

**Outcome of Trimodality Protocol for invasive bladder cancer patients at Karachi, Pakistan**

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**Abstract**

**Objectives:** To evaluate the outcomes of patients with muscle invasive bladder cancer managed by trimodality protocol with assessment of factors that may predict treatment response, risk of recurrences and survival of such patients in our population.

**Methods:** A prospective, single arm study was conducted between July 2006 and December 2009 at the Sindh Institute of Urology and Transplantation, Karachi. One hundred and sixteen patients with muscle invasive bladder cancer T2-T3N0M0 were treated with concurrent chemoradiation (total dose 6500 cGy) after maximal transurethral resection. Complete response was defined as no tumour seen on check 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:** At the median follow up of 36 months (14-43), out of total 116, 62(51.6%) surviving patients the bladder was functioning well, while 18(15%) had local recurrence; in 9 patients superficial tumour recurred and required further transurethral resection and intravesical drug therapy and nine patients who had muscle invasive recurrence; underwent radical cystectomies. Concurrent chemoradiation was well tolerated. The overall survival at 3 years was 54%. Initial complete response, primary tumour stage and absence of hydronephrosis were the most important prognostic factors for survival (all  $p < 0.0001$ ).

**Conclusion:** Trimodality treatment was found to be an effective therapy in patients with invasive bladder cancer and complete TURBT, tumour stage and no hydronephrosis at time of presentation were found important prognostic factors for treatment response, disease free and over all survival rates.

**Keywords:** Urinary bladder, Preservation, Transurethral resection, Concurrent chemoradiation, Survival, Prognostic factors, Karachi (JPMA 61:874; 2011).

## Introduction

In Pakistan, bladder cancer is the 4th and the 15th most common cancer in men and women, respectively and smoking is main cause of bladder cancer according to the Karachi Cancer Registry.<sup>1</sup> Due to the lack of country based cancer registries, exact incidence remains doubtful in most developing countries including Pakistan; but bladder cancer is the most common urologic malignancy according to a dedicated urology tertiary referral setting.<sup>2</sup> According to the treatment, bladder cancer is categorized into, superficial (non-invasive), muscle invasive and metastatic disease.<sup>3</sup> 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>4</sup> An alternative, trimodality treatment, including transurethral resection of bladder tumour (TURBT) and concurrent chemoradiation (CCRT) has been suggested as a bladder-preserving therapy in invasive bladder cancer over the past two decades.<sup>5-7</sup> However for combined chemoradiation treatment, the patient selection is very important. Full bladder capacity, no hydronephrosis and lower T stage are the pre-requisites for bladder preservation.<sup>8</sup> In the Asian population, there is insufficient data regarding the bladder preservation for muscle invasive bladder cancer.

To determine the clinical effectiveness of this trimodality treatment and assessment of factors that may predict treatment response, risk of recurrences and survival, we conducted the present study of concurrent chemoradiation incorporating weekly cisplatin following maximal transurethral resection of bladder tumour for muscle invasive bladder cancer.

## Patients and Methods

Between the period of July 2006 and December 2009, one hundred and sixteen patients with muscle invasive bladder cancer T2-T3N0M0 were prospectively treated after taking written consent from patients and approval by institutional ethics review committee.

### Eligibility criteria:

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 T2-T3N0M0, (4) Full capacity functioning bladder (5) maximum transurethral resection of bladder tumour (TURBT) at time of concurrent chemoradiotherapy (CRT) (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) 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.

### Treatment Protocol:

#### Transurethral resection:

Maximal TURBT was performed in one or more attempts. Completeness of TURBT was assessed according to residual tumour status. Complete TURBT was defined as no residual tumour, whereas incomplete TURBT was defined as macroscopic residual tumour.

#### Concurrent chemoradiation and dose modifications:

Patients underwent CRT within 6 weeks after maximal TURBT. All patients were simulated on virtual simulator and three dimensional (3D) conformal planning was performed. Radiotherapy was given with shrinking field technique (Figure-1), (1) first phase included whole pelvis, covered by four fields ( anteroposterior (AP),

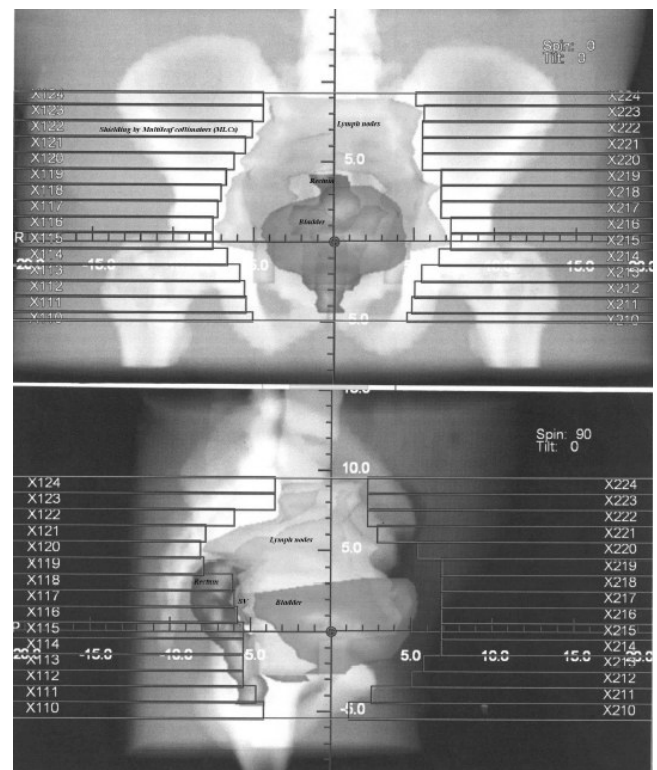


Figure-1: Initial phase pelvic box field technique covering gross tumour volume and pelvic lymph nodes in anteroposterior and lateral fields.

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 cephalic, 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 residual bladder gross tumour volume (GTV) 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> weekly prior to radiotherapy for six doses. During CRT, dose modifications were also calculated.

**Toxicity and assessment evaluation:**

During CRT, for grading the acute side effects (persisting for less than 90 days) the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 was used. The Radiation Therapy Oncology Group (RTOG) Late Radiation Morbidity Scoring Criteria was used to score radiation toxicity that persisted beyond 90 days from the completion of radiotherapy.

Check cystoscopy was performed four weeks after completion of radiotherapy. Patients were considered to have achieved a complete response (CR) if no evidence of visible tumour on cystoscopy and if biopsy/urine cytology showed no malignancy. Patients with CR or only superficial tumour (Ta, Tis, or T1) at a new site were followed with 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 CRT, and then every 3 months for first year and every 6 months for the following years.

The data was collected and completed during January 2010 to July 2010. The primary endpoints were the overall survival, disease free survival and the secondary points were, the 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 analysis was performed using the computer programme SPSS (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, III, USA).

**Results**

From July 2006 to December 2009, a total 100 males and 16 females with mean age 61.95 ± 10.53 years (range 40-85) with muscle invasive bladder cancer were treated. Radiological stage of 69 (59.5%) patients was T3N0M0 (Figure-2). Thirty five (30.2%) patients had hydronephrosis at the time of enrollment, and they underwent percutaneous nephrostomy (PCN). Complete TURBT was performed in 88(75.9%) patients in one or more attempts. All patients had good performance status (Eastern Co-operative Oncology Group {ECOG} 0-2).

Acute grade 3 side effects of concurrent chemoradiation were nausea, vomiting, diarrhoea and cystitis in 10.6%, 12.7% and 12.7% cases respectively. The

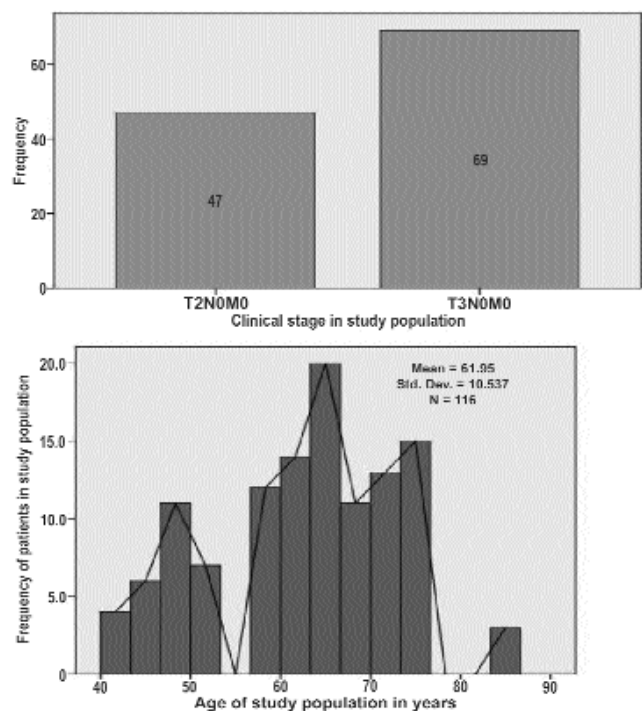


Figure-2: Graphical representation of baseline TNM stage and age stratification in the study population.

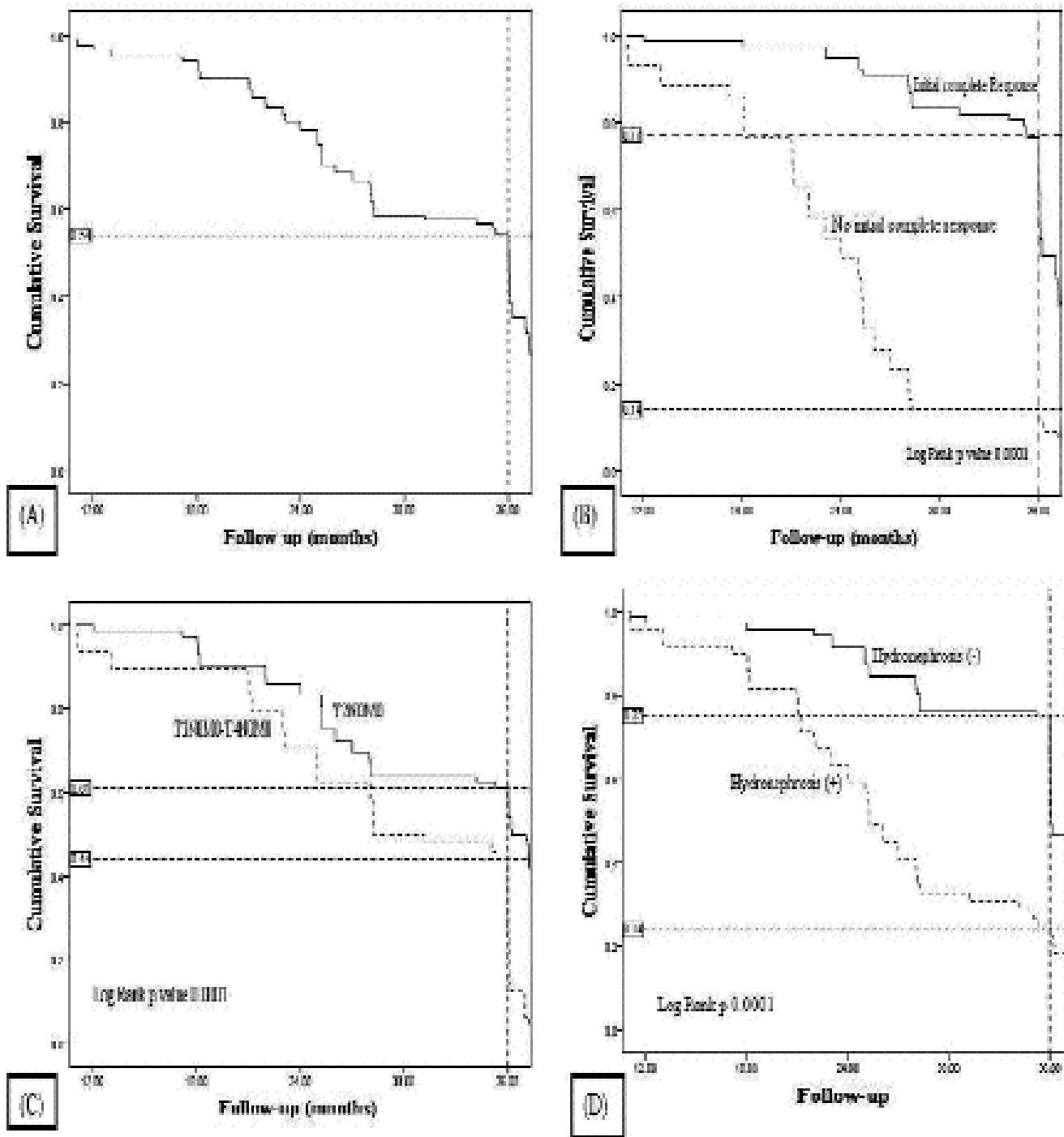


Figure-3: (A) Kaplan Meier survival curves (at 3 year) for patients underwent concurrent chemoradiation and Survival difference between (B) initial complete responders and non responders using Log Rank (C) stage T2N0M0 and >T2N0M0 and (D) presence and absence of hydronephrosis.

G4 side effects were only cystitis seen in 3.7% cases. The weekly cisplatin was omitted for one course in 6 (5.2%) patients; however no dose reduction was seen during the course of radiation.

The complete response on check cystoscopy/tumour

site biopsy following concurrent chemoradiation was seen in 90 patients (75%, 95% confidence interval 60-92). Of 30 patients, who did not achieve CR, 16 patients (with tumours at initial cancer site) underwent salvage cystectomies and 14 patients (all had tumours at initial cancer site) were

found still inoperable and were treated with salvage chemotherapy.

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

At the median follow-up period of 36 months (14-43 months), local recurrences were seen in 18 patients (7.5%) out of 90 initial complete responders. Nine had superficial bladder cancers (pT1, G2) (3 patients recurred within initial site and 6 patients developed recurrence in initially normal sites) and were treated with complete TURBT followed by intravesical Bacillus Calmette-Guerin (BCG). Nine had muscle invasive cancer (7 patients had disease within initial site and only two patients recurred in previously normal sites), for which salvage cystectomy was performed.

The distant metastases in bones were seen in 9 patients (7.5%); and were treated with salvage chemotherapy, palliative radiotherapy for pain relief and bisphosphonates.

At the time of analysis 62(51.6%) initial responders were retaining their original bladder and were free of disease. Using the Kaplan-Meier method, the 3 year actuarial survival was found to be 54% (Figure-3A).

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), initial complete response and incomplete TURBT (log-rank p 0.001) (Figure-3B,C,D). Hydronephrosis, tumour stage and initial complete response were found important prognostic factors during univariate and multivariate analysis.

## Discussion

Over the last two decades, some centers in the United States and Europe adopted a trimodality treatment for patients who are seeking alternate to radical cystectomy. The rationale for combining radiotherapy with chemotherapy after TURBT is twofold. First, certain cytotoxic agents (cisplatin, gemcitabine and 5-fluorouracil) may have the ability to sensitize cancer cells to radiation and to inhibit repopulation during radiotherapy. Second, high rates of occult metastases require efforts to eradicate them, that have already developed in as many as 50% of muscle-invasive cancer.<sup>9</sup> This multimodality strategy of concurrent chemoradiation following maximal TURBT resulted in 3 year survival rate of 54% and intact bladder survival 52.1%. The complete response rates, local control and bladder preservation rates were as good as previously published similar trials.<sup>10-12</sup>

To our knowledge, no study with enough sample size regarding bladder preservation in muscle invasive bladder cancer has been documented in the Asian population. The selection of ideal candidates for concurrent chemoradiation is an important factor for better bladder preservation. Few studies have been undertaken to identify clinical factors that help distinguish candidates for trimodality treatment and have shown the completeness of TURBT, primary tumour size (<5 cm), early tumour stage, absence of hydronephrosis and no evidence of pelvic lymph node metastases.<sup>13-17</sup> In our study incomplete TURBT was performed in 28 patients (24.1%) and was found an important prognostic factor (3 year survival with complete TURBT 44% vs. 61% with incomplete TURBT p<0.0001). Further the initial complete response, hydronephrosis and higher T stage were found to be poor prognostic factors on multivariate analysis; subgroup analysis showed poor survival rates at 3 year; 14%, 24% and 44 % respectively for no initial complete response, radiological stage >T3N0M0 and with hydronephrosis at time of presentation. Radiological stage >T3 with hydronephrosis is a common presentation in our part of the world as mentioned previously.<sup>2</sup> Institutional urologists performed aggressive resections in one or more attempts to accomplish the visible complete TURBTs. However our study did not evaluate the DNA ploidy, tumour grade and HER 2 over expression, which are considered additional poor prognostic factors.<sup>18,19</sup>

## Conclusion

The trimodality protocol was found to be an effective treatment option for patients with a muscle-invasive bladder cancer and complete TURBT, T stage and hydronephrosis at presentation were found important prognostic factors for disease free and overall survival. For better bladder preservation, not only a proper case selection is advised, but also close follow up is required for the patients who achieved complete response after concurrent chemoradiation.

## Acknowledgement

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