

**Bladder preservation by neoadjuvant chemotherapy followed by concurrent chemoradiation for muscle-invasive bladder cancer: Experience at Sindh Institute of Urology & Transplantation (SIUT)**

Mutahir Ali Tunio,<sup>1</sup> Altaf Hashmi,<sup>2</sup> Mansoor Rafi,<sup>3</sup> Abdul Qayyum,<sup>4</sup> Rehan Masood<sup>5</sup>

Department of Radiation Oncology,<sup>1,3</sup> Department of Urology,<sup>2,5</sup> Department of Medical Oncology,<sup>4</sup> Sindh Institute of Urology & Transplantation (SIUT), Karachi.

**Abstract**

**Objective:** To identify any additional benefit and note the safety profile of neoadjuvant chemotherapy prior to concurrent chemoradiation in muscle-invasive bladder cancer.

**Methods:** Forty three patients with T2b-T4N0M0 bladder cancer underwent maximal TURBT followed by neoadjuvant chemotherapy cisplatinum 75mg/m<sup>2</sup> D1+ gemcitabine 1000mg/m<sup>2</sup> D1, D8 & D15 repeated every 28 days for three cycles followed by concurrent radiation 65Gy and weekly cisplatinum 30mg/m<sup>2</sup> or gemcitabine 100mg/m<sup>2</sup>. Complete response (CR) was defined as no tumour seen on cystoscopy and biopsy. The disease control and overall survival were determined by Kaplan and Meier method and statistical inferences with the log-rank test. Cox regression analysis was used to find different prognostic factors.

**Results:** Out of 43, thirty two patients (78.04%) achieved CR at time of cystoscopic evaluation. Six patients who did not achieve CR (14.63%) underwent salvage cystectomies, remaining were not operable. At the median follow up of 36 months, overall survival was 61%. Local recurrences were seen in 3 patients (10%) (2 pT1, 1pT2), distant metastases were seen in 2 patients (6.6%); 27/41 were alive, of whom 23 (56.1%) were retaining intact disease free bladders. The Tumour stage, incomplete TURBT and presence of hydronephrosis were important prognostic factors (log-rank p values 0.0001, 0.0001 and 0.001 respectively).

**Conclusion:** Neoadjuvant chemotherapy followed by concurrent chemoradiation was tolerable with better bladder preservation and overall survival.

**Keywords:** Neoadjuvant chemotherapy, gemcitabine, cisplatinum, concurrent chemoradiation, muscle invasive bladder(JPMA 61:6; 2011).

**Introduction**

Muscle invasive bladder cancer is traditionally treated with radical cystectomy. Even the new surgical techniques including construction of neobladder with continent urinary diversion cannot substitute for the original bladder.<sup>1</sup> An alternative trimodality treatment incorporating radical transurethral resection (TUR) and concurrent chemoradiation (CCRT) has demonstrated similar overall survival and disease free survival to radical cystectomy.<sup>2-4</sup>

The current trend of bladder preservation is concurrent chemoradiation after complete TUR followed by adjuvant chemotherapy rather than neoadjuvant chemotherapy with estimated five year survival rates 50-60%.<sup>5,6</sup> The rationale for neoadjuvant chemotherapy as suggested is to treat low burden micrometastasis.<sup>7</sup> However four previously reported randomized trials of neoadjuvant chemotherapy have reported no survival benefit to neoadjuvant chemotherapy that preceded radiation therapy, cystectomy, or preoperative radiation therapy and cystectomy.<sup>8-11</sup> However three large meta-analyses studies have shown survival benefit and improved disease free survival associated with platinum based

neoadjuvant chemotherapy after excluding trials in which neoadjuvant cisplatinum monotherapy was used.<sup>12-14</sup>

We aimed to see the additional benefit of cisplatinum and gemcitabine (GC) based neoadjuvant chemotherapy following maximal transurethral resection of bladder tumour (TURBT) prior to concurrent chemoradiation.

**Patients and Methods**

Total 43 patients with T2b-T4N0M0 muscle invasive bladder cancer were accrued to receive neoadjuvant chemotherapy following maximal TURBT prior to concurrent chemoradiation during July 2006 to January 2007. These patients were followed till January 2010.

Inclusion criteria were defined as; (1) histological proven muscle invasive transitional cell carcinoma of bladder, (2) European Cooperative Oncology Group (ECOG) performance status 0-2, (3) American Joint Committee on Cancer (AJCC) stage T2b-T4aN0M0, (4) Full capacity functioning bladder (5) maximum transurethral resection of bladder tumour (TURBT) at time of neoadjuvant chemotherapy and CCRT (small residual after second sitting of

TURBT were eligible), (6) normal haematology; haemoglobin  $\geq 10$  gm/dl, white blood cells(WBC)  $\geq 4000/\text{mm}^3$ , platelets  $\geq 100,000/\text{mm}^3$  and (7) normal renal functions (serum creatinine  $\leq 2.0$  mg/dl or creatinine clearance  $\geq 60\text{ml}/\text{min}$ ) and normal electrolyte values. Patients excluded were, (1) any lymphadenopathy or distant metastasis, (2) ECOG status 3-4, (3) no prior chemotherapy, radiotherapy or prior history of malignancy. Hydronephrosis was not an exclusion criteria. Attempts were made to correct renal functions by percutaneous nephrostomy (PCN) or urinary diversion.

Neoadjuvant chemotherapy was started within one week of complete TURBT. Patients received cisplatin 75 mg/m<sup>2</sup> on day 1 plus gemcitabine 1,000 mg/m<sup>2</sup> on days 1, 8 and 15, according to dose regimen by Von der Maase H et al.<sup>15</sup> Chemotherapy was repeated every 28 days for three cycles. As antiemetic regimen, all patients received dexamethasone 20 mg in 50 ml saline given as an intravenous infusion over 15 min, 45 min before cisplatin and ondansetron 16 mg as an intravenous infusion over 15 min. The dose modifications of gemcitabine and cisplatin were also calculated.

### **Concurrent chemoradiation and dose modifications:**

Patients underwent CCRT within 6 weeks after completion of neoadjuvant chemotherapy. All patients were simulated on virtual simulator and three dimensional (3D) conformal planning was performed. Radiotherapy was given with shrinking field technique, (1) first phase included whole pelvis, covered by four fields (anteroposterior (AP), posteroanterior (PA), two opposing lateral fields (right and left lateral) to encompass the entire bladder, prostate, and pelvic lymph nodes. The field borders were at the L5-S1 interspace cephalad, at laterally 1 cm beyond bony pelvis, and the inferior margin of obturator foramen caudally. The dose given was 45 Gy with fraction size 1.8 Gy in 25 fractions, five days/a week, (2) in second phase; field was reduced to cover the bladder tumour volume with 1 cm margin around with multiple fields. The dose was given 20 Gy with fraction size 2 Gy in ten fractions to complete 65 Gy. The maximum dose to the posterior rectal wall and to the femoral heads were kept  $<55$  Gy and  $<45$  Gy, respectively. All radiation was delivered by 6 to 15 MV photons from multileaf collimator (MLC) based linear accelerator.

Patients underwent concurrent chemotherapy with weekly cisplatin 40mg/m<sup>2</sup> or gemcitabine 100 mg/m<sup>2</sup> IV prior to radiotherapy for six doses.

During CCRT, dose modifications were also calculated.

### **Toxicity and assessment evaluation:**

During neoadjuvant chemotherapy, records were

evaluated for weight, performance status, haematology/chemistry and other related symptoms. During CCRT, for grading the acute side effects (persisting for  $< 90$  days) The National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0, were used.<sup>16</sup> The Radiation Therapy Oncology Group (RTOG) Late Radiation Morbidity Scoring Criteria were used to score radiation toxicity that persisted beyond 90 days from the completion of radiotherapy.<sup>17</sup>

Check cystoscopy was performed when radiotherapy was completed. Patients were considered to have achieved a complete response (CR) if there was no evidence of visible tumour on cystoscopy or if biopsy showed no malignancy. Patients with CR or only superficial tumour (Ta, Tis, or T1) at a new site were followed as bladder preservation. Patients with any residual tumour at the original tumour site or muscle-invasive tumour (T2 or greater) at a new site were considered candidates for salvage cystectomy. During the follow up period, patients underwent check cystoscopy 6 weeks after completion of concurrent chemoradiation, and then every 3 months for first year and every 6 months for following years.

The primary endpoints were the overall survival, disease free survival and the secondary points were the effectiveness of the neoadjuvant chemotherapy, complete response rates, local recurrence and distant metastasis. The times to last follow up evaluation, appearance of local and distant relapse and death were calculated from date of starting treatment. Disease free survival (DFS) was defined as the duration between the entry date and the date of documented disease reappearance, death from cancer and/or last follow-up (censored). Overall survival (OS) was defined as the duration between the entry date and the date of patient death or last follow-up (censored). Probabilities of local and distant control, disease free and the overall survival were determined with the Kaplan-Meier method. The comparisons for various endpoints were performed using log rank test and Cox regression analysis was used to detect any prognostic factors. Statistical analyses were performed using the computer program SPSS (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago,III, USA).

### **Results**

Patient characteristics are shown in Table-1.

A total of 33 males and 10 females with mean age  $60.06 \pm 10.61$  years (range 36-75) with muscle invasive bladder cancer were treated. Thirty (69.8%) patients were with radiological stage  $\geq T3aN0M0$ . 30.2% patients had hydronephrosis at time of enrollment, for which they underwent percutaneous nephrostomy (PCN) prior to neoadjuvant chemotherapy. Complete TURBT was performed in 33 patients (76.7%) in one or more attempts. All patients had good performance status.

**Table-1: Patient characteristics.**

| Variables                               | Number (%)                      |
|---|---------------------------------|
| Mean Age                                | 60.06±10.61 years (range 36-75) |
| <b>Gender</b>                           |                                 |
| Male                                    | 33 (76.7)                       |
| Female                                  | 10 (23.3)                       |
| <b>Radiologic Stage</b>                 |                                 |
| T2bN0M0                                 | 13 (30.2)                       |
| T3aN0M0                                 | 9 (20.9)                        |
| T3bN0M0                                 | 12 (27.9)                       |
| T4aN0M0                                 | 7 (16.3)                        |
| T4bN0M0                                 | 2 (4.7)                         |
| <b>Hydronephrosis</b>                   |                                 |
| No                                      | 30 (69.8)                       |
| Yes                                     | 13 (30.2)                       |
| <b>Visible complete TURBT performed</b> |                                 |
| Yes                                     | 33 (76.7)                       |
| No                                      | 10 (23.3)                       |
| <b>ECOG</b>                             |                                 |
| 0-2                                     | 43 (100)                        |
| 4-Mar                                   | 0                               |

ECOG= European Co-operative Oncology Group.

Of 43 patients, 41 completed three cycles of neoadjuvant chemotherapy. Almost all the planned doses of neoadjuvant chemotherapy were administered. Two patients received only two courses of the chemotherapy owing to grade 4 neutropenia and thrombocytopenia and prolonged recovery. Subsequently these patients were withdrawn from the study protocol. There were two episodes of delay for cisplatin in two patients because of grade 3 renal toxicity. The neutropenia attributable to neoadjuvant chemotherapy were grade 3 in 6 (14.6%) patients and febrile neutropenia in 2 (4.9%) patients. The frequency of grade 3 toxicity profile was as, thrombocytopenia 4.9%, nausea and vomiting 17.1%, anorexia 7.1% and renal toxicity in 4.8% cases.

Acute grade 3 side effects of concurrent chemoradiation were nausea and vomiting, diarrhoea and cystitis in 15.6%, 18.7% and 18.7% cases respectively. The

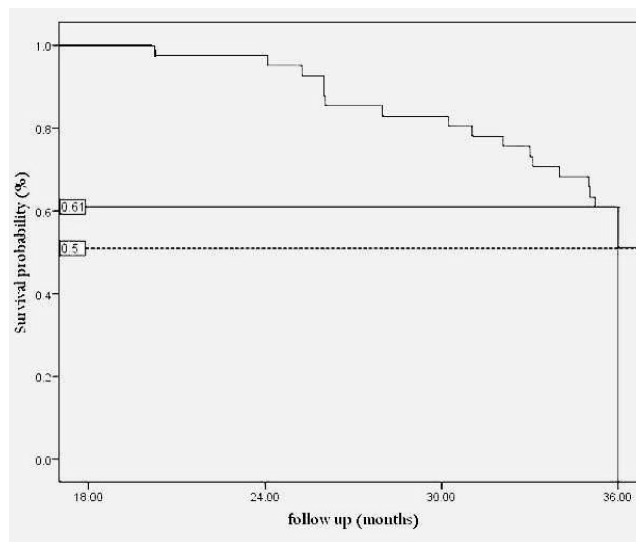


Figure: Overall survival at 3 years using Kaplan & Meir method.

G4 side effects were only cystitis in 3.7% cases. The weekly cisplatin and gemcitabine was omitted for one course in six patients; however no dose reduction was seen during the course of radiation.

The complete response on check cystoscopy/tumour site biopsy following neoadjuvant chemotherapy and concurrent chemoradiation was seen in 32 patients (78.04%, 95% confidence interval {CI} 62-94). Of 9 patients, who did not achieve CR, 6 underwent salvage cystectomy and 3 were found still inoperable and were treated with salvage chemotherapy.

Late side effects were seen in 6 patients and were mild irritative bladder symptoms. No delayed gastrointestinal or haematological toxicity were reported.

At the median follow-up period of 36 months (24-38months), local recurrences were seen in 3 patients (10%)

**Table-2: Comparison of results of present study with other previously published studies.**

| Study (reference)             | Patients | Follow/up (months) | Protocol   | Initial CR | Pelvic failure | Distant metastasis | Bladder preservation | Survival |
|-------------------------------|----------|--------------------|--|------------|----------------|--------------------|----------------------|----------|
| RTOG 85-12 <sup>18</sup>      | 42       | 36                 | Concurrent cisplatin + RT  | 67%        | 28%            | 32%                | 48%                  | 64%      |
| Lin CC, et al <sup>19</sup>   | 30       | 47                 | Neoadjuvant CF X 3 cycles ± paclitaxel 'cisplatin or paclitaxel + RT | 73.3%      | 10%            | 10%                | 50%                  | 77%      |
| Cervek J, et al <sup>20</sup> | 47       | 23                 | Neoadjuvant CMV x 3-4 cycles ' RT alone                              | 62%        | 32%            | -                  | 53%                  | 73%      |
| Kuafman et al <sup>21</sup>   | 53       | 48                 | Neoadjuvant CMV x 3 cycles ' cisplatin + RT                          | 58%        | 13.3%          | 42%                | 58%                  | 48%      |
| Present study                 | 43       | 30                 | Neoadjuvant GC X 3 cycles ' cisplatin/gemcitabine + RT               | 78.04%     | 10%            | 6.6 %              | 56.1%                | 61%      |

RTOG= Radiation Therapy Oncology Group, CR= complete response, DFS= Disease free survival, CMV= cisplatin, methotrexate and vinblastine, CF= cisplatin, 5-Flourouracil, GC= gemcitabine, cisplatinum , RT= Radiation therapy.

out of 30 initial complete responders. Two had superficial bladder cancers (pT1, G2) and were treated with complete TURBT followed by intravesical bacillus Calmette-Guerin (BCG). One had muscle invasive cancer, for which salvage cystectomy was performed.

The distant metastases in bones were seen in 2 patients (6.6%); and were treated with salvage chemotherapy, palliative radiotherapy for pain relief and bisphosphonates.

At the time of analysis, 27/41 were alive. Of whom 23(56.1%) were retaining their original bladder and are free of disease. Using the Kaplan-Meier method, the 3 year actuarial survival was 54% (Figure).

On Cox-regression analysis, significant differences in survival were found between the subgroups of hydronephrosis (log-rank p 0.0001), Tumour stage (log-rank p 0.0001) and initial complete response (log-rank p 0.001).

### Discussion

This multimodality regimen of neoadjuvant cisplatin and gemcitabine based chemotherapy followed concurrent chemoradiation resulted in 3 year survival rate of 61% and intact bladder survival rate 56.1%. The complete response rates, local control and bladder preservation rates were as good as or better than previously published similar trials shown in Table-2.

In the present study, majority of patients were with radiological stage >T3a 70%, hydronephrosis 30.2% and with post TURBT residuals in 23.3% cases, which are generally considered poor candidates for bladder preservation protocols.<sup>22,23</sup> Radiological stage >T3a with hydronephrosis is common presentation in our part of the world and constitute major referral for radiation.<sup>24</sup> Institutional urologists performed aggressive resections in one or more attempts to accomplish the visible complete TURBTs. We found hydronephrosis, incomplete TURBT and tumour stage as important prognostic factors. However our study did not evaluate the DNA ploidy, tumour grade and HER 2 over expression which are recently considered additional poor prognostic factors.<sup>25-27</sup>

The improved CR rates (78.04%, 95% CI62-94) in this study could be attributed to better tolerance and completion rates of the protocol as compared to traditionally used CMV regimen by RTOG trials which failed to demonstrate the benefit of neoadjuvant chemotherapy. Contrary Lin CC, et al reported better CR rates, lower local recurrences, distant metastasis and better bladder preservation with newer cisplatin and 5-fluorouracil ± paclitaxel based neoadjuvant chemotherapy.<sup>17</sup>

However our study had few limitations. (a) Interval cystoscopy immediate after neoadjuvant chemotherapy was

not carried in our patients (b) complete response rates were not separated after neoadjuvant chemotherapy and CCRT (c) salvage cystectomies were carried out in few patients, justification could be the religious and socioeconomic factors.

Though not powered enough and with short follow up period, this trial of cisplatin and gemcitabine based neoadjuvant chemotherapy followed by concurrent chemoradiation has shown encouraging results in bladder preserving approach, however a large randomized, multi-institutional prospective trial is warranted.

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