ADVANCING PATIENT-CENTERED OUTCOMES IN SURGERY: DEVELOPMENT OF A RESEARCH AGENDA ON PATIENT-REPORTED OUTCOMES IN SURGERY AND CREATION OF A PATIENT-CENTERED DECISION AID FOR STOMA FORMATION DURING LOW ANTERIOR RESECTION.

A Thesis

Presented to the Faculty of the Weill Cornell Graduate School

of Medical Sciences

in Partial Fulfillment of the Requirements for the Degree of

Masters of Clinical Epidemiology

by

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May 2016

ABSTRACT

Background: Greater integration of patient-centered outcomes in surgery remains paramount in the current medical climate. Patient-reported outcomes have emerged as a useful tool to assess subjective outcomes such as pain, function, and quality of life. In order to determine areas of crucial research on patient-reported outcomes and advance cross-disciplinary collaboration, a research agenda was created through a Delphi survey of stakeholders in collaboration with the inaugural Patient-Reported Outcomes (PROS) in Surgery Conference. In the second part of this study, a decision model was created to simulate patient-centered outcomes after low anterior resection for rectal cancer. Randomized controlled trials support the use of defunctioning ileostomies as it reduces the morbidity and mortality of anastomotic leakage; however, they are associated with greater risk for readmission, complications (bowel obstruction, stomal hernia) and impact patient quality of life. Assimilating these data can be difficult for clinicians. To this end, a decision analysis was developed to evaluate the impact of defunctioning ileostomy on patient quantity and quality of life.

Methods: To create a research agenda, an iterative Web-based interface was used to create a conference-based, modified Delphi survey. Participation was limited to PROS conference registrants, which included surgeons, PRO researchers, payers and other stakeholders. In the first round, research items were generated from qualitative review of responses to open-ended prompts. In the second and third rounds, items were ranked using a Likert scale. The top 20 items by mean rating were selected for the research agenda. In the decision analysis, a decision tree compared defunctioning ileostomy creation to no defunctioning ileostomy creation after low anterior resection for rectal cancer. The base case for model analysis was a 65-year-old man with resectable, stage II-III rectal cancer at 8cm from the anal verge status post neoadjuvant

chemoradiation therapy. Long term health states after surgery were stoma, no stoma or death. The primary outcome measure was quality-adjusted life-years (QALYs). Model probabilities and health-state utilities were obtained from the literature using a priori search criteria. The probabilities and utilities were varied over their plausible ranges through sensitivity analyses of one, two and three variables.

Results: In round one of the Delphi Survey, participants submitted 459 items, which were reduced through qualitative review to 53 distinct items across seven themes of PROs research. A research agenda was formulated after two successive rounds of ranking. The research agenda identified three themes important for future PROs research in surgery: (1) PROs in the decision-making process, (2) integrating PROs into the EHR and (3) measuring quality in surgery with PROs. For the decision analysis, defunctioning ileostomy creation was the preferred strategy (8.81 *vs.* 8.73 QALYs). In one-way sensitivity analyses, defunctioning ileostomy remained the preferred strategy over the plausible range of all variables with four exceptions: if the risk of clinical leak was less than 8.9%, if the leak-associated mortality was less than 4.1 %, if the one-year ileostomy reversal rate was less than 70% or if the utility of a stoma was less than 0.69.

Conclusion: A research agenda on PROs in surgery was created using a modified Delphi survey of stakeholders that will help researchers, surgeons, and funders identify crucial areas of future PROs research in surgery. In the decision analysis, low anterior resection with defunctioning ileostomy is the preferred treatment strategy, however for a subset of patients, no ileostomy may be the preferred if patient perception and risk are accounted. The quality of life with a stoma, the probability of a clinical leak and the rate of stoma reversal significantly impacted model preferences, and should be considered in decisions on ileostomy formation during rectal resection.

BIOGRAPHICAL SKETCH

Michael L. Pezold, MD is a clinical research fellow at Memorial Sloan Kettering Cancer Center and concurrently a fellow in Clinical Epidemiology and Health Services Research at the Weill Cornell Graduate School of Medical Sciences. He graduated with his medical degree from the University of Colorado School of Medicine in 2011, and is completing his residency in General Surgery at New York Presbyterian-Weill Cornell Medicine. Throughout medical school and during his residency, Dr. Pezold's research interests have focused on patient/provider decision-making, patient quality of life, patient-reported outcomes, and performance measures in colorectal surgery. As a research fellow at Weill Cornell Medicine, Dr. Pezold's research has focused on determining factors important for patients and providers in the creation of a defunctioning stoma during low anterior resection. His thesis project identifies a research agenda on Patient-Reported Outcomes in Surgery through a Delphi survey of stakeholders, and examines ileostomy creation during low anterior resection for rectal cancer using a decision tree.

DEDICATION

This thesis is dedicated to my mother who showed me ‘true grit’, my father who kindled interest in science through summers of fish, turtles and snakes, my wife who has consistently supported me through seemingly endless training, and to my children, Ellee and Hunter, who bring me tremendous pride and joy.

ACKNOWLEDGEMENTS

Funding for this study was made possible through grants from The Plastic Surgery Foundation and the Agency for Healthcare Research and Quality (Grant numbers 1R13 HS023357-01 and T32HS000066). This work was supported, in part, by NIH/NCI Cancer Center Support Grant P30 CA008748. David Sewell provided editorial review of the manuscript and figures. Dr. Andrea Pusic provided content review and was a PROS Conference organizer. Dr. Wes Cohen helped in the analysis of Delphi responses. Finally, these works would not be possible without the generous contributions from Drs. Larissa Temple and James Hollenberg of both their time and mentoring.

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CHAPTER ONE

INTRODUCTION

PROs, as defined by the FDA, are "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."[1] In practice, this entails measuring a subjective outcome like function after knee arthroplasty with a questionnaire. Publications on patient-reported outcomes (PROs) in the surgical literature have tripled during the last decade. The growing recognition among surgeons that many postoperative outcomes like functional improvement or symptom severity are best measured by the patient and the increased availability of measures for historically subjective topics have undoubtedly contributed to this surge in publications.[2–4] PROs now play an important role in the planning of comparative effectiveness research and are currently used as primary outcomes in surgical trials.[5] The Institute of Medicine and the National Quality Forum have long advocated that patient-centered care should be a requirement in modern health care, and this perspective has influenced health care deliberations during the last decade.[6] Furthermore, the Affordable Care Act has encouraged patient-reported data collection in surgery by creating new payment models through the Centers for Medicaid and Medicare Services (CMS) and by targeted funding of research from the Patient-Centered Outcomes Research Institute.[7,8] These new models underscore the growing importance of PROs in surgery.

Despite the potential value of PROs in surgical care, many methodological and logistical concerns remain.[9] Addressing these issues is difficult in a research climate of increasingly scarce funding.[10] Thus, researchers and funding agencies need input and clarity from stakeholders, in order to better prioritize research and improve collaboration between institutions. Furthermore, options for surgical techniques and technologies are rapidly expanding while healthcare resources are shrinking. To better

understand the outcomes of surgery from the patient perspective, there is no better time than now for the surgical and research communities to come together and reach consensus regarding the most important and timely issues with PROs research in surgery.

To address these issues, the Patient-Reported Outcomes in Surgery Conference was formed, with sponsorship from The Plastic Surgery Foundation and the Agency for Healthcare Research and Quality. The conference brought together stakeholders from diverse fields, including payers, patient advocates, surgeons, researchers, industry representatives, regulators, and health information technology vendors. The two-day conference was held in Washington, D.C. (Jan 29-30, 2015) and included panel discussions on current PROs research in surgery within the areas of clinical care, comparative effectiveness, patient access, psychometric development, surgical trials, and quality, as well mapping out the future directions for each field. The specific goals of the conference were to improve the accessibility and interpretability of PROs data for patients and providers, to develop a consensus around methodological issues of PROs measurement, and to develop a research agenda for PROs measurement in surgery. The formation of a research agenda should prioritize research questions deemed to be timely and important by stakeholders to guide future collaboration and funding. To meet this aim, the conference leadership conducted a Delphi survey of stakeholders to develop an agenda on future PROs research in surgery.

METHODS

This study used a modified Delphi survey to achieve formal group consensus, maximizing dialogue through anonymous, structured feedback.[11,12] To facilitate the use of the Delphi model, an expert panel was assembled before the opening of the

conference. The panel, composed of conference leaders and methodological experts, developed the study schema and consensus criteria on the basis of a three-round, Web-based survey (Figure 1.1). The study was approved by the Memorial Sloan Kettering Cancer Center Institutional Review Board (prospective waiver X15-004).

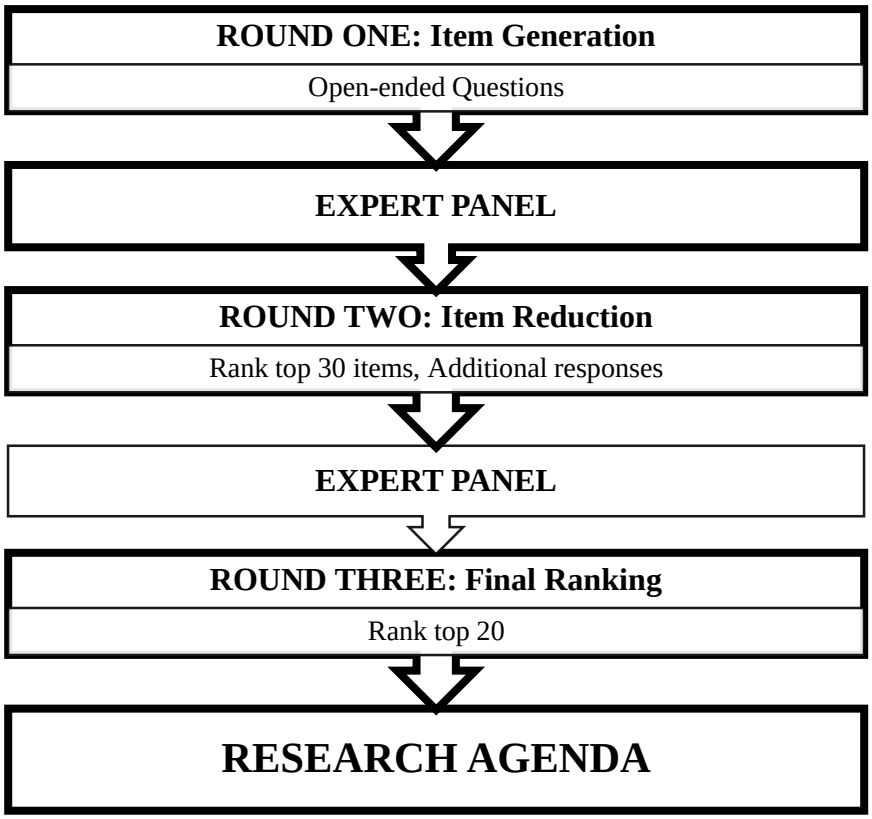

Figure 1.1 Flow chart for the three rounds of the modified Delphi survey

Emails containing a link to a Web-based survey were distributed to all conference registrants 1 week before the start of the conference (round one), which was held January 29–30, 2015. Participants were asked to anonymously identify timely and important PROs research topics through seven open-ended questions related to clinical care, comparative effectiveness, patient satisfaction, and quality metrics. There was no limit to the length of the responses. Item submissions were reviewed in parallel by two researchers (M.P. and W.C.). This involved separating

compound responses into individual items, summarizing submissions into concise items, and categorizing items into generic themes. After all submissions were reviewed, identical items were deleted and similar items with overlapping content were consolidated into broader concepts. The expert panel then evaluated the consistency of each researcher's item reduction and endorsed the selection of research items for round two.

All conference attendees were invited to participate in a Web-based survey during the conference (round two). Participants were given the final research items from round one, in randomized order, and were asked to rank the items by research importance using a 5-point Likert scale, with high and low research priority as anchors. In addition, an open-ended question prompt at the conclusion of the survey allowed participants to submit additional research questions. Mirroring the process in round one, all new research questions submitted in round two were subjected to qualitative review and consolidation into final research items. Round two concluded with the completion of the conference.

Following the conference, all attendees were asked, via email, to participate in a Web-based survey, regardless of whether they participated in previous rounds. Email reminders to complete the survey were distributed weekly, and each registrant was limited to one survey response each. The top 30 items by mean priority score from round two, along with new item submissions, were distributed for final ranking by research priority, in order to reach the a priori goal of a 20 item research agenda. To reduce the possibility of a ceiling effect, a 3-point Likert scale was utilized in the final round and participants were encouraged to rate only 10 items as 'high research priority'. As in round two, item order was randomized. The top 20 items by mean Likert score were selected as the consensus research agenda.

RESULTS

Of the 143 people registered for the conference, 137 provided valid email addresses. Potential subjects were invited to participate during each round. There was a wide range of attendants including individuals from several surgical subspecialties, payers, regulators and patient advocates with the three most common groups identified as being plastic surgeons (19%), general surgeons (13%) and researchers (17%). Table 1.1 presents the basic demographic characteristics of respondents by round. During item generation (rounds one and two), participants were given the option to specify their occupation (Table 1.2). Specific occupation demographics were not collected during round three as there was a desire to keep the survey as short as possible in order to increase response rates. In the first round, 83 participants (61% of conference registrants with email addresses) submitted 356 responses to open-ended questions. After review, a total of 459 research items were submitted, with a mean of 5.5 items submitted per participant.

Table 1.1 Characteristics of survey responders by round

	Round		
Characteristic	**One**	**Two**	**Three**
Registrant %, (no.)	61 (83)	39 (54)	42 (59)
Age			
<40	49	39	42
41–60	39	44	51
≥61	12	17	7
Conference role			
Speaker	18	24	26
Registrant	82	76	74
Occupation			
Surgeon	64	54	59
Non-surgeon	36	46	41
PROs experience			
<3 years	40	35	44
4–6 years	22	17	17
>7 years	39	48	39

Data are % of conference registrants with a valid email address (N=137). Percentage totals may not equal 100 due to rounding. PROs, patient-reported outcomes.

Table 1.2 Occupations of conference registrants and survey responders

Table 1.2 Occupations of conference registrants and survey responders

Occupation	Conference Registrants	Round 1	Round 2
Surgeon			
Breast Surgery	7	2	0
Colorectal Surgery	7	7	2
General Surgery	19	12	8
Neurosurgery	1	1	1
Orthopedic Surgery	9	1	0
Otolaryngology	7	2	2
Plastic Surgery	28	14	9
Surgical Oncology	4	1	0
Thoracic Surgery	2	0	1
Urology	8	3	1
Vascular Surgery	1	0	0
Nonsurgeon			
Health IT Vendor	2	2	2
Funding Agency	2	1	1
Federal Regulator	5	1	0
Patient Advocate	2	1	1
Policymaker	2	0	1
Researcher	25	20	15
Research Fellow/Trainee	4	2	4
Research Staff/Manager	8	3	2
Total	143	73	50

Disclosure of specific occupations remained optional. Thus, the number of participants who disclosed their occupation in Rounds 1 and 2 was less than the total number of participants for both rounds.

After item reduction was performed and the expert panel reviewed the results, there were 53 items within seven themes: clinical care, comparative effectiveness, data management, ethics, performance measurement, education, and other. In the second round, 54 participants (39% of emailed registrants) responded to email invitations during the conference. Responders ranked the 53 items by research priority and submitted 9 new items, which were reviewed and consolidated to 3 new items. In the third round, 57 participants (42% of emailed registrants) responded to survey invitations. The top 20 items from round three were selected as the consensus research agenda for future PRO research (Table 1.3). Ranking of item importance remained stable between rounds, with only 2 items from the top 20 of Round 2 failing to make the final research agenda. Stakeholder participation from Rounds 2 and 3 was predominantly from experienced PROs researchers with more than 60% of participants reporting > 7 years experience.

Table 1.3 The final research agenda, from 459 items initially submitted

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Rank	Mean	Item
1	2.52	Impact of PROs on patient and/or provider decision making.
2	2.49	Accuracy of measuring quality in surgery with PROs versus clinical quality metrics.
3	2.46	Efficacy of patient-reported performance measures to reduce costs and improve quality.
4	2.41	Improve PROs data collection, integration, and presentation into the EHR.
5	2.36	Impact of patient expectations on their satisfaction with surgery.
6	2.35	Optimize presentation of PROs data to providers for rapid interpretation and action.
6	2.35	Efficient integration of PROs data collection and reporting into the clinical workflow.
8	2.33	Determine optimal method for transitioning PROMs from research tools to performance measures.
9	2.29	Create systems that use PROs data to alert providers to patient needs and flag actionable items.
10	2.27	Influence of patient-reported data on patient satisfaction with decision-making.
11	2.23	Establish PROs benchmarks in surgical care.
12	2.22	Effect of preoperative education on patient satisfaction with surgery.
13	2.21	Improve utilization of PROs among nonacademic providers and institutions.
14	2.19	Influence of patient-reported data on patient satisfaction with clinical care.
14	2.19	Develop strategies for better patient engagement and improved response rates.
16	2.17	Accuracy of patient-reported data as a primary outcome in surgical trials.
17	2.15	Role of PROs data in patient education.
18	2.13	Explore if patient access to PROs data improves quality.
18	2.13	Risk adjust and standardize PROs data.
20	2.11	Identify barriers to successful implementation of PROs measures in clinical trials.

EHR, electronic health record; PROs, patient-reported outcomes; PROMs, patient-reported outcome measures.

DISCUSSION

Using a modified Delphi approach, we engaged an international stakeholder group of surgeons, researchers, patient advocates, funding agency representatives, health information technology vendors, and regulators to reach consensus on future PROs research priorities in surgery. The final results of the survey contain the top 20 items from over 450 topics initially submitted by participants. Our results represent the first consensus-driven, surgery-focused PRO research agenda to date. Within the research agenda, three themes emerged as priorities for future research in surgery: (1) PROs in the surgical decision-making process, (2) challenges to integration of PROs in the electronic health record (EHR), and (3) PROs and the measurement of quality (Figure 1.2). Among all items, the decision-making process was rated of high importance, with “Impact of PROs on patient and/or provider decision-making” the top-ranked item for both rounds.

Figure 1.2 Most important themes for PROs research in surgery identified from the Delphi survey

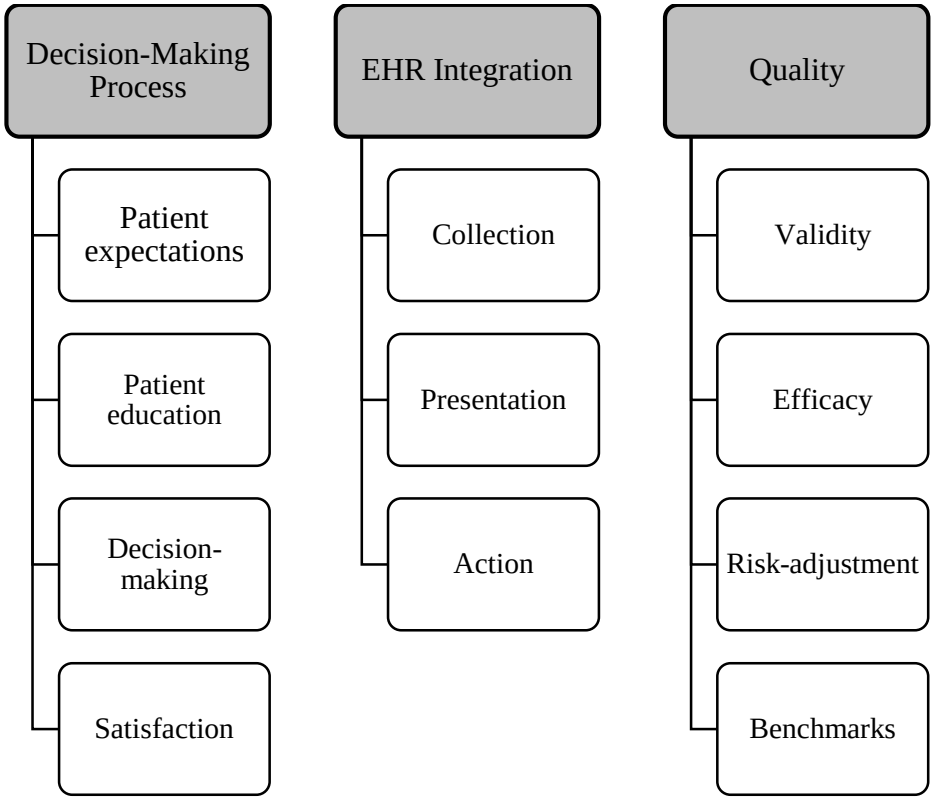

Figure 1.2 Most important themes for PROs research in surgery identified from the Delphi survey

Priority 1: Incorporating PRO data into the Decision Making Process

It is not surprising that the use of PROs in the clinical decision-making process was the highest importance. Decision-making in surgery has traditionally relied on surgeon experience and established objective measures such as 30-day mortality and hospital length of stay. Although currently underutilized, PROs have proven to be effective at measuring subjective outcomes after surgery.[13,14] In this respect, PROs data provide an added dimension to the evaluation of new surgical techniques and technology, which may enable surgeons to better understand subjective outcomes. For example, outcomes in randomized controlled trials comparing open and laparoscopic hernia repair techniques have previously focused on visual analogue scores of pain, hernia recurrence, complications, and operative time.[15,16] As the differences between emerging techniques become more nuanced (e.g., robotic vs. laparoscopic), traditional measures may be insensitive to improvements in patient disability and well-being, both of which are central to arguments for minimally invasive surgery. Additionally, the inclusion of patients in shared decision-making requires health care that aligns with patient preferences and values.[17] Routine and accurate measurement of PROs in surgical trials and clinical care provides a valued outcome for surgeons and expands patient involvement in decision-making.

Improving decision-making in surgery will require more than just greater implementation of PROs in surgical trials and clinical care. This study identified problematic aspects within the theoretical framework for decision-making—specifically, the relationship between decision-making and patient expectations, education, and satisfaction. Understanding the effects of patient expectations on the decision-making process requires accurate measurement of expectations, as well as honest assessment of the ability to recalibrate these expectations through preoperative education.[18] A randomized trial of hip and knee arthroplasties showed that

preoperative education can influence patient expectations of postoperative recovery.[19] Furthermore, Ho et al. reported that patient satisfaction with preoperative information was the strongest predictor of satisfaction with the overall outcome—stronger even than the method of surgery and whether complications occurred.[20] Yet, thus far, patient expectations have inconsistently correlated with patient satisfaction after surgery, and there is no accepted method for capture of perioperative expectations.[21] Studying the relationship between treatment decision-making and patient education, expectations, and satisfaction has become paramount, given that patient satisfaction, which has been measured for the past decade, is now being used to calibrate surgeon and institutional reimbursement.[22] Future research will need to further explore the theoretical framework for the decision-making process and identify measurable factors that surgeons and institutions can use to improve care.

Priority 2: Integrating PRO data into the Electronic Health Record

Concerns remain regarding the integration of PROs into the EHR. Paper administration and processing of PROs can be time-consuming, costly, and too burdensome for a busy surgical practice. EHR integration improves the logistics of administration, although it raises additional concerns related to the security of patient and provider information. Existing research has focused primarily on PROs measurement, rather than on the EHR interface with patients and providers.[23] Effective systems must optimize the presentation of PROs data to enable surgeons to effectively interpret this information for decision-making. Likewise, enhanced feedback to patients may help validate the time commitment required to complete patient-reported measures and may potentially improve patient response rates. Without significant collaborative efforts to develop and improve EHR platforms, the effective use of patient-reported data by providers is unlikely to increase.

The NIH Patient Reported Outcomes Measurement Information System (PROMIS) may provide some insight for institutions collaborating on the electronic integration of PROs data collection and presentation. As a collective effort between institutions, PROMIS uses a centralized, Web-based system for PROs data collection and features immediate, standardized scoring using a shared item bank.[24,25] Despite the success of PROMIS with electronic administration and scoring across multiple institutions, they are not uniformly calibrated nor validated for measuring the impact of surgical procedures. Future systems that measure PROs in surgery should incorporate the advances made by PROMIS, as well as address the issues identified by our Delphi survey, including presentation of PROs data to patients that is responsive to education level and language abilities, enabling easy interpretation by surgeons for immediate action, and improving the integration of PROs systems into the EHR.

Priority 3: Patient Reported Outcomes and Quality Assessment

PROs and the measurement of quality emerged as the final theme from the Delphi survey and raised concerns about the validity, efficacy, and risk adjustment of PROs measures in surgery. Foremost, the survey identified the validity of measuring quality with PROs versus traditional clinical outcome measures as a significant consideration for stakeholders. Moreover, the efficacy of PROs instruments to improve quality and lower costs has not been extensively studied. System-wide introduction of PROs instruments should follow thoughtful research initiatives that demonstrate their effectiveness. To address this need for validation, the CMS Innovation Center could be a potential resource in evaluating the efficacy of selected PROs measures to improve quality, as it has already seen success in assessing new reimbursement strategies for Accountable Care Organizations.[22] Emerging evidence has begun to show a correlation between patient satisfaction and surgical outcomes, however comparison of selected PROs measures between providers, surgical groups,

and institutions will require thorough risk and case adjustment.[26] Furthermore, to alleviate potential skepticism within the surgical community, the establishment of benchmarks will necessitate adequate transparency with regard to reasoning and methodologies. Successful use of PROs in performance measurement of surgery will require a thoughtful and open collaboration among stakeholders.

Measuring performance with PROs, however, is not a new concept. During the past decade, the UK National Health Service Patient Reported Outcome Measures initiative has collected health-related quality of life (HR-QOL), patient satisfaction, and functional data after inguinal hernia repair, hip and knee arthroplasty, and varicose vein ablation.[27] Internationally, the Patient Reported Outcome Measures initiative is perhaps the most ambitious quality improvement project to date and has started to evaluate the changes in HR-QOL and patient satisfaction after surgery, at the provider and institution level.[28] In a comparable move, CMS plans to encourage providers and institutions to routinely collect PROs data through funding models, such as the Meaningful Use and Physician Quality and Reporting System. The funding models initially incentivize PROs data collection through physician and institution reimbursements; however, after an introductory period, the models penalize participants who do not meet reporting/collection requirements. It remains to be determined whether routine measurement and comparison of PROs data will improve outcomes and lower costs in the long run.

There are several limitations to this study, many of which are inherent to the Delphi process. The qualitative round of the survey was susceptible to influence from both the expert panel and the reviewers. To address this, the independent reviewers worked separately, without interaction with the expert panel. Final review by the expert panel looked for differences between reviewers, which is an accepted method for item generation and review and has been implemented by other groups in creating

a research agenda.[11,29] In addition, the survey was susceptible to nonresponder bias. Studies have demonstrated that the demographic characteristics and survey results of responders are not equivalent to those of nonresponders.[30] There were no qualitative differences in occupation between responders and nonresponders; however, there may have existed subtle differences between these groups that were not measured. Despite this limitation, the survey did receive robust participation for all three rounds, and the sample size was comparable to or greater than that of similar conference-based surveys.[31,32] Finally, the PROS conference relied on patient advocacy groups as a surrogate for the 'patient voice'. Ideally, one could envision incorporating non-advocacy patients in a national research agenda; however, patient advocates represent the best practice currently to promote patient concerns in policy discussions, and this study remains one of the few Delphis to incorporate the 'patient voice'. Ongoing efforts to increase the patient voice in PRO research and implementation will be required for meaningful incorporation of PROs into surgical care, measurement and research.

CONCLUSION

In an era of patient-centered care, PROs can serve as a useful complement to ongoing discussions on health care expenditures by including the patient voice, and they have considerable potential in the determination of quality in an evolving health care system. The incredible growth of PROs in clinical care and surgical trials has led to many potential research endeavors and collaborations. The PROS Conference developed a research agenda for researchers, surgeons, and funding agencies, to help prioritize research on PROs measurement in surgery, in order to direct funding and institutional collaboration. Future research initiatives should address PROs in the

decision-making process, challenges to integrating PROs into the EHR, and PROs and the measurement of quality.

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CHAPTER TWO

When to divert? Defunctioning ileostomy creation during low anterior resection for rectal cancer: A decision analysis.

CHAPTER TWO

INTRODUCTION

Over the past two decades, sphincter preserving surgery has eclipsed abdominoperineal resection as the treatment of choice for rectal cancer.[1–4] Improved screening, surgical technique and multimodality therapy have undoubtedly contributed to this trend, yet patient aversion to stomas has remained the foremost catalyst for change. Sphincter preservation, however, comes at considerable risk for anastomotic leak, which can lead to significant morbidity and mortality. To mitigate this risk, proximal diversion of the enteric stream has emerged as the primary procedure to reduce both the incidence and severity of anastomotic leaks. Non-randomized observational data, as well as one adequately-powered randomized-controlled trial, have demonstrated an over 50% reduction in the development of leaks and more than 90% reduction in associated mortality.[5–9] In light of these data, creation of a defunctioning ileostomy during low anterior resection is now ubiquitous.

Although principally a risk-reducing procedure, temporary defunctioning ileostomies are not without risk for morbidity, nor are they always temporary. Recent literature has suggested a greater likelihood for readmission for dehydration or stomal complications.[10–15] A defunctioning ileostomy mandates a second operation for reversal, which is itself associated with a small, but not insignificant risk. Additionally, patients must accept a temporary lower quality of life (QOL) on the grounds that it will reduce the risk and severity of anastomotic leak, and improve their long term quantity and quality of life. And yet, not every patient who undergoes low anterior resection is at high risk for anastomotic leaks; there may exist a population of unnecessary defunctioning stomas. Furthermore, despite a commitment by the patient and surgeon to avoid a permanent stoma, some patients may develop metastatic

disease or comorbid conditions that preclude reversal of a temporary ileostomy, thereby becoming permanent. Growing evidence has shown that anywhere from 10-30% of defunctioning ileostomies are never reversed.[14,16–19]

Regardless of the limitations of existing data, clinical practice has shifted towards routine stoma formation during sphincter preserving surgery.[4,20] Assimilating the risk for anastomotic leak and related mortality with the possibility of stomal complications and ileostomy nonreversal, not to mention the QOL implications for each strategy, can be difficult to incorporate into preoperative patient discussions. There may be clinical scenarios in which the survival and long-term QOL benefit of a temporary, defunctioning stoma is negligible. A patient-centered approach to decision-making would incorporate the risk/benefits of defunctioning ileostomy creation and remain responsive to the clinical scenario. To examine the tradeoff between the risks and benefits for each strategy, we developed a decision analysis to determine the best strategy (defunctioning ileostomy vs no defunctioning ileostomy) during low anterior resection for rectal cancer using overall survival and long-term QOL as the primary outcome (quality-adjusted life years), and identified clinical variables influential to this decision.

METHODS

Study Design

We created a decision analytic model to simulate postoperative outcomes after low anterior resection for rectal cancer using published guidelines.[21–23] We compared the strategy of defunctioning ileostomy vs. no defunctioning ileostomy creation, and the effect it had on anastomotic and stomal complications (Figure 2.1). The model simulated outcomes along three identified phases of postoperative care: 30 days post-surgery, 90 days post-surgery, and 1 year post-surgery, in which anastomotic leaks for

their part occur primarily within the first 30 days, whereas other complications including stoma-related may occur within the first 90 days. The primary outcome was quality-adjusted life-years (QALYs), which were calculated using health-state utilities derived from the literature and the base case life expectancy adjusted for age and disease using the Declining Exponential Approximation of Life Expectancy (DEALE) method.[24] The age- and disease-specific life expectancies were obtained from the Centers for Disease Control and Prevention (CDC) Life Tables and the Surveillance Epidemiology and End Results (SEER) Cancer Statistics Review.[25,26] Utilizing a decomposed approach, health outcomes were separated into short- and long-term outcomes. Long-term health outcomes were simplified into three categories: no stoma, stoma, or death. Short-term outcomes reflected the temporary negative impact of complications or reoperations on QOL. The short-term disutility for specific complications or procedures were assessed using the average, published length of in-hospital stay in years, and reflects the loss of time in perfect health.

The decision tree, model probabilities, and utilities were assessed for clinical validity by colorectal surgeons. The decision tree analysis and sensitivity analyses were performed using TreeAge Pro 2016 (TreeAge Software, Williamstown, Mass).

Figure 2.1 Abridged diagram of the decision tree showing model progression and the timeline for outcomes

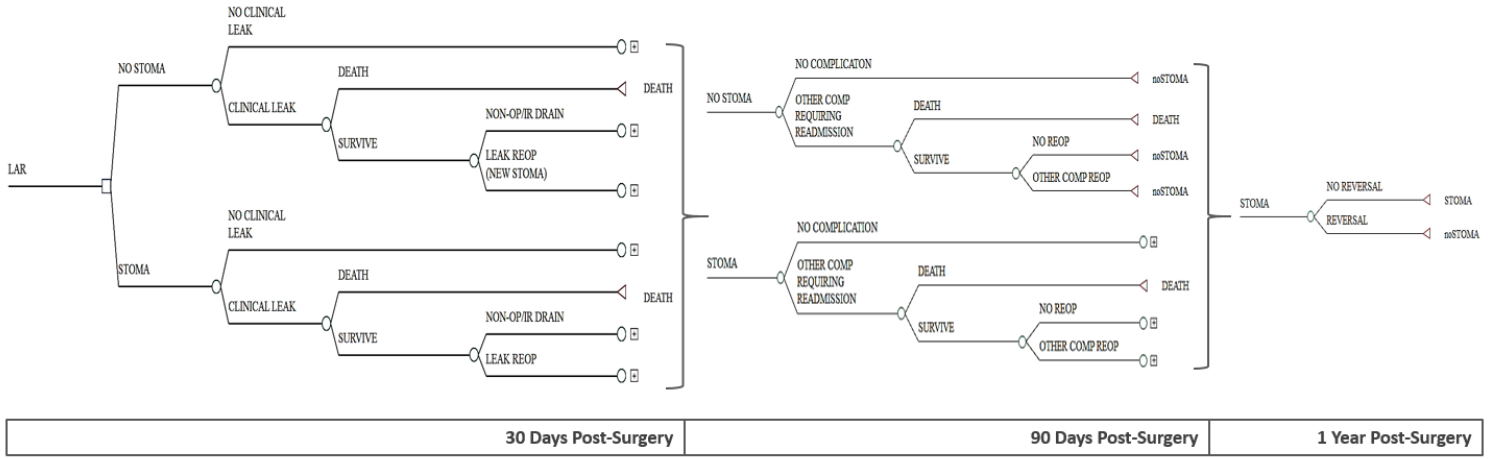


Figure 2.1 Abridged diagram of the decision tree showing model progression and the timeline for outcomes. On the left, a decision node (square) denotes the decision between stoma and no stoma formation during LAR. The brackets correspond to model progression from a chance node (circles) to a relevant subtree. The terminal nodes (triangles) are predefined end points: no stoma, stoma and death.

Base Case

The base case for model analysis was a 65 year-old patient with resectable, stage II-III rectal cancer at 8cm from the anal verge, who received standard neoadjuvant radiation therapy. Elective low anterior resection was planned with or without a defunctioning ileostomy. The technique for specimen removal was total mesorectal excision with grossly negative distal and radial margins. The method of resection (i.e. open, MIS, MIS-assisted) is not specified and no intraoperative complications occurred.

Model Assumptions

For most, if not all decision analyses, model assumptions must be made to simplify a clinical scenario into a unified construct and to determine model parameters when insufficient or little data exists. In both cases, model assumptions were developed by a team of researchers to address these concerns.

1. *Long-term health outcomes:* We assumed patients reached their long-term health outcome within one year of surgery. Existing high-quality evidence shows that > 95% of stomas are reversed within 12 months of surgery.[19,27,28] To this end, patients were assumed to reach three outcomes by the end of year one: no stoma, stoma or death. Death in this context refers to complication-related mortality, and not as a result of disease.
2. *Complications:* To account for differences in the incidence and severity of clinical leaks, as well as the morbidity associated with defunctioning ileostomies, we separated complications into 'clinical leaks' and 'other complications'. Clinical leaks were defined as any signs or symptoms of anastomotic leak requiring intervention (antibiotics, percutaneous drainage, or operation) within the first 30 days. Management of a clinical leak was dichotomized into non-operative (antibiotics or percutaneous drainage; Grade A/B anastomotic leak) and operative interventions (Grade C anastomotic leak), and does not include potential

management of chronic anastomotic leaks such as mucosal advancement flaps, fibrin glue, etc. 'Other complications' were included only if they were serious enough to require readmission within 90 days, which was based on evidence that most complications including stoma-related occur within 90 days of surgery[9,14,17,29,30]. The need for reoperation from a complication other than clinical leak was assumed to be equivalent between treatment groups. Finally, reoperation for a complication other than clinical leak in a patient with an existing stoma such as small bowel obstruction, stomal herniation, and fascial dehiscence was assumed to result in stoma reversal.

3. *Stoma Formation*: We assumed urgent reoperation for a clinical leak would uniformly result in the creation of a stoma. This was demonstrated in both the Rectal Cancer Trial On DEfunctioning Stoma (RECTODES) study and the Danish Colorectal Cancer Group's database, in which a stoma was consistently created during urgent reoperation for clinical leak if there was no defunctioning ileostomy during the initial low anterior resection[6,31]. Urgent reoperation for a clinical leak in the presence of an existing defunctioning ileostomy, although unlikely, would not intuitively result in reversal of the existing ileostomy at the time of emergent reoperation. We refer to a stoma created as a result of urgent reoperation for a clinical leak as a 'secondary stoma', whereas ileostomy created during index operation are referred to as a primary stoma. By defining these as 'secondary', we are acknowledging the greater likelihood for colostomy or end ileostomy formation, which in the literature has shown significantly lower likelihood of reversal than loop ileostomy.[6,19,27,31–33]

Data Sources

Model probabilities and utilities used for base case analysis and sensitivity analyses were obtained from the literature (Table 2.1 and Table 2.2). A systematic literature

search of the Embase/Medline databases from 2005 to 2015 identified articles reporting comparative outcomes for defunctioning stoma creation during low anterior resection. Preference was given to larger and prospectively-collected data (randomized control trials, $n \geq 75$; prospective observational cohorts, $n \geq 200$; retrospective observational cohorts, $n \geq 400$). Case studies, case-control studies, and systematic literature reviews were excluded. Results were screened for manuscripts that reported dichotomized outcomes for defunctioning ileostomy creation during low anterior resection. The literature search criteria, results and selected manuscripts are listed in Appendix 1 and 2.

Table 2.1 Model Probability Estimates

Table 2.1 Model Probability Estimates

Model Parameter	*Base case*	*Plausible Range*	*Values*	*References*
Clinical leak 30-d				Eriksen 2005, Gastinger 2005, Peeters 2005, Matthiessen 2007, Eberl 2008, den Dulk 2009, Bakkar 2014
No stoma	15%	5 – 30%	6 – 28%	
Stoma	7.5%	2 – 20%	2 – 23%	
Clinical leak 30-d mortality				Eriksen 2005, Gastinger 2005, Peeters 2005, Eberl 2008, den Dulk 2009
No stoma	10%	1 – 15%	0– 22%	
Stoma	1%	0 – 5%	0 – 4.7%	
Urgent reoperation after clinical leak				Gastinger 2005, Peeters 2005, Matthiesen 2007, Eberl 2008, Bakkar 2014
No stoma	85%	50 – 100%	71 – 96%	
Stoma	30%	5 – 50%	8 – 60%	
Stoma after clinical leak reoperation	100%	80 – 100%	96 – 100%	Matthiessen 2007, Tortorelli 2011, Krarup 2014
Other complication requiring readmission				Gastinger 2005, Bakkar 2014
No stoma	20%	10 – 50%	20%	
Stoma	30%	20 – 50%	25 – 34%	
Other complication 30-d mortality	1%	0 – 5%	0 – 2%	Williams 2006, Matthiessen 2007, Parikh 2008
Reoperation after Other complication	30%	10 – 50%	29	Bakkar 2014
Stoma reversal at 1 year				den Dulk 2007, Matthiessen 2007, Lindgren 2011, Lim 2013, Krarup 2014
Primary stoma	85%	70 – 100%	83 – 90%	
Secondary stoma	35%	20 – 80%	28 – 49%	
Median time to stoma reversal (yrs)				Gastinger 2005, Wong 2005, Matthiessen 2007, den Dulk 2007, Messaris 2012
Primary	0.30	0.3 – 1.0	0.26 – 0.42	
Secondary	0.83	0.5 – 2.0	0.83	

Table 2.2 Health State Utilities

Table 2.2 Health State Utilities

Model Parameter	*Base Case*	*Plausible Range*	*Values*	*References*
Long-Term Utilities				
No stoma	0.85	0.80 – 0.99	0.73-0.86	van den Drink 2004, Bossema 2008
Stoma	0.80	0.60 – 0.90	0.63-0.95	van den Drink 2004, Bossema 2008, Smith 2006, Shiroiwa 2009
Death	0.0	NA	NA	NA
Short-term Disutilities				
Readmit/Non-op comp	0.01	0.005 – 0.25	0.008 – 0.024	Williams 2005, Foster 2006, Matthiessen 2007, Parikh 2008
Stoma reversal	0.01	0.005 – 0.25	0.010 – 0.014	Wong 2005, Chow 2009
Other comp reoperation	0.03	0.01 – 0.05	0.019 – 0.036	Williams 2005, Foster 2006, Parikh 2008
Leak reoperation	0.05	0.03 – 0.10	0.049	Matthiessen 2007

Other model parameters include complications other than clinical leak occurring within the first 90 days, primary vs. secondary stoma reversal, and health state utilities after low anterior resection. In order to determine the incidence, mortality, length of stay and need for urgent surgery for complications other than anastomotic leak, several large observational studies reporting complications after large bowel surgery were utilized. Similarly, the incidence of primary or secondary stoma reversal at one year, median length of stay and time to stoma reversal was obtained from the broader colorectal literature. Health state utilities were obtained from manuscripts reporting the postoperative QOL associated with a stoma and/or no stoma after low anterior resection through standard methodology (i.e. standard gamble, time tradeoff method, or visual analogue scale).

Sensitivity Analyses

Model robustness was examined through a series of deterministic sensitivity analyses. All model parameters and health state utilities were varied over plausible ranges in one-way sensitivity analyses. Sensitive model parameters or utilities were further examined through two-way sensitivity analyses when clinically relevant. A three-way sensitivity analysis further examined the relationship between three sensitive model probabilities.

RESULTS

The average life expectancy and quality-adjusted life years for each strategy are listed in Table 2.3. For the base case, in which a patient 65 years old with rectal cancer at 8 cm from the anal verge received neoadjuvant radiation, average life expectancy was greater for stoma formation (10.45 vs. 10.32 life years). When adjusted for QOL,

stoma formation remained the preferable strategy over no stoma formation (8.81 vs. 8.77 QALYs); however, equated to only one quality-adjusted life month difference between strategies.

Table 2.3 Base case analysis

	Stoma	*No Stoma*	*Difference*
Life-years	10.45	10.32	0.13
Quality-adjusted life-years	8.81	8.73	0.08

All model parameters were evaluated through one-way sensitivity analyses along there range of plausible values. Sensitive variable are listed in Table 2.4. No stoma formation was preferred when the risk for anastomotic leak and leak-related mortality was less than 9.0% and 4.1%, when the likelihood of ileostomy reversal was less than 70%, and when the predicted QOL with an ileostomy was poor (Health State Utility < 0.69). The tornado diagram in Figure 2.2 depicts the influence each model parameter has on the expected value (QALYs).

Table 2.4 Sensitive Variables

Model Parameter	*Threshold*
Clinical leak	8.90%
Clinical leak mortality	4.10%
Primary stoma reversal at one-year	70%
QOL with stoma health state utility	0.69

Figure 2.2 Tornado Diagram of model probabilities and utilities

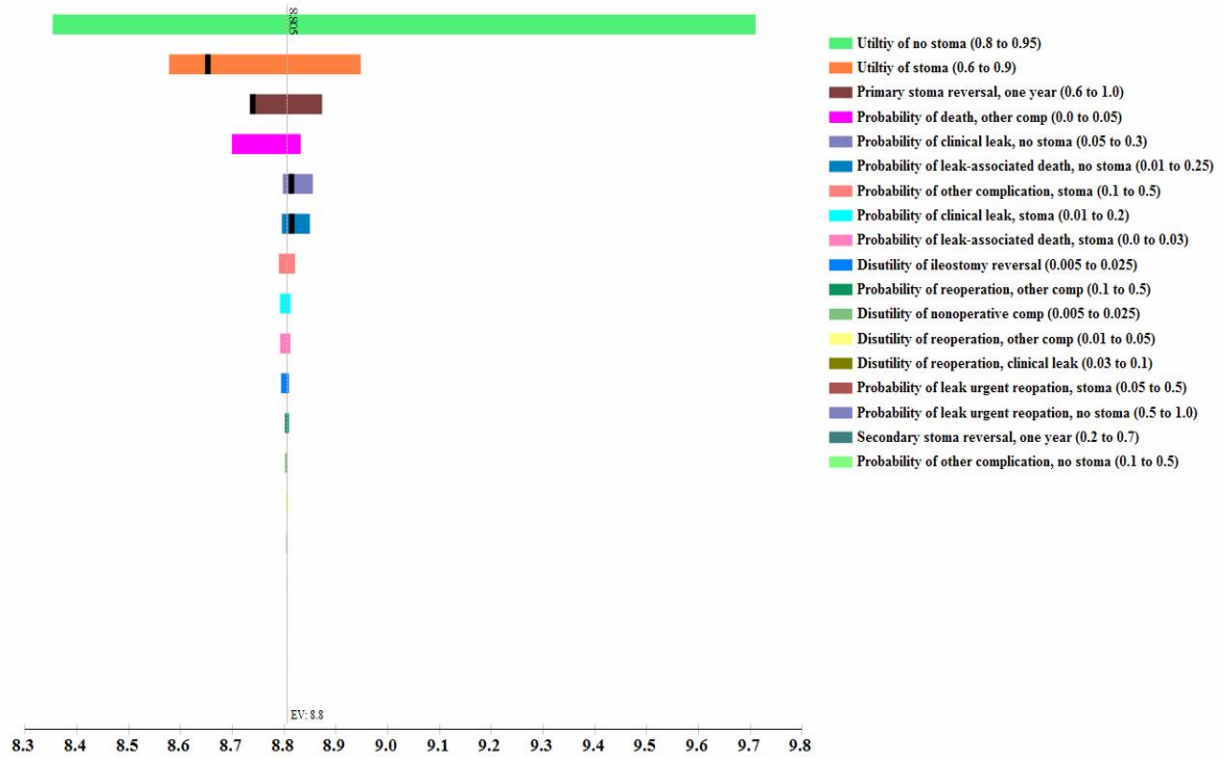


Figure 2.2 Tornado Diagram, illustrates the influence of model probabilities and utilities on the expected value (QALYs) of the preferred strategy. Black bars correspond to the threshold for model change for specific variables: stoma utility, primary stoma reversal at one year, probability of clinical leak (no stoma), and leak-associated death (no stoma).

Variables sensitive in one-way analyses were further evaluated in two-way sensitivity analyses. Figure 2.3 illustrates the interaction between the probability of clinical leak and the utility of a permanent stoma, and the probability of clinical leak and leak-related mortality. A three way analysis of sensitive variables (clinical leak risk, leak-related mortality and primary stoma reversal) is depicted in Figure 2.4.

Figure 2.3 Results of two-way sensitivity analyses

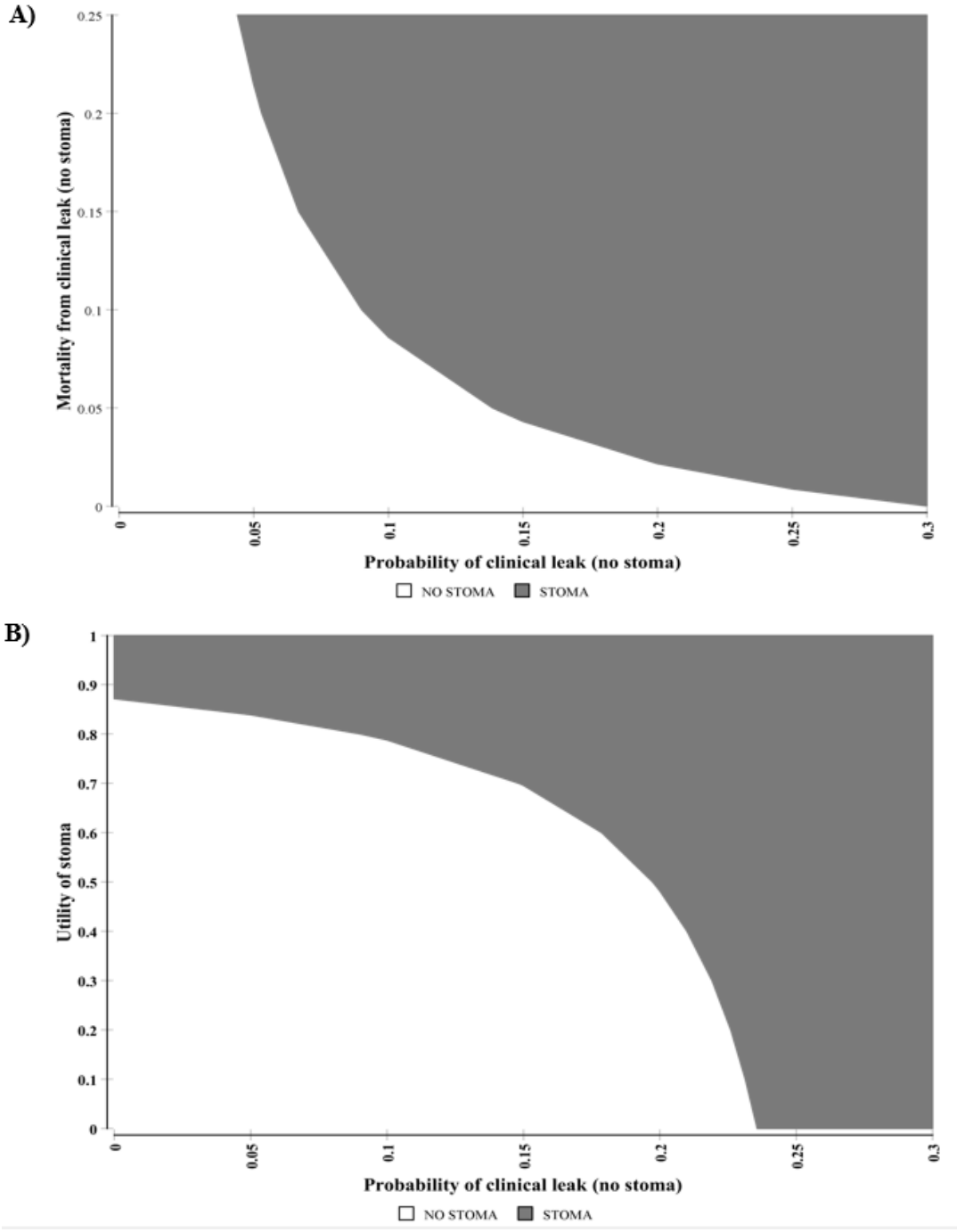


Figure 2.3 Results of two-way sensitivity analyses, in which the probability of clinical leak and A) the associated mortality, B) the utility of a permanent stoma is varied along plausible ranges. The color of the graph plot corresponds to the preferred strategy for selected scenario.

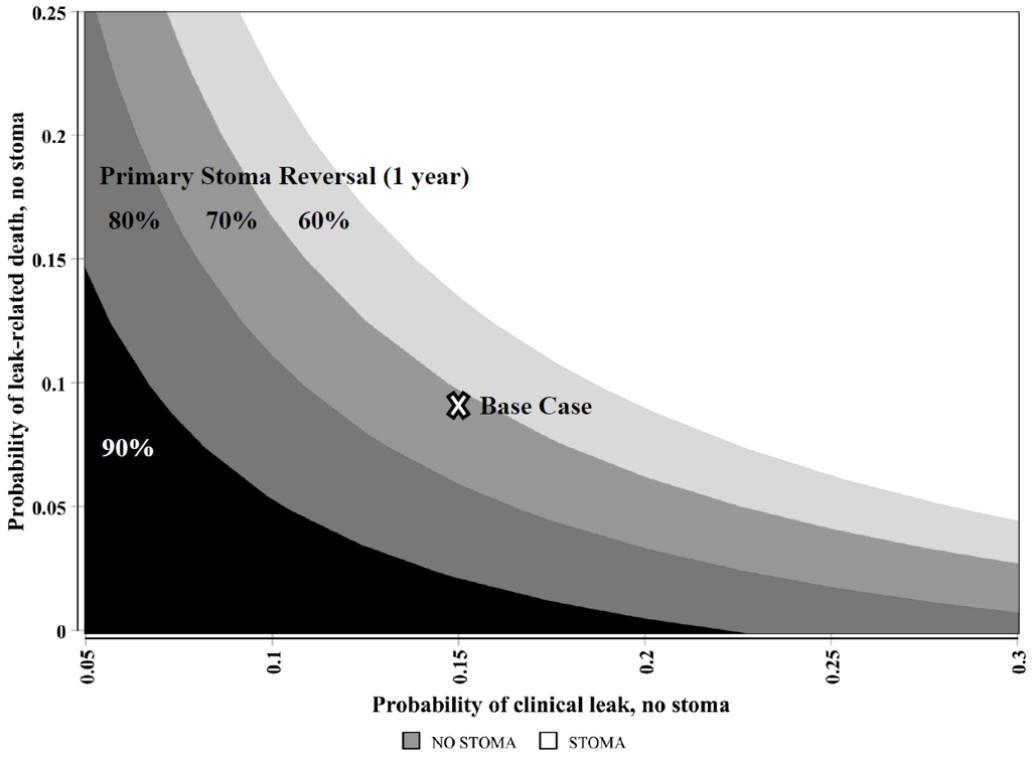


Figure 2.4 Three-way sensitivity analysis of the probability of clinical leak, leak-related death and primary stoma reversal at one year.

DISCUSSION

For the base case, the decision model suggests that creation of a defunctioning ileostomy during low anterior resection for rectal cancer results in greater quality and quantity of life than no stoma creation. This is consistent with nine meta-analyses and one Cochrane review that found ileostomy creation to be a beneficial strategy to reduce the incidence and morbidity of anastomotic leaks.[34–43] Three recent randomized-controlled trials demonstrated a significant reduction in the incidence and morbidity of anastomotic leaks; however, only one trial was adequately randomized.[6,44,45] More recently in a large propensity score matched retrospective cohort, ileostomy creation significantly reduced urgent reoperation for anastomotic leaks, but did not significantly reduce leak incidence. Despite the abundance of existing research, this model represents the first attempt to integrate both the upfront

risks associated with anastomotic leaks with the short- and long-term morbidity associated with routine stoma formation. After assimilating these risks, the benefit of ileostomy creation was modest with only one quality-adjusted life month difference between strategies. Interpreting the significance of this difference is difficult and specific to the unique time frame and clinical scenario of this decision. In the setting of cancer care, the literature supports a life-expectancy gain of two months as significant particularly when a comparable risk reduction in clinical trials would be considered clinically significant.[46] Although the benefit of stoma formation was modest, our model identified clinical scenarios, in which it was the definitive strategy. No stoma was favored when the risk for anastomotic leak was less than 9%, when the leak-related mortality was less than 4%, when the likelihood of ileostomy reversal was less than 70%, and when the QOL with an ileostomy was poor (health state utility < 0.69).

The risk for anastomotic leak remains a foremost consideration in the decision to create an ileostomy, and it was unsurprising that it played an influential role in our model. The interpretation of this value in the clinical setting remains a challenge to surgeons as patients rarely present with definitive risk stratification. Unlike predicting the risk for stroke in the setting of atrial fibrillation, no risk calculator exists for predicting anastomotic leak after low anterior resection. Conversely, risk stratification has largely relied on surgeon assessment, which is less a definitive value and more a subjective assignment of low, moderate and high risk. There are real consequences to reliance entirely on surgeon assessment as a growing body of literature has recognized that surgeon risk-taking behavior has a profound impact on their decision-making. In a survey of general surgeons, those demonstrating greater tolerance for risk-taking were more likely to report common bile duct injuries.[47] On the other end of the spectrum, risk-averse colorectal surgeons are more likely to create a stoma in response to a series

of clinical vignettes.[48] In real practice, this may produce considerable variation in the treatment strategies among surgeons. Snijders et al. demonstrated this phenomenon among hospitals performing colorectal surgery in the Netherlands, in which significant variation existed in the formation of stomas during sphincter preserving surgery.[20] Among high and low outlier hospitals, in which the rate of stoma formation ranged from 26 to 88%, no significant differences were found in the rate of anastomotic leak or mortality even after adjustment for case-mix. Objective determination of anastomotic leak risk could optimize patient outcomes after rectal cancer surgery and potentially reduce differences in treatment strategies between surgeons. The National Surgical Quality Improvement Project currently allows surgeons to determine patient-specific risk for a core set of postoperative complications, and it is not ill-conceived to reason that surgeons would welcome a similar tool to assess anastomotic leak risk.

Despite current limitations in risk assessment, there exists a large body of retrospective data that has identified risk factors for anastomotic leak such as very low anastomosis (< 6cm), neoadjuvant radiation, male sex, and intraoperative complications.[5,6,49,50] In a prospective, Norwegian study, anastomotic height was a strong predictor with less than 5% of anastomoses greater than 10cm from the anal verge developing an anastomotic leak, whereas the probability was greater than 15% for anastomoses less than 6cm.[49] From a practical perspective, both this model and the results of these observational studies suggest that defunctioning stomas are unlikely to be beneficial in patients with high rectal tumors (>10cm) and without preoperative risk factors such as radiation, male sex or intraoperative complications.

The primary aim for this decision analysis was to determine when the risk for anastomotic leak and related morbidity and mortality were great enough to warrant a temporary loss of QOL with a temporary ileostomy, itself associated with a not insignificant morbidity and potential for permanent diversion. To address this, a three-

way sensitivity analysis was performed of sensitive variables potentially relevant to clinical registries: probability of anastomotic leak, anastomotic leak-related mortality and ileostomy reversal at one year. For moderate to high risk for clinical leak and leak-related mortality, the overwhelming majority of clinical scenarios favored stoma formation when the likelihood of ileostomy reversal was greater than 80%. However, no ileostomy formation was the preferred strategy for a majority of clinical scenarios when the likelihood of stoma reversal was less than 60%. This is particularly important when considering the significant variation in defunctioning ileostomy reversal (10 – 40%) reported in the literature.[14,30,51–53] This analysis suggests that reversal of more than 80% of defunctioning ileostomies represents a suitable goal for surgeons and institutions to advance patient outcomes.

Finally, this analysis identified QOL associated with a stoma as an influential variable in decision-making. When examined in a two-way analysis, poor QOL associated with a stoma was acceptable when the risk for clinical leak was high; conversely, if there was marginal clinical benefit, then no stoma creation was preferable. Interpreting the importance of health state utilities in clinical practice, though, is challenging. Bossema et al. measured the patient perception of stoma QOL in patients with and without a stoma, and found significant divergence between groups (0.92 vs. 062).[54] Of interest, the perception of the QOL with a stoma in patients, who had a prior stoma and have been subsequently reversed, approached that of the no stoma group. This underscores the importance of response shift, in which difficulties from a stoma may not be perceived as serious within the context of cancer treatment.[55] Stoma-related morbidity has not been shown to significantly impact global QOL in longitudinal assessments either; however, patients are more likely to report a significant impact on function (role, physical and sexual) that recovers after stoma reversal.[56,57] In preoperative decision-making, discussions should emphasize the

impact an ileostomy may have on function (role, physical and sexual) and the likely return to their baseline quality of life after reversal.

There were several limitations to this decision analysis. We chose a decision tree over a Markov state transition model based on the relatively short time horizon for events. Decision trees are appropriate when clinically important events happen within a short, fixed period of time following the decision and when each event generally happens only once. However, some patients may develop more than one serious complication after surgery. Furthermore, others may develop late complications including subclinical leaks, anal stenosis and bowel dysfunction. These complications were modeled indirectly through health state utilities, and were the principal reason the utility for 'no stoma' was less than one. Disutilities were calculated using existing analytic methodology, however length-of-stay may not be an appropriate surrogate for the disutility of complications in this cohort, and has not been fully investigated.

CONCLUSION

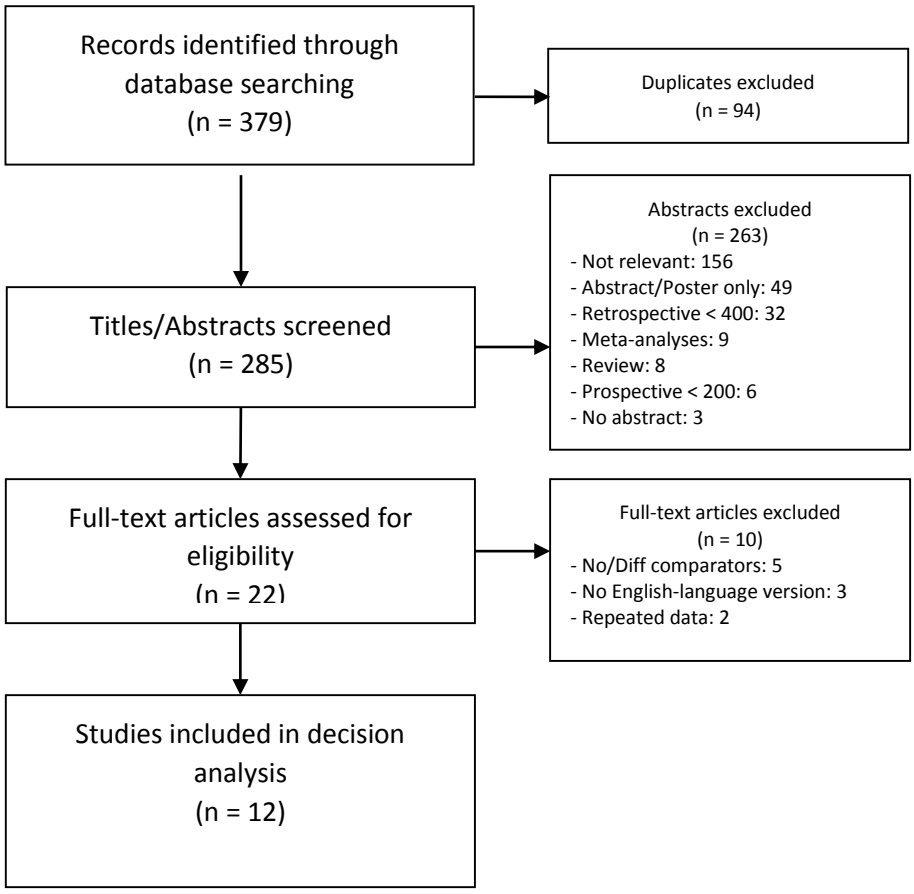
This decision analysis suggests that the benefits of a defunctioning ileostomy for most cases are modest, and underscores the importance of personalizing the treatment strategy. The model identified clinical scenarios, in which no stoma was a preferable strategy; these scenarios occurred when the risk for clinical leak and leak-related death was low, the probability of ileostomy reversal was low, and when the predicted quality of life with an ileostomy was poor. This analysis highlights the need for anastomotic leak risk stratification tools. Preoperative patient discussions should emphasize a patient's risk for anastomotic leak and ileostomy nonreversal, as well as examine patient perceptions of stoma quality of life.

APPENDIX 1

Literature Search

Embase/Medline
2005 – 2016
('rectal' OR 'rectal' OR 'rectum’ 'rectum') AND
('neoplasm' OR 'tumor' OR 'cancer' OR 'carcinoma') AND
('lar' OR 'low anterior resection' OR 'rectum resection' OR 'rectal resection') AND
(‘defunctioning' OR 'protective') AND
('ileostomy' OR 'stoma' OR 'ostomy') AND

PRISMA Diagram



APPENDIX 2

Literature Search Results

First Author	Year	Study design	Interval	Population	Median Tumor Height (cm)		Patients		Clinical Leak (%)		Clinical Leak Mortality (%)		Clinical Leak Reoperation (%)		Stoma Closure (%)	
					No DS	*DS*	*No DS*	*DS*	*No DS*	*DS*	*No DS*	*DS*	*No DS*	*DS*	*No DS*	*DS*
Eriksen	2005	Retrospective cohort	1993 – 1999	Norwegian Rectal Cancer Registry	-		1336	622	12.3	10.3	**7.9**	**4.7**	-	-	-	-
Peeters	2005	Retrospective review of RCT	1996 – 1999	Dutch TME Trial	8.4[12]		401	523	**16.0**	**8.2**	13.9	14.1	**93.8**	**60.5**	-	-
Gastinger	2005	Retrospective cohort	2000 – 2001	Working Group Colon/Rectum Carcinoma, Germany	9.6[1]	7.9[1]	1848	881	14.2	14.5	**14.2**	**6.3**	**71.1**	**25**	-	-
Matthiessen	2007	RCT	1999 – 2005	REctal Cancer Trial On DEfunctioning Stoma (RECTODES), Sweden	10	10	118	116	**28.0**	**10.3**	0	0	**91**	**83.3**	28.6	86.2
Eberl	2007	Retrospective cohort	1986 – 2006	Single Institution, Austria	-		362	110	12.4	3.6	2.2	0	**95.6**	**50**	-	-
Chude	2008	RCT[3]	2001 – 2008	Single Institution, Greece	4.5[2]		120	136	10	2.2	-[4]	0	16.7	0	-	-
Asteria	2008	Retrospective cohort[5]	2005	Multi-institution, Italy	-		226	294	16	14	-	-	36.2	15.6	-	-
den Dulk	2009	Retrospective review of RCTs	1996 – 2003	Dutch TME Trial, CAO/ARO/AIO-94Trial , EORTC 22921 Trial, Polish RC Trial, Swedish RC Trial[6]	-		1067	1226	**11.6**	**7.8**	8.9	5.8	-	-	-	-
Bakker	2014	Retrospective cohort	2011 – 2012	Dutch Surgical Colorectal Audit	8[1]	8[1]	657	1319	**12**	**9**	-	-	80	50	-	-
Thoker	2014	RCT[3]	2008 – 2010	Single Institution, India	-		44	34	11.4	5.9	-	-	-	-	-	-
Tortorelli	2015	Retrospective cohort	1991 – 2010	Single Institution, Italy	8.5[2]		311	164	8.6	9.8	0	0	**77.8**	**12.5**	71.5	98.2
Shiomi[7]	2015	Prospective cohort, PSM	2010 - 2012	Multi-institution, Japan (Japanese Society for Cancer of the Colon and Rectum)	6.5	6	165 (542)	165 (394)	15.8	14.5	-	-	**57.7**	**4.2**	-	-

DS, defunctioning stoma; PSM, propensity score matching; RCT, randomized-control trial; TME, total mesorectal excision.
Bolded values denotes statistical significance.
[1] Value represents mean, not median.
[2] Median tumor height for No DS/DS not dichotomized.
[3] Significant omissions in methodology and statistical analysis. Quality of randomization and analysis uncertain.
[4] Two deaths were reported, however do not specify if following leak.
[5] Results were self-reported via survey by participating institutions. Quality of abstraction not provided.
[6] No information on stoma formation was reported for the Swedish Rectal Cancer trial and is excluded from the stoma/no stoma analysis.
[7] Reported results are after PSM.

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