

Bladder preservation by neoadjuvant chemotherapy followed by gemcitabine as radiosensitizer for muscle-invasive transitional cell carcinoma of the urinary bladder after maximal TURBT

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Abstract: Objectives: To evaluate prospective phase II study of neoadjuvant chemotherapy and gemcitabine as radiosensitizer in conservative management of muscle-invasive transitional cell carcinoma of the urinary bladder. **Patients and methods:** Forty eight patients with transitional cell carcinoma, stage T2b-T4aN0M0, bladder cancer underwent maximal TURBT followed by neoadjuvant chemotherapy carboplatin AUC5 D1 and gemcitabine 1000 mg/m² D1 and D8 repeated every 21 days for 2 cycles followed by concurrent radiation 65Gy with Gemcitabine given intravenously at 100 mg/m² on days 1, 8, 15, 22, 29, 36. The end points were tumor response, toxicity and survival. **Results:** The neoadjuvant as well as concurrent chemoradiotherapy were tolerated with low toxicity rates as the following. Urinary Bladder irritative symptoms developed in 2 patients (4.1%) and successfully managed with antimuscarinic. Neutropenia occurred in 4 patients (8.3%) while febrile neutropenis in 1 patient (2%). Nausea and vomiting occurred in 6 patients (12.5%) while nephrotoxicity occurred in 2 patients (4.1%). Complete response was noted in 28 patients (58.3%). Partial response was observed in 15 patients (31.25%). At time of analysis, there were fourteen deaths (29.1%) due to bladder cancer. Three-year cancer specific survival (CSS) and overall survival (OS) were 69.9% and 66.6%. Twenty one patients (43.7%) were tumor free and kept their bladder at time of analysis. **Conclusion:** Neoadjuvant chemotherapy followed by gemcitabine as radiosensitizer for muscle-invasive transitional cell carcinoma of the urinary bladder was tolerable with good bladder preservation and overall survival.

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1. Introduction

Bladder cancer is the 9th most common cancer worldwide. Bladder cancer is the thirteenth most common cause of death, with approximately 145,000 deaths annually worldwide [1]. The gold standard treatment modality for muscle invasive disease is radical cystectomy [2].

Urinary bladder substitution has been established to improve quality of life after cystectomy. Even with advancement in reconstruction techniques, neobladder cannot substitute for the patient's original bladder. Organ preservation protocols are introduced to keep the balance between achieving local cure with no compromise in survival. Transurethral resection of the bladder tumor (TURBT), chemotherapy or radiotherapy when used alone cannot ensure adequate disease control. Several reports tried to combine all three treatment options, with salvage cystectomy in case of incomplete response or recurrence [3].

The rationale for combining the three modalities is that certain chemotherapeutic agents may act as sensitizer for tumor cells to radiation; second, the high incidence of occult metastases requires eradication by multiple modalities. [3]

Gemcitabine has been shown to be active in bladder cancer and is used in combination with platinum as a standard of care in the neoadjuvant and metastatic settings [2, 4, 5]. Many reports have suggested the combination of gemcitabine and radiotherapy with good initial results. However, the clinical use of this combination has to be applied cautiously due to high possibilities of toxicity. We present the results of our prospective study in Bladder preservation by using neoadjuvant chemotherapy followed by chemoradiation after maximal TURBT

2. Patient and methods

Between January 2010 and July 2014, forty eight patients diagnosed as muscle invasive bladder cancer T2b-T4aN0M0 and not amenable or refuse radical cystectomy were enrolled in this prospective study. Eligibility criteria included ECOG (Eastern Cooperative Oncology Group) performance status 0-2, haemoglobin > 10 gm/dl, white blood cells (WBC) > 3000/mm³, platelets > 100,000/mm³, creatinine clearance < 60 ml/min. Patients who received chemotherapy, radiotherapy or had prior history of malignancy were excluded from the study. An

approval of local ethics committee and an informed consent from all patients were obtained.

Neoadjuvant chemotherapy

All patients underwent routine laboratory and radiological work up for staging and assessment of performance status. Maximal TURBT was carried out for all patients followed by neoadjuvant chemotherapy within 1 week. Patients received carboplatin AUC5 on day 1 followed gemcitabine 1,000 mg/m² on day 1 and 8 repeated every 21 days for 2 cycles.

Radiation and radiosensitizer

Radiotherapy started within 4 weeks after completion of neoadjuvant chemotherapy. Gemcitabine 100 mg/m² was given as radiosensitizer 3 hours before radiotherapy in the course of radiotherapy on days 1, 8, 15, and 22, 29 and 36.

All patients were simulated on virtual simulator and three dimensional (3D) conformal planning was performed. Sixty five Gy was given according to shrinking field technique [6].

Phase I; 45 Gy in 25 fractions five days/week, with borders to include bladder and drainage lymph node (whole pelvis) as the following:

Anterior–posterior field: Superior: between L5-S1. Inferior: at the level of the bottom of the obturator foramina (if bladder neck and/or prostatic urethra involvement: 1.5 cm below obturator foramina). Lateral: bony pelvis + 1.5–2 cm.

Lateral fields: Superior and inferior: same as anterior–posterior fields. Anterior: extends to the anterior bladder wall with a 1.5- to 2-cm margin. Posterior: at least 1–3 cm posterior to tumor which will incorporate the presacral lymph nodes. Anterior–posterior field: femur heads are shielded; lateral fields: two-thirds of posterior rectum and small intestines are shielded.

In phase II; the dose was given 20 Gy in ten fractions to the following volume (Boost field): Bladder + 1.5–2 cm margin.

Follow up cystoscopy and biopsy was performed 4-6 weeks after completion of radiotherapy cycles and then every 3 months for the first year and every 6 months for the following years. Salvage cystectomy is performed if Patient has any residual tumor or recurrence of disease during the follow up period. Chest radiography abdominal and pelvic CT were performed every 6 months for 5 years after treatment.

Outcome

1- The National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0, were used to assess toxicity [7]. Late Radiation Morbidity Scoring Criteria were used to score toxicity according to The Radiation Therapy Oncology Group (RTOG) [8]. The assessment of toxicities were assessed every

week in regular clinic visits during treatment and every month after treatment

2- Outcome was evaluated at follow up cystoscopy and tumor site biopsy done after completion of treatment. Response assessment was assessed according to response evaluation criteria in solid tumors (RECIST): Complete response (CR): complete regression of all evidence of tumors. Partial response (PR): an estimated decrease in tumors size of 50% or more. Stable disease (SD): less than 50% in tumor size or more than 25% of pretreatment tumor size. Progressive disease (PD): more than 25% increase in pretreatment tumor size [9].

Endpoints:

The primary endpoints were tumor response and toxicity. Secondary end point was the overall survival (OS) and Cancer-specific survival (CSS). OS was measured from the date of initiation of treatment to the date of death from any cause; detecting recurrences or metastases. CSS was measured from the date initiation of treatment to the date of death from Cancer related cause.

Statistical analysis:

The unpaired student -t- test or chi-squared (χ^2) test was used for data expression. Survival was evaluated and statistically analyzes using Kaplan-Meier curves and the log-rank test with $p < 0.050$ considered as statistically significant. All statistical analyses were done by MedCalc software, version 14.8.1.

3. Results

A total of 50 patients were enrolled in this study. Two patients were excluded because of prior radiotherapy for another malignancy, making the final number 48 patients. The mean \pm SD age of the patients was 62.4 \pm 5.7. Two thirds of patients had performance status I, while one third had performance status II. Thirty two patients (66.6%) were stage T3N0M0, while T4aN0M0 was found in 6 patients (12.5%). Patients' demographics and pretreatment criteria are displayed in **table 1**.

Neoadjuvant Chemotherapy and chemo-radiotherapy was successively accomplished in all patients. Neutropenia occurred in 4 patients (8.3%) while febrile neutropenia in 1 patient (2%). Nausea and vomiting occurred in 6 patients (12.5%) while nephrotoxicity occurred in 2 patients (4.1%). Acute toxicities during chemoradiotherapy was Bladder irritative symptoms developed in 2 patients (4.1%) and successfully managed with antimuscarinic, proctitis was 8.3% , dermatitis was 12.5% and diarrhea 12.5%.while late toxicities were proctitis was 4.1% and cystitis 8.3% as in tables (2,3,4) below.

Table (1) Distribution of Patient's characteristics.

Parameter	No. or Mean \pm SD	Percentage or Range
Number of patients	48	100%
Age (years)	62.4 \pm 5.7	41 – 75
Sex:		
Male	38	79.16%
Female	10	20.8%
Performance status		
PSI	34	70.8%
PSII	14	29.16%
Tumor Grade		
GII	40	83.3%
GIII	8	16.6%
Stage		
II	10	20.8%
III	32	66.6 %
Via	6	12.5%
Hydronephrosis		
-Yes	4	8.3%
-No	44	91.7%

Table 2: Toxicities during chemotherapy

Toxicity	Number of patients	%
Neutropenia	4	8.3
Nausea and vomiting	6	12.5
Nephrotoxicity	2	4.1
Febrile neutropenia	1	2

Table 3: Acute toxicities during chemoradiotherapy

Toxicity	Number of patients	%
Cystitis (Urinary Bladder irritative symptoms)	2	4.1
Proctitis	4	8.3
Dermatitis	6	12.5
Diarrhea	6	12.5

Table 3: Late toxicities after chemoradiotherapy

Toxicity	Number of patients	%
Cystitis	4	8.3
Proctitis	2	4.1

Complete response with disappearance of all evidence of tumor in CT images and during cystoscopy with negative tumor site biopsy was noted in 28 patients (58.3%). Partial response was observed in 15 patients (31.25%). Eight of them (16.6 %) underwent salvage cystectomy and the other 7

(14.5%) were found still inoperable and were treated with chemotherapy. Progressive disease was reported in 5 patients (10.4 %) with concomitant metastasis to lung and brain and treated with palliative radiotherapy and chemotherapy. **Table (5)** shows different protocols in bladder preservation technique.

Table (5) Comparison of results of present study and different bladder preservation trails

Study	Patients	Follow up by month	Initial CR	Preservation techniques
RTOG 85-12 (10)	42	36	67%	Concurrent cisplatin + RT
Lin CC, <i>et al.</i> (11)	30	47	73.3	Neoadjuvant CF X 3 cycles \pm paclitaxel, cisplatin
Kuafman <i>et al.</i> (12)	53	48	58%	Neoadjuvant CMV x 3 cycles + cisplatin + RT
Our study	48	31 \pm 3.7	58.3%	Neoadjuvant gem/carboplatin x 2 cycles and gem +RT

RTOG =Radiation Therapy Oncology Group, CR= complete response, RT= Radiation therapy CMV= cisplatinum, methotrexate and vinblastine

Patient's response to treatment is displayed in **figure 1**. The mean \pm SD months of follow up were 31 ± 3.7 months ranged (24-36 months). Three patients developed local recurrence of muscle invasive disease, detected during follow up cystoscopy and underwent salvage cystectomy at 11, 19 and 32 months. Two patients (4.1 %) developed bone metastasis at 25 and 31 months and were

managed with palliative radiotherapy. Two patients died due to cerebrovascular accident at 20 and 27 months. At time of analysis, there were fourteen deaths (29.1%) due to bladder cancer. Three-year CSS and OS were 69.9% and 66.6%. Twenty one patients (43.7%) were tumor free and kept their bladder at time of analysis. Detailed survival analysis is displayed in **figure2**.

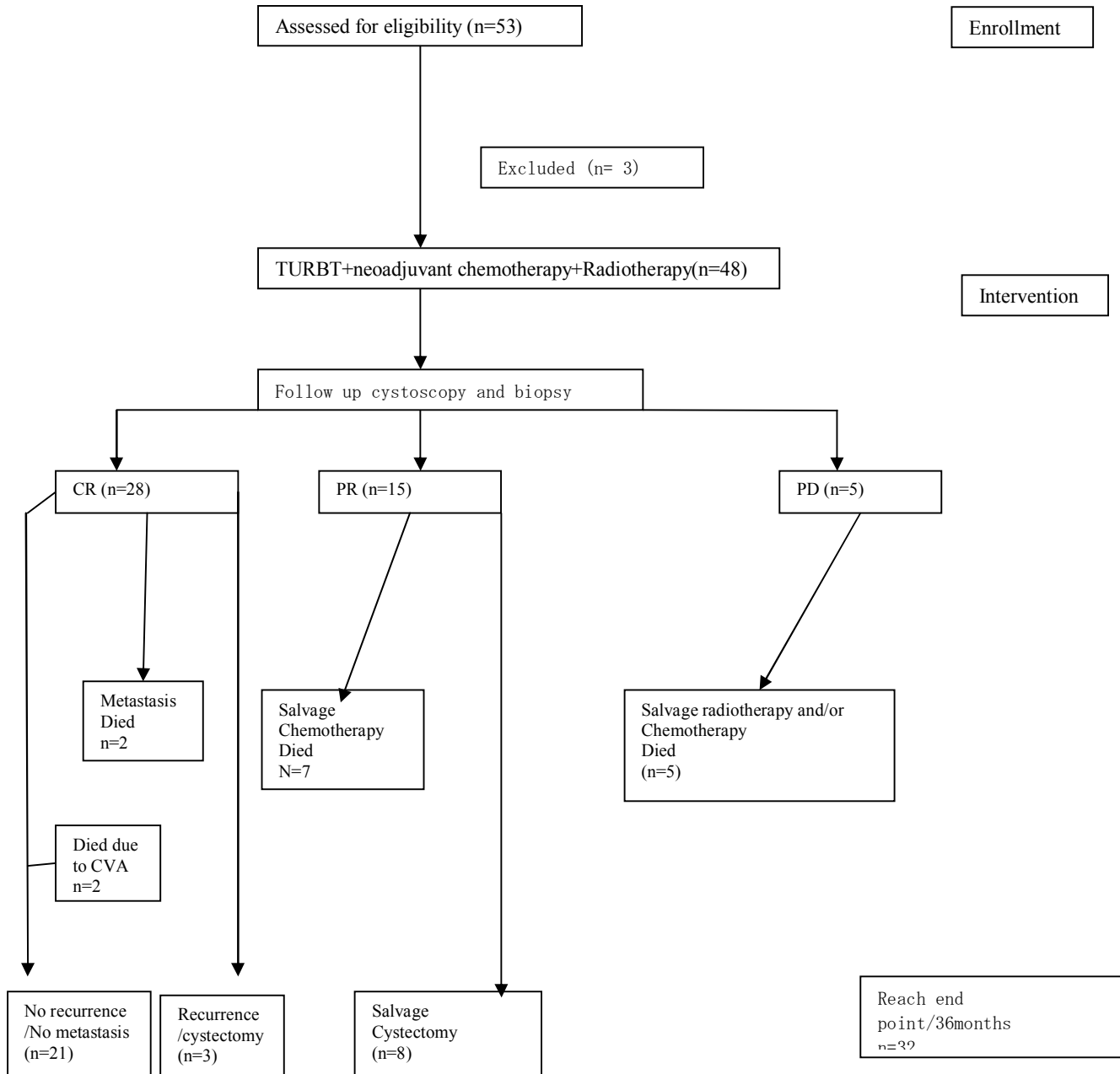


Figure 1: Patients' response to treatment

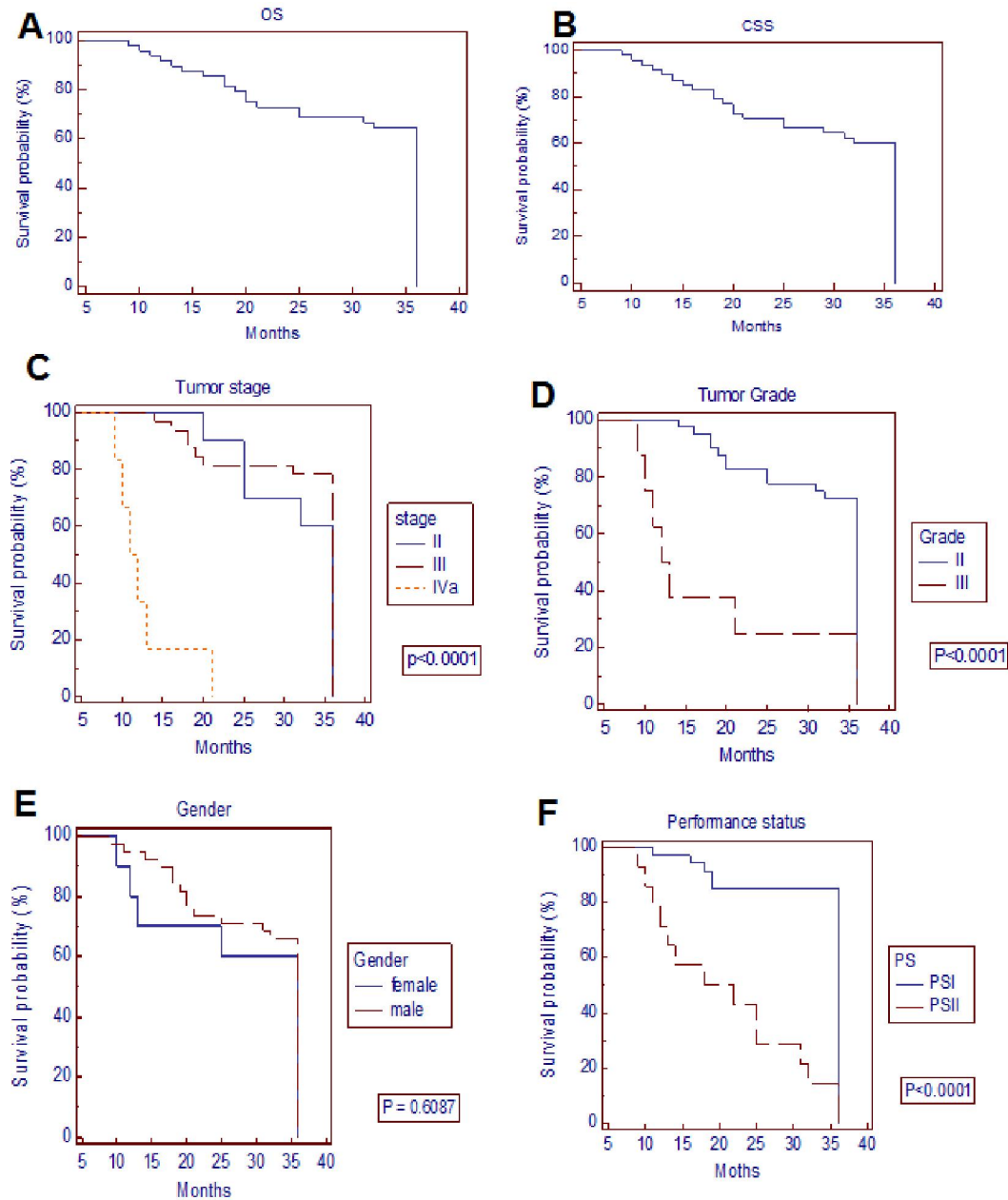


Figure 2: Detailed survival A: overall survival, B: cancer specific survival, C: Tumor stage, D: Tumor grade, E: Gender, F: performance status

4. Discussion

One of the modalities of care for localized muscle-invasive bladder cancer is radical cystectomy; however, although this procedure is associated with excellent local control, it has high risk of complications and, poor quality of life [13]. The era of organ preservation in muscle-invasive bladder cancer has been investigated in several prospective series [4]. Most strategies use combination of complete TUR of the tumor, chemotherapy and/or radiotherapy [4]. *In vitro* and *in vivo* studies have

revealed that gemcitabine is an effective radiosensitizer, and its potency has been confirmed in several types of cancer, including bladder tumors [4].

In our prospective phase II study of muscle invasive bladder cancer the multimodality regimen of neoadjuvant carboplatin and gemcitabine based chemotherapy followed by gemcitabine as radiosensitizer results were: the complete response was 58.3%, partial response was 31.25% and three-year cancer specific survival (CSS) and overall

survival (OS) were 69.9% and 66.6% respectively. Twenty one patients (43.7%) were tumor free and kept their bladder at time of analysis but in study done by Mutahir *et al.* the complete response was (78.04%) at time of cystoscopic evaluation of gemcitabine and cisplatin as neoadjuvant chemotherapy followed by gemcitabine as radiosensitizer protocol of treatment and at the median follow up of 36 months, overall survival was 61% [14]. Another study done by Ananya Choudhury *et al.* achieved a complete endoscopic response (88%) but with different protocol where conformal hypofractionated radiotherapy with concurrent Gemcitabine in muscle invasive bladder cancer was used and the 3 year cancer specific survival and overall survival was 82% 75% respectively [15].

In our study acute toxicities with neoadjuvant chemotherapy was neutropenia occurred in 4 patients (8.3%) and febrile neutropenis in 1 patient (2%). Nausea and vomiting occurred in 6 patients (12.5%) while nephrotoxicity occurred in 2 patients (4.1%) which was less than side effects of Mutahir study were the neutropenia attributable to neoadjuvant chemotherapy were grade 3 in 6 (14.6%) patients and febrile neutropenia in 2 (4.9%) patients, thrombocytopenia 4.9%, nausea and vomiting 17.1%, anorexia 7.1% and renal toxicity in 4.8% cases [14]. Acute toxicities with chemoradiotherapy of our study was bladder irritative symptoms which developed in 2 patients (4.1%) and successfully managed with antimuscarinic, proctitis was 8.3%, dermatitis was 12.5% and diarrhea 12.5% and late side effect was proctitis 4.1% and cystitis 8.3%. In Mutahir study the acute grade 3 side effects of concurrent chemoradiation were nausea and vomiting, diarrhoea and cystitis in 15.6%, 18.7% and 18.7% of cases respectively and late side effects were seen in 6 patients and were mild irritative bladder symptoms. No delayed gastrointestinal or haematological toxicity were reported in Mutahir study [14]. Many researchers have tried to use Carboplatin instead of cisplatin to decrease toxicities. Iwasaki *et al.* reported less non-hematologic toxicity and nephrotoxicity with or gemcitabine than MVAC [16].

The gemcitabine dose was one tenth of the usual systemic dose of used as the neoadjuvant in MIBC. Thus, the effect of gemcitabine on response rate in our prospective phase II study was radiosensitization, for which improved survival is likely a result of increased local control [12]. The limitation of our study was the small number of patients and few numbers of patients and equipments as cystoscopes.

Bladder preservation is the ultimate goal in many studies. In their report on 99 patients Shipley *et al.* reported 73% bladder preservation rate [17].

While Chauvet *et al.* in a study on 109 patient reported 37% only with intact bladder [18]. In our study bladder preservation rate was 43.7%. A potential limitation of our study is the relatively small sample size and non-comparative design of the study.

Conclusion

Neoadjuvant chemotherapy followed by Gemcitabine as radiosensitizer for muscle-invasive transitional cell carcinoma of the urinary bladder was tolerable with good bladder preservation and overall survival

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