# Extended hospital stay after radical cystectomy with enhanced recovery protocol

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*Introduction:* To evaluate the reasons leading to an extended hospital stay (EHS) in patients undergoing radical cystectomy (RC) with postoperative enhanced recovery after surgery (ERAS) protocol.

*Materials and methods:* A total of 509 patients underwent RC and urinary diversion with ERAS between May 2012 and March 2017. The protocol includes no bowel preparation, early feeding, predominantly non-narcotic pain control and  $\mu$  opioid antagonists. Non-consenting/ lost to follow up patients, and those with non-urothelial carcinoma were excluded. We defined EHS as  $\geq$  5 postoperative days and compared the cohort to those with a LOS of  $\leq$  4 days. Demographics including modifiable and non-modifiable factors as well as in-house complications as possible contributing factors to EHS was reviewed. **Results:** There were 279/509 (54.8%) patients had an EHS. Median age was 73 years, 82.4% were male, and 36.6% had a Charlson comorbidity index (CCI) of > 2. Univariate analysis demonstrated that age > 65 years, CCI > 2, increased operative time, anemia requiring transfusion and non-orthotopic diversion were associated with EHS. On multivariate analysis, advanced age, operative time, postop transfusion, CCI > 2 as well as surgeon specific preferences was associated with EHS. Within EHS patients, 86% stayed due to an in-house complication; ileus (34.3%), anemia requiring transfusion (8.5%). Canada and an atrial fibrillation (8.5%).

**Conclusions:** Advanced age, operative time, postop transfusion, CCI > 2 and surgeon-specific preferences are associated with an EHS following RC with ERAS. The common causes of EHS are in-house complications, mainly ileus.

**Key Words:** bladder cancer, complications, enhanced recovery after surgery, radical cystectomy, hospital stay

# Introduction

With over 79,000 new cases diagnosed in 2017, bladder cancer remains one of the most common malignancies in the United States.<sup>1</sup> The gold standard therapy for muscle invasive disease remains radical cystectomy,<sup>2</sup> which is associated with significant morbidity and a lengthy hospital stay.<sup>36</sup> Modern improvements in

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surgical technique, coupled with a greater focus on perioperative care, have decreased the length of stay (LOS). This has historically been upwards of 17 days in European series and 8-9 days by U.S. Nationwide Inpatient Sample estimates.<sup>4,5</sup>

Enhanced recovery after surgery (ERAS) protocols are being increasingly adopted to shorten LOS yet concerns over earlier discharge exist. These include an increased risk for outpatient complications and readmission rates with a subsequent need for greater resources in the post hospital setting.<sup>7,8</sup> Population based series during the ERAS era have shown a consistent decline in LOS following cystectomy without a meaningful change in complication rates.<sup>6,9</sup> Similarly,

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we have previously shown the benefit of an ERAS protocol following radical cystectomy with a shortened median hospital stay of 4 days with no change in 30day complication or readmission rate.<sup>10</sup> A large and recent study of Medicare beneficiaries undergoing major inpatient surgery showed that savings from shorter postsurgical hospitalizations are not met by a compensatory increase in payments for post discharge care.<sup>11</sup> All the more, prolonged length of stay has been shown to place patients at risk for worse overall survival.<sup>12</sup> Thus, the impetus remains for physicians to improve ERAS protocols and reduce LOS.

In this study, we evaluate the reasons for and predictors of extended hospital stay (EHS) in patients undergoing radical cystectomy within an ERAS protocol.

# Materials and methods

We designed a retrospective cohort study of prospectively maintained database to evaluate patients undergoing radical cystectomy, pelvic lymphadenectomy and urinary diversion between May 2012 and March 2017 at a single academic institution. Both open and robotic cystectomies were included. Five hundred and nine patients were identified. Seventy-nine were excluded due to the following reasons: lost to follow up, nonconsenting, and patients with a prolonged postoperative intubation status that prohibited early feeding, and thus inability to adhere to the ERAS protocol. Those undergoing cystectomy for a non-urothelial primary malignancy, and patients undergoing concomitant nephroureterectomy were also excluded. These generally comprises of < 10% of all cystectomy patients, of which < 5% has been for curative intent.

The ERAS protocol at our institution has been previously described.<sup>13</sup> Briefly, this practice includes extensive preoperative education and counseling, intraoperative fluid optimization and removal of the nasogastric tube upon extubation. Early postoperative feeding is encouraged, and there is a preference towards non-opioid pain control. Patients receive alvimopan, a  $\mu$ -receptor opioid antagonist to help prevent the opioid effects on the gastrointestinal system. Other prokinetic agents, such as neostigmine, are administered as well. Upon discharge, the protocol delivers intravenous fluid hydration via a midline intravenous catheter for three weeks and subcutaneous prophylactic enoxaparin injections.

In this study, patients were stratified into a group of those with a LOS of 4 days or less and an extended hospital stay (EHS≥5 days) group, as our previous study showed a median hospital stay of 4 days for consecutive cystectomy patients.<sup>10</sup> In both groups, data was collected on gender, age, race, Charlson comorbidity index (CCI), American Society of Anesthesiologists (ASA) physical status classification, neoadjuvant chemotherapy, operative time (including anesthesia time), type of diversion, intraoperative blood loss, and postoperative transfusion rates. Pathologic details including lymph node status, presence of lymphovascular invasion (LVI), margin status, and presence of multi-focal disease were also identified. Within the EHS group, data regarding in-house complications were collected.

Additionally, outcome analysis for enrolled patients were evaluated according to surgeon preference. Surgeries were done by six fellowship trained surgeons; three in open and three via robotic-assisted laparoscopy.

Univariate analysis between means to compare the EHS group to those discharged at 4 days or less was conducted using Chi-squared analysis and Fisher's exact test. After a step-wise selection, multivariable logistic regression modeling was used to characterize the independent associated of factors contributing to an EHS. Subsequently, univariate and multivariate analysis was performed to compare each of the six surgeons, while controlling for the independently associated risk factors already established. A statistically significant difference was defined as a p value of less than 0.05. Statistical analysis was performed using SAS software, version 9.0.

## Results

Over a 4-year period, 588 consecutive patients who underwent radical cystectomy in the ERAS era were identified retrospectively. Seventy-nine patients were excluded due to lost to follow up, non-consenting, those undergoing cystectomy for a non-urothelial malignancy, concomitant nephroureterectomy, and patients with a prolonged postoperative intubation status that prohibited early feeding. The remaining 509 patients enrolled in this study.

EHS group comprised of 279 patients (54.8%) whose hospital LOS was 5 days or more. Median age was 73 years, 82.4% were male, and 36.6% had a CCI of > 2. The other 230 patients (45.2%) (non-EHS cohort) were discharged in 4 days or less. Demographic and comparison data between both groups is detailed in Table 1.

Univariate analysis via chi-squared analysis and Fisher's exact test showed statistically significant difference comparing EHS and non-EHS groups in several demographic aspects including age greater than 65 years (p < 0.0001), CCI greater than 2 (p < 0.0002), prolonged operative time (p < 0.0001), non-orthotopic urinary diversion (p < 0.0001), and postoperative anemia requiring transfusion (p < 0.0001). Neither

	Extended hospital stay (279 patients) LOS ≥ 5 davs		Non extended hospital stay (230 patients) LOS ≤ 4 davs		
	<b>#</b> of patients	%	<b>#</b> of patients	%	
		(out of 279)		(out of 230)	p value
Age					< 0.0001
Median	73	n/a	68	n/a	
≤ 65 years	68	24.4	94	40.9	
> 65 years	211	75.6	136	59.1	
Gender					0.65
Male	230	82.4	186	80.9	
Female	49	17.6	44	19.1	
CCI					< 0.0001
CCI ≤ 2	177	63.4	177	77.0	
CCI > 2	102	36.6	53	23.0	
Neoadjuvant	83	29.8	67	29.1	0.88
Surgical approach					< 0.0001
Open	167	59.9	192	83 5	< 0.0001
Robotic	112	40.1	38	16.5	
Operative time	6.4 hours	10.1	57 hours	10.0	< 0.0001
	0.4 1100115		5.7 Hours		< 0.0001
lype of diversion	100	40 F		04.0	< 0.0001
lleal conduit	138	49.5	57	24.8	
Continent cutaneous	8 100	2.9	11	4.8	
Studer neobladder	133	4/./	162	70.4	
Estimated blood loss	514 mL		459 mL		0.31
Postop transfusion	109	39.1	41	17.8	< 0.0001
Pathologic stage					0.06
Organ confined	170	60.9	163	70.9	
Extra-vesical disease	45	16.1	28	12.2	
Lymph node (+)	64	22.9	39	17.0	
LOS = length of stay; CCI = C	Charlson comorbidit	y index			

TABLE 1. Demographic features of extended hospital stay patients compared to non-extended hospital stay patients (n = 509)

neoadjuvant chemotherapy, nor pathologic stage/ surgical margin status were significantly different between the two cohorts, Table 1.

In a stepwise approach, a multivariate regression model was then performed to reveal the independent predictors of an extended hospital stay. Advanced age (OR 5.86, 95% CI 2.72-13.01, p < 0.0001), operative time (OR 1.31, 95% CI 1.12-1.56, p = 0.001), postoperative transfusion (OR 3.12, 95% CI 1.96-5.06, p < 0.0001) and CCI > 2 (OR 1.23, 95% CI 1.03-1.47, p = 0.02) were associated with EHS. Neoadjuvant chemotherapy and type of diversion had no statistically significant association with increased LOS, Table 2. Given that individual surgeon preferences and variations in postoperative care may also play a role in LOS, subsequent analysis was performed to compare the six surgeons who conduct radical cystectomy, diversion and lymphadenectomy under the ERAS protocol. Univariate analysis showed a statistically significant difference between the surgeons (p < 0.0001). Controlling for the independent predictors of EHS (advanced age, operative time, and postoperative transfusion), multivariable regression model was then conducted between surgeon "A" and the remaining surgeons. Surgeon "A" has contributed the highest of patients in the cohort (54% of the total group), and

Extended hospital stay after radical cystectomy with enhanced recovery protocol

Subgroup analysis	Odds ratio (95% confidence interval)	p value
Age ≥ 80 years	5.86 (2.72-13.01)	< 0.0001
Postop transfusion	3.12 (1.96-5.06)	< 0.0001
Operative time	1.31 (1.12-1.56)	0.001
Charlson comorbidity index > 2	1.23 (1.03-1.47)	0.02
Type of diversion	1.58 (0.97-2.59)	0.005
Neoadjuvant chemotherapy	0.99 (0.61-1.61)	0.96

TABLE 2.	Multivariable	logistic	regression	modeling o	f extended	hospital	stay patien	ts
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with 80% of patients in the non-EHS group. So, this surgeon has been selected as the benchmark upon which other surgeons were compared. Statistically significant differences with an EHS were observed in two surgeons, each with differing surgical approaches (p = 0.02 and p < 0.0003). No differences were seen in the remaining three surgeons (one open, two robotic). This implies that surgeon specific nuances, beyond the choice of open or robotic approach, contributes to an EHS.

The majority of EHS patients remained in house due to an immediate postop complication; ileus (34.3%), anemia requiring transfusion (9.8%), urinary tract infections (9.4%), atrial fibrillation (8.5%), and uncontrolled pain (4.3%).

#### Discussion

The adoption of ERAS protocols has dramatically changed the recovery of radical cystectomy patients. These are multimodal pathways that aim to optimize all elements of perioperative care to decrease stress, streamline predictable recovery patterns and accelerate recovery following surgery.<sup>14</sup> Despite the demonstrated improvements with ERAS, radical cystectomy remains a morbid operation and a need for improvement remains.

In this study, we identified independent predictors of EHS, and showed that the most common reason for an extended hospital stay is an in-house, or immediate postoperative, complication. Postoperative ileus was the most prevalent and occurred in one third of those who stayed longer than 4 days. A retrospective review by Pietzak et al found prolonged LOS (> 12 days) to be associated with a greater number of postoperative complications, again with ileus being the most common in 13 of 56 (23.2%) patients.<sup>12</sup> Similarly, a study by Chang et al in 2002 found ileus to be the most common cause of an increased hospital stay at a rate of 53 of 77 (68.8%) patients who stayed longer than a target 8 hospital days.<sup>15</sup> Though these studies were done in the setting of a clinical pathway, they were not in the contemporary ERAS era. In the pathway used by Chang et al, all patients were given a bowel preparation, and while NGT decompression was not routinely done, patients were kept on a no oral intake diet until return of bowel function.

As described previously, our protocol includes omission of NGT without preoperative bowel preparation, pre and postoperative use of alvimopan and early feeding.<sup>10</sup> These are all evidence-based interventions<sup>16-18</sup> with the most robust data existing for alvimopan, which has been shown in randomized controlled trials to significantly reduce ileus.<sup>19</sup> Although rates of ileus were lower in our cohort, it remains the primary reason for EHS. Other immediate postoperative complications in the EHS group included anemia requiring transfusion (9.8%), urinary tract infections (9.4%), atrial fibrillation (8.5%), and uncontrolled pain (4.3%). These values are consistent with our previously published 90-day complication findings following radical cystectomy with ERAS.<sup>13</sup>

Forty percent of the patients with an EHS had postoperative anemia requiring blood transfusion, which was indeed found to be associated with EHS on multi-variable analysis. A strict transfusion protocol exists at our institution based off high level evidence supporting a restrictive transfusion strategy over a liberal one<sup>20</sup> and given concerns in oncologic outcomes as pertains to bladder cancer specifically.<sup>21</sup> Unsurprisingly, the cohort of patients in our series who received transfusion also had prolonged and complicated hospital stays. The specific factors leading to blood transfusion were not examined in this study, but practice patterns may explain this trend. Hematocrit levels are followed closely in the postoperative period, and if down trending, a transfusion often withheld until the patient displays signs of symptomatic anemia. Blood product transfusion time, along with time spent thereafter checking further values to ensure stability, invariably lengthens the hospital stay.

In addition to anemia, advanced age was also identified to be a predictor of EHS. Age is well known to be an independent predictor of morbidity following radical cystectomy<sup>22</sup> and prior series have also shown advanced age to be associated with prolonged hospital stays.<sup>12,23,24</sup> While age is certainly not a modifiable factor when considering treatment options for patients with invasive bladder cancer, our results further emphasize the importance of preoperative counseling of these patients.

Comorbid conditions reflected as CCI portended an EHS on univariate analysis. CCI weighs a patient's comorbid conditions to quantify their disease burden. This has been validated as a prognostic indicator of mortality, and especially applicable to cystectomy patients who carry multiple comorbid conditions in addition to bladder cancer. Undoubtedly, patients with comorbid conditions are at higher anesthetic risk, and prone to postoperative complications. Similarly, patients receiving a non-orthotopic urinary diversion had an increased length of stay on univariate, but not on the multivariate analysis. In our institution, we lean more toward a continent diversion (orthotopic or continent cutaneous) compared to national data; 2/3 of our patients get continent diversions. Hepatic dysfunction, renal insufficiency, and cognitive impairment as well as positive frozen urethral margin are contraindications to orthotopic diversion, so those receiving an ileal conduit are an inherently sicker population of patients. Therefore, an extended hospital stays in patients with a CCI > 2, or those ineligible for a continent diversion due to contraindications, was not unexpected.

The effect of increased operative time was also a clear and statistically significant predictor of EHS in this study. Again, our reported operative time was anesthesia time, including time for intubation and line placement. In 2014, Lavallee et al established that an operative time of > 6 hours for cystectomy was independently associated with perioperative complication.<sup>25</sup> A highly powered SEER study by Filson et al provided the details behind increased operative times.<sup>26</sup> While this data was derived from anesthesia administrative claims, large hospitals and academic centers was noted to have the longest operative times. Other features such as female sex, increased CCI and extended lymphadenectomy, quantified by lymph node yield, showed longer operative times. In addition, continent diversions were approximately 35 minutes longer than ileal conduits. Interestingly, perioperative procedures such as arterial line or central venous catheter placement was also a significant contributor to prolonged operative times. While the details behind lengthy operative times were not established in our study, the independent factors established by Filson et al help explain this association to EHS. Increased operative times in this study may be attributed to non-modifiable patient factors, academic interests in education (i.e., postgraduate residents/fellows in urology and anesthesia), and extent of lymphadenectomy.

However, in our cohort, the majority of EHS patients had an ileal conduit urinary diversion. This should technically show a faster operative time than orthotopic diversion, regardless of robotic or open approach. Yet, EHS patients had operative times that were statistically longer as well. Our data does not clarify this discrepancy, except that non-modifiable morbid factors related to the patient were more common in EHS group. This can commonly lead to increased anesthesia preparation time before surgery. Both CCI and advanced age were predictors in themselves for EHS.

Employment of robotic assistance is a known factor to increase operative times, but this must be considered in the context of surgeon preference and practice patterns. Our institutional ERAS protocol is considered standard of care for all patients, but implementation of each intervention is at the discretion of the surgeon. A review of patients undergoing colorectal resection using the National Surgical Quality Improvement Program found significant variation in factors that may have attributed to extended LOS.27 Their conclusion was that risk adjusted LOS is most likely a reflection of differences in practice style and that efforts should focus on efficiency of care. In our cohort, there were six surgeons who performed the majority of cystectomy cases, and three are exclusively via the robotic approach. The data reflect a statistical difference between the six surgeons, attributed mainly towards variation in postoperative practice patterns. Moreover, the statistical difference elicited was between surgeons, and not between surgical approach. It is not possible to tease these two features apart as each surgeon exclusively used one approach or the other in this study. While our multivariable analysis did show an association of longer operative times and EHS, accounting for individual surgeon practices (i.e., a combination of surgical approach and postoperative care patterns) revealed that both open and robotic surgeons may be associated with EHS. This illustrates that a surgeon's individual care postoperatively, even while adhering to ERAS, may account for difference in hospital stays. Postoperative care is not formulaic, but highly nuanced and tailored to each patient. Longer operative times and the link to robotic assistance will predictably, and likely, diminish in the years to come.<sup>28</sup>

Limitations of our study include a single institution design and retrospective review of outcomes. Additionally, patients with non-urothelial pathology, concurrent nephroureterectomy, and simple cystectomy patients were excluded from the IRB approved data set. This population is a small number, but since they typically had ERAS driven post-operative care, omitting these patients may have contributed to a bias in predicting EHS factors.

While data was collected in a prospective fashion with granular details for each case, it is challenging to eliminate biases such as individual physicians practice patterns. Intraoperative details that may have led to a complicated hospital course were not explicitly recorded, and specific co-morbid conditions beyond the CCI classification were not established either. Future work will examine each of the individual factors influencing EHS and attributed costs.

## Conclusions

Advanced age, longer operative time, postoperative transfusion, CCI > 2 and surgeon preference practices of ERAS are associated with extended hospital stay following radical cystectomy with enhanced recovery protocol. The most common cause of extended hospital stay is in-house complication. This information can help to identify patients prone to EHS and improve discharge planning to better control the resources of hospitalization after radical cystectomy.

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