CAIRO UNIVERSITY
FACULTY OF MEDICINE

NEMROCK

Original Article

Chemoradiotherapy For Operable Transitional Cell Carcinoma Of The Urinary Bladder: A Bladder Sparing Technique

Ali Abd-Elrahman *, Alaa Abd-Elrhman Abd-Elhafez **.

*department Of Clinical Oncology,** Department Of Urology, South Valley University, Egypt.

Abstract

Background: Bladder cancer constitutes 30.3% of all cancer cases. Radical cystectomy is the standard treatment for invasive bladder cancer. A combination of transurethral resection, and concomitant radio-chemotherapy (cisplatin& 5-FU) produced the most promising results as bladder sparing protocols for patients with invasive bladder cancer. Completeness of TUR, clinical stage and tumor grade, were all significant prognostic factors. We performed a phase II study to evaluate the safety and tolerability of concomitant radio-chemotherapy after TUR, in patients with stage II & III muscle invasive transitional cell carcinoma of urinary bladder and to evaluate the complete response rate, disease free survival and overall survival after a minimum follow up of one year.

Patients and methods: Thirty patients with operable muscle invasive transitional cell carcinoma of the bladder were treated by transurethral resection followed 3 to 4 weeks later by radiochemotherapy *(Phase1)*:.external beam irradiation, (twice daily treatment), 1.6 Gy was given to the pelvis in the first treatment followed by an interfraction period of at least 4-6 hours, then the second treatment, 1.5 Gy was given to the whole bladder, this treatment was given in days 1- 5 & 8- 12 & 15, 16 17. 5-fluorouracil (400 mg/m2) was administered as a 24- hour infusion on days 1, 2, 3 and 15, 16, 17. Cisplatin (15 mg/m2) was infused over 60- minutes on days 1, 2, 3, 8, 9, 10, 15, 16, 17. *Phase II* (weeks 8, 9): radiotherapy was given twice daily for 8 days, day 1, 2, 3, 4, 5, 8, 9, 10 with a minimum 4 hours interval. 1.5 Gy was delivered to the pelvic field, the radiation dose given during phase II was 24 Gy. Total dose of radiation after phase I and phase II treatment delivered to the bladder would be 64.3 Gy. 5- flourouracil (400 mg/m2) was given on days 1, 2, 3, 8, 9, 10. Cisplatin (15 mg/m2) was given on days 1, 2, 8, 9

Results: All patients underwent transurethral resection, (TUR was complete in 8 patients and incomplete in 22 patients) followed by radio-chemotherapy as an initial treatment. Most of patients were T2b &T3a, Tumor grade II was found in 18 patients (60%) and 12 patients (40%) were in GIII. After end of phase 1treatment, 15 patients (50%) had complete response, 7 patients had partial response (23.3%), 7 patients had stationary response (23.3%) and one patient had a disease progression (3.3%). Completeness of transurethral resection and early tumor stage were the most significant factors (p- values: 0.012 and 0.021 respectively). No life threatening acute toxicity was noticed due to combined radio-chemotherapy. One patient experienced G IV increased creatinine level as a late squeal. At the end of treatment, 15 patients were free of disease and with preserved bladder and 15 patients did not have CR, of whom, 14 patients underwent salvage cystectomy (one patient refused cystectomy). At the end of follow up, number of patients free of disease was 23 patients (76.6%). Overall survival for the preserved bladder patients at the end of follow up (30 months) was 92% and for the salvage cystectomy patients 84%, (P-0.63).

Conclusions: The strategy for bladder preservations used in our study is capable of achieving complete response in patients with operable invasive transitional cell carcinoma. The high response rate was achieved in patients with complete TUR, early stage, no obstructive uropathy, but the results were significant with the first 2 criteria only. This can help to ideally select cases for bladder preservation. Patients who were not completely responding and who experienced local invasive

recurrence after complete response, can be saved by salvage cystectomy. Recurrence free survival rate at the end of follow up was 70%, and overall survival was 84%, these results are comparable to other studies performed for bladder preservation.
Key words: *Bladder sparing, TUR, chemoradiotherapy*

INTRODUCTION:

Bladder cancer constitutes 30.3% of all cancer cases treated at Egyptian National Cancer Institute (1). Radical cystectomy is the standard treatment for invasive bladder cancer irrespective of its association with schistosomiasis. Different reports showed that tumor stage, grade of differentiation and nodal status are independent prognostic factors after adjusting for all relevant clinicopathological characteristics. In Egyptian reports, local recurrences account for 60% of treatment failure after radical cystectomy alone, while distant metastasis at 5 years has been estimated to be 23% (2). Alternatives to radical cystectomy include, operations providing continent urinary diversions, combined modality approaches with transurethral resection or partial cystectomy in conjunction with chemotherapy and/or radiotherapy. Cumulative results of studies incorporating two or more modalities showed a trend toward higher response rates (3) .An Australian / United Kingdom trial of 288 patients with T2- T4, transitional cell carcinoma randomized to receive cisplatin accompanied by radiotherapy or radiotherapy alone with salvage surgery for non responders demonstrated no difference between the two arms with respect to survival or organ preservation (4). Many studies of radiotherapy and chemotherapy ± conservative surgery have been conducted. Rates of bladder preservation at 5 years ranged from 18% to 44% and 5 years survival, irrespective of local control, was equivalent to that seen with historical cystectomy series. Synergistic bladder and bowel toxicities were not observed, and most patients completed the planned therapy without dose attenuation. Reversible nephrotoxicity and myelosuppression were the main toxicities encountered (5). The development of new treatment techniques, including concomitant chemotherapy and radiotherapy appears to achieve higher response rates in advanced bladder cancer. Previous studies have suggested that continuous infusion chemotherapy and concomitant radiotherapy act synergistically to increase tumor cell destruction. With the combination of 5- FU and radiotherapy, local control rate of transitional cell carcinoma was 70% with a 5 year survival rate of 36% to 62% .Concomitant cisplatin and radiotherapy improved the control of locally advanced bladder cancers with no effect on distant metastasis (6). A combination of transurethral resection, and concomitant radio-chemotherapy (cisplatin& 5-FU) produced the most promising results in bladder sparing protocols for patients with invasive bladder cancer. Completeness of TUR, clinical stage and tumor grade, were all significant prognostic factors, it was obvious that smaller tumors did better than bigger tumors and also that patients with complete resection fared better than with incomplete resection (7).

The aim of the work is to evaluate the safety and tolerability of concomitant radio-chemotherapy after TUR, in patients with stage II & III muscle invasive transitional cell carcinoma of urinary bladder and assess the complete response rate, disease free survival and overall survival.

Patients and methods

This study was performed in Clinical Oncology Department, Faculty of Medicine, South Valley University, during the period from September 2002 to April 2005. Thirty patients with operable muscle invasive transitional cell carcinoma of the bladder were included in this study and were treated by transurethral resection followed by radiochemotherapy. Eligibility criteria

- Age: 18- 65 years Disease characteristics
- Performance status: 0-2 (8).
- Histologically confirmed transitional cell carcinoma of the bladder.
- T2- T4a, No(no evidence of nodal disease), Mo(no evidence of distant metastases). resectable disease, prostatic urethral involvement with transitional cell carcinoma if completely resected, no stromal invasion.
- Hemoglobin ? 10 g/dl & WBC count ? 3000/ mm3 (neutrophil count ? than 1000/ mm3) & platelet count ? 100,000/mm3, bilirubin < 1.5 mg/dl & liver enzymes within normal values, creatinine < 1.5 mg/dl.
- No prior systemic chemotherapy or pelvic radiotherapy and no concurrent drugs that have potential nephrotoxicity.

Pretreatment evaluation: Baseline investigations before treatment included clinical history, physical examination, chest x-ray, bone scan, abdominal and pelvic CT scans, complete blood count, alkaline phosphatase, SGOT, , bilirubin, blood urea, serum creatinine, urinalysis, 24 hour (or calculated) creatinine clearance, pregnancy test for female patients of childbearing potential, 72 hours prior to study entry, bimanual examination under anesthesia, cystoscopic evaluation and transurethral resection for the bladder tumor, Four quadrant bladder and prostatic urethra mucosal biopsies were taken.

Phase I of radiochemotherapy (weeks 1- 3) started within 3 to 4 weeks after transurethral resection. External beam irradiation, (twice daily treatment), was given on days 1- 5 & 8- 12 & 15, 16, 17. 1.6 Gy was given to the pelvis in the first treatment followed by an interfraction period of at least 4-6 hours, then, the second treatment, 1.5 Gy was given to the whole bladder. Target volumes: Pelvic field included the entire bladder, total bladder tumor volume, prostate, prostatic urethra, and regional lymph nodes. Bladder field included the whole bladder, defined by, the cystogram and the bladder wall thickness calculated from the CT scan. A four field technique with the patient supine was used. These fields were designed by using SLS SIMULATOR MEDIO 50 CPH PHILIPS, while the patient was having a 40 to 50 ml air contrast cystogram with contrast material in the rectum. Linear accelerator SL75.5 PHILIPS 6 MV was used in treating the patients (figs 1-4). Dose of radiotherapy and isodose distribution were calculated by using the MULTIDATA computer planning system. The isodose distribution that covered the target structures should be minimum 95%, and maximum 107%. Total doses of radiotherapy delivered to the patients after phase I treatment were: 2080 cGy to the whole pelvis and 1950 cGy to the whole bladder. Chemotherapy: 5-fluorouracil and cisplatin combined with radiotherapy began 3- 4 weeks following the transurethral resection. On days of chemotherapy administration, patients were instructed to increase their fluid intake over the 12 hours prior to chemotherapy. I.V. hydration with neutral saline at a rate of 500 cc /hour was given before cisplatin injection. 5- fluorouracil (400 mg/m2) was administered as a 24- hour infusion on days 1, 2, 3 and 15, 16, 17.Cisplatin (15 mg/m2) was given as a 60- minutes infusion on days 1, 2, 3, 8, 9, 10, 15, 16, 17.Post cisplatin i.v hydration should consist of NS of 500 cc over one hour. On days when both chemotherapy and two fractions of radiation therapy were given, the first radiation fraction was given before chemotherapy and the second fraction after chemotherapy, while maintaining the minimum four hour interfraction interval. Anti-emetic regimens included ondansetron or granisetron, metoclopramide and dexamethasone. Phase II of radiochemotherapy started on weeks 8, 9. Radiotherapy was given twice daily for 8 days, day 1, 2, 3, 4, 5, 8, 9, 10 with a minimum 4 hours interval. 1.5 Gy was delivered to the pelvic field including the bladder, the radiation dose given during phase II would be 24 Gy. Total dose of radiation after phase I and phase II treatment delivered to the bladder would be 64.30 Gy and to the pelvis 44.80 Gy. Chemotherapy given during phase II included, 5- fluorouracil (400 mg/m2) was given on days 1, 2, 3, 8, 9, 10. Cisplatin (15 mg/m2) was given on days 1, 2, 8, 9. The maximum radiation dose allowed to the posterior wall of the rectum should not exceed 55 Gy and to the femoral heads should be 45 Gy. We utilized the Common Toxicity Criteria (CTC) for grading of chemotherapy and acute radiation toxicity (9). Patients were evaluated in week 7 following the start of phase I radiochemotherapy (3 weeks after end of phase one). Evaluation included bimanual examination, cystoscopy, tumor site transurethral biopsy, and CT scan. Patients with complete response or partial response (equal or more than 50% decrease tumor size), would receive phase II radiochemotherapy in weeks 8, 9. Patients with stationary disease or progressive, but still operable disease, were sent for salvage radical cystectomy. Patients who achieved complete pathologic response after phase I treatment were evaluated by cystoscopy in week 17 after completion of phase II treatment, and thereafter every 3 months. Patients who achieved partial response after phase I treatment were evaluated by cystoscopy within 3- 4 weeks after ending phase II treatment. In case of complete response, the patient would be regularly followed up. Patients who failed to achieve complete response but still having an operable disease were referred for salvage cystectomy.

Statistical analysis:

Major endpoints of the study were locoregional control, disease free survival , one year overall survival ,response and toxicity. The statistical analysis of patients survival and disease free survival were based on a comparison of Kaplan-Meier curves by the log rant test. Survival was estimated from the date of first treatment day to

death or last follow-up visit. Disease free survival was estimated from the date of first treatment day to first evidence of disease progression. Fisher exact test was used for the additional analysis of categorical and continuous variables. P value < 0.05 was considered significant

Results:

In this study, 30 patients with operable transitional cell carcinoma of the bladder underwent maximum transurethral resection followed by radio-chemotherapy as an initial treatment.

Patients' characteristics

As shown in table (1): age of patients ranged from 35-72 y with median 56 years. Twenty four patients were male (80%) and 6 patients were female (20%). Performance status ranged from 0- 2, 22 patients were scale 1 (73.3%), 5 patients scale 2 (16.6%) and 3 patients were scale 0 (10%). All patients underwent transurethral resection, complete TUR in 8 patients and incomplete TUR in 22 patients (26.6%, 73.3% respectively). 6 patients presented with obstructive uropathy (20%).

Tumor characteristics

As shown in table (2): most of patients were T2b &T3a, distributed as follows, 2 patients in stage T2a (6.6%), 9 patients in stage T2b (30%), 11 patients in stage T3a (36.6%), 7 patients in stage T3b 23.3 % and one patient in stage T4a (3.3%). Tumor grade II was found in 18 patients (60%) and 12 patients were in GIII (40%).Pathology associated with bilharziasis was observed in 13 patients (43.3%).

Response

Initial response after phase I of treatment: Thirteen patients had complete response (43.3%), 9 patients had partial response (30%) with an overall response rate 73.3%, Seven patients had stationary response and one patient had disease progression (3.3%) (table3). Eight patients (26.6%) underwent salvage cystectomy. Final response after phase II of treatment: After end of treatment, 15 patients (50%) had complete response, 7 patients had partial response (23.3%), 7 patients had stationary response (23.3%) and one patient had a disease progression (3.3%). 14 patients (who were not in complete response) underwent salvage cystectomy; one patient refused cystectomy and received other treatment (table 4). Figs (5&6) show pre and post treatment CT findings. Predictive clinical and pathologic factors influencing the response are listed in the table 5. We found that completeness of transurethral resection (p- value: 0.012), and early tumor stage (p- value: 0.021) the most significant factors. Table 6 shows that, no life threatening acute toxicity was noticed due to combined radio-chemotherapy. Anemia GI occurred in 3 patients (10%), GII in 5 patients (16.6%), and those patients were treated by Iron, no patient received blood transfusion. Leucopenia GI occurred in 6 patients (20%), GII in 2 patients (6.6%), recovery occurred without treatment, and GIII occurred in one patient (3.3%) when prophylactic antibiotics were given till recovery. Thrombocytopenia GI occurred in one patient (3.3%), GII in one patient (3.3%). Gastrointestinal toxicity was noticed in many patients but no life threatening, GIII, or IV toxicities were detected. GIII bladder toxicity was noticed in 3 patients, and the rest had GI & II toxicity, those patients were managed by symptomatic treatment. Ten patients experienced increased creatinine level (8 patients were GI, and 2 patients were GII, and improved by I.V hydration. Seven patients had (GI) radiation dermatitis. The percentage of patients sustaining chronic sequelae noticed during the follow up period of this study is listed in the (table 7). One patient experienced G IV increased creatinine level (associated with impaired renal parenchyma) and referred for dialysis, and one patient had GI and was kept under follow up with no further deterioration. Two patients (13.3%) had GI dysuria, and 5 patients (33.3%) GII. Eight out of 15 bladder preserved patients (53.3%) had GI frequency and two patients (13.3%) had GII, and were treated with antispasmodic. Five patients experienced proctitis G1, and one patient (6.6%) had GII. Disease free survival: Follow up period ranged from 12 to 30 months with median 17 months. After the end of treatment, 15 patients were free of disease and with preserved bladder and 15 patients did not have CR, 14 patients underwent salvage cystectomy (one patient refused cystectomy). During the period of follow up, 4 patients with preserved bladder showed disease recurrence and 2 patients salvaged by cystectomy had disease recurrence. The actuarial disease free survival curve for complete and non complete responders at median follow up (17 months) was 70% for the preserved bladder patients and 75% for the salvage cystectomy ones (fig 6). Pattern of relapse in the whole group of patients: During the follow up of the complete responding patients (15 patients), 4

patients had a disease recurrence (table 8), one patient had superficial recurrence and treated by transurethral resection and followed by BCG, 2 patients had invasive recurrence and underwent salvage cystectomy, and one had distant metastasis. Two patients out of 14 treated by salvage cystectomy relapsed, one locally, and the other had distant metastasis. At the end of follow up, number of patients free of disease was 23 patients (76.6%). Table (9) shows Correlation between the disease free survival of the preserved bladder patients and certain prognostic factors. Grade of the tumor was found to be significant (p-value 0.007). DFS of T2 patients at 17 months was 80% and T3 patients was 53% (p- value 0.05) (fig 10). Table (10) shows that tumor grade was the only significant factor affecting the disease free survival of the whole series (p- value 0.01). Over all survival: Fig. (11) shows that over all survival for the whole series was 92% and 84% for the preserved bladder patients at the end of follow up (30 months).

DISCUSSION:

The optimal treatment for invasive bladder cancer has been radical cystectomy; sophisticated techniques for urinary diversion have been developed to improve patients' quality of life. However, even neobladder cannot substitute for the patient's original bladder. Several groups have reported the value of combined- modality therapy, including TUR, radiotherapy, and systemic chemotherapy. Cystectomy has been reserved for patients with incomplete response or local relapse after combined- modality treatment (10). In our study, 30 patients with operable invasive TCC of the urinary bladder underwent trimodality therapy, including TUR and concomitant radio-chemotherapy, aiming to eradicate the disease and preserve their bladders. The median age for these patients was 56 years, comparable with those reported in the Egyptian series, (11-14), and lower than the western series, (10,15,16), who reported median age 67 & 66 & 67.5 (respectively). Male to female ratio in our study was 4: 1, similar to what reported by Nazli, et al; 2001 and others (10, 15, 14), who found male to female ratio, 5:1 & 4:1 & 3:1 & 5:1, respectively. In the present series, the patients had transitional cell carcinoma; most of them had T3 (60%). Sauer, et al; 1998, reported that, 73% had T2 and 9% had T3 & Arias, et al; 2000, found 32% cases with T3, while R?del, et al; 2002, found T3 in 7% of their cases. Abdel-Hameed, 2004, found T3 in 52% of his cases, and sakr, 2003, who reported on 46.6% patients having T3. In our study, patients with grade II were 60%, and patients with grade III were 40%, these results matched with the other series (14). On the other hand Zaghloul, et al; 2003(17) reported that patients with GI were 1.1%, patients with GII were 55.3%, and patients with GIII were 42.4%. In Western series, Rodel, et al; 2002 found the patients with G II were 47.5%, and patients with G III were 52.5%. We found in our study, that 43.3% of tumours had associated bilharziasis, Abdel-Hameed, 2004, reported that 64% of patients were associated with bilharziasis, Sakr, 2003, Reported that, bilharzial ova were documented in 40% of the patients (70% of patients had history of bilharziasis). Multimodality treatment was used in the form of TUR, followed by radio-chemotherapy, TUR was complete in 26.6% of patients and incomplete in 73.3%, these results were similar to Sakr, 2003, who reported 30% of patients had complete TUR, Cervek, et al; 1998(18), and Matos, et al; 2000(19), who reported complete TUR in 26% of patients. Abdel-Hameed, 2004, reported complete TUR in 36% of patients. Other studies reported higher percentage of complete TUR (5, 10), where TUR was complete in 46% & 49%, respectively. Chemotherapy (5-FU & cisplatin), concomitant with twice daily fractionated radiotherapy (accelerated hyperfractionation) was used in our series. After initial treatment (phase I), the total responders were 73.3% of patients, which conforms to results reported by reported by Abdel-Hameed, 2004 (76%). After the end of treatment, complete response in the present study was found in 50% of patients, partial response was found in 23.3% of patients, the total response was 73.3%, these results were observed by Tester, et al; 1996(20), who used 2 cycles of CMV followed by concomitant radiotherapy and cisplatin, and reported 53% CR rate. An Italian study (21), in which patients received 2 cycles of CMV, followed by radiotherapy and concurrent cisplatin, found 50% complete response rate after induction treatment. Given, et al; 1995(22), treated their patients by TUR followed by 2-3 cycles of chemotherapy then followed by radiotherapy, reported 53% complete response rate, the same results were reported by Kaufman, et al; 1993, (23)who treated 53 patients by TUR followed by radiotherapy and concurrent cisplatin. Higher complete response rates than ours were reported by R?del, et al; 2002, who used concurrent radiotherapy and 5-FU & cisplatin, (the complete response rate was 72%). Zietman,

et al; 1997 (24), used bifractionated radiotherapy together with cisplatin and 5-FU for potential bladder preservation and reported 77% complete response rate. This difference between our results and those mentioned above may be attributed to advanced tumors, and presence of bilharziasis and obstructive uropathy in a percentage of our patients, which was not found in mentioned trials. The lowest result achieved by sakr, 2003, who reported 37% complete response rate, may be attributed to the different clinico-pathological features (mixed tumor), also he used sequential chemotherapy and radiotherapy. In the present study, we investigated certain prognostic factors and their association with the response, (age & sex & TUR & association of bilharzias & tumor stage & grade & presence of obstructive uropathy). We found that completeness of TUR and early stage of the tumor had the strongest impact on the response, these results are similar to R?del, et al, 2002, and Sauer, et al, 1998, who reported that disease stage, grade and the extent of TUR were the most significant prognostic factors affecting the response. In Abdel-Hameed, 2004, early stage, completeness of TUR, presence of ureteric obstructive uropathy and bilharziasis were found to be significant prognostic factors. In this study, patients experienced acute toxicity in the form of hematological, GIT, bladder toxicity. No life threatening toxicity was noticed due to concomitant radio-chemotherapy.The recurrence rate was 20% during the period of 30 months of follow up. These results were near to the results reported by Shipley, et al; 1999(25), R?del, et al; 2002 and Abdel-Hameed, 2004, who found that, the recurrence rates at the same period of follow up were 14, 20.9 and 16%, respectively. Recurrence free survival for the preserved bladder patients at the end follow up (30 months) was 70% and 75% for those salvaged by cystectomy, (P-0.74). Recurrence free survival for the whole group of patients was 70%. Similar results were reported by R?del, et al; 2002, who found that recurrence free survival for the preserved bladder patients (at the same period) of follow up was 75%. Housset, et al, 1993, Peyromaure, et al; 2004, (26) reported the recurrence free survival at 3 years were 62%, 63% respectively. Higher results were reported by Arias, et al; 2000, who found 85% recurrence free survival at 3 years. Tumor stage and grade were the most important prognostic factors affecting the recurrence free survival in the current study. R?del, et al; 2002, found that, early T- stage and completeness of TUR were the most important factors affecting recurrence free survival. Brunner, 2001 ((27), reported that completeness of TUR, stage and grade were the most significant factors. However, Zapatero, et al; 1997 (28), found the initial response was the most important risk factor associated with survival. Abdel-Hameed, 2004, reported that the stage of the tumor was the only significant factor affecting recurrence free survival.At the end of follow up, 80% of complete responders preserved their bladders, similar to Sauer, et al; 1998, R?del, et al; 2002 and Abdel-Hameed, 2004, who reported the rate of bladder preservation at the same period of follow up were 79%, 79% and 81.5%, respectively. Higher results were reported by Arias, et al; 2000 and Kaufman, et al; 1993, who found the rate of bladder preservation as 90% and 89% (at 3 years) respectively.In this study overall survival for preserved bladder patients at the end of follow up was 92% and for non complete responders who underwent salvage cystectomy was 84% (P-0.63), respectively. The over all survival for the whole group of patients after end of follow up was 84%, this is similar to Zietman, et al; 1997, Kaufman, et al; 2000 and Arias, et al; 2000, who reported that overall survival at the same period of follow up were 83%, 83% and 82%, respectively. No randomized trials have been performed yet, to compare the combined modality therapy with primary radical cystectomy.

Conclusions

The strategy for bladder preservations used in our study is capable of achieving complete response in patients with operable invasive transitional cell carcinoma, in spite of small number of patients, more advanced disease and short period of follow up. The high response rate was achieved in patients with complete TUR, early stage, no obstructive uropathy and no bilharziasis, but the results were significant with the first 2 criteria only. This can help to ideally select cases for bladder preservation. Patients who were not completely responding and who experienced local invasive recurrence after complete response, can be saved by salvage cystectomy. Recurrence free survival rate at the end of follow up was 70%, and overall survival was 84%; these results are comparable to other studies performed for bladder preservation.

Recommendations

More studies to confirm the results of this trial are needed with bigger number of patients and with

better selection of cases according to the proved prognostic factors. Evaluating different strategies for combined modality therapy, including the use of altered fractionation compared with conventional fractionation and uses of different types of chemotherapy such as gemcitabine and taxanes, to improve safety and increase efficacy is recommended.

Table (1): Patients characteristics

Characteristics	No. of patients	%
***Age**		
(median=56Ys)		
-<median	13	43.3
->median	17	56.6
***Sex**		
-male	24	80
-female	6	20
***Performancestatus**		
-0	3	10
-1	22	73.3
-2	5	16.6
***Transurethral resection.**		
-complete	8	26.6
-incomplete	22	73.3
***Obstructive uropathy.**		
-yes	6	20
-no	24	80

Table (2): Tumour characteristics

characteristics	No. of patients	%
***stage**		
-T2a	2	6.6
-T2b	9	30
-T3a	11	36.6
-T3b	7	23.3
T4a	1	3.3
***grade**		
-II	18	60
-III	12	40
***Bilharzial type**		
-yes	13	43.3
-no	17	56.6

Table (3): Initial response after phase I of treatment

Complete response		Partial response		Stationary response		progression		Salvage cystectomy	
No	%	No	%	No	%	No	%	No	%
13	43.3	9	30	7	23.3	1	3.3	8	26.6

Table (4): Final response after phase II of treatment

Complete response		Partial response		Stationary response		progression		Salvage cystectomy	
No	%	No	%	No	%	No	%	No	%
15	50	7	23.3	7	23.3	1	3.3	14	46.6

Table 5:Correlation between the response and certain prognostic factors

Factor	No of patients		All responders		Complete responders		(stationary and progression)		p-value
	No	%	No.	%	No.	%	No.	%	
Age									
-<med.	13	43.3	8	61.5	5	38.4	5	38.4	0.4
->med.	17	56.6	14	82.3	10	58.8	3	17.6	8
Sex									
-male	24	80	17	70.8	11	45.8	7	29	0.8
-female	6	20	5	83.3	4	66.6	1	16.6	1
TUR									
complete	8	26.6	8	100	8	100	0	0	0.0
incomplete	22	73.3	14	63.6	7	31.8	8	36.3	12
Bilharzial									
-yes	13	43.3	7	53.8	5	38.4	6	46	0.1
-no	17	56.6	15	88.2	10	58.8	2	11.7	8
Stage									
-T2	11	36.6	11	100	10	90.9	0	0	0.0
-T3	18	60	10	55.5	5	27.7	8	44.4	21
-T4a	1	3.3	1	100	0	0	0	0	
Grade									
-II	18	60	15	83.3	9	50	3	16.6	0.2
-III	12	40	7	58.3	6	50	5	41.6	3
Obstructive uropathy									
-yes	6	20	3	50	2	33.3	3	50	0.1
-no	24	80	19	79	13	54.1	5	20.8	8

Table (6) Acute toxicity

Acute toxicity	I		II		III	
	No.	%	No.	%	No.	%
*Anemia	3	10	5	16.6	0	0
*leucopenia	6	20	2	6.6	1	3.3
*Thrombocytopenia	1	3.3	1	3.3	0	0
*Diarrhea	12	40	2	6.6	0	0
*Nausea	20	66.6	5	16.6	0	0
*Vomiting	13	43.3	4	13.3	0	0
*Anorexia	15	50	5	16.6	0	0
*Colitis	10	33.3	5	16.6	0	0
*Poctitis	18	60	3	10	0	0
*Dysuria	10	33.3	18	60	2	6.6
*Cystitis	9	30	5	16.6	0	0
*Frequency/Urgency	12	12	6	20	1	3.3
*Increase creatinine level.	8	26.6	2	6.6	0	0
*Increase bilirubin level.	0	0	0	0	0	0
*Increase liver enzymes.	0	0	0	0	0	0
*Radiation dermatitis	7	23.3	0	0	0	0

Table (7) late toxicity

Late toxicity	I		II		III		IV	
	No.	%	No.	%	No.	%	No.	%
Dysuria (in bladder preserved patients)	2/15	13.3	5/15	33.3	0	0	0	0
Frequency (in bladder preserved patient)	8/15	53.3	2/15	13.3	0	0	0	0
Proctitis	5/30	16.6	1/30	6.6	0	0	0	0
Increase creatinine level	2/30	6.6	0	0	0	0	1/30	3.3

Table (8): pattern of relapse in the preserved bladder patients

Superficial recurrence		Invasive recurrence		Distant metastasis		No. of patients with intact bladder	
No	%	No	%	No	%	No	%
1/15	6.6	2/15	13.3	1/15	6.6	12/15	80

Table (9): Correlation between the disease free survival of the preserved bladder patients and certain prognostic factors.

Factor	Patients in C.R		Patients with disease recurrence		Disease free survival %	p-value
	No	%	No.	%		
Age						
-<median	5	33.3	2	40	60	0.30
->median	10	66.7	2	20	76	
Sex						
-male	11	73.3	2	18	79	0.18
-female	4	26.7	2	50	50	
transurethral resection						
complete	8	53.3	2	25	75	0.99
incomplete	7	46.7	2	28.6	64	
Bilharzial						
-yes	5	33.3	2	40	40	0.35
-no	10	66.7	2	20	80	
Stage						
-T2	10	66.7	2	20	80	0.05
-T3	5	33.3	2	40	53	
Grade						
-II	9	60	0	0	100	0.007
-III	6	40	4	66.6	33	
Obstructive uropathy						
-yes	2	13.3	0	0	100	0.42
-no	13	86.7	4	30.7	66	

Table (10):Correlation between disease free survival of the whole series (preserved bladder and salvage cystectomy) with certain prognostic factors

Factor	No. of patients		No. of Patients with recurrence		DFS %	p-value
	No	%	No.	%		
Age						
-<median	13	43.3	4	30.7	65	0.27
->median	17	46.7	2	11.7	80	
Sex						
-male	24	80	4	16.7	77	0.25
-female	6	20	2	33.3	66	
TUR						
complete	8	26.7	2	25	75	0.72
incomplete	22	37.3	4	18.8	70	
Bilharzial						
-yes	13	43.3	3	23	60	0.45
-no	17	56.7	3	17.6	79	
Stage						
-T2	11	36.7	3	27.2	70	0.84
-T3	18	60	3	16.6	75	
-T4a	1	3.3	0	0	100	
Grade						
-II	18	60	1	5.5	93	0.01
-III	12	40	5	41.6	42	
Obstructive uropathy						
-yes	6	20	0	0	100	0.21
-no	24	80	6	25	67	
Initial rsponse						
-CR	13	43.3	3	23	73	0.96
-No. CR	17	56.7	3	17.6	73	

Fig (1): Whole pelvis fields (lateral

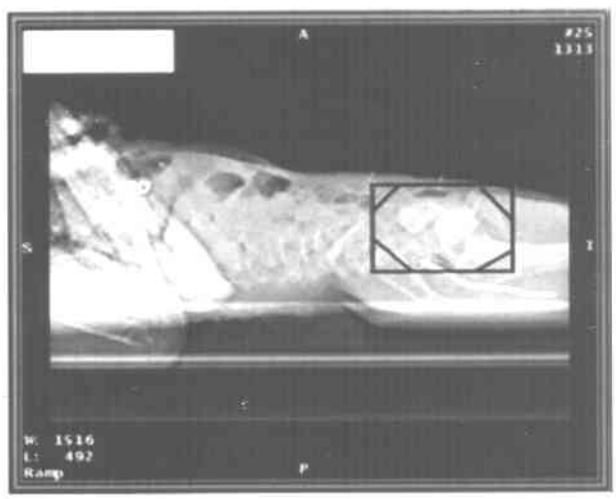


Fig (2): Whole pelvis fields (anterior)

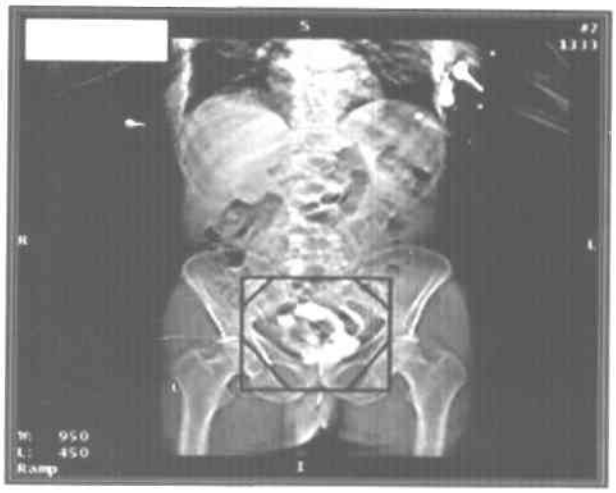


Figure (3):- lateral bladder field.

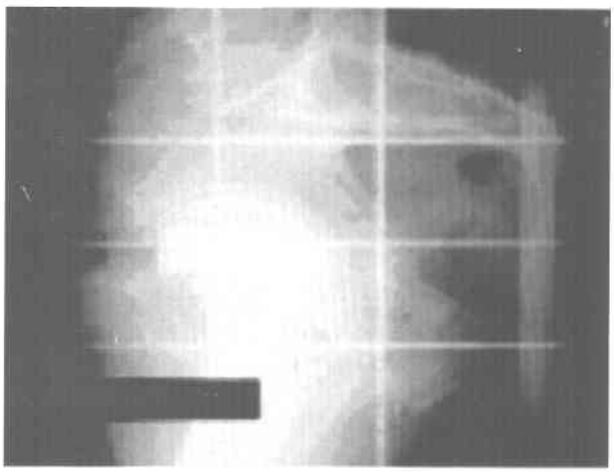


Figure (4):anterior bladder field.

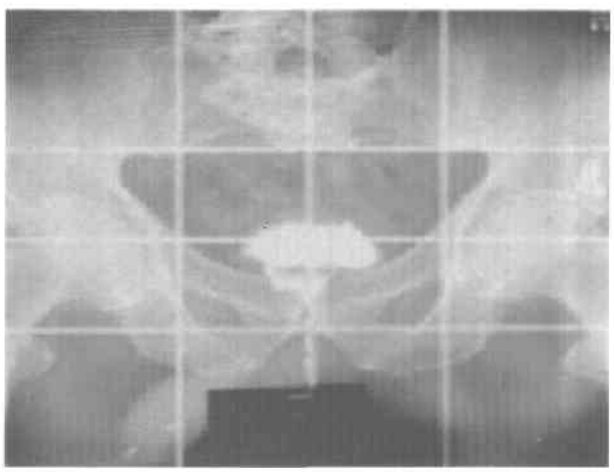


Fig (5): pretreatment

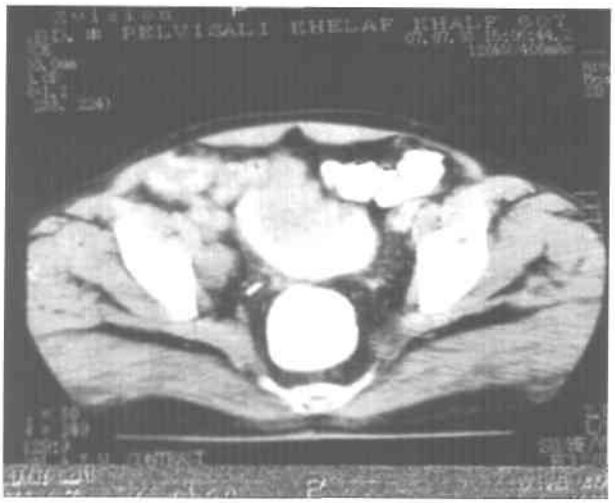


Fig (6): post treatment

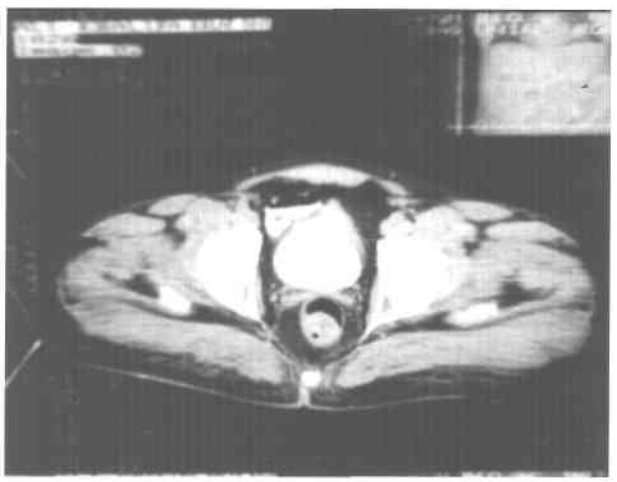
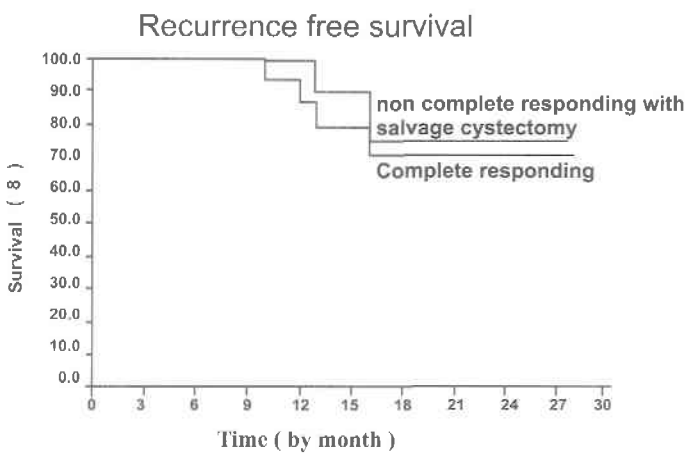


Fig (7): Actuarial survival for complete and non complete responders



References

1) Abdel-Hameed M.: bladder preserving approach by chemo-radiotherapy in patients with muscle-invading transitional cell carcinoma 2004; MD thesis, Radiotherapy department. South Egypt Cancer Institute. Assiut University.
2) Abol-Enein H, Ghoneim M.: Functional results of orthotopic ileal neobladder with serous lined extramural reimplantation: experience with 450 patients. J Urol 2001; 165: 1427-1432.
3) Arias F, Dominguez MA, Martinez E, et al.: Chemo-radiotherapy for muscle invading bladder cancer. Final report of a single institutional organ-sparing program. Int J Radiat Oncol Biol Phys 2000; 47: 373-378.
4) Brunner T.: Radiotherapy plus chemotherapy-bladder cancer survival. 42nd Annual Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO) 2001; Vol. 10, No 3 (March).
5) Cervek J, Cufer T, Zakotnik B, et al.: Invading bladder cancer: our experience with bladder sparing approach. Int J Radiat Oncol Biol Phys 1998; 41: 273-278.
6) Fellin G, Graffer U, Bolner A, et al: Combined chemotherapy and radiation with selective organ preservation for muscle- invasive bladder carcinoma. A Single Institution Phase II Study. 1997; Br. J. Urol; 80 (1): 44-49.
7) Given RW, Parsons JT, McCarley D, et al: Bladder sparing- multimodality treatment of muscle-invasive bladder cancer: a five year follows up. Urology 1995; 46 (4): 499-504.
8) Hossfeld k, Sherman JR, Bosch FX.: Manual of clinical oncology. 5th edition (Middle East ed.), Springer- Verlag/ UTCC Agreement. 1993; pp. 109.
9) Housset M, Maulard C, Chretier YC, et al.: Combined radiation and chemotherapy for invasive transitional cell carcinoma of the bladder: A prospective study. J Clin Oncol 1993; 11: 2150-2157.
10) Kaufman DS, Shipley WU, Griffin PP, et al: Selective bladder preservation by combination treatment of invasive bladder cancer. New England Journal of Medicine 1993; 329 (19): 1377-1382.
11) Khaled HM, Zaghloul MS, Ghoneim M, et al.: Gemcitabine and cisplatin as neoadjuvant chemotherapy for invasive bladder cancer: Effect on bladder preservation and survival. 2002; Pros Am Soc Oncol; 22: 411 (abstract 1625).
12) Matos T, Cufer T, Cervek J, et al.: Prognostic factors in invasive bladder carcinoma treated by combined modality protocol (organ sparing approach). Int J Radiat Oncol Biol Phys 1995; 46: 403-409.
13) Nazli GM, El-Bolkainy MM, Khaled HM.: Bladder cancer in Africa: update Semin Oncol 2001; 28: 174-178.
14) Paul B, Saint F.: Simultaneous chemotherapy and radiotherapy in locally advanced bladder cancer. J Prog Urol, 2001; Feb; 11 (1): 132-140.
15) Peyromaure M, Slama J, Beuzeboc P, et al: Concurrent chemo/radiotherapy for clinical stage T2 bladder cancer: report of a single institution. Urology 2004; 63 (1): 73-77.
16) Rödel C, Grabenbaver GG, Kuhn R, et al: Combined modality treatment and selective organ preservation in invasive bladder cancer: Long term results. Journal of Clinical Oncology 2002; Vol. 20, No. 14 (July 15): 3061-3071.
17) Sakr HM.: Use of combination chemotherapy (gemcitabine and cisplatin), and radiotherapy after transurethral resection for treatment of invasive bladder carcinoma. 2003; MD thesis in radiotherapyand nuclear medicine department, Al-Azhar university.
18) Sauer R, Berkenhage S, Kuhn R, et al.: Efficacy of Radio/chemotherapy with platin derivatives compared to radiotherapy alone in organ sparing treatment of bladder cancer. Int J Radiat Oncol Biol Phys 1998; 40: 121-127.
19) Scher HI, Norton L.: Chemotherapy for urothelial tractmalignancies: Breaking the dead lock. Semin Surg Oncol 1992; 8: 316-341.
20) Scher HI, Shipley WU, Herr HW.: Cancer of the bladder 1996; in Devita VT, Hellmann S, Rosenberg SA. (Eds): Cancer principles and practice of oncology, 5th ed. Pp 1300- 1321. Philadelphia, Lippincott-Raven.
21) Shipley WU, Kaufman DS, Heney NM, et al.: An update of combined therapy for patients with muscle invading bladder cancer using selective bladder preservation or cystectomy 1999; J Urol; 162: 445-450.
22) Tester W, Caplan R, Heaney J, et al.: Neoadjuvant combined modality program with selective organ preservation for invasive bladder cancer: Results of Radiation Therapy Oncology Group Phase II Trial 8802. 1996; J Clin Oncol; 14: 119-126.
23) Thurman SA, Deweese TL.: Multimodality therapy for the treatment of muscle invasive bladder cancer 2000; Semin Urol Oncol, Nov; 18 (4): 313-322.
24) Zaghloul MS, Awaad KH, Akoush HH, et al: Post-operative radiotherapy of carcinoma in Bilharzial bladder: Improved disease free survival through Improving local control 1992; Int. J. Radiat. Oncol. Biol. Phys; 23511-517.
25) Zaghloul MS, Nouh A, Moneer MM, et al.: Pathological types and time trends in bladder cancer 2003; SIU meeting, Sharm El-Sheik, Egypt.
26) Zapatero A, Pinar B, Arellano R, et al: Conservative treatment with Chemotherapy and radiotherapy in bladder cancer invading the muscle: preliminary results of a prospective study

1997; Arch Esp Urol; 50 (5): 448- 454; discussion 454- 456.

27) Zietman AL, Kaufman DS, Shipley WU, et al.: A phase I/II trial of TUR plus cisplatin and radiation therapy followed either by selective bladder preservation or radical cystectomy for patients with muscle-invading bladder cancer but without hydronephrosis 1997; Proc Am Soc Therapeutic Radiol Oncol, Abstract # 42, Int J Radiat Oncol Biol Phys; suppl 2.

28) Haskell CM, Berek JS.: Grading of toxicity 2001; in: cancertreatment, 5th edition W.B. Saunders Co, Philadelphia, appendix B.