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Review

Evidence of Atypical Recurrences After Robot-Assisted Radical Cystectomy: A Comprehensive Review of the Literature

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Abstract. Robot-assisted radical cystectomy (RARC) has seen remarkable growth in the last decade. Despite a low level of evidence, numerous publications reporting on outcomes after RARC are now available. While definitive data on the long-term oncologic safety and efficacy of this technique are still lacking, similar oncological and functional outcomes compared to open radical cystectomy (ORC) have been reported. Several studies have also reported on atypical recurrences after RARC, including peritoneal carcinomatosis, extra-pelvic lymph node metastasis and port-site metastasis. While distant metastases overall do not appear to be affected by technique, it is possible that RARC may be associated with an increased risk of some atypical recurrences and this should be prospectively studied in RARC. However, atypical recurrences are rare events and are infrequent in their description. To date, there is no convincing evidence that, in the hands of equally experienced surgeons who treat bladder cancer routinely, a skillfully performed RARC is less oncologically efficacious than a skillfully performed ORC.

Keywords: Radical cystectomy, atypical recurrence, robotic-assisted

INTRODUCTION

Open radical cystectomy (ORC) with regional lymph node dissection is the gold standard treatment for localized muscle invasive bladder cancer and high-risk non-muscle invasive bladder cancer [1]. Despite aggressive management, it is associated with a recurrence-free and overall survival rate of 68% and 66% at 5 years, respectively [2]. Most local and distal recurrences occur during the first 2 years after surgery, with a lethal impact on survival [3].

Since first reported in 2003 [4], robot-assisted radical cystectomy (RARC) with regional lymph node dissection has gained momentum with increased utilization in the United States, from 0.6% in 2004 to 12.8% in 2010 [5]. With the evolving landscape of this surgical technique, the concern of safety and oncological control has been raised. Due to data limitations, until recently, RARC was considered as an investigational procedure, with the aim to improve perioperative outcomes, hospital stay and recovery.

However, recently, experience and publications regarding RARC are more abundant in the literature, including systematic reviews [6, 7], randomized controlled trials [8–11] and international multicentric studies [12–14]. While definitive data on the long-term oncologic safety and efficacy of this technique are still lacking, similar oncological and functional outcomes compared to ORC were reported and there have been outcomes favorable to RARC, namely less estimated blood loss and lower analgesic requirements [15].

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Nevertheless, some studies raised concern that atypical recurrences, including peritoneal carcinomatosis, extra-pelvic lymph node metastasis and port-site metastasis, could be more frequent after RARC. The aim of this article was to comprehensively review the current available data regarding atypical recurrences after RARC.

DEFINITION OF ATYPICAL RECURRENCES

Contemporary open cystectomy has a 5–15% probability of pelvic recurrence and 50% of distal recurrence [16]. Nearly 90% of distant recurrence appears within the three first years after radical cystectomy, mainly in the two first years. The most likely sites for distal recurrence are lymph nodes, lungs, liver and bones, and these locations are found in at least 95% of the patients with metastatic disease [17]. In the literature, atypical recurrence sites usually include peritoneal carcinomatosis, extra-pelvic lymph node metastasis and port-site metastasis [18]. However, in autopsy and clinical studies, almost all organs were shown to be involved by metastases in at least some patients [17, 19].

In these series, peritoneal carcinomatosis was found in 16–19% of bladder cancer patients, and tumors with variant histology were more likely to be present at the peritoneal metastases. Of note, the number of metastatic sites was significantly higher among patients with peritoneal involvement (mean of 4 sites) than patients without peritoneal involvement (mean of 2 sites). Patients with peritoneal involvement, irrespective of the histologic subtype of the tumor, had a shorter metastasis-free interval (median time: 2 months [range: 0–28] *vs*. 10 months [range: 0–192] for the patients without peritoneal involvement; $p = 0.0002$) and had most often multi-organ involvement [17].

The lymph nodes are the most common sites of metastasis from bladder cancer. Clinical studies found a sequentially decreasing incidence of involvement of nodes as distance from the bladder increased [17]. While intrathoracic and supraclavicular lymph nodes metastases were not infrequent (respectively 20% and 10% of patients with pathologically proven metastases), these events were rare in the absence of prior pelvic or abdominal adenopathy (1.3%). Overall, only 3% of patients had metastatic disease elsewhere without metastasis at one of these sites: lymph nodes, lungs, liver, bone or peritoneum.

Port-site metastases are a rare complication of minimally invasive surgery. The first report of urologic tumor port seeding occurred after a laparoscopic lymphadenectomy for urothelial carcinoma of the bladder [20]. In a survey following minimally-invasive procedures for genito-urinary malignant disease, the authors reported an incidence of 10 cases out of 10,912 procedures (0.09%), including 3 nephroureterectomies for urothelial carcinoma [21]. Reports of tumor implantation after laparoscopic procedures in patients with intra-abdominal malignancies are a concern. This fear has been a major factor precluding the initial widespread use of laparoscopy in the treatment of malignant disease and this is still a matter of concern in regards with RARC. The incidence of tumor seeding in general laparoscopic surgery was up to 21%, with 3 abdominal-wall metastases in a series of 14 laparoscopic hemicolectomies reported in *The Lancet* in 1994 [22]. However, most authors report an incidence of 0.5%, comparable to the rate for surgical wound metastases (0.4–1.5%) in conventional open methods [23–25].

RATIONALE FOR ATYPICAL RECURRENCES

Laparoscopic surgery has been associated with a minimal risk of peritoneal tumor spread, as well as port-site metastasis, and 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 tumor seeding related to pneumoperitoneum or insufflation [26]. Many clinical and experimental studies have tried to explain the mechanism and the potential risk of laparoscopy and robot-assisted surgery for the occurrence of atypical metastasis. Several possible causes have been suggested, including intrinsic factors, such as tumor aggressiveness and natural behavior in cases of extravesical disease or extensive nodal involvement, local process in the wound and host immune response [23, 27]. But laparoscopy-related factors are still a matter of concern. Evidence derived from experimental studies suggests that CO_2 pneumoperitoneum may inhibit the peritoneal immune response against malignant urothelial cells and may contribute to recurrence in the pelvis and at port sites [28]. Furthermore, tumor cell seeding may be enhanced via aerolization of the tumor cells into the peritoneal cavity due to repeated gas insufflation and desufflation [29]. Leakage of the

gas around the port, could also result in accumulation of tumor cells at the port site (chimney effect) [30], as well as contamination of the port site from the repeated introduction of the laparoscopic instruments used for dealing with the tumor [31]. Many centers are now using devices such as the AirSeal®, which is aimed at decreasing smoke and fogging of the lens during laparoscopy but also provides higher CO_2 flow. In theory, this may have some impact on tumor seeding and close evaluation is recommended.

Finally, technical issues and breaching of oncologic surgical principles, including vigorous surgical manipulation, specimen morcellation, entry into the bladder and the retrieval method, have also been investigated as potential explanations. Of note, a study from the International Robotic Cystectomy Consortium showed that the incidence of early oncologic failure after RARC, including atypical recurrences, decreased with time from 10% in 2006 to 6% in 2015 [13]. If these recurrences are surgery related, this trend might be explained by the evolution of the technique of RARC, the learning curve, experience with the procedure and comfort with the robot-assisted platform for surgery. In order to prevent this risk in an operation with high oncologic stakes, it is mandatory to strictly follow oncological principles, such as no tumor violation, minimal handling, prevention of urine spillage, or use of retrieve bag.

ATYPICAL RECURRENCES AFTER RARC IN THE LITERATURE

The first case report of port-site metastasis after RARC was published back in 2005 [32]. In this case, a 52-year old patient underwent an uneventful procedure, without morcellation, with an extra-corporeal neobladder reconstruction. The final pathology was pT3bN0M0. Ten months after surgery, the patient presented an isolated 4 cm abdominal wall mass at the site of the 10 mm port at the left midclavicular line, with no evidence of local recurrence. A needle biopsy confirmed the urothelial metastasis. The patient was given only palliative analgesics as he refused the options of local excision with adjuvant radiotherapy and/or chemotherapy. The authors of this report suggest that a proper selection of low stage (cT1-T2) and low grade disease might decrease such risk of port site metastases. They also recommend careful manipulation of the mass and proper trocar fixation to prevent gas leakage. Since then, six more cases were reported in the literature [13, 33] (Table 1).

In a meta-analysis including 87 surgical series of RARC, Yu et al. reported on oncological outcomes and found a disease-free survival at 1, 2, 3 and 5 years of 79–96%, 67–81%, 67–76%, and 53–74%, respectively [7]. These results compare favorably with similar rates for ORC. However, an important limitation was a selection bias toward smaller tumors and a mean follow-up between 6 and 84 months. In the 5 series with median follow-up of >36 months, rates of local recurrence without distant disease ranged between 0% ($n=15$) and 9% ($n=99$) [34–38]. Of note, no port-site recurrence was reported in these series.

In their initial study published in 2015, Nguyen et al. compared 263 RARC cases to 120 ORC cases in order to evaluate the effect of surgical technique on the risk of recurrence [39]. In this retrospective, monocentric analysis, the authors found no large difference within 2 years of surgery in the number of local recurrences between ORC and RARC patients (23% vs 18%), and the distribution of local recurrences was similar between the two groups. Similarly, the number of distant recurrences did not differ between the groups (36% vs 29%). However, there were distinct patterns of distant recurrence. Extrapelvic lymph node locations were more frequent for RARC than ORC (23% vs 15%). In addition, two recurrences in the RARC group were detected in the cervical chain and one in the mediastinum. Furthermore, peritoneal carcinomatosis was found in 8% of ORC patients with distant recurrence, in contrast to 21% of RARC patients with distant recurrence. In detail, five RARC patients had peritoneal carcinomatosis only, all diagnosed with abdominopelvic computed tomography and histologically confirmed in three patients. Four RARC patients with multiple recurrence locations also had peritoneal carcinomatosis, confirmed histologically in one case. The two cases of peritoneal carcinomatosis in ORC patients were diagnosed by CT only. No port-site metastasis was documented in the RARC cohort. Although RARC was not a predictor of recurrence in multivariable analyses and despite selection bias, this study raised concerns that an association between RARC and recurrence could not be excluded with certainty.

The same group published an updated report after accruing further cases [18]. In the updated analysis, including 310 patients treated with RARC, they found a total of 19 isolated local recurrences, 33 distant recurrences and 29 atypical recurrences (peritoneal carcinomatosis and extrapelvic lymph node metastases). Tumor stage and lympho-vascular

Table 1
Atypical recurrences after RARC in the literature

Study	Year	Atypical recurrence	Number of cases	Frequency among all recurrences	Delay after surgery
El Tabey et al. [32]	2005	Port site metastasis	1	NA	10 months
Nguyen et al. [18]	2016	Peritoneal carcinomatosis	13	16%	Median: 10 months (IQR: 4–11)
		Extrapelvic LN metastasis	21	26%	Median: 11 months (IQR: 3–18)
Gandaglia et al. [40]	2016	Peritoneal carcinomatosis	2	4%	NA
Hussein et al. [13]	2017	Peritoneal carcinomatosis	17	1%	6 cases <3 months
		Port site metastasis	5	0.4%	3 cases <3 months
Khetrapal et al. [33]	2017	Port site metastasis	1	NA	2 months
Collins et al. [14]	2017	Peritoneal carcinomatosis	5	1.4%	Risk of 0.3% at 3 months, 0.7% at 12 months and 0.7% at 24 months
		Port site metastasis	2	0.6%	Risk of 0.3% at 12 months and 0.3% at 24 months

IQR: Interquartile range.

invasion were the strongest predictors of recurrence, including atypical recurrence. On multivariate analysis adjusting for tumor stage and lymphovascular invasion, the predictors of atypical recurrences were a lower estimated glomerular filtration rate and perioperative blood transfusion (HR: 2.21, 95% CI: 1.03–4.74, $p = 0.04$ and HR: 2.85, 95% CI: 1.31–6.18, $p = 0.008$, respectively). However, predictors of atypical recurrences were not different than those of distant recurrences at common locations, and the authors suggested that the main factor that influenced recurrence was the pathologic tumor characteristics and not the surgical technique.

Similarly, Gandaglia et al. published the results of 155 consecutive patients who received RARC for localized bladder cancer in a high-volume robotic center and found a 5-year recurrence-free survival rate of 53.7% [40]. Among patients who experienced recurrence, 12% had local recurrence, 4% had peritoneal recurrence, and 84% had distant recurrence. Considering the low rate of peritoneal metastases observed in this series, together with the majority of recurrences after RARC occurring at distant sites, the authors advocated the ability of RARC to provide local control with good safety. Again, tumor stage and nodal status represented independent predictors of recurrence and cancer specific mortality in patients treated with RARC.

Of the four published randomized controlled trials comparing RARC and ORC [8–11], only one analyzed the oncological outcomes [11], while the other focused on feasibility, lymph node yield and perioperative complications. This study included 20 patients in the RARC arm, 20 in the ORC arm and 19 in the laparoscopic arm. At 12 months, 10 patients had disease recurrence with no significant difference between the different arms. In the RARC patients there were 5 recurrences; 2 patients had nodal recurrence, 2 had distal recurrence and 1 had both. There were no port-site metastasis reported.

The International Robotic Cystectomy Consortium, a prospectively populated quality-assurance database, included more than 2,000 patients from 37 institutions in 17 countries who were treated for localized bladder cancer with RARC from 2003. A long-term oncologic outcomes analysis was published in 2015, including 743 patients with more than 5 years of follow-up data [12]. With a median time of follow-up of 67 months, the overall recurrence rate was 29%, which included an 11% local recurrence rate. Only seven patients were found to have peritoneal carcinomatosis, which represents 3.5% of all the distal recurrences, with a mean time to recurrence of 178 days. One incision/port-site recurrence was also reported 88 days after surgery. All the patients with atypical recurrence had disease greater than pT2 and 5/8 were pN+. Overall, the long-term oncologic outcomes appeared similar to historical ORC data.

The same group investigated the factors associated with early recurrence (relapse within 3 months after RARC) [13]. Out of 1,380 patients treated with RARC, 305 patients (22%) experienced disease relapse, 220 (16%) had distant recurrence, 154 (11%) had local recurrence, 17 (1%) had peritoneal carcinomatosis and 5 (0.4%) had port-site recurrence, at a mean follow-up of 24 months. Early recurrence developed in 71 patients (5%), and on multivariate analysis, any complication, extravesical disease and nodal involvement were significant predictors of early recurrence. Of note, 8 patients experienced early recurrence despite having organ confined disease (<pT3N0) and in 3 of these cases a breach of

oncologic surgical principles was noted (spillage of urine or tumor in 2 cases, specimen not retrieved in bag in 1 case). Furthermore, early recurrence decreased from 10% in 2006 to 6% in 2015, suggesting an improvement of the safety of the procedure with the learning curve.

As most of the published series used extracorporeal reconstruction, the European Association of Urology Robotic Urology Section (ERUS) focused on patients who underwent totally intracorporeal RARC [14]. Among 717 patients, recurrence at any site was found in 4.1% of patients at 3 months, 19.8% at 12 months, and 25.4% at 24 months, similar to rates seen in ORC series. Regarding atypical recurrence patterns, five patients (0.7%) had peritoneal carcinomatosis and two patients (0.3%) had metastasis at the port-site (wound site), which are of low incidence. Patients with peritoneal carcinomatosis and port-site metastasis had all high-grade disease. 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. Finally, no unusual recurrence patterns after RARC were identified in this multi-institutional study and the results suggest that peritoneal carcinomatosis due to tumor seeding is related to tumor biology rather than the pneumoperitoneum or other effects of an RARC approach.

CONCLUSION

In the last decade, RARC has seen remarkable growth. Outcomes have been evaluated in several retrospective studies and in four randomized controlled trials. While distant metastases overall do not appear to be affected by technique, it is possible that RARC may be associated with an increased risk of some atypical recurrences, especially peritoneal carcinomatosis, and this should be prospectively studied in RARC. However, atypical recurrences were described in a very low number of cases and to date, there is no convincing evidence that, in the hands of equally experienced surgeons who treat bladder cancer routinely, a skillfully performed RARC is less oncologically effective than a skillfully performed ORC.

CONFLICT OF INTEREST

None.

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