

## Single Institutional Experience of Bladder-Preserving Trimodality Treatment for Muscle-Invasive Bladder Cancer

The authors designed this study to determine the clinical effectiveness of trimodality treatment, i.e., transurethral resection of a bladder tumor (TURBT) and concurrent chemoradiotherapy (CRT). Twenty patients with a muscle-invasive bladder cancer were treated by TURBT followed by concurrent cisplatin (75 mg/m<sup>2</sup> day), administered on weeks 1 and 4 of radiotherapy. According to residual tumor status after TURBT, patients were classified into patients with a complete TURBT group and incomplete TURBT group. Response to treatment was evaluated by restaging TURBT at 4 weeks after completing CRT (post-CRT). Fifteen patients (75%) achieved complete remission (CR) at restaging; 10 patients (50%) remained continuously free of tumor recurrence. Disease-specific and overall survivals were 51.1% and 38.6% at 5 yr post-CRT, respectively. Of 16 patients in the complete TURBT group, 14 patients (87.5%) achieved CR, which was significantly different from that observed in the incomplete TURBT group, in which only 1 (25%) of 4 patients achieved CR ( $p=0.032$ ). Five-year disease-specific and overall survivals were 71.6% and 53.5%, respectively. Ten patients (90.9%) maintained their own bladder among the 11 surviving patients. Trimodality treatment was found to be an effective treatment in patients who underwent complete TURBT for a muscle-invasive bladder cancer.

**Key Words :** Urinary Bladder Neoplasms; Cisplatin; Combined Modality Treatment

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Received : 4 September 2007  
Accepted : 10 December 2007

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\*This study was supported by a National Cancer  
Center Grant, No. 0510200.

### INTRODUCTION

Radical cystectomy is considered the standard treatment for muscle-invasive bladder cancer, and over recent years surgical techniques have improved and urinary diversion has been introduced, which have undoubtedly improved quality of life. However, even the construction of a neobladder with continent urinary diversion cannot substitute for the original bladder. Resultantly, trimodality treatment, including transurethral resection of bladder tumor (TURBT) and chemoradiotherapy (CRT) has been suggested as a bladder-preserving therapy in invasive bladder cancer over the past two decades (1-4). To my knowledge, no study has been reported on a prospectively designed trimodality protocol for muscle-invasive bladder cancer in Korean patients. To determine the clinical effectiveness of this trimodality treatment, we designed the present study of concurrent CRT incorporating cisplatin following TURBT for the treatment of muscle-invasive bladder cancer.

### MATERIALS AND METHODS

#### Patient selection

Patient with cT2-3 bladder cancer and an eastern cooper-

ative oncology group (ECOG) of <2 were enrolled in this study. Initial evaluations included chest radiography, computed tomography (CT) scan of abdomen and pelvis, complete blood count (CBC) and serum chemistry, and creatinine clearance. A white blood cell (WBC) of >4,000/ $\mu$ L, a platelet count of >100,000/ $\mu$ L, bilirubin <1.5 mL/dL, and a creatinine clearance of >60 mL/min were mandatory. Patients were excluded if there was evidence of distant metastases, or prior pelvic irradiation, or if cisplatin chemotherapy was contraindicated.

A trimodality treatment was recommended as an alternative treatment to radical cystectomy only to patients who underwent complete TURBT. On the other hand, radical cystectomy was strongly recommended as a standard treatment to patients if complete TURBT was deemed impossible. When patients refused to undergo an operation designed to remove the native bladder, they were considered for the present study. After giving written informed consent, patients were enrolled for the concurrent CRT protocol, which was initiated 3-4 weeks after TURBT.

#### Treatment protocol

##### TURBT

TURBT was performed layer by layer, which produced three

separate specimen groups according to depth, i.e., the superficial layer from mucosa and submucosa, deep layer from superficial muscle, and a bottom layer from deep muscle. Completeness of TURBT was assessed according to residual tumor status. Tumor infiltration in the deep layer with no tumor infiltration in the bottom layer was defined as microscopic no residual tumor. Scant tumor infiltration (up to 2 foci per high power field,  $\times 400$ ) in the bottom layer and prominent tumor infiltration in the deep layer was defined as microscopic residual tumor, and gross residual tumor on the resection surface or prominent tumor infiltration even in the bottom layer was defined as macroscopic residual tumor. Therefore, complete TURBT was defined as microscopic no residual tumor or microscopic residual tumor, whereas incomplete TURBT was defined as macroscopic residual tumor.

#### Concurrent chemoradiotherapy

Radiotherapy was initiated 3–4 weeks after TURBT using 6- to 10-MV photons and a four-field box technique with individually shaped portals and daily fractions of 1.8 Gy on 5 consecutive days. Planned target volumes (PTV) consisted of the bladder and tumor with a 2-cm contoured margin. PTV were sometimes modified after administering a dose of 40 or 45 Gy and a cone down boost was given to exclude the uninvolved part of the bladder, provided the tumor was unifocal and well lateralized. The total dose given during the induction period was 45 Gy in 1.8 Gy daily fractions over 5 weeks and 20 Gy in 1.8 Gy daily fractions over 2 weeks during the consolidation period. Therefore, total doses administered to whole bladder and pelvic lymph node ranged from 45 and 65 Gy. As concurrent chemotherapy, cisplatin 75 mg/m<sup>2</sup> was administered by slow intravenous infusion in conjunction with adequate hydration on weeks 1 and 4 of radiotherapy.

#### Response evaluation and salvage treatment

Four weeks after completing CRT (post-CRT), initial response was evaluated by restaging TURBT of the former tumor region, and by urine cytology and CT. Complete remission was diagnosed when no evidence of residual tumor was found on restaging TURBT, no cancer cells were found by urine cytology, and there was no evidence of tumor recurrence by CT. Patients were regarded as having local failure if they had superficial recurrence or persistent invasive cancer by restaging TURBT at 4 weeks post-CRT, and were regarded as having distant failure if they had developed metastasis by CT. In case of persistent invasive cancer at initial evaluation after CRT, salvage cystectomy was preferentially recommended.

#### Follow-up schedules

In case of complete response at 4 weeks post-CRT, patients were followed up at 3-months intervals by CT, urine cytology, and by cystoscopic biopsy (the latter was performed when cystoscopic findings were suspicious). Follow-up was performed on a 3 monthly basis for the first 3 yr, 6 monthly for the next

3 yr, and then annually. In addition, acute hematologic and non-hematologic toxicities were assessed weekly during CRT according to the National Cancer Institute Common Toxicity Criteria, version 2.0, and late complications were noted during follow-up.

#### End points and statistical analysis

The major statistical endpoints of this study were; the CR rate at 4 weeks post-CRT, disease-specific survival (DSS) at 5 yr, and overall survival (OS) at 5 yr. Actuarial survival rates were calculated from the end of CRT to the time of the last follow-up visit or death, using the Kaplan-Meier method. The Mann-Whitney U test was used to analyze continuous variable and the chi-square or Fisher's exact tests were used to analyze categorical variables. Statistical significance was accepted at the  $p < 0.05$  (two-sided) level. Statistical analysis was performed entirely using the Statistical Package for the Social Sciences for Windows, version 11 (SPSS Inc, Chicago, IL, U.S.A.).

## RESULTS

#### Patient characteristics

From March 2000 to January 2006, 22 patients with muscle-invasive cT2-3 bladder cancer were enrolled in this prospective study. Of these, 20 patients completed the CRT protocol and two patients were excluded because they refused to continue with the study protocol during radiotherapy induction in the absence of complications. CRT was actively recommended as an alternative treatment to radical cystectomy in 16 pa-

Table 1. Patient characteristics (n=20)

Variables	No. of patients (%)
Male vs. female	11 (55) vs. 9 (45)
Primary tumor	10 (50)
Recurrent tumor	10 (50)
Tumor size	
<5 cm	8 (40)
$\geq 5$ cm	12 (60)
Multiplicity	
Single	10 (50)
Multiple	10 (50)
Clinical stage	
T2N0M0	12 (60)
T3N0M0	8 (40)
Grade (WHO grade)	
1-2	4 (20)
3	16 (80)
Associated CIS	1 (5)
Residual tumor status	
No microscopic residual tumor	3 (15)
Microscopic residual tumor	13 (65)
Macroscopic residual tumor	4 (20)

WHO, World Health Organization; CIS, carcinoma in situ.

tients with complete TURBT. On the other hand, radical cystectomy was preferentially recommended in 4 patients with incomplete TURBT. However, these 4 patients strongly want to preserve the native bladder and voluntarily enrolled in this study. The characteristics of the 20 patients are outlined in Table 1.

**Initial response and salvage treatment**

In terms of initial response at 4 weeks post-CRT, 15 patients (75%) achieved CR and 5 patients (25%) had a persistent invasive cancer at 4 weeks post-TURBT. In terms of response to CRT according to the completeness of TURBT, 14 (87.5%) of 16 patients with complete TURBT achieved CR whereas only 1 (25%) of 4 patients with incomplete TURBT achieved CR, which was significant ( $p=0.032$ ). Radical cystectomy was preferentially recommended as a salvage treatment to 5 patients who failed to achieve CR as an initial response to CRT. However, only one patient accepted our suggestion; the other 4 chose CMV (cisplatin, methotrexate, and vinblastine) chemotherapy rather than an operation.

**Tumor recurrence after complete remission**

Of 15 patients with CR at initial response, tumor recurrence (both local and distant) occurred in 7 patients. Two patients showed invasive tumor recurrence at the preserved bladder 6 months and 52 months post-CRT. The patient with later recurrence developed a recurrent superficial cancer before an

invasive cancer. For salvage treatment of invasive cancer, both patients requested chemotherapy rather than salvage cystectomy, and they remained in a locally controlled state with no evidence of distant metastasis by cystoscopy or CT scan at 6 months after chemotherapy using MVAC regimen. On the other hand, isolated superficial recurrences were found in another 2 patients. Of these, one patient experienced superficial recurrences on three occasions, which were managed by TUR and intravesical chemotherapy. The other patient showed experienced a single recurrence at 48 months post-CRT. In another 3 patients, isolated distant metastases to brain, lung and liver developed at 6, 10 and 24 months post-CRT, and underwent MVAC (methotrexate, vinblastine, adriamycin, and cisplatin) for the treatment of distant metastasis. Subsequently, they died of progression to bladder cancer. Treatment outcomes are summarized in Fig. 1.

**Survival and bladder preservation**

After 33 months (range, 8-62 months) of median follow-up period for all study subjects, 9 deaths had occurred. All 4 patients with incomplete TURBT died of bladder cancer progression at a median 12 months (range, 8-43 months) post-CRT. On the other hand, of the 16 patients with complete TURBT, 3 patients died of bladder cancer progression and 2 of other causes (lung cancer and a heart attack). DSS and OS rates for all 20 patients were 51.1% and 38.6% at 5 yr, respectively, and those of the 16 patients with complete TURBT were 71.6% and 53.5%, respectively. DSS and OS

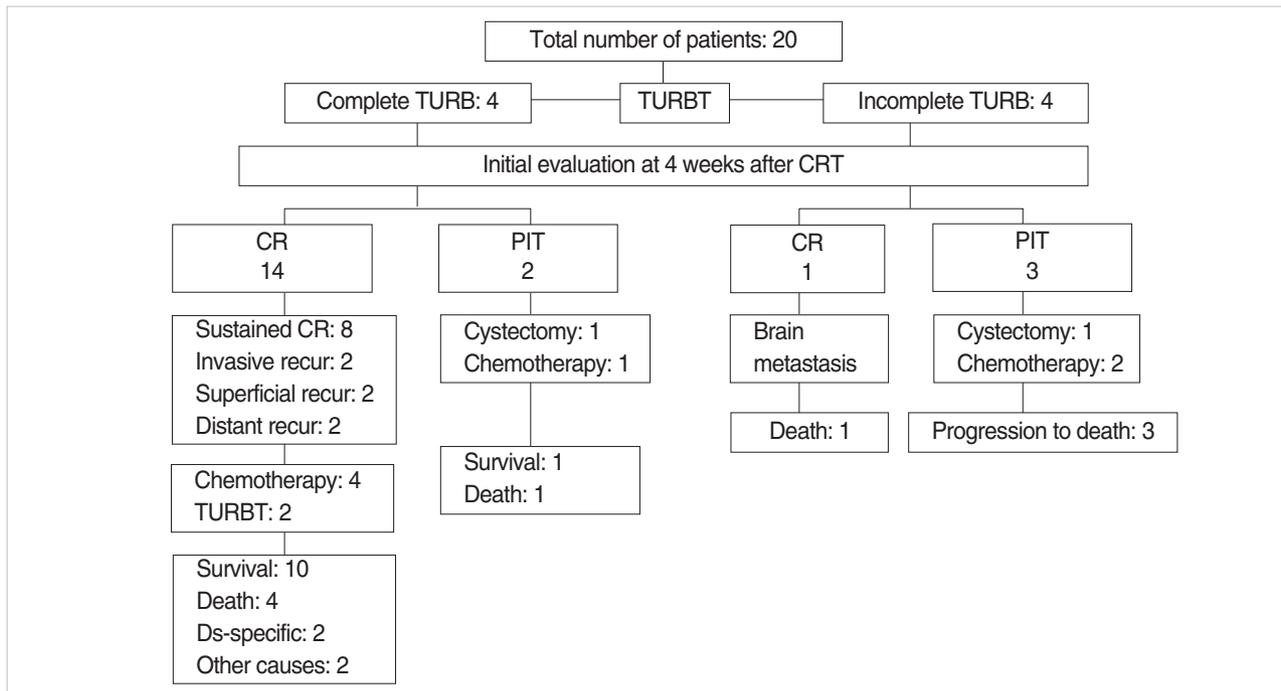


Fig. 1. Treatment outcomes. TURBT, transurethral resection of bladder tumor; CR, complete remission, PIT, persistent invasive tumor; recur, recurrence; Ds, disease.

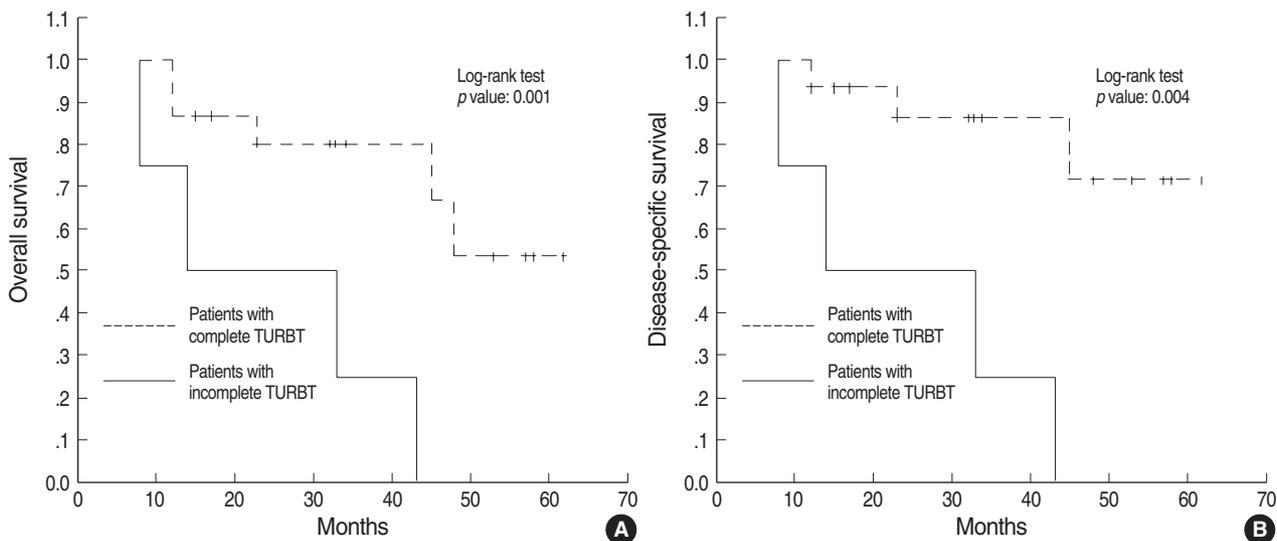


Fig. 2. Kaplan-Meier estimates of likelihood of overall survival (A) and disease-specific survival (B) for patients with complete TURBT vs. incomplete TURBT.

Table 2. Treatment-related acute toxicity according to the National Cancer Institute Common Toxicity Criteria

Variables	No. of patients (%)
Hematologic	
Neutropenia	1 (5)
Leukopenia	5 (25)
Thrombocytopenia	2 (10)
Anemia	2 (10)
Non-hematologic	
Diarrhea	7 (35)
Irritative voiding symptoms	11 (55)
Nausea and vomiting	2 (10)

rates showed significant differences according to the completeness of TURBT (DSS,  $p=0.004$ ; OS,  $p=0.001$ ) (Fig. 2). Of the 11 surviving patients, 10 patients (90.9%) retained their own bladders at the time of analysis.

#### Treatment-related toxicities

Toxicities are briefly presented in Table 2. In terms of hematologic toxicities, neutropenia, leukopenia, thrombocytopenia, and anemia were reported in 1 (5%), 5 (25%), 2 (10%), and 2 (10%) patients, respectively. Only one patient (5%) required a dose reduction due to neutropenia, and recovered within 2 weeks. In terms of non-hematologic toxicities, diarrhea was most frequently reported and occurred in 7 (35%) patients. No case of grade 3-4 non-hematologic toxicity was encountered. All patients who experienced a non-hematologic toxicity recovered with conservative treatment. In terms of bladder function, mild dysuria, urgency, and nocturia were registered in 20-55% of patients, but these were temporary and improved 3 months post-CRT. No remarkable late complication occurred, though one patient complained of noctur-

nal frequency due to a decreased functional bladder capacity.

## DISCUSSION

Traditionally, transitional cell carcinoma (TCC) is known to be sensitive to cisplatin-based chemotherapy (5). In addition, radiation therapy has been administered to patients who appear to be unsuitable for radical cystectomy (6). However, in the case of muscle-invasive bladder cancer, adequate cancer control cannot be achieved by TURBT, chemotherapy, or radiotherapy alone. Over the last two decades, some centers in the United States and Europe adopted a trimodality treatment (1-4).

The rationale for combining radiotherapy with chemotherapy after TURBT is twofold. First, certain cytotoxic agents may have the ability to sensitize cancer cells to radiation and to inhibit repopulation during radiotherapy. Second, high rates of occult metastases require that efforts to eradicate occult metastases that have already developed in as many as 50% of muscle-invasive cancer (7).

There are two main concerns about CRT. The selection of optimal regimens and ideal candidates are main issues following bladder-preserving therapy, but optimal regimens have not been established. In general, cisplatin and 5-FU (fluorouracil) are still recommended by many investigators, because both agents have been shown to have radiosensitizing activities and acceptable toxicities (8). In addition, to these two drugs, newer chemotherapeutic agents, particularly gemcitabine and taxanes, have also been shown to be potent radiation sensitizers (9). Furthermore, recent studies have established that gemcitabine in combination with radiotherapy as a feasible regimen for bladder sparing treatments, and other series have shown that concurrent CRT using platinum and paclitaxel or doc-

etaxel was also an effective regimen (10, 11). Recently, the relation between radiosensitization and the inhibition of oncogene products, such as, H-ras and c-erbB-1, has been the focus of attention (12, 13).

The selection of ideal candidates for CRT is another important issue for successful bladder-preserving treatment. Some studies have been undertaken to identify clinical factors that help distinguish candidates for trimodality treatment. Rodell *et al.* concluded that the completeness of TURBT is one of the most potent factors of survival after CRT for patients with invasive bladder cancer (14). In our patients with complete TURBT, the rate of CR was 87.5% and the 5-yr disease-specific and overall survivals were 71.6% and 53.5%, respectively. Our patients with complete TURBT were found to be more likely to respond to CRT and to have a higher survival rate than the 4 patients with incomplete TURBT. These findings are comparable with those of other studies on CRT, which achieved overall survivals of 45-60% (7, 14-16). Other clinical factors that have been considered when choosing patients for bladder preserving surgery include; small tumor size (<5 cm), early tumor stage, absence of ureteral obstruction, and no evidence of pelvic lymph node metastases (7). In addition to clinical factors, several promising molecular markers, such as p53, bcl-2, bax, and pRB may help predict response to specific cytotoxic therapies (17-19).

In terms of the timing of evaluating initial response to CRT, there are two strategies, *i.e.*, early and delayed evaluation. In our study, delayed evaluation was performed at 4 weeks post-CRT. In a study by Erlangen and several others, responses were evaluated 4 to 6 weeks post-CRT by restaging TURBT (1-3). Conversely, according to the Massachusetts General Hospital (MGH) and Radiation Therapeutic Oncology Group (RTOG) protocols, response evaluation should be performed much earlier, *i.e.*, after approximately 40 Gy of induction radiation therapy (20-22). In the literature, salvage cystectomy plays an important role in patients with a persistent tumor after CRT. In this study, we also preferentially recommended cystectomy, but the majority of patients with a persistent tumor at initial evaluation after CRT refused a salvage operation. Thus, we performed cystectomy as a salvage treatment in only 1 of the 5 patients with a persistent tumor at initial evaluation after CRT. In the Erlangen series, which used a late-response evaluation at 4 to 6 weeks post-CRT (1-3), the disease-specific survival rate at 5 yr for patients treated by salvage cystectomy for invasive relapse was 51%. Similarly, in the Boston series, the 5-yr disease-specific survival rate for patients that ultimately underwent salvage cystectomy, but after early-response evaluation, was approximately 50% (23). Thus, available findings reveal no difference in survival after salvage cystectomy according to the time of initial evaluation after CRT.

In our subjects, 4 of 15 patients that achieved CR at initial evaluations after CRT developed a recurrent tumor at the preserved bladder. Of these 4 patients, 2 had a superficial cancer

and 2 had an invasive cancer. Two patients with superficial recurrence were easily managed by TURBT and survived with bladder preservation at the time of analysis. Of two patients with superficial recurrence, one patient showed experienced a single recurrence at 48 months post-CRT. Moreover, 3 of 15 patients that achieved CR at initial evaluations after CRT developed isolated distant metastasis. Thus, close follow-up of patients after organ-preserving treatment is mandatory in patients who achieve CR at initial evaluations after CRT for a long time. Generally, 30% of patients who achieved initial CR after CRT developed a recurrent tumor in the preserved bladder, and about a half of these recurrent cancer were superficial (7).

We found that the common acute side effects by CRT are transient diarrhea and voiding symptoms (frequency and urgency), which were common but easily managed with supportive treatment. Moreover, these symptoms usually resolved within 2 or 3 weeks of completing treatment. In this study, 55% and 35% of patients experienced voiding symptoms and diarrhea, respectively. At the time of analysis, no patient required cystectomy for bladder contraction by radiation, but in the largest series conducted to date by Erlangen, 2% of patients required cystectomy for bladder shrinkage, 10% reported some degree of incontinence or increased micturition frequency, and 1.5% of patients experienced a late gastrointestinal toxicity (bowel obstruction) requiring surgical intervention (14).

The present study is limited by the small number of patients recruited, which is why we could not analyze results with respect to clinical factors, especially the completeness of TURBT. A study with a greater number of patients is required to identify factors that distinguish candidates for bladder-preserving treatment. In our study, we could not perform salvage cystectomy on patients with a persistent tumor after CRT, and number of patients with incomplete TURBT was too small to reach the conclusion of survival differences with respect to the completeness of TURBT. However, considering that salvage cystectomy was performed in only 2 patients, 5-yr disease-specific and overall survivals for the 16 patients with complete TURBT were better than those reported by large studies in the US and Europe (1-4). Furthermore, the 5-yr overall survival rate was comparable to the results of radical cystectomy from large surgical series, which showed 48% from the University of Southern California and 45% from Memorial Sloan-Kettering Cancer Center (24).

The trimodality treatment was found to be an effective treatment option for patients with a muscle-invasive bladder cancer who underwent complete TURBT. Close follow-up of patients after CRT is mandatory even in those patients who achieved CR at initial response evaluations.

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