Author's Accepted Manuscript

Early Oncologic Failure after Robot-assisted Radical Cystectomy: Results from the International Robotic Cystectomy Consortium

Ahmed A. Hussein , Matthias Saar , Paul R. May , Carl J. Wijburg , Lee Richstone , Andrew Wagner , Timothy Wilson , Bertram Yuh , Joan Palou Redorta , Prokar Dasgupta , Mohammad Shamim Khan , Mani Menon , James O. Peabody , Abolfazl Hosseini , Franco Gaboardi , Alexandre Mottrie , Koon-ho Rha , Ashok Hemal , Michael Stockle , John Kelly , Thomas J. Maatman , Abdullah Erdem Canda , Peter Wiklund , Khurshid A. Guru

PII: S0022-5347(16)31985-1
DOI: 10.1016/j.juro.2016.12.048
Reference: JURO 14266

To appear in: *The Journal of Urology*

Please cite this article as: Hussein AA, Saar M, May PR, Wijburg CJ, Richstone L, Wagner A, Wilson T, Yuh B, Redorta JP, Dasgupta P, Shamim Khan M, Menon M, Peabody JO, Hosseini A, Gaboardi F, Mottrie A, Rha Kh, Hemal A, Stockle M, Kelly J, Maatman TJ, Canda AE, Wiklund P, Guru KA, Early Oncologic Failure after Robot-assisted Radical Cystectomy: Results from the International Robotic Cystectomy Consortium, *The Journal of Urology*® (2017), doi: 10.1016/j.juro.2016.12.048.

Early Oncologic Failure after Robot-assisted Radical Cystectomy: Results from the International Robotic Cystectomy Consortium

Ahmed A. Hussein[1,2], Matthias Saar[3], Paul R. May[1], Carl J Wijburg[4] , Lee Richstone[5], Andrew Wagner[6], Timothy Wilson[7], Bertram Yuh[7], Joan Palou Redorta[8], Prokar Dasgupta[9], Mohammad Shamim Khan[9], Mani Menon[10], James O. Peabody[10], Abolfazl Hosseini[11], Franco Gaboardi[12] , Alexandre Mottrie[13], Koon-ho Rha[14], Ashok Hemal[15], Michael Stockle[3], John Kelly[16], Thomas J. Maatman[17], Abdullah Erdem Canda[18], Peter Wiklund[11], Khurshid A. Guru[1]

[1]Roswell Park Cancer Institute, Buffalo, NY, [2]Cairo University, Egypt, [3]University of the Saarland, Homburg Saar, Germany, [4] Rijnstate Hospital, Arnhem, the Netherlands, [5]The Arthur Smith Institute for Urology, New York, NY, [6]Beth Israel Deaconess Medical Center, Boston, MA, [7]City of Hope and Beckman Research Institute, Duarte, CA, [8]Fundacio Puigvert, Barcelona, Spain, [9]Guy's Hospital and King's College London School of Medicine, London, UK, [10]Henry Ford Health System, Detroit, MI, [11]Karolinska University Hospital, Stockholm, Sweden, [12]Luigi Sacco University Hospital, Milan, Italy, [13]Onze-Lieve-Vrouw Ziekenhuis, Aalast, Belgium, , [14]Yonsei University Health System Severance Hospital, Seoul, Korea, [15]Wake Forest University Baptist Medical Center, Winston-Salem, NC, [16]Division of Surgery and Interventional Science, University College London, Department of Urology, [17]Michigan Urological Clinic, Grand Rapids, MI., [18]Yildirim Beyazit University, School of Medicine, Ankara Ataturk Training and Research Hospital, Ankara, Turkey

Corresponding Author:

Khurshid A. Guru, MD

Elm & Carlton St Buffalo, NY 14263

Tel: 716-845-4155;

Fax:716-845-3300

Khurshid.guru@roswellpark.org

Professor of Oncology

Department of Urology, Roswell Park Cancer Institute

A.T.L.A.S (Applied Technology Laboratory for Advanced Surgery) Program

Keywords: Robot-assisted, cystectomy, recurrence, relapse, early, port-site, peritoneal carcinomatosis, outcomes, technique

Background: We sought to investigate the prevalence and variables associated with Early Oncologic Failure (EOF).

Methods: Retrospective review of the IRCC database of patients who underwent robot-assisted radical cystectomy (RARC) since 2003. The final cohort comprised 1894 patients (23 institutions from 11 countries). EOF was defined as any disease relapse within 3 months of RARC. All institutions were surveyed for the pneumoperitoneum pressure used, breach of oncological surgical principles and technique of specimen and lymph node removal. Multivariate model was fit to evaluate predictors of EOF. The Kaplan Meier method was used to depict disease-specific (DSS) and overall survival (OS) and Cox proportional regression analysis to evaluate predictors of DSS and OS.

Results: 305 patients (22%) experienced disease relapse, 220 (16%) distant, 154 (11%) local recurrence, 17 (1%) peritoneal carcinomatosis and 5 (0.4%) port-site recurrences. Seventy-one patients (5%) from 10 institutions developed EOF, and the incidence of EOF decreased from 10% in 2006 to 6% in 2015. On multivariate analysis, presence of any complication (OR 2.87; 95% CI 1.38-5.96; p=0.004), ≥pT3 disease (OR 3.73, 95% CI 2.00-6.97, p<0.001), and nodal involvement (OR 2.14, 95% CI 1.21-3.80, p=0.008) were significant predictors of EOF. Patients with EOF demonstrated worse DSS and OS (23% and 13%) at 1 and 3 years when compared to patients who experienced later or no recurrences (log rank p<0.001)

Conclusion: The incidence of EOF following RARC has decreased with time. Disease-related rather than technical-related factors play a major role in occurrence of EOF after RARC.

Introduction

Radical cystectomy (RC) with pelvic lymph node dissection (pLND) represents the gold standard for management of non-metastatic muscle invasive bladder cancer (MIBC) and refractory non-muscle invasive disease. More interest has been spurred in robot-assisted radical cystectomy (RARC) aiming to improve perioperative outcomes, including blood loss, transfusion rates, hospital stay and recovery without compromising oncological efficacy [1,2]. Consequently, the past decade has witnessed a paramount shift in the utilization of RARC (from <1% in 2004 to 13% in 2010) [2]. Nevertheless, much of the criticism to RARC has been attributed to lack of long term oncologic outcomes and patient selection bias. There have also been concerns regarding adherence to key oncologic tenets and induction of local pelvic, peritoneal and port-site recurrences during minimally invasive approaches to RC [3].

Despite aggressive management, more than half of patients with MIBC will relapse (locally or systemically), usually within the first 2 years after surgery with deleterious impact on survival [4]. Extent of the disease at the time of surgery or the breach of oncologic surgical may contribute to disease relapse. Known predictors of disease relapse include perioperative chemotherapy, extent of pLND, pathological T stage, lymph node status, and positive soft tissue surgical margins at cystectomy [5].

In this study we queried the multi-national, prospectively maintained, quality assurance database—the International Robotic Cystectomy Consortium (IRCC) to investigate the prevalence of early oncologic failure (EOF) after RARC. EOF was defined as any disease relapse within the first 3 months following surgery, among patients who underwent RARC over more than a decade, and further to investigate the possible factors contributing to EOF. To our

knowledge, this is the first paper to address possible early recurrences related to technical faults after RARC.

Methods

A retrospective review of 2460 patients from 29 institutions included in the IRCC database (I-97906) was performed. Institutions (n=566) that failed to provide updated data were excluded from the study. The final cohort comprised 1894 patients from 23 institutions across 11 countries who were treated with RARC since 2003 (Figure 1). Data were reviewed for age, gender, body mass index [BMI], and American Society of Anesthesiologists [ASA] score, preoperative characteristics (neoadjuvant chemotherapy, prior abdominal surgery, and clinical staging), operative variables (type and technique of diversion, operative time, estimated blood loss, and blood transfusion), perioperative outcomes (complications, readmissions, hospital and intensive care unit stay), and pathologic outcomes (staging, lymph node yield and soft tissue surgical margins). Technique of RARC and urinary diversion, and follow up differed among institutions.

Disease relapses were defined in terms of recurrence type (local, distant, port-site or peritoneal carcinomatosis), anatomical site, and timing since cystectomy (EOF—defined as any disease relapse within 90 days following RARC; versus later; or no recurrences). Ninety days was chosen as a cut off for EOF so that these recurrences are most likely related to the surgical technique rather than the disease severity. All patients had at least 3 months of follow up. Institutions having patients with EOF were surveyed for their use of pneumoperitoneum pressure, breach of oncological principles during RARC including spillage of urine during the procedure, and the technique of specimen and lymph node removal.

Descriptive statistics were used to summarize the data. Univariable associations were statistically assessed using Pearson Chi-square or Fisher's Exact test. Univariate and multivariate (stepwise variable selection) logistic regression models were fit to evaluate preoperative, operative, and postoperative predictors of EOF following RARC. The Kaplan Meier method was used to depict disease-specific (DSS) and overall survival (OS) for patients with EOF versus those who did not exhibit EOF. All tests were two-sided, with statistical significance defined as $p<0.05$. All statistical analyses were performed using SAS software (version 9.4, SAS Institute Inc., Cary, NC).

Results

Of the 1894 patients included in the study, 30 patients died because of non-cancer related causes and 484 had incomplete recurrence data. A total of 1380 patients had complete data were included in the final analysis (Figure 1). After a mean follow up of 24 months, 305 patients (22%) experienced disease relapse; 220 (16%) developed distant, 154 (11%) local recurrence, 17 (1%) peritoneal carcinomatosis and 5 (0.4%) port-site recurrences. Seventy-one patients (5%) from 10 institutions developed EOF, and the incidence of EOF decreased from 10% in 2006 to 6% in 2015 (Figure 2). Compared with patients who developed later or no recurrences, patients who experienced EOF significantly experienced higher estimated blood loss, received blood transfusion and adjuvant chemotherapy more frequently, and demonstrated higher complication rate. EOF patients when compared to those who developed recurrences > 3 months and those without any recurrences, had higher prevalence of pT3, (75% versus 68% and 31%, respectively, $p<0.001$), and positive nodal disease (42% versus 36% and 15%, respectively, $p<0.0001$). They had higher positive soft tissue surgical margins compared to patients who did not have any

recurrences (13% versus 6%, p<0.001) (Table 1). Eight patients experienced EOF despite having organ confined disease (<pT3 and N0). Of these, 3 had breech of oncologic surgical principles.

Overall, the pelvis was the commonest site for local recurrence (51%). The lung was the most common site for distant recurrence (24%) followed by bone metastasis (21%) and extrapelvic lymph node (20%). When compared to those who developed later recurrences, patients with EOF experienced more pelvic recurrences (37% versus 22%, p=0.02), extrapelvic lymph node metastasis (23% versus 12%, p=0.03), and bone metastasis (24% versus 12%, p=0.03) (Table 2).

We surveyed the 10 institutions that had patients with EOF. Four institutions operated at higher pneumoperitoneum pressures (≥14 mmHg), while the remaining operated at ≤12 mmHg. Of patients who developed EOF, 4 patients from 2 institutions had possible disseminated disease on preoperative metastatic work up. Breaching of oncologic principles occurred in 6 patients (Table 3).

On multivariate analysis, presence of any complication (Odds ratio [OR] 2.87; 95% confidence interval [CI] 1.38-5.96; p=0.004), extravesical disease (OR 3.73, 95% CI 2.00-6.97, p<0.001), and nodal involvement (OR 2.14, 95% CI 1.21-3.80, p=0.008) were significant predictors of EOF (Table 4). Patients with EOF demonstrated worse DSS (32% and 26%) and OS (23% and 13%) at 1 and 3 years when compared to patients who experienced later recurrences (DSS 81% and 39%; OS 74% and 25%) and no recurrences (DSS 99% and 96%; OS 93% and 82%) (log rank p<0.001) (Figures 3 and 4). On Cox proportional hazards analysis, patients with pT≥3, nodal involvement, and presence of positive soft tissue surgical margins

exhibited worse DSS and OS. Patients who received neobladders demonstrated better OS (HR 0.49, 95% CI 0.31-0.75, p=0.001) (Table 5).

Discussion

Despite aggressive management, disease relapse after RC will occur in half of the patients which significantly reduces survival. The pathogenesis of recurrence following RC is yet to be determined but it is probably multifactorial. Tumor aggressiveness, occult metastatic disease at the time of surgery, inhibited host immune response, laparoscopy-related factors (gas insufflation and desufflation), or breaching of oncologic surgical principles (vigorous surgical manipulation, specimen morcellation, entry into the bladder, and retrieval method) have been investigated [6-8]. The contribution of carbon dioxide (CO_2) pneumoperitoneum deployed in minimally invasive surgery remains unknown. Prior animal studies suggested that CO_2 pneumoperitoneum may inhibit peritoneal immune response against malignant urothelial cells and may be contributing to recurrences within the pelvis and at port sites [9].

We identified and characterized patients who developed EOF after RARC. Five percent of our patients experienced EOF, of these 63 (89%) had advanced disease (≥pT3 +/- positive nodal disease), and oncologic principles were breached in 6 (8%), 3 of them had organ confined disease (<pT3/N0). For any RC performed (open and RARC), tumor stage, nodal involvement, lympho-vascular invasion and positive soft tissue surgical margins are the most powerful predictors of tumor recurrence [1,10]. On multivariable analysis, patients with extravesical or nodal disease were at least twice as likely to develop EOF. During RC, tumor spillage may occur with extravesical disease, extensive nodal involvement, or due to technical error, which may risk seeding the peritoneal cavity with urothelial cell carcinoma (UCC). The potential seeding of

tumor cells as a source for the local recurrences is a concern during open and minimally invasive RC. While much attention has been given to reporting negative soft tissue surgical margins, measures to prevent urine leakage from the urethra or the ureters should be routine [11]. A survey of 162 members of the Society of Urologic Oncology revealed that 71% use urethral catheterization, 44% clamp the urethra and 22% ligate or clip the urethra at RC to prevent urine spillage [12]. The Roswell Park Cancer Institute group initiated a novel approach to objectively evaluate the presence of cancer cells and their gene-related products in the pelvis and pneumoperitoneum during RARC [13]. UCC, presumably from tumor spillage during transurethral resection of bladder tumor (TURBT) or after open RC, or from circulating tumor cells, has been reported in abdominal wounds, suprapubic tube sites, in the pelvic cavity (resection bed), and on the psoas muscle [14-16]. The use of intravesical instillation of chemotherapy after TURBT to prevent tumor seeding and decrease recurrence inspired some surgeons to use sterile water to induce hypotonic lysis of any remaining UCCs despite the unproven efficacy [17]. This raises questions about the possible role of intraperitoneal chemotherapy similar to ovarian, gastric and colorectal malignancies [18,19]. The use of prophylactic radiation or systemic chemotherapy in the setting of UCC spillage remains unclear with significant potential morbidity.

It is worth mentioning that the incidence of EOF decreased with time (from 10% in 2006 to 6% in 2015). If these recurrences are surgery-related, then this trend might be explained by the evolution of the technique of RARC, the learning curve, experience with the procedure, and comfort with the robot-assisted platform for surgery [20]. Blood transfusion and poor renal function have been proposed to induce recurrences by affecting the immunity and DNA repair [21]. Although patients who had any recurrence received blood transfusion more frequently, it did not reach statistical significance on multivariable analysis. Patients who received neobladders

exhibited better OS (HR 0.49). Possible explanation is patient selection, where patients who received neobladders are generally of better health and less comorbidities, and further explains why the type of diversion affected OS and not CSS. Patients who developed postoperative complications were approximately 3 times more likely to develop EOF. Complications (especially intraoperatively or early in the postoperative period) may be a result of suboptimal surgical performance and therefore impact cancer control and patient survival [22].

To our knowledge, no study reported early oncologic failures, but time to oncologic failure has been shown to be a significant predictor of OS after open RC [4]. Nine percent early unexpected relapses were observed in a cohort of patients with favorable pathology (pT2 N0 Ro or less) in the European Association of Urology Section of Uro-Technology (ESUT) cohort [23]. Similar to our study, they found that disease stage rather than technical factors is the main reason for early failures. However, they defined early failure as disease recurrence within 24 months after surgery. Since most recurrences after RC develop within the first 2 years after surgery, a period of 24 months will make it harder to differentiate recurrences that occur due to tumor biology from those that may have occurred due to breech of oncologic surgical principles. For this reason, we defined EOF as any disease relapse that occurred within the first 3 months after RARC. Patients with EOF demonstrated worse DSS and OS when compared to patients who experienced later recurrences and no recurrences (log rank $p<0.0001$). Early failures may be a result of unrecognized metastatic disease before surgery, or occurs as a result of tumor spillage during the procedure. Current imaging techniques lack adequate sensitivity and specificity, especially in low-volume metastatic disease. Moreover, it has been shown that in patients with presumably organ confined disease; micrometastatic disease was detected using RT-PCR studies in up to one third of patients with histologically negative lymph nodes [24,25]. Similarly, patients

with colorectal, ovarian and urothelial cancers with local relapse, port site seeding and early metastasis after minimally invasive surgery have been previously reported [20,26]. It remains difficult to determine whether such recurrences occurred due to the primary tumor stage or as a result of the surgical procedure itself. The use of quality scoring can objectively assess and quantify surgical performance and assess the surgical factors that may be contribute to EOF [22].

Interestingly, pneumoperitoneum pressure was not associated with EOF. Prior reports suggested that high and/or pulsatile pneumoperitoneum, especially in lengthy procedures, may enhance migration tumor cells from the venous plexus of the bladder (whose pedicles are squeezed throughout the procedure) and contribute to early tumor recurrence [6,27,28]. Identifying patients who are at higher risk for EOF will provide valuable information for technique modification, preventive measures, patient counselling, risk stratification and prognostication.

Despite the emerging role of RARC as a viable alternative to the open traditional approach, criticisms regarding the RARC literature include lack of long term survival data, inherent patient selection bias, in addition to longer operative times and associated cost. In our cohort, EOF patients experienced more extrapelvic lymph node metastasis when compared to later recurrences (23% versus 12%, p=0.03). Nguyen et al suggested that recurrence patterns may differ between open and RARC. They reported higher incidence of extrapelvic lymph node metastasis and peritoneal carcinomatosis with RARC [29]. Less thorough lymph node dissection with RARC and possible peritoneal dissemination of malignant urothelial cells with pneumoperitoneum have been considered responsible for these findings [30]. However, the lymph node yield in the same study was similar for either approach and the differences reported were not statistically significant. Additionally, the approach to performing cystectomy was not a significant predictor on multivariable analysis [30]. In our cohort, peritoneal carcinomatosis

occurred in less than 1% of all patients, and represented 4% of all recurrences. The difference in peritoneal carcinomatosis rates may be in part attributed to variation in defining carcinomatosis, sample size, follow up duration and perhaps surgical technique.

Despite the uniqueness of this study, the retrospective study design and the multi-institutional and multi-national databases have their recognized limitations. Recall bias may be an issue when looking at the surgical factors affecting EOF. Also, heterogeneity in surgical techniques, pathological examination and institutional follow-up protocols may lead to variation in reporting outcomes. However, the IRCC represents the largest multinational database for RARC that captures and reflects real-world practices. The lack of similar open reports examining early failures in open RC literature limits any comparison with RARC.

Conclusion

The incidence of EOF following RARC is low and has decreased with time. Disease-related rather than technical or laparoscopy-related factors play a major role in occurrence of EOF after RARC.

Acknowledgements: Vattikuti Foundation Collective Quality Initiative and Roswell Park Cancer Institute Alliance Foundation

References

1. Raza SJ, Wilson T, Peabody JO, et al. Long-term oncologic outcomes following robot-assisted radical cystectomy: results from the International Robotic Cystectomy Consortium. *Eur Urol.* 2015;68(4):721-728.
2. Leow JJ, Reese SW, Jiang W, et al. Propensity-matched comparison of morbidity and costs of open and robot-assisted radical cystectomies: a contemporary population-based analysis in the United States. *Eur Urol.* 2014;66(3):569-576.
3. Karam JA, Sagalowsky AI. Minimally invasive radical cystectomy for bladder cancer? *Lancet Oncol.* 2008;9(4):317-318.
4. Sonpavde G, Khan MM, Lerner SP, et al. Disease-free survival at 2 or 3 years correlates with 5-year overall survival of patients undergoing radical cystectomy for muscle invasive bladder cancer. *J Urol.* 2011;185(2):456-461.
5. Huguet J. Follow-up after radical cystectomy based on patterns of tumour recurrence and its risk factors. *Actas Urol Esp.* 2013;37(6):376-382.
6. Jacobi CA, Wenger FA, Ordemann J, Gutt C, Sabat R, Muller JM. Experimental study of the effect of intra-abdominal pressure during laparoscopy on tumour growth and port site metastasis. *Br J Surg.* 1998;85(10):1419-1422.
7. Stolla V, Rossi D, Bladou F, Rattier C, Ayuso D, Serment G. Subcutaneous metastases after coelioscopic lymphadenectomy for vesical urothelial carcinoma. *Eur Urol.* 1994;26(4):342-343.
8. Tsivian A, Sidi AA. Port site metastases in urological laparoscopic surgery. *J Urol.* 2003;169(4):1213-1218.
9. Ost MC, Patel KP, Rastinehad AR, et al. Pneumoperitoneum with carbon dioxide inhibits macrophage tumor necrosis factor-alpha secretion: source of transitional-cell carcinoma port-site metastasis, with prophylactic irrigation strategies to decrease laparoscopic oncologic risks. *J Endourol.* 2008;22(1):105-112.
10. Kluth LA, Rieken M, Xylinas E, et al. Gender-specific differences in clinicopathologic outcomes following radical cystectomy: an international multi-institutional study of more than 8000 patients. *Eur Urol.* 2014;66(5):913-919.
11. Williams SB, Kamat AM, Lamm DL. Pelvic recurrence after radical cystectomy: a call to arms. *BJU Int.* 2015;116(2):172-173.
12. Via KJ, Burns KM, Lamm DL. Tumor implantation: a rare but potentially preventable cause of death in cystectomy patients. *Can J Urol.* 2010;17(3):5216-5218.
13. Hussein AA, Ma Y, Azabdaftari G, et al. MP 38-05 Tumor dessimination during robot-assisted radical cystectomy: does the emperor have no clothes? *The Journal of Urology.* 2016;195(4, Supplement):e534-e535.
14. Breul J, Block T, Breidenbach H, Hartung R. Implantation metastasis after a suprapubic catheter in a case of bladder cancer. *Eur Urol.* 1992;22(1):86-88.
15. Chakravarti A, Day DW, MacDermott S. Extravesical transitional cell carcinoma as a result of implantation after perforation of the bladder. *BJU Int.* 2000;85(9):1150-1151.
16. Engilbertsson H, Aaltonen KE, Bjornsson S, et al. Transurethral bladder tumor resection can cause seeding of cancer cells into the bloodstream. *J Urol.* 2015;193(1):53-57.
17. Abaza R, Keck RW, Selman SH. Intraperitoneal chemotherapy for the prevention of transitional cell carcinoma implantation. *J Urol.* 2006;175(6):2317-2322.

18. Jaaback K, Johnson N, Lawrie TA. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. *Cochrane Database Syst Rev.* 2016(1):CD005340.
19. Kang LY, Mok KT, Liu SI, et al. Intraoperative hyperthermic intraperitoneal chemotherapy as adjuvant chemotherapy for advanced gastric cancer patients with serosal invasion. *J Chin Med Assoc.* 2013;76(8):425-431.
20. El-Tabey NA, Shoma AM. Port site metastases after robot-assisted laparoscopic radical cystectomy. *Urology.* 2005;66(5):1110.
21. Nguyen DP, Al Hussein Al Awamlh B, O'Malley P, et al. Factors impacting the occurrence of local, distant and atypical recurrences after robot-assisted radical cystectomy: a detailed analysis of 310 patients. *J Urol.* 2016.
22. Hussein AA, Dibaj S, Hinata N, et al. Development and Validation of a Quality Assurance Score for Robot-assisted Radical Cystectomy: A 10-year Analysis. *Urology.* 2016.
23. Albisinni S, Fossion L, Oderda M, et al. Critical Analysis of Early Recurrence after Laparoscopic Radical Cystectomy in a Large Cohort by the ESUT. *J Urol.* 2016;195(6):1710-1717.
24. Tarin TV, Power NE, Ehdaie B, et al. Lymph node-positive bladder cancer treated with radical cystectomy and lymphadenectomy: effect of the level of node positivity. *Eur Urol.* 2012;61(5):1025-1030.
25. Marin-Aguilera M, Mengual L, Burset M, et al. Molecular lymph node staging in bladder urothelial carcinoma: impact on survival. *Eur Urol.* 2008;54(6):1363-1372.
26. Carmignani CP, Sugarbaker PH. Regional lymph node metastasis from port site implants after laparoscopic surgery. *Surg Endosc.* 2004;18(12):1818.
27. Kazemier G, Bonjer HJ, Berends FJ, Lange JF. Port site metastases after laparoscopic colorectal surgery for cure of malignancy. *Br J Surg.* 1995;82(8):1141-1142.
28. Hewett PJ, Thomas WM, King G, Eaton M. Intraperitoneal cell movement during abdominal carbon dioxide insufflation and laparoscopy. An in vivo model. *Dis Colon Rectum.* 1996;39(10 Suppl):S62-66.
29. Nguyen DP, Al Hussein Al Awamlh B, Wu X, et al. Recurrence patterns after open and robot-assisted radical cystectomy for bladder cancer. *Eur Urol.* 2015;68(3):399-405.
30. Pourmalek F, Abdi H, Black PC. Re: Daniel P. Nguyen, Bashir Al Hussein Al Awamlh, Xian Wu, et al. Recurrence Patterns After Open and Robot-assisted Radical Cystectomy for Bladder Cancer. Eur Urol 2015;68:399-405. *Eur Urol.* 2016;69(3):e35.

Table 1. Demographics, clinical characteristics and perioperative outcomes of patients who experienced EOF after RARC versus those who did not.

Preoperative parameters	**EOF**	**Later Recurrence**	**No Recurrence**	**p-value**
N of patients (%)	71	234	1075	-
Age at cystectomy, mean (SD) (yr)	64 (13)	68 (10)	67 (10)	0.02
Gender, Males n (%)	47 (66)	176 (75)	788 (74)	0.31
Body Mass Index, mean (SD) (kg/m^2)	26.7 (5.1)	27.2 (5.5)	27.7 (5.2)	0.20
ASA score, mean (SD)	2 (0.70)	2 (0.65)	2 (0.67)	0.38
Prior abdominal/pelvic surgery, n (%)	26 (52)	69 (46)	299 (48)	0.76
Neo-adjuvant chemotherapy, n (%)	16 (25)	45 (20)	207 (21)	0.68
Perioperative outcomes				
Type of diversion, Ileal conduit, n (%)	55 (86)	188 (87)	810 (81)	0.08
Technique of diversion, Intracorporeal, n (%)	39 (75)	127 (72)	642 (82)	0.007
Operative time, median (min) (IQR)	392 (328-474)	373 (316- 454)	374 (311- 451)	0.65
Estimated blood loss, mean (ml)	541 (690)	498 (417)	383 (411)	<0 .001
Blood Transfusion, n (%)	7 (10)	25 (11)	67 (6)	0.038
Adjuvant chemotherapy, n (%)	29 (45%)	94 (44%)	72 (8%)	< 0.001
Hospital stay, mean (SD) (d)	12 (10)	12 (9)	12 (12)	0.32
Intensive Care Unit stay, mean (SD) (d)	1 (3)	1 (3)	1 (2)	0.70
Postoperative complications, n (%)				
• Any complication	53 (75)	147 (63)	615 (57)	0.007
• Clavien 3-5	14 (20)	27 (12)	131 (12)	0.159
• 30-d complications	29 (41)	76 (33)	294 (27)	0.001
• 30-90 d complications	7 (10)	17 (7)	60 (6)	
• > 90-d complications	4 (6)	28 (12)	75 (7)	
Follow up, median (months) (IQR)	4 (3-11)	15 (9-27)	19 (8-32)	< 0.001
Time to recurrence, median (months) (IQR)	2 (1-3)	8 (5-17)	-	
Pathological outcomes				
Pathologic T stage, ≥pT3, n (%)	51 (75)	148 (68)	317 (31)	< 0.001
Lymph node yield, mean	16 (10)	18 (12)	18 (11)	0.402
N positive, n (%)	30 (42)	84 (36)	159 (15)	< 0.001
Positive surgical margins, n (%)	9 (13)	31 (13)	65 (6)	< 0.001
EOF, early oncologic failure; SD, standard deviation; Kg/m^2, Kilogram per square meters; Ml, milliliter				

Table 2. Sites of disease relapse as a proportion of all relapses (distant+local)

Local recurrence	**EOF**	**Later recurrences**	**p-value**
Pelvis	26 (37)	52 (22)	0.02
Vagina	1 (1)	3 (1)	1.00
Rectum	4 (6)	9 (4)	0.51
Perineum	4 (6)	8 (3)	0.49
Urethra	0	6 (3)	0.34
Penile	2 (3)	0	0.06
Neobladder/Conduit	2 (3)	2 (1)	0.24
Kidney	1 (1)	3 (1)	1.00
Multiple Local	7 (10)	15 (6)	0.48
Unidentified site	2 (3)	34 (15)	NA
Distant recurrence	**EOF**	**Later recurrences**	**p-value**
Nodal	16 (23)	27 (12)	0.03
Lung	11 (15)	41 (18)	0.83
Liver	10 (14)	15 (6)	0.07
Bone	17 (24)	29 (12)	0.03
Brain	3 (4)	2 (1)	0.09
Abdominal wall	2 (3)	5 (2)	0.67
Multiple distant	17 (24)	24 (10)	0.006
Unidentified site	7 (10)	88 (38)	NA
Peritoneal carcinomatosis	6 (8)	11 (5)	0.25
Port-site recurrence	3 (4)	2 (1)	0.09
Local and distant recurrence	20 (28)	53 (23)	0.43

Table 3. Surveys collected from the lead surgeons of the institutions whose patients experienced EOF.

Survey	**n (%)**
Patients with EOF, n	71
Institutions, n	10
Suspicious preoperative metastatic work up, n (%)	3 (4)*
Pneumoperitoneum pressure used (12 or less mmHg), n (%)	13 (18)
Inadvertent Bladder Entry	1 (1)
Urine spillage	2 (3)
Tumor Spillage	2 (3)
Ureters and urethra not clipped before extirpation	0
Specimen (bladder/Lymph nodes) not retrieved in a bag	1 (1)
* Two patients had possible nodal disease and 1 had possible lung metastasis on preoperative metastatic work up	

Table 4. Univariate and multivariable regression modeling predictors for EOF (stepwise variable selection)

Variables [Reference]	Univariate			Multivariate		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Preoperative parameters						
Age at cystectomy	0.97	(0.95, 0.99)	0.01	-	-	-
Gender [Female]	0.69	(0.43, 1.14)	0.14	-	-	-
Body Mass Index	0.97	(0.92, 1.02)	0.18	-	-	-
ASA score	0.77	(0.52, 1.13)	0.18	-	-	-
Neo-adjuvant chemotherapy	1.28	(0.72, 2.29)	0.41	-	-	-
Operative						
Type of diversion [Ileal Conduit]	0.73	(0.36, 1.50)	0.39	-	-	-
Technique of diversion [Extracorporeal]	0.73	(0.38, 1.40)	0.35	-	-	-
Operative time	1.08	(0.94, 1.23)	0.28	-	-	-
Estimated blood loss	1.05	(1.00, 1.09)	0.03	-	-	-
Blood Transfusion	1.45	(0.64, 3.25)	0.37	-	-	-
Adjuvant therapy	4.45	(2.66, 7.47)	< 0.001	-	-	-
Intensive care unit stay	1.02	(0.90, 1.16)	0.76	-	-	-
Hospital stay	1.00	(0.98, 1.02)	0.91	-	-	-
Any complication	2.11	(1.22, 3.65)	0.006	2.87	(1.38, 5.96)	0.004
Clavien ≥ 3 complications	1.79	(0.97, 3.29)	0.06	-	-	-
Pneumoperitoneum pressure [12mmHg]	1.47	(0.79, 2.76)	0.22	-	-	-
Breaching of oncologic principles [No]	1.52	(0.86, 2.71)	0.15	-	-	-
Pathologic						
≥pT3 stage	4.95	(2.82, 8.67)	< 0.001	3.73	(2.00, 6.97)	< 0.001
pN1	3.21	(1.96, 5.25)	< 0.001	2.14	(1.21, 3.80)	0.008
Lymph Node Yield	0.99	(0.96, 1.01)	0.22	-	-	-
Positive surgical margins [No]	1.83	(0.88, 3.80)	0.10	-	-	-

RARC, robotic-assisted laparoscopic radical cystectomy; SD, standard deviation; NA, odds ratio calculation impossible due to zero cell count(s)

Table 5. Cox proportional hazards modelling predictors of DSS and OS

Overall survival			
Parameter	HR	95% CI	p-value
≥pT3	3.302	2.56-4.25	<.0001
pN1	1.796	1.40-2.30	<.0001
Positive margins	1.578	1.13-2.21	0.0076
Neobladders	0.484	0.31-0.75	0.0012
Disease-specific survival			
Parameter	HR	95% CI	p-value
≥pT3	4.94	3.30-7.40	<0.0001
pN1	2.26	1.58-3.22	<0.0001
Positive margins	1.64	1.03-2.63	0.04

Figure 1. Study cohort

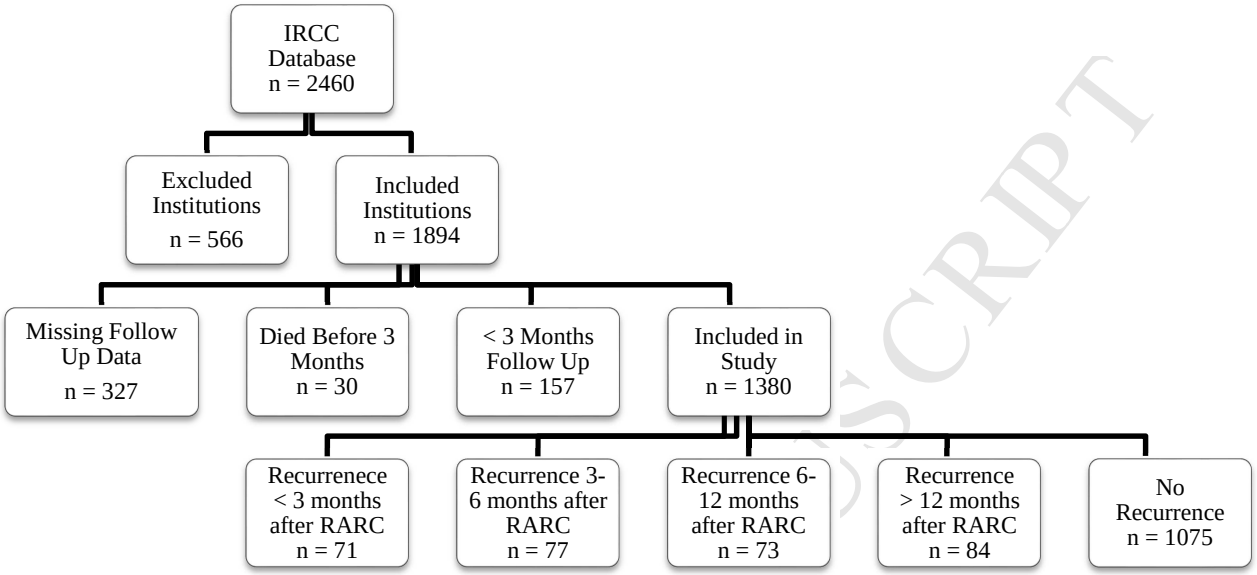


Figure 2. EOF cases as they occurred with time (Linear Regression Test p = 0.15)

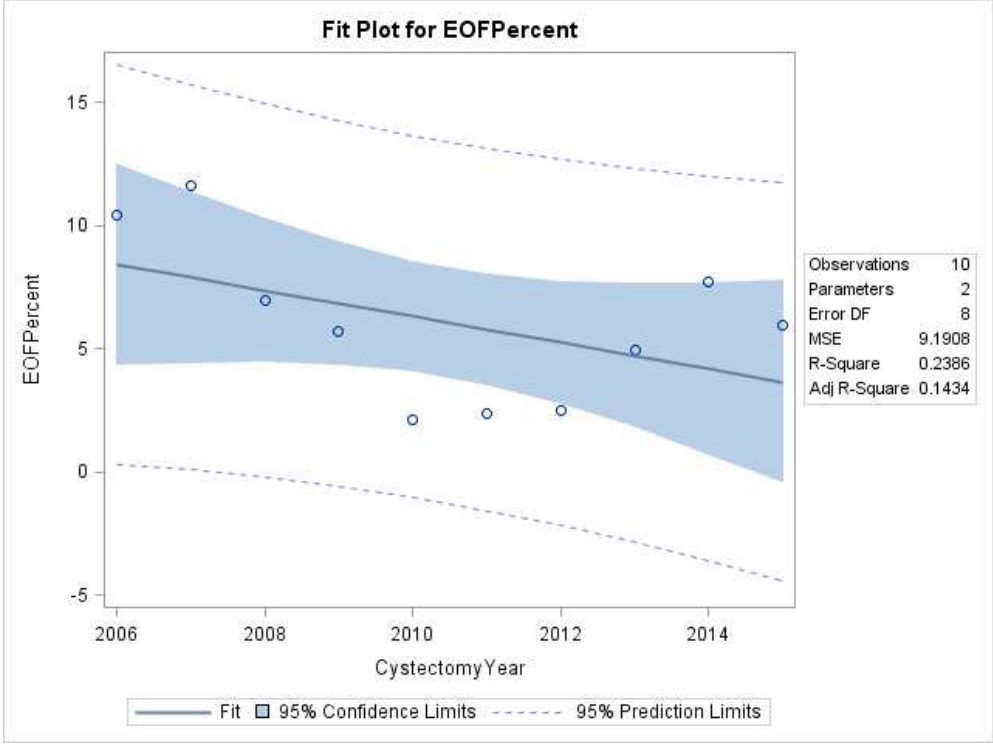
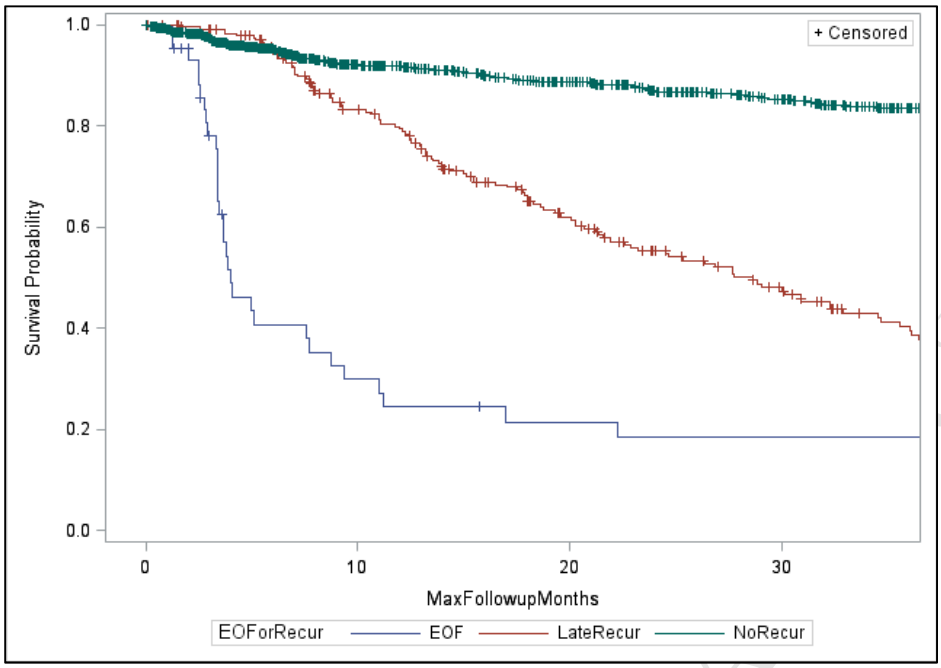


Figure 3. Kaplan Meier curves for OS (log rank p <0.001)



EOF Patients

Months	0-6	6-12	12-18	18-24	24-30	30-36
Patients At Risk	71	30	12	8	6	6
Patient Deaths	36	14	3	2	0	0
Survival %	46.6	22.8	16.7	12.5	12.5	12.5

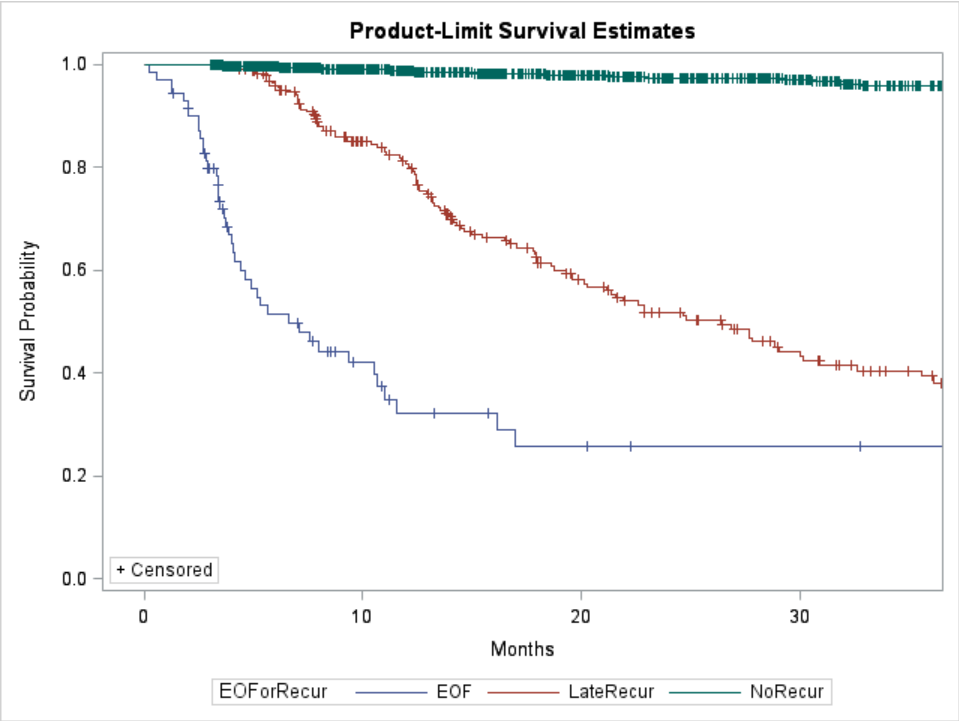
Later Recurrence

Months	0-6	6-12	12-18	18-24	24-30	30-36
Patients At Risk	234	211	152	100	68	49
Patient Deaths	14	42	40	24	14	10
Survival %	93.9	74.4	54.1	40.6	31.8	24.8

No Recurrence

Months	0-6	6-12	12-18	18-24	24-30	30-36
Patients At Risk	1075	894	698	552	434	312
Patient Deaths	28	32	23	15	10	12
Survival %	97.2	93.4	90.0	87.3	85.0	81.5

Figure 4. Kaplan Meier curves for DSS (log rank p <0.001)



EOF Patients

Months	0-6	6-12	12-18	18-24	24-30	30-36
Patients At Risk	71	30	12	8	6	6
Patient Deaths	31	9	2	0	0	0
Survival %	51.4	32.2	25.8	25.8	25.8	25.8

Later Recurrence

Months	0-6	6-12	12-18	18-24	24-30	30-36
Patients At Risk	234	211	152	100	68	49
Patient Deaths	9	31	32	16	9	5
Survival %	96.0	80.8	62.6	51.8	44.3	39.4

No Recurrence

Months	0-6	6-12	12-18	18-24	24-30	30-36
Patients At Risk	1075	894	698	552	434	312
Patient Deaths	4	7	4	3	20	3
Survival %	99.6	98.7	98.1	97.5	96.9	95.9

List of Abbreviations

- Robot-assisted radical cystectomy (RARC)
- Early Oncologic Failure (EOF).
- Radical cystectomy (RC)
- Pelvic lymph node dissection (pLND)
- Muscle invasive bladder cancer (MIBC)
- International Robotic Cystectomy Consortium (IRCC)
- Body mass index (BMI)
- American Society of Anesthesiologists (ASA)
- Odds ratio (OR)
- Confidence interval (CI)
- Transurethral resection of bladder tumor (TURBT)
- Urothelial carcinoma (UCC)
- Disease-specific (DSS)
- Overall survival (OS)