

Research Report

Readmission Rate and Causes at 90-Day after Radical Cystectomy in Patients on Early Recovery after Surgery Protocol

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Abstract.

Background: Radical cystectomy (RC) is associated with high risk of early and late perioperative complications, and readmissions. The Enhanced Recovery After Surgery (ERAS) protocol has been applied to RC showing decreased hospital stay without increased morbidity.

Objective: To evaluate the specific causes of hospital readmissions in RC patients treated before and after adoption of an ERAS protocol at our institution.

Methods: We retrospectively evaluated the outcome of 207 RC patients on ERAS protocol at the Stanford University Hospital from January 2012 to December 2014. We focused on early (30-day) and late (90-day) postoperative readmission rate and causes. Results were compared with a pre-ERAS consecutive series of 177 RC patients from January 2009 to December 2011.

Results: In the post-ERAS time period a total of 56 patients were readmitted, 41 within the first 30 days after surgery (20%) and 15 within the following 60 days (7%). Fever, often associated with dehydration, was the most common reason for presentation to the hospital, accounting for 57% of all readmissions. At 90 days infection accounted for 53% of readmissions. Of all the patients readmitted during the first 90 days after surgery, 32 had positive urine cultures, mostly caused by *Enterococcus faecalis* isolated in 18 (56%). Readmission rates did not increase since the introduction of the ERAS protocol, with an incidence of 27% in the post-ERAS group versus 30% in the pre-ERAS group.

Conclusions: Despite accurate adherence to most recent perioperative antibiotic guidelines, the incidence of readmissions after RC due to infection still remains significant.

Keywords: Cystectomy, patient readmission, infection, alvimopan

INTRODUCTION

Radical cystectomy (RC) with pelvic lymph node dissection and urinary diversion is the standard treatment for muscle invasive and high-risk non-muscle invasive bladder cancer [1, 2]. The procedure is

associated with a high risk of early and late perioperative complications, and readmissions [3].

Patient outcome improved with advances in surgical and anesthetic management, but the 90-day complications rate still exceeds 60% [4]. The Enhanced Recovery After Surgery (ERAS) protocol has been recently applied to RC and has been shown to decrease hospital stay [5]. First introduced in colorectal surgery, the ERAS protocol aims to accelerate patient recovery through evidence-based multimodal

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pathways of perioperative care, including avoiding preoperative bowel preparation and nasogastric tube, reduced narcotic pain medication, careful fluid management, and early oral feeding and mobilization [6, 7] Recent studies reporting on the 30-day outcome of RC patients on ERAS protocol have reported shorter hospital stay and fewer gastrointestinal problems with no increase in other complications or hospital readmissions compared to patients on standard clinical care pathways [8, 9].

In this study we wished to evaluate the specific causes of hospital readmissions in patients treated before and after adoption of an ERAS protocol at our institution.

MATERIALS AND METHODS

We retrospectively evaluated the outcome of 207 RC patients on ERAS protocol at the Stanford University Hospital from January 2012 to December 2014. Complications were reported according to the Clavien-Dindo classification system. We focused on early (30-day) and late (90-day) postoperative readmission rate and causes. Results were compared with a pre-ERAS consecutive series of 177 RC patients from January 2009 to December 2011. All postoperative complications and readmission data were collected from both local and outside hospital and physician office records.

Stanford ERAS protocol is a three-phase multimodal care pathway that includes pre-, intra- and post-operative steps, supported by published data [10] The protocol includes preoperative education, no bowel prep, 24 hour perioperative antibiotics with cefoxitin begun within 1 hour of incision, epidural postop analgesia with minimization of narcotics, careful fluid management, no nasogastric tube and early feeding. Alvimopan, a gastrointestinal opioid receptor antagonist, was introduced in the protocol in July 2013 and was used in the last 101 patients. Patients did not routinely go to the ICU and home intravenous hydration was not used. We excluded from the analysis 4 patients who remained intubated post-operatively and could not be started on oral feeding. Results were compared with a pre-ERAS consecutive series of 177 RC patients from the three years prior to institution of the ERAS protocol, January 2009 to December 2011. Data were analyzed with SPSS[®], version 19.0. A logistic regression model was performed to identify independent variables associated with readmission. The Institutional

Review Board waived requirement of a separate informed consent for this study.

RESULTS

A total of 207 RC patients between January 2012 and December 2014 were included in the post-ERAS group, and 177 in the pre-ERAS group. Details of the patient composition of each group are described in Table 1. Fewer patients in the ERAS time period underwent ileal conduit diversion (75% vs 63%) and robotic-assisted surgery (25% vs 15%), and more received neoadjuvant chemotherapy (6% vs 63%). Median hospital length of stay decreased from 7 to 6 days following the institution of the ERAS program, and to 5 days with the addition of alvimopan in the last 101 patients ($p=0.001$). Within the first 90 days postoperatively, all patients experienced at least one complication, though most were low-grade. The highest grade complication was \geq Clavien grade 3 in 25% in the pre-ERAS group, and 23% in the post-ERAS group. The 90-day readmission rate was not significantly different between the pre-ERAS and post-ERAS time periods, occurring in 30% and 27% respectively.

In the post-ERAS time period a total of 56 patients were readmitted, 41 within the first 30 days after surgery (20%) and 15 within the following 60 days (7%). Eleven patients had multiple readmissions in the first 90 days. Median time from discharge to readmission was 15 days (range 1 to 87). Median readmission hospital stay was 4 days (range 2 to 18). Fever was the most common reason for readmission, accounting for 57% of all readmissions. Other causes were abdominal pain and/or gastrointestinal symptoms (25%), dyspnea or chest pain, flank pain, or urinary retention (18% combined).

A summary of the diagnoses for the patients with 30 and 90-day readmissions is shown in Table 2. Of the 41 patients readmitted within 30 days of surgery, infection accounted for 63% of the admissions, often associated with dehydration. Other common diagnoses were dehydration, acute kidney injury, small bowel obstruction and constipation. Of the 26 patients with at least one infection, 8 patients had febrile UTI and 11 had urosepsis. An additional 10% had a UTI diagnosed without fever during the readmission. Beside urinary infection, five patients had *C. difficile* colitis, three pelvic abscesses, and two other infections (pneumonia, cholecystitis).

Table 1

Demographics, surgery and outcome in radical cystectomy patients, before and after the adoption of ERAS protocol without (group 1) and with Alvimopan (group 2)

Patients demographics	Pre-ERAS		Post-ERAS	
	Jan 09 – Dec 11	Jan 12 – Jun 13	w/Alvimopan Jul 13 – Dec 14	Total Jan 12 – Dec 14
Patients number	177	106	101	207
Median age	70 (33–91)	72 (33–90)	67 (43–89)	69 (43–89)
Male	130 (73%)	83 (78%)	77 (76%)	160 (77%)
Female	47 (27%)	23 (22%)	24 (24%)	47 (23%)
Median BMI (range)	27 (14–55)	27 (19–55)	26 (18–47)	27 (19–55)
Smoking history	118 (67%)	74 (70%)	70 (70%)	144 (70%)
Charlson comorbidity index:				
≤2	84 (47%)	47 (44%)	47 (46%)	94 (45%)
≥3	93 (53%)	59 (56%)	54 (54%)	113 (54%)
Heart disease	23 (13%)	21 (19%)	13 (13%)	34 (16%)
Diabetes	58 (15%)	13 (12%)	14 (14%)	27 (13%)
Cronic kidney insufficiency	30 (17%)	37 (35%)	22 (22%)	59 (28%)
Neoadjuvant chemo	11 (6%)	76 (72%)	54 (54%)	130 (63%)
Prior pelvic radiation	11 (6%)	10 (9%)	4 (4%)	14 (7%)
Prior abdominal surgery	62 (35%)	43 (41%)	37 (37%)	80 (39%)
Surgery				
Robot assisted	45 (25%)	30 (28%)	1 (1%)	31 (15%)
Diversion type:				
Ileal conduit	132 (75%)	79 (75%)	51 (51%)	130 (63%)
Orthotopic neobladder	39 (22%)	25 (24%)	46 (46%)	71 (34%)
Continent cutaneous diversion	6 (3%)	2 (1%)	4 (3%)	6 (3%)
Trasfusion (%)	84 (47%)	38 (36%)	51 (51%)	88 (43%)
Tumor stage:				
T2 or less	232 (60%)	64 (60%)	77 (77%)	141 (68%)
T3, T4	75 (42%)	42 (40%)	24 (23%)	66 (32%)
Nodal metastasis	29 (16%)	24 (23%)	15 (15%)	39 (19%)
Outcome				
Median days (range):				
Ambulation	3 (1–20)	2 (1–10)	2 (1–6)	2 (1–6)
Flatus	3 (1–13)	3 (1–8)	2 (1–7)	
Bowel movement	5 (2–19)	5 (3–16)	4 (2–7)	3 (2–16)
Regular diet	5 (2–36)	5 (3–17)	4 (2–7)	5 (2–17)
Hospital stay (range)	7 (3–78)	6 (3–27)	5 (3–36)	6 (3–36)
30-day readmission	48 (27%)	23 (22%)	18 (18%)	41 (20%)
90-day readmission	53 (30%)	31 (29%)	25 (25%)	56 (27%)
90-day mortality	4 (1%)	2 (2%)	1 (1%)	3 (1%)
90-day minor complications (Clavien 1-2)	280 (73%)	79 (75%)	80 (80%)	159 (77%)
90-day major complications (Clavien 3-5)	104 (27%)	27 (25%)	21 (20%)	48 (23%)

At 90 days infection accounted for 53% of readmissions. Genitourinary complications increased compared to the 30-day readmission group, from 29% to 47% of the readmissions. Urine leak and hydronephrosis were the most common GU complications in the late readmission group.

Of all the patients readmitted during the first 90 days after surgery, 32 had positive urine cultures, mostly caused by *Enterococcus faecalis* isolated in 18 (56%). Other common pathogens were *E. coli* (28%), *Klebsiella* (25%), *Staphylococcus* (16%), *Candida* (16%) and *Pseudomonas* (9%). Several patients had polymicrobial infections.

When we compared the incidence of the different infections between the pre-ERAS and post-ERAS

group during readmissions, we found the same distribution in both cohorts, except for the UTI rate that was higher post-ERAS ($p=0.037$). Readmission rates did not increase since the introduction of the ERAS protocol, with an incidence of 27% in the post-ERAS group versus 30% in the pre-ERAS group.

On a multivariable analysis, only age and Charlson comorbidity index correlated with the risk of readmission with a p value of 0.018 (OR 0.37) and 0.042 (OR 3.33) respectively (Table 3).

DISCUSSION

The incidence of readmissions after RC is still high after the adoption of the ERAS protocol, 27% in our

Table 2

Causes of readmission among 56 patients in the post-ERAS group readmitted during the first 90 days from surgery. Forty-one patients readmitted between day1 and day30 and 15 between day31 and day90

	<30 day – n (% of 41)	31–90 day n (% of 15)
Infectious Causes	26 patients (63%)	8 patients (53%)
Febrile UTI (without sepsis)	8 (20%)	2 (13%)
Urosepsis	11 (27%)	3 (20%)
Abscess	3 (7%)	1 (7%)
<i>C. difficile</i> colitis	6 (15%)	2 (13%)
Other (pneumonia, etc)	2 (5%)	1 (7%)
UTI without fever	4 (10%)	4 (27%)
Multiple infections	4 patients (10%)	3 patients (30%)
Noninfectious causes	23 patients (56%)	10 patients (67%)
Dehydration/AKI	15 (37%)	3 (20%)
GU complications (urine leak, etc)	12 (29%)	7 (47%)
Bowel problems (SBO, constipation)	8 (20%)	3 (20%)
CV problems (angina, hypotension)	6 (15%)	1 (7%)
Tromboembolism	2 (5%)	–
Multiple diagnosis	12 patients (29%)	5 patients (33%)

Table 3

Output from a logistic regression model with readmission as the dependent variable. Age and Charlson comorbidity index score correlated with readmission

Readmission	Odds Ratio	Standard Error	P value	95% Confidence Interval	
Age	0.372	0.154	0.018	0.165	0.841
Sex	0.777	0.367	0.595	0.307	1.965
Smoking Hx	1.116	0.438	0.779	0.516	2.412
BMI	1.101	0.450	0.813	0.494	2.455
Heart disease	1.824	0.976	0.261	0.639	5.209
CKI	0.342	0.218	0.093	0.098	1.196
Diabetes	1.759	1.084	0.359	0.525	5.889
Charlson score	3.331	1.966	0.042	1.047	10.596
Prior radio-tp	0.919	0.706	0.920	0.180	4.680
Prior chemo-tp	1.769	0.706	0.153	0.808	3.869
Alvimopan	0.507	0.228	0.133	0.209	1.228
Robot-assisted	1.286	0.710	0.648	0.435	3.798
Diversion type	1.353	0.585	0.484	0.579	3.159
Pathology	0.829	0.319	0.628	0.390	1.764
Post-op abx	0.733	0.363	0.531	0.278	1.935
Tansfusion	0.937	0.382	0.874	0.421	2.086
LOS	0.762	0.317	0.515	0.337	1.724
Clavien at 90d	4.548	1.863	0.000	2.037	10.152

series. Since the introduction in colorectal surgery, ERAS protocols have been shown to improve recovery of bowel function and shorten hospital stay [5, 11–13]. Advantages of the use of these pathways in RC patients has now been reported in a number of centers, with slight variations in the protocols used, but none has shown a decrease in readmission rates with these interventions [5, 8, 9, 14].

At our institution, we introduced an ERAS protocol in January 2012, and since the addition of alvimopan in July 2013 we have observed a decrease in median LOS of 2 days from 7 to 5 days. The potential of increased readmissions associated with earlier discharge have not been realized in other series [5]. Our data similarly show that the early discharge did not

result in increased readmissions, which were 27% in the pre-ERAS group versus 20% in the ERAS group at 30 days. We extended the follow-up to 90-day and observed similar results in late readmissions (30% versus 27% respectively). A recent report of 247 patients who underwent robot-assisted cystectomy showed a median initial length of stay of 9 days with a 40% 90-day readmission rate. In that series UTI was the most common cause of readmission in the continent diversion patients, and second to dehydration in the ileal conduit patients [15].

We focused on the specific causes of early and late readmissions in the hope to identify an intervention plan to reduce those readmissions. The principal cause of readmission was fever, reported in almost

60% of the readmitted patients, mostly caused by urinary infections. The most common pathogen was *Enterococcus faecalis*, isolated in almost 60% of the positive urine cultures. An *E. coli* infection was diagnosed in less than 30% of patients. We found a lower rate of *E. faecalis* resistance to ciprofloxacin than reported in the literature, only 11% in our patients. However, the *E. coli* resistance to ciprofloxacin exceeded 20%. It is not clear if a change in perioperative antibiotic choice or duration might impact these acquired postoperative infections. In a recent series, Pariser et al. suggest broadening perioperative antibiotics as an approach to decreased postoperative infections. Based on institutional data, they changed from cefoxitin to broader, culture-directed antimicrobial prophylaxis including routine use of antifungals [16].

However, it is unclear if patients are indeed being infected at the time of surgery (such that perioperative antibiotics would help) or if the infection is acquired later in the hospital stay or at home. In our series, all patients present with sterile urine at surgery and in accordance with the AUA best practice guidelines, we administered a second/third generation cephalosporin for 24 hours. The AUA guidelines also suggest the alternate use of an aminoglycoside with metronidazole or clindamycin. This combination may carry problematic renal toxicity for bladder cancer patients who often have compromised renal function. In addition, as a pilot we sent urine cultures at discharge on 50 consecutive patients and found that there was little correlation between discharge culture and the bacteria causing infection on readmission. Our fear of using broader-spectrum or longer-term antibiotics is the potential development of highly resistant organisms in this group of patients.

Other observed infections were *C. difficile* colitis (14%), pelvic abscess (7%), pneumonia and cholecystitis (5%). When we compared the incidence of the different infections between the ERAS and pre-ERAS group we found the same distribution in both the early and late complications. Only the early febrile UTI rate was higher in the ERAS group, possibly related to a higher percentage of neobladders performed in this group.

The main limitation of this study is its retrospective design. We made every effort to obtain records including all cultures for patients admitted to outside hospitals, but it is possible that some admissions were missed. This was particularly true for the comparison group prior to 2012, where in a few patients we were not able to obtain complete data about

causes of readmission. In addition there are differences between the groups that could have an impact on complications, such as the percentage treated with neoadjuvant chemotherapy, undergoing continent diversion or robotic surgery. However, in our multivariable analysis we did not find that any of these factors appeared to be associated with the readmission or infection rates. Future directions will focus on the design of additional strategies to prevent and manage the development of infections after RC.

In conclusion, using the ERAS protocol with alvimopan we decreased the median hospital stay by 2 days without increasing the readmission rate. Despite accurate adherence to most recent perioperative antibiotic guidelines, the incidence of readmissions after RC due to infection still remains significant. About 60% of the UTIs in our patients were caused by *Enterococcus*. Prospective studies are needed to test potential interventions that may decrease the rate of hospital readmission in these patients.

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CONFLICT OF INTEREST

The authors have no conflict of interest or financial support to report.

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