Published in final edited form as:

Eur Urol. 2016 December ; 70(6): 995–1003. doi:10.1016/j.eururo.2016.05.031.

Enhanced Recovery Pathways Versus Standard Care After Cystectomy: A Meta-analysis of the Effect on Perioperative Outcomes

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Abstract

Context—Enhanced recovery after surgery (ERAS) protocols aim to improve surgical outcomes by reducing variation in perioperative best practices. However, among published studies, results show a striking variation in the effect of ERAS pathways on perioperative outcomes after cystectomy.

Objective—To perform a systematic review of the literature and a meta-analysis comparing the effectiveness of ERAS versus standard care on perioperative outcomes after cystectomy.

Evidence acquisition—We performed a literature search of PubMed, EMBASE, Web of Science, Google Scholar, the Cochrane Library, and the health-related grey literature in February 2016 according to the Preferred Reporting Items for Systematic Review and Meta-analysis and the Cochrane Handbook. Studies were reviewed according to criteria from the Oxford Centre for Evidence-Based Medicine. Thirteen studies (1493 total patients) met the inclusion criteria (ERAS: 801, standard care: 692). A pooled meta-analysis of all comparative studies was performed using inverse-weighted, fixed-effects models, and random-effects models. Publication bias was

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Author contributions: Mark D. Tyson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tyson, Chang.

Acquisition of data: Tyson.

Analysis and interpretation of data: Tyson, Chang.

Drafting of the manuscript: Tyson.

Critical revision of the manuscript for important intellectual content: Chang.

Statistical analysis: Tyson.

Obtaining funding: Tyson.

Administrative, technical, or material support: None.

Supervision: Chang.

Other: None.

Financial disclosures: Mark D. Tyson certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

graphically assessed using contour-enhanced funnel plots and was formally tested using the Harbord modification of the Egger test.

Evidence synthesis—Pooled data showed a lower overall complication rate (risk ratio [RR]: 0.85, 95% confidence interval [CI]: 0.74–0.97, $p = 0.017$, $I^2 = 35.6\%$), a shorter length of stay (standardized mean difference: -0.87 , 95% CI: -1.31 to -0.42 , $p = 0.001$, $I^2 = 92.8\%$), and a faster return of bowel function (standardized mean difference: -1.02 , 95% CI: -1.69 to -0.34 , $p = 0.003$, $I^2 = 92.2\%$) in the ERAS group. No difference was noted for the overall readmission rates (RR: 0.74, 95% CI: 0.39–1.41, $p = 0.36$, $I^2 = 51.4\%$), although a stratified analysis showed a lower 30-d readmission rate in the ERAS group (RR: 0.39, 95% CI: 0.19–0.83, $p = 0.015$, $I^2 = 0\%$).

Conclusions—ERAS protocols reduce the length of stay, time-to-bowel function, and rate of complications after cystectomy.

Patient summary—Enhanced recovery after surgery pathways for cystectomy reduce complications and the amount of time patients spend in the hospital.

Keywords

Clinical pathways; Collaborative care; Cystectomy; Enhanced recovery; Fast track

1. Introduction

In recent years, a shift has occurred in the perioperative management of patients undergoing cystectomy with urinary diversion. The previous tradition-based, nonstandardized components of perioperative care, which included different forms of bowel preparation, preoperative fasting routines, gastrointestinal decompression, and postoperative bowel rest, have evolved in the past decades into clinical pathways that attempt to minimize variation in care. Commonly referred to as enhanced recovery after surgery (ERAS) pathways, these steps can accelerate postoperative convalescence, decrease costs, and maintain quality [1]. Initially described in the late 1990s [2], ERAS pathways are standardized, multimodal, interdisciplinary protocols that aim to improve surgical outcomes by reducing variation in perioperative best practices [3]. Given the emphasis that healthcare systems are currently placing on cost reduction and the transparency of surgical outcomes, ERAS pathways for cystectomy patients have tremendous clinical value and important implications for health systems at large.

Despite the enthusiasm for ERAS pathways in urologic surgery, however, the evidence supporting their use in cystectomy patients is not robust. Although several studies have been published, striking variation exists in the effect of ERAS protocols on perioperative outcomes [4–15]. For example, some studies show that ERAS pathways can reduce the length of stay [4,6,10,11,14,16], whereas others do not [7,9,12,16]; some studies show that ERAS pathways can shorten the time to recovery of bowel activity [7,9,12], yet others do not [6,11]; some studies show that ERAS pathways can lower the rates of readmission [6,12,13]; but yet again, others do not [9,11,14].

In light of this tremendous variability in study results, as well as the absence of experimental data from randomized, controlled trials, a clear rationale exists for the quantitative synthesis

of the available evidence regarding the comparative effect of ERAS pathways on postoperative outcomes after cystectomy and urinary diversion. In this context, we performed a systematic review of the literature and a meta-analysis to evaluate the comparative effectiveness of ERAS versus standard care (SC) on various perioperative outcomes of interest after cystectomy and urinary diversion. We hypothesized that the pooled analysis would favor ERAS for length of stay, time-to-bowel activity, complications, and readmission rates.

2. Evidence acquisition

2.1. Study aims

The aim of the study was to evaluate the comparative effectiveness of ERAS pathways versus SC in reducing the length of stay, complications, readmission, and time-to-bowel activity after cystectomy and urinary diversion. We prepared a protocol of a priori methods that followed the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols 2015 checklist [17] and the Cochrane Handbook [18]. Accordingly, this protocol is registered at the International Prospective Register of Ongoing Systematic Reviews (registration number: CRD42016033882).

2.2. Literature search

An English-language literature search of observational studies and randomized controlled trials was performed in the electronic databases of Medline (PubMed), EMBASE, Web of Science, Google Scholar, the Cochrane Library, and an index of abstracts from the American Urological Association and the European Urological Association for the past 5 yr. The health-related grey literature was similarly searched using the GreySource Index. We used, in various relevant combinations, keywords and medical subject headings pertinent to the intervention of interest: “cystectomy,” “enhanced recovery after surgery,” and “collaborative care pathways.” The last search was performed on February 1, 2016. To ensure literature saturation, we scanned the reference lists of the included studies or relevant reviews for additional candidate articles. A flow diagram showing article selection as the review progressed is presented in the Supplementary Figure 1.

2.3. Inclusion and exclusion criteria

Two members of the investigative team (M.D.T. and S.S.C.) independently assessed the eligibility of candidate articles for inclusion in the study. The following inclusion criteria were used: (1) studies comparing ERAS with standard postoperative pathways after cystectomy, (2) ERAS protocols if they had standardized preoperative, intraoperative, and postoperative pathways that included patient education, goal-directed fluid management, prevention of nausea and vomiting, early ambulation, early oral nutrition, and early hospital discharge, and (3) at least one of the main outcomes of interest (readmission, complications, time-to-bowel function, or length of stay). The specific details of each ERAS protocol are summarized for each study in Supplementary Table 1. Studies were excluded if: (1) the inclusion criteria were not met, and (2) no outcomes of interest were reported or were impossible to calculate or extrapolate. Studies using robotic approaches to cystectomy were allowed provided the distribution of laparoscopic technology was equal in both the ERAS

and SC groups. In other words, studies comparing patients whose care was managed with ERAS after a laparoscopic procedure to patients whose care was managed with SC after an open cystectomy were not allowed because of the confounding effect of minimally invasive approaches on the outcomes of interest.

2.4. Data extraction

One investigator (M.D.T.) independently extracted data from the primary texts, supplementary appendixes, and protocols using data abstraction forms that contained fields for authors, publication year, country, study design, matching factors (age, proportion of men, body mass index, American Society of Anesthesiologists score, clinical stage, diversion type, prior major pelvic or abdominal surgery, and receipt of neoadjuvant chemotherapy), and outcomes of interest. The outcomes of interest were readmission rates (30 d and 90 d), perioperative complication rates, length of stay, time-to-bowel movement, and analgesia requirements. Because only two studies reported analgesia requirements, this outcome was not assessed in the pooled analysis. Complications were classified into Grade 2 and Grade 3 according to the Clavien-Dindo classification. Disagreements between the two reviewers were resolved by consensus after discussion.

2.5. Assessment of quality

M.D.T. independently rated the level of evidence of the included studies according to the criteria provided by the Oxford Centre for Evidence-Based Medicine [19]. The methodological quality of the studies was assessed using the Newcastle-Ottawa scale for observational comparative studies [20].

2.6. Handling of missing variance estimates

For studies presenting continuous data as median and range or interquartile range, the means and standard deviations were calculated using the method described by Wan et al [21]. For studies that reported means and p values without standard deviations or ranges, the standard error was estimated using the corresponding t value (as estimated from the p value and degrees of freedom). The standard deviation was then calculated using the standard error, as previously described [18]. For studies with missing p values, t values, confidence intervals, and standard errors, we imputed the pooled standard deviation using the average of the standard deviations across the other studies in the meta-analysis, as described by Furukawa et al [22].

2.7. Statistical analysis

The meta-analysis was performed using the metan package in Stata 14/MP (StataCorp LP, College Station, TX, USA) [23]. All statistical methods followed the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions [18]. The standardized mean difference (SMD) and risk ratios (RRs) were used to compare continuous and dichotomous variables, respectively. The following rule of thumb has been proposed for interpreting standardized mean differences: 0.2 represents a small effect, 0.5 represents a moderate effect, and 0.8 represents a large effect [18,24]. The number needed to treat is computed using the inverse of the assumed control risk multiplied by the RR subtracted

from 1 [18,24]. All results were reported with 95% confidence intervals (CIs). Statistical heterogeneity between studies was assessed using the χ^2 test, with a p value of less than 0.1 considered to indicate statistical significance, and heterogeneity was quantified using the inconsistency (I^2) statistic. A random-effects model was used for outcomes that displayed significant heterogeneity with I^2 values greater than 50%; otherwise, an inverse-weighted, fixed-effects model was used. To test the impact of imputation on the study findings, a sensitivity analysis was performed, which excluded the studies for which variance parameters had to be imputed (three studies in total). Publication bias was assessed using contour-enhanced funnel plots [25]. Because the visual interpretation of funnel plot asymmetry is inherently subjective, we also formally tested funnel plot asymmetry using the Harbord modification of the Egger test [26].

3. Evidence synthesis

3.1. Characteristics and quality of included studies

The literature yielded 13 comparative studies that fulfilled the inclusion criteria and were considered suitable for meta-analysis. This resulted in 801 ERAS participants and 692 controls who received SC ($N = 1493$). Table 1 summarizes the characteristics of the studies included, and Supplementary Table 2 summarizes the clinical and demographic features of the patient population in each study.

3.2. Readmissions

Overall, ERAS did not significantly reduce the likelihood of patients being readmitted after cystectomy. In raw terms, approximately 14.9% (59/396) of patients in the ERAS group were readmitted within 90 d compared with 15.9% (60/376) of patients in the SC group. Furthermore, pooled data from the random-effects model demonstrated no significant difference between the ERAS and SC groups (RR: 0.74, 95% CI: 0.39–1.41, $p = 0.36$, $I^2 = 51.4\%$; Fig. 1). In a stratified analysis, 30-d readmission rates favored ERAS (RR: 0.39, 95% CI: 0.19–0.83, $p = 0.015$, $I^2 = 0\%$), whereas 90-d readmission rates favored the SC groups (RR: 1.22, 95% CI: 0.83–1.79, $p = 0.31$, $I^2 = 1.3\%$), although the latter comparison was not statistically significant.

3.3. Complications

Overall, the complication rate favored the ERAS group. In raw terms, approximately 39.6% (209/527) of the ERAS patients had a complication compared with 51.5% (237/461) of patients in the SC group. Furthermore, pooled data from the fixed-effects model favored the ERAS group (RR: 0.85, 95% CI: 0.74–0.97, $p = 0.017$, $I^2 = 35.6\%$; Fig. 2). The number needed to treat to prevent one complication is approximately 14. When stratified by the Clavien-Dindo classification, most of the variation between groups was attributable to a reduction in the risk of low-grade complications (Clavien-Dindo Grade I or II) among ERAS participants (Supplementary Table 3). The 90-d mortality rate did not differ between the groups (RR: 0.97, 95% CI: 0.36–2.62, $p = 0.96$, $I^2 = 0\%$).

3.4. Length of stay and time-to-bowel activity

Pooled data from 12 studies that assessed length of stay in 1381 patients strongly favored the ERAS group (SMD: -0.87 , 95% CI: -1.31 to -0.42 , $p = 0.001$, $I^2 = 92.8\%$; Fig. 3). The estimated mean difference between groups for length of stay was approximately 5.4 d in favor of ERAS. Pooled data from seven studies assessing the time to return of bowel function (five assessing time-to-bowel movement and two assessing time to flatus) in 554 patients favored a faster return of bowel function among the ERAS participants (SMD: -1.02 , 95% CI: -1.69 to -0.34 , $p = 0.003$, $I^2 = 92.2\%$; Fig. 4). The estimated mean difference in return of bowel function between groups was 1.1 d in favor of ERAS.

3.5. Publication bias and small-study effects

Funnel plots were used to investigate the presence of small-study effects and publication bias. Figure 5 shows the contour-enhanced funnel plots of the studies included in this meta-analysis for readmissions, complications, length of stay, and time-to-bowel activity. The Harbord modification of the Egger test provided evidence that the assessment of complications may be confounded by publication bias ($p = 0.046$). Minimal bias was detected for readmissions ($p = 0.23$), length of stay ($p = 0.52$), and time-to-bowel activity ($p = 0.91$).

3.6. Sensitivity analysis

Because the standard deviations had to be imputed for select studies involving the outcomes of interest (length of stay [4] and time-to-bowel movement [6,12]), we repeated the analysis excluding the three studies for these outcomes of interest. We did not find any significant qualitative difference when this analysis was compared with our main analysis.

4. Conclusions

The principle finding of this study is that the implementation of standardized, perioperative pathways for cystectomy patients reduces the length of the index hospitalization, lowers the rate of low-grade complications, and improves the time-to-bowel function. No difference in overall readmission rates was noted. We believe these data have important clinical implications and lend further evidence for the implementation of standardized, evidence-based perioperative protocols in centers not presently using them.

There are several theoretical reasons why ERAS protocols would improve perioperative outcomes. First, many of the principles of ERAS have a physiologic basis. For example, preoperative carbohydrate loading improves perioperative insulin sensitivity and helps maintain lean body mass and muscle strength [27], goal-directed fluid management has been shown to reduce the incidence of ileus by maintaining splanchnic perfusion [28], body temperature monitoring, the maintenance of normothermia, early mobilization, and early oral feeding reduce complications by maintaining body homeostasis [29]. Secondly, ERAS pathways are adaptive, evidence-based responses to specific problems and care needs at the organizational level. Unlike national guidelines, which are not based on local professional consensus, ERAS pathways are designed to implement current best practices tailored to fit the specific needs of the population served by the organization. Finally, standardized

protocols have the potential advantage of reducing variation in care, even if the protocols differ. ERAS pathways are integrated management strategies that set goals for certain outcomes and provide the sequence and timing of actions necessary to attain such goals with optimal efficiency. Previous research has suggested that implementation of standardized protocols can not only improve compliance with recommended processes of care but can also improve patient outcomes [30]. In surgical literature, for example, standardized protocols have been shown to improve outcomes for multiple procedures across various disciplines, including general surgery, orthopedics, vascular surgery, and colorectal surgery [31]. Healthcare organizations that use electronic medical records for computerized entry of physician orders may have even greater improvements in compliance, quality, and efficiencies of care. As a result, ERAS pathways improve outcomes primarily through the promotion of effective strategies that reduce clinical performance variations.

The issue that arises from an analysis such as this is the uncertainty about which pathway is best. Each study included in this meta-analysis used a perioperative pathway that is distinct in some way from all pathways used in the other studies. Can these data really be synthesized and can meaningful results truly be gleaned from the pooled estimates? We would counter that the aim of this study was not to suggest which pathway was best or which elements should be universally adopted. Rather, the purpose of this meta-analysis was to determine whether these pathways have an effect at all. The differences in the pathways notwithstanding, this study demonstrates that merely adopting a standardized, multimodal, interdisciplinary protocol for the perioperative management of cystectomy patients may be as important to improving perioperative outcomes as any individual element by itself. A similar finding was recently reported by the Department of Health Enhanced Recovery Partnership Program for length of stay across four different surgical specialties in the UK [32].

Despite these promising results, however, these findings should be interpreted within the context of several study limitations. Firstly, the main limitation is that all of the studies included were observational studies, and most used historical controls. This almost certainly biased the pooled estimates in favor of ERAS. There is no question that in the current era providers have become more conscious of the length of stay, complications, and readmission rates irrespective of perioperative pathways. A randomized study or a retrospective study using a difference-in-differences approach would more accurately quantify the effect of ERAS on perioperative outcomes of interest. Although one randomized trial was identified, it did not evaluate any of the primary outcomes of interest [33]. Nevertheless, there were clear and meaningful effects of ERAS pathways that emerged after the pooling of the data, which are compelling and are consistent with what has been reported in colorectal literature. Secondly, for some of the outcomes of interest, fewer than 10 studies have been published, which results in a low test power for assessing funnel plot asymmetry. However, we also interpreted the test results in the context of visual inspection of the funnel plots. Thirdly, while we evaluated most of the clinical outcomes of interest, we did not evaluate costs and patient-reported outcomes, such as quality of life, mainly because of the relative absence of these data in the cystectomy population.

Despite these limitations, we believe these data are clinically relevant for quality improvement efforts for organizations that care for cystectomy patients. The data support the development of integrated, multidisciplinary clinical pathways in an effort to improve patient outcomes, reduce errors, and increase patient and provider satisfaction. Although a randomized trial may not be feasible because of the lack of clinical equipoise in this setting, this study substantially improves the evidence for ERAS pathways in the cystectomy population.

ERAS pathways for patients undergoing cystectomy and urinary diversion reduce the length of the index hospitalization, the time to recovery of bowel function, and complications. These data have important clinical implications and should lend further evidence for the implementation of standardized, evidence-based perioperative protocols in centers not presently using them.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Tyson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. This work was in part supported by the National Cancer Institute, Grant 5T32CA106183.

Funding/Support and role of the sponsor: None.

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Take home message

M.D. Tyson, S.S. Chang

Cystectomy patients whose care is managed perioperatively with enhanced recovery after surgery pathways experience a shorter hospitalization, quicker recovery of bowel function, and lower complication rates. These findings lend further support for implementing standardized, multimodal, evidence-based, perioperative collaborative-care pathways for cystectomy patients.

Fig. 1.

Forest plot displaying a random-effects meta-analysis of the effect of enhanced recovery after surgery (ERAS) on readmission rates within 30 d and 90 d after cystectomy. Weights are from random-effects analysis.

CI = confidence interval; RR = risk ratio; SC = standard care.

Fig. 2.

Forest plot displaying a fixed-effects meta-analysis of the effect of enhanced recovery after surgery (ERAS) on complication rates after cystectomy.

CI = confidence interval; RR = risk ratio; SC = standard care.

Fig. 3.

Forest plot displaying a random-effects meta-analysis of the effect of enhanced recovery after surgery (ERAS) on length of stay after cystectomy. Weights are from random-effects analysis.

CI = confidence interval; SC = standard care; SMD = standardized mean difference.

Fig. 4.

Forest plot displaying a random-effects meta-analysis of the effect of enhanced recovery after surgery (ERAS) on time to bowel function after cystectomy. Weights are from random-effects analysis.

CI = confidence interval; SC, standard care; SMD, standardized mean difference.

Fig. 5.
Contour-enhanced funnel plots for (A) complications, (B) length of stay, (C) readmission,
and (D) time-to-bowel movement.

Table 1

Study characteristics

First author, yr	Country	Design	No. of patients		Matching/comparable variables ^a	Quality score Σ (*) ^b	Level of evidence
			ERAS	Non-ERAS			
Pruthi et al, 2003 [4]	USA	Retrospective	40	30		*****	3b
Maffezzini et al, 2007 [5]	Italy	Retrospective	71	40	1, 2, 4, 7, 8	*****	3b
Arumainayagam et al, 2008 [6]	England	Retrospective	56	56	1, 2, 4, 5, 6, 8	*****	3b
Mukhtar et al, 2013 [7]	England	Prospective	51	26	1, 2, 3, 4, 5, 7, 8	*****	3b
Saar et al, 2013 [8]	Germany	Prospective	31	31	1, 2, 3, 4, 5, 8	*****	3b
Cerruto et al, 2014 [9]	Italy	Prospective/retrospective	9	13	1, 2, 3, 4, 8	*****	3b
Daneshmand et al, 2014 [10]	USA	Prospective/retrospective	110	110		*****	3b
Guan et al, 2014 [16]	China	Retrospective	60	55	1, 2, 3, 7	*****	3b
Smith et al, 2014 [11] ^c	England	Retrospective	27	69	1, 2, 3, 4, 6	*****	3b
Perrson et al, 2015 [12]	Sweden	Prospective/retrospective	31	39	1, 2, 3, 4, 5, 6, 7, 8	*****	3b
Koupparis et al, 2015 [13] ^d	England	Prospective/retrospective	56	56	1, 2, 4, 6, 8	*****	3b
Collins et al, 2016 [14]	Sweden	Prospective	135	86	1, 2, 3, 4, 5, 6, 7, 8	*****	3b
Xu et al, 2015 [15]	USA	Prospective/retrospective	124	81	1, 2, 7	*****	3b

ERAS = enhanced recovery after surgery; Σ = Newcastle-Ottawa Scale.

^a1, age; 2, sex; 3, body mass index; 4, American Society of Anesthesiologists score; 5, history of previous surgery; 6, neoadjuvant chemotherapy; 7, clinical stage; 8, diversion type.

^bStars are awarded such that the highest-quality study is awarded up to 9 stars.

^cIncludes data from non-ERAS control patients and phase 2 ERAS participants. Phase 1 ERAS participants were excluded because phase 2 was chosen as the comparator.

^dIncludes data from non-ERAS control patients and phase 2 ERAS participants. Phase 1 ERAS participants were excluded because of prior publication, and the cohort of patients who underwent robotic procedures was excluded because of the impact of the robotic approach on outcomes of interest (control patients underwent an open approach).