

# Pattern of Failure in Bladder Cancer Patients Treated with Radical Cystectomy: Rationale for Adjuvant Radiotherapy

Thus far, the role of adjuvant radiotherapy (RT) after radical cystectomy (RC) in urinary bladder cancer patients has yet to be defined. The purpose of this study is to analyze patterns of failure, and suggest the rationale for RT. Between 1986 and 2005, a total of 259 patients treated with RC and pelvic lymph node dissection was enrolled. The age range was 27-82 yr (median, 62 yr). Node positivity increased according to tumor staging. Patients were divided into the following two groups based on pathologic analysis: organ-confined disease group (n=135) and extravesical/lymph node-positive disease group (n=80). Pelvic failures (PF) were observed in 8 (4.9%) in organ-confined disease group, and 21 (21.7%) in extravesical/lymph node-positive disease group. Five-year PF-free survival rates were 91.2% in organ-confined disease group and 68.0% in extravesical/lymph node-positive disease group. Five-year cancer-specific survival rates were 86.2% in organ-confined disease group and 53.9% in extravesical/lymph node-positive disease group. In conclusion, a relatively high PF rate was observed in extravesical lymph node-negative and lymph node-positive disease patients in this study. Adjuvant pelvic RT may be considered to reduce pelvic failures in extravesical lymph node-positive bladder cancer. Future prospective trials are required to test the clinical benefit of adjuvant RT.

**Key Words :** *Urinary Bladder Neoplasms; Radical Cystectomy; Pelvic Failure; Radiotherapy, Adjuvant*

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## INTRODUCTION

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is the standard surgical procedure for muscle-invasive bladder cancer. RC also provides an accurate evaluation of primary bladder tumors as well as regional lymph nodes. This evaluation allows for adjuvant treatment strategies based on clear pathologic staging rather than clinical staging, the latter of which has been associated with significant errors in 30-50% of patients (1-3). Many investigators have reported that RC with PLND provides excellent local control (4-8).

Although we often experience locoregional failure after RC, there has not been a clinicopathological study of bladder cancer from the radiation oncology perspective of this disease. The purpose of this study was to provide the rationale of adjuvant radiotherapy (RT) through analysis of pathologic findings of RC and patterns of failure in bladder cancer patients.

## MATERIALS AND METHODS

### Patients

We have maintained a database of all bladder cancer patients treated with RC at Severance Hospital, Yonsei University Health System, which contains detailed and comprehensive clinical and pathologic information since 1986. The records of 404 consecutive patients with a date of cystectomy on or before December 2005 were reviewed.

The retrospective collection of clinical data was approved by the Institutional Review Board for Clinical Research at Severance Hospital (4-2009-0476). To review a more homogeneous cohort of patients with transitional cell carcinoma (TCC) of the urinary bladder who received RC, the ineligibility criteria contained the following: history of previous malignancy (n=1), non-TCC bladder cancers (n=5), multiple primary tumors in the urinary tract (n=15), synchronous metastasis (n=4), preoperative systemic chemotherapy or RT (n=83),

postoperative RT (n=2), partial cystectomy (n=6), death from postoperative complications (2), and loss of follow up (n=27). Finally, 259 patients who underwent RC without adjuvant RT for primary TCC of the bladder were analyzed in this study.

### Treatment

Standard surgical procedures consisted of an en bloc RC with meticulous PLND and urinary diversion. PLND included the internal and external iliac and obturator lymph nodes. The boundaries of dissection included the circumflex iliac vein inferiorly, pelvic side wall laterally, bladder wall medially, and iliac bifurcation superiorly. Postoperative chemotherapy was administered selectively for muscle-invasive or node-positive disease in the adjuvant setting. Chemotherapeutic regimens consisted of methotrexate-vincristine-adriamycin-cyclophosphamide or gemcitabine and carboplatin (64 patients, 24.7%).

### Pathologic analysis

All en bloc cystectomy specimens were examined using the same pathologic protocol. Multiple sections were obtained from the tumor, bladder wall, and mucosa adjacent to and distant from the tumor along with the ureters and regional lymph nodes. All bladder tumors were primary TCC, with some demonstrating prominent histologic features of glandular differentiation. Histologic grading was determined according to the World Health Organization/International Society of Urological Pathologists grading system (9). Pathologic staging of primary bladder tumors and regional lymph nodes were re-evaluated according to the 2002 tumor-node-metastasis classification.

### Outcome analysis

We classified patterns of treatment failure into the following categories: local failure (LF), pelvic lymph node failure (PNF), paraaortic lymph node failure (PANF), and distant metastasis (DM). Recurrence in the soft tissue field of the exenteration and urethra was defined as LF. Nodal recurrence inside the pelvis was defined as PNF. Pelvic failure included LF and PNF. PANF was defined as nodal recurrence in the paraaortic lymph node chain. DM was defined as recurrence in solid organs, such as the bones, lungs, liver, or brain.

Pelvic failure-free survival (PFFS) and cancer-specific survival (CSS) rates were calculated using the Kaplan-Meier method, and differences were compared using log-rank test. CSS was calculated from the date of diagnosis to cancer-related death or last visit, and PFFS was calculated from the date of diagnosis to PF or last visit. Univariate analysis was used to define the prognostic factors influencing survival. The relative importance of the covariates in determining prognostic factors was also assessed by means of a multivariate Cox pro-

portional hazards model. *P* values  $\leq 0.05$  were considered significant.

## RESULTS

### Patient characteristics and clinical profiles

Patient characteristics and clinical profiles are listed in Table 1. Age ranged from 27 to 82 yr (median, 62 yr) and 88.4% of the population was male. The distribution of T staging was as follows: 15.8% were T0/Ta/Tis, 20.1% were T1, 30.9% were T2, 24.3% were T3, and 8.9% were T4. High tumor

Table 1. Patient characteristics

Characteristics	No. of patients (n=259)	%
Age (yr)		
Median	62	
Range	27-82	
Sex		
Male	229	88.4
Female	30	11.6
Tumor stage		
T0/Ta/Tis	41	15.8
T1	52	20.1
T2	80	30.9
T3	63	24.3
T4	23	8.9
Tumor grade		
Low	70	27.0
High	137	52.9
Unknown	52	20.1
Tumor shape		
Exophytic	122	30.0
Infiltrative	285	70.0
Lymphovascular involvement		
Yes	45	17.4
No	214	82.6
Resection margin		
Positive	17	6.6
Negative	242	93.4
No. of dissected LN (median)	11	
Nodal stage		
N0	224	86.5
N1	21	8.1
N2	12	4.6
N3	2	0.8
Stage		
0	6	2.7
I	49	22.3
II	71	32.3
III	52	23.6
IV	42	19.1
Adjuvant chemotherapy	64	24.7

LN, lymph node.

grade and lymphovascular permeation were observed in 52.9% and 17.4% of patients. Seventeen (6.6%) cases had positive resection margins, mainly at the urethra and ureter. The median number of dissected nodes was 11. The incidence of pathologic node positivity was 13.5%. Node positivity remarkably increased from 0% and 3.8% in T0/Ta/Tis and T1 to 27.0% and 34.8% in T3 and T4 (Fig. 1).

**Pattern of treatment failure and survival outcome**

During the median follow-up duration of 51 months (range, 5-257 months), 59 patients experienced treatment failure. Of 37 PF patients, 15 patients (40.5%) were diagnosed as computed tomography without symptoms, and other patients presented with urethral bleeding (12 patients, 16.2%), abdominal pain (4 patients, 10.8%), small bowel obstruction (4 patients, 10.8%), back pain (3 patients, 8.1%), and penile pain (3 patients, 8.1%). We investigated salvage therapy that 16 patients received for PNF; chemotherapy in 3 patients, RT in 1 patients, and symptomatic treatment in the other patients. After salvage therapy in these patients, 8 distant metastases to solid organs, 1 pelvic nodal progression, 1 paraaortic LN progression, and 1 carcinomatosis were observed, respectively. Five-year PFFS and CSS rates for all patients were 83.0% and 76.0%, respectively. According to T staging and node positivity, patient groups were defined as organ-confined disease with negative lymph node (T0, Ta, Tis, T1, T2; organ-confined group) and extravesical disease with negative lymph node (T3, T4) or lymph node-positive disease (extravesical/node-positive group). No significant differences were seen in LF between groups (8.2% vs. 10.3%). However, the incidence of PNF was significantly higher in the extravesical/node-positive group (14.0%) compared to the organ-confined group (4.1%). No differences were observed in PANF and DM between the 2 groups (Fig. 2).

Univariate analysis was performed to determine the significant prognostic indicator of PFFS and CSS (Table 2). Tumor

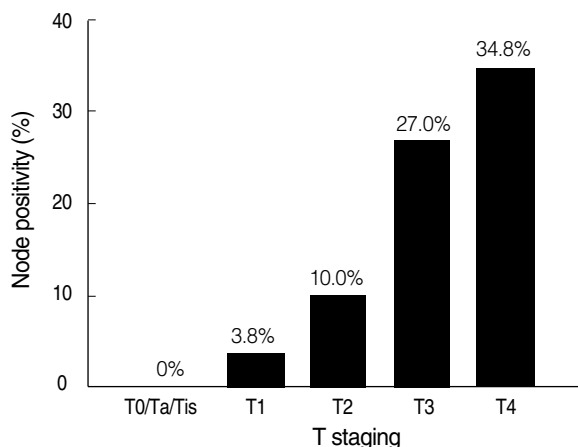


Fig. 1. Node positivity according to T staging.

grade, lymphovascular permeation, T staging, and node positivity were found to be the significant prognostic factors. However, administration of chemotherapy was the poor prognostic factor for PFFS and CSS. The extravesical/node-positive group had much poorer 5-yr PFFS and CSS rates compared to the organ-confined group (Fig. 3). We attempted to further identify independent prognostic factors influencing PFFS and CSS using Cox regression analysis. On multivariate analysis, patient grouping remained the independent prognostic factors in PFFS (the extravesical/node-positive group, hazard ratio=2.8), but not CSS. Rather, high-grade (hazard ratio=2.8) and positive lymphovascular permeation (hazard ratio=1.7) were found to be significant prognostic factors in CSS, as well as in PFFS (Table 3).

**DISCUSSION**

RC with PLND provides the most accurate pathological data on primary bladder tumors and regional lymph nodes. These pathologic determinants may be based on classification of pathologic subgroups that provide risk stratification and decide the necessity of adjuvant therapy in each patient. Pathologic subgroups are commonly defined as organ-confined tumors, non-organ-confined (extravesical) tumors, and lymph node-positive disease.

The role of adjuvant chemotherapy after cystectomy was not clear until now. Of the adjuvant studies in bladder cancer, five randomized trials used adjuvant chemotherapy. Advanced Bladder Cancer Meta-analysis Collaboration conducted a systemic review and meta-analysis of 491 patients from six trials, representing 90% of all patients randomized in cisplatin based combination chemotherapy trials. The analysis showed the overall hazard ratio for all trials of 0.75 suggests an absolute improvement in survival of 9% at 3 yr. However, the current evidence is clearly limited with too few trials and too few patients on which to base reliable treatment decisions (10). On-going studies, such as EORTC 30994 trial and the

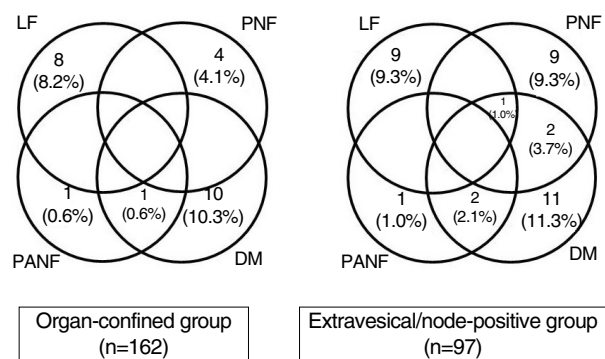
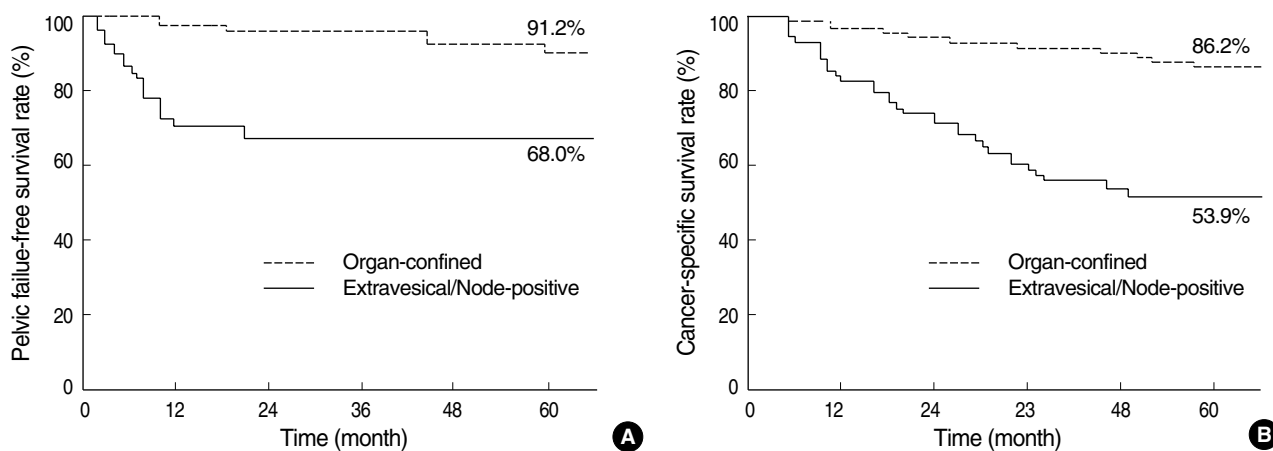


Fig. 2. Diagrams showing the difference in failure patterns between patient groups. LF, local failure; PNF, pelvic lymph node failure; PANF, paraaortic lymph node failure; DM, distant metastasis.

**Table 2.** Univariate analysis of prognostic factors

Prognostic Variables	No. of patients	5-yr pelvic failure-free survival		Statistical significance	5-yr cancer-specific survival		Statistical significance
		%	95% CI		%	95% CI	
Age (yr)							
<62	123	91.5	86.5-96.5	NS	78.7	70.7-85.7	NS
≥62	136	91.2	86.2-96.2		71.9	62.9-80.9	
Sex							
Male	229	92.5	88.5-96.5	NS	76.1	70.1-82.1	NS
Female	30	82.8	68.8-96.8		70.0	52.0-88.0	
Grade							
Low	66	100	-	0.01	92.8	85.8-99.8	0.01
High	137	86.0	80.0-92.0		62.0	52.0-72.0	
Lymphovascular permeation							
Yes	45	74.1	60.1-88.1	0.00	40.7	24.7-58.7	0.00
No	214	94.7	91.3-98.1		82.7	76.7-88.7	
Resection margin							
Positive	17	91.6	87.6-95.6	NS	69.6	43.6-95.6	NS
Negative	242	87.1	70.1-100		75.0	69.0-81.0	
Tumor staging							
T0, Ta, Tis, T1, T2	173	98.6	96.6-100	0.00	86.3	80.3-92.3	0.00
T3, T4	86	74.2	63.2-85.2		48.8	35.8-61.8	
Node positivity							
Positive	35	80.8	66.4-95.2	0.02	56.0	36.0-76.0	0.00
Negative	234	92.9	89.1-96.7		78.0	71.6-84.4	
Patient group							
Organ-confined	162	98.5	96.5-100	0.00	86.2	80.0-92.4	0.00
Extravesical/node-positive	97	77.6	67.6-87.6		53.9	41.9-65.9	
Chemotherapy							
No	195	97.9	95.9-99.9	0.00	88.3	83.3-93.3	0.00
Yes	64	67.5	52.5-82.5		36.3	22.3-50.3	

CI, confidence interval; NS, not significant.



**Fig. 3.** Five-year pelvic failure-free survival (A) and cancer-specific survival rates (B) according to patient groups.

USC p53 trial, are expected to answer the question definitely. In spite of insufficient evidence, investigators generally agree that for patients with positive nodes and even with negative node and high pathological stage of the primary tumor. Adjuvant chemotherapy is already being used in the treatment of

patients with invasive bladder cancer. In this study, administration of chemotherapy had negative influence on PFFS and CSS, because chemotherapy was administered selectively for muscle-invasive or node-positive disease.

To our knowledge, there is one randomized trial to investi-

Table 3. Multivariate analysis of prognostic factors

Prognostic variables	5-yr pelvic failure-free survival		Statistical significance	5-yr cancer-specific survival		Statistical significance
	Risk ratio	95% CI*		Risk ratio	95% CI	
Grade	4.9	2.9-6.9	NS†	9.1	7.7-10.5	0.00
Lymphovascular permeation	2.0	1.0-3.0	NS	3.0	2.4-3.6	0.00
Extravesical/node-positive	8.0	6.4-9.6	0.00	1.7	0-2.0	NS

CI, confidence interval; NS, not significant.

gate the value of postoperative RT as an adjuvant measure for RC (11). Patients with non-organ confined tumors were randomized into three groups after RC: 1) no further treatment, 2) multiple daily fractionation (3 fractions per day, 37.5 Gy/12 days), and 3) conventional fractionation (50 Gy/5 weeks). Two groups treated with adjuvant RT presented excellent five-year local control rates compared with the surgery alone group. Therapeutic benefits of postoperative RT were consistent for all tumor types, histological grades, and pathological stages for both disease-free survivals and local controls. Because there has been no further study to prove the clinical significance of postoperative RT after RC, most physicians do not accept RT as the standard adjuvant therapy after RC.

In a University of Southern California report, 5-yr recurrence-free survival rates of pathologic subgroups were 80%, 46%, and 35%, respectively (6). In addition, several institutional studies, including our series, also reported excellent local control rates. Most studies reported overall local control rates without distinction of stage. Recently, Stein et al. reported long-term oncological outcomes in 205 women undergoing RC for bladder cancer. The tumors consisted of 73 organ-confined (61%), 18 extravesical (15%), and 29 lymph node positive diseases. Even though lymph node positive diseases have significantly worst recurrence-free survival, only two patients had local recurrences (12). However, Dhar et al. reviewed 685 patients treated with RC, and analyzed 130 pelvic recurrences without concomitant distant metastasis. The median time from RC to PF was 7.3 months, and median survival from the time of PF to death was 4.9 months. Pelvic side wall and pelvic masses were the most common locations of pelvic recurrences. They suggested PF correlated with pathological and nodal stage. Patients with extravesical tumors without node involvement suffered from significantly higher pelvic recurrences within 12 months. In addition, node positive tumors also had higher pelvic recurrences irrespective of tumor stage (13).

In our series, pelvic lymph node metastasis correlated with advanced tumor staging, and extravesical or lymph node positive disease patients experiences significantly more PNF. Even though radical surgery provides accurate pathologic status through macroscopical resection, microscopic disease is still likely to remain in the pelvis. Therefore, most PFs occurred in the extravesical/node-positive group within 12 months, and were unfortunately too advanced at that time to be salvaged with re-treatment including chemotherapy and RT.

This study has several drawbacks to suggest the rationale postoperative RT after RC. This study is a retrospective collection of data for a long period of time. There are considerable heterogeneities of the surgical technique, administration of chemotherapy, and so on. In addition, our data showed the extravesical/node-positive group had significantly poor 5-yr PFFS, not CSS. This pattern of survival parameters may be explained by difference of PNE, not PANF and DM according to patient grouping. Even though grade was unknown in 20% of patients, high grade tumor and lymphovascular involvement were thought to be powerful prognostic factors on patterns of failures, PFFS and CSS in the present study. Therefore, patients with high grade tumor and lymphovascular involvement should be included in the future study to investigate the clinical significance of adjuvant RT after RC in addition to extravesical/node-positive group.

Clinical significance of postoperative RT may be important to relieve serious problems of quality of life due to intractable pain and discomfort from PF. We think the present study can not provide the confirmative role of postoperative RT, but suggests the rationale of RT in such patients who are likely to develop LF or PNF after RC. RT may be considered an adjuvant treatment in addition to adjuvant chemotherapy. Prospective clinical trials are needed to investigate such clinical and survival benefits of adjuvant RT in the future.

Adjuvant RT is believed to increase the incidence of postoperative complications such as small bowel toxicity in bladder cancer. Generally, radiation oncologists have used a variety of techniques to avoid small bowel obstruction when RT is delivered to the pelvis. Of the various techniques, bladder filling is the most effective method to push small bowel out of radiation field. Unfortunately, the small bowel comes down from the abdomen to the pelvic cavity in such patients without a bladder. Therefore, a much higher incidence of small bowel obstruction was reported in patients who received postoperative RT compared with patients without postoperative RT (14). Intensity-modulated RT (IMRT) has been proven to significantly reduce irradiation dose to the small bowel in gastrointestinal and gynecologic cancers (15-17). Whole pelvic IMRT using conformal avoidance techniques can deliver lower irradiation doses to the small bowel, and is expected to significantly reduce small bowel toxicity. Thus far, IMRT (50 Gy/5 weeks) is thought to be the safe and effective modality to cover whole pelvis and minimize bowel toxicity.

In conclusion, relatively high PF rate was observed in

extravesical lymph node-negative and lymph node-positive disease patients in this study. Adjuvant pelvic RT may be considered to reduce pelvic failures in extravesical/lymph node-positive bladder cancer. Future prospective trials are required to test the clinical benefit of adjuvant RT.

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