Patterns of Locoregional Recurrence after Radical Cystectomy for Stage T3-4 Bladder Cancer: A Radiation Oncologist's Point of View

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Purpose: Adjuvant radiotherapy (RT) has been performed to reduce locoregional failure (LRF) following radical cystectomy for locally advanced bladder cancer; however, its efficacy has not been well established. We analyzed the locoregional recurrence patterns of post-radical cystectomy to identify patients who could benefit from adjuvant RT and determine the optimal target volume.

Materials and Methods: We retrospectively reviewed 160 patients with stage ≥ pT3 bladder cancer who were treated with radical cystectomy between January 2006 and December 2015. The impact of pathologic findings, including the stage, lympho-vascular invasion, perineural invasion, margin status, nodal involvement, and the number of nodes removed on failure patterns, was assessed.

Results: Median follow-up period was 27.7 months. LRF was observed in 55 patients (34.3%), 12 of whom presented with synchronous local and regional failures as the first failure. The most common failure pattern was distant metastasis (40%). Among LRFs, the most common recurrence site was the cystectomy bed (15.6%). Patients with positive resection margins had a significantly higher recurrence rate compared to those without (28% vs. 10%, *p*=0.004). The pelvic nodal recurrence rate was < 5% in pN0 patients; the rate of recurrence in the external and common iliac nodes was 12.5% in pN+ patients. The rate of recurrence in the common iliac nodes was significantly higher in pN2−3 patients than in pN0−1 patients (15.2% vs. 4.4%, *p*=0.04).

Conclusion: Pelvic RT could be beneficial especially for those with positive resection margins or nodal involvement after radical cystectomy. Radiation fields should be optimized based on the patient-specific risk factors.

Key Words: Urinary bladder neoplasms, adjuvant radiotherapy, cystectomy, recurrence

INTRODUCTION

Bladder cancer is the sixth most common male cancer worldwide, and the eighth most common male cancer in Korea.[1,2] Radical cystectomy plus pelvic lymph node dissection (PLND) with or without neoadjuvant chemotherapy is a standard treatment option for muscle-invasive bladder cancer (MIBC) without distant metastases. Despite radical cystectomy, MIBC patients have a poor prognosis, with a 5-year overall survival (OS) rate of 50−60%.[3-6] Historically, locoregional failure (LRF) after radical cystectomy for MIBC was reported in 15−35% of patients with pathologic stage T3 disease.[4,7] Neoadjuvant and adjuvant chemotherapy have been previously attempted to improve clin-

ical outcomes; however, treatment failure is still common in these patients, and oncologic outcomes remain unaltered.[5] The Southwest Oncology Group (SWOG)-Intergroup trial reported a 5-year actual LRF rate of 32% for MIBC with no benefit from methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy in terms of locoregional recurrence.[4]

Adjuvant pelvic radiotherapy (RT) has been used as local treatment to reduce LRF and improve outcomes. In an observational cohort study involving 15124 locally advanced bladder cancer patients from the National Cancer Database (NCDB), adjuvant RT was associated with improved OS.[8] However, planning adjuvant RT is challenging in clinical practice, as the bowel may replace the cystectomy bed and pelvic cavity, and routine RT to the whole pelvis could result in unnecessary gastrointestinal (GI) and genitourinary (GU) toxicities.[9] The benefit of adjuvant RT is still controversial, and therefore, RT is selectively implemented in clinical practice. Only 3.3% of the 15124 patients in the NCDB received adjuvant RT after cystectomy.[8]

In the current study, we aimed to identify the patients who could benefit from pelvic irradiation by analyzing the patterns of failure after radical cystectomy; we also aimed to suggest appropriate target volumes for RT.

MATERIALS AND METHODS

Study population

Patients who underwent radical cystectomy for MIBC between January 2006 and December 2015 were identified from the database of our institution. In total, 223 consecutive patients who were diagnosed with pT3 or pT4 stage disease were retrospectively reviewed. Those who received neoadjuvant RT (n=11) or adjuvant RT (n=3), presented with distant metastasis at the initial diagnosis (n=30), or had a history of double primary cancer (n=4) were excluded. Patients who died perioperatively (n=6) or did not undergo follow-up after surgery (n=19) were also excluded. Finally, 160 patients were included in this study. Pathological stage was assigned in accordance with the 8th American Joint Committee on Cancer staging system.[10] Pathological analysis of cystectomy specimens was performed by an experienced uropathologist at our institute. This retrospective study received approval from the Institutional Review Board of Yonsei University Severance Hospital (IRB No. 4-2020-0786).

Treatment

Standard surgical procedures consisted of en bloc radical cystectomy with extended PLND and urinary diversion. The boundaries of extended PLND included the nodes between aortic bifurcation and common iliac vessels proximally, genitofemoral nerve laterally, circumflex iliac vein distally, and internal iliac vessels posteriorly.[11] However, in some patients, the extent of PLND was changed or PLND was not performed dur-

ing operation due to severe adhesion or according to the clinician's judgment. Gemcitabine (1000 mg/m² of body-surface area) was administered intravenously on days 1, 8, and 15 of each cycle. Cisplatin (70 mg/m²) was administered on day 1 every 28 days. Adjuvant MVAC chemotherapy was administered to 20 patients: methotrexate (30 mg/m² of body-surface area) on days 1, 15, and 22; vinblastine (3 mg/m²) on days 2, 15, and 22; and doxorubicin (30 mg/m²) and cisplatin (70 mg mg/m²) on day 2. The doses were adjusted if toxicities occurred.

Treatment failure

After surgery, regular follow-ups were conducted every 3 months during the first 2 years and every 6 months over the next 3 years. Regular follow-up evaluations included computed tomography (CT) of the chest and abdomen, magnetic resonance imaging (MRI) of the pelvis, and positron emission tomography (PET) or PET-CT. All available imaging data were reviewed for evidence of treatment failure. Recurrences were documented based on the first site identified on imaging studies during the entire follow-up period. Patients with two or more local, regional, or distant failures within the same 3-month period were considered to have synchronous failure.

Local failure was defined as a soft tissue recurrence in the pelvis according to three predefined subsites: cystectomy bed, rectosigmoid region, and "other," which included subsites that were unsuitable for categorization into the first two sites. Regional failure was defined as pelvic lymph node (LN) recurrence below the aortic bifurcation. It was categorized according to six subsites: common iliac, internal iliac, external iliac, obturator, pelvic side wall, and presacral LNs. Nodal recurrences cephalad to the aortic bifurcation or within the inguinal area were scored as distant metastases.

Delineation of locoregional failures

We delineated locoregional recurrent tumors based on the vascular structure on reference CT images. As a reference image, we used a set of CT images from a patient whose vascular anatomy was considered to be the closest to the standard without anatomic variation. We depicted the contours of recurrent tumors from 55 patients on axial and coronal views of the reference CT images. To show common recurrence sites, we drew figures overlapping the heatmap of the cumulative histogram over a CT image according to cancer stages IIIA and IIIB (Fig. 1). Normalization was applied based on the maximum cumulative frequency, as there was a difference in cumulative frequency between each histogram. Cumulative frequency was represented by the following colors: blue (20%≤recurrence rate<40%), cyan (40−60%), yellow (60−80%), and red (≥80%).

Data and statistical analyses

Univariate and multivariate Cox regression analyses were performed to identify the prognostic factors related to LRF. The impact of pathologic findings, including stage, lympho-vascu-
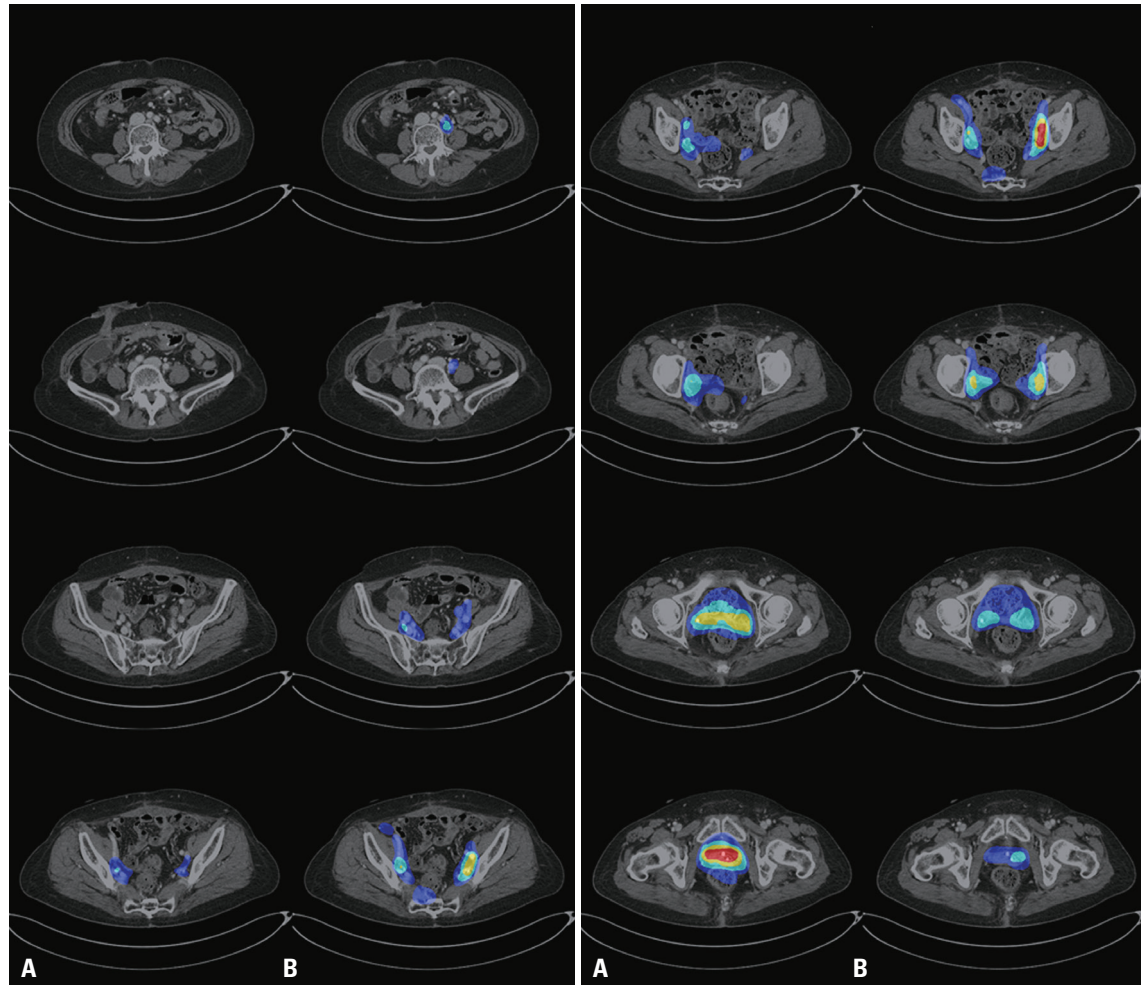
Fig. 1. Volume of loco-regional recurrent tumor in stage IIIA patients (A) and stage IIIB patients (B) on axial CT images. Every CT image of the same level is displayed in parallel. All recurrent tumor volumes are delineated based on vessel and bony landmarks. The colors represent cumulative frequencies: blue (20%≤recurrence rate<40%), cyan (40–60%), yellow (60–80%), and red (≥80%).

lar invasion, perineural invasion, margin status, nodal involvement, number of nodes removed, and the use of adjuvant chemotherapy, was assessed. LRF-free survival, progression-free survival (PFS), and OS were calculated from the date of surgical resection to the corresponding events. Kaplan-Meier method was used to plot the survival outcomes. For comparison of failure rates according to risk factors, p values based on the χ^2 test, Fisher's exact test, or linear-by-linear association were used. All statistical tests were two-sided, with significance defined as p value<0.05. All data were analyzed using the IBM SPSS software version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics are listed in Table 1. The median age was 69 years (range, 35–91 years), and 135 (84.4%) patients were male. The most common histopathology was urothelial cell carcinoma (96.2%), with the exception of six cases: squamous

cell carcinoma, two cases; small cell carcinoma, two cases; signet-ring cell carcinoma, one case; and undifferentiated carcinoma, one case. LN metastasis was pathologically confirmed in 64 patients (40%). Resection margin involvement was noted in 50 patients (31.3%): R1 resection, 48 patients and R2 resection, two patients. Positive resection margins were more frequently observed in pT4 patients than in pT3 patients (44% vs. 25%, p=0.014). Treatment details are also summarized in Table 1. The median number of LNs removed was 14 [interquartile range (IQR), 8–19]. Chemotherapy was administered either pre- or postoperatively in 113 patients (70.6%): 24 before surgery, 99 after surgery, and 10 patients before and after surgery. Most patients were administered gemcitabine/cisplatin (GC) chemotherapy: preoperatively in four, postoperatively in 81, and both in five patients. For those who received both neoadjuvant and adjuvant GC chemotherapy, two or three cycles of GC chemotherapy was performed as neoadjuvant treatment followed by four to six cycles of adjuvant GC chemotherapy. All five patients were treated between 2007 and 2009, and their

Table 1. Patient Characteristics and Treatment

Age, yr, median (range)	69 (35–91)
Sex	
Male	135 (84.4)
Female	25 (15.6)
Repeated TURB (≥2)	
Yes	47 (29.4)
Clinical T stage	
cT2	33 (20.6)
cT3	100 (62.5)
cT4	27 (16.9)
Clinical N stage	
cN0	123 (76.9)
cN1	16 (10.0)
cN2	20 (12.5)
cN3	1 (0.6)
Histology	
Urothelial cell carcinoma	154 (96.2)
Squamous cell carcinoma	2 (1.3)
Small cell carcinoma	2 (1.3)
Other	3 (1.3)
Pathologic T stage	
pT3	108 (67.5)
pT4	52 (32.5)
Pathologic N stage	
pN0	96 (60.0)
pN1	18 (11.3)
pN2	39 (24.4)
pN3	7 (4.4)
Pathologic AJCC stage	
Stage IIIA	114 (71.2)
Stage IIIB	46 (28.8)
No. of nodes removed	
<10	56 (35.0)
10–19	72 (45.0)
20–29	25 (15.6)
≥30	7 (4.4)
LVI	
Yes	93 (35.6)
No	57 (58.1)
Unknown	10 (6.3)
PNI	
Yes	65 (40.6)
No	85 (53.1)
Unknown	10 (6.3)
Resection margin	
R0	110 (68.7)
R1	48 (30.0)
R2	2 (1.3)
Chemotherapy	
NACT	4 (2.5)
ACT	99 (61.8)
NACT+ACT	10 (6.3)
No	47 (29.4)

TURB, transurethral resection of the bladder; AJCC, The American Joint Committee on Cancer; LVI, lymphovascular invasion; PNI, perineural invasion; NACT, neoadjuvant chemotherapy; ACT, adjuvant chemotherapy.
Data are presented as n (%).

Table 2. Patterns of First Recurrence

Site	No. of patients	% of total patients
Local failure		
Cystectomy bed	25	15.6
Rectosigmoid region	8	5.0
Other	8	5.0
Regional failure		
Common iliac node	12	7.5
Internal iliac node	6	3.8
External iliac node	12	7.5
Obturator node	4	2.5
Pelvic side wall node	7	4.4
Presacral node	1	0.6
Distant metastasis		
Lung	8	5.0
Liver	4	2.5
Bone	11	6.9
Peritoneal seeding	6	3.8
Non-regional LN	17	10.6
Disseminated	17	10.6
Brain	1	0.6

LN, lymph node.

treatments were performed at the clinician's discretion.

Recurrences were observed in 93 patients (58.1%). LRF was observed in 55 patients (34.3%), 12 of whom had synchronous local and regional failures as the first failure pattern. The median time to LRF was 6.9 months (IQR: 3.0–12.9). Distant metastasis was the most common pattern of failure, observed in 64 patients (40%). The median time to distant metastasis was 8.5 months (IQR: 3.9–18.7). Two or more local, regional, or distant metastases were observed simultaneously in 33 patients (35.5% of all failures). The individual sites of failure according to the predefined subsites are summarized in Table 2. As an individual failure site, the cystectomy bed was the most common (25 patients, 15.6%). External and common iliac LN metastases were the most commonly found regional failures (12 patients, 7.5%). Among distant metastases, bone metastasis as a single solid organ metastasis was the most frequent, whereas 10.6% of patients had disseminated failure.

We investigated pelvic recurrence rates according to the pathologic T and N stages and resection margin status. LRF rates at each subsite by pathologic stage and resection margin status are summarized in Table 3. Regardless of the stage, cystectomy bed was the most common failure site among pelvic failures. Especially, recurrences in the cystectomy bed were significantly frequent in patients with a positive resection margin (10% vs. 28%, *p*=0.004).

In terms of nodal recurrences, the rates of recurrence at all LN subsites were approximately 5% or below in pN0 patients. Among pN+ patients, the rates of recurrence at the external iliac LNs were 11.4% and 13.8% in pT3 and pT4 patients, respectively. Furthermore, the rate of recurrence at the common iliac

Table 3. Loco-Regional Failure Rates by Pathologic Stage and Resection Margin

	Stage					Stage			Resection margin		
	pT3N-	pT3N+	pT4N-	pT4N+	*p* value	IIIA	IIIB	*p* value	Negative	Positive	*p* value
Common iliac nodes	4.1	5.7	4.3	20.7	0.014	4.4	15.2	0.040*	6.4	10.0	0.418
Internal iliac nodes	4.1	2.9	0.0	6.9	0.801	3.5	4.3	>0.999*	0.9	10.0	0.012*
External iliac nodes	5.5	11.4	0.0	13.8	0.376	5.3	13.0	0.105*	9.1	4.0	0.257
Obturator nodes	2.7	0.0	0.0	6.9	0.429	2.6	2.2	>0.999*	2.7	2.0	>0.999
Pelvic side wall nodes	4.1	0.0	0.0	13.8	0.119	3.5	6.5	0.411*	3.6	6.0	0.678
Presacral nodes	0.0	0.0	0.0	3.4	0.090	0.0	2.2	0.287*	0.0	2.0	0.312
Cystectomy bed	15.1	20.0	13.0	13.8	0.813	17.5	10.9	0.293	10.0	28.0	0.004
Rectosigmoid region	2.7	5.7	4.3	10.3	0.148	3.5	8.7	0.228*	4.5	6.0	0.696
Other	4.1	2.9	13.0	3.4	0.615	5.3	4.3	>0.999*	5.5	4.0	0.696

Data are presented as %.
*Fisher's exact test.
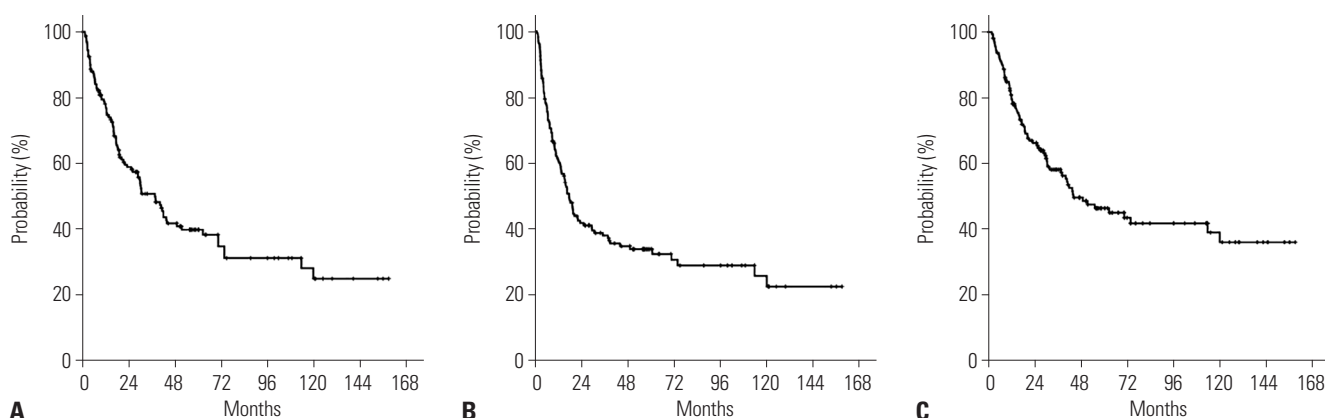
Fig. 2. Kaplan-Meier survival curves for locoregional failure-free survival (A), progression-free survival (B), and overall survival (C).

LNs was remarkably high (20.7%) in pT4N+ patients. To depict the recurrence patterns according to nodal stage, we divided the patients into two groups: stage IIIA vs. stage IIIB (Table 3). The rates of recurrence at the internal iliac, obturator, and pelvic side wall LNs were similar between the two groups. However, the rate of recurrence at the common iliac LNs was significantly high in stage IIIB patients (stage IIIA 4.4% vs. IIIB 15.2%, *p*=0.040). Fig. 1 shows the LRF sites in stage IIIA and IIIB patients. The extent of external iliac LN recurrence was wider in stage IIIB patients than in stage IIIA patients, and the level of recurrence was more cephalad up to the common iliac LN level.

As for the resection margin status, the recurrence rates for all LN subsites were similar, except those for the internal and common iliac LNs (Table 3). Recurrence rates for the internal and common iliac LNs were both 10% in patients with positive resection margins, but were 0.9% and 6.4%, respectively, in patients with negative resection margins. The difference in recurrence rates for the internal iliac LNs was statistically significant between patients with positive and negative resection margins (*p*=0.012).

Median follow-up duration was 27.7 months (range, 1.9–158) for all patients. The 1-, 2-, and 5-year OS rates of the entire cohort were 80.8%, 66.1%, and 46.3%, respectively (Fig. 2).

The 1-, 2-, and 5-year PFS rates were 60.0%, 41.8%, and 33.9%, respectively. Moreover, the median PFS was 17.3 months. The 1-, 2-, and 5-year LRFS rates were 76.7%, 59.0%, and 40.0%, respectively.

The risk factors for LRF are summarized in Table 4. On univariate analysis, sex, history of repeated transurethral resection of the bladder (TURB; ≥2), use of adjuvant chemotherapy, LN metastases, resection margin status, and perineural invasion were significantly associated with LRF. On multivariate analysis, sex [hazard ratio (HR): 2.86; 95% confidence interval (CI): 1.4–5.9; *p*=0.004], history of repeated TURB (HR: 2.17; 95% CI: 1.2–4.0; *p*=0.015), adjuvant chemotherapy (HR: 0.17; 95% CI: 0.1–0.3; *p*<0.001), LN metastases (HR: 2.74; 95% CI: 1.4–5.3; *p*=0.003), and resection margin status (HR: 2.46; 95% CI: 1.4–4.5; *p*=0.003) were associated with LRF. On univariate analysis of OS, nodal metastasis and adjuvant chemotherapy were significantly associated with the outcome. On multivariate analysis, both nodal metastasis and adjuvant chemotherapy were associated with OS. The use of chemotherapy decreased the mortality risk (HR: 0.34; 95% CI: 0.21–0.56; *p*<0.001), while nodal metastasis increased the mortality risk (HR: 2.57; 95% CI: 1.57–4.20; *p*<0.001).

Table 4. Univariate and Multivariate Analyses of Local-Regional Failure

Variable	2-yr LFFS rate (%)	Univariate		Multivariate	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value
Sex		2.39 (1.3–4.3)	0.003	2.86 (1.4–5.9)	0.004
Male	65.4				
Female	39.6				
Age (yr)		1.20 (0.7–2.0)	0.495		
<70	63.5				
≥70	57.8				
Histology		0.42 (0.1–3.0)	0.369		
Urothelial carcinoma	60.3				
Non-urothelial carcinoma	83.3				
Repeated TURB before surgery		2.05 (1.2–3.5)	0.008	2.17 (1.2–4.0)	0.015
<2	66.7				
≥2	46.4				
Neoadjuvant chemotherapy		1.41 (0.6–3.3)	0.423		
No	61.3				
Yes	57.0				
Adjuvant chemotherapy		0.32 (0.2–0.5)	<0.001	0.17 (0.1–0.3)	<0.001
No	41.4				
Yes	69.4				
Clinical T stage			0.297		
cT2	62.4				
cT3	63.3				
cT4	51.5				
Pathologic T stage		1.33 (0.8–2.3)	0.293		
pT3	62.9				
pT4	57.3				
LN metastasis		1.79 (1.1–3.0)	0.027	2.74 (1.4–5.3)	0.003
No	68.0				
Yes	49.3				
No. of LNs removed		1.35 (0.7–2.5)	0.345		
<20	64.5				
≥20	41.2				
Resection margin		2.07 (1.2–3.5)	0.006	2.46 (1.4–4.5)	0.003
Negative	68.1				
Positive	45.4				
LVI		1.39 (0.8–2.5)	0.266		
No	66.2				
Yes	59.2				
PNI		1.65 (0.9–2.9)	0.077	1.17 (0.6–2.2)	0.614
No	70.6				
Yes	52.8				

LFFS, local failure-free survival; HR, hazard ratio; CI, confidence interval; TURB, transurethral resection of the bladder; LN, lymph node; LVI, lymphovascular invasion; PNI, perineural invasion.

DISCUSSION

In this study, we investigated the patterns of failure in stage pT3-4 bladder cancer patients who underwent radical cystectomy, focusing primarily on the LRF. Even after radical cystectomy, approximately 60% of the patients experienced treat-

ment failure, 34% of which involved LRF. The most common site of LRF was the cystectomy bed, followed by the internal/external iliac LNs. LRF patterns were affected by pathologic risk factors, including margin status and pathologic T/N stage.

There have been several studies which investigated the pelvic failure after radical cystectomy in MIBC patients. Reddy, et

al.[12] reported 12.8% of LRF among 334 patients who underwent radical cystectomy for pT3-4 bladder cancer. Baumann, et al.[13] reported 28% of the 5-year cumulative incidence of pelvic failure in stage ≥pT3 patients. Our study showed similar or slightly higher LRF rates than those from previous studies investigating pelvic failure after radical cystectomy in MIBC patients. This may be because in our study, failures were detected more frequently due to active imaging evaluation using MRI, PET, or CT during follow-up.

Consequently, many authors have tried to identify the risk factors related to LRF.[6,14-17] Christodouleas, et al.[18] proposed risk stratification for LRF using the SWOG 8710 cohorts, and reported pT stage, margin status, and the number of dissected lymph nodes as prognostic factors. In the study by Reddy, et al.,[12] LN involvement, pathologic stage, and margin status were significant prognostic factors for LRF, similar to our results.

To reduce pelvic recurrences, several studies have investigated the efficacy of adjuvant RT. Although their results corroborate the use of adjuvant RT for improving locoregional control and disease-free survival or OS, the findings are not definitive due to their small sample sizes, retrospective study design, and heterogeneities.[9,19,20] Two historical prospective randomized trials from Egypt have demonstrated that postoperative RT improved locoregional control and disease-free survival; the 5-year locoregional control rate was 93% in the postoperative RT group and 50% in the observational group ($p<0.05$).[9,19] However, this study was limited by the fact that only 20% of the patients had urothelial cell carcinoma, and that an old RT technique (2D RT) was used. A large observational cohort study by Fisher-Valuck, et al.[8] evaluated the effectiveness of adjuvant RT using data from the NCDB. They showed that adjuvant RT was independently associated with improved OS: 19.8 months in the RT group vs. 16.9 months in the no-RT group ($p=0.03$).

Despite of these results, adjuvant RT is still limited in the real practice. A major concern inhibiting the use of adjuvant RT is toxicity. In the previous studies using outdated RT techniques, GI toxicities were high in up to 37% of patients, making adjuvant RT unacceptable.[9,21,22] However, recent studies using modern RT technique have reported relatively low rates of GI or GU toxicity. The results from a French multicenter study reported 5.2% and 9% of Grade ≥3 acute and late GI toxicity, respectively.[23] Another study by Zaghloul, et al.[24] also reported 7% of late Gr 3 GI toxicities.

Furthermore, an appropriate RT target volume is warranted to reduce RT-related toxicities. Baumann, et al.[13] reported pelvic failure patterns among 442 urothelial cell carcinoma patients and suggested an appropriate clinical target volume for adjuvant RT. They showed that >10% of recurrences occurred in the iliac and obturator nodes in stage ≥pT3 patients, and that only positive margin status was associated with a significant increase in local failure involving the cystectomy bed. Based on these results, they recommended that RT should tar-

get at least the iliac and obturator nodes in stage ≥pT3 patients with negative margins; coverage of the presacral nodes and cystectomy bed may be necessary for stage ≥pT3 patients with positive margins. Reddy, et al.[12] also evaluated pelvic failure patterns in pT3-4 bladder cancer patients according to risk factors including pT and pN stages; however, no variations were found despite significant differences in clinical outcomes. Our results confirmed those of Baumann's study, and showed that the failure site may differ depending on the pT and pN stages and resection margin status.

Our study had some limitations in addition to its retrospective nature. First, recurrences might have been underestimated due to the patients' irregular visiting schedules and small-sized lesions in the nodal basin that were difficult to recognize radiographically. Second, a small number of patients with non-urothelial cell carcinoma were included in this study; however, this may mimic the real clinical situation considering the need for adjuvant RT even for such cancers. Third, the evaluation of complete surgical resection could not be standardized due to the retrospective nature of the study. In the surgical evaluation of the primary lesion, recurrence was evaluated based on the resection margin, but the extent of LN dissection was not standardized. Future research should be conducted to evaluate the extent of recurrence by standardizing the evaluation of the extent and completeness of surgical resection.

Our results suggest the potential efficacy of adjuvant RT in selective patients who underwent radical cystectomy for stage pT3-4 bladder cancer. This study may suggest that it would be better to include cystectomy bed in the target volume for adjuvant RT, considering the high recurrence rate at this site. In patients with pN+ disease, the external iliac LNs are recommended to be included in the target volume, while no nodal irradiation may be needed in pN0 patients. Especially, the nodal target volume is recommended to extend cephalad up to the presacral and common iliac LNs in those with pT4 disease or positive resection margins. Furthermore, the pelvic nodal area may need to be fully covered by RT in pN2-3 patients who have shown extensive recurrence in the external iliac and common iliac LNs.

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AUTHOR CONTRIBUTIONS

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