Analysis of Intravesical Recurrence After Bladder-preserving Therapy for Muscle-invasive Bladder Cancer

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Objective: The aim of the present study was to analyze the pattern of recurrences after bladder-preserving therapy for muscle-invasive bladder cancer.

Methods: The subjects were 77 patients with T2-3N0M0 bladder cancer whose bladder was preserved by intra-arterial chemotherapy and radiation. The patterns of the first recurrences were retrospectively analyzed.

Results: With a median follow-up of 38.5 months, 17 patients (22.1%) experienced intravesical recurrence without metastasis, 14 (82.4%) of which were cases of non-muscle-invasive bladder cancer recurrence and 3 (17.6%) of which were muscle-invasive bladder cancer recurrences. Muscle-invasive bladder cancer recurred at the same site as the initial tumor site in all three cases, whereas non-muscle-invasive bladder cancer recurred at different sites in 64% of the patients in that group. The peak hazard of the non-muscle-invasive bladder cancer recurrence was observed at around a year after treatment. Recurrent non-muscle-invasive bladder cancer was of a significantly lower histological grade with lower Ki-67-labeling indices than the initial muscle-invasive bladder cancer. Twelve (85.7%) of 14 patients with non-muscle-invasive bladder cancer recurrence achieved disease-free status. The multivariate analysis revealed that multiplicity, grade and tumor size were significantly correlated with the recurrence (P = 0.0001, 0.0442 and 0.0412, respectively).

Conclusions: Most of the recurrences after bladder-preserving therapy were cases of non-muscle-invasive bladder cancer. The recurrence pattern and characteristics of the tumors did not differ from those of primary non-muscle-invasive bladder cancer. Patients with high-risk factors would be candidates for prophylactic intravesical therapy for non-muscle-invasive bladder cancer recurrence.

Key words: drug therapy – preservation – radiation – recurrence – urinary bladder neoplasms
INTRODUCTION

Radical cystectomy with urinary diversion has long been considered a gold-standard treatment for muscle-invasive bladder cancer (MIBC) (1,2), with a reported 5-year survival rate of ~40–60% (3–5). Although complications and mortality rates have decreased due to advances in surgical techniques and perioperative patient care, these operations have the potential for lowering the quality of life (5–7). Therefore, a substantial subset of patients experience great anxiety regarding the removal of their bladder. In addition, due to advanced age and co-morbidities, some patients are considered unsuitable for cystectomy. Thus, bladder-preserving therapy with curative intent using multimodality treatment consisting of transurethral resection of the bladder tumor (TURBT), chemotherapy and radiation was developed in the early 1980s (8,9). Since then, several groups including ours modified their own protocols of bladder-preserving therapy, leading to quite favorable outcomes (10–21). These bladder-preserving therapies are now listed in the clinical guidelines [evidence level of categories 2B and 3 in the National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines, respectively] (1,2). To select patients with favorable indications, the tumor control rate ranged from 70 to 90%, the 5-year cause-specific survival rate from 60 to 80% and the overall survival rate from 50 to 75% (10–19). However, there remain clinical issues with a bladder-preserving approach. Preserved bladders always harbor the risk of subsequent intravesical recurrence. Indeed, non-MIBC (NMIBC) recurrence and MIBC recurrence have been reported in 4 to 26% and 5 to 15% of patients, respectively (10–15).

Primary NMIBCs are generally treated by TURBT, but intravesical recurrences very frequently occur after TUR, i.e. at a rate of 30–60% at 1 year (22). After repeated intravesical recurrence, the tumors occasionally progress to MIBC and/or metastases (2). Timing of NMIBC recurrence after TURBT was reported to have two phases; the early phase was during the first 500 days and the late phase was between 500 and 800 days (22,23). To prevent intravesical recurrence, single instillation of chemotherapy or maintenance of instillation of bacillus Calmette–Guérin (BCG) is recommended following risk classification and presents the prophylactic effects on the early phase and/or late phase (1,2). Thus, the patterns of intravesical recurrences after TURBT for primary NMIBC and the effects of intravesical instillation on the intravesical recurrences have been enthusiastically examined in the literature, but the pattern of intravesical recurrences after the treatment of MIBC remains to be known. In the present study, we first elucidated the pattern of intravesical recurrence after bladder-preserving therapy for MIBC in our bladder-preserving methods using arterial infusion of chemotherapy with irradiation. Furthermore, we analyzed the characteristic differences between the initial and recurrent tumors and the risk of intravesical recurrences after bladder-preserving therapy.

PATIENTS AND METHODS

PATIENTS AND TREATMENT PROTOCOL

Bladder-preserving therapy was performed in patients with T2-3N0M0 urothelial bladder cancer at Tsukuba University Hospital, Japan. The clinical stages were determined by TURBT, computed tomography (CT), magnetic resonance imaging and bone scintigram. Patients who had previously been treated, who had other active malignant disease or who had severe co-morbidities were excluded from the protocol. In principle, patients with severe hydronephrosis and/or carcinoma in situ were also excluded. Informed consent was obtained from all patients before treatment.

A detailed protocol of the bladder-preserving therapy was previously described elsewhere (21). Briefly, patients were first treated by TURBT of the initial MIBC to debulk the tumor and to confirm the histology as well as its invasion into the muscularis propria. Three cycles of intra-arterial chemotherapy at intervals of 3 weeks consisting of cisplatin at 50 mg/m² and methotrexate at 30 mg/m² and concurrent X-ray irradiation (41.4 Gy in 23 divided doses) to the small pelvis were then performed. An interim evaluation for initial tumor control was then performed by imaging studies, urine cytology, TUR biopsy and, in a part of the patients, whole-layer needle biopsy. If there were no more viable tumors, the site of the initial tumor was finally subjected to a boost irradiation by X-ray (19.8 Gy) (n = 35) or proton (36.3 GyE) (n = 42). After the completion of the treatment, patients were followed by urinary cytology, cystoscopy and chest X-ray every 3 months for the first 2 years, then every 6 months for the next 2 years and then annually. An abdominal ultrasound or CT scan was performed every 6 months. When intravesical recurrence was detected, the treatment depended on whether muscle was involved. For MIBC recurrence, cystectomy was strongly recommended. For NMIBC recurrence, radical cystectomy was recommended from 1993 to 1997. Thereafter, however, we gradually changed our policy towards a further conservative approach, including TURBT with or without BCG instillation therapy.

From 1993 to 2010, 111 patients with T2-3N0M0 urothelial bladder cancer were treated at our hospital. Among the 102 evaluable patients, the planned protocol achieved a complete disappearance of tumor on the interim evaluation in 84. Of these, 77 completed the full-course protocol, and these patients were the subjects of the present study. The background characteristics of the subjects (i.e. patients with T2-3N0M0 urothelial carcinoma of the bladder who completed the protocol and whose bladder could be preserved) are summarized in Table 1. The T stage of the initial tumor was T2 in 49 patients and T3 in 28. The grade of the initial tumor was G3 in most of the patients (80.5%). About half of
the patients (40 patients) had tumor equal to or exceeding 3 cm in size.

**IMMUNOHISTOCHEMICAL ANALYSIS**

To evaluate the cell proliferation, the Ki-67-labeling index was determined immunohistochemically using paired samples of five patients from both the initial MIBC and the recurrent NMIBC groups.

After pretreatments including antigen retrieval by microwave heating, 4 μm-thick sections from paraffin-embedded tissue blocks were incubated overnight at 4°C with anti-human Ki-67 monoclonal antibody (Dako Japan Inc., Tokyo, Japan) diluted 1:100. Then, the sections were treated with N-Histofine® Simple Stain MAX PO (Nichirei Biosciences Inc., Tokyo, Japan) according to the manufacturer’s instructions. Immunostaining without primary antibody was used as a negative control. Counterstaining was performed using hematoxylin. At least 300 nuclei per tumor were visually assessed for the staining positivity. The Ki-67-labeling index was calculated by dividing the number of positive nuclei by the total number of nuclei assessed, and the index was expressed as a percentage.

**STATISTICAL ANALYSIS**

Clinical factors and pathological information were obtained from medical records. The relationships among the background variables, recurrence pattern and the type of boost irradiation were assessed using Fisher's exact probability test or the Wilcoxon test. The proportion of NMIBC and of MIBC recurrence was compared by one-tailed binominal test. Characteristics of the initial MIBC and those of the recurrent tumors were compared for each patient by paired t-test or Wilcoxon’s signed-rank test. Risk factors for the NMIBC recurrence were analyzed by the Cox proportional hazard model. The time to event was defined as the interval from the treatment initiation to the occurrence of the earliest events. These analyses were performed with JMP®9 software (SAS Institute Inc., Cary, NC, USA), and values of P < 0.05 were considered statistically significant. Smoothed hazard of the first recurrence was estimated by a kernel function method under the condition of bandwidth = 270 days (22,24).

**RESULTS**

Of the 77 patients who completed bladder-preserving treatment by chemoradiation, 17 (22.1%; X-ray boost in 8 and proton boost in 9) suffered an intravesical recurrence without distant metastasis and 5 (6.5%; X-ray boost in 1 and proton boost in 4) suffered a distant metastasis. No relationship was observed between the failure pattern and the type of boost irradiation (P = 0.4694). The pathological findings for the first intravesical recurrence were as follows: 14 (18.2%; Ta in 6, Tis in 2 and T1 in 6) cases of an NMIBC phenotype, and 3 (3.9%; T2 in 1 and T3 in 2) cases of an MIBC phenotype. Significantly, more frequent NMIBC recurrences than MIBC recurrences were observed (P = 0.0064). Next, the characteristics of the first intravesical recurrence were analyzed. Among the MIBC recurrences, the median time to recurrence was 29.7 (8.6–32.9) months, and tumors developed at the initial tumor site in all three patients. In contrast, among the NMIBC recurrences, the median time to recurrence was 14.1 (range, 6.6–137.2) months, and tumors recurred only at the initial tumor site in five patients (35.7%) and at different sites in nine patients (64.3%). In patients with NMIBC recurrence, the histological grade and cell proliferation of the intravesical recurrent tumor were compared with those of the initial tumors. The tumor grade was significantly lower in the recurrent tumor (G2 in 11 patients and G3 in 3 patients,
The cell proliferation of both tumors was evaluable in five patients and revealed that the Ki-67-labeling index was $32.7 \pm 16.7\%$ in the initial MIBC and $14.3 \pm 10.3\%$ in the recurrent NMIBC, with the latter value being significantly lower ($P = 0.0462$).

The patterns of the NMIBC recurrence were analyzed by the estimated smoothed hazard curve. As shown in Fig. 1, the peak hazard was observed at around a year of follow-up, and most recurrences were observed within the first 2 years. As regards the clinicopathological risk factors affecting the recurrences, the multiplicity significantly correlated with the recurrence, with a $P$ value of 0.0002 on univariate analysis (Table 2). $P$ values regarding tumor grade and size were not statistically significant, but were considered marginal (0.0633 and 0.0826, respectively). We also performed a multivariate analysis using these three variables, which revealed all three as significant risk factors.

Finally, we analyzed the follow-up status of the 14 patients with NMIBC recurrence. Three of these patients underwent immediate cystectomy at the first NMIBC recurrence, and the other seven patients were treated with intravesical BCG instillation. Salvage cystectomy was needed to treat the subsequent MIBC or NMIBC recurrence in three patients. None of these 14 patients experienced a distant metastasis or died of disease during 76-month follow-up period.

### DISCUSSION

At present, bladder-preserving therapy for MIBC is listed as an option in EAU/NCCN guideline, and the incidence of bladder-preserving therapy for muscle-invasive bladder cancer

<table>
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<th>Clinicopathological variable</th>
<th>Category</th>
<th>Patient no.</th>
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<th>3-year recurrence-free</th>
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<th>Multivariate</th>
<th>Risk ratio</th>
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<td></td>
<td>G3</td>
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<td>21.0</td>
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MIBC recurrence has been reported to range from 5 to 15% (10,11,19,25). However, one problem is that there is a wide variety among their protocols, and the standard methods are not yet decided. The most important finding of the present study was that the rate of MIBC recurrences was 3.9%; lower than any previous protocols (10,11,19,25). This high success rate to control MIBC might be partly due to differences in treatment protocols. We administered cisplatin and methotrexate intra-arterially and also treated with the total radiation dose as high as 77.7 GyE with proton therapy or 61.2 Gy with X-ray treatment, which was the relatively higher-dose irradiation than the previous reports (10,11,19,25). On the other hand, the incidence of NMIBC recurrences is reported to be 4–26% after bladder-preserving therapy for MIBC (10,11,19,25), which is similar to one in the present study (18.7%). These data may indicate that higher-dose irradiation or arterial infusion was not effective to prevent NMIBC recurrence.

To elucidate the pattern of NMIBC recurrences, the recurrent risk over time was analyzed using smoothed hazard function plots. This statistical approach has revealed variations in the patterns of intravesical recurrence among diverse clinical conditions (22,23,26). For example, after TURBT for the primary NMIBC, two peaks of intravesical recurrence were detected in the early phase (i.e. during the first 500 days) and the late phase (500–800 days) (22,23). Interestingly, induction therapy of BCG reduced the risk of recurrence in the early phase after TUR, and maintenance BCG therapy has prophylactic effects against both the early phase and the late phase (22,23,27). NMIBC recurrences were observed after nephroureterectomy against upper-tract urothelial tumors. Smoothed hazard function plots demonstrated that NMIBC recurrence is most often seen within 2.5 years after treatment (26). In the present study, the smoothed hazard function plots revealed a peak of recurrence hazard after bladder-preserving therapy for MIBC within 2 years, although the hazard risk persisted at a low level for a long period of time. This recurrence pattern was very similar to those observed after treatment for the primary NMIBC or upper-tract urothelial tumors, but not to those after BCG instillation therapy. These data might also support our hypothesis that higher-dose irradiation or arterial infusion was not effective to prevent NMIBC recurrence, unlike BCG. However, because of the small number of events in the present study, further studies are necessary to confirm this hypothesis.

When an NMIBC recurs after bladder-preserving therapy, it is difficult to choose salvage radical cystectomy or TURBT with/without intravesical instillation. In the early phase of the present study, we adopted salvage cystectomy for patients with an NMIBC recurrence because we worried about the risk of progression. However, after Massachusetts General Hospital reported low progression rate (10%) and high successful bladder-preserving rate (75%) in the patients with NMIBC recurrences (25), we tried to preserve the bladder in the most of our patients with NMIBC recurrences using TURBT with/without intravesical instillation. Thus, we were able to successfully preserve the bladder in 8 of the 14 patients with NMIBC recurrence. In fact, our data of the histological grade in initial and recurrent tumors suggested that the recurrent tumor was less aggressive than the initial MIBCs. This finding was also supported by the results of the Ki-67-labeling index, although the sample number is limited because the initial TURBTs were often performed in other hospitals. Taking into consideration that the background of the patients in this study suggested a very high risk of recurrence, these findings might be due to the effect of chemoradiation and/or the potential heterogeneity of the initial MIBCs. On the other hand, it is also important to note that we observed two cases of progression after several times of intravesical recurrences during follow-up. As for risk factors regarding NMIBC recurrences, statistical analysis indicated that the large-sized tumor (more than 5 cm), multifocality and Grade 3 were significantly related with NMIBC recurrences. These data indicating careful and lifelong follow-up remain mandatory and also it may be important to control for NMIBC recurrences using TURBT and the intravesical instillation of BCG for high-risk patients with NMIBC recurrence.

In conclusion, intra-arterial chemotherapy with higher dose of irradiation achieved a high tumor control rate of MIBC, but was less effective in preventing NMIBC recurrence. As recurrent NMIBC exhibited less malignant potential than the initial MIBC, a large population of such patients could be still bladder preserved using TURBT with intravesical instillation. Close collaboration between urologists and radiation oncologists is important to achieve high-quality bladder-preserving therapy.

**Conflict of interest statement**

None declared.

**References**


