



Original Article

Gynecologic organ involvement and incidental gynecologic organ neoplasms in female patients with urothelial carcinoma of the bladder undergoing anterior pelvic exenteration in Rajavithi Hospital

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Female, urothelial carcinoma of bladder, anterior pelvic exenteration, gynecologic organ

Abstract

Objective: To evaluate the pathological data of the bladder and gynecologic organs obtained from anterior pelvic exenteration and review the incidence of gynecologic organ involvement and primary gynecologic tumor.

Materials and Methods: The clinicopathological data of 70 patients who were diagnosed with bladder transitional cell carcinoma and underwent anterior pelvic exenteration in Rajavithi Hospital between January 2008 and October 2020 were analyzed to examine and determine any correlations.

Results: Thirteen (18.5%) patients had gynecologic organ involvement. This consisted of 4 cases (5.7%) involving the uterus, 7 (10%) involving the vagina, 2 (2.8%) involving the ovaries, and 10 (14.2%) involving the cervix. Female patients with gynecologic organ invasion were more likely to have a high pathological T stage ($p < 0.001$), and have pre-operative hydronephrosis ($p = 0.002$). From multivariate logistic regression, pre-operative hydronephrosis was associated with increased risk of gynecologic organ invasion (odds ratio 9.57; 95% confidence interval, 1.86 - 49.18; $p = 0.007$). There were 23 (32%) female patients incidentally diagnosed with benign gynecologic tumors, specifically 16 (22%) cases of myoma uteri, 7 (10%) of adenomyosis and 4 (2.8%) with ovarian cysts. No patient was diagnosed as having primary gynecologic malignancy.

Conclusions: The incidence of gynecologic organ involvement in female patients who had undergone anterior pelvic exenteration for urothelial carcinoma of the bladder was 18.5%. Pre-operative hydronephrosis was a risk factor associated with increased risk of gynecologic organ involvement. Information from this study may allow better identification of candidates for gynecologic organ sparing surgery.

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Introduction

Bladder cancer is the ninth most common cancer worldwide.¹ More than 60% of all bladder cancer cases and half of all the bladder cancer deaths occur in the less developed regions of the world. Three-quarters of all bladder cancer cases occur in men.¹ Despite having a lower incidence of bladder cancer, females have more advanced tumors at the time of diagnosis.²

Anterior pelvic exenteration is the standard treatment for recurrent high grade or muscle-invasive bladder cancer. This operation in women involves en bloc removal of the bladder, entire urethra and adjacent vagina, uterus, distal ureters, and regional lymph nodes.³ Despite good oncologic outcomes, anterior pelvic exenteration has a great impact on functional outcomes.⁴ Even though the literature regarding involvement of the gynecologic organs in female patients with bladder cancer reported relatively low rates of gynecologic organ involvement, the data in the literature tends to be from small sample sized studies and information about risk factors for gynecologic organ involvement is limited.⁵⁻⁸ Currently, there are no standard guidelines for preservation of the uterus or other gynecologic organs in anterior pelvic exenteration.⁹ It is recognized and advisable that gynecologic organ preservation should be considered for younger women who desire to retain their fertility.¹⁰

In this study, we aimed to investigate the incidence of gynecologic organ involvement at the time of anterior pelvic exenteration, which may allow better identification of candidates for gynecologic organ sparing surgery.

Materials and Methods

We retrospectively reviewed the records of female patients diagnosed with bladder cancer who underwent anterior pelvic exenteration including removal of the bladder, bilateral pelvic lymph nodes, uterus, fallopian tubes and anterior vaginal wall from January 2008 to October 2020 at Rajavithi Hospital. The research was approved by the ethics committee of Rajavithi Hospital (Study Code: 63236).

The patients were excluded from further analysis if non-urothelial primary malignancy was found in the final pathology, there was a prior total abdominal hysterectomy with bilateral salpingo-oophorectomy and no gynecologic

organs were present in the final cystectomy specimen, or data from hospital records was incomplete.

We collected the clinicopathological and radiological data from hospital charts. Tumor staging was performed according to the American Joint Commission on Cancer TNM classification, 8th edition.¹¹ All cystectomy specimens were examined by an experienced pathologist.

The baseline data of patients were analyzed. Descriptive statistics are reported as number, percentage, mean, median, standard deviation, minimum and maximum. In the case of inferential statistics, quantitative data which was normally distributed were analyzed by Student T-test and abnormally distributed by Mann-Whitney U test. Qualitative information comparisons were analyzed by Chi-square test or Fisher's Exact test. Binary logistic regression was performed to evaluate the association between each of the clinicopathologic variables and the risk of gynecologic organ involvement.

A p-value less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS version 22.0.

Results

In this study, 95 female patients underwent anterior pelvic exenteration between January 2008 and October 2020. 25 patients were excluded due to primary adenocarcinoma (6), squamous cell carcinoma (3) and sarcoma (1) of bladder, incomplete clinical data (11), previous gynecologic surgery (4).

Therefore 70 female patients remained for analysis. Their clinicopathologic data are reported in Table 1. Mean age was 64.80 years. Thirteen (18.5%) patients had any gynecologic organ involvement, including 4 (5.7%) involving the uterus, 7 (10%) involving the vagina, 2 (2.8%) involving the ovaries, and 10 (14.2%) involving the cervix.

Data of gynecologic organ involvement are reported in Table 2. There were 23(32%) female patients incidentally diagnosed as benign gynecologic tumor; this consisted of 16 (22%) myoma uteri, 7 (10%) adenomyosis, 4 (2.8%) ovarian cyst (Table 3). Between the non-gynecologic organ invasion and gynecologic organ invasion groups, there were no significant differences with regard to age, body mass index, hypertension and diabetes



history, neoadjuvant chemotherapy history, glomerular filtration rate, smoking history, pathological grade. There was a correlation between female patients with advanced pathological T stage ($p < 0.001$), and pre-operative hydronephrosis ($p = 0.002$) and gynecologic organ involvement (Table 4).

From the multivariate logistic regression, pre-operative hydronephrosis was associated with increased risk of gynecologic organ invasion (odds ratio 9.57; 95% confidence interval, 1.86 - 49.18; $p = 0.007$).

There were 6 patients with no gynecologic organ involvement diagnosed with pathologic stage T4. These included 3 cases involving the abdominal wall and 3 involving the adjacent colon. There were no incidental primary gynecologic malignancies in the patients.

Discussion

Approximately 75% to 85% of bladder cancer cases present with non-muscle invasive bladder tumors and 20 to 30% of bladder cancer cases present with muscle-invasive disease or beyond.^{12,13} Anterior pelvic exenteration in female patients historically included resection of the bladder, urethra, anterior vagina, uterus, and cervix. This allows for adequate resection. It should also be noted that initial presentation in women is usually at a more advanced stage of disease in comparison to men.^{14,15} Although bladder cancer is rarely diagnosed before the age of 40, female patients who undergo premenopausal oophorectomy may have cardiometabolic disease, bone resorption issues, sexual dysfunction, and cognitive disorders.^{12,16} Furthermore prolonged hormone replacement therapy used to alleviate symptoms and minimize these risks has been associated with increased incidence of breast cancer, especially if used for more than 5 years.¹⁷

The rate of involvement of gynecologic organs is variable. Gregg et al. reported that 32 (23%) out of 139 patients with no prior history of hysterectomy had genital organ involvement.¹⁸ Whereas Chen et al. reported 5.2% of 115 patients had gynecologic organ involvement.⁸ In this study, the incidence of involvement of the gynecologic organs in association with bladder cancer was 13 (18.5%) (Table 5).

Some prior studies investigated the risks of gynecologic organ involvement to determine

Table 1. Demographic and clinical characteristics of the study patients

Data	Total (N = 70)
Characteristics	Mean \pm SD (min-max)
Age (years)	64.80 \pm 10.53 (24-88)
Body mass index	23.31 \pm 4.16 (15.8-36.4)
Glomerular filtration rate	66.27 \pm 25.42 (7-110)
	Number (%)
Hypertension	29 (41.4)
Diabetes mellitus	16 (22.9)
Smoking	2 (2.9)
Neoadjuvant chemotherapy	6 (8.6)
Pre-operative hydronephrosis	32 (45.7)
Pathological data	Number (%)
Pathologic stage	
Ta	1 (1.4)
T1	11 (15.7)
T2	23 (32.9)
T3	16 (22.9)
T4	19 (27.1)
Pathologic grade	
Low	6 (8.6)
High	64 (91.4)
Pelvic lymph node involvement	17 (24.3)

Table 2. Gynecologic organ involvement at pathologic examination

	Total (N = 70) Number (%)
Gynecologic organ involvement	13 (18.5)
Vagina	7 (10)
Uterus	4 (5.7)
Ovaries	2 (2.8)
Cervix	10 (14.2)
Single organ involvement	5 (7.1)
Multiple organ involvement	8 (11.4)

Table 3. Primary gynecologic organ neoplasm at pathologic examination

	Total (N = 70) Number (%)
Primary gynecologic organ neoplasm	23 (3.3)
Myoma uteri	16 (2.3)
Adenomyosis	7 (10)
Ovarian cyst	4 (28)
Single gynecologic organ neoplasm	20 (28.6)
Multiple gynecologic organ neoplasm	3 (4.3)

Table 4. Correlation between patient characteristics

	Gynecologic organ involvement		
	Yes (n=13)	No (n=57)	P-value
	Mean ± SD		
Age (years)	66.23±8.19	64.47±11.02	0.591
BMI (kg/m²)	22.44±4.59	23.51±4.07	0.405
GFR (ml/min)	61.92±26.14	67.26±25.37	0.498
	Number and percentage		
Hypertension	6 (20.7)	23 (79.3)	0.702
Diabetes mellitus	4 (25)	12 (75)	0.476
Smoking	1 (50)	1 (50)	0.339
Neoadjuvant chemotherapy	1 (16.7)	5 (83.3)	1.000
Pre-operative hydronephrosis	11 (65.6)	21 (34.4)	0.002
Pathologic stage			< 0.001
Ta	0 (0)	1 (100)	
T1	0 (0)	11 (100)	
T2	0 (0)	23 (100)	
T3	0 (0)	16 (100)	
T4	13 (68.4)	6 (31.6)	
Pathologic grade			1.000
Low	1 (16.7)	5 (83.3)	
High	52 (81.3)	12 (18.8)	
Pelvic lymph node involvement	6 (35.3)	11 (64.7)	0.069

Table 5. Gynecological organ involvement

References	Patient numbers N	Countries	Invasion n (%)
Chen et al. (1997) ⁸	115	USA	6 (5.2)
Tran et al. (2004) ²⁷	221	USA	11 (5.0)
Varkarakis et al. (2007) ¹⁰	54	Austria	3 (5.7)
Djaladat et al. (2012) ⁵	267	USA	20 (7.5)
Gregg et al. (2016) ¹⁸	139	USA	32 (23)
Choi et al. (2017) ¹⁹	112	South Korea	11 (9.8)
Huang et al. (2019) ⁹	49	China	5 (10.2)
This study	70	Thailand	13 (18.5)

which patients are likely candidates for gynecologic organ sparing cystectomy. Choi et al. reported that tumor location at the trigone or bladder neck at TUR-BT, maximum tumor size > 4.8 cm from CT, and hydronephrosis from CT were independent predictors of female organ involvement.¹⁹ Gregg et al stated that lack of trigonal or bladder floor tumor, intraoperative palpable posterior mass, and clinical lymphadenopathy were associated with absence of female pelvic organ involvement. Taylor et al. reported that the presence of gynecologic organ involvement during anterior pelvic exenteration was associated

with advanced pathologic T stage.²⁰ Djaladat et al. retrospectively reviewed 267 patients and found that palpable mass and hydronephrosis were among the preoperative clinical factors associated with reproductive organ involvement.⁵ Chen et al. examined 115 patients and reported that vaginal and cervical invasion both showed a correlation with stages T3b and T4 of disease.⁸ Varkarakis et al. retrospectively reviewed 54 women with clinical organ confined transitional cell bladder cancer and found that 3 (5.7%) patients had tumor invasion to gynecologic organs. There were no preoperative risk factors found



in their study.¹⁰ In our retrospective study, we found that pre-operative hydronephrosis was associated with increasing risk of gynecologic organ invasion

In this study, one patient developed low grade transitional cell carcinoma with gynecologic organ involvement. Stage progression and tumor-related mortality of low grade bladder transitional cell carcinoma were approximately 10% and 5% respectively.²¹ In muscle invasive bladder cancer there is usually a high incidence of high grade transitional cell carcinoma but application of histologic grade to the invasive component provided no additional prognostic information.^{22,23} However, this is retrospective study and there were several pathologists involved in the interpretation of the specimens leading to some potential variation.

Gynecologic organ sparing surgery in female patients had been reported by few studies. Ali-El et al. reported 15 cases which had undergone gynecologic organ sparing surgery with good functional outcomes and with no recurrence developing in the retained gynecologic organs.²⁴ Moursy et al. reported 18 pre-menopausal women who underwent radical cystectomy and orthotopic urinary diversion with preservation of gynecologic organs and found 14 of these patients were able to void satisfactorily, while four patients needed clean intermittent catheterization. Sexual life remained unchanged in 15 cases, while three patients reported dyspareunia and there was no local recurrence.²⁵

The overall incidence of gynecologic malignancies was reported as being very low in previous studies. Chang et al. reported 1 case (2.5%) of an incidental low-grade stromal sarcoma.⁷ Ali-El-Dein et al. detected no primary gynecologic malignancies in 609 female patients in their study.²⁶ Tran et al identified clinically unexpected malignant or premalignant gynecologic lesions in 8 out of 221 patients (3.6%).²⁷ In our study, there was no incidental primary gynecologic malignancies found in the patients.

Benign gynecologic organs neoplasm reported by Tran et al. and Ali-El-Dein et al. were commonly recognized entities, uterine leiomyomas and simple serous cysts being respectively the most common.^{25,26} Our study discovered 23 patients had benign ovarian neoplasms, of which myoma uteri were the most common.

The limitations of this study are that it was a single-center study with limited number of patients. It was also retrospective in nature which can result in some variation due to the number of different health professionals involved in the original examinations and procedures.

Conclusion

The incidence of gynecologic organ involvement in female patients who undergo anterior pelvic exenteration for urothelial carcinoma of the bladder in this study was 18.5%. Pre-operative hydronephrosis was a risk factor associated with increasing risk of gynecologic organ involvement. Information from this study may allow better identification of candidates for gynecologic organ sparing surgery. Further large multi-center studies are needed to appropriately define the criteria for gynecologic organ sparing surgery.

Conflict of interest

The authors declare no conflict of interest.

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