT for other neurologic indications shows, that it might be useful to adapt treatment intervals individually to the patients' needs [Dressler *et al.* 2015]. However shorter treatment intervals go along with an increased risk of antibody formation against BoNT resulting in treatment failure [Lange *et al.* 2009].

Safety and tolerability

Adverse effects (AEs) of BoNT are usually related to the injection, systemic AEs are very rare [Silberstein, 2016]. Injection-related AEs are usually mild and transient and rarely lead to

abortion of therapy. Among the reported AEs in the PREEMPT studies, neck pain (4.3%), injection site pain (2.1%), eyelid ptosis (1.9%), muscular weakness (1.6%) were most common [Aurora *et al*. 2014]. Data from various clinical studies document that treatment with onabotulinumtoxinA is tolerable [Cernuda-Morollón *et al*. 2014; Kollewe *et al*. 2016; Silberstein *et al*. 2005].

Conclusion

OnabotulinumtoxinA is the substance that has been best studied in the prophylactic treatment of CM. There is good clinical evidence that treatment with onabotulinumtoxinA leads to a reduction of monthly headache days and improves quality of life. Treatment with onabotulinumtoxinA is well tolerated by the patients. Further research is needed to elucidate the analgesic mechanism of onabotulinumtoxinA in CM.

Conflict of interest statement

CE states that he has no conflict of interest. LP received travel grants from Ipsen (Boulogne-Billancourt, France) and Merz (Frankfurt/M, Germany). DD received honoraria for consultations from Allergan (Irvine, California, USA), Bayer (Leverkusen, Germany), Eisai (Tokio, Japan), IAB-Interdisciplinary Working Group for Movement Disorders (Hamburg, Germany), Ipsen, Merz and UCB (Monheim, Germany). He is shareholder of Allergan and holds several patents on botulinum toxins.
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An evidence-based review of botulinum toxin (Botox) applications in non-cosmetic head and neck conditions

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Summary

Botulinum toxin (Botox) is an exotoxin produced from *Clostridium botulinum*. It works by blocking the release of acetylcholine from the cholinergic nerve end plates leading to inactivity of the muscles or glands innervated. Botox is best known for its beneficial role in facial aesthetics but recent literature has highlighted its usage in multiple non-cosmetic medical and surgical conditions. This article reviews the current evidence pertaining to Botox use in the head and neck. A literature review was conducted using The Cochrane Controlled Trials Register, Medline and EMBASE databases limited to English Language articles published from 1980 to 2012. The findings suggest that there is level 1 evidence supporting the efficacy of Botox in the treatment of spasmodic dysphonia, essential voice tremor, headache, cervical dystonia, masticatory myalgia, sialorrhoea, temporomandibular joint disorders, bruxism, blepharospasm, hemifacial spasm and rhinitis. For chronic neck pain there is level 1 evidence to show that Botox is ineffective. Level 2 evidence exists for vocal tics, trigeminal neuralgia, dysphagia and post-laryngectomy oesophageal speech. For stuttering, 'first bite syndrome', facial nerve paresis, Frey's syndrome, oromandibular dystonia and palatal/stapedial myoclonus the evidence is level 4. Thus, the literature highlights a therapeutic role for Botox in a wide range of non-cosmetic conditions pertaining to the head and neck (mainly level 1 evidence). With ongoing research, the spectrum of clinical applications and number of people receiving Botox will no doubt increase. Botox appears to justify its title as 'the poison that heals'.

Introduction

Botulinum toxin (Botox) is a protease exotoxin produced from *Clostridium botulinum*. It works by blocking the release of acetylcholine from cholinergic nerve endings causing inactivity of muscles or glands. Its effects are transient and may be graded by varying the dose and frequency of administration. Botox is one of the most potent naturally occurring biological poisons and in the

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past has been responsible for many accidental deaths prior to its discovery in medicine. Its first medical use was to treat strabismus in 1980. Nine years later, the cosmetic effects of the toxin on wrinkles were noted, but it was only in 2002, following Food and Drug Administration approval, that Botox gained widespread popularity as an alternative to cosmetic surgery.[1]

Recently, the therapeutic uses of Botox have expanded exponentially to include a wide range of medical and surgical conditions. This has been aided by a greater understanding of its underlying physiology as well as improved efficacy and safety. This review examines the evidence on Botox usage in non-cosmetic conditions of the head and neck.

Methods

The Cochrane Controlled Trials Register, Medline and EMBASE databases were searched from 1980 to 2012. The medical subject heading search terms were 'botox' and 'larynx' or 'dysphonia' or 'dystonia' or 'tremor' or 'oral' or 'myoclonus' or 'temporomandibular' or 'sialorrhoea' or 'bruxism' or 'oesophagus' or 'dysphagia' or 'speech' or 'face' or 'autonomic nervous system' or 'sweating' or 'torticollis' or 'pain' or 'migraine' or 'headache' or 'myalgia' or 'neuralgia' or 'nose' or 'rhinitis'. A total of 997 English language abstracts were reviewed and 88 relevant articles identified. Further references were obtained through their bibliographies. Evidence levels, based on those suggested by the Oxford Centre for Evidence-Based Medicine (Table 1),[2] are shown in the text inside [ ]. The highest level of evidence pertaining to Botox treatment for each of the ENT conditions is presented in Table 2.

Results and discussion

Laryngeal conditions

Spasmodic dysphonia

Spasmodic dysphonia is due to inappropriate glottic closure or opening due to spasm of intrinsic laryngeal muscles. Symptoms include hoarseness and strangled speech breaks (adductor type) or hypophonia and breathy voice (abductor type).[3] A meta-analysis of 30 randomized controlled trials (RCTs) involving Botox therapy in adductor spasmodic dysphonia revealed an improvement to about one standard deviation across the dependent voice-related Quality of Life (QoL) variables studied [1a].[4,5] A subsequent RCT also confirmed the beneficial effects of Botox in spasmodic dysphonia with the greatest improvements present in those patients who were most profoundly impaired [1b].[6] In addition, a recent prospective study ($n = 133$) has demonstrated a mean Voice Handicap Index improvement of 9.6% following laryngeal Botox injection in patients with spasmodic dysphonia.[7]

Essential voice tremor

Essential voice tremor is characterized by rhythmic activation of mainly the intrinsic laryngeal muscles. The voice is affected by breaks in pitch, diminished fluency and arrests. It naturally accompanies the ageing process, but may also occur with spasmodic dysphonia.[8] Electromyography (EMG)-guided Botox injection into the thyroarytenoid muscles was shown to have beneficial effect in a RCT ($n = 13$) [1b],[9] in a prospective crossover study ($n = 10$) [3b][10] and a case report [4].[11]

Stuttering or stammering

This refers to a disorder of speech-motor control in which the flow of speech is disrupted by involuntary repetitions and prolongations of sounds, syllables, words or phrases, with occasional involuntary silent pauses, collectively caused by poor coordination between lingual, labial, laryngeal and respiratory muscles. There is only one case series that has shown that intralaryngeal Botox injection improves fluency in speech therapy failures so its value in treating this disorder is questionable and requires further research [4].[12]

Vocal tics (Gille de la Tourette syndrome)

Repetitive dyskinetic movements of the laryngeal musculature lead to the production of embarrassing speech known as vocal tics. This is commonly seen in Gille de la Tourette syndrome. There is one RCT showing that Botox injections into the thyroarytenoid muscles is efficacious in reducing the frequency and urge of vocal and motor tics ($n = 18$) [2b], but the patients did not report an overall benefit from the treatment.[13–15] Again, further research is mandated to assess the efficacy of Botox for vocal tics.

Table 1
Levels of evidence based on those suggested by the Oxford Centre for Evidence-Based Medicine

Level of evidence	*Type of study*
1a	Systematic review (SR) (with homogeneity*) of randomized control trials (RCTs)
1b	Individual RCT (with narrow confidence interval)
1c	All or none†
2a	SR (with homogeneity*) of cohort studies
2b	Individual cohort study (including low quality RCT; e.g. <80% follow-up)
2c	'Outcomes' Research; ecological studies
3a	SR (with homogeneity*) of case-control studies
3b	Individual case-control study
4	Case-series, case reports and poor quality cohort or poor quality case-control studies‡
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

*This refers to a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need to be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a '-' at the end of their designated level
†Met when all patients died before the treatment became available, but some now survive on it; or when some patients died before the treatment became available, but none now die on it
‡This refers to a cohort study that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. Poor quality case-control study refers to one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders

Pain

Headache

Numerous multicentre double-blind placebo-controlled trials support the use of Botox as a prophylactic therapy for migraine [1a].[16–18] The technique involves injections into muscles innervated by the facial or trigeminal nerves (e.g. procerus, corrugator, frontalis, temporalis and suboccipital), specific sites of pain distribution or a combination of both.[19] Significant reductions from baseline were observed in patients in the Botox trial arm with regard to headache and migraine days, cumulative hours of headache and frequency of moderate/severe headache days. A recent meta-analysis confirmed these beneficial effects of Botox but only in the treatment of chronic daily headaches and chronic migraines (>15 episodes per month) [1a]. Adverse effects including blepharoptosis, skin tightness, paraesthesias, neck stiffness, muscle weakness and neck pain can occur at injection sites but these were minimal and transient.[20]

Cervical dystonia or spasmodic torticollis

This refers to sustained neck muscle contraction resulting in involuntary movements of the head and neck associated with significant cervical pain and abnormal cervical postures. It can be primary or secondary to other neurological disorders.[21] The evidence supporting the use of Botox in the treatment of cervical dystonia consists of two Cochrane systematic reviews of 13 (677 participants for Botox A) and three (308 participants for Botox B) high-quality RCTs, respectively [1a].[22,23] These meta-analyses showed that single injection of Botox is effective (as evident from both objective and subjective rating scales) and can be safely repeated if necessary. Since then, there have been further RCTs confirming the efficacy and safety of Botox in the treatment of cervical dystonia in both previously treated as well as Botox-naive patients [1b].[24] It is worth noting that Botox not only reduces abnormal movements and contractures but can also prevent secondary degenerative changes of the cervical spine and associated radiculopathy.[25,26]

Masticatory myalgia

Masticatory pain can be explained by chronic nociceptive irritation of the tendons and fascias of the masseter, temporalis and medial pterygoid muscles.[27,28] There are three RCTs showing Botox to be more effective than placebo (saline) in reducing masticatory myalgia [1b].[29–31] The most recent of these three RCTs also evaluated with EMG the action potentials of the masseter and temporalis muscles and showed that these decreased by nearly 80% on day 14, and by 25% on day 28 following Botox injection.[30] Botox causes a disuse atrophy of the affected muscle which relieves tension, improves aerobic metabolism

Table 2
Levels of evidence for the role of Botox in various head and neck conditions

Condition	*Highest level of evidence*
Laryngeal	
Spasmodic dysphonia[4,5]	1a
Essential voice tremor[9]	1c
Stuttering[12]	4
Vocal tics[13–15]	2b
Pain	
Headache[16–18,20]	1a
Cervical dystonia/spasmodic torticollis[22,23]	1a
Masticatory myalgia[29–31]	1b
Chronic neck pain[33] (non-beneficial)	1a
Trigeminal neuralgia[34–36]	2b
First bite syndrome[40,41]	4
Oesophageal	
Oesophageal speech postlaryngectomy[44–47]	2c
Dysphagia[51–53]	2c
Oral	
Sialorrhoea[55–57]	1b
Temporomandibular joint disorders[29,31,59]	1b
Bruxism[29]	1b
Oromandibular dystonia[63,64]	4
Palatal/stapedial myoclonus[65,66]	4
Facial	
Blepharospasm[69–71]	1b
Hemifacial spasm[75]	1b
Facial nerve paresis[76–78]	4
Nasal	
Rhinitis[79–82]	1b
Autonomic	
Frey's syndrome[85–90]	4

and enables decompression of afferent nociceptive neurons through reduction of substance P-mediated neurogenic inflammation.[31,32]

Chronic neck pain (no benefit with Botox)

Several studies have assessed the role of intramuscular Botox injections in chronic neck pain; however, no significant beneficial effect has been demonstrated. A recent Cochrane systematic review of nine trials (503 participants) showed that Botox alone was no better than the placebo (saline) for patients with subacute or chronic neck pain and concluded that the available evidence does not support the use of Botox either as a monotherapy or in combination with any other treatment in patients with subacute or chronic neck pain [1a].[33]

Trigeminal neuralgia

The role of Botox in the treatment of drug-refractory trigeminal neuralgia has been evaluated in three studies ($n = 15$, $n = 12$, $n = 8$, respectively).[34–36] All three studies (including a low-quality RCT) found Botox to be an effective treatment with the majority of the patients reporting a reduction or even disappearance of the pain [2b].[34–36] Botox was found to be effective in combination with pharmacotherapy, prior to considering more invasive therapies such as surgery or gamma knife radiosurgery.[34] As such, Botox is a particularly valuable treatment for elderly patients and those with adverse anaesthetic comorbidities.[37,38]

First bite syndrome

This is the development of facial pain after the first bite of each meal and is seen after surgery in the parapharyngeal space, especially deep lobe parotidectomy.[39] It is probably due to autonomic dysfunction of salivary myoepithelial cells. Intraparotid Botox injection was found to significantly decrease symptom severity and improve the patients' QoL in a case series of five patients and a case report [4].[40,41]

Oesophageal conditions

Oesophageal speech post-laryngectomy

Tracheoesophageal puncture in laryngectomy patients allows excellent quality speech development in most cases. The procedure involves cricopharyngeal myotomy and valve placement. However, postoperative pharyngo-oesophageal spasm can cause failure of tracheoesophageal speech and dysphagia.[42] Traditionally, this was treated with dilation of the pharyngo-oesophageal segment (POS), pharyngeal myotomy and/or pharyngeal neurectomy.[43] More recently, EMG-guided Botox administration that chemically denervates the cricopharyngeus muscle facilitating tracheoesophageal speech and relieving dysphagia has been reported. There are several

prospective[44–47] and retrospective outcomes research studies[48] assessing the efficacy of Botox using both subjective (videotaped recordings) and objective (videostroboscopy) outcome measures [2c]. In corroboration, the largest and most recent prospective study consisting of 34 laryngectomized patients showed Botox therapy to be effective in POS voice restoration, especially when combined with speech therapy [2c].[44] The effects of Botox were shown to be long-lasting with only one patient needing to be re-injected every three months.[44] These results are promising but further, higher quality studies are needed to establish the true value of Botox in oesophageal speech post-laryngectomy.

Dysphagia

Incoordination of cricopharyngeal contractions at the initiation of swallowing can result in dysphagia, especially in the elderly population. EMG-guided Botox injections either percutaneously[49] or endoscopically[50] to the cricopharyngeus muscle were found to be effective in the treatment of dysphagia in a number prospective and retrospective outcomes research studies [2c].[51–53] Effective toxin administration can predict a successful surgical outcome following cricopharyngeal myotomy.[51,54] Again, like with oesophageal speech post-laryngectomy, these results are promising but further, higher quality studies are needed before the true value of Botox in dysphagia is determined.

Oral conditions

Sialorrhoea

Sialorrhoea may occur in neurological and other akinetic disorders such as Parkinson's disease and cerebral palsy. There are several RCTs where the efficacy of Botox injections to the parotid and/or submandibular glands in such patients has been demonstrated [1b].[55–57] The effects last 3–6 months and can be repeated. Injections can also be used for sialorrhoea caused by salivary fistulas and sialadenitis.[58]

Temporomandibular joint disorders

Spasm of the lateral pterygoid muscles may cause temporomandibular joint (TMJ) disc displacement anteriorly resulting in exquisite pain and clicking. The evidence supporting the use of Botox in the treatment of such TMJ disorders includes multiple RCTs [1b].[29,31,59] However, injection of Botox into the lateral pterygoid muscle may cause a 'fixed' smile due to diffusion into the superficial facial muscles.[60]

Bruxism

This is characterized by non-functional contact of the mandibular and maxillary teeth resulting in clenching or tooth grinding due to repetitive, unconscious contraction of the masseter and temporalis muscles.[61] There is one RCT ($n = 30$) which has shown Botox to be efficacious in reducing myofascial pain symptoms in bruxers compared with control patients receiving saline placebo injections[29] with a second one currently underway [1b].[62]

Oromandibular dystonia

This disorder is characterized by involuntary, action-induced, tonic or clonic spasms of the masticatory, lingual and pharyngeal musculature. Symptoms include dysphagia, dysarthria, bruxism and tempomandibular joint subluxation. There are case series and case reports [4] showing favourable effects of Botox injections into the lateral pterygoid, anterior belly of digastric, masseter and temporalis muscles.[63,64] Thus, further higher quality studies are needed to establish the true role of Botox in the treatment of oromandibular dystonia.

Palatal and stapedius myoclonus

Palatal myoclonus is characterized by involuntary palatal contractions, causing clicking tinnitus due to the action of soft palate muscles on the membranous Eustachian tube. Similarly, stapedius myoclonus can cause clicking tinnitus due to the contractions of the stapedius muscle. There are two case reports, one for each type of myoclonus where the use of Botox has been shown to be beneficial in relieving the patients' symptoms [4]. For palatal myoclonus, Botox was injected in the soft palate under EMG guidance,[65] while for stapedius myoclonus, Botox was placed trans-tympanically into the middle ear on a piece of gelfoam.[66] In the latter case, the beneficial effects of Botox lasted for four months.

Facial conditions

Blepharospasm

Involuntary contraction of the eyelid muscles typically occurs bilaterally and in patients over 60 years. The orbicularis oculi muscle is most commonly implicated, but upper facial muscles can also be affected. The therapeutic use of Botox in blepharospasm was first described in 1985[67] and it has since become the treatment of choice.[68] There are three RCTs demonstrating the superiority of Botox over placebo [1b].[69–71] A recent Cochrane systematic review has concluded that doing more RCTs to prove the effectiveness of Botox over the placebo (saline) would be unethical due to the high efficacy and obvious benefits of Botox in treating blepharospasm.[72]

Hemifacial spasm

This is characterized by unilateral, recurrent, involuntary movements of the muscles innervated by the facial nerve. It is usually due to compression of the facial nerve near its origin by an aberrant branch of the posterior inferior cerebellar artery.[73] The first study to assess Botox in hemifacial spasm was in 1986.[74] Since then, there have been several studies, including one RCT which showed Botox to be an effective and safe treatment.[75] This RCT involved 11 patients and clearly demonstrated the beneficial effect of the Botox over the placebo [1b].

Facial nerve paresis

Botox may be used to induce therapeutic ptosis, thereby protecting the cornea during the acute phase of facial nerve paresis. This is achieved by transcutaneous injection into Mueller's muscle and the levator palpebrae superioris. There are two case series of therapeutic chemodenervation with Botox of these muscles comprising three and 10 patients, respectively.[76,77] Both showed that Botox administration is beneficial in preventing damage as well as healing of the cornea [4]. In addition, there is one case series of 30 patients showing Botox to reduce synkinesis in aberrant facial nerve regeneration following facial nerve paresis.[78] In that study, Botox was injected to several synkinetic muscles of patients with facial nerve paresis and all 30 patients experienced improvement after treatment [4].

Nasal conditions

Rhinitis

In a RCT of 39 patients with allergic rhinitis, Botox therapy provided better symptomatic control than steroid injections into each inferior turbinate, both in terms of the duration and degree of symptoms [1b].[79] In another RCT of 20 patients with idiopathic (vasomotor) rhinitis, topical application of Botox on a sponge significantly reduced rhinorrhoea compared with placebo (saline) but nasal congestion remained unchanged.[80] Furthermore, in a study of 38 patients with idiopathic rhinitis, Botox displayed a similar degree and duration of efficacy with regard to hypersecretion symptoms to ipratropium bromide.[81] Middle and inferior turbinate injections of Botox were shown to be a highly effective, safe and simple intervention in a RCT of 30 patients with vasomotor rhinitis [1b].[82] Hence, the role of Botox seems promising in the treatment of allergic and idiopathic rhinitis though several limiting factors prevent its widespread use. These include the mode of administration which can be associated with the requirement of specialized skills and the potential for significant pain (particularly with injection to the inferior and/or middle turbinates) in addition to its high cost.[83]

Autonomic conditions

Frey's syndrome

This typically occurs after parotid surgery and is caused by aberrant regeneration of postganglionic parasympathetic fibres innervating sympathetic cholinergic sweat glands. The result is sweating, flushing and piloerection while eating (gustatory sweating).[84] Several case series have demonstrated the efficacy of Botox in Frey's syndrome [4].[85–90] The procedure involves injecting the areas of gustatory sweating identified by an iodine-starch test. Further research is needed to assess the efficacy of Botox as a treatment for Frey's syndrome.

Conclusion

The literature highlights a therapeutic role for Botox in a wide range of non-cosmetic conditions pertaining to Otorhinolaryngology and Head & Neck Surgery. With ongoing research, the spectrum of clinical applications and number of

people receiving Botox will no doubt increase. Botox appears to justify its title as 'the poison that heals'.

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Use of chemodenervation in dystonic conditions

ABSTRACT

Dystonia, an uncommon movement disorder that causes sustained muscle contractions and painful body positions, is a difficult diagnostic challenge; misdiagnosis is common. Classification may include etiology, area of physical involvement, or age of onset. Bodily distribution is varied, and dystonias can present as primary (genetic) or secondary (caused by other disease processes or use of neuroleptic drugs). Although there is no cure, the use of botulinum toxins for chemodenervation provides symptomatic relief and is considered the treatment of choice in focal dystonia. The dose of botulinum toxin may be titrated to provide significant relief for 12 weeks or more.

Dystonia is a movement disorder in which involuntary sustained muscle contractions cause twisting movements that place the body in abnormal, sometimes painful, positions. Dystonia is believed to arise from an abnormality in the basal ganglia and an inherent or acquired defect in the processing of neurotransmitters.[1]

Dystonia is uncommon, although its exact prevalence is unknown. Nutt et al concluded that at least 250,000 people were affected by idiopathic dystonia in the United States, but prevalence is likely higher because misdiagnosis is not uncommon.[2] A more recent European study found the prevalence of primary dystonia in the general population aged 50 years or more to be 732 per 100,000.[3] The Epidemiological Study of Dystonia in Europe (ESDE) Collaborative Group found that the estimated prevalence of cervical dystonia was 50 to 200 per 1 million individuals.[4] Also known as spasmodic torticollis, this is the most commonly diagnosed form of focal dystonia.

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CLASSIFICATION OF DYSTONIA

Accurate classification of dystonia is important, since this informs approaches to management as well as prognosis. The three most important means by which dystonia is classified are (1) etiology, including primary dystonia, which encompasses a variety of genetic variables, and secondary dystonia; (2) bodily distribution of symptoms; and (3) age at onset.

Etiology

Most primary or idiopathic dystonia appears to be hereditary. Early-onset primary dystonia is most frequently caused by a mutation in the *DYT1* gene, although other genetic mutations are possible.[5] Patients with primary dystonia have no other underlying disorder; involuntary muscle contractions are the sole symptom. A thorough history should include a review of perinatal and early developmental history, prior neurologic illness, and exposure to drugs known to cause acquired dystonia. Physical examinations (encompassing intellectual, pyramidal, cerebellar, and sensory domains) and laboratory tests reveal no specific cause for the dystonic symptoms. Primary dystonia is also most frequently action-induced; at rest, the affected body region may appear to be normal.

Secondary dystonia occurs as a symptom of another disease process. Multiple sclerosis or any one of several hereditary neurologic disorders, such as Wilson disease, may be implicated. Secondary dystonia also may result from trauma to the brain, as might occur during an automobile accident; from heavy-metal or carbon monoxide poisoning; or as an adverse effect of medication. It may be psychogenic or related to Parkinson disease or Parkinson-plus syndromes, a group of neurodegenerative disorders with parkinsonian features. Tardive dystonia, the most common adult form of secondary dystonia, may occur following exposure to certain neuroleptic drugs; tardive dystonia is a type of tardive dyskinesia that describes any involuntary neurologic movement disorder.

Bodily distribution

Dystonia is further classified by location of symptoms. Focal dystonias, which are usually primary dystonias, describe symptoms that are limited to a region of the body, such as a specific arm. There are several variations.

TABLE 1
Common dystonia misdiagnoses

Type of dystonia	Misdiagnosed as…
Blepharospasm	Tic, dry eye syndrome
Cervical dystonia	Arthritis, stiff neck, subluxation of cervical vertebrae, tumor of posterior fossa
Dystonia, all forms	Stress, anxiety, nervousness; psychogenic disorders
Laryngeal dystonia	Laryngitis, sore throat, vocal abuse
Oromandibular dystonia	Temporomandibular joint disorder
Writer's cramp	Carpal tunnel syndrome, muscle strain, lateral epicondylitis

Cervical dystonia affects the head and neck, is the most common adult-onset dystonia, and affects more women than men. Blepharospasm, or involuntary contractions of the eyelids, potentially leads to extended eye closure and functional blindness and often involves other facial muscles. Laryngeal dystonia affects the muscles in the larynx. Limb dystonia, such as writer's or musician's cramp, affects muscles in the arm, hand, leg, or foot. Limb dystonia is often task-specific action dystonia, and can be primary or secondary.

Segmental dystonia describes a group of involved muscles that are contiguous, such as cranial to neck to cervical to arm. Oromandibular dystonia, affecting the face, mouth, and jaw, often with unusual tongue movements (ie, lingual dystonia), is a type of segmental dystonia, although some consider it a focal dystonia. Meige syndrome is the combination of blepharospasm and oromandibular dystonia. Certain limb and cranial dystonias are considered segmental dystonias. Dystonia that affects two or more noncontiguous muscle groups in different parts of the body is multifocal. Hemidystonia describes unilateral symptoms.

Symptoms that have advanced from a focal presentation to affect additional regions of the body characterize generalized dystonia. The symptoms potentially advance to include the trunk and limbs. The muscular contractions are usually sustained, are often both repetitive and painful, and worsen with activity.[6] In severe cases, muscular contractions may occur even while resting. Early-onset myoclonus dystonia is a generalized hereditary dystonia whose symptoms include dystonic contractions of the neck and shoulders and rapid jerking movements.[7] Of note diagnostically, early-onset dystonia in a leg typically begins at age 8 to 9 years and is more likely than other early-onset presentations to progress to generalized dystonia. Early-onset dystonia that begins in an arm typically presents later, at age 12 to 14 years, and is less likely to progress to generalized dystonia. Late-onset dystonia (> 27 years of age), by contrast, rarely begins in a leg and tends to remain either focal or segmental.[8]

Age of onset

A third useful classification scheme identifies early-onset (childhood to young adult) and late-onset varieties of dystonia.

THE DIAGNOSTIC CHALLENGE

Accurate diagnosis of dystonia is challenging because of its relative rarity and the variety of etiologies that pertain to this heterogeneous family of disorders. Patterns of inheritance are not straightforward and primary dystonia can be difficult to diagnose even with the benefit of genetic testing. There is no identifiable pathologic abnormality in many patients, and negative genetic tests do not necessarily mean that the dystonia is not primary. In the face of these challenges it is not surprising that dystonia is frequently misdiagnosed **(Table 1)**. Nevertheless, certain findings can guide the diagnosis toward primary or secondary dystonia.

Consider primary dystonia if perinatal and developmental histories, intellect, strength, and perception of sensations are normal. There should be no prior history of neurologic illness or exposure to neuroleptic drugs whose adverse effects include secondary dystonia. In primary dystonia, diagnostic studies are negative and dystonia is the only symptom. If onset of symptoms is associated with activity, then primary dystonia should be considered. In the case of early- or late-onset limb dystonia, testing should be performed for the *DYT1* gene. If the results are negative, then a trial for dopa-responsive dystonia should be undertaken with levodopa.

Consider secondary dystonia if the patient has been exposed to neuroleptic drugs, symptoms are distributed unilaterally, or the presentation is unusual for age or distribution of symptoms. For example, cranial dystonia in a child would raise the index of suspicion for secondary dystonia. If tardive dystonia is part of the differential diagnosis, consider magnetic resonance imaging (MRI), serum ceruloplasmin measurement, or slit-lamp diagnostic testing. Suspicion of a structural lesion affecting the central nervous system warrants examination with MRI, computed tomography, or angiography. Certain metabolic and neurologic hereditary disorders cause secondary dystonia, in which case dopa-responsive dystonia should be ruled out. Psychometric testing should also be considered.

SYMPTOMATIC TREATMENT WITH CHEMODENERVATION

In the absence of a cure, treatment options for dystonia are necessarily symptomatic and supportive. Titratable chemodenervation agents are injected directly into the muscle or motor nerve, temporarily weakening the local muscle and easing dystonia symptoms. Chemodenervation agents include phenol, ethyl alcohol, and botulinum toxin types A (BTX-A; onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA) and B (BTX-B; rimabotulinumtoxinB).

Phenol and ethyl alcohol injections targeted perineurally or as a motor point block have been employed for dystonia and cause nonselective tissue destruction, muscle necrosis, and highly variable durations of response. Perineural microcirculation may be damaged, possibly leading to long-term defects.

Clostridium botulinum bacteria produce seven serologically distinct neuroparalytic toxins. They are the most powerful such toxins currently known and temporarily prevent acetylcholine vesicles from docking into the presynaptic neuromuscular junction. Use of BTX-A for treatment of dystonia was recommended in a National Institutes of Health consensus statement in 1990.[9] It has been studied for a variety of dystonias, including blepharospasm, hemifacial spasm, laryngeal dystonia, oromandibular dystonia, and cervical dystonia, among other focal dystonias. Lew et al reported in 1997 on the successful use of BTX-B for cervical dystonia in a double-blind, single-treatment study,[10] and confirmatory studies followed.[11,12]

Varying indications for botulinum toxin

US Food and Drug Administration–approved indications for the toxins vary. The three BTX-A products and the single BTX-B product are approved for the treatment of cervical dystonia in adults to reduce the severity of abnormal head position and neck pain. OnabotulinumtoxinA is approved for treatment of blepharospasm and strabismus associated with dystonia; and incobotulinumtoxinA is approved for blepharospasm in patients who have previously been treated with onabotulinumtoxinA. BTX-A has also been found to be safe and effective for the management of focal dystonias. These botulinum toxin agents are not equivalent in dosing units, so caution must be observed when switching brands.

Patients selected to receive BTX for dystonia should meet three criteria:

- The dystonia should interfere with their functioning, comfort, or care to the degree that causes impairment and affects activities of daily living;
- Focal weakening following administration of the drug should not decrease their level of function; and
- The patient should understand that use of BTX may not completely address positioning, posturing, or secondary deformities.

Contraindications include pregnancy, lactation, comorbid neuromuscular disease (eg, amyotrophic lateral sclerosis or myasthenia gravis), and use of an aminoglycoside.

The need for BTX therapy should be reevaluated prior to each treatment; clinical benefit lasts 3 months or more. Electromyography may facilitate the location of target muscles, particularly since involved musculature may not be palpable and is often not superficial.[13] In-office tools that help document baseline and posttreatment results, including videotaping dystonic limb movements and the use of rating scales, can be important for evaluating the patient's progress.[14]

Relief for cervical dystonia

The treatment of choice for focal dystonias and focal aspects of generalized dystonia is BTX. Both BTX-A and BTX-B offer effective palliative treatments for cervical dystonia by improving neck position, reducing pain, and decreasing disability in sufferers.[11,15–18] The BTX solution is injected directly into the dystonic muscle at several locations, temporarily weakening the overactive muscle. The BTX dose is approximately proportional to the size of the muscle, although smaller muscles typically responsible for precision movement may require a relatively larger dose **(Table 2)**. Doses may be modified according to clinical factors such as muscle bulk and severity of dystonia **(Table 3)**.

TABLE 2
Botulinum toxin-A for cervical dystonia: Starting doses[a]

Potential muscles involved	Starting dose (units)	Starting range (units)	Approximate number of injection sites
Sternocleidomastoid	40	15–75	2
Scalene complex	30	15–50	3
Splenius capitis	60	15 or 30–100	4
Splenius cervicalis	30	20–60	2
Semispinalis capitis	60	30–100	4
Longissimus capitis	60	30–100	4
Trapezius	40	20 or 55–100	3
Levator scapulae	40	20–100	3

[a]In this example, the botulinum toxin-A is onabotulinumtoxinA.

TABLE 3
Potential botulinum toxin dose modifiers

Clinical situation	A *decrease* may be indicated	An *increase* may be indicated
Patient weight	Low	High
Likely duration of therapy	Chronic	Acute
Muscle bulk	Very small	Very large
Dystonia severity	Mild	Severe
Number of muscles injected	Many	Few

Relief following BTX injection for cervical dystonia occurs about 1 week later, with the greatest effect seen at about 2 to 6 weeks following injection; relief may last 12 to 16 weeks. Reinjections are not normally administered prior to 12 weeks' duration in order to reduce the possibility of antibody formation. Concomitant interventions addressing depression and anxiety may have a significant effect on overall quality of life.[19] Patients may also try several sensory tricks, called gestes antagoniste, which may temporarily reduce or alleviate the dystonia. However, these tactile procedures—such as placing a hand on top of the head—lose their effectiveness over time.

Treatment of blepharospasm, focal limb dystonia

The use of BTX-A for blepharospasm is a significant improvement over the former clinical reliance on various oral medications, which, with the exception of baclofen, proved largely ineffective.[20] Surgical treatments result in damage to muscular and nervous tissues, and so are reserved only for nonresponders to BTX-A therapy.[21]

BTX-A can provide effective relief and is the treatment of choice for focal limb dystonias.[22] Goals of treatment include functional improvement, correction of abnormal posture, and relief from discomfort. Although a variety of oral medications may also be prescribed, drug toxicity and adverse effects can outweigh the benefit and are usually only used in cases of severe dystonia. Oral medications used for limb dystonia include anticholinergics, dopamine agonists and antagonists, baclofen, clonazepam or other benzodiazepines, and muscle relaxants.

Antibodies may bind to the drug in a small percentage of patients who regularly receive injections of BTX, rendering additional injections of that specific serotype of BTX ineffective. This immunoresistance can be avoided if clinicians inject only the smallest quantity of BTX that achieves clinical efficacy, avoid administering booster injections before the end of the minimum 12-week lockout period, and extend the period between treatments as long as possible. If immunoresistance does occur, the BTX should be exchanged for a different serotype.

Testing for nonresponse

Patients are said to be nonresponders to BTX therapy if at 4 to 6 weeks following injection they show no reduction in muscle tone. A functional test for nonresponse is to inject a small amount of BTX into either the frontalis or sternocleidomastoid muscle prior to starting treatment; asymmetric weakness demonstrates a response, indicating that either injection technique or muscle selection is the problem. In addition to the development of neutralizing antibodies, other possible reasons for nonresponse include a dose that is too low or an alteration in the pattern of muscles involved in the dystonic movement.

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