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*ORIGINAL ARTICLE*

# Elective bladder preservation with multimodality treatment for bladder cancer

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## Summary

***Purpose:*** *To observe the outcome of maximal transurethral resection of bladder tumor (TURBT) followed by induction chemotherapy and concurrent chemoradiotherapy in medically inoperable patients with bladder cancer.*

***Methods:*** *This study included 30 patients with stage T 2-4 bladder cancer. The patients were first treated with TURBT, and then received 2 cycles of induction chemotherapy with gemcitabine and cisplatin, followed by concurrent chemoradiotherapy with gemcitabine.*

***Results:*** *Median follow up was 28.9 months. Radiologically, complete and partial response rates were 60 and 36.7%, while cystoscopically they were 40 and 30%, respectively. Local progression (4 cases) and distant metastasis (11 cases) were noted. Median overall survival and progression-free survival were 32 and 21 months, respectively. One -and 2-year overall survival and progression-free survival rates were 97.60% and 83.49%, respectively.*

***Conclusion:*** *The multimodal treatment performed in this study was well tolerated and achieved a high rate of bladder preservation in selected patients with bladder cancer.*

**Key words:** bladder cancer, concurrent chemoradiotherapy, gemcitabine, induction chemotherapy

## Introduction

Regardless of clinical stage, radical cystectomy remains the standard approach for the majority of patients with muscle-invasive transitional cell carcinoma of the bladder, which requires creation of any type of urinary diversion [1]. The rates of perioperative mortality and early complications range between 3 and 28%, respectively [2]. Late morbidity, including impaired sexual function, is usually due to the type of the urinary diversion [3]. Furthermore, this therapy achieves a 5-year overall survival of only about 50%. In addition, quality of life issues have created a trend toward the development of bladder preservation methods [2].

Bladder-preserving approaches are reasonable alternatives to cystectomy for selected patients who are medically unfit for surgery and those seeking an alternative treatment, with survival rates similar to those achieved with radical cystectomy, but with a clear quality of life advantage [4,5]. With these approaches, cystectomy has been reserved for patients with inadequate response to treatment or local relapse [6]. Options include aggressive endoscopic TURBT alone, transurethral resection followed by chemotherapy alone, radiotherapy (RT) alone, or a combination of chemotherapy and radiotherapy [4].

Although some reports show favorable results with radical TURBT as monotherapy in selected patients [7], guidelines on muscle-invasive bladder cancer do not recommend TURBT, RT or chemotherapy alone as potential bladder-sparing approaches in most patients [2,4]. Recent organ-preservation strategies consist of combined TURBT, chemotherapy and RT [2]. However, the optimal chemotherapy regimen and combination with RT remains to be established [6,8]. Newer chemotherapy regimens and advances in conformal RT techniques may improve the protocol compliance to multimodality treatment protocols and result to an improvement in bladder preservation. If needed, salvage cystectomy and urinary diversion is performed later [9].

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Gemcitabine, a nucleotide analog, is a newer chemotherapeutic agent, now being tested in combination with RT, and may further improve organ preservation in bladder cancer [1,10]. This drug has shown significant single-agent activity against urothelial tumors and is a potent radiation sensitizer [1,2,4,10].

The aim of this non-controlled, prospective study was to observe the initial outcomes of maximal TURBT followed by induction chemotherapy, consisting of cisplatin and gemcitabine and followed by concurrent chemoradiotherapy with gemcitabine in a selected group of patients with bladder cancer.

## Methods

This study included 30 patients medically inoperable because of comorbid diseases or who refused surgical therapy. Patient accrual started in September 2006 and ended in January 2008.

*Inclusion/exclusion criteria*

Inclusion criteria included age > 18 years, ECOG performance status of 0-2, histological diagnosis of transitional cell carcinoma of the bladder and eligibility for transurethral resection. Patients were ineligible if they had evidence of distant metastases, WBC count < 4,000/$mm^3$, platelet count < 100,000/$mm^3$ and creatinine clearance < 50 mL/min.

Pretreatment evaluation included history and physical examination, chest radiography, complete blood cell count, blood urea nitrogen, creatinine clearance, liver function tests and abdominal computed tomography (CT). All patients underwent cystoscopic examination

*Treatment*

After maximal TURBT, 2 cycles of induction chemotherapy followed by chemoradiotherapy was planned to be given to the patients included in the study.

*Chemotherapy*

Two cycles 3 weeks apart of the combination of gemcitabine and cisplatin were administered. Gemcitabine was administered at 1250 mg/$m^2$/day on days 1, 8, 22 and 29 and, cisplatin was given at 75 mg/$m^2$/day on days 1 and 22 with appropriate hydration, together with gemcitabine.

During chemotherapy, all patients were evaluated with complete blood count, hepatic and renal function tests, as well physical examination before each chemotherapy cycle. Side effects related to chemotherapy and chemoradiotherapy were graded according to the National Cancer Institute - Common Toxicity Criteria (NCI-CTC).

In the presence of hematologic (anemia, neutropenia and thrombocytopenia), neurologic or renal toxicity due to chemotherapy, cisplatin dose was decreased by 10-20%. Manipulations such as stoppage of chemotherapy for a while were necessary in some cases.

*Concurrent chemoradiotherapy*

Chemoradiotherapy was initiated after 2 cycles of gemcitabine plus cisplatin chemotherapy. Gemcitabine was administered at a flat dose of 200 mg/weekly on days 1, 8, 15, 22, 29 and 36, beginning from the first day of RT.

Conventional RT was delivered using linear accelerator (GE Saturn) in 26 patients, while Siemens Oncor system with 3D-CRT was used in 6 patients. RT was given as conventional therapy, 2 Gy per fraction with 6-15 mV photon, 5 days a week, for a total of 66 Gy in 33 fractions.

The planned target volume (PTV) was designed to cover the pelvic lymph nodes with 2 cm safety margin according to radiologic imaging data obtained after chemotherapy. After 46 Gy to PTV, a 20 Gy boost was delivered to achieve a total RT dose of 66 Gy. In patients who received conventional RT, the first 23 fractions were given by the box technique (anterior and 2 opposed lateral fields). For boost treatment the small box technique, the 3 areas (anterior and 2 opposed lateral fields) or oblique areas were used. Dose calculation and treatment planning were done by the "Target II treatment planning system" in 24 patients and by the "CMS Xio-Planning system" in 6 patients.

*Treatment evaluation*

The clinical course and tumor response to treatment were evaluated with imaging studies (CT, MRI) or cystoscopy after completion of chemoradiotherapy. Urinalyses were done monthly in the first 6 months, 3-monthly during the next 2 years and every 6 months thereafter. Cystoscopy was performed every 6 months. Responses to therapy were defined as complete response, partial response, stable disease and progressive disease according to WHO criteria.

*Statistical analyses*

Survival analyses were done using the Kaplan-Meier method. Cox proportional hazard model was used to evaluate the variables connected with overall survival. Comparison of the different clinicopathologic parameters were done using chi-square test.

## Results

The median patient age was 71 years (range 55-80). Of the patients included in this study, 96.7% were > 60 years. There were 26 (86.7%) male and 4 (13.3%) female patients. Twenty-four (80%) patients had T2 tumors, one (3.3%) T3 tumor and 5 (16.7%) T4 tumors. All patients had transitional epithelial cell carcinoma. ECOG performance status [11] was 1 in 29 (96.7%) patients and 2 in 1 (3.3%). Positive smoking history gave 80% of the patients. The most frequently reported symptoms were dysuria (15 patients; 50%), hematuria (15 patients; 50%) and difficulty in urination (8 patients; 26.7%). The patient characteristics are shown in Table 1.

*Response*

Complete and partial radiologic responses were noted in 60% and 40% of the patients, respectively. Cystoscopy could not be performed in 9 (30%) patients due to social problems. Of the patients who underwent cys-

**Table 1.** Patient characteristics

| *Characteristics* | *Patients, N* | *%* |
|---|---|---|
| Sex | | |
| Male | 26 | 86.7 |
| Female | 4 | 13.3 |
| Age (years) | | |
| ≤60 | 1 | 3.3 |
| >60 | 29 | 96.7 |
| pT stage | | |
| T2 | 24 | 80 |
| T3 | 1 | 3.3 |
| T4 | 5 | 16.7 |
| ECOG performance status | | |
| 0-1 | 29 | 96.7 |
| 2 | 1 | 3.3 |
| Smoking | | |
| Yes | 24 | 80 |
| No | 6 | 20 |
| Complaints on admission | | |
| Difficulty in urination | 8 | 26.7 |
| Dysuria (any grade) | 15 | 50 |
| Hematuria (any grade) | 15 | 50 |

toscopy, complete response was noted in 12 (40%) and partial response in 9 (30%) (Table 2).

Median overall survival was 32 months (95% CI 16-48). One-and 2-year overall survival was as 97 and 60%, respectively.

The median progression free survival was 21 months (95% CI 5-37) and the 1- and 2-year progression free survival was 83 and 49%, respectively. Overall survival and progression free survival are shown in Figures 1 and 2.

Four (13.3%) patients had local disease progression and 11 (36.7%) developed distant metastasis. The most common metastatic sites were bones (5 patients), liver (3 patients), brain (3 patients), and lung, adrenal gland and peritoneum in one patient each. Local relapse free survival in the first and second year from treatment termination was 100 and 61.1%, respectively (Table 3).

**Table 2.** Response to therapy

| *Response* | *Patients, N (%)* |
|---|---|
| Radiologic | |
| Partial response | 12 (40) |
| Complete response | 18 (60) |
| Total | 30 (100) |
| Cystoscopic | |
| Partial response | 9 (30) |
| Complete response | 12 (40) |
| Unknown | 9 (30) |
| Total | 30 (100) |

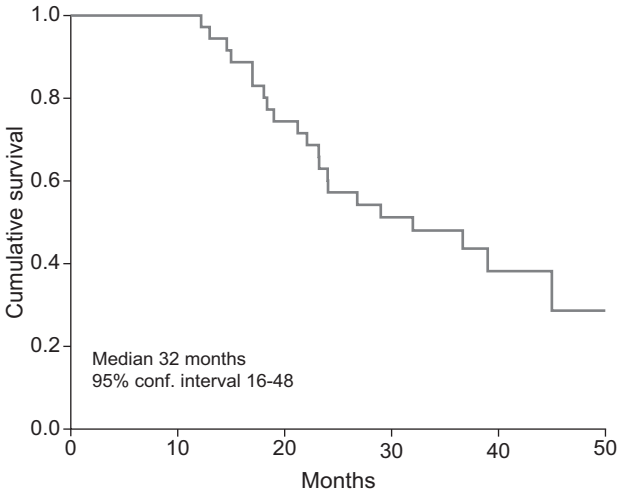


**Figure 1.** Overall survival.

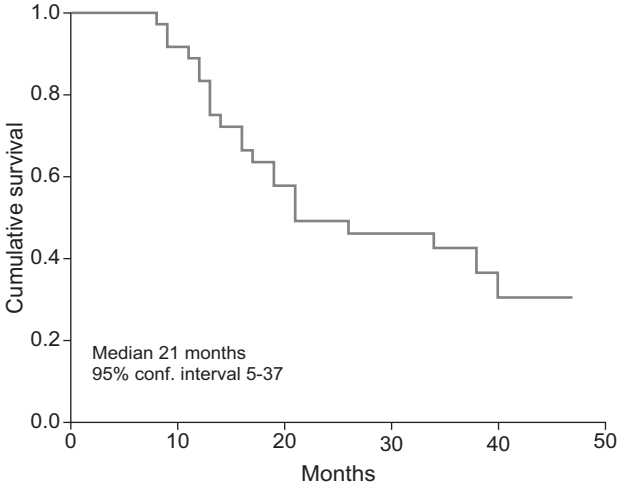


**Figure 2.** Progression-free survival.

During a median follow-up of 28.9 months (range 12-50), one patient underwent cystectomy due to the development of contractile bladder. The remaining patients lived with normal bladder.

**Table 3.** Distribution of metastatic locations and rates of local control

| *Metastatic locations* | *Patients, N (%)* |
|---|---|
| Distant metastasis | 11 (36.7) |
| Bone | 5 (16.6) |
| Liver | 3 (10) |
| Brain | 3 (10) |
| Lung | 3 (10) |
| Adrenal gland | 1 (3.3) |
| Peritoneum | 1 (3.3) |
| Local failure | 4 (13.3) |
| Local control (%) | |
| First year | 100 |
| Second year | 61.1 |

**Table 4.** Univariate analysis for overall survival

| *Characteristics* | *Patients, N* | *%* | *Median survival time (mo)* | *p-value* |
|---|---|---|---|---|
| Sex | | | | 0.199 |
| Male | 26 | 86.7 | 29 | |
| Female | 4 | 13.3 | NR | |
| Age (years) | | | | 0.117 |
| ≤60 | 1 | 3.3 | 18 | |
| >60 | 29 | 96.7 | 37 | |
| pT stage | | | | 0.591 |
| T2 | 24 | 80.0 | 32 | |
| T3 | 1 | 3.3 | 21 | |
| T4 | 5 | 16.7 | NR | |
| ECOG performance status | | | | 0.158 |
| 0-1 | 29 | 96.7 | 32 | |
| 2 | 1 | 3.3 | 22 | |
| Smoking history | | | | 0.299 |
| Yes | 24 | 80.0 | 29 | |
| No | 6 | 20.0 | NR | |
| Histological grade | | | | 0.823 |
| 1-2 | 12 | 40.0 | 37 | |
| 3 | 18 | 60.0 | 29 | |

NR: not reached, mo: months

In univariate analysis (Table 4) no statistical significance was noted between survival and smoking, grade, T stage, age and performance status. No independent prognostic factor was identified in multivariate analysis (Table 5).

*Toxicity*

Induction chemotherapy was administered to all patients. The RT component of chemoradiotherapy (which lasted for 6 weeks) was completed in all but one patient who stopped at 56 Gy due to grade 3 rectitis. Chemotherapy was given only for 3 weeks in one patient who suffered from severe diarrhea. Chemotherapy doses were not decreased in the other patients.

Hematologic and non hematologic toxicities were tolerable. Anemia (all grades) was noted in 4 (13.3%) patients and grade 1-4 leukopenia was recorded in 6 (20%). None of the patients developed febrile neutropenia. Non hematologic toxicities were nausea and vomiting in 8 (26.7%) patients, dermatologic reactions in 5 (16.7%), grade 1-2 uremia in 2 (6.6%), dysuria in 14 (46.7%), grade 1-2 diarrhea in 12 (40%) and rectitis in 4 (13%) patients. No ototoxicity or allergic reactions were recorded. RT had not to be stopped for a while due to side effects. The adverse effects in our series are detailed in Table 6.

## Discussion

External RT is the most commonly used method as bladder-preserving treatment in the last 30 years [12]. RT has been usually suggested for inoperable patients due to age, comorbidities and metastasis. Several authors have reported that 5-year overall survival rate and local control rate with RT alone in operable patients were 20-40% and 50% respectively, lower than those with radical surgery. RT has not been usually offered as single treatment in bladder cancer patients [2,4,12].

As a treatment model, preoperative RT has been first evaluated in the early 1980s. Lately, a randomized prospective study designed by the Southwest Oncology Group (SWOG) demonstrated that there is no survival advantage with preoperative RT [13,14]. It has also been shown that intestine damaged by RT could not be used for urinary reservoir, thus preoperative RT is not an attractive method [2,4,9].

**Table 5.** Multivariate analysis for overall survival

| | *B* | *SE* | *Wald* | *df* | *Sig.* | *Exp(B)* | *95.0% CI for Exp(B)* | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | *Lower* | *Upper* |
| Gender | 1.227 | 1.190 | 1.063 | 1 | 0.303 | 3.412 | 0.331 | 35.164 |
| Age | 2.594 | 1.109 | 5.473 | 1 | 0.119 | 13.388 | 1.523 | 117.679 |
| Smoking history | 0.119 | 0.951 | 0.016 | 1 | 0.900 | 1.126 | 0.175 | 7.258 |
| T stage | | | 4.030 | 3 | 0.258 | | | |
| T1 | –2.745 | 2.002 | 1.881 | 1 | 0.170 | 0.064 | 0.001 | 3.248 |
| T2 | 0.084 | 1.043 | 0.007 | 1 | 0.936 | 1.088 | 0.141 | 8.408 |
| T3 | 1.524 | 1.499 | 1.034 | 1 | 0.309 | 4.591 | 0.243 | 86.720 |
| Histological grade | | | 0.126 | 2 | 0.939 | | | |
| grade 1 | –12.402 | 597.201 | 0.000 | 1 | 0.983 | 0.000 | 0.000 | |
| grade 2 | –0.197 | 0.557 | 0.125 | 1 | 0.723 | 0.821 | 0.276 | 2.445 |
| Performance status | | | 0.764 | 2 | 0.683 | | | |
| ECOG 1 | –1.166 | 1.592 | 0.537 | 1 | 0.464 | 0.312 | 0.014 | 7.053 |
| ECOG 2 | –1.327 | 1.560 | 0.724 | 1 | 0.395 | 0.265 | 0.012 | 5.643 |

**Table 6.** Toxicities

| *Toxicity grades* | *Patients, N* | *(%)* |
|---|---|---|
| Anemia | | |
| 1-4 | 4 | 13.3 |
| Leukopenia | 6 | 20 |
| 1-2 | 3 | 10 |
| 3-4 | 3 | 10 |
| Non-hematologic | | |
| Nausea | 8 | 26.7 |
| 1 | 6 | 20 |
| 2 | 2 | 6.7 |
| Diarrhea (1-2) | 12 | 40 |
| Dermatologic reactions | 5 | 16.7 |
| 1 | 5 | 16.7 |
| 2 | 0 | 0 |
| Dysuria | 14 | 46.7 |
| 1-2 | 11 | 36.7 |
| 3-4 | 3 | 10 |
| Rectitis | 4 | 13 |
| 1-2 | 4 | 13 |
| 3-4 | 0 | 0 |
| Uremia (1-2) | 2 | 6.6 |
| Ototoxicity | – | – |
| Allergic reactions | – | – |

In the last decade, several trials using neoadjuvant chemotherapy followed by radical cystectomy gave improved results concerning survival [15,16]. A SWOG trial has shown that 3 cycles of neoadjuvant MVAC chemotherapy before radical cystectomy achieved a survival advantage compared with radical cystectomy alone [17].

A recently published meta-analysis included 11 randomized studies and showed that neoadjuvant chemotherapy decreased the relative mortality risk by 9% in 2492 patients [18]. Subgroups analyses dealing with patients treated with cisplatin-based regimens showed increase of this rate to 13% and also increased absolute 5-year survival by 5%.

It has been shown that RT has a synergistic effect when combined with chemotherapy, thus, it should be considered in the bladder-preserving treatment [19].

One of the studies dealing with bladder-preserving treatment designed by Kachnic et al., 5-year overall survival and disease free survival rates were 52 and 60%, respectively, and the 5-year overall survival rate of patients with intact and fully functioning bladder was 43% [20]. The necessity of induction chemotherapy for bladder-preserving treatments remains to be answered [12,19, 21,22].

The RTOG 89-03 study has tested directly the contribution of induction chemotherapy to chemoradiotherapy [21]. One hundred twenty-three eligible patients with TNM stage from T2 to T4a NXM0 were randomized to receive 2 cycles of MCV combination chemotherapy followed by pelvic RT with 39.6 Gy with concurrent cisplatin 100 mg/m$^2$ for 2 courses 3 weeks apart (arm 1, n=61). Patients assigned to arm 2 (n=62) did not receive MCV before concurrent cisplatin and RT. Overall survival rates were the same (48 and 49%) and survival rates with intact bladder were similar in the 2 groups (36 vs. 40%).

Three phase II studies have shown that the combination of gemcitabine and cisplatin had a high activity in the treatment of advanced or metastatic transitional cell bladder cancer. Complete response rates of these studies were 18, 28 and 21%, respectively [24-26].

A randomized study designed by Von der Maase et al. had compared the gemcitabine-cisplatin combination chemotherapy with MVAC chemotherapy. The response and survival rates were similar in both arms but the toxicity of gemcitabine-cisplatin regimen was lower [27]. Moreover, the radiosensitizing activity of gemcitabine has been shown in several *in vitro* studies [28,29] and occurred in subcytotoxic doses [30,31].

An Italian study reported by Caffo et al. [32] in 16 patients with T2 NXM0 bladder cancer, cisplatin was administered at a dose of 100 mg/m$^2$ every 3 weeks and gemcitabine at a starting dose of 200 mg/m$^2$/week, reaching 500 mg/m$^2$ by adding 100 mg/m$^2$ each week; RT with 54 Gy in 30 fractions was delivered after transurethral resection. Intestinal perforation was noted in one of the patients receiving 500 mg/m$^2$ gemcitabine, while another patient with the same gemcitabine dose died from intractable diarrhea.

In a phase I study Kent et al. administered gemcitabine 10-33 mg/m$^2$ twice a week simultaneously with RT (2 Gy/daily fractions, total dose 60 Gy). No toxicity was reported at a dosage of 10-27 mg/m$^2$. Fifteen (65%) of 23 patients were alive with intact bladder and without metastasis after a follow up period of 43 months [1].

In another phase I study Sangar et al. [33] used simultaneously hyperfractionated conformal RT (54 Gy in 30 fractions) and gemcitabine in 8 patients. They concluded that the maximum tolerated dose of gemcitabine was 100 mg/m$^2$. Complete response was achieved in 7 (87.5%) of 8 patients and all of them were disease free at a median follow up of 19.5 months (range 14-23).

In our study, 1- and 2-year overall survival rates were 97 and 60%, respectively. Median time to progression was 21 months. One- and 2-year overall survival rates without disease progression were 83 and 49%, respectively. All of the patients but one had intact bladder. The outcomes obtained in the present study are comparable with those of the literature. In addition, hematologic and non-hematologic adverse effects were rather mild and tolerable.

In conclusion, chemoradiotherapy with concurrent gemcitabine after induction therapy with gemcitabine and cisplatin combination is a promising bladder-sparing approach in patients with invasive disease who had undergone maximal TURBT; this therapy may also be an acceptable alternative to radical cystectomy in patients who are not eligible for surgery.

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