

**Original
Article**

**MULTIMODALITY TREATMENT FOR MUSCLE INVASIVE TRANSITIONAL CELL
CARCINOMA OF BILHARZIAL BLADDER**

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ABSTRACT

Introduction: To study the possibility of bladder sparing treatment for invasive transitional cell carcinoma (TCC) of bilharzial bladder.

Patients and Methods: Between April 2003 and February 2008, 29 patients with TCC carcinoma of the urinary bladder associated with bilharziasis were treated at Alazhar department of clinical oncology. Multimodality treatment approach has been offered to those patients as they were medically unfit for or refused radical cystectomy. The treatment protocol consisted of maximal Transurethral resection (TUR) followed in 2-4 weeks by concomitant radiotherapy 61 Gy over 6.5 weeks period in 2 phases, with concomitant cisplatin, or carboplatin on days 1 and 21. All patients had weekly clinical assessment during the treatment period to monitor acute toxicity, six to eight weeks after treatment, cystoscopy and biopsy was done to assess the immediate response.

Results: The median follow up period was 25.4 months (range 7.6-50.3); The median progression free survival was 29.5 months (95% CI 25.8-33.3) with 2 and 3-year progression free survival rates of 64.3% and 30.4% respectively. The median overall survival was 34.7 months (95% CI 28.5-40.9); the overall survival rate at 2 years was 87% while the 3-year survival rate was 41.8%. Clinical tumor stage, pathologic grade, hydronephrotic changes and immediate response to treatment have been shown to significantly affect the outcomes in univariate analysis.

Conclusions: Multimodality treatment is a reasonable treatment option for patients with invasive TCC of bilharzial bladder unfit or refuse radical cystectomy, careful patient selection may further improve the results of this treatment approach.

Key Words: Bladder, TCC, bilharzial, multimodality treatment, bladder sparing.

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INTRODUCTION

Bladder cancer is one of the most common cancers among Egyptian males, its relative frequency in recently published studies ranged from 9.4 % to 11.7%^{1,2}. This frequency is significantly higher than a published frequency rate of 4.6% from USA³.

The histopathological profile of bladder cancer in Egypt has changed significantly over the past 26 years, historically, squamous cell carcinoma was the predominant form of bladder cancer in Egypt; transitional cell carcinoma has become the most frequent type⁴ However, Bilharzial cystitis is still diagnosed in at least 55% of cases².

Muscle invasive bladder cancer is a disease associated with low cure rate and several unresolved therapeutic questions still exist⁵. Radical cystectomy is still the standard treatment of choice in Egypt as well as USA and Europe⁶⁻⁸. Over the past 20 years multimodality organ sparing treatment has become the standard of care for many malignancies, including laryngeal cancer, soft tissue sarcoma and others, this has arisen a question about the possibility of replacing primary cystectomy as

a treatment of choice for invasive bladder cancer by an organ sparing approach⁹.

Several studies have reported the value of combined modality therapy, including transurethral resection, radiation therapy and systemic chemotherapy. With these programs; cystectomy has been reserved for patients with incomplete response or local relapse following combined-modality treatment. These studies concluded that combined modality treatment achieved bladder preservation in the majority of patients with survival data comparable to that of primary cystectomy series¹⁰⁻¹².

We are reviewing our experience with multimodality treatment approach in patients with invasive TCC on top of bilharziasis to investigate the possibility of bladder preservation.

PATIENTS AND METHODS

Between April 2003 and February 2008, 29 patients with TCC carcinoma of the urinary bladder associated with bilharziasis were treated at Alhussien university

hospital (departments of clinical oncology and urology); the diagnosis of bilharziasis was made based on histopathologic manifestation of bilharzial cystitis in the TURBT spacemen. Multimodality treatment approach has been offered to those patients as they were medically unfit for or refused radical cystectomy.

Prior to treatment, all patients were subjected to complete staging work up in the form of detailed history and physical examination, plain chest X ray, CT scan of the abdomen and pelvis with contrast and radionuclide bone scan, as well as laboratory assessment in the form of complete blood picture, blood urea and creatinine and liver function tests.

The treatment protocol consisted of maximal TURBT followed in 2-4 weeks by radiotherapy 61 Gy in 33 fractions over 6.5 weeks period in 2 phases, 45 Gy in 25 fraction over 5 weeks were delivered to the bladder and pelvic lymphatics along with concomitant cisplatin 80 mg/m² on days 1 and 21. Carboplatin at an AUC of 5 replaced Cisplatin for elderly patients (≥ 70 years) or patients with impaired renal functions. Phase I radiotherapy was followed by a boost dose of 16 Gy in 8 fractions over 1.5 weeks to the urinary bladder defined by ascending cystogram with 2 cm safety margin in all directions. Treatment planning was done with 2D treatment planning system using three fields technique “anterior and two laterals” throughout the whole treatment course, radiation doses were calculated at the isocenter. Radiation therapy was delivered using a Linear Accelerator machine with 6-MV photon energy. Patients were treated on a comfortably full bladder to minimize inter-fraction variation in bladder position and to keep small bowel out of the radiation field as much as possible.

All patients had weekly clinical assessment during the treatment period to monitor acute toxicity. Six to eight weeks after treatment a thorough clinical assessment was done including cystoscopy and biopsy and CT scan of the abdomen and pelvis to assess the immediate response. Follow up was then carried out with regular visits every 3 months. Cystoscopy and abdomino-pelvic CT scan were done every 6 months.

The Kaplan-Meyer method was used for calculation of survival, univariate analysis of different clinical, pathologic and treatment factors affecting survival was done using the Log Rank test, P value of ≤ 0.05 was considered significant. Multivariate analysis was not done as the sample size was too small to give reliable results.

RESULTS

Twenty nine patients were included, 27 males and two females, all patients were ≥ 40 years old and most of them (79%) were smokers. Disease was staged clinically based

on the TNM staging system (AJCC 1997)¹³. There were no radiologic evidence of nodal disease in all patients and T2 disease was the most commonly encountered stage (66%). Complete TUR was achievable in 14 patients (48%) and sixteen patients (55%) were found to have back pressure changes before treatment. Table (1) summarizes the clinical and pathologic profiles.

Table 1: Clinico-pathologic criteria of 29 patients with invasive TCC of bilharzial bladder.

		No. (%)
Age	Median	63 years
	Range	(40-75)
Gender	Male	27 (93)
	Female	2 (7)
History of smoking	Yes	23 (79)
	No	6 (21)
KPS	90	25 (86)
	80	4 (14)
Presenting symptom	Heamaturia	18 (62)
	Dysuria	11 (38)
Complete TUR	Yes	14 (48)
	No	15 (52)
Grade	II	17 (59)
	III	12 (41)
Stage	T2	19 (66)
	T3	10 (34)
Hydronephrosis	Yes	13 (45)
	No	16 (55)

The median follow up period was 25.4 months (range 7.6-50.3); 12 patients (41%) experienced treatment failure, ten patients had isolated local disease recurrence/progression, while the remaining two patients had local disease progression as well as distant metastasis “bone”. The median progression free survival was 29.5 months (95% CI 25.8-33.3) with 2 and 3-year progression free survival rates of 64.3% and 30.4% respectively. The progression free survival curve is presented in (Fig. 1)

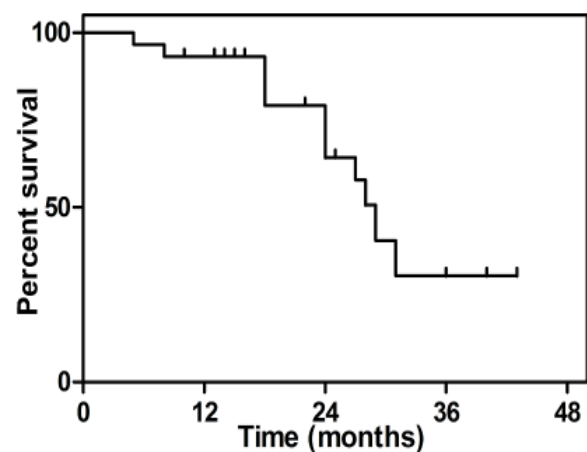


Fig. 1: Progression free survival curve.

Six to eight weeks after the end of chemo-radiotherapy, assessment of the disease response was carried out, fourteen patients (48%) showed pathologically confirmed complete response and 15 patients (52%) showed partial response. Partial responders were kept under close follow up until first sign of disease progression. Among

the complete responders, five patients experienced disease recurrence with a median disease free survival of 31 months, compared to seven of the non complete responders with a median time to disease progression of 24 months. At disease relapse/progression, patients have been referred to the urology department for salvage cystectomy. Only three patients had completed cystectomy at the time of disease relapse, the remaining nine patients were kept under supportive care.

On univariate analysis, T2 disease, complete response on immediate post treatment assessment, lower pathologic grade, absence of hydronephrosis and completeness of TUR were associated with significantly improved progression free survival, tumor stage had the highest effect with a P value of 0.00001. Table (2)

Table 2: Univariate analysis of clinical and pathologic factors affecting progression free survival.

Factor	N/E	Median Survival	95% CI	P value	
Pathologic grade	II	17/4	30.9	28.2-33.7	0.01
	III	12/8	24	19.3-28.6	
Stage	T2	19/6	31	27.6-34.2	0.00001
	T3	10/6	18	8.3-27.6	
Hydronephrosis	Present	13/7	24	18-30	0.03
	Absent	16/5	31	24-38	
Complete TUR	Yes	14/3	NR	---	0.03
	No	15/9	27	18.7-35.4	
Chemotherapeutic agent	Cisplatin	20/8	31	22.5-39	0.3
	Carboplatin	9/4	28	21.7-34	
Immediate response	CR	14/5	31	27.6-34.3	0.02
	PR	15/7	24	15.3-32.6	

-N/R= Not reached

The median overall survival was 34.7 months (95% CI 28.5-40.9); the overall survival rate at 2 years was 87% while the 3-year survival rate was 41.8%. Figure (2) is showing the overall survival curve.

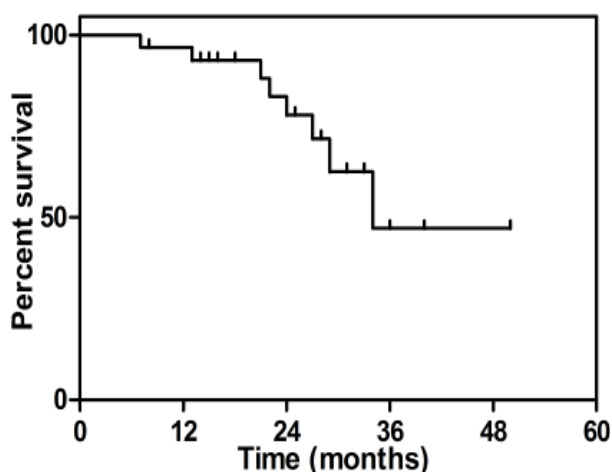


Fig. 2: Overall survival curve.

Univariate analysis of various clinical, pathologic and treatment variables showed that stage of the disease had the most statistically significant effect on overall survival (P= 0.004), while the extent of TUR had no significant effect. Table (3) is summarizing the results of univariate analysis of factors affecting the overall survival.

Table 3: Univariate analysis of clinical and pathologic factors affecting the overall survival.

Factor	N/E	Median Survival	95% CI	P value	
Pathologic grade	II	17/1	NR	0.02	
	III	12/7	29.4	23-35.7	
Stage	T2	19/4	34.7	28.5-41	0.004
	T3	10/4	22	21-23	
Hydronephrosis	Present	13/5	32	---	0.02
	Absent	16/3	NR	---	
Complete TUR	Yes	14/2	NR	---	0.1
	No	15/6	32	24-40	
Chemotherapeutic agent	Cisplatin	20/5	NR	---	0.3
	Carboplatin	9/3	34.7	28.5-41	
Immediate response	CR	14/2	NR	---	0.01
	PR	15/6	32	22.7-41	

-N/R= Not reached

All patients had completed the prescribed treatment; Treatment related toxicity was reported according to the NCI Common Toxicity Criteria (CTC V2.0). Three patients developed grade 3 acute radiation reaction (frequency and/or dysuria) accordingly they were subjected to treatment breaks for a median time of 7 days with supportive treatment. The frequency of grade 3/4 hematologic and non hematologic toxicity as well as acute radiation induced side effects are listed in (table4).

Table 4: Frequency of grade 3/4 acute toxicity.

	Grade 3		Grade 4	
	No.	%	No.	%
Heamatologic	4	13	1	3
Nausea/ vomiting	3	10	0	0
Frequency/Dysuria	3	10	0	0
Diarrhea	1	3	0	0

Late radiation reaction defined as adverse events occurred more than 90 days after radiation therapy was limited to 2 patients (7%) who developed grade 3 bladder toxicity in the form of sever frequency and dysuria.

DISCUSSION

Radical cystectomy is the standard treatment of choice for invasive bladder cancer in Egypt irrespective to its association with bilharziasis¹⁴. The results of radical cystectomy has been reported in a large series of 2,090 patients, the 5-year survival rate was 55% with

2.6% operative mortality⁶ local recurrence and distant metastasis account for 60% and 32% of treatment failure respectively¹⁵. Radical cystectomy is also considered the standard treatment for invasive bladder cancer in USA as well as Europe^{7,8,16,17}. Data from western studies showing slightly better results, in a series of 1054 patients with bladder cancer treated with radical cystectomy, the reported 5- and 10-year overall survival rates were 66 and 43%¹⁸. This series, however, included 213 patients (20%) with non-invasive (T0, Ta, Tis) bladder cancer and excluded 112 patients with inoperable tumor, unradical surgery, or intra-operative detection of distant metastases.

Over the past 10 years, the concept of organ preservation by conservative surgery and combined radio- and chemotherapy has been investigated in several prospective series from single centers and cooperative groups. Results of modern European series have demonstrated five-year survival rates in the range of 50 to 60%, and about three-quarters of the surviving patients maintained their own bladder¹⁹.

In one of the earliest studies on multimodality treatment for invasive bladder cancer, Housset and coworkers from Paris reported the results of a prospective trial of TUR followed by radio-chemotherapy, using 5-fluorouracil and cisplatin and concomitant bifractionated split-course radiation therapy in T2 to T4 disease. Complete responders were considered candidates for bladder preservation, the complete response rate was 74% and the 3-year disease free survival rate was 62%¹⁰.

Rodel et al. from the University of Erlangen-Germany reported on the largest experience with combined modality treatment for bladder preservation, 415 patients with bladder cancer (including 89 patients with high risk T1 and 326 with T2 to T4 disease) were treated with TUR followed by radiation therapy in 126 patients or radio-chemotherapy in 289 patients, 72% of the whole study group have achieved complete response as documented by restaging TUR six weeks after treatment. The 5-year overall survival rate was 50% with a 5-year bladder preservation rate of 42%¹².

The Radiation Therapy Oncology Group (RTOG) has completed 6 successive protocols of multimodality treatment in patients with invasive bladder cancer who were candidates for cystectomy; the primary objective has been to maximize overall cure rates. As 60-80% of patients entered to these protocols achieved complete response based on cystoscopic re-evaluation and tumor site re-biopsy, selective bladder preservation was the secondary objective. The RTOG 89-03 protocol was a phase III study that included 123 patients and was designed to compare concomitant chemoradiotherapy after TUR with or without neo-adjuvant chemotherapy. The complete response rate was 59%, the 5-year overall survival rate was 49% and the 5-year bladder preservation

rate was 38% with no statistically significant effect from the addition of neo-adjuvant chemotherapy²⁰.

The current study showed a complete response rate of 51%, 3-year overall survival of 41.8% and 3-year progression free survival (which correlate to bladder preservation rate at 3-year) of 30.4%. These results are obviously inferior to the reported western studies. This may be due to the patient's characteristics as the present study included many patients with adverse prognostic criteria, 42% had disease with high pathologic grade, and 43% had obstructive uropathy.

In the current study, early tumor stage, low pathologic grade, absence of obstructive uropathy and complete response at the immediate post treatment assessment were found to be associated with a statistically significant higher overall survival rates on univariate analysis. The prognostic value of clinical tumor stage was found to be one of the most important prognostic factors for patients with invasive bladder cancer treated either by radical cystectomy²¹ or conservative approaches^{12,22,23}. Pathologic grade and Obstructive uropathy were also found by others to have a prognostic impact on survival in patients with invasive bladder cancer²⁴.

Immediate complete response to chemoradiotherapy is a direct indicator of the tumor sensitivity and it has served as the basis for selection for bladder preservation in the RTOG trials on trimodality treatment approach²⁰ its prognostic significance on survival has been confirmed by others⁵.

The extent of TUR has been considered by some authors as prognostic factor²⁵, complete TUR was associated with statistically significant improvement of overall survival at 5 and 10-years as compared to incomplete TUR¹². In the present study there was no statistically significant effect of the extent of TUR on overall survival, this finding is in agreement with Matos et al²⁴, who suggested that the controversy about the prognostic significance of extent of TUR is due to the inconsistent evaluation of the completeness of TUR, as additional biopsy samples should be taken from the resection margins as well as tumor bed at the time of TUR to reliably assess its completeness which was not for all patients in that study nor in our patients.

Cisplatin is the most active chemotherapeutic agent against cancer bladder; it is also characterized by gastrointestinal, renal, neurologic and otologic toxicity and requires the intravenous administration of large amounts of fluid, which can cause a fluid overload that is particularly detrimental in elderly patients. Because of these side effects, cisplatin might be replaced by carboplatin, which has a better toxicity²⁶.

Studies of chemotherapy for locally advanced and metastatic bladder cancer reported lower response rates

with the use of carboplatin based chemotherapy as compared to cisplatin^{26, 27}. In the present study there was no statistically significant difference in either progression free or overall survival between patients treated with cisplatin use compared to carboplatin this may be attributed to small sample size, only 9 patients received carboplatin.

On the basis of the current study we can conclude that multimodality treatment was tolerated with acceptable toxicity profile and more than 30% of the patients were alive with functioning bladder at 3-year despite inclusion of patients with adverse prognostic factors, careful patients selection based on the prognostic factors identified in the current study can result in improved rates of bladder preservation and overall survival in patients with invasive TCC of the bladder regardless its association with bilharziasis. Prospective randomized studies would be needed to further explore the relative merits of this treatment approach.

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