

Low Volume Lymph Node Metastases after Radical Cystectomy: Good Long-Term Survival

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Abstract

Objectives: To determine the long-term findings of patients with pathologically proven regional lymph node metastases undergoing radical cystectomy (RC) and pelvic lymph node dissection (PLND) for bladder cancer, and to analyze the impact of the number of lymph node metastases and adjuvant chemotherapy on the patient clinical outcome.

Methods: This study reviewed the data from 15 patients with lymph node metastases from 1994–2009. The overall survival (OS) after RC was measured using the Kaplan-Meier method.

Results: A median of 22 nodes (range, 9–37) were removed per patient. The median follow-up time was 34 months (range, 6–109) after RC. The 5-year OS of 15 patients with lymph node metastases was 58%, and that of patients with one or two positive nodes ($n=11$) was 83%, which was significantly better than patients with three or more positive nodes ($n=4$) ($p=0.00045$). A multivariate analysis showed the number of positive nodes to be an independent prognostic parameter ($p=0.038$).

Conclusions: Good long-term survival was observed in patients with low volume lymph node metastases after RC.

Key words : Bladder cancer, Lymph node metastasis, Overall survival, Radical cystectomy

Introduction

The therapeutic value of pelvic lymph node dissection (PLND) during radical cystectomy (RC) in bladder cancer patients with positive nodes has historically been controversial. Although even one positive lymph node was originally thought to be associated with systemic disease, a poor prognosis and not to benefit from local treatment, Skinner¹⁾ showed that some patients with node-positive bladder cancer achieved a favorable outcome with a meticulously performed PLND at RC. Furthermore, Vieweg et al²⁾ found that patients with single node metastasis benefitted from PLND and RC in comparison to those with node-negative disease and a similar pathological stage of the primary tumor.

Recent studies demonstrated that not only the number of positive nodes but also the number of nodes removed

were independent predictors of overall survival (OS) and disease-specific survival (DSS)³⁾. The present study evaluated the clinical characteristics and long-term survival of node-positive patients with bladder cancer that underwent RC and PLND at this institution.

Patients and Methods

Patients

One hundred thirty patients with bladder cancer underwent RC at this institution between January 1994 and December 2009. PLND was performed in all patients according to the standard protocol (including removal of external iliac and obturator nodes). Twenty-one of these (16%) patients had pathologically proven regional lymph node metastases (pN+). Six of these cases were complicated by upper urinary tract cancer, distant metastases or other malignancy so they were excluded

from the analysis.

Survival analysis

OS was measured from RC until the date of death or the last follow-up. Comparisons were made between patient survival and various parameters. The different comparisons included those patients with one or two positive nodes (≤ 2 pN+ group) versus those with three or more positive nodes (≥ 3 pN+ group); those with a lymph node density (LND), that is the ratio of positive lymph nodes to the total number of lymph nodes removed, of 10% or less (LND $\leq 10\%$ group) versus those with a LND greater than 10% (LND $>10\%$ group); and those that received adjuvant chemotherapy versus those without adjuvant chemotherapy.

The Kaplan-Meier method was used for the survival analysis. Differences between groups were evaluated by the log-rank test. Statistical significance was defined as $p < 0.05$. A multivariate analysis of parameters predicting OS, was performed using Cox’s proportional hazards model.

Results

Patient characteristics

Patient characteristics are shown in Table 1. Patients included 11 males and 4 females with a median age of 69 years (range, 46–80 years). All patients had urothelial carcinoma (UC) of the urinary bladder, and, one had a

small cell carcinoma (SmCC) component and another had a squamous cell carcinoma (SCC) component. A median of 22 nodes (range, 9–37) was removed per patient. Nine patients (60%) had one positive node, two (13%) had two positive nodes, and four (27%) had three or more positive nodes. The median LND was 9.1% (range, 2.7–95.5%).

Treatment outcomes

Treatment outcomes are shown in Table 2. Ten (67%) of the 15 patients received two to three cycles of adjuvant chemotherapy, which included methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) in eight patients, gemcitabine and cisplatin (GC) in one, and etoposide and cisplatin (EP) in another (UC>SmCC case).

Four (27%) of the 15 patients underwent five to 21 cycles of salvage chemotherapy, which included MVAC in one patient, GC in one, EP in one, and paclitaxel and gemcitabine (PG) plus GC in the other. Six patients died of bladder cancer (DOD) and two died of other causes (DOC). Four patients showed no evidence of disease (NED) and the remaining three were alive with disease (AWD).

Survival analysis

The median follow-up time was 34 months (range, 6–109 months) after RC. The 5-year OS of patients with

Table 1 Patient characteristics

Case	Age	Sex	Histology type	Grade	pT	Number of positive nodes	Number of nodes removed	Lymph node Density (%)
1	74	F	UC	2	3b	1	37	2.7
2	62	M	UC	2	2a	2	22	9.1
3	70	M	UC	2>3	2a	1	10	10.0
4	80	M	UC	2>3	3b	2	16	12.5
5	79	F	UC>SCC	2>3	3a	1	17	5.9
6	49	M	UC	3>2	4a	1	17	5.9
7	46	M	UC	3>2	2b	1	22	4.5
8	70	M	UC	3	2b	7	27	25.9
9	62	M	UC	2>3	2b	1	9	11.1
10	62	M	UC	3	3a	1	24	4.2
11	67	M	UC	3	3a	1	22	4.5
12	70	F	UC>SmCC	3	2b	1	19	5.3
13	69	M	UC	2=3	3b	22	28	78.6
14	62	M	UC	3	4a	21	22	95.5
15	75	F	UC	2>3	4a	3	15	20.0

UC, urothelial carcinoma. SmCC, small cell carcinoma. SCC, squamous cell carcinoma.

Table 2 Treatment outcomes

Case	Chemotherapy		Prognosis	Survival (months)
	Adjuvant	Salvage		
1	MVAC 2 x		DOC	109
2	MVAC 2 x		NED	66
3	MVAC 3 x	P G 16 x, GC 5 x	DOD	64
4			AWD	62
5			NED	44
6	MVAC 3 x	GC 5 x	AWD	41
7	MVAC 3 x		NED	40
8	MVAC 3 x	MVAC 6 x	DOD	36
9			AWD	34
10	GC 3 x		NED	34
11	MVAC 3 x		DOD	32
12	EP 2 x	EP 5 x	DOD	30
13	MVAC 3 x		DOD	18
14			DOD	7
15			DOC	6

NED, no evidence of disease. AWD, alive with disease. DOC, died of other cause. DOD, died of disease.

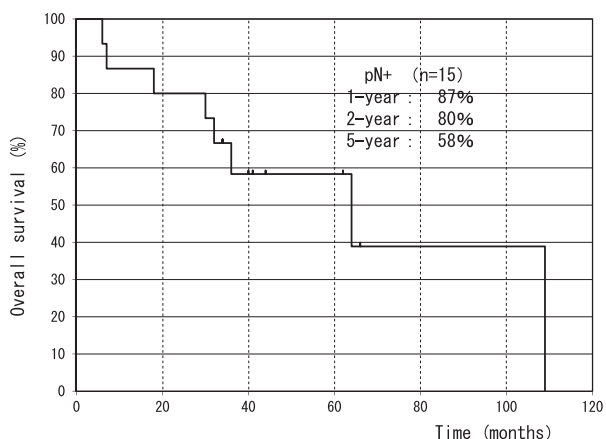


Fig. 1 Overall survival of node-positive bladder cancer patients.

pN+ was 58% (Fig. 1) in comparison to 83% for the ≤ 2 pN+ group, which was significantly better than the ≥ 3 pN+ group (0%), ($p=0.00045$, Fig. 2). The 5-year OS of the LND $\leq 10\%$ group and the LND $>10\%$ were 78% and 25%, respectively, which was not statistically significant ($p=0.054$, Fig. 3). There was also no significant difference between the 5-year OS of patients with and without adjuvant chemotherapy (58% versus 60%, respectively; $p=0.728$).

The multivariate analysis demonstrated that the number of positive nodes was an independent predictor of OS ($p=0.038$; Table 3).

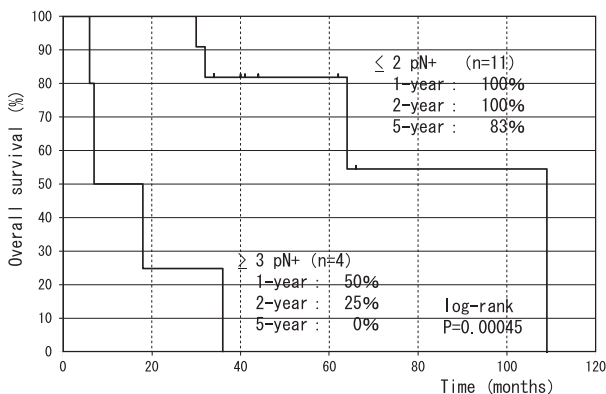


Fig. 2 Overall survival of node-positive bladder cancer patients according to the number of positive nodes: one or two (n=11) versus three or more (n=4) ($p=0.00045$).

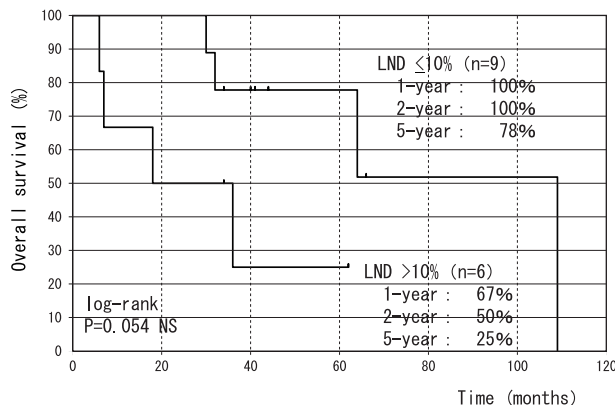


Fig. 3 Overall survival of node-positive bladder cancer patients according to the lymph node density (LND): 10% or less (n=9) versus more than 10% (n=6) ($p=0.054$).

Table 3 Multivariate analysis of parameters predicting overall survival in node positive patients

Parameter	n	Risk ratio	95% Confidence Interval	Multivariate P value	
Histology type	Pure UC UC + other histologic component	13 2	5.575	0.148–210.4	0.354
Grade	2 or 2>3 2=3, 3>2 or 3	7 8	20.484	0.387–1084.6	0.136
Pathological T stage	≤ 2 ≥ 3	6 9	3.724	0.288–48.18	0.314
Number of positive nodes	≤ 2 ≥ 3	11 4	125.906	1.315–1258	0.038
Number of removed nodes	≥ 20 < 20	8 7	15.725	0.500–494.4	0.117
Adjuvant chemotherapy	with without	10 5	0.387	0.017–8.636	0.549

UC, urothelial carcinoma.

Discussion

Previous Japanese large-scale multi-institutional studies^{4),5)} showed that patients with pN+ were found in 16–18% of bladder cancer patients that received RC with PLND. These node-positive cases had a lower 5-year OS rate (30–35%) than node-negative cases (64–76%)^{4),5)}. The 5-year OS of pN+ patients in the current series was 58%, which is consistent with the previous reports, perhaps because of the high proportion of patients with low volume pN+ and low LND (median, 9.1%).

The long-term OS of bladder cancer patients largely depends on the number of positive nodes^{3),6)}. Steven et al.⁶⁾ reported that the recurrence-free survival rate was significantly higher in patients with up to five involved lymph nodes. Similarly, the current findings showed that patients with one or two positive nodes had a significantly better 5-year OS rate of 83% in comparison to that of patients with three or more positive nodes.

An improved survival is also associated with a larger number of nodes removed, and more lymph nodes were removed in the current series than many previous studies (22 in this study in comparison to nine, 11 and 14^{3),7),8)}). Herr⁷⁾ found that DSS in bladder cancer patients with pN+ was improved if 13 or more nodes were examined, while Honma et al.³⁾ concluded that the removal of 13 or more pelvic lymph nodes was essential for a more accurate pathologic examination to predict patient

outcome and also contributed to an increased chance of survival. Koppie et al.⁸⁾ carried out a multivariable analysis and thus showed the number of lymph nodes removed to be predictive of survival.

LND was designed to classify the status of lymph node metastasis. Most studies establish an LND cutoff of 20% or 25%⁹⁾, and Osawa et al.¹⁰⁾ previously reported a 5-year OS for patients with an LND ≤25% of 39.6% in comparison to 10.3% for patients with an LND >25%. The present study found that an LND ≤10% was associated with a good 5-year OS of 78%. Kassouf et al.¹¹⁾ concluded that LND was superior to the TNM staging and to the absolute number of positive lymph nodes in predicting survival in bladder cancer patients with pN+ after RC.

The current small study found no survival benefit of adjuvant chemotherapy, but this has been observed in some large-scale studies of pN+ bladder cancer^{5),12)}. Takahashi et al.⁵⁾ reported that adjuvant chemotherapy significantly improved the 5-year OS (43% versus 17%), while Bruins et al.¹²⁾ used multivariate analysis to show that adjuvant chemotherapy was an independent significant predictor of recurrence-free survival in patients with pN+ after RC.

In conclusion, this study demonstrated that a good long-term survival was found after RC and PLND in patients with low volume pN+ bladder cancer.

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