

## Transurethral Resection of Bladder Tumor (TUR-BT) then Concomitant Radiation and Cisplatin Followed by Adjuvant Gemcitabine and Cisplatin in Muscle Invasive Transitional Cell Carcinoma (TCC) of the Urinary Bladder

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### ABSTRACT

**Purpose:** To evaluate the efficacy, safety, and tolerance of bladder preservation trimodality protocol combining maximal transurethral resection of bladder tumor (TUR-BT) with concomitant chemoradiation (CCRT) followed by adjuvant chemotherapy in patients with muscle invasive transitional cell carcinoma (TCC) of the bladder.

**Patients and Methods:** Between January 2004 and May 2006, 40 patients with invasive TCC (T2-T4a) presented to the Radiation Oncology and Urology departments - Ain Shams University hospitals and were enrolled in this prospective phase II study. Patients were treated using concurrent cisplatin and 45Gy radiotherapy (induction phase) after maximal TUR-BT. Patients were re-evaluated 2 weeks after induction CCRT, by cystoscopy, repeated biopsy and urine cytology. Those with complete pathologic response (CR) received consolidation CCRT to 64.8Gy. Patients with less than CR were advised to undergo radical cystectomy (RC). Four cycles of adjuvant gemcitabine 1250mg/m<sup>2</sup> on days 1 and 8 and cisplatin 70mg/m<sup>2</sup> on day 1, repeated every 3 weeks, were given following definitive therapy.

**Results:** Twenty-four patients achieved CR after initial 45Gy CCRT, 22 of them received additional consolidation CCRT. Eight of 14 patients who did not achieve CR after induction CCRT underwent RC. A total of 30 patients (75%) received adjuvant chemotherapy. Twenty percent (20%) and 13.7% of patients experienced at least one severe (grade 3) toxicity during induction and consolidation phase of CCRT, respectively, mainly neutropenia, cystitis, proctitis and nausea and vomiting, while 46% experienced at least one severe (grade 3 or 4) toxicity during adjuvant chemotherapy, mainly neutropenia (32%), thrombocytopenia (11%) and nausea and vomiting (29%). Local and/or regional failure was recorded in 40% of patients

and distant metastasis was reported in 25%. Eighteen patients (45%) retained functioning and healthy urinary bladder at the end of follow-up. The 2-year actuarial survival and progression free survival (PFS) were 67% (95% CI 52.2%-82.7%) and 58% (95% CI 42.3%-74.0%), respectively. There was significantly better 2 year survival for patients having complete TUR-BT before CCRT.

**Conclusion:** Trimodality approach is a reasonable and safe alternative to RC with manageable toxicities. Longer follow-up with a larger number of patients is necessary to assess its impact on overall and disease-free survival.

**Key Words:** Bladder cancer – Chemoradiotherapy – Cisplatin – Gemcitabine.

### INTRODUCTION

The standard of care for muscle invasive transitional-cell carcinoma (TCC) of the bladder is radical cystectomy (RC). Radical surgery results in long-term survival rates of 40%-60% [1-3]. Sophisticated techniques for urinary diversion have been developed to improve patients' quality of life; however, this cannot substitute for the patient's original bladder [4]. Attempts to obtain bladder preservation are only justified when they have a high likelihood of achieving local cure with no compromise in survival rates. Transurethral resection of the bladder tumor (TUR-BT) alone, chemotherapy alone or radiation therapy alone provide inferior outcomes to radical cystectomy with only 20% to 40% local control rates in muscle invasive TCC. Several groups have reported the value of combining all three modalities, with salvage cystectomy being reserved for patients with incomplete response or local relapse [5,6].

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The initial study of the Radiation Therapy Oncology Group (RTOG) 85-12 treated 42 patients with daily conventional radiation therapy and concurrent cisplatin (CCRT), and reported greater than 50% 5-year survival. This approach was feasible, well tolerated by the patients and resulted in 42% long term survival with intact bladder [7]. Sauer et al. from the University of Erlangen reported in their experience of 162 patients treated with TUR-BT followed by daily radiation with concurrent platinum compound [8]. Results were similar to those of RTOG with 55% 5-year overall survival and 44% survival with intact bladder. RTOG 95-06 evaluated the accelerated hypofractionated irradiation schemes in combination with concurrent outpatient chemotherapy. In the later trial, 21% of patients developed grade 3 or 4 hematological toxicity and 15% had grade 3 bowel toxicity. Moreover, of the 20 patients who completed CCRT with a complete response (CR), 9 patients (45%) developed in-bladder recurrences [9]. The available data indicate that differences in local control between different radiation schedules, conventional hyperfractionation, accelerated fractionation or accelerated hypofractionation, are more related to the total dose than to the fractionation regimen [5]. Protocol RTOG 85-12 was the first protocol to use what was established to be the classic RTOG approach for patients who candidates for cystectomy.

However, the prognosis still remains poor with CCRT because it is technically difficult to irradiate the whole tumor target to cancericidal dose without exceeding the tolerance of critical structures. In an overview of RTOG bladder cancer trials, up to 70% of patients who completed the CCRT regimens were rendered tumor-free in the bladder at the initial post-treatment cystoscopy examination. However, during follow-up, approximately one fourth of these individuals developed a new superficial or invasive lesion requiring additional therapy [10]. In addition, the majority of patients who relapse following definitive local therapy have distant, rather than local, relapse. The distant metastasis rate was >50% especially in patients with high risk features like T3, high grade tumor or vascular invasion indicating the likelihood of microscopic metastatic disease at the time of local therapy [11]. Thus, the use of systemic chemotherapy, either neoadjuvant or adjuvant, should be employed in an attempt to potentiate the

effect of local therapy and to eradicate such microscopic disease.

In the RTOG 89-03 protocol, patients were treated with two cycles of neoadjuvant MCV (methotrexate, cisplatin, vinblastine) chemotherapy, followed by concurrent cisplatin and radiotherapy. This regimen failed to improve survival or local tumor eradication, compared with concurrent cisplatin and radiotherapy alone. Moreover, because of toxicity, the protocol completion rate for MCV neoadjuvant arm was only 67% [12]. As a result, some subsequent studies employed adjuvant rather than neoadjuvant chemotherapy. In RTOG 97-06, patients were treated with concomitant CCRT followed by three cycles of adjuvant CMV chemotherapy. Although a high complete response rate was reported in this trial, but this was associated with poor compliance and tolerance to chemotherapy [13].

Gemcitabine and cisplatin had been extensively investigated in cancer urinary bladder [14-16]. Recently, gemcitabine/cisplatin combination has been compared to methotrexate, vinblastin, doxorubicin, and cisplatin (MVAC) in a phase III study and the two combinations had similar efficacy in metastatic disease but the gemcitabine/cisplatin combination was better tolerated and led to fewer hospital days for the treatment of toxic side effects [14].

Based on the above-mentioned information, we conducted this prospective phase II study on patients with muscle invasive TCC of the urinary bladder to evaluate the efficacy, safety, and tolerance of bladder preservation protocol. For this study, maximal TUR-BT was followed by concomitant conventional radiation therapy and cisplatin. Prompt radical cystectomy (RC) was offered for those whose tumors responded incompletely to concomitant chemoradiation at the time of interval assessment after 45Gy. Patients who completed the concomitant chemoradiation or underwent RC received additionally four cycles of adjuvant gemcitabine/cisplatin combination chemotherapy. The primary end points were overall survival (OS) and progression free survival (PFS) and the secondary endpoints were failure rate and toxicity.

## **PATIENTS AND METHODS**

This trial included 40 patients with histopathologically proven muscle-invasive TCC of

the bladder who presented to the Radiation Oncology and Urology departments - Ain Shams University hospitals between January 2004 and May 2006.

*Pre-treatment evaluation:*

Initial evaluation included history and complete physical examination including performance status evaluation by ECOG criteria [17], and baseline audiometry. Laboratory studies (no more than 4 weeks prior to study entry) included complete blood count, serum chemistries and urine cytology. Radiological evaluation (no more than 6 weeks before treatment start) included chest X-ray, intravenous pyelogram (IVP) and pelvi-abdominal computerized tomographic scan (CT scan). Other additional imaging investigations [e.g. bone scan, brain or chest CT or magnetic resonance imaging (MRI)] were performed if clinically indicated. Cystoscopic evaluation by the participating urologist was done under general or regional anaesthesia and included as thorough as possible maximal TUR-BT, bimanual examination under anaesthesia, four quadrant bladder mucosal biopsies, as well as a biopsy of the base of the resected tumor site with an adequate sample of muscle.

*Eligibility:*

Eligible patients were required to have T2-T4a bladder cancer according to the AJCC staging system, 2002 [18]. Other eligibility criteria included age >18 but ≤70 years old, ECOG performance status 0-2, adequate bone marrow function (Hb ≥10g/dl, an absolute neutrophil count (ANC) ≥1500/μL and platelet count ≥100,000/μL), adequate renal functions (serum creatinine ≤1.5mg/dl, creatinine clearance (Cr Cl) ≥60ml/min), adequate hepatic functions (serum bilirubin ≤1.5mg/dl, transaminases ≤3x the institutional upper limit of normal). Patients were ineligible for this study if they had distant metastases, pelvic lymph node metastasis, evidence of tumor-related hydronephrosis, severe irritative bladder symptoms, active infection, associated serious medical or psychiatric illness, prior or concurrent malignancy of any other site unless the patient was disease free for ≥5 years, previous systemic chemotherapy or pelvic irradiation, and pregnant or lactating female patients. Each patient gave written informed consent before entering the study.

*Treatment plan:*

*Concomitant chemoradiotherapy (CCRT):*

Radiotherapy was given using CO-60 or linear accelerator (6 or 10MV) photon beams. The patients were asked to completely empty their bladders immediately before any imaging was done for treatment planning purpose and before delivery of each radiation fraction. The initial clinical target volume encompassed the entire bladder, paravesical tissues and pelvic lymph nodes. Radiation was delivered with anterior, posterior, right lateral and left lateral fields. The anterior and posterior treatment fields started at the level of midsacrum superiorly to the lower edge of the obturator foramina inferiorly and laterally to a distance of 10-15mm outside the bony margin of the pelvis at its widest point. Barium in the rectum was useful in the simulation of the posterior border of the lateral fields which excluded the posterior rectal wall. The anterior border of the lateral fields was at the anterior aspect of the symphysis pubis. Shielding was used in the corners of the fields to exclude the small bowel and femoral heads. This initial treatment phase (induction phase) was given as 1.8Gy/fraction/day for a total dose of 45Gy in 25 fractions over 5 weeks. After a 2-week break in the treatment to allow tumor regression, restaging was performed. This re-evaluation included examination under anaesthesia, cystoscopy with tumor site biopsy, and urine cytology. Patients were considered to have achieved CR, according to WHO criteria [19], if no clinical, radiological or histological evidence of tumor was found. Those patients with interval CR received an additional reduced field boost (consolidative phase) to the entire bladder and initial site of the tumor to a total dose of 64.8Gy. Therapy started 1-2 weeks after cystoscopic re-evaluation. This boost was given using one anterior and two lateral wedged fields. The maximum dose allowed to the posterior wall of the rectum was 55Gy and to the femoral heads was 45Gy. Patients with less than CR after cystoscopic re-evaluation were advised to undergo RC before their disease progressed and before they had received radiation doses that might make surgery more difficult.

On the first 2 days of each week of radiotherapy treatment, cisplatin 20mg/m<sup>2</sup>/day, 30-minute IV infusion, was administered 30 minutes to 60 minutes before radiotherapy session. If the Cr Cl was <60mL/min or the patient

developed  $\geq$  grade 3 otologic toxicity or  $\geq$  grade 2 neurologic toxicity, cisplatin was stopped totally and the patient was withdrawn from the protocol. If grade 3 or more haematological toxicity developed, both chemotherapy and radiotherapy were discontinued for one week and resumed when ANC returned to  $\geq 1500/\mu\text{L}$  and the platelet count returned to  $\geq 100,000/\mu\text{L}$ . If the blood counts failed to recover in three consecutive weekly measurements, the patient was considered to be off protocol.

#### *Adjuvant chemotherapy:*

Patients received adjuvant chemotherapy 8 weeks following the end of CCRT or cystectomy. It consisted of 4 cycles of gemcitabine  $1250\text{mg}/\text{m}^2$  administered as a 30min IV infusion on days 1 and 8, and cisplatin  $70\text{mg}/\text{m}^2$  given on day 1. Cisplatin was given intravenously, with standard pre and post-treatment hydration. Cisplatin was administered during a 2-hour period of forced hydration. Dexamethazone was also administered intravenously or orally at a dose of  $4\text{mg}/6$  hours until the following morning. Antiemetics including ondansetron or granisetron were administered IV during a period of 30 minutes before starting chemotherapy. Complete blood count with differential, LFTs, and KFTs were performed before each cycle of chemotherapy.

#### *Dose adjustment:*

A new cycle of chemotherapy was postponed until recovery if ANC was  $<1500/\mu\text{L}$  and platelet count was  $<100,000/\mu\text{L}$ , then a 25% dose reduction in subsequent cycles of gemcitabine and cisplatin in case of grade 3-4 neutropenia and/or thrombocytopenia developed. For patients with Cr Cl between 40 to  $60\text{mL}/\text{min}$ , carboplatin targeting an area under the curve of 5 (Calvert formula) was to be substituted for cisplatin. If the Cr Cl was  $<40\text{mL}/\text{min}$  or the patient developed  $\geq$  grade 3 otologic or  $\geq 2$  neurologic toxicity, chemotherapy was stopped totally.

#### *Follow-up:*

Patients underwent cystoscopic re-evaluation beginning 6 weeks after consolidation. Follow-up evaluations included clinical examination, cystoscopy with biopsy of the tumor site, urine cytology, liver function tests, creatinine, electrolytes, chest radiography, and imaging of the abdomen and pelvis. Patients were followed

quarterly for the first year, at 4-month intervals for the second year, and every 6 months for an additional 3-year period or if clinically indicated. Patients treated with CCRT were promptly considered for radical cystectomy for an invasive recurrence. If a positive cytology was documented in a patient with a normal bladder, an evaluation of the upper tracts with selective washings and a prostatic urethral biopsy were recommended.

#### *Morbidity evaluation:*

Radiation-related toxicity was graded according to RTOG/EORTC radiation morbidity scheme [20]. Toxicity due to chemotherapy was assessed according to the National Cancer Institute (NCI) toxicity scale [21].

#### *Survival and statistical analysis:*

The 2-year overall survival (OS) and 2-year progression free survival (PFS) were estimated using the Kaplan-Meier method [22]. Overall survival was estimated from the date of treatment start till death or last follow-up visit. PFS was estimated from the date of treatment start till first evidence of loco/regional and/or distant failure. The  $X^2$  test was used to determine  $p$ -value and was considered significant if it was  $\leq 0.05$ .

## RESULTS

The pre-treatment patients and tumor characteristics of the 40 eligible patients including age, sex, performance status, tumor grade and AJCC staging are detailed in Table (1). Twenty two patients (55%) were  $\geq 60$  years of age, 33 (82.5%) were males and 20 (50%) had ECOG score 0 performance status. Grade III and IV TCC were encountered in 31 patients (77.5%), and 21 patients (52.5%) had T3 tumors. A visibly completed TUR-BT was possible in 24 patients (60%). One patient was lost to follow-up. Eight patients (20%) had a history of antibilharzial treatment.

#### *Protocol completion and response:*

The induction phase of CCRT was accomplished in 38 patients. Two patients did not complete it, one because of disease progression and the other due to development of acute renal failure. Post induction urologic evaluation revealed no evidence of disease (CR) in 24 (60%) patients and residual disease in 14 patients. Consolidation CCRT was completed in 22 of

the 24 patients with CR, and 2 patients refused to continue consolidation CCRT because of poor compliance and tolerance to initial induction CCRT. Eight of the 14 patients with residual disease after induction CCRT underwent cystectomy, 6 of them were found to have foci of squamous metaplasia during the pathological examination of the cystectomy specimen. No patients received postoperative irradiation. Of the remaining 6 patients with residual disease after induction CCRT, 2 patients refused surgery and 4 were found to be medically inoperable. These 10 patients who had disease progression (1 patient), or developed renal failure during radiation (1 patient), refused to continue treatment (2 patients) or surgically inaccessible (6 patients) received off protocol chemotherapy, radiation, chemoradiation, or best supportive care and were considered failure.

Thirty patients were eligible to receive adjuvant gemcitabine/cisplatin chemotherapy according to protocol, 22 patients completed consolidation CCRT and 8 patients underwent cystectomy. Nineteen patients (63%) completed 4 courses of chemotherapy, 9 patients experienced toxicities and received 1-3 cycles and 2 patients refused to receive the adjuvant course.

#### *Morbidity evaluation:*

No treatment related deaths had been recorded. The patients tolerated the induction and consolidation CCRT very well. A total of 8 out of 40 patients (20%) and 3 out of 22 patients (13.7%) experienced at least one severe (grade 3) toxicity during induction and consolidation phase of CCRT, respectively. During the induction phase (Table 2A) grade 3 cystitis and proctitis were recorded in 7.5% and 2.5%, respectively. Hematologically, grade 3 neutropenia occurred in 3 patients (7.5%) while grade 3 thrombocytopenia and anemia were encountered each in one patient. One patient developed acute renal failure. During the consolidation phase, only two of 22 patients developed grade 3 cystitis, 2 patients had grade 3 nausea and vomiting and one patient developed grade 3 neutropenia (Table 2A). As regards the reported late toxicities. 2 patients (5%) had grade 3 cystitis but none required cystectomy for bladder contraction and one patient (2.5%) exhibited partial small intestinal obstruction (RTOG grade 2 toxicity).

The incidence of toxicity during adjuvant chemotherapy was greater. A total of 13 patients out of 28 patients (46%) receiving chemotherapy experienced at least one severe (grade 3 or 4) toxicity. Grade 3-4 neutropenia was recorded in 9 patients (32%) with two cases developing febrile neutropenia that necessitated hospital admission, broad spectrum antibiotics and colony stimulating factor administration. Grade 3-4 thrombocytopenia was observed in 3 patients (11%) necessitating platelet transfusion in one patient, while two patients (7%) developed grade 3 anemia. Eight patients (29%) developed severe nausea and vomiting and one patient (4%) developed grade 3 diarrhea that necessitated hospital admission and fluid replacement. Details of acute toxicities are shown in Table (2B).

#### *Failure patterns:*

Sixteen out of 40 eligible patients (40%) developed loco-regional and/or distant failure (Table 3). Four patients (10%) had local failure only, 10 patients (25%) had locoregional failure, 2 patients (5%) had regional failure (pelvic nodal recurrence) and 10 patients (25%) developed distant metastasis. All the in-bladder failures were of the invasive type. All the patients who developed distant metastasis had an element of regional failure. Originally, 10 patients did not complete the planned CCRT or RC and were considered local failure, 8 of them ultimately developed regional progression during follow-up. Four of the 22 patients who completed the planned chemoradiation course failed during the follow-up period, 2 of them developed local recurrences and were referred for salvage cystectomy and 2 patients had locoregional recurrences. Two of the 8 patients who underwent RC because of incomplete response to induction chemoradiation developed regional recurrences during the follow-up period, one of them had later on lung metastasis. At the end of the follow-up period, 18 patients (45%) retained intact functional urinary bladder.

#### *Survival:*

At the time of analysis, the median follow-up period was 24 months (4-36 months). The 2-year actuarial survival and PFS rates were 67% (95% CI 52.2%-82.7%) and 58% (95% CI 42.3%-74.0%), respectively. Survival curves are shown in Fig. (1). A correlation between the 2 year actuarial survival and the different

clinicopathologic and treatment related factors (age, sex, tumor stage, tumor grade and completion of TUR-BT) revealed that only completeness of TUR-BT was a significant determinant of overall survival (Table 4). The 2 year actuarial survival was 92% for T2 versus 57% for T3-4a (Fig. 2A), however the differences were not statistically significant,  $p=0.154$ . On the other side, the 2-year actuarial survival was 87% for patients who underwent complete resection of the tumor at the time of pretreatment transurethral resection versus 40% for those who underwent only partial resection (Fig. 2B), the difference was statistically significant,  $p=0.008$ .

Table (1): Patients and disease characteristics.

No. of patients	40
Age (years): Mean $\pm$ SD	55.8 $\pm$ 11.2
Sex: Male/Female	33/7
ECOG performance status:	
0	20 (50%)
1	17 (42.5%)
2	3 (7.5%)
Tumor grade:	
GII	9 (22.5%)
GIII	26 (65%)
GVI	5 (12.5%)
Tumor stage (T) according to AJCC staging system:	
T2	12 (30%)
T3	21 (52.5%)
T4a	7 (17.5%)
TUR-BT:	
Complete	24 (60%)
Incomplete	16 (40%)
History of anti-bilharzial treatment	8 (20%)

Table (2-A): Acue toxicity (grade 3) during induction and consolidation chemoradiation.

Toxicity	Induction (40 patients)	Consolidation (22 patients)
Cystitis	3 (7.5%)	2 (9%)
Proctatitis	1 (2.5%)	0
Nausea and vomiting	3 (7.5%)	2 (9%)
Neutropenia	3 (7.5%)	1 (4.5%)
Anemia	1 (2.5%)	0
Thrombocytopenia	1 (2.5%)	0

Table (2-B): Acute toxicity (grade 3 or 4) during adjuvant chemotherapy (28 patients).

Toxicity	Grade 3	Grade 4	Total
Neutropenia	7	2	11 (32%)
Thrombocytopenia	2	1	3 (11%)
Anaemia	2	–	2 (7%)
Nausea/vomiting	7	1	8 (29%)
Diarrhea	1	–	1 (4%)

Table (3): Pattern of treatment failure.

Failure	No. (%)
Local failure only	4 (10%)
Regional failure	2 (5%)
Loco-regional failure	10 (25%)
Distant metastasis:	10 (25%)
Lung	5
Bone	4
Liver	1

Table (4): Survival in relation to prognostic factors.

Category	Number of cases	2-year survival (%)	<i>p</i> -value
Age (years):			
$\leq 60$	23	66.9	0.748
$> 60$	17	67.9	
Sex:			
Males	33	74.5	0.348
Females	7	33.3	
Grade:			
II	9	77.8	0.686
III & IV	31	63.9	
Stage:			
T2	12	91.7	0.154
T3 & 4a	29	56.5	
TUR-BT:			
Complete	24	86.7	0.008
Incomplete	16	40.1	

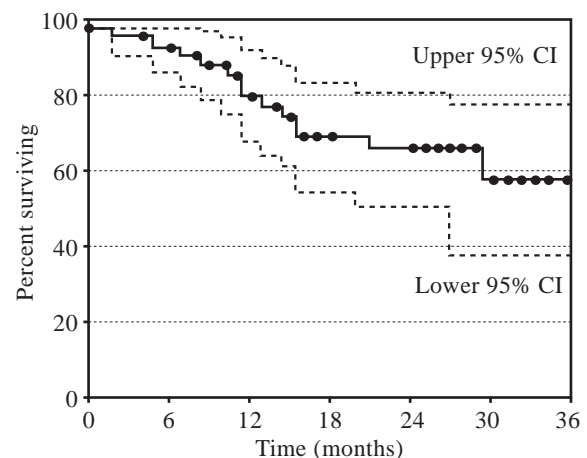


Fig. (1): 2-year actuarial survival.

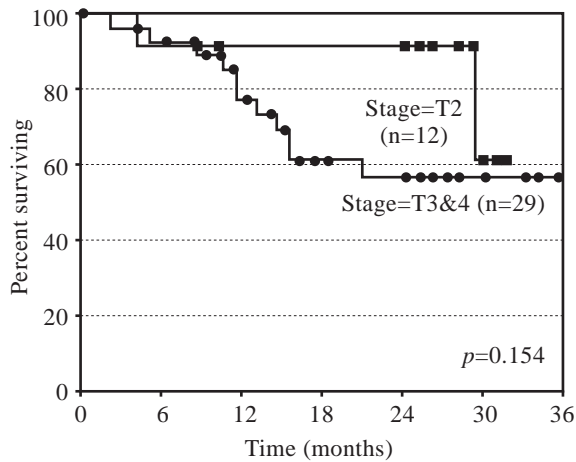


Fig. (2-A): 2-year actuarial survival for T2 Vs T3-4a patients.

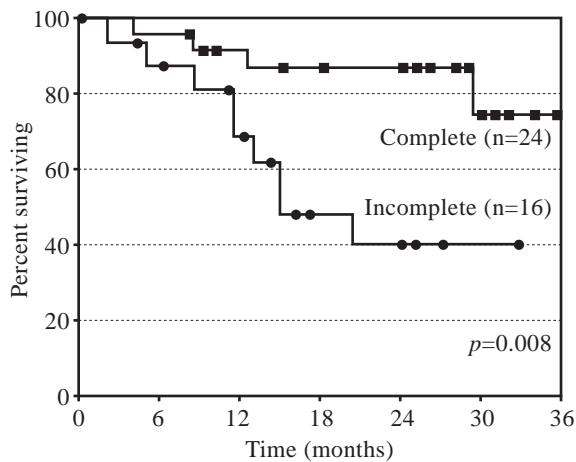


Fig. (2-B): 2-year actuarial survival for complete Vs incomplete TUR-BT.

### DISCUSSION

Trimodality bladder sparing protocol, including TUR-BT, radiation therapy and chemotherapy is an attractive alternative to primary cystectomy in muscle invasive bladder cancer. The CR rate after induction CCRT, in the present study, was achieved in 60% of patients. The CR rates, after induction CCRT, for different trimodality bladder-conserving trials varied between 59% and 74% [9,12,13,23,24]. Hagan et al., investigated the efficacy of concurrent twice daily hyperfractionated radiation and cisplatin followed by three cycles of adjuvant CMV chemotherapy. They reported a CR rate after induction CCRT of 74% [13]. Recently RTOG started a trial (99-06) using paclitaxel and cisplatin concomitant with twice daily irradiation followed by either selective bladder preservation

or RC and 4 cycles of adjuvant chemotherapy with gemcitabine and cisplatin. Preliminary results from this study have been reported in an abstract form, the CR rate after induction therapy was 87% for 47 assessable patients [25]. Weiss et al., treated 112 patients with CCRT using 5 fluorouracil and cisplatin and reported a complete pathological response rate of 88.4% after full course CCRT [26]. However, in the RTOG 97-06 trial [13], it included only patients with stage T2 and T3 while in the current study, 17.5% of our patients had stage T4a. In the Weiss et al., trial, 95% of patients had T1 or T2 muscle invasive tumor. Additionally, clinical understaging at initial evaluation and incomplete regression at time of assessment may limit obtaining high CR rates after CCRT. Ghoneim et al., reported a clinical understaging error in 20.4% of cases compared with postcystectomy pathological staging [27]. Moreover, the kinetics of regression are likely to depend on both the fractionation scheme and the interval to observe response. Several reports have noted additional CRs at cystectomy for failed induction [5,6]. In the present study, we selected the interval assessment for bladder response 2 weeks after induction CCRT to avoid long delay between induction and consolidation CCRT. The split course radiotherapy is of some radiobiologic concern since tumor cell repopulation may occur during interruption. This is contrary to other RTOG trials that wait for 3 weeks before assessment of response to chemoradiation. However, incomplete regression is difficult to measure because not all patients with induction failure proceeded to cystectomy. It is of interest that 6 of 8 patients who underwent surgeries were found to have foci of squamous metaplasia, of which radiosensitivity is questionable, during the pathological examination of the cystectomy specimen.

Grade 3 cystitis, proctitis, nausea and vomiting and neutropenia in the present study, were recorded in 7.5%, 2.5%, 7.5% and 7.5%, respectively, during induction CCRT and in 9%, 0%, 9% and 4.5%, respectively, during consolidation CCRT. These figures compared favourably to the toxicity profile of bladder preserving CCRT protocols [7,12]. The RTOG 95-06 trial evaluated the accelerated hypofractionated (3Gy/fraction) irradiation schemes in combination with concurrent outpatient chemotherapy. In this trial, 21% of patients developed grade

3 or 4 hematological toxicity and 15% had grade 3 bowel toxicity [9]. In RTOG protocol 97-06 [13] that incorporated accelerated radiotherapy but with a reduced dose per fraction (1.5-1.8Gy/fraction) compared with RTOG 95-06, grade 3 and 4 cystitis, proctitis and small bowel toxicity were recorded in 17%, 6% and 4%, respectively, after CCRT. None of our patients required cystectomy for bladder shrinking after radiation. In the largest series from the University of Erlangen, where Rodel et al., treated 415 patients with TUR-BT followed by CCRT (platinum and 5 fluorouracil) [28], 2% of patients required cystectomy for shrinking bladder, 10% reported some degree of incontinence or increased frequencies of micturition, and 1.5% of patients experienced late gastrointestinal toxicity (bowel obstruction) requiring surgical intervention.

The incidence of toxicity during adjuvant chemotherapy was greater. Grade 3-4 neutropenia, thrombocytopenia, anemia, nausea and vomiting were recorded in 32%, 11%, 7% and 29%, respectively. The rate of completion of 4 cycles adjuvant gemcitabine/cisplatin was 63%. In RTOG 97-06, only 40% of patients went to receive a full three cycles of adjuvant CMV chemotherapy and 77% of patients developed Grade 3 or 4 toxicity [13]. Grade 3-4 neutropenia, thrombocytopenia, and nausea and vomiting were recorded in 59%, 14%, and 5%, respectively. On the contrary, in the study of Flechon et al. [29], who tested gemcitabine/cisplatin in the adjuvant setting after cystectomy, 90% of eligible patients received four cycles of chemotherapy. It thus appears that the poor patient tolerance to adjuvant chemotherapy may be limited by the cumulative toxic effects of concurrent CCRT.

The incidence of loco-regional and/or distant failure was recorded in 40% of patients in the present study. Ten percent had only invasive in-bladder persistent or recurrent disease, 25% had locoregional failure and 5% had only regional failure (pelvic nodal recurrence). The in-bladder failure figure is equivalent to that of neoadjuvant trials which ranged from 32% to 40% [12,14,30] but it is inferior to the local failure in RTOG 97-06 that reported only 13% (6/47) in bladder failure [13]. Additionally, the regional failure rate is higher than that reported in the RTOG series that ranged from 11% to 15% [9,13]

and this can be explained by the fact that there is a higher incidence of T4a local tumor in the present study which may be associated with a higher incidence of subclinical nodal disease, in addition to the probable clinical understaging error. Distant metastasis developed in 25% of patients, all of whom had regional nodal recurrences. However, the relatively short follow-up period may mask the proper incidence of distant metastasis as adjuvant chemotherapy may delay rather than lower the appearance of distant metastasis. The incidence of distant metastasis in RTOG trials that utilized conventional radiation concomitant with cisplatin as the sole line of treatment after maximal TUR-BT was 39% to 43% at 5 years [7,12] that was lowered to the 22% to 29% in RTOG 97-06 and Zietman et al. [13,31] trials that utilized adjuvant CMV chemotherapy which reflected the great impact of adding more chemotherapy to the local treatment for improving the distant metastasis rate.

The actuarial 2-year survival and PFS rates, in the present study, were 67% and 58%, respectively, with 45% of patients maintaining their intact functioning bladder. The 5-year OS in different RTOG series of bladder preservation technique was 50%-60% and 5-year OS with intact bladder ranged from 40 to 44% [7,9,12,30]. The results of a large long-term study by Rodel et al., from the University of Erlangen achieved 5-year OS of 50% and bladder preservation in more than 80% of survivors [28]. However, 25% of their patients had high risk T1 disease. Two small series treated patients with concomitant radiotherapy and chemotherapy, cisplatin, 5-fluorouracil in one series and cisplatin or paclitaxel in the other and reported 3-year OS of 69% and 60%, respectively [32,33]. In the RTOG 97-06 trial, the actuarial 3-year OS rate was 61% and 48% of patients who maintained intact bladder [13]. A correlation between the 2-year survival and the different clinicopathologic and treatment related factors revealed that, although smaller tumor volume had a trend for better survival, only pretreatment completeness of TUR-BT was a significant determinant of 2-year survival. The actuarial 2-year survival was 92% for T2 versus 57% for T3-4a, the differences were not statistically significant may be because of the relatively smaller number of patients in each category. On the other side, the actuarial 2-year survival was 87% for patients

who underwent complete resection of the tumor at the time of pretreatment transurethral resection versus 40% for those who achieved only partial resection, the difference was statistically significant. In a series of 190 patients treated with selective bladder preservation, 5-year OS was 62% for T2 and 47% for T3 and T4a, the difference was statistically significant [24]. In a series from the University of Erlangen, 5-year OS was 56% for T2 and 17% for T4, the difference was statistically significant [28]. Additionally, the ability to completely resect visible tumor was a strong predictor of OS in univariate and multivariate analyses [5].

In conclusion, selective bladder preservation protocol is an alternative to radical cystectomy. This approach contributes significantly to the quality of life of patients so treated. Ideal candidates for this treatment are those patients with early stage disease in whom a complete TUR-BT is accomplished. A clear question is raised about the ability of this approach to reduce in-bladder and regional failure. It is important to emphasize on the aggressiveness of TUR-BT and possibility to repeat it when induction is delayed, in addition to trying to minimize the clinical staging errors. Translational researches to detect molecular markers that may better identify a tumor's true malignant potential as well as its response to chemoradiotherapy are strongly needed. Whether this approach may increase survival needs prospective randomized trials with larger number of patients and longer follow-up periods.

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