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DOI:

[10.1016/j.juro.2016.12.048](https://doi.org/10.1016/j.juro.2016.12.048)

*Document Version*

Peer reviewed version

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*Citation for published version (APA):*

Hussein, A. A., Saar, M., May, P. R., Wijburg, C. J., Richstone, L., Wagner, A., ... Guru, K. A. (2017). Early Oncologic Failure after Robot-assisted Radical Cystectomy: Results from the International Robotic Cystectomy Consortium. *Journal of Urology*, 197(6), 1427-1436. <https://doi.org/10.1016/j.juro.2016.12.048>

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

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PII: S0022-5347(16)31985-1  
DOI: [10.1016/j.juro.2016.12.048](https://doi.org/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.

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

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

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

19 **Corresponding Author:**

20 Khurshid A. Guru, MD

21 Elm & Carlton St Buffalo, NY 14263

22 Tel: 716-845-4155;

23 Fax:716-845-3300

24 [Khurshid.guru@roswellpark.org](mailto:Khurshid.guru@roswellpark.org)

25 Professor of Oncology

26 Department of Urology, Roswell Park Cancer Institute

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

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

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

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

58 **Results:** 305 patients (22%) experienced disease relapse, 220 (16%) distant, 154 (11%) local  
59 recurrence, 17 (1%) peritoneal carcinomatosis and 5 (0.4%) port-site recurrences. Seventy-one  
60 patients (5%) from 10 institutions developed EOF, and the incidence of EOF decreased from  
61 10% in 2006 to 6% in 2015. On multivariate analysis, presence of any complication (OR 2.87;  
62 95% CI 1.38-5.96;  $p=0.004$ ),  $\geq pT3$  disease (OR 3.73, 95% CI 2.00-6.97,  $p<0.001$ ), and nodal  
63 involvement (OR 2.14, 95% CI 1.21-3.80,  $p=0.008$ ) were significant predictors of EOF. Patients  
64 with EOF demonstrated worse DSS and OS (23% and 13%) at 1 and 3 years when compared to  
65 patients who experienced later or no recurrences (log rank  $p<0.001$ )

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

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## 70 Introduction

71 Radical cystectomy (RC) with pelvic lymph node dissection (pLND) represents the gold  
72 standard for management of non-metastatic muscle invasive bladder cancer (MIBC) and  
73 refractory non-muscle invasive disease. More interest has been spurred in robot-assisted radical  
74 cystectomy (RARC) aiming to improve perioperative outcomes, including blood loss, transfusion  
75 rates, hospital stay and recovery without compromising oncological efficacy<sup>1,2</sup>. Consequently,  
76 the past decade has witnessed a paramount shift in the utilization of RARC (from <1% in 2004 to  
77 13% in 2010)<sup>2</sup>. Nevertheless, much of the criticism to RARC has been attributed to lack of long  
78 term oncologic outcomes and patient selection bias. There have also been concerns regarding  
79 adherence to key oncologic tenets and induction of local pelvic, peritoneal and port-site  
80 recurrences during minimally invasive approaches to RC<sup>3</sup>.

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

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

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

#### 94 **Methods**

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

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

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

## 122 **Results**

123 Of the 1894 patients included in the study, 30 patients died because of non-cancer related  
124 causes and 484 had incomplete recurrence data. A total of 1380 patients had complete data were  
125 included in the final analysis (Figure 1). After a mean follow up of 24 months, 305 patients  
126 (22%) experienced disease relapse; 220 (16%) developed distant, 154 (11%) local recurrence, 17  
127 (1%) peritoneal carcinomatosis and 5 (0.4%) port-site recurrences. Seventy-one patients (5%)  
128 from 10 institutions developed EOF, and the incidence of EOF decreased from 10% in 2006 to  
129 6% in 2015 (Figure 2). Compared with patients who developed later or no recurrences, patients  
130 who experienced EOF significantly experienced higher estimated blood loss, received blood  
131 transfusion and adjuvant chemotherapy more frequently, and demonstrated higher complication  
132 rate. EOF patients when compared to those who developed recurrences  $> 3$  months and those  
133 without any recurrences, had higher prevalence of pT3, (75% versus 68% and 31%, respectively,  
134  $p < 0.001$ ), and positive nodal disease (42% versus 36% and 15%, respectively,  $p < 0.0001$ ). They  
135 had higher positive soft tissue surgical margins compared to patients who did not have any



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

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

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

149 On multivariate analysis, presence of any complication (Odds ratio [OR] 2.87; 95%  
150 confidence interval [CI] 1.38-5.96;  $p=0.004$ ), extravesical disease (OR 3.73, 95% CI 2.00-6.97,  
151  $p<0.001$ ), and nodal involvement (OR 2.14, 95% CI 1.21-3.80,  $p=0.008$ ) were significant  
152 predictors of EOF (Table 4). Patients with EOF demonstrated worse DSS (32% and 26%) and  
153 OS (23% and 13%) at 1 and 3 years when compared to patients who experienced later  
154 recurrences (DSS 81% and 39%; OS 74% and 25%) and no recurrences (DSS 99% and 96%; OS  
155 93% and 82%) (log rank  $p<0.001$ ) (Figures 3 and 4). On Cox proportional hazards analysis,  
156 patients with  $pT\geq 3$ , nodal involvement, and presence of positive soft tissue surgical margins

157 exhibited worse DSS and OS. Patients who received neobladders demonstrated better OS (HR  
158 0.49, 95% CI 0.31-0.75, p=0.001) (Table 5).

## 159 **Discussion**

160 Despite aggressive management, disease relapse after RC will occur in half of the  
161 patients which significantly reduces survival. The pathogenesis of recurrence following RC is yet  
162 to be determined but it is probably multifactorial. Tumor aggressiveness, occult metastatic  
163 disease at the time of surgery, inhibited host immune response, laparoscopy-related factors (gas  
164 insufflation and desufflation), or breaching of oncologic surgical principles (vigorous surgical  
165 manipulation, specimen morcellation, entry into the bladder, and retrieval method) have been  
166 investigated<sup>6-8</sup>. The contribution of carbon dioxide (CO<sub>2</sub>) pneumoperitoneum deployed in  
167 minimally invasive surgery remains unknown. Prior animal studies suggested that CO<sub>2</sub>  
168 pneumoperitoneum may inhibit peritoneal immune response against malignant urothelial cells  
169 and may be contributing to recurrences within the pelvis and at port sites<sup>9</sup>.

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

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

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

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

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

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

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

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

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

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

## 258 **Conclusion**

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

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

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

<b>Preoperative parameters</b>	<b>EOF</b>	<b>Later Recurrence</b>	<b>No Recurrence</b>	<b>p-value</b>
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 <sup>2</sup> )	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
<b>Perioperative outcomes</b>				
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)	-	
<b>Pathological outcomes</b>				
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<sup>2</sup>, Kilogram per square meters; MI, milliliter

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

<b>Local recurrence</b>	<b>EOF</b>	<b>Later recurrences</b>	<b>p-value</b>
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
<b>Distant recurrence</b>	<b>EOF</b>	<b>Later recurrences</b>	<b>p-value</b>
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	

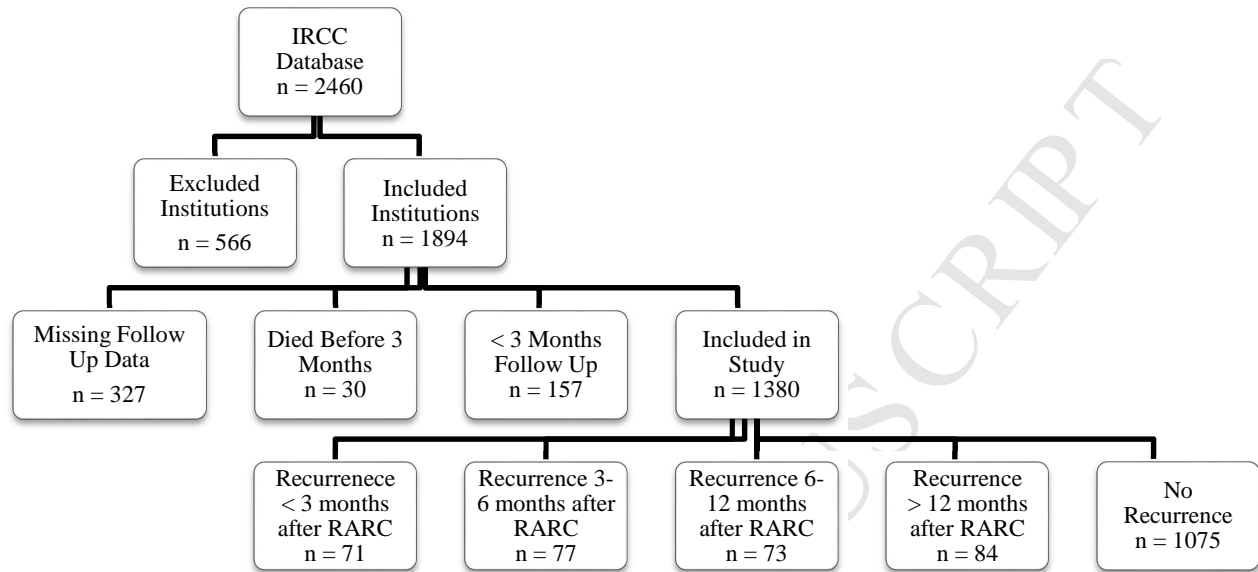
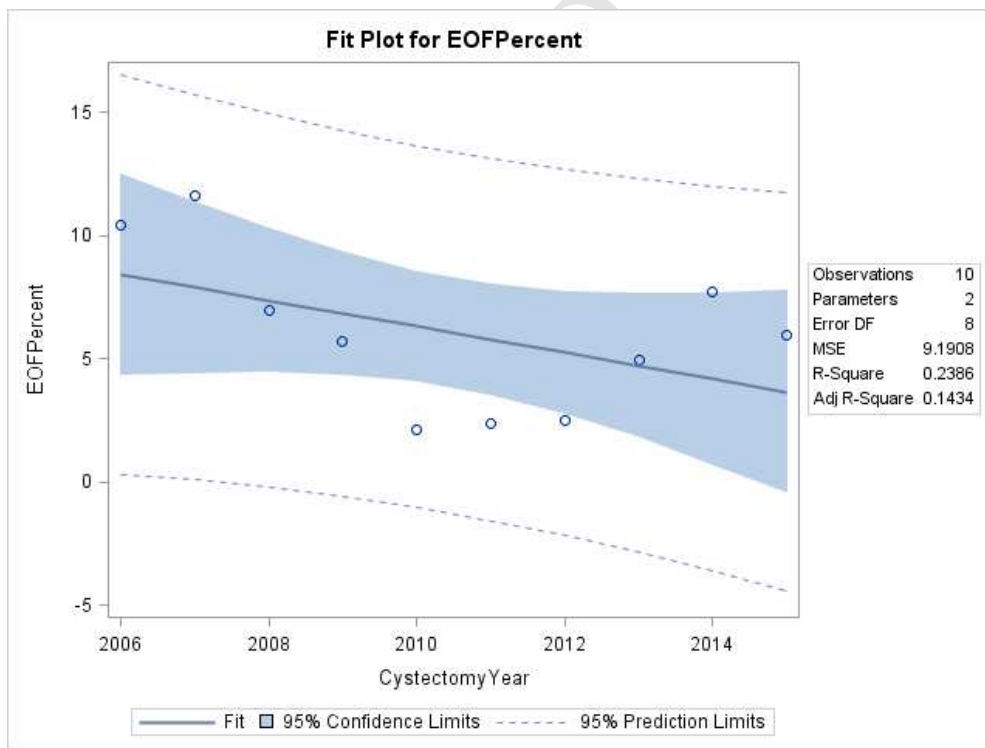
**Table 4.** Univariate and multivariable regression modeling predictors for EOF (stepwise variable selection)

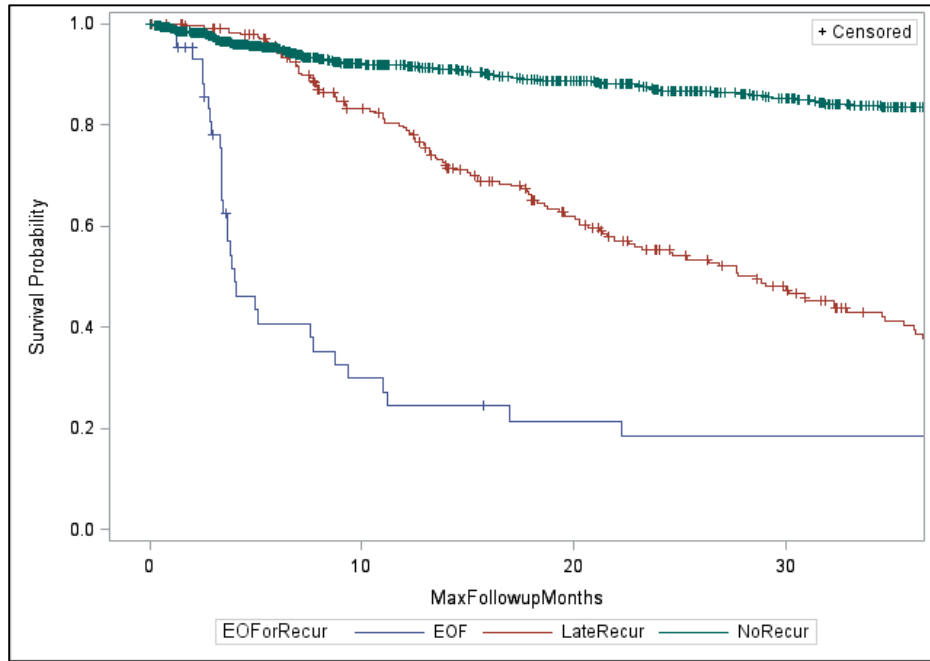
Variables [Reference]	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
<b>Preoperative parameters</b>						
Age at cystectomy	0.97	(0.95, 0.99)	0.01	-	-	-
Gender [Female]	0.69	(0.43, 1.14)	0.14	-	-	-
Body Mass Index	0.97	(0.92, 1.02)	0.18	-	-	-
ASA score	0.77	(0.52, 1.13)	0.18	-	-	-
Neo-adjuvant chemotherapy	1.28	(0.72, 2.29)	0.41	-	-	-
<b>Operative</b>						
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 $\geq$ 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	-	-	-
<b>Pathologic</b>						
$\geq$ 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

<b>Overall survival</b>			
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
<b>Disease-specific survival</b>			
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

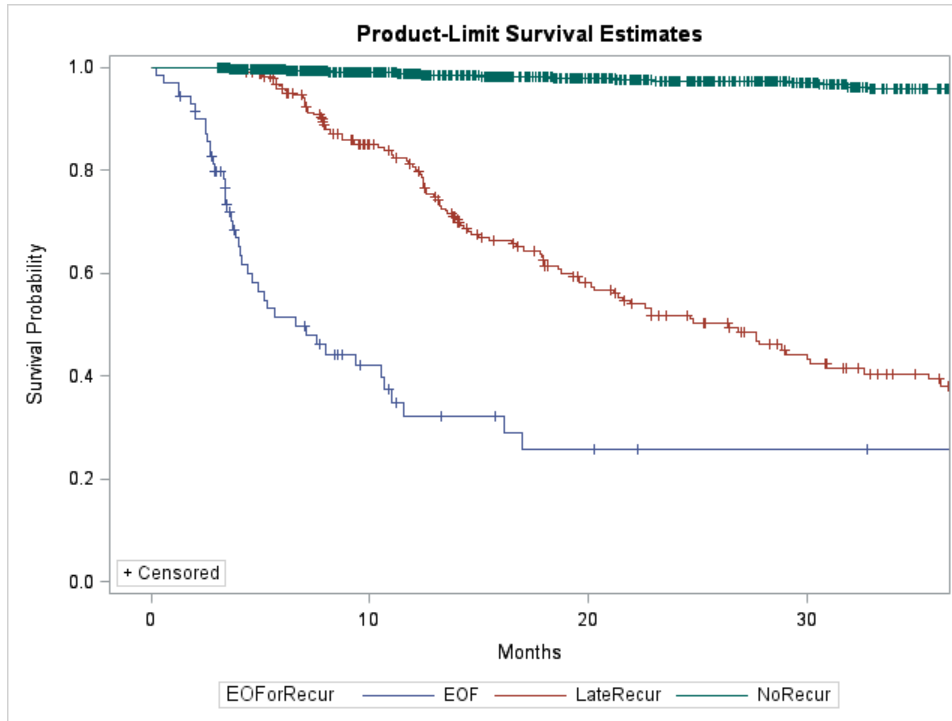
Months	0-6	6-12	12-18	18-24	24-30	30-36
Patients At Risk	71	30	12	8	6	6
Patient Deaths	36	14	3	2	0	0
Survival %	46.6	22.8	16.7	12.5	12.5	12.5

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)