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

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Abstract

Background: There have been concerns regarding incidences of peritoneal recurrences and adherence to key oncologic tenets during minimally invasive approaches to radical cystectomy

Objective: To investigate the prevalence and variables associated with Early Oncologic Failure (EOF).

Design, setting and participants: Retrospective review of the IRCC database (I-97906) which comprises 2648 patients was conducted. The final cohort included in this study comprised 1894 patients from 23 institutions across 11 countries treated with RARC since 2003

Intervention: EOF was defined as any disease relapse within 3 months of RARC. All institutions were surveyed for the pneumoperitoneum pressure used, breach of any oncological principle during RARC, the technique of specimen and lymph node removal, and whether urine spillage occurred.

Outcome Measurements and Statistical Analysis: 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 overall survival for patients with EOF and Cox proportional hazards regression analysis to evaluate predictors of disease-specific and overall survival.

Results and limitations: 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. EOF patients 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). On multivariate analysis, presence of

any complication (OR 2.87; 95% 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. 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 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.

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 at improving 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 [3]. There have been concerns regarding adherence to key oncologic tenets and induction of local pelvic, peritoneal and port-site recurrences during minimally invasive approaches to RC [4].

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 [5,6]. These relapses may be related to the disease aggressiveness or breaching of oncologic principles during surgery. Predictors of disease relapse include perioperative chemotherapy, extent of pLND, pathological T stage, lymph node status, and positive soft tissue surgical margins at cystectomy [7].

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). 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.

Methods

A retrospective review of 2648 patients from 29 institutions included in the IRCC database (I-97906) was performed. Six institutions (n=556) that failed to provide updated data were excluded from the study. The final cohort comprised 1894 patients from 23 institutions across 11 countries treated with RARC since 2003 (Figure 1). Data were reviewed for demographics (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 differed by institution.

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). All patients had at least 3 months of follow up. For all EOF patients, institutions were surveyed for their use of pneumoperitoneum pressure, any breach of oncological principles during RARC, technique of specimen and lymph node removal, and whether urine spillage occurred during the procedure.

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 and overall survival 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 were excluded. A total of 1380 patients had complete data and 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. Patients with EOF when compared to patients who developed recurrences > 3months and those without any recurrences, they 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).

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 the 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 invariably occur in half of the patients which significantly reduces survival. The exact pathogenesis of recurrence following

RC is yet to be determined. Tumor aggressiveness, 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 [8-10]. 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 [11].

We identified and characterized patients who developed EOF after RARC. Five percent of our patients experienced EOF. All of these patients but 8 (11%) had advanced disease (≥pT3 +/- positive nodal disease), and oncologic principles were breached in 6 (8%). For any RC performed (open and RARC), tumor stage, nodal involvement, lympho-vascular invasion and positive margins are the most powerful predictors of tumor recurrence [1,12]. Similarly, on multivariable analysis, patients with extravesical or nodal disease were at least twice more likely to develop EOF. During RC, tumor spillage may occur with extravesical, extensive nodal involvement, or due to technical error, which risks seeding the peritoneal cavity with TCC. Although its efficacy is unproven, a common practice reported is to irrigate the abdomen with sterile water, presumably to induce hypotonic lysis of any remaining TCCs [13]. 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 [14]. Recurrent TCC, presumably from tumor spillage during TURBT or after 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 [15-18]. The use of prophylactic radiation or systemic

chemotherapy in the setting of TCC spillage remains unclear with significant potential morbidity. This raises questions about the possible role of intraperitoneal chemotherapy similar to ovarian, gastric and colorectal malignancies [19,20]. 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 with time, and increased experience and comfort with the robot-assisted platform [21]. Blood transfusion and poor renal function have been also suggested to induce recurrences by affecting the immunity and DNA repair [22]. 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). Patients who developed postoperative complications were approximately 3 times more likely to develop EOF. Complications (especially early in the postoperative period) may be a result of inadequate surgical performance and therefore may affect cancer control and patient survival [23]. Patients who receive neobladders are generally of better health and less comorbidities. This may explain why the type of diversion affected OS and not CSS.

Time to oncologic failure has been shown to be a significant predictor of overall survival [6]. Early unexpected relapse was 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 [24]. However, they defined early progression as any disease recurrence within 24 months after surgery. Since most recurrences after RC develop within the first 2-3 years after surgery, a period of 24 months will make it harder to differentiate recurrences that occur due to advanced disease from those that may have occurred due to breech of oncologic surgical principles. In our study, 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 [25,26]. Similarly, patients with colorectal, ovarian and urothelial cancers with local relapse, port site seeding and early metastasis after laparoscopic surgery have been previously reported [21,27]. It remains difficult to contemplate whether such recurrences occurred due to the primary tumor 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 [23].

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 [8,28,29]. 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 [30]. Less thorough lymph node dissection with RARC and possible peritoneal dissemination of malignant urothelial cells with pneumoperitoneum have been implicated [31]. However, the lymph node yield in the same study was the same for either approach and the differences reported were not statistically significant. Additionally, the approach to cystectomy was not a significant predictor on multivariable analysis [31]. In our cohort, peritoneal carcinomatosis occurred in less than 1% of all patients, and represented 4% of all recurrences. This difference may be in part attributed to differences in defining carcinomatosis, sample size, follow up 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. Also, heterogeneity in institutional protocols, surgical techniques, and pathological examination may lead to variation in reporting outcomes. However, the IRCC represents the largest multinational database for RARC that captures and reflects real-world practices.

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.

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

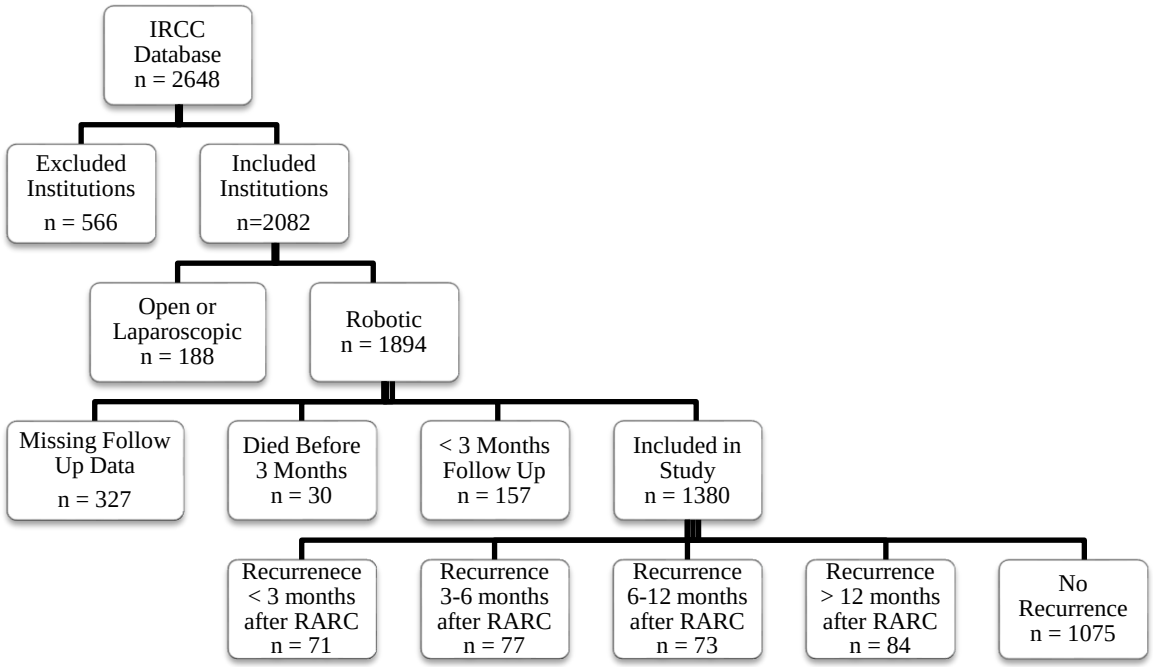


Figure 2. EOF cases as they occurred with time (Linear Regression Test p = 0.15)

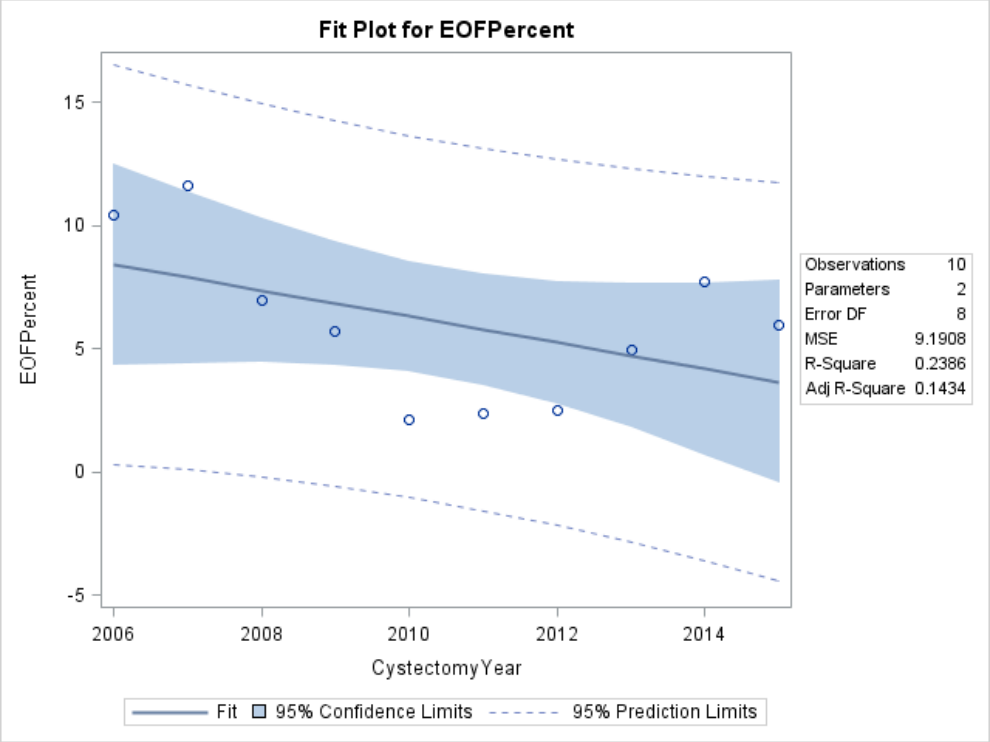
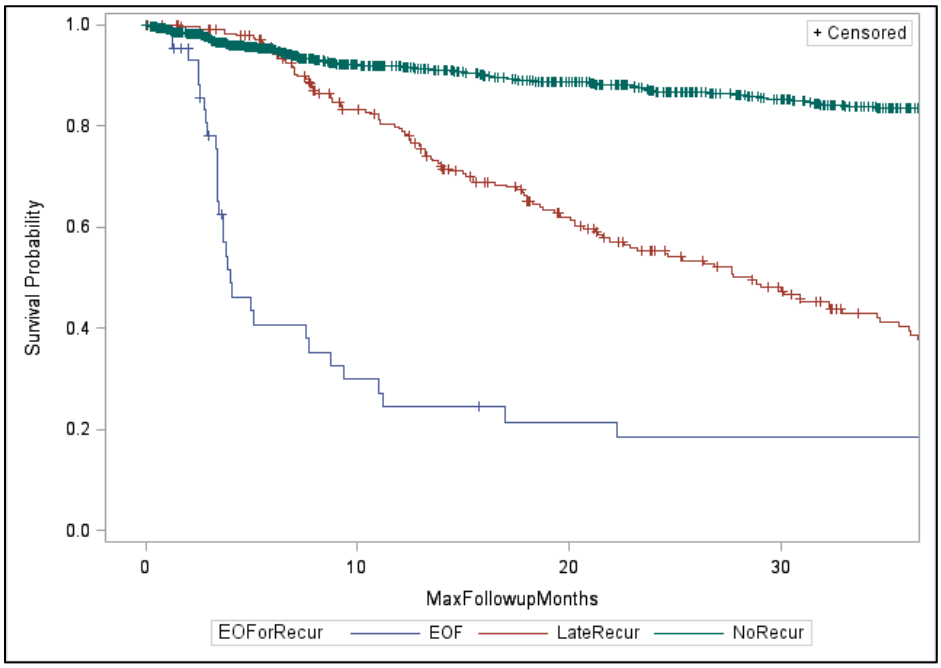


Figure 3. Kaplan Meier curves for OS (log rank p <0.001)



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

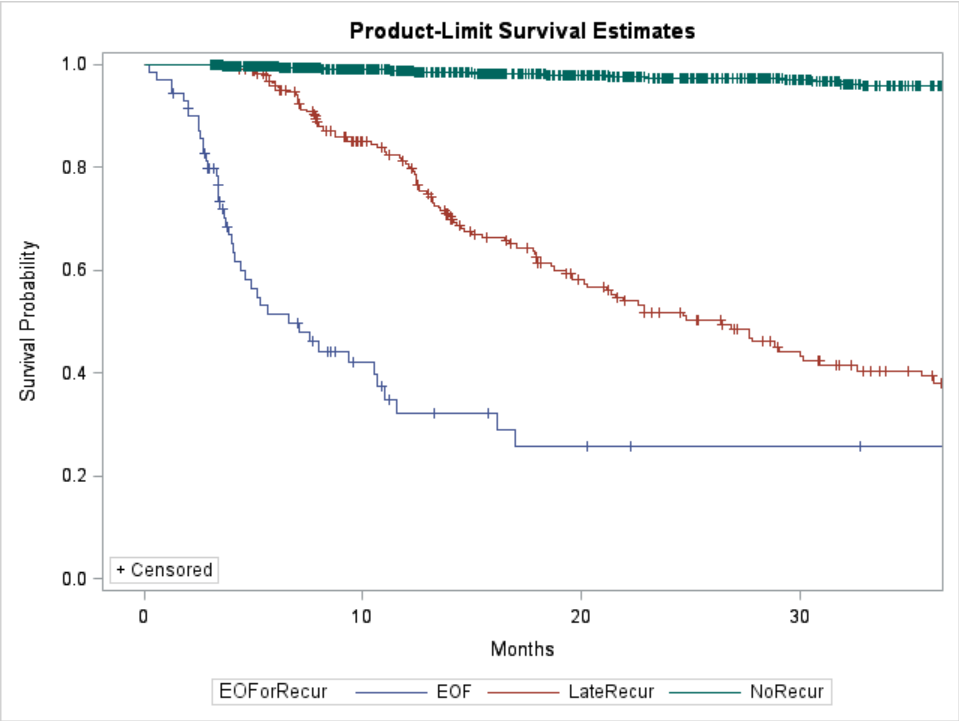
Later Recurrence

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

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