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**Prospective implementation of Enhanced Recovery After Surgery (ERAS) protocols to Radical Cystectomy**

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**Abstract**

**Background:** Multimodal enhanced recovery after surgery (ERAS) regimens have improved outcomes from colorectal surgery.

**Objective:** We report the application of ERAS to patients undergoing radical cystectomy (RC).

**Design, Setting and Participants:** Prospective collection of outcomes from consecutive patients undergoing RC at a single institution.

**Intervention:** Twenty-six components including prehabilitation exercise, same day admission, carbohydrate fluid loading, targeted intra-operative fluid resuscitation, regional local anesthesia, cessation of NG tubes, omitting oral bowel preparation, avoiding drain use, early mobilization, chewing gum use and audit.

**Outcome Measurements and Statistical Analysis:** Primary outcomes were length of stay and readmission rate. Secondary outcomes included intra-operative blood loss, transfusion rates, survival and histopathological findings.

**Results and Limitations:** 453 consecutive patients underwent RC, including 393 (87%) with ERAS. Length of stay was shorter with ERAS (median (IQR): 8 (6-13) days) than without (18 (13-25), $p<0.001$). Patients with ERAS had lower blood loss (ERAS: 600 (383-969) mls vs. 1050 (900-1575) mls for non-ERAS, $p<0.001$), lower transfusion rates (ERAS: 8.1% vs. 25%, Chi sq. $p<0.001$) and fewer readmissions (ERAS: 15% vs. 25%, Chi sq. $p=0.04$) than those without. Histopathological parameters (e.g. tumor stage, node count and margin state) and survival outcomes did not differ with ERAS use (all $p>0.1$). Multivariable analysis revealed ERAS use was ($p=0.002$) independently associated with length of stay.

**Conclusions:** The use of ERAS pathways was associated with lower intra-operative blood loss and faster discharge for patients undergoing RC. These changes did not increase readmission rates or alter oncological outcomes.

**Patient summary:** Recovery after major bladder surgery can be improved by using enhanced recovery pathways. Patients managed by these pathways have shorter length of stays, lower blood loss and lower transfusion rates. Their adoption should be encouraged.

## Introduction

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is the gold standard treatment for muscle invasive BC [1], plays a key role in managing local failure after radiotherapy [2] and is an option for high risk local non-muscle invasive BC [3]. RC is a morbid procedure that often performed in older patients with co-existing cardiopulmonary disease. Many patients develop post-operative complications, including 13% (grade 3-5) that require further intervention [4]. Consequently, patients who could benefit from RC do not always receive this option [5, 6]. Whilst centralization of major cancer services increases radical treatments and subsequent outcomes [7], the morbidity from RC still limits its use.

In colorectal surgery, the use of multimodal Enhanced Recovery after Surgery (ERAS) regimens has reduced post-operative morbidity and length of stay [8, 9]. ERAS introduces a number of pre-, peri- and post-operative steps to improve the patient pathway [10]. Many ERAS components are generic to abdominal surgery and so have been implemented in RC without prospective evidence [11]. However, RC includes surgery to the urinary and gastrointestinal tracts and so not all ERAS components may be suitable.

There have been several reports of ERAS in RC cohorts [10-14] and one RCT [15]. This RCT found ERAS improved quality of life and reduced morbidity in patients undergoing RC, but did not shorten post-operative length of stay (LOS). Here we report the prospective adoption of ERAS in a large UK centre, where the opioid receptor antagonist Alvimopan [16] is not available and healthcare design does not incentivize rapid discharge.

## Materials and methods

*Patients*

Consecutive patients undergoing RC and urinary reconstruction were enrolled in a prospective institutional database. From February 2007 to October 2016, a 25 point ERAS regimen was implemented. The regimen (table 1) was derived from available evidence and practice within colorectal surgery [10]. Data were collected prospectively and all patients undergoing RC were included in the study. The use of ERAS reflected the date of surgery. During the transition period, patients were identified as using the ERAS pathway if they had pre-operative carbohydrate loading, were allowed fluids until 2 hours prior to surgery, planned to avoid NGT, used a smaller incision had early post-operative mobilization with diet on the ward.

*ERAS Protocol*

*Pre-operative:* Counselling in the outpatient setting was performed by the surgeon (JWFC), a cancer nurse specialist, an anaesthetist (RG) when needed, and a stoma therapist. Typical consultations included wide ranging treatment discussions and lasted 30-45 minutes. Patients were advised to maintain a normal diet until the night before surgery, to reduce cigarette smoking and alcohol intake, and were given an information booklet regarding their expected recovery. Increasing exercise activity (prehabilitation) was stressed as an important aspect of recovery and patients asked to walk 1 hour per day (once or twice) between their initial consultation and surgery. Patients whose anaesthetic fitness was uncertain were reviewed by an Anaesthetist and cardiopulmonary exercise (CPEX) testing used in selective cases. Pre-morbidities were optimized where possible. Anemia was treated with intravenous iron transfusion. Prior to surgery, patients attended clinic for stoma marking, to obtain 6 carbohydrate dinks (e.g. PreOp ™, Nutricia) and to collect a single injection of low molecular weight heparin (LMWH e.g. dalteparin 5,000 iu s/c). Patients self-administered dalteparin the evening before surgery and undertook carbohydrate fluid loading for the 18 hours prior to surgery. Patients were allowed oral fluids up to 2 hours pre-operatively and food 6 hours pre-operatively.

*Per-operative:* At induction, a pre-planned anaesthetic protocol was used (supplementary table 1). Important elements included limited fluid administration targeted to losses, the use of vasopressors to maintain blood pressures, the avoidance of nasogastric tubes (NGT) and hypothermia (e.g. using Bair Hugger ™). Typically, only 500-1000mls intravenous crystalloid was administered prior to bladder removal. Intra-operative steps taken to reduce the impact of surgery included the use of small incisions (typically 10cm) or robot assisted laparoscopy, the use of vessel sealers (e.g. Ligasure™ impact), clips and fastidious haemostasis. Post-operative analgesia commenced with the insertion of rectus sheath local anaesthetic blocks (usually 60mls of 0.125% bupivacaine) and tunnelled cannulae (lateral and superior to the incision prior to wound closure) for a 48 hour bupivacaine infusion. Closure was performed using a 2/0 PDS rectus sheath suture and 4/0 monocryl subcuticular skin suture. Antibiotic prophylaxis (1.2g intravenous co-amoxiclav) was administered for 24 hours in men and for 48 hours in women (due to higher contamination from vaginal flora). DVT prophylaxis was administered from 6-12 hours prior to surgery and for at least 28 days after surgery or until discharge (whichever was longer).

*Radical cystectomy:* In males, cystoprostatectomy was performed in an antegrade manner to include the seminal vesicles. In females, anterior pelvic exenteration included the uterus, fallopian tubes and anterior vaginal wall. Ovaries were spared, when possible in younger women and in those with low stage disease. Lymphadenectomy was performed after bladder removal and included the obturator, internal and external iliac chains to the level of the ureteric crossing of the mid common iliac vessels. Ureteroileal anastomosis was by a Bricker technique and the Studer technique used for a neobladder.

*Post-operative:* Management was undertaken using a pre-specified ERAS regimen (table 1). During the regimen's introduction, an ERAS nurse audited compliance. On post-operative day (POD) #1 patients were allowed chewing gum, one clear boiled sweet/candy per hour and 30mls clear non-fizzy oral fluids per hour, as comfort allowed. Intake was reduced in patients feeling nauseous or uncomfortable. Patients were sat out of bed and encouraged to walk 10-20 meters. Additional analgesia was allowed through on demand patient controlled analgesic (PCA) intravenous opiates. On POD#2 patients aimed to walk 100 meters and were allowed to drink clear fluids as tolerated. Nausea or vomiting were treated with reduced fluid intake and rest, rather than NGT. NGT were administered for repeated vomiting with epigastric discomfort or in the presence of ileus/obstruction. Light diet was introduced when the patient passed flatus or had a bowel movement. Patients without flatus or bowel movement on POD#3, had a glycerine suppository administered per rectum. Total parenteral nutrition (TPN) was started on patients not tolerating diet by POD#7, or sooner if post-operative complications were apparent. Abdominal and pelvic CT scan was undertaken on POD#5 if patients were not progressing according to expectation or in the presence of signs of intra-abdominal complications. Discharge occurred when the patients were comfortable, self-caring with their stoma, mobile, and when they had resumed full diet with bowel motion.

*Statistical analysis*

Primary outcomes were LOS and post-discharge readmission rates. Secondary outcomes included intra-operative blood loss, intra- and post-operative blood transfusion rates, operative duration, overall and bladder-cancer specific survival. For analysis, BMI was stratified as underweight (BMI <18.5), healthy (BMI 18.5–24.9), overweight (BMI 25–29.9) and obese (BMI ≥30) [17]. Pre-operative anaemia was defined as hemoglobin <12g/dl in both sexes and renal impairment as estimated GFR <40mls/min, as per our national registry database. Multivariable analysis for a ≤7-day LOS was performed using logistic regression with factors significant from univariable analysis. To test ERAS through any learning curve, cases were divided into quartiles by time, and variables analysed using logistic regression.

## Results

*Patients and recovery components*

453 consecutive patients underwent radical cystectomy (table 2, figure 1). The median (IQR) age was 70 years (64-76) and 14% of patients were ≥80 years old. Ninety-eight were female (22%) and 50 (11%) received a neobladder reconstruction. Around one quarter of patients had renal impairment (eGFR <40mls/min in 107 (24%)) prior to surgery, 100 (22%) had hydronephrosis or were anephric, the median (IQR) BMI was 29 (26.0-32.8) and 177 (39%) had Charlson Comorbidity index (CCI) of 4 or higher. Twenty-eight patients underwent robot assisted surgery, of which 25 had intracorporeal reconstruction. Fifty-nine patients received neoadjuvant chemotherapy (NAC), 18 received adjuvant chemotherapy and 29 palliative chemotherapy. 135 patients had invasive cancer at TUR, were younger than 80 years of age, had normal renal function and a good performance status (CCI 0-3)). As such, the use of NAC in these suitable cases was 57/135 (42%) and did not differ by ERAS use (42% vs. 44% (non-ERAS)). Histological outcomes were similar in patients with and without ERAS recovery (supplementary table 2, figures 2a and b). In particular, the lymph node count (mean ± st. dev: 10.7 ± 4.7 for ERAS vs. 10.3 ± 5.8 non-ERAS, T test p=0.6) and circumferential margin status (positive in 2.5% (ERAS) vs. 1.7%, Chi sq. p=0.4) were similar.

ERAS components were used in 393 (87%) patients (figure 1a). Direct admission from home to surgery occurred in 376 (83%), rectus sheath local anaesthetic infusions used in 241 (53%), NGT avoided in 382 (84%), pre-operative oral bowel preparation avoided in 390 (86%) and drains not used in 20 (4.4%) patients. Carbohydrate fluid loading was used in 364 (80%) and drinking until 2 hours prior to anaesthesia allowed in 284 (63%). Patients with ERAS were older (median (IQR) 71 years (65-76)) than those without (60 (61-70), Mann-Whitney U test p<0.001), more commonly female (23% vs. 13%) and less often underwent neobladder reconstruction (6.4% vs. 42%), but otherwise the two groups were similar (table 2).

*Length of stay and readmission*

Length of stay differed significantly for patients with ERAS (median (IQR) 8 (6-13) days) and without ERAS (18 (13-25)) recovery (supplementary figure 1 and p<0.001). Over the series, LOS reduced from a median of 17 days to 6 days (figure 1b) and varied with a number of factors (table 3). Longer stays were seen in females (12 days vs. 9 for males, p=0.004), with neobladder reconstruction (19 days vs. 9 for ileal conduit, p=0.001), those with an abnormal BMI (p=0.001), in those receiving a blood transfusion (14 days vs. 10 for no transfusion, p=0.03) and in those with comorbidities (P=0.001) (see table 3 for details). Shorter stays were seen with robot-assisted surgery (7 days vs. 10 for open, p=0.03). In univariable analysis (table 3) male gender (p<0.001), ileal conduit diversion (p<0.001), low BMI (p=0.01), normal renal function (p<0.001), low CCI (p<0.001), no transfusion (p=0.03), no drain (p=0.04) and all components of the ERAS regimen (p<0.001) were associated with a LOS of ≤7days. Multivariable analysis revealed that female gender (logistic regression p<0.001), neobladder reconstruction (p=0.02), BMI (p<0.001), comorbidity (CCI: p<0.001) and non-ERAS use (grouped into a single parameter, p=0.002) were independently associated with a LOS of ≥7days. In only neobladder cases (25 ERAS and 25 non-ERAS), sub-group analysis revealed that ERAS use was still associated with shorter LOS (median (IQR) 15 (8-20) (ERAS) vs. 24 (18-28) days (non-ERAS), Mann-Whitney U test p<0.001).

Readmission occurred in 21% of patients (88/417 with readmission outcomes). Twenty-two patients (25%) stayed 1 day and 24 (27%) more than 10 days. Most readmissions were within 30 days of discharge (60/88 (68%)). Patients with ERAS had fewer readmissions (15%) than those without ERAS (25%, Chi sq. p=0.04). Readmission rates declined over time to 11% for the last 100 cases (figure 1d). We did not demonstrate differences in readmission length of stay by ERAS use (supplementary figure 2). ERAS use was significantly associated with shorter LOS and lower readmission rates, once adjusted for covariates (including learning curve, logistic regression p<0.05).

*Secondary outcomes*

Intra-operative blood loss (median (IQR)) was lower for ERAS (600 (383-969) mls) than non-ERAS (1050 (900-1575) mls) patients (Mann-Whitney U test p<0.001). Consequently, transfusion rates were lower for ERAS (n=32 (8.1%)) than for non-ERAS (n=15 (25%)) patients (Chi sq p<0.001). Blood loss reduced across the series from an average of 1,237 (first 50 cases) to 557mls (last 50 cases, figure 1c). The median (IQR) operative duration was lower in the ERAS (2.9 (2.5-4.0)) vs non-ERAS (5.0 (4.5-6.0)) (Mann-Whitney U test p<0.001, supplementary figure 2). ERAS use was significantly associated with lower blood loss (logistic regression p<0.01), but not faster operative times (p=0.5), once adjusted for learning curve.

*Mortality*

At median (IQR) follow up of 19 (8.3-37) months, 335 (77%) patients were alive and under surveillance (17 missing). There were 77 deaths (17%) from BC (median (IQR) of 15 (7.2-22) months after surgery) and 24 from other causes (median (IQR) 19 (6.1-34) months). The 30-day mortality rate was 1.7% (1 case) for non-ERAS and 0.3% (1 case) for ERAS patients (Chi sq. p=0.14). There were 3 (5%) deaths in the non-ERAS and 8 (2.1%) in the ERAS cohort within 90-day of cystectomy. Of the 90-day deaths, 8/11 (73%) were from metastatic BC. In univariable and Multivariable analysis, neither 30-day nor 90-day mortality rates differed with ERAS use (Chi Sq. and Logistic regression p>0.60). There was no difference in overall or bladder cancer specific survival when stratified by ERAS use (figure 2c and d).

## Discussion

Since introduction into colorectal surgery, enhanced recovery programs have improved the outcomes for many patients undergoing a diverse array of surgical procedures (reviewed in [10]). The ERAS Society (www.erassociety.org) has protocols within several surgical specialities, including RC. Since many RC patients develop complications during recovery [4], these patients may benefit more than most from refinements in post-operative management. Our data support the use of ERAS, demonstrate excellent improvements in post-operative recovery and confirms its oncological safety.

There has been one prospective RCT of ERAS in RC patients [15], in which ERAS use led to fewer complications, a faster improvement in return of quality of life, more rapid bowel recovery and shorter stays in intermediate care, but no change in LOS. These findings support and conflict with the field. For example, whilst others also found ERAS leads to accelerated bowel recovery and fewer complications, many report shorter hospital stays [11, 12, 18]. Within the USA, Daneshmand et al. reported ERAS using 110 patients and found its use reduced median LOS to 4 days [12]. With the UK, Arumainayagam et al. found ERAS reduced median LOS by around 4 days [19]. LOS can reflect healthcare design as well as rehabilitation. In the UK, patients do not pay for healthcare and most are discharged home. As such, there can be reluctance for rapid discharge. In the US, expensive hospital stays incentivise discharge home or to cheaper skilled nursing facilities (occurred in 16% Daneshmand et al. cohort). Within the German healthcare setting, reducing the LOS is not an economic pressure and so may not have changed in the ERAS population.

Within our series, ERAS improved recovery, accelerated discharge home and also reduced the burden of care to the patient and their medical/nursing teams. Faster discharge brings many benefits, including more rapid access to adjuvant chemotherapy when necessary. Key elements to the success of ERAS involved staff, patients and infrastructure. Firstly, a multidisciplinary approach was vital. Surgical staff engaged with anaesthetic staff to plan/anticipate patient care, nursing staff were engaged in implementing ERAS on the ward and auditing pathway compliance, whilst stoma/neobladder reconstruction nurses attended clinics and the ward to expedite competency. Unfit patients or those at increased risk of complications benefitted from additional surgeon/anaesthetist interaction. Secondly, pro-active patient engagement was vital. This included explaining anticipated recovery timeframes, creating an ERAS booklet that patient's read and completed during their recovery, engaging in prehabilitation exercise regimens for the patient (and involving their next of kin in these exercises), and planning discharge before admission (e.g. stocking up with food before admission, planning care and support once discharged). With regards to infrastructure, it was important to identify the pathway as new and different to traditional care. This helped staff feel comfortable with rapid changes in practice, allowed a change in patient flow (same day admission, rapid mobilisation and discharge), and justified resource to study implementation (auditing pathway compliance during introduction was very useful for the less experienced medical and paramedical staff).

There are important limitations to our data. Firstly, the design precludes a meaningful Multivariable analysis of ERAS elements as most components were used together rather than in different permutations. However, our analyses do reveal the importance of the patient (e.g. BMI and comorbidity), which makes clinical sense and matches our experience. Secondly, these data are derived from a single team and so include a learning curve. Figure 1 shows that the rate of improvement in all outcomes slows after 150 cases and changes most rapidly around the implementation of ERAS. Improvements in these outcomes are associated with ERAS use, after adjustment for learning curve and other covariates. As such, we feel key drivers for change include both a learning curve and ERAS use. Smaller, shorter series (and so less impact from learning curves) support our belief (e.g. [12] [19]). Thirdly, the ERAS and non-ERAS cohort are imbalanced for reconstruction choice. This reflects a change in practice prompted by data suggesting QOL is similar in many patients with ileal conduit and neobladder (unpublished from http://www.abdn.ac.uk/urology/research/otis/ and [20]) and the increased use of RC in older, less fit patients table 2) once ERAS improvements became apparent. We believe less fit patients need the simplest, least morbid surgery with the fastest recovery. A direct comparison using only neobladder cases confirmed that ERAS use was still associated with shorter LOS and faster operations. Overall our rate of neobladder use is similar or higher than the UK average (for example, the 2009 BAUS complex surgery database shows 5.7% received a neobladder in the UK).

## Conclusion

We found that changes to the RC pathway made dramatic improvements to patient recovery without affecting oncological outcomes. In particular, enhanced recovery use was associated with shorter length of stay, lower blood loss and transfusion rates, and fewer readmissions after surgery.

## Take home messages

Making the care of patient's undergoing bladder removal simpler and more uniform improves their outcomes. In particular, it can be associated with shorter stays and fewer readmissions after discharge.


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## References

[1] Chavan S, Bray F, Lortet-Teulent J, Goodman MM, Jemal A. International Variations in Bladder Cancer Incidence and Mortality. Eur Urol. 2014;66:59-73.

[2] Witjes JA, Comperat E, Cowan NC, De Santis M, Gakis G, Lebret T, et al. EAU guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2013 guidelines. Eur Urol. 2014;65:778-92.

[3] Kulkarni GS, Hakenberg OW, Gschwend JE, Thalmann G, Kassouf W, Kamat A, et al. An updated critical analysis of the treatment strategy for newly diagnosed high-grade T1 (previously T1G3) bladder cancer. Eur Urol. 2010;57:60-70.

[4] Shabsigh A, Korets R, Vora KC, Brooks CM, Cronin AM, Savage C, et al. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. Eur Urol. 2009;55:164-74.

[5] Gore JL, Litwin MS, Lai J, Yano EM, Madison R, Setodji C, et al. Use of radical cystectomy for patients with invasive bladder cancer. J Natl Cancer Inst. 2010;102:802-11.

[6] Galsky MD, Stensland K, Sfakianos JP, Mehrazin R, Diefenbach M, Mohamed N, et al. Comparative Effectiveness of Treatment Strategies for Bladder Cancer With Clinical Evidence of Regional Lymph Node Involvement. J Clin Oncol. 2016;34:2627-35.

[7] Hounsome LS, Verne J, McGrath JS, Gillatt DA. Trends in operative caseload and mortality rates after radical cystectomy for bladder cancer in England for 1998-2010. Eur Urol. 2015;67:1056-62.

[8] Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg. 2002;183:630-41.

[9] Lemanu DP, Singh PP, Stowers MD, Hill AG. A systematic review to assess cost effectiveness of enhanced recovery after surgery programmes in colorectal surgery. Colorectal Dis. 2014;16:338-46.

[10] Patel HR, Cerantola Y, Valerio M, Persson B, Jichlinski P, Ljungqvist O, et al. Enhanced recovery after surgery: are we ready, and can we afford not to implement these pathways for patients undergoing radical cystectomy? Eur Urol. 2014;65:263-6.

[11] Azhar RA, Bochner B, Catto J, Goh AC, Kelly J, Patel HD, et al. Enhanced Recovery after Urological Surgery: A Contemporary Systematic Review of Outcomes, Key Elements, and Research Needs. Eur Urol. 2016;70:176-87.

[12] Daneshmand S, Ahmadi H, Schuckman AK, Mitra AP, Cai J, Miranda G, et al. Enhanced recovery protocol after radical cystectomy for bladder cancer. J Urol. 2014;192:50-5.

[13] Dutton TJ, Daugherty MO, Mason RG, McGrath JS. Implementation of the Exeter enhanced recovery programme for patients undergoing radical cystectomy. BJU Int. 2014;113:719-25.

[14] Smith J, Pruthi RS, McGrath J. Enhanced recovery programmes for patients undergoing radical cystectomy. Nat Rev Urol. 2014;11:437-44.

[15] Karl A, Buchner A, Becker A, Staehler M, Seitz M, Khoder W, et al. A new concept for early recovery after surgery for patients undergoing radical cystectomy for bladder cancer: results of a prospective randomized study. J Urol. 2014;191:335-40.

[16] Lee CT, Chang SS, Kamat AM, Amiel G, Beard TL, Fergany A, et al. Alvimopan accelerates gastrointestinal recovery after radical cystectomy: a multicenter randomized placebo-controlled trial. Eur Urol. 2014;66:265-72.

[17] Nepogodiev D, Chapman SJ, Glasbey J, Kelly M, Khatri C, Drake TM, et al. Determining Surgical Complications in the Overweight (DISCOVER): a multicentre observational cohort study to evaluate the role of obesity as a risk factor for postoperative complications in general surgery. BMJ Open. 2015;5:e008811.

[18] Aning J, Neal D, Driver A, McGrath J. Enhanced recovery: from principles to practice in urology. BJU Int. 2010;105:1199-201.

[19] Arumainayagam N, McGrath J, Jefferson KP, Gillatt DA. Introduction of an enhanced recovery protocol for radical cystectomy. BJU Int. 2008;101:698-701.

[20] Ali AS, Hayes MC, Birch B, Dudderidge T, Somani BK. Health related quality of life (HRQoL) after cystectomy: comparison between orthotopic neobladder and ileal conduit diversion. Eur J Surg Oncol. 2015;41:295-9.

## Figure legends

**Figure 1. The use of ERAS following radical cystectomy.** ERAS Components and outcomes are aligned for the 453 consecutive patients. (a). Individual elements from the 26 elements of ERAS are shown for each patient including robotic assisted surgery (RARC), omission of a pelvic drain, the use of oral bowel preparation, same day admission to surgery, regional local anaesthesia (rectus sheath blockade), epidural use, nasogastric tube (NGT), small incision for open surgery, pre-operative carbohydrate loading and designating their pathway as ERAS to facilitate audit. The lower line indicates the extent of ERAS compliance (shades of white (6) to dark grey (10) for use of ERAS). (b). Length of stay (days) and (c). blood loss (mls) across the series are shown as median and interquartile ranges for each 10 consecutive cases. (d). Readmission rates for each 10 consecutive cases across the series.

**Figure 2. Oncological outcomes stratified by the use of ERAS.** Within this cohort of 453 patients, there was no difference in pathological (a). Lymph node count or (b). Margin status or (c). Overall survival or (d). Bladder cancer specific survival) outcomes according to the use of ERAS.

Table 1. Elements of the ERAS protocol used within this report.

| Domain | Item | Elements |
|---|---|---|
| **Clinic** | **1. Preoperative counseling and education** | Advice abour maintaining activity levels |
| | | Dietary and alcohol advice |
| | | Details of admission and recovery |
| | | Written material detailing post-op recovery plan |
| | **2. Prehabilitation exercise** | Walking for 1 hour per day |
| | **3. Preoperative medical optimization** | Optimization of co-morbidities |
| | | Smoking cessation advice |
| | | Plan social aspects of dicharge. Who will help care for patient? |
| | **4. Correction of anemia** | Oral Iron supplements or I/V Iron |
| **Prior to admission** | **5. Oral mechanical bowel preparation** | Omitted. Normal diet until pre-op fasting |
| | **6. Self administered thromboprophylaxis** | Single LMWH injection 12 hours prior to surgery administerd at home |
| | **7. Pre-operative carbohydrate loading** | Carbohydrate loading (6 cartons of drink (e.g. Nutricia PreOp) over the 18 hours prior to surgery). Careful use in diabetic patients |
| **Admission** | **8. Pre-operative oral intake** | Clear fluid until 2 hours pre-op |
| | | Solid foods until 6 hours pre-op |
| | **9. Pre-anaesthesia medication** | Avoidance of long-acting sedatives |
| **Anaesthesia** | **10. Standard anesthetic protocol** | |
| | **11. Anti-microbial prophylaxis** | 24 hours IV Augmentin |
| | **12. Skin preparation** | Two stage preparation: Spray alcoholic 2% chlorhexidine gluconate and paint aqueous 10% povidone-iodine |
| | **13. Thromboembolic prophylaxis** | Thromboembolic compression stockings |
| | | 28 days pharmacological prophylaxis with LMWH starting day before |
| | | Intra-operative pneumatic compression stockings |
| | **14. Regional analgesia** | Epidural anaesthesia omitted |
| | | Rectus sheath catheters (0.125% bupivicaine) for first 48 hrs |
| | **15. Perioperative fluid management** | Avoid overhydration. Vasopressors to maintain arterial hypotension. Administer <1l crystalloid until bladder removed. |
| | **16. Nasogastric intubation** | No NGT or it is removed at the end of surgery |
| | **17. Preventing intraoperative hypothermia** | Use of a warming blanket (Full body Bair Hugger TM 3M) |

| | | |
|---|---|---|
| **Surgery** | **18. Minimally invasive approach** | Mini-Open Cystectomy incision<br>RARC |
| | **19. Resection site drainage** | Consider omitting pelvic drain |
| | **20. Urinary drainage** | Ureteral stents or transurethral neo-bladder catheter should be used.<br>Stents removed as an out patient at 10 days. Catheter removed after cystogram for neobladder |
| | **21. Wound closure** | 2/0 polydioxanone suture (Ethicon) to rectus sheath. 3/0 subcuticular Monocryl (poliglecaprone) suture (Ethicon) to skin. |
| **Post-operative** | **22. Post-operative diet** | Chewing gum to start at 4 hours after surgery<br>Oral fluids to start evening of surgery - 30mls/hour of clear non-fizzy fluids<br>Resume diet when passing flatus, mobile and pain controlled. |
| | **23. Prevention of PONV** | Anti-emetics as needed<br>Early resumption of oral fluids |
| | **24. Postoperative analgesia** | Rectus sheath catheters (0.125% bupivicaine)<br>Patient controlled opiate<br>I/V Paracetamol/Acetaminophen 1g qds until diet resumed |
| | **25. Early mobilization** | 6 Hours out of bed on POD 1<br>Walk 10-20m on POD 1<br>Walk 100m on POD 2<br>Walk >100m on POD 3+ |
| | **26. Audit** | Audit compliance. Understand problems. Keep resource within team |

LMWH: Low molecular weight heparin
NGT: Nasogastric tube
POD: Post-operative day
PONV: post-operative nausea and vomiting
iRARC: Robot assisted Radical Cystectomy with intra-corporeal reconstruction
I/V: Intravenous

Table 2. Details of the patients within this series.

| | | ERAS | | Non-ERAS | | |
|---|---|---|---|---|---|---|
| | | n | % | n | % | p-value * |
| Sex | Male | 303 | 77% | 52 | 87% | |
| | Female | 90 | 23% | 8 | 13% | **0.01** |
| Age | Median (IQR) | 71 | 65-76 | 66 | 60.8-70.3 | **<0.001** |
| Age ≥80 | Yes | 60 | 15% | 2 | 3.3% | |
| | No | 333 | 85% | 58 | 97% | **0.01** |
| BMI | Underweight <18.5 | 2 | 0.5% | 0 | 0.0% | |
| | Healthy 18.5-24.9 | 96 | 24% | 18 | 30% | |
| | Overweight 25-29.9 | 105 | 27% | 14 | 23% | |
| | Obese >30 | 97 | 25% | 13 | 22% | |
| | Missing | 93 | 24% | 15 | 25% | 0.9 |
| Pre-op Hb (g/dl) | Median (IQR) | 131 | 120-142 | 129 | 118-136.5 | 0.6 |
| Renal Function | Normal | 285 | 73% | 26 | 43% | |
| | eGFR <40mls/min | 102 | 26% | 5 | 8.3% | |
| | Unknown | 6 | 1.5% | 29 | 48% | 0.2 |
| Upper tracts | Normal | 294 | 75% | 42 | 70% | |
| | Unilateral hydronephrosis | 70 | 18% | 8 | 13% | |
| | Bilateral hydronephrosis | 17 | 4.3% | 0 | 0.0% | |
| | Anephric/solitary | 5 | 1.3% | 0 | 0.0% | |
| | Unknown | 7 | 1.8% | 10 | 17% | 0.4 |
| Charlson CI score | 0-3 | 201 | 51% | 30 | 50% | |
| | 4-5 | 117 | 30% | 13 | 22% | |
| | 6-7 | 16 | 4.1% | 3 | 5.0% | |
| | ≥8 | 23 | 5.9% | 5 | 8.3% | |
| | Unknown | 36 | 9.2% | 9 | 15% | 0.6 |
| Pre-op BC phenotype | Low-risk NMI | 5 | 1.3% | 1 | 1.7% | |
| | High-risk NMI | 165 | 42% | 20 | 33% | |
| | Muscle invasive BC | 223 | 57% | 39 | 65% | 0.4 |
| Reconstruction | Ileal conduit | 368 | 94% | 35 | 58% | |
| | Neobladder | 25 | 6.4% | 25 | 42% | **<0.001** |

Abbreviations: NMI Non-muscle invasive, BC Bladder cancer, Hb hemoglobin

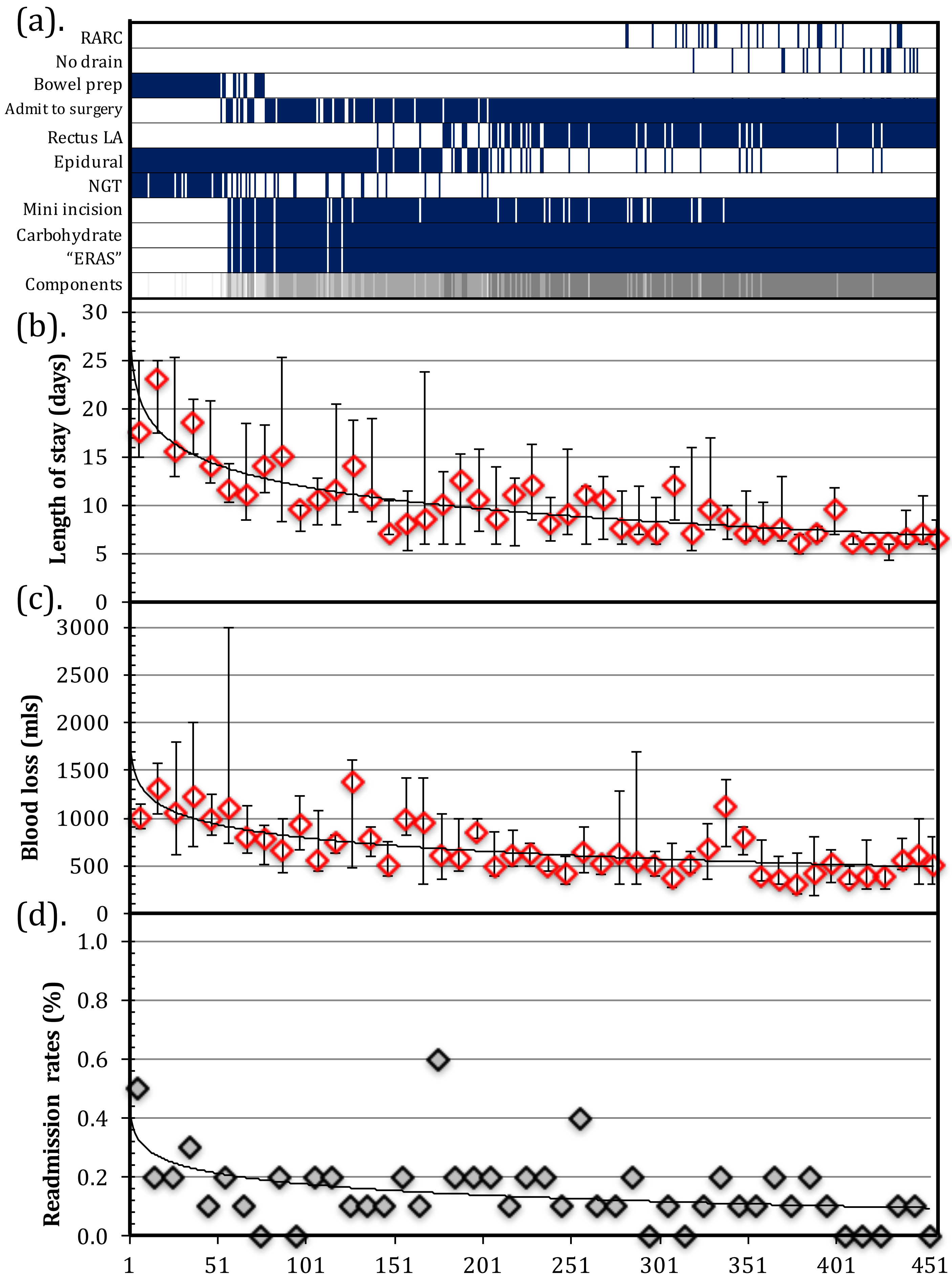
* Statistical tests: Chi square for categorical & Mann-Whitney U or t-test for continuous data.

Table 3. Factors associated with length of stay within this cohort.

| | | | | Length Of stay | | | Univariable* | | | | Multivariable * | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Element | | Number | % | Median | IQR | | OR | 95% CI | | p value | OR | 95% CI | | p value |
| Age (continous) | Median (IQR) | 70 (64-76) | 100% | 10 | 6 | 15 | 0.98 | 0.95 | 1.0 | 0.2 | | | | |
| Tumor phenotype | Low-risk NMI | 6 | 1.3% | 7 | 6 | 17.5 | | | | | | | | |
| | High-risk NMI | 185 | 41% | 10 | 7 | 16 | | | | | | | | |
| | Muscle invasive BC | 262 | 58% | 10 | 6 | 15 | 2.9 | 0.5 | 16.4 | 0.2 | | | | |
| Sex | Male | 355 | 78% | 9 | 6 | 15 | | | | | | | | |
| | Female | 98 | 22% | 12 | 7.8 | 16 | 2.2 | 1.3 | 3.7 | **<0.001** | 3.9 | 1.9 | 7.8 | **<0.001** |
| Robot assisted | Yes | 28 | 6.2% | 7 | 6 | 10 | | | | | | | | |
| | No | 425 | 94% | 10 | 6 | 16 | 2.0 | 0.9 | 4.3 | 0.08 | | | | |
| Reconstruction | Ileal conduit | 403 | 89% | 9 | 6 | 13 | | | | | | | | |
| | Neobladder | 50 | 11% | 19 | 12 | 25.3 | 6.4 | 2.5 | 16.4 | **<0.001** | 5.5 | 1.3 | 22.6 | **0.02** |
| Body Mass Index (continous) | Median (IQR) | 29 (26-32) | 76% | 8 | 6 | 16 | 1.0 | 0.9 | 1.0 | 0.4 | | | | |
| Hb Pre-operation (g/dl) | Anemia | 120 | 26% | 7.5 | 6 | 14 | | | | | | | | |
| | Normal | 175 | 39% | 8 | 6 | 12 | | | | | | | | |
| | Missing | 158 | 35% | 13 | 8 | 19 | 0.9 | 0.6 | 1.5 | 0.7 | | | | |
| Renal Funtion | Normal | 311 | 69% | 6 | 8 | 14 | | | | | | | | |
| | eGFR <40mls/min | 107 | 24% | 11 | 7 | 15 | | | | | | | | |
| | Unknown | 35 | 7.7% | 15 | 12 | 19 | 2.1 | 1.3 | 3.3 | **<0.001** | 1.5 | 0.8 | 3.0 | 0.2 |
| Hydronephrosis | None | 336 | 74% | 10 | 6 | 15 | | | | | | | | |
| | Unilateral | 78 | 17% | 10 | 7 | 13.3 | | | | | | | | |
| | Bilateral | 17 | 3.8% | 12 | 7 | 15.5 | | | | | | | | |
| | Anephric/Solitary | 5 | 1.1% | 6 | 5 | 11.5 | | | | | | | | |
| | Unknown | 17 | 3.8% | 15 | 7.5 | 21.5 | 0.2 | 0.0 | 1.4 | 0.1 | | | | |
| Charlson CI | 0-3 | 231 | 51% | 7 | 6 | 12 | | | | | | | | |
| | 4-5 | 130 | 29% | 10 | 7 | 13 | | | | | | | | |
| | 6-7 | 19 | 4.2% | 12 | 7 | 19 | | | | | | | | |
| | ≥8 | 28 | 6.2% | 26 | 22.3 | 31 | | | | | | | | |
| | Unknown | 45 | 9.9% | 15 | 12 | 17 | 32.4 | 4.3 | 242.5 | **<0.001** | 55.8 | 6.3 | 493.0 | **<0.001** |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Transfusion | Yes | 47 | 12% | 14 | 8 | 21 | | | | | | | | |
| | No | 406 | 88% | 10 | 6 | 14 | 2.2 | 1.1 | 4.4 | **0.03** | 0.7 | 0.3 | 2.2 | 0.6 |
| "ERAS Pathway" | Yes | 393 | 87% | 8 | 6 | 13 | | | | | | | | |
| | No | 60 | 13% | 18 | 13 | 25 | 45.5 | 6.2 | 331.3 | **<0.001** | 295 | 7.5 | 11649 | **0.002** |
| Pre-Op counselling | Yes | 288 | 64% | 7 | 6 | 12 | | | | | | | | |
| | No | 165 | 36% | 13 | 9 | 20.5 | 5.8 | 3.6 | 9.5 | **<0.001** | | | | |
| Prehabilitation exercise | Yes | 239 | 53% | 7 | 6 | 12 | | | | | | | | |
| | No | 214 | 47% | 12 | 8 | 19 | 3.9 | 2.6 | 5.9 | **<0.001** | | | | |
| Mini-Incision | Yes | 374 | 83% | 8 | 6 | 13 | | | | | | | | |
| | No | 79 | 17% | 16 | 12 | 24 | 5.3 | 2.6 | 10.6 | **<0.001** | | | | |
| NGT Tube | Yes | 71 | 16% | 19 | 13 | 25 | | | | | | | | |
| | No | 382 | 84% | 8 | 6 | 13 | 13.2 | 4.7 | 36.8 | **<0.001** | | | | |
| Rectus sheath LA | No | 212 | 47% | 13 | 8 | 20 | | | | | | | | |
| | Yes | 241 | 53% | 7 | 6 | 12 | 3.8 | 2.5 | 5.7 | **<0.001** | | | | |
| Same day Admission | Yes | 376 | 83% | 8 | 6 | 13 | | | | | | | | |
| | No | 77 | 17% | 16 | 12.5 | 23 | 31.0 | 7.5 | 127.9 | **<0.001** | | | | |
| Oral bowel preparation | Yes | 63 | 14% | 16 | 13 | 24 | | | | | | | | |
| | No | 390 | 86% | 8 | 6 | 13 | 48.1 | 6.7 | 352.7 | **<0.001** | | | | |
| Carbohydydrate loading | Yes | 364 | 80% | 8 | 6 | 12 | | | | | | | | |
| | No | 89 | 20% | 16 | 12 | 22 | 14.2 | 5.7 | 35.9 | **<0.001** | | | | |
| Fasting pre-op | 2hrs pre-op | 284 | 63% | 7 | 6 | 12 | | | | | | | | |
| | 6hrs pre-op | 169 | 37% | 13 | 9.0 | 20.5 | 4.9 | 3.1 | 7.8 | **<0.001** | | | | |
| Drain | Yes | 433 | 96% | 10 | 6.0 | 15.5 | | | | | | | | |
| | No | 20 | 4.4% | 7 | 5.3 | 11.5 | 2.6 | 1.0 | 6.4 | **0.04** | | | | |
| Closure | Mass PDS 0 | 331 | 73% | 11 | 7.0 | 17 | | | | | | | | |
| | Sheath PDS 2/0 | 122 | 27% | 7 | 6.0 | 12 | 3.0 | 1.9 | 4.9 | **<0.001** | | | | |
| Oral Fluids from day 1 | Yes | 403 | 89% | 9 | 6.0 | 13 | | | | | | | | |
| | No | 50 | 11% | 19 | 14.0 | 25.3 | 11.3 | 3.5 | 37.0 | **<0.001** | | | | |
| Chewing gum/candy | Yes | 393 | 87% | 8 | 6.0 | 13 | | | | | | | | |
| | No | 60 | 13% | 18 | 13.0 | 25 | 45.5 | 6.2 | 331.3 | **<0.001** | | | | |

* Univariable: Mann–Whitney U or Kruskal–Wallis tests. Multivariable: Logistic regression for staying ± 7 days
Abbreviations: Hb Hemoglobin, NMI Non-muscle invasive



(a).
RARC
No drain
Bowel prep
Admit to surgery
Rectus LA
Epidural
NGT
Mini incision
Carbohydrate
"ERAS"
Components
(b).
Length of stay (days)
0
5
10
15
20
25
30
(c).
Blood loss (mls)
0
500
1000
1500
2000
2500
3000
(d).
Readmission rates (%)
0.0
0.2
0.4
0.6
0.8
1.0
1
51
101
151
201
251
301
351
401
451


Figure 1

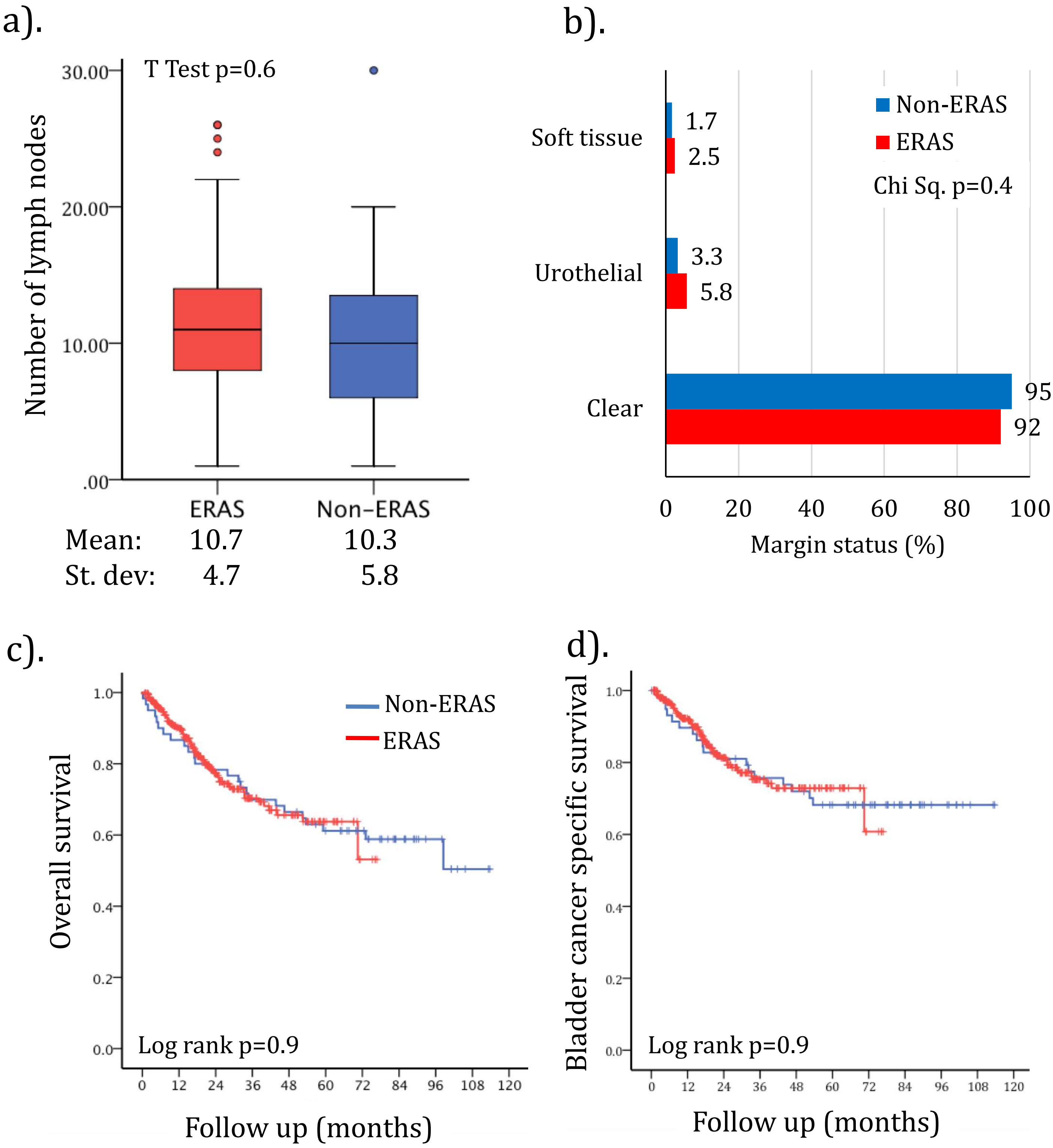
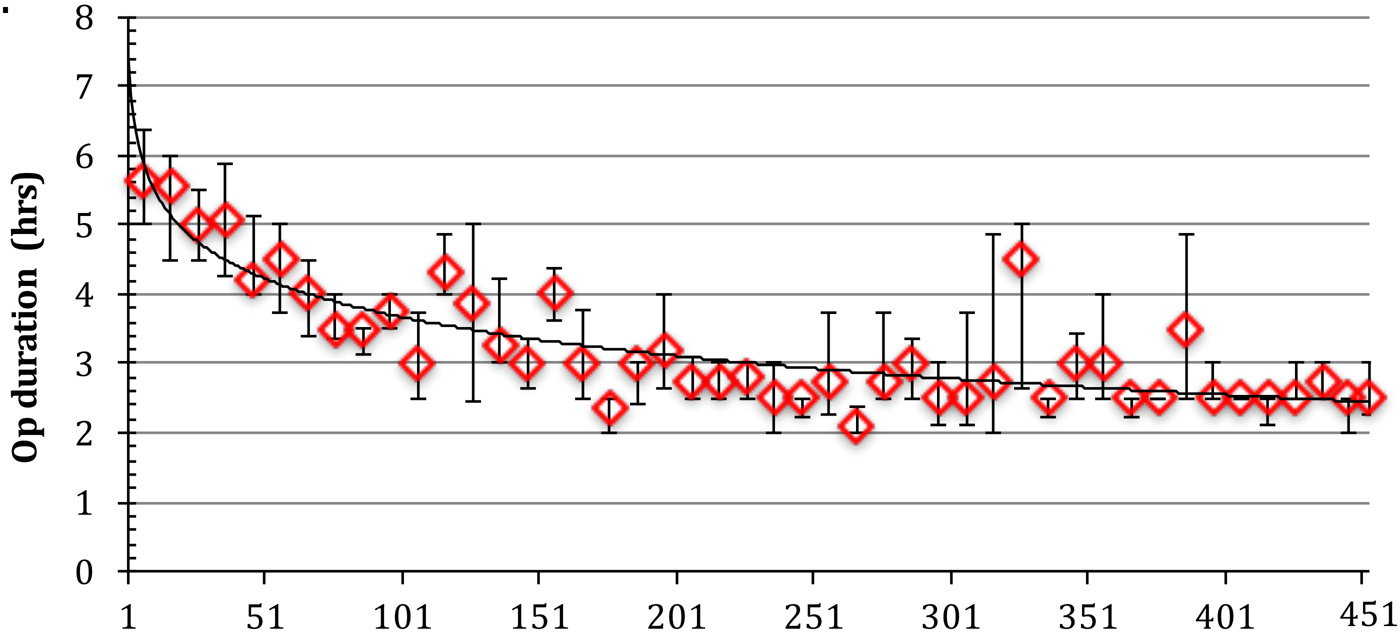
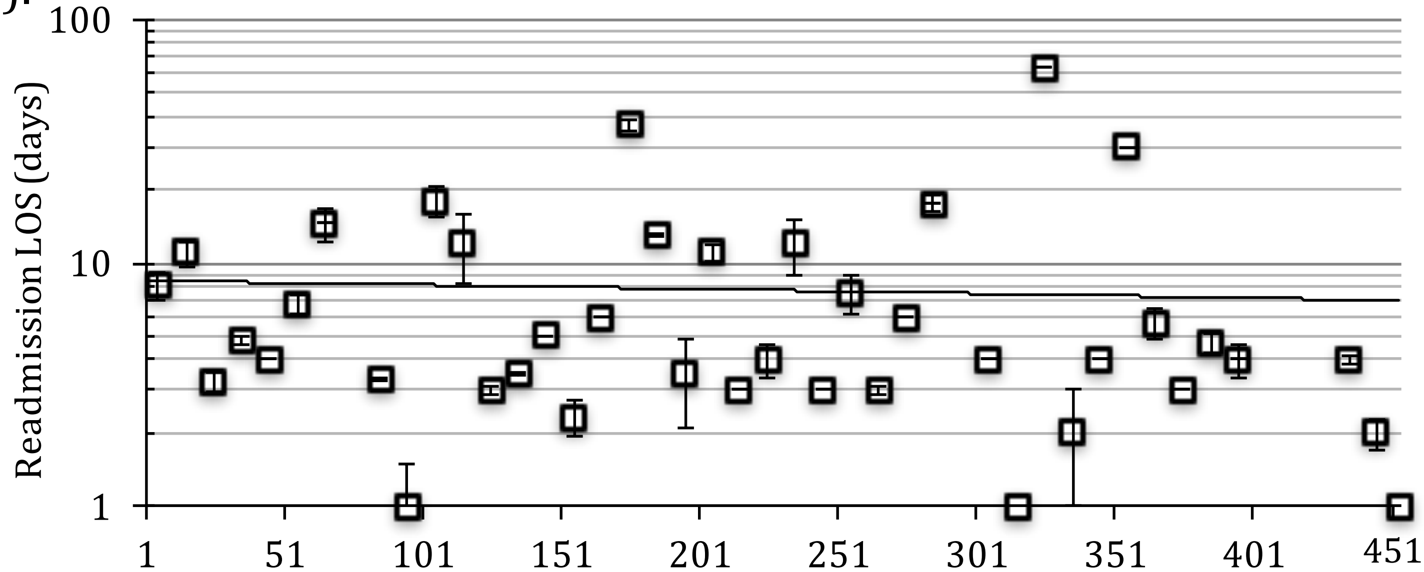

a).
T Test p=0.6
Number of lymph nodes
30.00
20.00
10.00
.00
ERAS
Non-ERAS
Mean: 10.7 10.3
St. dev: 4.7 5.8
b).
Soft tissue
Urothelial
Clear
1.7
2.5
3.3
5.8
95
92
Non-ERAS
ERAS
Chi Sq. p=0.4
0
20
40
60
80
100
Margin status (%)
c).
Overall survival
Non-ERAS
ERAS
Log rank p=0.9
Follow up (months)
d).
Bladder cancer specific survival
Log rank p=0.9
Follow up (months)

Figure 2

(a).




(b).




Supplementary Figure 1