Original Article

Clinical Predictive Factors for Reproductive Organ Involvement in Females with Muscle Invasive Bladder Cancer: A Retrospective Review of Radical Cystectomy Cases from Two Tertiary Centers

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What's Known

- For female patients undergoing radical cystectomy for bladder cancer, identifying preoperative predictors of reproductive organ involvement (ROI) is crucial. Given its substantial long-term implications, this assessment helps determine eligibility for genital-sparing surgery.
- Current predictors, such as lymph node involvement, are primarily pathological variables that become identifiable postoperatively, limiting their utility in preoperative patient selection.

What's New

- The present study assessed clinical predictors of ROI in female bladder cancer patients using preoperative transurethral resection of tumor (TURT) reports and imaging findings. The results provided practical tools to guide surgical planning.
- In addition to existing literature, the findings of the present study identified tumor size (>5 cm), carcinoma *in situ* (CIS), and lymphovascular invasion as significant independent risk factors for ROI.

Abstract

Background: The preservation of reproductive organs in females with muscle-invasive bladder cancer (MIBC) might improve reproductive and sexual function. This study aimed to identify potential clinical risk factors for reproductive organ involvement (ROI) using preoperative data from transurethral resection of tumor (TURT) reports and imaging findings.

Methods: This retrospective analysis was conducted on 143 women with bladder cancer who underwent radical cystectomy (RC) at Modarres and Labafinejad Medical Centers in Tehran, Iran, between 2010 and 2019. Demographic, clinical, and pathological data, along with follow-up reports, were collected from medical records and analyzed.

Results: The mean age of the participants was 69.17±10.62 years, with an ROI rate of 16.8%. The vagina was the predominantly involved organ. Significant independent risk factors for ROI included clinical T stage (P=0.042), bladder neck or trigonal location of the tumor (P<0.001), tumor size> 5 cm (P=0.002), presence of carcinoma *in situ* (CIS) (P=0.014), lymphovascular invasion in TURT reports (P=0.002), and preoperative hydronephrosis in imaging (P<0.001). Patients with ROI demonstrated significantly lower 5-year survival rates than those without ROI, with overall survival rate of 20.8% versus 63.9% and cancer-specific survival rate of 19% versus 64.8%, respectively.

Conclusion: This study represented a comprehensive analysis of preoperative TURT and imaging predictors of ROI. Clinical T stage, tumor location, maximum tumor size, concomitant CIS, presence of lymphovascular invasion, and hydronephrosis were identified as significant preoperative clinical factors associated with ROI. These findings might help guide surgical planning for organ preservation in female MIBC patients.

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Keywords ● Carcinoma, transitional cell ● Cystectomy ● Genitalia, female ● Organ preservation

Introduction

Bladder cancer is a prevalent malignancy of the urinary system, with urothelial carcinoma (UC) accounting for approximately 90% of cases.[1, 2] As the second most prevalent genitourinary

malignancy, it accounted for an estimated 19,300 new cases among women in the United State in 2020.[3] Among these patients, nearly 25% present with muscle-invasive disease,[4] requiring radical cystectomy (RC) with lymph node dissection and anterior pelvic exentration (APE) as the standard treatment.[5]

Although APE has the potential to eradicate locally advanced bladder cancer or any non-diagnosed gynecologic malignancies, it frequently leads to over-treatment, given that reproductive organ involvement (ROI) occurs in only 3-8% of cases, and occult gynecologic malignancies are found in 0-2%.[4] Oophorectomy, even in post-menopausal women, was shown to increase cardiovascular mortality risk, adversely affect bone health, and impair sexual function.[6,7] Furthermore, with an increasing number of females undergoing orthotopic neobladder reconstruction, preserving reproductive organs was associated with higher continence rates and reduced necessity for clean intermittent catheterization (CIC) in appropriately selected patients.[8]

Given these considerations, selecting proper candidates for reproductive organ preservation during RC represents a clinically justified approach. However, there was a paucity of data regarding the appropriate indications for genital-sparing RC in women. All existing studies were retrospective and typically involved heterogeneous patient populations. Additionally, some risk factors for ROI mentioned in the literature were pathologic variables that only become evident postoperatively, making them impractical for preoperative patient selection. In this way, this study aimed to identify potential clinical factors in female bladder cancer patients that could predict ROI, thus enabling more accurate surgical planning and patient counseling.

Patients and Methods

Patient Population

This retrospective cohort study included female patients with bladder cancer who underwent RC with APE performed with curative intent. The surgical procedure involved removal of the bladder, bilateral pelvic lymph nodes, uterus, fallopian tubes, and anterior vaginal wall. The study protocol was approved by the Research Ethics Committee of Shahid Beheshti University of Medical Sciences (code: IR.SBMU.MSP.REC.1402.388). Written informed consent was obtained from all participants and documented in their medical records.

The study included patients who underwent surgery in two high-volume Tertiary Hospitals, Modarres and Labafinejad Medical Centers (Tehran, Iran) from 2010 to 2019. Patients with non-urothelial carcinoma (non-UC) or variant histologies, previous history of abdominal hysterectomy, palliative cystectomies, or incomplete medical records, as well as those lost to follow-up, were excluded. Non-UC and variant histologies were excluded as this study aimed to focus on the clinical behavior of UC, the most common form of bladder cancer. Additionally, patients with a prior hysterectomy were excluded given the potential alterations in pelvic anatomy and tumor progression dynamics. Palliative cystectomies, which diverge from curative oncologic approaches, were excluded to maintain analytical consistency. Following screening, the final cohort comprised 143 female patients (figure 1).

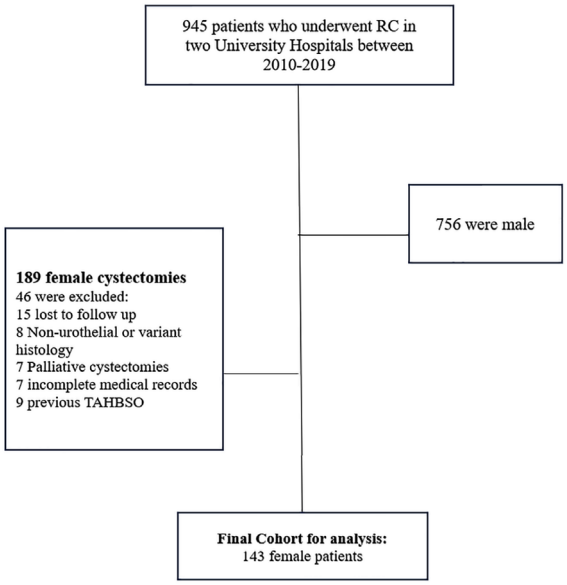

Figure 1: The figure illustrates the flowchart depicting the process of patient selection for the study. RC: Radical cystectomy; TAHBSO: Total abdominal hysterectomy bilateral salpingo-oophorectomy

Clinical data were extracted from the Hospital information system (HIS) (Tiraje Rayaneh Tehran [TRT®] Company, Tehran, Iran), including demographic information, clinical characteristics, and treatment details. Preoperative imaging studies, such as computed tomography (CT) scan, magnetic resonance imaging (MRI), or ultrasonography were reviewed to assess for hydronephrosis, clinical lymphadenopathy, and or local tumor extension. Data on lymphovascular invasion, concomitant carcinoma *in situ* (CIS), maximum tumor size, and clinical T stage were extracted from the transurethral resection of tumor (TURT) reports. Tumor characteristics, including the number and location, were obtained from the cystoscopy reports, and neoadjuvant chemotherapy information was gathered from clinical records.

Similar pathological protocols were used for examining cystectomy specimens, following standardized guidelines for prosection of the bladder and its adjacent organs. Pathological tumor grading and staging were performed according to the American Joint Committee on Cancer (AJCC) 2017 TNM classification system.[9]

Statistical Analysis

Data normality was assessed using the Kolmogorov-Smirnov test, while homogeneity of variances was evaluated with Levene's test. Comparative analyses between groups (with vs. without ROI) were performed using the Fisher exact test, Chi square test, and independent *t* test as appropriate. Potential risk factors for ROI were initially identified through univariate logistic regression analysis, and the identification of independent risk factors was accomplished through the application of multivariate logistic regression analysis. The Kaplan-Meier curve was used to calculate survival outcomes. All statistical analyses were performed using SPSS software (version 27, IBM Corp., Armonk, N.Y., USA), with a two-tailed P value less than 0.05 considered statistically significant.

Results

Of the 143 female patients with pure or mixed UC who underwent APE at the time of cystectomy, 24 (16.8%) cases exhibited ROI. The mean age of the participants was 69.17±10.62 years (range=29-91). The mean body mass index (BMI) was 25.01±3.53 Kg/m^2. Smoking history was reported in 22 (15.4%) patients. The TURT biopsy pathology revealed most tumors were multifocal, measuring less than 5 cm in size, predominantly staged as T2, and located in areas other than the trigone or bladder neck.

Table 1: Preoperative clinical data and postoperative pathological data of our study participants

Clinical Data		
Variable		**Frequency n (%)**
Clinical T stage (TURT)	T2	102 (71.3)
	T3	41 (28.7)
Number of Tumors	Single	39 (27.3)
	Multiple	104 (72.7)
Tumor location	Other	102 (71.3)
	Trigone or bladder neck	41 (28.7)
Maximum tumor size	≤5 cm	102 (71.3)
	>5 cm	41 (28.7)
Concomitant CIS	No	106 (74.1)
	Yes	37 (25.9)
Lymphovascular invasion	No	82 (57.3)
	Yes	61 (42.7)
Preoperative Hydronephrosis	No	93 (65)
	Yes	50 (35)
ROI	No	119 (83.2)
	Yes	24 (16.8)

Pathological Data			
Variable		**ROI**	
		No	**Yes**
		n (%)	**n (%)**
Positive margins	No (n=126)	109 (86.5)	17 (13.5)
	Yes (n=17)	10 (58.8)	7 (41.2)
Pathologic T stage	T1 (n=5)		
	T2 (n=83)		
	T3 (n=31)		
	T4 (n=24)		
ROI	Vagina		18 (52.9)
	Uterus		10 (29.4)
	Fallopian		4 (11.8)
	Ovarian		2 (5.9)
ROI	Single-Organ		13 (54.17)
	Multi-Organ		11 (45.83)

TURT: Trans-urethral resection of tumor; SD: Standard deviation, CIS: Carcinoma *in situ*; ROI: Reproductive organ involvement; N: Frequency

The type of diversion in our patients were ileal conduit in 121 (85%) cases, cutaneous ureterostomy in 22 (14.3%) cases, and continent ileal pouch in 1 (0.7%) case. No patients received orthotopic diversion. Complete clinical and pathological characteristics are detailed in table 1.

Significant differences were observed between patients with and without ROI for several clinical parameters: clinical T stage (P=0.042), location of the tumor (P<0.001), tumor size >5cm (P=0.002), CIS (P=0.014), lymphovascular invasion (P=0.002) and presence of hydronephrosis (P<0.001, table 2).

Univariate logistic regression analysis revealed that clinical T stage (P=0.046), tumor location (P<0.001), maximum tumor size (P=0.004), concomitant CIS (P=0.017), presence of lymphovascular invasion (P=0.004), and presence of hydronephrosis (P<0.001) were associated risk factors for ROI. After adjustment for potential confounders, multivariate regression analysis confirmed that all these variables were independent risk factors.

Multivariate analysis revealed significant associations between clinical parameters and ROI. Patients with clinical T3 stage tumors had a 4.4-fold increased risk of ROI compared to those with clinical T2 stage (P=0.040). The risk of ROI was 6.07 times higher in patients with tumors larger than 5 cm than those with tumors smaller than 5 cm (P=0.019). The presence of CIS increased the risk by 9.52-fold compared to its absence (P=0.005). Patients with lymphovascular invasion had a 15.51-fold increased risk of organ involvement (P=0.003). Tumors located at the trigon or bladder neck resulted in a 16.24-fold increased risk of ROI compared to tumors located in other bladder regions (P<0.001). Additionally, hydronephrosis was associated with an 8.68-fold increased risk of ROI compared to those without this condition (P=0.005) (table 3).

Among the 24 patients with ROI, pathological examination revealed vaginal involvement in 52.9% of cases and uterine involvement in 29.4% of the cases. No patient exhibited isolated ovarian or fallopian tube involvement. Furthermore, no primary gynecological malignancies were identified.

Survival analysis demonstrated significantly worse outcomes for patients with ROI. The 5-year overall survival for patients with and without ROI was 21% and 64%, respectively (P<0.001, figure 2). The 5-year cancer-specific survival rate for patients with and without ROI was 19% and 64.8%, respectively (P<0.001, figure 3).

Due to discrepancies between our HIS data and clinical records regarding neoadjuvant chemotherapy, lymph node involvement in preoperative imaging, and report of palpable pelvic mass during the preoperative examination, it was impossible to verify the validity of these variables and consequently excluded them from the final analysis.

Table 2: Frequency distribution of clinical data in study participants according to reproductive organ involvement

Variable		ROI		P value
		No	Yes	
		n (%)	n (%)	
History of Smoking	No (n=121)	101 (83.5)	20 (16.5)	0.765**
	Yes (n=22)	18 (81.8)	4 (18.2)	
Clinical T stage (TURT)	T2 (n=102)	89 (87.3)	13 (12.7)	0.042*
	T3 (n=41)	30 (73.2)	11 (26.8)	
Number of Tumors	Single (n=39)	34 (87.2)	5 (12.8)	0.437*
	Multiple (n=104)	85 (81.7)	19 (18.3)	
Tumor location	Other (n=102)	94 (92.2)	8 (7.8)	<0.001*
	Trigone or bladder neck (n=41)	25 (61)	16 (39)	
Maximum tumor size	≤5 cm (n=102)	91 (89.2)	11 (10.8)	0.002*
	>5 cm (n=41)	28 (68.3)	13 (31.7)	
Concomitant CIS	No (n=106)	93 (87.7)	13 (12.3)	0.014*
	Yes (n=37)	26 (70.3)	11 (29.7)	
Lymphovascular invasion	No (n=82)	75 (91.5)	7 (8.5)	0.002*
	Yes (n=61)	44 (72.1)	17 (27.9)	
Preoperative Hydronephrosis	No (n=93)	86 (92.5)	7 (7.5)	<0.001**
	Yes (n=50)	33 (66)	17 (34)	
Variable		**mean±SD**	**mean±SD**	**P value**
Age (year)		69.42±11.03	67.96±8.35	0.540***
BMI (Kg/m^2)		24.91±3.54	25.50±3.50	0.456***

TURT: Trans-urethral resection of tumor; ROI: Reproductive organ involvement; BMI: Body mass index; CIS: Carcinoma *in situ*; SD: Standard deviation; *Chi square; **Fisher exact test; ***Independent *t* test; P≤0.05 was considered statistically significant.

Table 3: The correlation between patients' clinical data with reproductive organ involvement

Variable		Unadjusted *		Adjusted**	
		OR (95% CI)	P value	OR (95% CI)	P value
Clinical T stage	T2 (Ref)	2.51(1.01-6.19)	0.046	4.40 (1.06-18.13)	0.040
	T3				
Tumor location	Other (Ref)	7.52 (2.89-19.57)	<0.001	16.24 (3.22-81.97)	<0.001
	Trigone/bladder neck				
Maximum tumor size	≤5 (Ref)	3.84 (1.54-9.52)	0.004	6.07 (1.35-27.31)	0.019
	>5 cm				
Concomitant CIS	No (Ref)	3.02 (1.21-7.54)	0.017	9.26 (1.92-44.59)	0.005
	Yes				
Lymphovascular invasion	No (Ref)	4.14 (1.59-10.76)	0.004	15.51 (2.62-91.81)	0.003
	Yes				
Hydronephrosis	No (Ref)	6.32 (2.40-16.65)	<0.001	8.68 (1.92-39.16)	0.005
	Yes				

OR: Odds ratio; CI: Confidence interval; Ref: Reference; CIS: Carcinoma *in situ*; *Univariate logistic regression test; **Multivariate logistic regression test; P<0.05 was considered statistically significant.

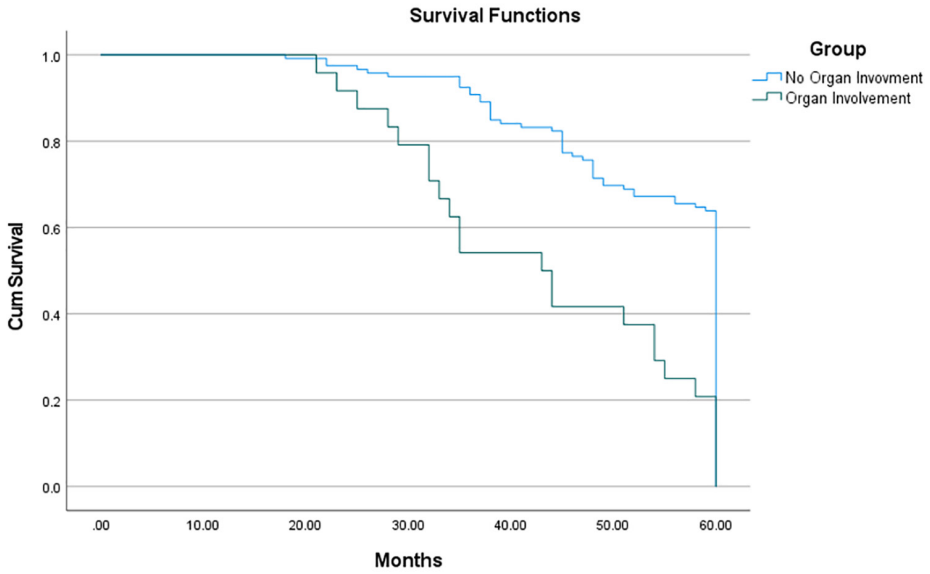

Figure 2: The figure displays the 5-year overall survival rates in patients with and without reproductive organ involvement. Survival rate was analyzed using Kaplan-Meier curves.

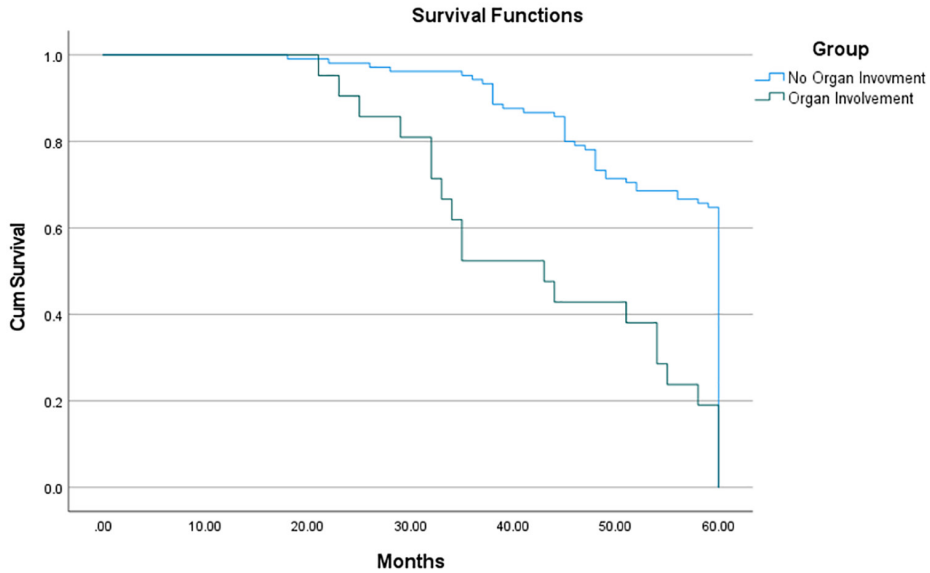

Figure 3: The figure displays the 5-year cancer-specific survival rates of patients with and without reproductive organ involvement. Survival rate was analyzed using Kaplan-Meier curves.

Discussion

The present study identified several preoperative clinical predictors of ROI, including clinical T stage, tumor location, tumor size>5, concomitant CIS, lympho-vascular invasion, and hydronephrosis. These factors might facilitate patient stratification to optimize selection for genital-sparing approaches.

According to the American Urological Association (AUA), American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology (ASTRO), and Society of Urologic Oncology (SUO) guidelines on the treatment of non-metastatic muscle-invasive bladder cancer (MIBC), adjacent reproductive organs should be removed during standard RC with curative intent in female patients, based on individual disease characteristics.[5] However, these guidelines provided no specific contraindications for organ preservation. Since preserving gynecologic organs during cystectomy can have a considerable effect on the quality of life, including sexual health, better continence rates, and improved cardiac condition, it is necessary to establish specific clinical indications for examining these patients.[6-8]

In the current cohort of 143 cases, the incidence of ROI was 16.8%, with vaginal involvement being the most frequently involved organ. This finding was consistent with most previous reports examining both UC and non-UC histology.[10-14] The absence of an isolated fallopian tube or ovarian involvement further supported the existing evidence, suggesting contiguous, stepwise bladder cancer spread through the reproductive organs.[10, 14]

Identifying reliable preoperative predictors of ROI is essential for appropriate patient selection for organ preservation. The present study was uniquely designed to focus exclusively on precystectomy data. To the best of our knowledge, this was the first investigation in which all preoperative TURT findings were included in the ROI analysis. Despite the existence of multiple series on female bladder cancer, potential predictive clinical factors for ROI were identified in only a limited number of studies (table 4).

Previous studies identified several clinical risk factors for ROI, including palpable mass in a bimanual examination, preoperative hydronephrosis, and bladder neck or trigonal location of the tumor.[10, 11, 13-16] Consistent with these findings, our study confirmed that the

Table 4: Potential clinical factors predictive of reproductive organ involvement in previous studies

Study	No. of pts	No. of ROI	Histology	Variables								
				Palpable mass	Clinical T stage	Preoperative hydronephrosis	Clinical LNP	Neoadjuvant chemotherapy	CIS in TURT	Max tumor size in TURT	Bladder neck or trigone location	Lymphovascular invasion in TURT
Chen[11] 1997	115	6 (5.2%)	UC	NR	NR	NR	NR	NR	NR	NR	Risk factors for urethral involvement	NR
Varkarakis[18] 2007	52	3 (5.7%)	UC	-	-	NR	-	NR	NR	NR	-	NR
Djaladat[10] 2012	411	21 (7.5%)	UC	+	-	+	NR	-	NR	NR	NR	NR
Gregg[16] 2016	160	32 (20%)	UC	+	NR	NR	-	NR	NR	NR	+	NR
Choi[15] 2017	112	11 (9.8%)	UC	NR	-	+	-	NR	NR	NR	+	NR
Whittum[13] 2018	118	17 (14%)	UC+ non-UC	NR	NR	NR	NR	-	NR	NR	+	+
Taylor[7] 2019	123	19 (15%)	UC+ non-UC	NR	NR	NR	NR	-	NR	NR	NR	NR
Bree[12] 2021	186	9 (4.8%)	UC	-	-	-	NR	Despite advanced stages in the neoadjuvant group, the rate of ROI was not different between the two groups.	NR	NR	NR	NR
Avulova[14] 2023	1335	70 (5.2%)	UC+ non-UC	NR	NR	+	NR	NR	NR	NR	+	NR

ROI: Reproductive organ involvement; CIS: Carcinoma *in Situ*; NR: Not reviewed; UC: Urothelial carcinoma, TURT: Trans-urethral resection of tumor; LNP: Lymph-adenopathy; Pts: Patients; +: Positive correlation; -: No correlation

presence of hydronephrosis and a trigonal or bladder neck location of the tumor were independent risk factors for ROI. Additionally, the presence of lymphovascular invasion (LVI) in the TURT specimen emerged as an independent predictor of ROI. This finding was in agreement with the findings of Whittum and colleagues' study which reported that 82% of ROI patients had LVI in the TURT biopsies.[13]

The clinical T stage (cT3 vs cT2) was identified as an independent risk factor in predicting ROI. Typically, clinical staging in bladder cancer is primarily conducted through TURT biopsy and physical examination under anesthesia, as imaging modalities remain limited for local and systemic staging. While the European Association of Urology (EAU) guidelines on MIBC[17] claimed that CT or MRI scans had a 90% sensitivity for local staging, lymph node detection sensitivity ranged from 48-87 %, and PET scans utility remained undefined. Given these limitations, TURT results alone were utilized for clinical T staging, which revealed that cT3 patients were associated with a 4.4 times greater risk of ROI than cT2 patients. The only study that demonstrated a positive correlation between clinical lymphadenopathy and ROI was conducted by Gregg and colleagues;[16] however, it was not an independent risk factor.

In this study, 29.7 and 31.7 % of patients with ROI had a maximum tumor size >5 cm and concomitant CIS in the TURT report, respectively. These factors were independently associated with organ involvement, a novel finding not previously reported. While the presence of CIS in a permanent pathology report was reported in some previous studies,[10, 15] none reported a significant correlation with ROI.

Regarding tumor size, Choi and colleagues established CT-measured size as an independent predictor (OR=2.2, 95% CI=1.3-4.2, P=0.005).[15] They calculated a threshold of 4.8 cm as the optimal threshold (sensitivity=81.8%, specificity=91.3%). The present study utilized their 5 cm tumor size cutoff for TURT specimen classification, which demonstrated an independent correlation with ROI (OR=6.07, 95% CI=1.35-27.31, P=0.019).

Most of the previous studies were conducted prior to the neoadjuvant chemotherapy era, limiting the assessment of its impact on ROI rates. Only a study by Bree and colleagues,[12] specifically evaluated the effect of neoadjuvant chemotherapy on ROI. Their findings demonstrated that despite the neoadjuvant group had higher-risk patients, the rate of ROI was comparable between the two groups. This observation could potentially indicate a protective effect of neoadjuvant chemotherapy against ROI.

Our survival analysis of patients with and without ROI clearly demonstrated that while preserving the genital organ could significantly enhance the quality of life, improper patient selection could lead to lower survival rates and compromised oncologic safety. An intriguing study by Avulova and colleagues classified patients with ROI according to the involvement of specific organs: vagina only, cervix/uterus, and fallopian tube/ovary.[14] They concluded that the 3-year cancer-specific survival rate was superior in the vagina-only group (39%, vs. 14%, vs. <1%, respectively). Given their similar clinical behavior to pT3b disease, they suggested that patients in the vagina-only group should be downgraded in AJCC pathologic staging.

This study had several important limitations inherent to its retrospective design, including potential selection and reporting biases. The non-randomized patient selection might limit generalizability to broader populations. Specific clinical data, particularly regarding neoadjuvant chemotherapy administration, were inconsistently available for analysis. Additionally, the multicenter nature of this study precluded centralized pathological review, which could affect diagnostic consistency across cases.

Conclusion

Genital organ preservation offered significant quality-of-life benefits for female cystectomy patients, including improved continence and overall health outcomes. To this end, identifying preoperative clinical variables is essential. The findings identified six preoperative clinical predictors of ROI: clinical T stage, tumor location, maximum tumor size (>5 cm), concomitant CIS, lympho-vascular invasion, and hydronephrosis. As neoadjuvant chemotherapy might influence tumor staging and potentially affect ROI rates, future prospective studies should specifically evaluate its impact on organ involvement patterns.

Authors' Contribution

N.Mah: Conception and design of the work; M.H.M: Interpretation of data for the work; P.M, K.V, S.I, and M.N: Acquisition of data, analysis; N.M: Conception and design of the work, interpretation of data for the work. All authors contributed to the drafting of the work and reviewing it critically for important intellectual content. All authors approved the final version to be published and agree to be accountable for

all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest: None declared.

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