Gynecological organ involvement at robot-assisted radical cystectomy in females: Is anterior exenteration necessary?

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Abstract

Introduction: We aimed to investigate patient and disease variables associated with gynecological organ invasion in females with bladder cancer at the time of robot-assisted radical cystectomy (RARC).
Methods: We conducted a retrospective review of female patients who underwent robot-assisted anterior pelvic exenteration (RAAE) between 2005 and 2016. Patients were divided into two groups: those with gynecological organ involvement at RAAE and those without. Data were reviewed for perioperative and pathological outcomes. Kaplan-Meier method was used to depict survival outcomes. Multivariable stepwise regression analysis was performed to identify predictors of gynecological organ involvement.
Results: A total of 118 female patients were identified; 17 (14%) showed evidence of gynecological organ invasion at RAAE. Patients with gynecological organ invasion had more lymphovascular invasion at transurethral resection of bladder tumour (TURBT) (82% vs. 46%; p=0.006), trigonal tumours at TURBT (59% vs. 18%; p=0.001), multifocal disease (65% vs. 33%; p=0.01), pN+ (71% vs. 22%; p<0.001), positive surgical margins (24% vs. 4%; p=0.02), and they less commonly demonstrated pure urothelial carcinoma at TURBT (18% vs. 66%; p<0.001). On multivariate analysis, significant predictors of gynecological organ invasion were pN-positive disease (odds ratio [OR] 6.48; 95% confidence interval [CI] 1.64–25.51; p=0.008), trigonal tumour location (OR 5.72; 95% CI 1.39–23.61; p=0.02), and presence of variant histology (OR 18.52; 95% CI 3.32–103.4; p=0.001).
Conclusions: Patients with trigonal tumours, variant histology, and nodal involvement are more likely to have gynecological organ invasion at RAAE. This information may help improve counselling of patients and better identify candidates for gynecological organ-sparing cystectomy.

Introduction

The gold standard for treatment of females with muscle-invasive bladder cancer (MIBC) and refractory non-muscle invasive disease is anterior pelvic exenteration.[1] Robot-assisted radical cystectomy (RARC) has been increasingly used, as it provides equivalent oncological outcomes to the conventional open approach, and provides superior perioperative outcomes in terms of less blood loss, transfusion rates, and improved convalescence.[2] Robot-assisted anterior pelvic exenteration (RAAE) has been shown feasible and reproducible.[3]

Recently, there has been growing interest in sparing the gynecologial pelvic organs at radical cystectomy (RC) to minimize adverse health-related quality of life (HRQoL) consequences, especially for younger patients. Prior studies have shown that anterior exenteration may pose a negative impact on females regardless of their age. Removing gynecological organs can cause early menopause, increasing risk of osteoporosis and or the need for hormone replacement therapy (HRT), which may increase risk of breast cancer.[4,5] Additionally, women may experience worse self-perceived body-image, more difficulties adapting to life, and decreased social functioning.[6] It also precludes female patients from future childbearing and adversely impacts their sexual lives.

Prior studies have investigated the prevalence of gynecological organ involvement at the time of open RC, with an estimated incidence of 3–8%.[7-9] Despite the relatively low incidence, use of gynecological organ-sparing surgeries remains limited. In this context, we aimed to investigate the prevalence of tumour invasion into adjacent gynecological organs, and identify predictors for gynecological organs involvement at RAAE, which may improve risk stratification and allow better counselling for patients who wish for gynecological organ-sparing surgery.

Methods

We retrospectively reviewed our prospectively maintained RARC quality assurance database (2005–2016) performed by a single surgeon (K.A.G.) at Roswell Park Cancer institute. All patients had RARC with curative intent and had non-metastatic disease on preoperative workup. Data were analyzed for demographics (age, body mass index [BMI], American Society of Anesthesiologists [ASA] score), preoperative disease-specific characteristics (neoadjuvant chemotherapy, prior abdominal/pelvic surgery, and prior radiation), operative variables (type and technique of urinary diversion; operative time, estimated blood loss [EBL]), and postoperative outcomes (adjuvant chemotherapy, hospital stay, intensive care unit [ICU] stay, complication, readmissions, mortality, and followup). All female patients were treated with RAAE, with surgical technique previously described.[10,11] Additional disease-specific parameters were collected from final pathology and most recent transurethral resection of the bladder tumour (TURBT) reports (tumour site, TNM staging, tumour grade, histological type, and lymphovascular invasion [LVI]).

Female patients were identified and divided into two groups: those with gynecological organ involvement at RAAE and those without. Univariable associations between baseline characteristics and outcome measurements were statistically assessed using Fisher exact test for categorical and Wilcoxon rank sum test for continuous variables. Stepwise multivariate logistic regression models were fit to evaluate preoperative, operative, postoperative, and pathological predictors of gynecological organs invasion. All statistical analyses were performed using SAS software (version 9.3, SAS Institute Inc., Cary, NC, U.S.). All tests were two-side, with statistical significance defined as $p \leq 0.05$.

Results

A total of 118 female patients underwent RAAE between 2005 and 2016, of whom 17 (14%) exhibited direct tumour invasion into their gynecological organs. Both groups were comparable in terms of preoperative and operative variables. There was no statistically significant difference between the two groups in terms of hospital or ICU stay, complications, readmissions, and mortality at 30 and 90 days. Patients who had gynecological organ invasion received adjuvant chemotherapy more frequently (41% vs. 9%; p=0.002) (Table 1). They more frequently demonstrated positive pelvic lymph nodes (pN+) (71% vs; 22%; p<0.001), LVI (82% vs. 46%; p=0.006), positive surgical margins (24% vs. 4%; p=0.02), variant/mixed histology tumours (83% vs. 34%;, p<0.001), trigonal tumour location (59% vs. 18%; p=0.001), and multifocal tumours (65% vs. 33%; p=0.01). Vaginal involvement was the most common site for female organ involvement (n=13, 76%) followed by the uterus (n=7, 41%) (Table 2). On multivariate analysis, significant predictors of gynecological organ invasion were pN+ (odds ratio [OR] 6.48; 95% confidence interval [CI] 1.64–25.51; p=0.008), trigonal tumour location on TURBT (OR 5.72; 95% CI 1.39–23.61; p=0.02), and presence of variant histology on TURBT (OR 18.52; 95% CI 3.32–103.4; p=0.001) (Table 3).

Discussion

The past decade has witnessed a dramatic increase in the use of RARC (<1 to >13 %).[12] However, studies from the open RC literature have demonstrated the feasibility and safety of gynecological organ preservation at RC, with paucity of studies investigating the prevalence of female organ involvement at RAAE (Table 4). Potential advantages of such an approach include avoidance of early menopause, especially in younger patients, which may pose an increased risk of cardiovascular disease and accelerated bone loss. While long-term HRT can combat these outcomes, it has been associated with long-term risk of breast cancer.[4,5] For patients of childbearing age, removing the uterus and adnexa precludes them from future pregnancies; it is important to note that studies have demonstrated that pregnancy is safe after gynecological organ-sparing cystectomy.[13,14] Such benefits are not limited to premenopausal women. Ali-El-Dein et al suggested that by preserving the reproductive organs, there is less damage to the pelvic fascia, thereby reducing the risk of pelvic floor prolapse.[15] Additionally, in patients who underwent neobladders, the risk of neobladder-vaginal fistula is significantly diminished even with only sparing the anterior vaginal wall.[16] From a quality of life standpoint, negative impacts of anterior exenteration have been studied and well-documented. In a retrospective cohort of 62 patients who underwent anterior pelvic exenteration, Roos et al found that more physical, sexual, and social problems were reported. Specifically, younger women in the study experienced greater difficulty adapting to daily life, and experienced worse body image and adverse impact on their sexual lives.[6] In the same context, a more recent study found that the construction of a neovagina has been associated with better self-confidence and allowed resumption of sexual function.[17,18]

Despite the benefits of gynecological organ-sparing surgery, the question remains whether oncological outcomes are in turn compromised. The largest cohort of patients who underwent uterus-, fallopian tube-, ovary-, and vagina-sparing cystectomy followed by U-shaped ileal neobladder construction included 30 women, of whom nine died from bladder cancer, one patient had local recurrence, and five patients experienced disseminated disease. One-third of the patients had extravesical disease and disease-specific survival was 70% at five years.[19] These findings highlight the need for

Table 1. Perioperative characteristic of 118 female patients who underwent RAAE and urinary diversion

Variable	No gynecological organ invasion	Gynecological organ invasion	p
Number of patients, n (%)	101 (85)	17 (14)	N/A
Preoperative characteristics			
Age at cystectomy, mean (SD) (years)	69 (11)	71 (10)	0.51
BMI, mean (SD) (kg/m^2)	28 (6)	28 (6)	0.95
ASA score ≥3, n (%)	55 (57)	13 (76)	0.14
Prior abdominal/pelvic surgery, n (%)	77 (77)	10 (63)	0.23
Prior radiation, n (%)	2 (2)	0	1.00
Neoadjuvant chemotherapy, n (%)	17 (17)	6 (35)	0.10
Operative outcomes			
Type of diversion, ileal conduit, n (%)	89 (88)	17(100)	0.45
Technique of diversion, intracorporeal, n (%)	68 (67)	13 (76)	0.45
Operative time, median (IQR) (minutes)	370 (300–448)	356 (315–393)	0.55
Estimated blood loss, mean (SD) (ml)	300 (110–500)	250 (113–475)	0.96
Postoperative outcomes			
Adjuvant chemotherapy, n (%)	9 (9)	7 (41)	0.002
Hospital stay, median (IQR) (days)	9 (7–12)	9 (7–9)	0.54
ICU stay, median (IQR) (days)	1 (1–2)	1 (1–2)	0.65
30-days overall complications, n (%)	51 (51)	8 (47)	0.79
30-day high-grade complications, n (%)	18 (18)	2 (12)	0.73
90-day overall complications, n (%)	63 (62)	10 (59)	0.78
90-day high-grade complications, n (%)	23 (23)	2 (12)	0.52
30-day readmissions, n (%)	19 (19)	2 (12)	0.73
90-days readmissions, n (%)	29 (29)	3 (18)	0.56
30-day mortality, n (%)	0	0	1.00
90-day mortality, n (%)	6 (6)	1 (6)	1.00
Followup, median (IQR) (months)	23 (8–45)	9 (6–13)	0.03

ASA: American Society of Anesthesiologists; BMI: body mass index; ICU: intensive care unit; IQR: interquartile range; RAAE: robot-assisted anterior pelvic exenteration; SD: standard deviation.

identification of better selection criteria for patients undergoing gynecological organ-sparing surgeries. Menon et al published a series of three cases that underwent robot-assisted gynecological organ-sparing RC, but relapse rates or survival were not reported.[20] The prevalence of gynecological organ invasion in our study is 14%, which is higher than previously reported.[7,8] Ali-El-Dein et al attempted to identify predictors of gynecological organ involvement at RC in a cohort of 609 women who underwent open anterior exenteration. They found that the risk of the genital organ involvement was low, with only 16 patients (3%) experiencing gynecological organ invasion. Gynecological organ involvement was more frequent with high-grade tumours and urothelial cell type cancers.[21] In a similar study that included 54 women, only three (6%) patients experienced gynecological organ involvement, however, they were unable to find any predictors of gynecological organ involvement, likely because of the small patient cohort.[8] We also observed a similar pattern of prior gynecological organ involvement, where the vagina is the most common site involved.[9]

We found that pN-positive disease, trigonal tumour location at TURBT, and presence of variant histology at TURBT were significant predictors of gynecological organ invasion at RAAE. The adverse impact of pN-positive status and the presence of variant histology on oncologic outcomes have been previously described.[22] The trigonal location may be associated with gynecological organ invasion, given the anatomical proximity to the vagina posteriorly. Tumour location and presence of variant histology can be known preoperatively as part of clinical staging, and therefore, can be used for better counselling of patients about the feasibility of genital-sparing surgery.

Although the vast majority of female patients do not have gynecological organ invasion at anterior pelvic exenteration, currently, the decision to perform a gynecological sparing procedure is mainly based on patient and surgeon preferences. Surgeons usually rely on clinical staging (prior TURBTs and/or imaging studies) to determine the eligibility of patients for such procedure. Identifying factors associated with gynecological organ involvement may help improve risk stratification, and identify women who can safely undergo gynecological organ-sparing surgery rather than depriving all women of maintaining their gynecological organs upon cystectomy. Higher-risk women would continue to undergo radical surgery, given the adverse impact of disease stage on disease outcomes.

Table 2. Pathological outcomes of 118 female patients who underwent RAAE

Variable	No gynecological organ invasion	Gynecological organ invasion	p
Number of patients, n (%)	101 (85)	17 (14)	NA
TURBT findings			
Lymphovascular invasion, n (%)	42 (46)	14 (82)	0.006
Positive surgical margins, n (%)	4 (4)	4 (24)	0.02
Pure urothelial cell carcinoma, n (%)	67 (66)	3 (18)	<0.001
Urothethlial mixed carcinoma, n (%)	27 (27)	12 (71)	<0.001
Non-urothethlial carcinoma, n (%)	7 (7)	2 (12)	0.62
Tumour location at TURBT			
Lateral wall, n (%)	63 (63)	14 (83)	0.11
Posterior wall, n (%)	39 (39)	10 (59)	0.12
Trigone, n (%)	18 (18)	10 (59)	0.001
Dome of the bladder, n (%)	20 (20)	2 (12)	0.74
Anterior wall, n (%)	31 (31)	6 (35)	0.71
Multifocal, n (%)	33 (33)	11 (65)	0.01
Gynecological organ involvement at RAAE			
Vagina, n (%)	N/A	13 (76)	-
Cervix, n (%)	N/A	1 (6)	-
Uterus, n (%)	N/A	7 (41)	-
Adnexa, n (%)	N/A	6 (35)	-
Perivascular fat, n (%)	31(31)	4 (24)	0.55
Pathology after RAAE			
Lymph node yield, mean (SD)	21 (11)	20 (12)	0.63
Positive lymph nodes, n (%)	22 (22)	12 (71)	<0.001

N/A: not available; RAAE: robot-assisted anterior pelvic exenteration; SD: standard deviation; TURBT: transurethral resection of bladder tumour.

Despite the uniqueness of this study, several limitations exist. The retrospective study design has its recognized limitations. This is a single institution study; therefore, generalization of the results may not be appropriate. In spite of the relatively small cohort of patients, to the best of our knowledge, this is the largest series of female patients with gynecological organ invasion that has been reported after RAAE.

Conclusion

Trigonal tumour location and presence of variant histology at TURBT were significantly associated with gynecological organ involvement in female patients at RAAE. These results may help improve risk stratification and better identify candidates for gynecological organ-sparing cystectomy.

Table 3. Univariate and multivariate stepwise logistic regression models for predictors of gynecological organ invasion

Variable	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Lymph node yield	0.99	0.95, 1.04	0.74			
Positive lymph nodes (N-)	8.62	2.74, 27.09	<0.001	6.48	1.64, 25.51	0.008
Lymphovascular invasion	5.44	1.46, 20.24	0.01			
Positive surgical margins (negative)	7.46	1.66, 33.51	0.009			
Variant histology (pure urethelial)	9.20	2.47, 34.2	0.001	18.52	3.32, 103.4	0.001
Perivesicular fat invasion	0.70	1.29, 2.30	0.02			
Multifocal tumour	3.78	1.29, 11.10	0.02			
Tumour location						
Trigone	6.59	2.21, 19.63	<0.001	5.72	1.39, 23.61	0.02
Dome	0.54	0.11, 2.56	0.65			
Lateral wall	2.82	0.76, 10.43	0.12			
Anterior wall	1.23	0.42, 3.63	0.36			
Posterior wall	2.27	0.80, 6.46	0.12			

CI: confidence interval; OR: odds ratio.

Table 4. Review of prior studies investigation gynecological organ-sparing cystectomies[22]

Reference	Pts, n	FU median* (IQR)	T stage ≥3 (%)	Positive surgical margins	Local recurrence	Distant recurrence	Disease-specific mortality (%)	DSS (%)	OS (%)
Open approach									
Ali-El-Dein et al (2013)[21]	15	72 (37–99)	15 (100%)	NR	1 (6.7%)	2 (13%)	3 (20%)	5-yr: 80%	5-yr: 80%
Horenblas et al (2001)[23]	3	42 (24–72)	1 (7.7%)	NR	0	0	0	NR	NR
Koie (2010)[19]	30	41 (4–98)	10 (33.3%)	0%	1 (3.3%)	5 (16.7)	9 (30%)	5-yr: 70%	NR
Kulkarni et al (2008)[24]	14	24.5 (12–65)	-	NR	1 (7%)	1 (7%)	2 (14%)	NR	NR
Wishahi et al (2015)[25]	13	132 (80–180)	3 (23%)	0%	NR	NR	NR	5-yr: 100% 10-yr: 62%	5-yr: 100% 10-yr: 62%
Robot-assisted approach									
Menon et al (2004)[20]	3	NR	3 (100%)	0	NR	NR	NR	NR	NR

*Followup period is measured in months. DSS: disease-specific survival; FU: followup; NR: not reported; OS: overall survival; pts: patients.

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