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Original Article

Propensity-score-matched comparison of soft tissue surgical margins status between open and robotic-assisted radical cystectomy

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Abstract

Introduction: The use of robotic-assisted radical cystectomy (RARC) is becoming more widespread. While its safety is accepted, its oncological efficacy as compared to the current standard, open radical cystectomy (ORC), remains debatable.

Materials and methods: The aim of this study is to compare the rates of positive soft tissue surgical margins (STSM), between patients treated with RARC or ORC, using a large contemporaneous collaborative database. We included 2,536 patients with urothelial carcinoma of the bladder treated at 26 institutions. A propensity-score matching 1:1 was performed with 3 ORC patients matched to 1 RARC patient. The final cohort included 1,614 patients. Uni- and multivariable logistic regression analyses tested the impact of surgical technique on STSM status, before and after propensity-score matching.

Results: Overall, 870 (34%) patients underwent RARC and 1,666 (66%) ORC. The overall STSM rate was 11%; 10% in the ORC group and 13% in the RARC group. Within the propensity-score-matched cohort, the positive STSM rate were 14% and 13% in the ORC and RARC group, respectively ($P = 0.1$). In multivariable analysis, after propensity match RARC approach was not associated with the risk of a positive STSM ($P = 0.1$). These results were confirmed in the subgroup of patients with pathologic non−organ-confined or organ-confined diseases.

Conclusions: While treatment with RARC is associated with a higher absolute rate of STSM, the difference did not remain after adjustment for the effects of other established prognostic factors. Results from ongoing trials are awaited to assess the validity of these findings.

Keywords: Bladder cancer; Robotic-assisted; Open; Radical cystectomy; Soft tissue surgical margins; Propensity score

1. Introduction

Open radical cystectomy (ORC) with pelvic lymph node dissection is the standard of care treatment for very high-risk non−muscle-invasive and muscle-invasive urothelial carcinoma of the bladder (UCB), providing durable local cancer control [1−3]. Even when performed by experienced surgeons, it is associated with significant morbidity including bleeding, pain associated with the incision and prolonged abdominal wall retraction, as well as major fluid shifts [4]. Additionally, visibility of the surgical field can be difficult in the deep pelvic and retrovesical spaces [5−9]. Minimally invasive approaches such as laparoscopic and robotic-assisted radical cystectomy (RARC) have been shown to result in lower estimated blood loss, reduced morbidity, improved convalescence, and earlier initiation of adjuvant systemic therapies if deemed necessary [5,7−12]. RARC has also been shown to be better tolerated in high risk patients [13,14].

Despite these potential perioperative benefits, the safety and oncologic efficacy afforded by RARC remain debated because of the lack of well-designed comparative effectiveness studies with mid/long-term follow-up [5,15,16]. Surgical factors such as soft tissue surgical margins (STSM) and extent of lymph node dissection are well-established quality of care indicators that are associated with oncologic outcomes after radical cystectomy [RC] [17]. To date, the studies that compared the rates of STSM between RARC and ORC are limited by small sample sizes, single-center design and/or lack of control for disease severity [18].

The aim of the current study was to compare the differential rates of positive STSM between patients treated with RARC as compared to ORC, using a large contemporaneous multicenter cohort. In order to adjust for selection bias inherent to the retrospective design of the study, we used a propensity-score-matched analysis.

2. Patients and methods

2.1. Patients

We reviewed an initial cohort of 9,867 patients with nonmetastatic UCB treated with RC and lymphadenectomy at 26 institutions between 2006 and 2015. Patients with pT0 disease on final pathology, treated before 2006 (year of introduction of RARC program in our multicenter collaboration) incomplete follow-up or those who underwent neoadjuvant chemotherapy or radiotherapy were excluded resulting in 2,536 potential patients for analysis.

2.2. Pathological evaluation

All surgical specimens were processed according to standard pathologic procedures at each institution. Tumors were restaged according to the 2009 American Joint Committee on Cancer-Union Internationale Centre le Cancer (AJCC/UICC) TNM classification. Tumor grade was reassessed according to the 2003 WHO/International Society of Urologic Pathology consensus classification. STSM was defined as the presence of tumor at inked areas of soft tissue on the RC specimen [19,20]. Urethral and ureteral margins were not classified as STSM. Lymphovascular invasion (LVI) was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls [21].

2.3. Statistical analysis

Comparison of the RARC and ORC cohorts were assessed using Fisher's exact and chi-square tests (categorical variables). Differences in continuous variables were assessed using the Kruskall-Wallis test.

Uni- and multivariable logistic regression analyses were performed to evaluate the association of clinical and pathologic characteristics with positive STSM.

Owing to inherent differences between patients undergoing ORC and RARC in terms of baseline patient and disease characteristics, we used a 1:1 propensity-score-matched analysis to adjust for the effects of these selection related differences. The use of the propensity score method reduces the customary bias associated with the conventional multivariable modeling approach. The variables adjusted for were tumor grade, pathological stage, lymph node status, and age at surgery [22].

All P values were 2-sided and statistical significance was defined as $P < 0.05$. Statistical analyses were conducted using STATA 11.0 statistical software (Stata Corp., College Station, TX).

3. Results

3.1. Clinicopathologic characteristics (entire cohort)

The clinical and pathologic characteristics of the 2,536 patients included in the study are shown in Table 1. Overall, 870 patients underwent a RARC (34%) and 1,666 underwent ORC (66%). ORC patients had higher tumor grade (high grade: 90% vs. 86%), higher rate of lymph node metastasis (23% vs. 19%), and higher rate of LVI (30% vs. 19%). The adjusted cohort is shown in Table 2 comprising 807 patients treated with RARC (50%) and 807 with ORC (50%).

3.2. Occurrence of soft tissue surgical margins in the entire cohort (unadjusted cohort)

The overall STSM rate was 11%; 10% in the ORC group and 13% in the RARC group. The unadjusted logistic regression uni- and multivariable analyses are shown in Table 3. In univariable logistic regression analyses, locally advanced disease (pT3–pT4), lymph node metastasis, higher tumor grade, concomitant CIS, and LVI were all associated with a higher occurrence of positive STSM. In multivariable analysis, locally advanced disease, lymph node metastases, and RARC approach were all independent predictors of positive STSM.

3.3. Occurrence of soft tissue surgical margins after propensity-score matching (adjusted cohort)

Propensity-score matching was performed to compare STSM between RARC and ORC. Three ORC patients were matched to each RARC patient, which resulted in a cohort of 1,614 patients (807 ORC and 807 RARC). Within the propensity-score-matched cohort, both groups had similar clinical and pathologic characteristics. The positive STSM rate in the entire adjusted cohort was 13%; 13% in the ORC group and 14% in the RARC group ($P = 0.1$).

The logistic regression analyses performed within the propensity-score matching cohort are shown in Table 4. In univariable logistic regression analyses, locally advanced disease (pT3–pT4), lymph node metastasis, higher tumor grade, and LVI were all associated with the occurrence of positive STSM. In

Table 1
Clinicopathologic demographics of 2,536 patients with urothelial carcinoma of the bladder treated with radical cystectomy

		RARC patients 870 (34%)	ORC patients 1,666 (66%)	All patients 2,536 (100%)	*P* value
Age (y)	Mean (SD)	68 (10.1)	68 (10.0)	68 (10.1)	0.5
	Median (IQR)	69 (61–75)	69 (62–76)	69 (62–76)	
Gender	Female	181 (21%)	353 (21%)	534 (21%)	0.4
	Male	689 (79%)	1313 (79%)	2002 (79%)	
Pathological T stage	pTa-pTis-pT1	410 (47%)	587 (35%)	997 (39%)	0.2
	pT2	148 (17%)	363 (22%)	511 (20%)	
	pT3	221 (25%)	506 (30%)	727 (29%)	
	pT4	91 (10.5%)	210 (13%)	301 (12%)	
Pathological grade	Low	60 (7%)	88 (5.3%)	148 (6%)	< 0.001
	High	747 (86%)	1554 (90%)	2301 (78%)	
Positive soft tissue surgical margins	No	758 (87%)	1493 (90%)	2251 (89%)	0.001
	Yes	112 (13%)	160 (10%)	272 (11%)	
Number of lymph nodes removed	Mean (SD)	19 (11)	18 (11)	18 (11)	0.01
	Median (IQR)	18 (12–25)	16 (10–24)	17 (11–24)	
Lymph node metastasis	No	706 (81%)	1284 (77%)	1990 (78%)	< 0.001
	Yes	164 (19%)	382 (23%)	546 (21%)	
Lymphovascular invasion	No	708 (81%)	1161 (70%)	1859 (73%)	< 0.001
	Yes	162 (19%)	505 (30%)	667 (26%)	
Administration of adjuvant chemotherapy	No	767 (88%)	1370 (82%)	2137 (84%)	< 0.001
	Yes	103 (12%)	296 (18%)	399 (16%)	

IQR = interquartile range; ORC = open radical cystectomy; RARC = robotic-assisted radical cystectomy; SD = standard deviation.

Table 2
Clinicopathologic characteristics of 1,614 patients with urothelial carcinoma of the bladder treated with radical cystectomy, comparing RARC and ORC cohorts after propensity match

		RARC patients 807 (50%)	ORC patients 807 (50%)	All patients 1,614 (100%)	*P* value
Age (y)	Mean (SD)	68 (10.1)	69 (9.7)	69 (9.9)	0.5
	Median (IQR)	69 (61−76)	70 (63−76)	69 (62−76)	
Gender	Female	167 (21%)	163 (20%)	330 (20%)	0.5
	Male	640 (79%)	644 (80%)	1284 (80%)	
Pathological T stage	pTa-pTis-pT1	363 (45%)	286 (35%)	649 (40%)	0.001
	pT2	145 (18%)	166 (21%)	311 (19%)	
	pT3	214 (26%)	237 (29%)	451 (28%)	
	pT4	85 (10%)	118 (15%)	203 (13%)	
Pathological grade	Low	60 (7%)	41 (5.1%)	101 (6.3%)	0.002
	High	444 (93%)	872 (90%)	1316 (82%)	
Positive soft tissue surgical margins	No	698 (86%)	702 (87%)	1400 (87%)	0.1
	Yes	109 (14%)	105 (13%)	214 (13%)	
Number of lymph nodes removed	Mean (SD)	19 (11.1)	11 (7.5)	15 (10.4)	0.001
	Median (IQR)	18 (12−25)	10 (6−13)	13 (8−20)	
Lymph node metastasis	No	649 (80%)	637 (79%)	1286 (80%)	0.5
	Yes	158 (20%)	170 (21%)	328 (20%)	
Lymphovascular invasion	No	649 (80%)	547 (68 %)	1196 (74%)	0.001
	Yes	158 (20%)	258 (32%)	416 (26%)	
Administration of adjuvant chemotherapy	No	709 (88%)	686 (85%)	1395 (86%)	0.1
	Yes	98 (12%)	121 (15%)	219 (14%)	

IQR = interquartile range; ORC = open radical cystectomy; RARC = robotic-assisted radical cystectomy; SD = standard deviation.
Propensity-score-matched analysis based on postoperative variables (1:1 match).

Table 3
Multivariable logistic regression analyses evaluating the association of clinical and pathological characteristics with the occurrence of soft tissue surgical margins in 2,536 patients with urothelial carcinoma of the bladder treated with radical cystectomy without neoadjuvant chemotherapy (unadjusted cohort)

	Univariable				Multivariable			
Effect	Odds ratio	Lower 95	Upper 95	*P* value	Odds ratio	Lower 95	Upper 95	*P* value
Male gender (vs. female)	1.10	0.82	1.48	0.5	1.03	0.74	1.43	0.8
Age (y)	1.01	0.99	1.02	0.4	1.01	0.99	1.02	0.4
RARC approach (vs. ORC)	1.27	0.99	1.27	0.06	1.71	1.22	2.40	0.002
Locally advanced disease (pT3-pT4 vs. pTa-pT2)	4.20	3.21	5.50	< 0.001	3.05	2.18	4.27	< 0.001
Lymph node involvement (vs. N0)	3.06	2.37	3.96	< 0.001	1.93	1.39	2.68	< 0.001
pGrade	1.27	1.05	1.52	0.01	1.03	0.84	1.27	0.7
Lymphovascular invasion	2.81	2.18	3.62	< 0.001	1.36	0.99	1.88	0.6
Concomitant carcinoma in situ	2.03	1.28	3.19	0.002	0.91	0.52	1.58	0.7

ORC = open radical cystectomy; RARC = robotic-assisted radical cystectomy.

Table 4
Multivariable logistic regression analyses evaluating the association of clinical and pathological characteristics with the occurrence of soft tissue surgical margins in 1,614 patients with urothelial carcinoma of the bladder treated with radical cystectomy without neoadjuvant chemotherapy (propensity-score-matched cohort 1:1)

	Univariable				Multivariable			
Effect	Odds ratio	Lower 95	Upper 95	*P* value	Odds ratio	Lower 95	Upper 95	*P* value
Male gender (vs. female)	0.94	0.66	1.35	0.7	0.92	0.61	1.39	0.6
Age (y)	1.01	0.99	1.02	0.2	1.01	1.00	1.03	0.1
RARC approach (vs. ORC)	1.04	0.78	1.39	0.7	1.36	0.95	1.94	0.1
Locally advanced disease (pT3-pT4 vs. pTa-pT2)	4.50	3.28	6.17	< 0.001	2.99	2.02	4.42	< 0.001
Lymph node involvement (vs. N0)	3.14	2.31	4.26	< 0.001	1.97	1.34	2.88	0.001
pGrade	1.32	1.09	1.59	0.004	1.22	0.97	1.52	0.09
Lymphovascular invasion	3.13	2.32	4.22	< 0.001	1.78	1.34	2.37	0.001
Concomitant carcinoma in situ	1.05	0.98	1.13	0.1	0.96	0.88	1.04	0.3

Table 5
Multivariable logistic regression analyses evaluating the association of clinical and pathological characteristics with the occurrence of soft tissue surgical margins in overall population and after propensity match score in organ-confined and non−organ-confined BCa diseases

	Multivariable overall				Multivariable propensity score			
Effect	Odds ratio	Lower 95	Upper 95	*P* value	Odds ratio	Lower 95	Upper 95	*P* value
RARC approach (vs. ORC) In ≥pT3 or N+	1.26	0.82	1.92	0.3	1.09	0.71	1.68	0.7
RARC approach (vs. ORC) In ≤pT2 N0	1.92	1.15	3.22	0.01	1.74	0.92	3.15	0.1

ORC = open radical cystectomy; RARC = robotic-assisted radical cystectomy.
Adjusted for gender, age, pGrade, lymphovascular invasion, and presence of concomitant carcinoma in situ.

multivariable analysis, RARC was not associated with of positive STSM ($P = 0.1$) and only locally advanced disease and lymph node metastasis retained an independent association.

3.4. Subgroup analyses in patients with organ-confined and non−organ-confined diseases

Table 5 shows the incidence of positive STSM rates stratified according surgical technique and pathological stage in the overall and matched cohort. RARC approach was not associated with an increased risk of positive STSM in the organ-confined (<=pT2) or non−organ-confined groups after propensity-score-matched cohorts (all $P > 0.1$).

4. Discussion

Despite the potential perioperative benefits associated with its use, the safety and oncologic efficacy afforded by RARC remains debated [7,23,24]. For UBC specifically, a disease where positive STSM has a lethal consequence [19,25], proponents of ORC argue that the oncologic equivalence of RARC remains questionable. We aimed to evaluate the difference of STSM, a widely accepted quality of care indicator, between patients treated with ORC and those treated with RARC.

Positive STSM at RC is a critical event almost unanimously associated with local recurrence, metastatic progression, and eventually death [19,20,26−28]. In 2004, Herr et al. [29] suggested benchmark recommendations of positive STSM rate of <10% and a lymph node yield of >10−14 based upon the oncologic outcomes of 16 experienced ORC surgeons at 4 institutions. The authors suggested that an acceptable positive STSM rates should be less than 10% across all cancers and less than 15% for advanced (pT3−pT4) tumors [29]. The rate of STSM was 13% and 10% in patients treated with RARC or ORC, respectively, in our study. These rates are in accordance with those reported in previous ORC and RARC series and met the criteria defined above [1,2,30−32]. However, when assessing STSM status, adjustment for pathologic stage is essential as more advanced stages are associated with a higher risk of positive STSM [20].

We found that in organ-confined UCB, 7.7% of patients treated with RARC harbored positive STSM as compared to 5.5% of ORC. In non−organ-confined tumors, the STSM rate was 17.5% vs. 12.3% for RARC vs. ORC. Such differences in higher stage patients have led some institutions to consider an open approach in more advanced tumor stages with an increased risk of STSM. These findings are in accordance with a previous report of the International Robotic Cystectomy Consortium showing that the STSM rates in patients with extravesical or locally advanced disease (pT3−pT4) was 16.6% [33]. Therefore, we assessed the rate of STSM within different tumor stages. When adjusted for the effects of pathologic features, we failed to detect an impact of the surgical approach (ORC vs. RARC) on STSM rates in both organ-confined and non−organ-confined tumors. However, sample size limitations may have limited the statistical power of our analyses. Using a propensity-score-matched analysis, we found that the RARC approach did not increase the risk of positive STSM compared to the open approach, when assessed in all patients and in the subgroups of patients with organ-confined (pT1−T2) or non−organ-confined (>pT2 or pN+) diseases. These STSM rates are probably overestimated compared to contemporary cohort that are represented by surgery performed in dedicated center with experienced surgeon after neadjuvant chemotherapy (NAC) (excluded in this series) and with an appropriate pelvic lymph node dissection.

These results are in accordance with previously published randomized controlled studies [23,34,35] and meta-analyses [32,36−38]. In the largest study to date ($n = 118$) that randomized patients to RARC ($n = 60$) vs. ORC ($n = 58$), overall positive STSM rates were 3.3% and 5.2% ($P = 0.6$), respectively. Similarly to our findings, the authors did not observe any differences between surgical approaches in the subgroup of patients with non−organ-confined disease [23]. In the most recent meta-analysis, Yuh et al. [32] assessed STSM status in 1,560 patients and found no significant difference between the RARC and ORC groups (OR: 0.71; 95% CI, 0.46−1.10; $P = 0.13$). However, the event rate was too low to allow solid

conclusions. Similarly, Matulewicz et al. [39] using the national cancer database compared 2,397 RARC and 9,639 ORC patients, reporting similar surgical margin rates.

All published meta-analyses suffer from selection biases due to the inclusion of early RARC cohorts that comprised well-selected patients with a tendency to avoidance of non−organ-confined disease and lymph node metastasis. However, they also suffered from the learning curve of RARC. Specifically, the incidence of pT3/pT4 disease in most early RARC series was approximately 25% compared with 35% to 50% in contemporary ORC series [1,40−44]. Similarly, the rate of metastatic lymph nodes involvement in early RARC series ranged from 9% to 29%, compared with 20% to 28% in ORC series [1,40−44]. In addition, early RARC cohorts included younger patients without history of prior pelvic treatments (i.e., surgery and radiation). These selection biases have made it difficult to meaningfully compare pathologic and survival outcomes in patients treated with RARC. In our study we included experienced open and robotic surgeons. In the current series, patients were propensity matched according to age, gender, T stage, and grade. Therefore, the propensity-score-matched analysis allowed us to overcome, at least, some of the limitations inherent to retrospective surgical selection bias. However, while STSM and extent of lymph node dissection are accepted surrogates of quality of surgery, stage-specific survival is more important in the management of bladder cancer patients. Ongoing prospective trials are mandatory to answer in a controlled manner the differential occurrence of STSM between ORC and RARC. Parekh et al. [45] recently presented the results of the RAZOR trial a randomized, open label, noninferiority phase 3 trial done in 15 medical centers in the United States comparing RARC and ORC. Authors reported no differences regarding surgical margin between the 2 techniques.

This is to our knowledge, the largest international multi-institutional contemporaneous cohort that assessed the STSM status between RARC and ORC. However, our study has noteworthy limitations. First and foremost are the limitations inherent to its design; while the data collection was prospective at most centers, the analyses were retrospective. In addition, we did not perform a central review of all specimens and therefore relied on the dedication and attention of the uropathologists. We did not show the role of center or individual surgeon volume since these data were only partially available in the study cohort. Second, historical patients were included in the ORC group and patients and tumor characteristics might differ from contemporary patients. Although we performed a propensity match analyses to try to mitigate for this effect, differences might exists between the 2 studied groups. Third, RARC group include early robotic experience of several surgeon and therefore the results might differ after an appropriate learning curve. However, no data regarding surgical expertise were included in our study and cannot be analyzed in this manuscript. Fourth, patients treated with NAC were excluded. That was due to avoid the risk of a down staging regarding the STSM status that might have influenced the results from our comparison. Finally, our experience does not represent a well-designed comparative effectiveness study of RARC vs. ORC.

5. Conclusion

Despite the higher absolute rate of STSM in RARC treated patients compared to ORC treated patients, there was no difference between these 2 approaches after adjustment for the effects of established prognostic factors. We could, thus, not find a statistically significant difference in the rate of STSM between ORC and RARC.

This finding was retained in subgroup analyses of organ-confined and non−organ-confined diseases as well as using propensity-score-matched analyses. While we attempted to adjust for all potential bias inherent to a retrospective design, ongoing well-designed, prospective, randomized trials are warranted.

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