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Platinum Priority – Brief Correspondence

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Early Recurrence Patterns Following Totally Intracorporeal Robot-assisted Radical Cystectomy: Results from the EAU Robotic Urology Section (ERUS) Scientific Working Group

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Abstract

Recurrence following radical cystectomy often occurs early, with >80% of recurrences occurring within the first 2 yr. Debate remains as to whether robot-assisted radical cystectomy (RARC) negatively impacts early recurrence patterns because of inadequate resection or pneumoperitoneum. We report early recurrence patterns among 717 patients who underwent RARC with intracorporeal urinary diversion at nine different institutions with a minimum follow-up of 12 mo. Clinical, pathologic, radiologic, and survival data at the latest follow-up were collected. Recurrence-free survival (RFS) estimates were generated using the Kaplan-Meier method, and Cox regression models were built to assess variables associated with recurrence. RFS at 3, 12, and 24 mo was 95.9%, 80.2%, and 74.6% respectively. Distant recurrences most frequently occurred in the bones, lungs, and liver, and pelvic lymph nodes were the commonest site of local recurrence. We identified five patients (0.7%) with peritoneal carcinomatosis and two patients (0.3%) with metastasis at the port site (wound site). We conclude that unusual recurrence patterns were not identified in this multi-institutional series and that recurrence patterns appear similar to those in open radical cystectomy series.

Patient summary: In this multi-institutional study, bladder cancer recurrences following robotic surgery are described. Early recurrence rates and locations appear to be similar to those for open radical cystectomy series.

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Radical cystectomy with extended pelvic lymph node dissection (PLND) provides the best chance of long-term survival for clinically localised muscle-invasive bladder cancer and high-grade recurrent noninvasive disease [1]. However, curative surgery remains challenging, with recurrence rates of 30–40% reported within 5 yr of surgery [2]. Recurrences often occur early; more than 80% occur within the first 2 yr after surgery, with average presentation occurring 10–15 mo after radical cystectomy [3].

Debate remains as to whether minimally invasive surgery negatively impacts survival outcomes due to inadequate resection, suboptimal lymph node dissection, or alteration of recurrence patterns due to tumour seeding related to pneumoperitoneum or insufflation [4]. A recent single-centre study compared open radical cystectomy (ORC) with robot-assisted radical cystectomy (RARC) and reported a similar incidence of overall transitional cell carcinoma (TCC) recurrences, with a higher frequency of peritoneal carcinomatosis and extraperitoneal lymph node recurrences among patients undergoing RARC [4].

It is recognised in ORC series that early recurrence is an indicator of poor prognosis that correlates closely with 5-yr recurrence-free survival (RFS) and overall survival [5]. The current evidence for long-term outcomes following RARC shows acceptable oncologic outcomes comparable to open series [2]. A multicentre study analysing data for 702 RARC patients with a minimum of 5-yr follow-up (median 67 mo) reported 5-yr RFS of 67%.

In the European Association of Urology Robotic Urology Section (ERUS) Scientific Working Group database, 717 patients at nine different institutions were identified who underwent totally intracorporeal RARC between December 2003 and March 2015. The follow-up protocol comprised history, physical examination, urine cytology, and laboratory measurements according to EAU guidelines. Diagnostic imaging was routinely performed at 4–6 mo for the first year, and at least annually thereafter, or more frequently when clinically indicated. The median follow-up was 31 mo (interquartile range [IQR] 20–46).

Patient demographics and oncologic outcomes are summarised in Table 1. Thirty-four patients (4.8%) had a positive surgical margin (PSM), of whom 31 (4.4%) had pT3/T4 disease. Three patients (0.4%) with organ-confined disease had a PSM. The median yield for extended PLND was 18 (IQR 13–25). Kaplan-Meier estimates were created for local and distant recurrence sites (Table 2). RFS at 3, 12, and 24 mo was 95.9%, 80.2%, and 74.6% respectively (Supplementary Fig. 1). Univariable and multivariable Cox regression was used to estimate hazard ratios for predictors of RFS (Supplementary material).

We observed early recurrences at any site in 4.1% of patients at 3 mo, 19.8% at 12 mo, and 25.4% at 24 mo, similar to rates seen in ORC series [5–7]. Distant recurrences were most frequent in the bones, lungs, and liver, while local recurrences were most common in pelvic lymph nodes. This is consistent with recurrence patterns seen in ORC and in autopsy series [6,7]. Regarding unusual recurrence patterns [4], five patients (0.7%) had peritoneal carcinomatosis and two patients (0.3%) had metastasis at the port site (wound site), which are both of low incidence and consistent with published ORC series [7]. In a recent review, RFS rates at 2 yr after surgery ranged from 67% to 81% in RARC series [8], and studies highlighting unusual recurrence patterns as a possible indicator of a detrimental effect have not shown a higher incidence of recurrences compared to ORC performed in the same institution [4].

It has been found at autopsy that peritoneal carcinomatosis incidence is as high as 19% among bladder cancer patients, but importantly it is most frequently associated with extensive metastases at multiple sites [6]. Review of the patients in our series with peritoneal carcinomatosis and port-site metastasis revealed that all had high-grade

Table 1 – Patient demographics and oncologic outcomes

Variable	Result
Patients (n)	717
Male/female (*n*)	78/22
Median age, yr (IQR)	68 (62–74)
ASA grade (*n*)	
1	17
2	51
3	31
4	1
Median BMI, kg/m^2 (IQR)	26 (23–28)
Median follow-up, mo (IQR)	31 (20–46)
Histology, *n* (%)	
Transitional cell carcinoma	680 (95.2)
Squamous cell carcinoma	20 (2.8)
Adenocarcinoma	9 (1.2)
Neuroendocrine	2 (0.3)
Small cell carcinoma	3 (0.4)
Missing data	3
Preoperative staging, *n* (%)	
Carcinoma in situ	34 (4.8)
Ta	25 (3.5)
T1	154 (21.6)
T2	370 (52.0)
T3	76 (10.7)
T4	19 (2.7)
Non–transitional cell carcinoma	34 (4.8)
Missing data	5
Received neoadjuvant chemotherapy, *n* (%)	176 (25.2)
Missing data	19
Pathological stage (%)	
pT0	136 (19.1)
pTis	76 (10.7)
pTa	34 (4.8)
pT1	72 (10.1)
pT2	162 (22.7)
pT3	163 (22.9)
pT4	69 (9.7)
Missing data	5
Soft tissue margin positive, *n* (%)	34 (4.8)
Missing data	2
PLND template, *n* (%)	
No PLND	35 (5.1)
Standard	144 (20.8)
Extended PLND	518 (74.3)
Missing	20
Pathologic nodal stage, *n* (%)	
Nx	35 (4.9)
N0	548 (77.1)
N1	58 (8.2)
N2	70 (9.8)
Missing	6

PLND = pelvic lymph node dissection.

Table 2 – Kaplan-Meier estimates of frequency of recurrence by site

	Estimated recurrence rate (%)		
	3 mo	12 mo	24 mo
Any recurrence	4.1	19.8	25.4
Local recurrence	1.8	8.2	10.7
Cystectomy bed	0.7	2.8	3.4
Distal ureteric	0.1	0.3	0.5
Urethral	0.0	0.1	0.5
Pelvic lymph nodes	1.0	5.3	7.2
Distant recurrences	3.0	13.9	17.8
Lung	1.1	4.6	6.2
Liver	0.8	4.1	5.5
Bone	1.0	5.2	6.4
Brain	0.1	0.6	1.0
Adrenal	0.0	0.3	0.7
Bowel	0.0	0.3	0.3
Pancreas	0.0	0.1	0.1
Extrapelvic lymph nodes	1.4	4.9	6.6
Peritoneal carcinomatosis	0.3	0.7	0.7
Port site	0.0	0.3	0.3
Skin	0.0	0.1	0.1
Muscle	0.0	0.2	0.2
Secondary urothelial cancer			
Upper urinary tract	0.0	0.3	0.3
Multiple recurrences	2.0	8.0	11.0

urethelial cancer. Four of the five patients with peritoneal carcinomatosis presented with multiple metastases, and 80% had postoperative upstaging of disease from organ-confined to non–organ-confined disease on the pathologic specimen report; only one of these patients (20%) received neoadjuvant chemotherapy. These findings indicate that peritoneal carcinomatosis due to tumour seeding is related to tumour biology rather than the pneumoperitoneum or other effects of an RARC approach.

It is important to replicate the oncologic principles of open surgery during RARC. Indications and contraindications for totally intracorporeal RARC, along with the preoperative work-up, patient preparation, and a standardised RARC surgical technique with extended PLND template, have previously been described [9]. Accepted early indicators of oncologic efficacy include PSM rates and lymph node yields [1,3]. Our multi-institutional database shows respectable PSM rates of 4.8% and median extended PLND yields of 18, consistent with open series [8]. On multivariable analysis the risk of recurrence was associated with positive compared to negative lymph nodes (N1 vs N0: hazard ratio [HR] 3.6, $p < 0.0001$; N2 vs N0: HR 5.6, $p < 0.0001$) and with pathologic non–organ-confined compared to organ-confined disease (HR 3.8, $p < 0.0001$), and was negatively associated with pT0 compared to organ-confined disease (HR 0.3, $p < 0.001$). On univariable analysis, PSMs (HR 4.49, $p < 0.0001$), selection for ileal conduit urinary diversion versus neobladder (HR 1.88, $p < 0.001$), and female gender (HR 1.63, $p < 0.01$) were all associated with a higher risk of recurrence. Neobladder patients are generally younger with less advanced disease [9], and female gender has been identified in ORC as an independent adverse prognostic factor for both recurrence and progression of bladder cancer [10]. These findings are consistent with findings in large ORC series, giving a further indication that early recurrences following RARC are primarily related to tumour biology [2]. Limitations of this study include the retrospective review, patient selection bias, and inclusion of learning curves. Despite the inclusion of learning curves, 32.6% of RARC patients had pT3/4 disease and 18.0% had positive lymph nodes.

No unusual recurrence patterns after RARC were identified in this multi-institutional study. Early recurrence rates and sites of recurrence appear similar to those for ORC series. Indicators of oncologic efficacy, namely PSM rates and PLND yields, are comparable to ORC series. Positive lymph nodes, non–organ-confined disease, and PSMs were associated with early recurrences, indicating that early recurrences following RARC are primarily related to tumour biology and not the modality of surgical treatment. Histopathologic stage pT0 was a positive prognostic factor for favourable oncologic outcomes.

Author contributions: Justin W. Collins had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Collins, Hosseini, Adding, Wiklund.
Acquisition of data: Collins, Hosseini, Adding, Koupparis, Rowe, Perry, Issa, Schumacher, Wijburg, Canda, Balbay, Decaestecker, Schwentner, Stenzl, Edeling, Pokupić, D'Hondt, Mottrie, Wiklund.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2016.10.030.

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