

high-grade invasive disease were cured and that most patients subsequently died of metastatic disease within 3 years of diagnosis [8,9]. Improvements in medical, surgical, and anesthetic therapy, however, have clearly reduced the morbidity and mortality associated with contemporary surgery, providing excellent results with regard to survival and prevention of local recurrence [6,7]. In the present study, we conducted a multi-institutional retrospective analysis to establish the clinical outcome of invasive bladder cancer treated with contemporary radical cystectomy in Japan.

2. Materials and methods

2.1. Patients characteristics

We registered all patients who underwent radical cystectomy between January 1990 and December 2000 at 32 Japanese institutions including three university hospitals (Kyoto University Hospital, Nagoya University Hospital, and Nara Medical University Hospital), containing detailed and comprehensive clinical and pathologic information. The clinical and pathological data that were collected from the medical records included age, gender, histologic grading according to the World Health Organization system, clinical staging and pathological (P) staging according to the 1997 TNM classification [10], and the presence of perioperative systemic chemotherapy.

As shown in Table 1, of these 1131 patients, 903 were males (79.8%) and 228 were females. The median age was 65.9 years (range 31–89 years). Updated follow-up information was obtained from patient records at every single center; for all those not followed until death or until the closing date of the study (December 31, 2001). Perioperative death occurred in 7 (0.6%) of 1131 patients. Median follow-up duration was 3.8 years. A total of 112 (9.9%) of the cases were lost to follow-up.

The follow-up procedures varied slightly among the institutions considered; however, some general statements should be made because of the long study period. All patients were followed for a period of 3–6 months between the follow-up visits during the first 2–3 years; the visits were every 6 months or annually thereafter. The follow-up included at each visit a physical examination (general and local). This prompted, when needed and according to the clinical suspicion of persisting/relapsing disease, the use of the same specific diagnostic tests performed during the baseline workup (e.g., ultrasonography, chest-XP, CT, and bone scan).

2.2. Study endpoints and statistical analysis

The overall survival was defined as the time from the radical cystectomy to any cause of death; all deaths from any causes were

counted as an event and patients still being alive were treated as censored at the date of last follow-up before December 31, 2001. The survival proportions were estimated with the Kaplan–Meier method. The log-rank test was performed to test associations between patient characteristics and survival according to pathological stage. To identify the prognostic factors independently associated with the overall survival and to estimate the hazard ratios, the Cox proportional hazards model was applied. Two-sided $p < 0.05$ was regarded as statistically significant. All statistical analyses were performed using SAS version 8 (SAS Institute, Cary, NC, USA).

3. Results

Among the 1131 consecutive TCC patients undergoing radical cystectomy, histopathological analysis demonstrated that 1042 patients (92.1%) harbored TCCs, whereas 89 patients (7.9%) presented non-TCCs; 38 SCCs, 23 adenocarcinoma, and 28 miscellaneous tumors. Mean patient age was 66.0 years (range 31–89) and 64.5 (range 37–85) in the TCC and non-TCC group, respectively. The male/female ratio and follow-up duration in both groups were similar, as shown in Table 1.

Pelvic LN dissection was performed in 1013 patients in total, and pathologically confirmed lymph node metastases were found in 162 (16.0%). LN involvement increased with a more advanced P category. The rate of having nodal metastases was significantly higher in patients with P3 or greater (37.0%) than in those with P2b or less (7.5%) ($p < 0.001$), but it did not correlate with the histological subtypes of the tumor (Table 2).

During the follow-up period, 288 cases were identified as definitive treatment failure (alive with or died of disease). Treatment failures were due to local recurrences in 65 cases (5.7%), distant metastasis in 204 (18.0%) or both in 13 (1.1%). Treatment failures were documented in a significantly higher frequency of patients with positive nodes (57.1%), than those with negative nodes (19.1%) ($p < 0.001$). As well, recurrence was observed in significantly higher frequency in patients with P3 or more (47.4%) than those with P2b or less (16.3%)

Table 1
Patient characteristics

Characteristics	Total	TCC	Non-TCC	Non-TCC		
				SCC	Adeno	Others
Total patients (%)	1131	1042 (92.1)	89 (7.9)	38 (3.4)	23 (2.0)	28 (2.5)
Mean age (years) (range)	65.9 (31–89)	66.0 (31–89)	64.5 (37–85)	62.9 (37–85)	68.4 (52–80)	63.5 (50–84)
Gender (M/F)	903/228	841/201	62/27	25/13	15/8	22/6
Median follow up duration (years)	3.8	3.8	3.7	3.5	3.4	7.9

Table 2
Lymph node involvement relative to P-stage and histology

Histology	P2 or less			P3 or more		
	pN0	pN+	%	pN0	pN+	%
TCC	633	51	7.5%	168	94	35.9%
Non-TCC	34	3	8.1%	16	14	46.7%
SCC	16	2	11.1%	7	9	56.2%
Adeno	8	1	11.1%	6	3	33.3%
Others	10	0	0.0%	3	2	40.0%
Total	667	54	7.5%	184	108	37.0%

($p < 0.001$), but histological subtypes showed no impact on treatment failure.

The overall survival for all 1131 patients at 5 years was 68.0%, and 95% confidence interval (CI) ranged between 64.8% and 71.2%, and most deaths (79.0%) occurred within 3 years. Kaplan–Meier analyses estimated the 5-year overall survival in each subgroup

Table 3
Five-year overall survival in different clinical and therapeutic subgroups of the entire series

Subgroups	No. patients	No. death	5-year survival (%)	<i>p</i> -value
Age (years)				
<70	691	186	71.4	
70–74	268	86	65.0	
75–79	110	39	59.7	
≥80	62	26	56.2	0.001
Gender				
Male	903	264	68.7	
Female	228	73	65.1	0.332
Histology				
TCC	1042	305	68.6	
Non-TCC	89	32	60.8	0.284
Grade				
G1	19	5	72.2	
G2	318	77	75.0	
G3	705	223	65.5	0.009
Clinical stage				
T1 or less	290	58	82.0	
T2	323	75	74.7	
T3	371	138	57.9	
T4	68	35	42.3	0.001
Pathological stage				
P2a or less	640	120	82.2	
P2b	149	54	60.2	
P3	237	109	47.8	
P4	94	50	28.0	0.001
LN involvement				
pN0	853	201	75.5	
pN+	163	90	35.1	0.001
LN dissection				
Without	121	54	54.1	
With	982	276	69.8	0.001

stratified with several variables including age, gender, histological subtype, grade, clinical stage, pathological stage, LN involvement and LN dissection. As shown in Table 3, 5-year survivals were significantly declined in correlation with age, grade, stage, the presence of LN involvement and the presence of LN dissection.

When comparing TCC and non-TCC, the 5-year survival for patients with TCC ($n = 1042$) and those with non-TCC ($n = 89$) was 68.6% and 60.8%, respectively (Table 3). On analyzing subgroups stratified with P-stages, the overall survivals were not significantly different between patients with TCC and those with non-TCC; the 5-year survival in stage P2b or less was 78.7% in TCC and 69.8% in non-TCC, respectively ($p = 0.20$), whereas that in stage pT3 or higher was 46.3% in TCC and 42.1% in non-TCC, respectively ($p = 0.51$) (Fig. 1a and b). When analyzing the patient group with TCC bladder cancers, the overall survival significantly declined as P and pN categories increased. The rates of 5-year survival for TCC patients without pathological lymph node involvement (pN0) were 84.5% for P2a or less, 64.9% for P2b, 58.5% for P3, and 43.4% for P4 patients, whereas those for TCC patients with pathological lymph node involvement (pN+) were 66.7% for P2a or less, 46.9% for P2b, 24.6% for P3, and 16.8% for P4 patients.

To identify the independent predictors of survival, multivariate analyses were performed, using various subsets of patients listed in Table 3. Factors significantly associated with better survival were age (70 years old or less), clinical stage (T3 or less), P-stage (P2a or less), negative LN involvement and cystectomy with LN-dissection, although gender and grade had no significant impact on survival (Table 4).

Table 4
Results of Cox regression analysis for overall survival

Factors	Category	Hazard ratio	95% CI	<i>p</i> -value
Age (years)	≤69	1.00		
	70–74	1.34	1.03–1.74	0.027
	75–79	1.44	1.01–2.06	0.044
	≥80	1.63	1.06–2.53	0.027
T	T3 or less	1.00		
	T4	1.61	1.09–2.38	0.017
pT	P2a or less	1.00		
	P2b	1.94	1.40–2.69	0.001
	P3	2.59	1.97–3.42	0.001
	P4	2.76	1.88–4.06	0.001
pN	pN0	1.00		
	pN1	1.50	1.03–2.18	0.037
	pN2–3	3.05	2.21–4.21	0.001
LN dessect	without	1.00		
	with	0.06	0.44–0.81	0.001

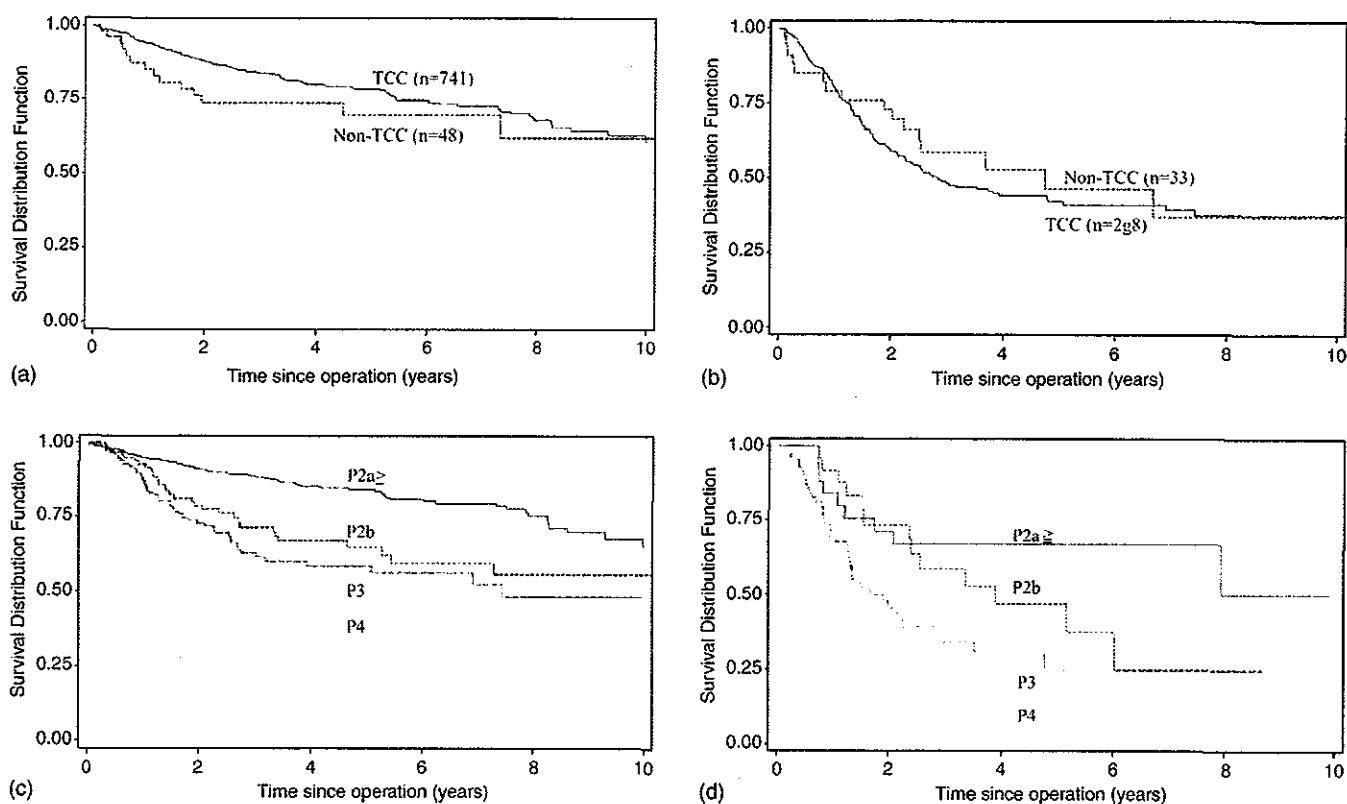


Fig. 1. Overall survival in TCC and non-TCC bladder cancers. Overall survivals were analysed by Kaplan–Meier estimates in pT2b or less (a) and pT3 or more (b). The five-year survival in pT2b or less was 78.7% and 69.8% in TCC and non-TCC ($p = 0.20$), whereas that in pT3 or greater was 46.3% and 42.1% in TCC and non-TCC ($p = 0.51$), respectively.

4. Discussion

Radical cystectomy has been established as a gold standard for locally advanced bladder cancer in the last two decades. Although only about 40% of patients survived at 5 years after the operation in the earlier studies [8,9] or from developing countries [11], recent advancements in medical and surgical therapy have clearly improved clinical results with overall survival rates of greater than 60% [6,7]. In our series of 1131 patients treated with radical cystectomy, the 5-year overall survival rate was 68.0%, which is comparable with those of other recent series [6,7].

In general, P-stage and LN status are well known as the most important predictors for survival [10]. The reported incidence of regional LN involvement varied between 14 and 27%, and this incidence correlated with the P-stage of the primary tumors [12–14]. In our entire series, the incidence of LN involvement was 16.0%. The rate of having nodal metastases was significantly higher in patients with P3 or greater (37.0%) than in those with P2b or less (7.5%) ($p < 0.001$). The reported 5-year survival following radical cystectomy and pelvic lymphadenectomy in patients with positive LNs ranged between 4 and 31% [6,7,15–17]. The

present findings demonstrated that radical cystectomy with LN dissection could provide a 5-year survival of 35.1% for node positive cases compared with 75.5% for node negative cases, a percentage comparable with other series [6,7,15–17]. Thus, LN involvement is definitely an unfavorable prognostic sign, but long-term survival was seen in 20–30% of patients, emphasizing that LN dissection can be curative in a subset of patients [7,16,18]. The clinical significance of LN dissection on survival was supported by the results of our multivariate analysis, in which radical cystectomy with LN dissection provide significantly better survival than that without dissection, although the bias of patient selection should be taken into consideration.

The findings of the present study also demonstrated that P-stage is an important survival determinant in patients undergoing cystectomy. The difference in survival between organ-confined tumors (P2b or less, according to the 1997 TNM system [10]) and extravesical tumors (P3 or more) is noteworthy [19]. In agreement with recent series [6,7,19], similar differences between organ-confined and non-organ-confined tumors were observed in our series: approximately 70% of patients with organ-confined disease were free of tumor at 5 years after the operation, whereas tumor

extension into perivesical fat or extravesical disease predicted a poor prognosis with less than 50% of 5 year overall survival.

Recently several studies reported the favorable clinical outcomes of large-scale patients with TCC bladder cancers [6,7]. To compare the present results in the same populations of patients, we evaluated the survival in TCC patients subgroups stratified with P- and pN-stages. The rates of 5 year survival were significantly lower for TCC patients with pN0 according with P-stage: 84.5% for less than P2a, 64.9% for P2b, 58.5% for P3, and 43.4% for P4 patients. Similar differences were noted when stratifying patients with pN+: 66.7% for less than P2a, 46.9% for P2b, 24.6% for P3, and 16.8% for P4 patients. The present results were comparable with the clinical outcomes of other recent large-scale series, in which 5-year overall survival was 62–78% for patients with organ-confined, lymph node-negative tumors (\leq pT2, pN0) and 47–49% for non-organ-confined, lymph node-negative tumors ($>$ pT2, pN0) [6,7]. This finding could provide validation of the new TNM nomenclature of 1997 with its distinction between P2b (deep muscle invasion) and P3a (microscopic invasion of perivesical fat).

Other than P-stage and LN status, there is no consensus on whether additional factors may significantly impact on the prognosis [6,7]. In the present series, multivariate analyses demonstrated that age and the presence of LN dissection are important survival predictors in cystectomy patients. Frazier et al. [20] based on the outcome analysis on a larger series of 531 patients, found age, grade, and the presence of positive margins to be additional independent predictors of disease specific survival. Gschwend et al. [21] demonstrated that the different independent variables impacted upon the outcome within the stratified patient category. The observed differences were most profound when comparing the prognostic variables of patients with organ-confined disease (P-stage, N-stage, age, and vascular invasion), N0 disease (P-stage, age, gender, tumor type, and vascular invasion) and N+ disease (only P-stage).

The patterns of treatment failure are important to realize the problems of radical cystectomy. Incidence of pelvic recurrences after radical cystectomy were reported recently to be an average of 10% (range 4% to 18%) [22]. Overall, the 5.7% local recurrence rate in the present series is at the lower end of this range. This is a result of earlier intervention, improved surgical technique, and better patient selection. Despite satisfactory local tumor control, distant metastases were observed in 208 patients among 228 patients presented as treatment failure. These findings suggest that reducing distant metastases is one of the most important

problems for further improvements of survival. Although there has been a huge increase in the knowledge of molecular mechanisms for bladder cancer and the large number of markers investigated [23], this has not yet brought about a reliable discrimination between high- and low-risk patients on an individual basis. Markers are needed to allow for a better stratification, for example, for adjuvant chemotherapy protocols.

The present series also disclosed clinical features of non-TCC bladder tumors in Japan. Bladder cancer comprises a broad spectrum of tumors, including TCCs, SCCs, adenocarcinomas, and miscellaneous subtypes. In Western countries including USA and Europe, TCCs are the more prevalent tumors and other histological types, including SCCs and adenocarcinomas, encompass a small percentage (2–3%) [1,2]. On the other hand, SCCs account for approximately 80% in areas of Africa and the Middle East [11]. In the present series, TCCs are the most prevalent tumor, accounting for greater than 90%, and SCCs and adenocarcinomas both encompassed only 2–3%, suggesting that the distributions of histological subtypes in Japan resembled those in Western countries.

The clinical outcome of non-TCC bladder tumors remains controversial, because of their rarity. Some studies reported that adenocarcinomas and SCCs are generally invasive and are considered to be unfavorable prognostic factors compared with TCCs [23,24], whereas other studies demonstrated that adenocarcinoma and SCCs have a clinical behavior similar to that of TCCs [25–27]. Recently, Ghoneim et al. [11] reported the clinical outcome of 608 patients with SCCs in Egypt, who were treated with radical cystectomy, demonstrating that the distribution of stage, the frequency of lymph node involvement and the prognosis in SCCs was not significantly different from those in TCCs. In the present series, the male/female ratio, the distribution of stage, and the frequency of lymph node-involvement in non-TCCs, including SCCs and adenocarcinoma, were all not significantly different from TCCs. Furthermore, univariate analysis and multivariate statistical analysis demonstrated that tumor histology had no impact on their prognosis.

5. Conclusions

The outcome reported from this large group of patients demonstrates that radical cystectomy provides good survival results, with excellent local tumor control. A 5-year overall survival is expected in 68% of cases. The results from this large series of patients provide sound data and a standard with which other

forms of therapy for invasive bladder cancer can be compared.

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