Analysis of open and intracorporeal robotic cystectomy shows no significant difference in recurrence patterns and oncological outcomes

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Abstract

Objectives

To report and compare early oncological outcomes and cancer recurrence sites among patients undergoing open radical cystectomy (ORC) and robotic assisted radical cystectomy with intracorporeal urinary diversion (iRARC).

Methods and materials

184 patients underwent radical cystectomy for bladder cancer. ORC cases (n=94) were performed between June 2005- July 2014 while iRARC cases (n=90) were performed between June 2011- July 2014. Primary outcome was recurrence free survival (RFS). Secondary outcomes were sites of local and metastatic recurrence and overall survival (OS).

Results

Median follow-up for patients without recurrence was 33.8 months (IQR: 20.5-45.4) for ORC; and 16.1 months (IQR: 11.2-27.0) for iRARC**.** No significant difference in age, gender, pre-cystectomy T stage, pre-cystectomy grade, or lymph node yield between ORC and iRARC was observed. The ORC cohort included more patients with ≥pT2 (64.8% ORC vs 38.9% iRARC) but fewer pT0 status (8.5% ORC vs 22.2% iRARC) due to lower preoperative chemotherapy use (22.3% ORC vs 34.4% iRARC). Positive surgical margin rate was significantly higher in the ORC cohort (19.3% vs 8.2%; p=0.042). Kaplan-Meir analysis showed no significant difference in RFS (69.5% ORC vs 78.8% iRARC), CSS (80.9% ORC vs 84.4% iRARC), or OS (73.5% ORC vs iRARC 83.8%) at 24 months. Cox regression analysis showed RFS, CSS and OS were not influenced by cystectomy technique. No significant difference between local and metastatic RFS between ORC and iRARC was observed.

Conclusion

This study has found no difference in recurrence patterns or oncological outcomes between ORC and iRARC. Recurrent metastatic sites vary, but are not related to surgical technique.

Keywords

Bladder Cancer; Intracorporeal urinary diversion; Open cystectomy; Outcomes; Recurrence; Robotic-assisted cystectomy

1. Introduction

Radical cystectomy with lymphadenectomy remains the gold standard of curative treatment for muscle invasive or recurrent high grade non-muscle invasive bladder cancer (1). Minimally invasive radical cystectomy has evolved to include robotic assisted laparoscopic techniques with intracoporeal urinary diversion, largely as a result of developments in robotic technology, and in a number of centers has become the surgical approach of choice in selected cases (2-4).

Evidence from retrospective case series that compare open radical cystectomy (ORC) to intracorporeal robotic assisted radical cystectomy (iRARC) reports that iRARC carries a lower risk of major complications and reduced transfusion rate (5). However, it is equally important that oncological outcomes following iRARC should at least be equivalent to ORC. It is also essential to determine if surgical technique influences the landing sites and pattern of recurrence following radical cystectomy.

Although no studies exist that compare iRARC to ORC, a recent systematic review suggests that early oncological outcomes after RARC were comparable to ORC (6). To date, published studies reporting oncological outcomes after iRARC comprise largely of case series, with few studies comparing the outcomes of robotic and open surgery (7, 8). Recently, in a series of 383 patients over 13 years, Nguyen et al. reported a larger proportion of extrapelvic lymph node metastasis and peritoneal carcinomatosis following RARC compared to ORC, although statistical significance was not reached (9). The authors found that RARC was not an independent predictor of recurrence after surgery (9). Non randomized comparative series have the potential for bias and, while a randomized controlled trail by Bochner et al. has been conducted comparing ORC and RARC, it was not designed to determine whether there is a survival benefit for RARC (10). The trial was intended to detect a reduction in Clavian grade 2-5 complication rate of ≥20% at 90 days but was closed early following a futility analysis.

In this study, we report early oncological outcomes of 184 consecutive open or iRARC cases within a tertiary referral center. Secondary objectives included a comparison of local versus metastatic recurrence and overall survival (OS) for ORC and iRARC.

2. Material and methods

2.1 Patient cohort

A retrospective analysis of 184 patients within a tertiary referral center underwent radical cystectomy for primary bladder cancer with curative intent. ORC cases (n=94) were performed from June 2005 to July 2014 while RARC cases (n=90) were performed from June 2011 to July 2014. Four cases were excluded based on the lack of histopathological data. Prior to 2013, RARC was performed at one of the two sites undertaking radical cystectomy. After 2013 all cystectomies were performed at one site. In 2014, 45 radical cystectomy cases were performed and in 2015 this increased to 63 cases. All three surgeons performing open cystectomy had performed ≥100 cases previously and the two iRARC surgeons, who also performed the ORC cases, performed 76 and 14 iRARCs respectively during the study period.

Inclusion criteria were patients with muscle invasive bladder cancer (MIBC) or high risk non-MIBC who had radical cystectomy and lymphadenectomy with curative intent. The type of urinary diversion was dependent on patient choice provided there were no absolute contraindications (11). All patients underwent preoperative laboratory investigations, cross sectional imaging for staging, and transurethral resection of bladder tumour (TURBT). Preoperative chemotherapy was recommended for patients with MIBC who had an Eastern Cooperative Oncology Group (ECOG) performance score ≤1, glomerular filtration rate (GFR) ≥60mL/min and no contraindication. Three cycles of Gemcitabine-Cisplatin (Gem-Cis) was typically used if tolerated. The use of adjuvant chemotherapy or adjuvant radiotherapy was based on the decision of the tumor board meeting.

The commencement of a robotic cystectomy program in June 2011 coincided with the start of the BOLERO trial, a phase II Cancer Research UK funded feasibility study on randomizing patients to ORC vs minimal invasive surgery (NCT01196403). At the start of the program, due to the expected learning curve, iRARC may have been avoided in comorbid patients. The number of iRARC cases increased year on year to 45.2%, 83.3% and 97.8% of cystectomy cases in 2012, 2013 and 2014 respectively.

2.2 Surgical technique

The standard technique for both ORC and iRARC has been described previously (4, 12). iRARC was performed using a 6 port transperitoneal approach with the patient in 27° Trendelenburg was used. Pelvic lymph node dissection included excision of obturator, external, internal and common iliac nodes. For RARC following cystectomy, the specimen was placed in an endocatch bag (Covidien, Dublin, Ireland) and removed after lymphadenectomy and urinary diversion were complete in males via the extended right iliac fossa port site, or via the vagina in females. The intracorporeal ileal conduit was constructed using 15 cm of terminal ileum, taken 15 cm from the ileo-cecal valve using a 60 mm laparoscopic intestinal stapler (Endo-GIA; Covidien, Dublin, Ireland). Intracorporeal continent diversion required 50 cm of terminal ilium which was detubularised and cross folded without an afferent limb. Uretero-ileal anastomosis was performed either using a Bricker (JDK) or a Wallace (TPB) anastomosis. 6F infant feeding tubes/ Bander stents were externalized and used as ureteric stents.

2.3 Patient covariates

Patient demographics, TURBT histopathology, radical cystectomy histopathology, type of surgery performed, neo-adjuvant chemotherapy (NAC) use and follow-up data were collected. Histopathological data included tumor type, grade (according to World Health Organization classification) (13), and tumor and nodal stage (according to 2002 TNM classification) (14). A positive surgical margin was defined as the presence of tumor at any soft tissue margin on the cystectomy specimen.

Follow-up for all patients included imaging by CT scan of the chest, abdomen and pelvis at 6 months, 12 months and then annually. Additional imaging was based on presence of symptoms suggestive of recurrent disease or post-operative complications. Outcome measures included overall survival (OS), cancer specific survival (CSS) and recurrence free survival (RFS). Local recurrence was defined as any soft tissue or bony disease within the surgical bed, surgical incision site, pelvis and nodal disease below the aortic bifurcation and distant recurrence was defined as metastasis at any site outside the pelvis and nodal disease beyond the aortic bifurcation. Only cases of urothelial cell

carcinoma (UCC) were included in RFS, CSS and OS analysis as non-UCC patients have a different prognosis.

2.4 Statistical analyses

Descriptive statistics including mean, standard deviation, chi-square analysis and paired t test were used to report continuous and categorical data. Kaplan- Meier analysis was used to calculate survival probabilities and differences in survival were assessed using log-rank test analysis. Multivariable Cox regression analysis was performed to determine which variables were independent predictors of oncological outcomes. Statistical significance was set at p value ≤0.05. Statistical analysis was performed using SPSS v16 (IBM, New York, USA).

3. Results

The overall median follow-up was 22.8 months (IQR: 12.5-35.6 months). The median follow-up for ORC and iRARC patients were 33.8 months (IQR: 20.5-45.4) and 16.1 months (IQR: 11.2-27.0) respectively. There was no significant difference in age and

gender between ORC and iRARC although significantly more patients had a continent urinary diversion in the iRARC cohort (p=0.001).

The majority of cases were UCC and there was no significant difference in pre-cystectomy pathological T stage (Table 1). 31/90 patients (34.4%) in the iRARC group where received preoperative chemotherapy compared to 21/94 patients (22.3%) in the ORC cohort, which showed a trend towards statistical significance (X^2=3.48, df=1 p=0.073). There was no significant difference between the use of NAC (iRARC: 83.9% vs ORC: 71.4%) and inductive chemotherapy (iRARC: 16.1% vs ORC: 28.6%) in ORC and iRARC cohorts (p=0.281).

The proportion of patients who were stage pT0 on post-operative histology was significantly higher in the iRARC cohort (iRARC: 22.2% vs ORC: 8.5%) (X^2=5.540, df=1 p=0.025) while positive soft tissue surgical margins were higher in the ORC cohort (iRARC: 8.2% vs ORC: 19.3) (X^2=4.133, df=1 p=0.042). There was no significant difference between number of lymph nodes resected between ORC and RARC patients. Two ORC patients received postoperative radiotherapy, one for positive surgical margin and the other for isolated metastatic iliac nodal disease. Four iRARC patients had postoperative radiotherapy; one for positive surgical margin, two for an isolated sacral metastasis and a patient for an isolated port site recurrence. Two patients (2.1%) in the ORC cohort and 5 patients (5.6%) in the iRARC cohort received adjuvant chemotherapy while a further 5 patients (5.3%) and 4 patients (4.4%) in the ORC and iRARC cohort received palliative chemotherapy respectively.

The analysis of RFS and OS was conducted on patients with UCC. There was no difference in RFS (65.9% ORC vs 75.2% iRARC), CSS (80.9% ORC vs 84.4% iRARC), or OS (72.5% ORC vs iRARC 79.2%) at 24 months (Figure 2-4). Propensity score adjustment for cystectomy pathological stage, lymph node status, use of preoperative chemotherapy and surgical margin status showed that there was no significant difference in recurrence free survival (p=0.210; OR: 0.58, 95% CI: 0.24-1.36), cancer specific survival (p=0.300; OR:0.62, 95% CI: 0.25-1.54) and overall survival (p=0.313; OR:0.64, 95% CIL 0.27-1.52) between ORC and iRARC.

Cox regression analysis showed that higher post-operative pathological stage and presence of nodal disease were independently associated with lower cancer RFS, CSS and OS (Table 2-4). Surgical technique was not significantly associated with RFS, CSS or OS. In addition, there was no difference in time to local recurrence [ORC (n=12): median: 8.4±13.0 months; IQR: 4.6-22.7 vs iRARC (n=10): median: 8.5±9.2 months; IQR: 4.1-16.1] or metastasis with/ without local recurrence [ORC (n=21): median: 8.5±15.9 months; IQR: 3.9-19.1 vs iRARC (n=10): median: 6.4±10.4 months; IQR: 4.3-17.9] (Figure 5A &4B).

In the ORC cohort 30 patients (31.9%) had recurrence and 22 patients (23.4%) died as a result of recurrent disease. Three patients (3.6%) died 90 days post-operatively while a further 8 patients (9.5%) died from non-cancer causes. Nine patients had local recurrence alone, 13 patients had distant metastasis alone with 8 patients having both local and metastatic recurrence.

In the iRARC group 17 patients (18.9%) developed recurrence which resulted in 11 deaths (12.2%). One patient (1.3%) died 90 days postoperatively and two patients (2.5%) died from non-cancer causes. Among patients who had iRARC, 7 patients had local recurrence alone, while 6 patients had distant metastasis alone and 4 patients had both local and distant metastasis. Table 4 describes the site of recurrence stratified according to surgical approach. Surgical bed, bone and lymph node were the most common sites of local recurrence for both ORC and iRARC. Site of metastatic recurrence varied, with a predisposition of lung and liver metastasis in the ORC cohort. In addition, in the ORC cohort there were one para-umbilical hernia site, one skin and one penile metastasis while in the iRARC cohort; there were one port site recurrence and one penile metastasis.

4. Discussion

The results of the present study suggest that short term oncological outcomes for iRARC, including RFS and OS, are not inferior to those of ORC. This is consistent with the findings of the recent Pasadena Consensus Group where a number of retrospective case series from high-volume institutions were examined and it was suggested that

intermediate oncological outcomes for extracorporeal RARC are similar to those of ORC (5). However, data on oncological outcomes of intracorporeal RARC are limited as the technique has not been widely adopted due to its technical challenges.

Tyritzis et al. and Desai et al. reported a 24 month RFS of 80.7% and 79% and an OS of 88.9% and 82.0% respectively in their iRARC series (2, 8). Desai et al. included patients from Tyritzis et al., hence the similarity in their results. We report a similar 24 month RFS rate of 78.8% and an OS rate of 83.8%. However, there were a higher proportion of ≥pT3, and a lower proportion of pT2 tumors at final cystectomy pathology in the present series when compared in the present series than either Desai et al, or Tyritzis et al's cohorts. This is surprising, as the present cohort describes a higher NAC uptake, in addition to a reduced proportion of patients with post-operative pT0 (22.5% vs 24.3-26.1%). Post cystectomy down-staging due to NAC is a well reported predictor of improved outcome and those who are ≥pT2 at cystectomy despite NAC are in fact non-responders with associated adverse oncological outcomes (15). Such an observation coupled with the present cohort's oncological staging might suggest that this cohort of patients have more adverse pathological characteristics compared to Tyritzis et al. and Desai et al. (2, 8).

In the present series, among the iRARC group there were significantly more patients who received a continent urinary diversion compared to patients who underwent ORC reflecting that a minimally invasive approach does not preclude orthotopic bladder reconstruction. In addition, there was a significant higher positive surgical margin rate in the ORC cohort, which might be explained by a higher proportion of patients with T4 tumors in this group.

Proponents of ORC have concerns that RARC patients might not receive as adequate a lymph node dissection compared to their ORC counterparts. However, similarly to Nix et al., we did not observe a difference between lymph node yield of our ORC and iRARC cohorts (16). This is an important point because although prognosis from nodal metastasis is poor, patient with localized bladder cancer with isolated nodal disease may be cured by surgery alone if an adequate lymphadenopathy is performed (17). In any curative cancer surgery, oncological outcomes are of paramount importance

especially where there are limited options for adjuvant treatment in bladder cancer (18). It is therefore encouraging that no significant difference in OS and RFS between ORC and iRARC was found in this study although there was a trend towards better OS in iRARC patients.

Although there was no difference in lymph node yield, the lymph node count for both ORC and iRARC were lower compared to contemporary series (2, 8). This could be due to interobserver variability and the fact we did not perform an extended lymphadenectomy. Currently, there is no conclusive evidence to support extended lymph node dissection. Results of phase III South West Oncology Group (SWOG) S1011 trial and German Association of Urologic Oncology trial where patients are randomized to either extended or standard lymph node dissection are eagerly awaited.

One concern that has been raised by bladder cancer surgeons regarding minimal invasive techniques, particularly intracorporeal reconstruction techniques, is the potential for port-site metastases and intraperitoneal seeding. Several plausible hypotheses for such occurrences have been suggested including seeding during extraction of the tumor, contact with contaminated laparoscopic instruments, and the effects of pneumoperitoneal desufflation (19-21). The recent retrospective analysis performed by Nguyen et al. suggested that patients treated with extracorporeal RARC had higher rates of extrapelvic lymph node recurrence [10/43 (23%) vs 4/26 (15%)] and peritoneal carcinomatosis [9/43 (21%) vs 2/26 (8%)] compared to ORC (9). They hypothesized that the robotic technique may result in altered lymphatic metastatic dissemination although they acknowledge this remains unproven. Eight of nine of patients with peritoneal carcinomatosis had ≥pT3 disease suggesting advanced disease. It would be interesting to know if patients with extrapelvic lymph node recurrence had pre-existing lymph node positive at cystectomy as this will make them at risk of lymph node recurrence. Analysis of data from the present study found no significant difference in the rate of local or metastatic RFS between ORC and iRARC groups. Of interest, in the iRARC series there were one port site recurrences and one penile metastasis; and in the ORC series, there was one case of recurrence in a para-umbilical hernia, penis and skin.

Our data suggests that regardless of the modality of surgery the potential for the development of subcutaneous metastasis may in fact reflect tumor biology rather than surgical technique. Our findings are supported by a review by Kadi et al. which has reported that although rare, laparoscopic and open techniques carry a similar risk of subcutaneous metastasis, and that tumor grade and stage are probably more important in predicting the occurrence of subcutaneous metastasis in this setting (22).

Certain limitations of the present study should be acknowledged, including the retrospective data collection. In addition, given the non-randomized nature of our study, differences in patient demographics, temporal patterns of referral and treatment as well as the nature of the tumors selected for a particular approach between the ORC and RARC groups are almost inevitable. Although there will be some inherent selection bias, since its introduction iRARC has been the default operation of choice at our institution, notwithstanding specific and contraindications to minimally invasive surgery, such as previous complex abdominal surgery. A difference in post-operative pathological tumor stage between ORC and iRARC was noted, which may be explained by stage migration as a result of a higher use of NAC in the iRARC cohort (RARC: 34.4% vs ORC: 23.0%). In this series, there was a trend towards significance between pT0 status and preoperative chemotherapy (preoperative chemotherapy: 23.1% vs no preoperative chemotherapy: 12.9%; p=0.087). This is evident in the higher proportion of ≤pT1 and pT0 patients in our iRARC cohort and confirmed by the fact that there were significantly more patients who were down-staged in the iRARC cohort (ORC: 17.4%; n=4/23 vs RARC: 51.6%; n=16/31) (p=0.01). Multivariate analysis was performed to attempt to account for other confounding variables although this is by no means a replacement of a randomize control trial. Additionally, our median follow-up in the RARC group was relatively short at 16.1 months.

5. Conclusions

The findings of this study suggest that iRARC has comparable short term oncological outcomes, and similar site of metastatic and local recurrence compared to ORC. However, the results for higher stage (≥pT2) disease should be interpreted with caution in view of the increased use of NAC in the iRARC group. Hence, results of larger prospective randomized studies, such as the RAZOR trial are eagerly awaited to support our findings of the oncological equivalence of iRARC to ORC (23).

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461 Table 1: Patient demographic data and pathological characteristics for ORC and iRARC

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Characteristic		ORC (n=94)	iRARC (n=90)	P value
Gender	**Male**	68 (72.3)	69 (76.7)	0.502
	Female	26 (27.7)	21 (22.3)	
Age	**Mean ± SD**	66.4 ±10.6	64.3 ± 12.3	0.290
Type of tumour	**Urothelial cell**	84 (89.4)	80 (88.9)	0.274
	Squamous cell	6 (6.4)	7 (7.8)	
	Adenocarcinoma	4 (4.2)	1 (1.1)	
	Other	0 (0)	2 (2.2)	
Salvage cystectomy	**Yes**	7 (7.4)	3 (3.3)	0.330
	No	87 (92.6)	87 (96.7)	
Pre-cystectomy staging	**Carcinoma in situ**	1 (1.1)	5 (5.6)	0.191
	pTa	9 (9.6)	5 (5.6)	
	pT1	23 (23.4)	29 (32.2)	
	pT2	45 (47.9)	42 (46.7)	
	pT3	14 (14.9)	8 (8.9)	
	pT4	3 (3.2)	1 (1.1)	
Tumour grade	**Carcinoma in situ**	1 (1.0)	5 (5.6)	0.207
	G2	7 (7.4)	4 (4.4)	
	G3	77 (81.1)	71 (78.9)	
	Non TCC	10 (10.5)	10 (11.1)	
Preoperative chemotherapy	**Yes**	21 (22.3)	31 (34.4)	0.073
	No	73 (77.7)	59 (65.6)	
Postoperative radiotherapy	**Yes**	2 (2.1)	4 (4.4)	0.376
	No	92 (97.9)	86 (95.6)	
Postoperative chemotherapy	**Yes**	7 (7.4)	9 (10.0)	0.539
	No	87 (92.6)	81 (90.0)	
Diversion type	**Ileal conduit**	81 (86.2)	60 (66.6)	0.001
	Continent	13 (13.8)	30 (33.4)	
Post-cystectomy stage	**pT0**	8 (8.5)	20 (22.2)	0.001
	Cis, pTa, pT1	25 (26.6)	35 (38.9)	
	pT2	22 (23.4)	8 (8.9)	
	pT3	23(24.4)	23 (25.6)	
	pT4	16 (17.0)	4 (4.4)	
pT0 status	**pT0**	8 (8.5)	20 (22.2)	0.025
	Disease present	86 (91.5)	70 (77.8)	
Lymph node status	**Positive**	18 (21.2)	13 (14.4)	0.229
	Negative	67 (78.8)	77 (85.6)	
Number of lymph nodes	**Mean ± SD**	12.6±10.9	14.9±10.0	0.461
	Range	0-48	0-51	
Soft tissue surgical margin	**Positive**	17 (19.3)	6 (8.2)	0.042
	negative	71 (80.7)	67 (91.8)	

463 ORC: open radical cystectomy; iRARC: intracorporeal robotic assisted radical
464 cystectomy

Table 2: Cox regression analysis comparing variables and recurrence free survival

Variables	P value	Hazard ratio	95% CI
Technique (ORC vs iRARC)	0.799	1.09	0.58-2.02
Surgical margin (- vs +)	0.217	1.62	0.75-3.50
Perioperative chemotherapy (no vs yes)	0.138	0.60	0.31-1.18
Cystectomy pathological stage (≤pT2 vs ≥pT3)	0.002*	3.38	1.57-7.26
Node positive disease (N0 vs N1-3)	0.010*	2.56	1.25-5.23

ORC: open radical cystectomy; iRARC: intracorporeal robotic assisted radical cystectomy

Table 3: Cox regression analysis comparing variables and cancer specific survival

Variables	P value	Hazard ratio	95% CI
Technique (ORC vs iRARC)	0.639	1.20	0.56-2.55
Surgical margin (- vs +)	0.236	1.65	0.72-3.76
Perioperative chemotherapy (no vs yes)	0.395	0.72	0.36-1.54
Cystectomy pathological stage (≥pT3 vs ≤pT2)	0.001*	7.08	2.39-21.00
Node positive disease (N0 vs N1-3)	0.022*	2.45	1.14-5.29

ORC: open radical cystectomy; iRARC: intracorporeal robotic assisted radical cystectomy

Table 4: Cox regression analysis comparing variables and overall survival

Variables	P value	Hazard ratio	95% CI
Technique (ORC vs iRARC)	0.624	1.19	0.601-2.34
Surgical margin (- vs +)	0.281	1.53	0.71-3.31
Perioperative chemotherapy (no vs yes)	0.417	0.75	0.37-1.51
Cystectomy pathological stage (≥pT3 vs ≤pT2)	<0.001*	4.64	1.97-10.95
Node positive disease (N0 vs N1-3)	0.020*	2.31	1.24-4.69

ORC: open radical cystectomy; iRARC: intracorporeal robotic assisted radical cystectomy

Table 5: Site of recurrence of patients with transitional cell carcinoma stratified according to ORC and iRARC

Site of recurrence	Site of recurrence	ORC N	iRARC N
Number of patients with recurrence:	**All sites**	**30**	**17**
	Local	**9**	**7**
	Distant	**13**	**6**
	Local and distant	**8**	**4**
Local recurrence site	**Bone**	**5**	**3**
	Lymph nodes	**6**	**5**
	Surgical bed	**10**	**8**
Distant recurrence site	**Adrenal**	**1**	**0**
	Brain	**2**	**0**
	Bone	**4**	**3**
	Liver	**8**	**1**
	Lung	**8**	**3**
	Lymph nodes	**2**	**3**
	Mesentery/peritoneum	**3**	**2**
	Paraumbilical hernia	**1**	**0**
	Port site	**0**	**1**
	Penile	**1**	**1**
	Scalp/ skin	**1**	**0**

ORC: open radical cystectomy; iRARC: intracorporeal robotic assisted radical cystectomy