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Original Article

Trimodality bladder-sparing approach versus radical cystectomy for invasive bladder cancer

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Abstract

Purpose: To compare the outcome among patients with invasive bladder cancer treated with cystectomy alone with outcome among those treated with combined-modality treatment in a randomised phase III trial.

Patients and methods: Patients with histologically confirmed invasive non-metastatic bladder cancer T2-3, N0 and M0 were randomly assigned to two arms: Arm 1: of which all patients underwent radical cystectomy (RC) alone; and Arm 2, of which all patients were subjected to maximal transurethral resection of bladder tumour, followed 2 weeks later by combined chemoradiotherapy. The whole pelvis received 46 Gy in 23 fractions over 4·5 weeks. Chemotherapy was administered concomitantly with radiotherapy with: cisplatin 70 mg/m^2 q. 3 weeks and Gemcitabine 300 mg/m^2 D 1, 8 and 15 q. 3 weeks for two cycles. Patients who had complete response were shifted to phase II treatment: 20 Gy/10 fractions/2 weeks to the bladder. Patients with residual tumour underwent RC.

Results: Of the 80 patients assigned Arm 2, a visibly completed transurethral resection of the bladder tumour was possible in 48 patients (60%). Phase I of combined chemoradiotherapy (CCRT) was accomplished in 74 patients. Post-induction urologic evaluation revealed no evidence of disease in 62 patients (83·8%) and residual disease in 12 patients (16·2%). Phase II of CCRT was completed in 58 of the 62 patients. The median follow-up for all patients is 27 months (range: 4–49). The 3-year overall survival (OS) for the combined-modality group and for the surgery group were 61 and 63%, respectively ($p = 0{\cdot}425$), whereas the disease-specific survival (DSS) for each group was 69 and 73%, respectively ($p = 0{\cdot}714$). The 3-year OS with bladder preservation for Arm 2 patients was 50%.
Multivariate analysis for the whole series showed that tumour stage and performance status (PS) were the only factors independently associated with DSS, although PS was the only factor independently associated with OS. In addition, residual disease after transurethral resection of the bladder tumour in Arm 2 patients was independently associated with both DSS and OS.
Acute toxicity was moderate and most of the late toxicities were grade 2 with no grade 4 toxicity and no treatment-related deaths, none required cystectomy for bladder contraction.

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Conclusion: This study demonstrates that trimodality bladder-preserving approach represents a valid alternative for suitable patients. The OS and DSS rates of patients treated with trimodality bladder-preserving protocol are comparable to the results reported on patients treated with immediate radical cystectomy.

Keywords: bladder sparing; invasive bladder cancer; trimodality approach

INTRODUCTION

The standard of care for transitional cell carcinoma invading the muscularis propria of the bladder is a bilateral pelvic lymph-node dissection and a cystoprostatectomy, with or without a urethrectomy in the male patient. In the female patient an anterior exenteration is performed, which includes the bladder and urethra, the ventral vaginal wall and the uterus.[1] Unfortunately, after this radical cystectomy (RC) for locally advanced bladder cancer, there is a significant rate of recurrence (56% among patients with pathological stage T3), most commonly as distant metastases.[2] In addition, this operation has been associated, sometimes, with poor quality of life results, as there is still no substitute for the patient's own fully functional bladder.[3]

Therefore, recent strategies have combined the three modalities: transurethral resection of the bladder tumour (TURBT), chemotherapy and radiation therapy in an attempt to improve long-term survival and bladder preservation rates,[4] with salvage cystectomy being reserved for patients with incomplete response or local relapse.[5,6]

We had updated our experience in Assiut university hospitals with trimodality bladder-sparing approach.[3] For all patients, overall survival (OS), cancer-specific survival and OS with bladder preservation (OSBP) rates at 5 years reached 58, 60 and 51%, respectively. These results, similar to those reported by other studies, support the use of bladder-sparing treatment in selected patients as a safe and an effective alternative to RC.[7–11]

Despite these encouraging results, the outcome of the organ-sparing approach needs to be compared with the surgical standard. Unfortunately, primary cystectomy has not been tested against trimodality approach in randomised trials.[4,12]

Purpose of the paper was to compare the outcome among patients with invasive bladder cancer treated with cystectomy alone, with outcome among those treated with combined-modality treatment in a randomised phase III trial. Secondary objectives were to quantify the rate of complete response after neoadjuvant chemoradiotherapy and survival with preserved bladder.

PATIENTS AND METHODS

Inclusion criteria

This trial included patients with histologically confirmed invasive non-metastatic bladder cancer. Inclusion criteria were clinical stage T2-3, N0 and M0, [AJCC TNM classification 7th edition 2010]; no prior radiotherapy and/or chemotherapy; Eastern Cooperative Oncology Group performance status (PS) $\leq$2; age at diagnosis of $\geq$18 years; and adequate bone marrow (absolute neutrophil count $\geq$1,500/m^3 and platelet count $\geq$100,000/m^3), renal (creatinine clearance $\geq$60 mL/minute, serum creatinine $\leq$1·3 mg/dL) and hepatic function (total bilirubin $<$1·5 mg/dL). Before the treatment, all patients received detailed oral information on the treatment protocol and possible side effects, and signed an informed consent. The trial was approved by the ethics committee of the Faculty of Medicine, Assiut University.

Patient evaluation

At baseline, all patients underwent history, physical examination, evaluation of PS, and complete blood count, kidney and liver function tests, and 24-hour urine collection for creatinine clearance. Histopathological diagnosis was established by cystoscopy and TURBT. Distant metastasis was excluded by pre-operative staging, including computed tomography (CT) scan of the chest, abdomen and pelvis. Bone scan was requested only when indicated.

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Treatment protocol

Patients were randomly assigned to two arms:

- Arm 1: of which all patients underwent RC alone.
- Arm 2: of which all patients were subjected to maximal TURBT, followed 2 weeks later by combined chemoradiotherapy (CCRT). Radiotherapy was delivered once per day, 5 days a week. The whole pelvis received 46 Gy in 23 fractions over 4 to 5 weeks. Three-dimensional CT-based treatment planning was carried out.

Chemotherapy was administered concomitantly with radiotherapy with GC: cisplatin 70 mg/m^2 q. 3 ws. and Gemcitabine 300 mg/m^2 D 1, 8 and 15 q. 3 ws. for two cycles.[13] All patients were pre-medicated for day 1 of each cycle with dexamethasone 20 mg intravenous (IV) injection, ondansetron 8 mg IV and ranitidine 50 mg IV. If the WBC was lower than $3{\cdot}0 \times 10^9$/L or the platelets below 100×10^9/L, or haemoglobin <9 g/dL, or other grade 3 toxicities on day 22, the subsequent cycle was delayed for 1 week.

Four to six weeks after the end of treatment, the patients were re-evaluated by taking a CT scan of the pelvis and second- look cystoscopy, where the base of the tumour was rebiopsied and examined histopathologically.

Patients who had complete response were moved to phase II treatment. Phase II: 20 Gy/10 fractions/2 weeks to the bladder. Patients with residual tumour underwent RC.

Radiotherapy techniques

The target volume in phase I included the bladder, the proximal urethra and the pelvic lymph nodes. The planning target volume extends in the cranial–caudal dimension from L5-S1 interspace to the lower pole of the obturator foramen and 0·5–1 cm beyond the pelvic bones laterally. The anterior border lies 1–2 cm in front of the anterior bladder wall and the posterior border at the mid-rectum. Booster treatment was then used in phase II, which included the whole bladder and a margin of 2 cm.

The patients were treated in the supine position checked by laser lights. Fixation with thermoplastic shells was used in obese patients and in patients having redundant abdomen. IV contrast was used to localise the bladder.

Field arrangement for the proposed target volume was carried out by computerised planning system, taking in consideration homogeneous distribution shape to the target volume and the tolerance dose to the critical organs. For whole-pelvic irradiation (phase I), treatment was administered, with the full bladder displacing the small bowel out of the pelvis. For phase II treatment, the patient was instructed to empty the bladder immediately before the treatment session to ensure that the bladder is inside the target volume. All patients were treated by photon linear accelerator 6 and/or 15 MeV. The total dose did not exceed 45 and 55 Gy to the femoral heads and the posterior rectal wall, respectively.

Surgery

- TURBT
- Definitive surgery included RC and urinary diversion. Urinary diversion was variable according to the PS and the relationship of the tumour with the bladder neck.

Pathologic analysis

Pathologic analysis of the RC specimen included extensive macroscopic and histologic evaluation. All the lymph nodes were entirely submitted for analysis per designated site and representative sections of surrounding fibroadipose tissue were, in addition, sampled.

Follow-up

During chemoradiotherapy, patients were evaluated weekly for acute toxicity and compliance with the protocol. If radiotherapy was interrupted, chemotherapy was not administered. Clinical examination and complete blood count were carried out. Toxic side effects were assessed according to National Cancer Institute Common Toxicity Criteria (version 2.0). Patients were followed every 3 months for the first 2 years after

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Table 1. Patients and disease characteristics in all cases

	Arm 1 ($n = 80$)	Arm 2 ($n = 80$)	*p*-value
Age in years (mean ± SD)	55·6 ± 10·8	58·6 ± 8·3	0·08
Age range	35–80	36–70	
Sex			
Male	62 (77·5%)	65 (81·2%)	0·68
Female	18 (22·5%)	15 (18·8%)	
History of smoking			
Non-smoker	49 (61·2%)	47 (58·8%)	0·63
Smoker	31 (38·5%)	33 (41·2%)	
ECOG performance status			
1	65 (81·2%)	61 (76·3%)	0·57
2	15 (18·8%)	19 (23·7%)	
Tumour site			
Single	66 (82·5%)	64 (80%)	
Anterior bladder wall	24 (30%)	21 (26·3%)	0·87
Left lateral wall	17 (21·3%)	13 (16·3%)	
Right lateral wall	11 (13·8%)	9 (11·3%)	
Dome	4 (5%)	6 (7·5%)	
Posterior wall	7 (8·8%)	10 (12·5%)	
Bladder neck	3 (3·8%)	5 (6·3%)	
Multiple	14 (17·5%)	16 (20%)	
History of Bilharziasis			
No	27 (33·8%)	20 (25%)	0·23
Yes	53 (66·2%)	60 (75%)	
Disease stage			0·85
T2	61 (76·3%)	60 (75%)	
T3	19 (23·7%)	20 (25%)	
Tumour grade (G)			
G_1 low grade	9 (11·2%)	9 (11·2%)	
G_2 intermediate grade	37 (46·3%)	33 (41·2%)	1·00
G_3 high grade	34 (42·5%)	38 (47·5%)	

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

the last cycle of adjuvant chemotherapy and thereafter every 6 months.

Statistical analysis

Data were analysed using Statistical Package for Social Sciences version 21.0. The 0·05 level was used as the cut-off value for statistical significance. Count and percentage were used for describing and summarising qualitative data. Arithmetic mean and standard deviation were used as measures of central tendency and dispersion for quantitative data, respectively. Univariate analysis for the most important factors regarding patients, tumour and complications were carried out using χ^2 and *t*-test analysis. The clinical-pathologic factors with proven statistical significance from the univariate analyses were further included in the multivariable Cox proportional hazard regression models. The Kaplan–Meier method with the log-rank test for statistical significance was used for survival analysis of individual prognostic factors.

Actuarial survival rates were calculated from the time of Cystectomy (Arm 1) or initial TURBT (Arm 2) to the time of the last follow-up visit or death. For the estimation of disease-specific survival (DSS), patients who died of unrelated causes were censored at death. Patients whose cause of death was unknown were assumed to have died of bladder cancer. The OSBP was defined as the probability of remaining alive and with a preserved bladder.

RESULTS

The patients and tumour characteristics are detailed in Table 1. Both arms, with 80 patients each, were demographically well balanced.

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Protocol completion and response

All patients of Arm 1 underwent RC and urinary diversion, which was variable according to the PS and the relationship of the tumour with the bladder neck. Urinary diversion among those patients was as follows: 47 patients underwent orthotopic neobladder, 21 patients underwent catheterisable neobladder, five patients underwent ureterosigmoidostomy and seven patients underwent ileal conduit.

Of the 80 patients assigned Arm 2, a visibly completed TURBT was possible in 48 patients (60%). Phase I of CCRT was accomplished in 74 patients. Six patients did not complete it: four because of treatment intolerance and the other two owing to the development of acute kidney injury. Post-induction urologic evaluation revealed no evidence of disease (complete response, CR) in 62 patients (83·8%) and residual disease in 12 patients (16·2%). Phase II of CCRT was completed in 58 of the 62 patients with CR and bladder preservation and four patients did not continue consolidation CCRT because of poor compliance and tolerance to CCRT. The remaining 12 patients (16·2%) who had residual disease after induction therapy plus those (six patients) who did not complete phase I included 13 patients (66·7%) subjected to salvage cystectomy, and five patients (33·3%); three patients refused surgery and two were surgically inaccessible because of disease progression. These five patients received off-protocol chemotherapy or best supportive care and were considered failure. The four patients who did not complete phase II were kept on follow-up.

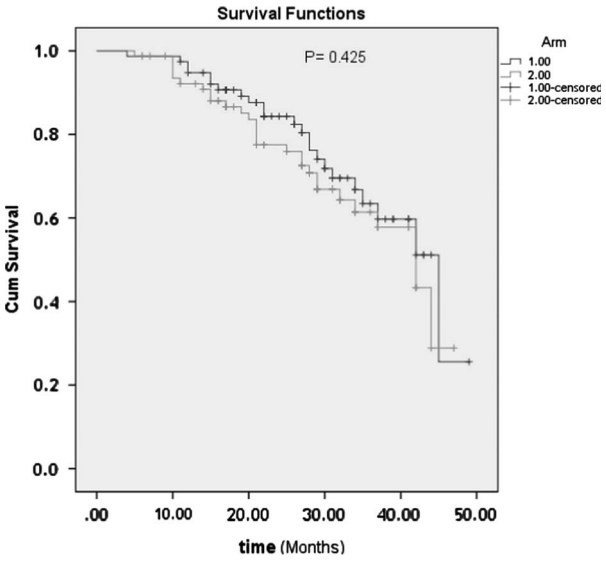

Figure 1. Overall survival.

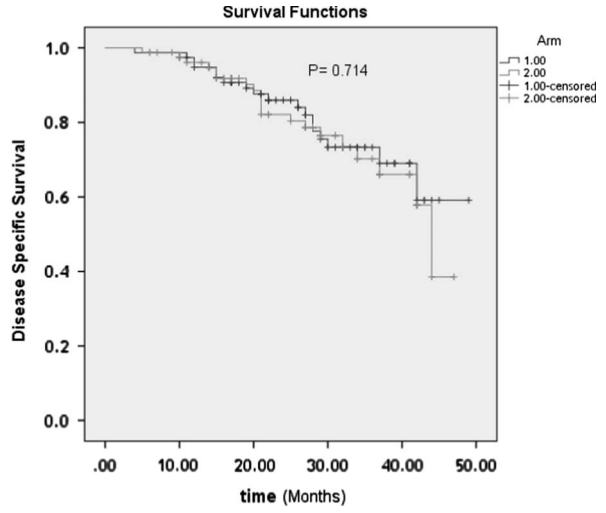

Figure 2. Disease-specific survival.

Outcome and pattern of failure

The median follow-up for all patients is 27 months (range: 4–49). The OS and DSS of the two treatment groups are shown in Figures 1 and 2. The 3-year OS for the combined-modality group and for the surgery group were 61 and 63%, respectively ($p = 0{\cdot}425$), whereas the DSS for each group was 69 and 73%, respectively ($p = 0{\cdot}714$). Thus, there was no significant difference in OS and DSS between both arms. The 3-year OSBP for Arm 2 patients was 50% (Figure 3).

Of the 80 Arm 1 patients, 23 (28·8%) patients experienced local pelvic recurrences and 13 (16·3%) patients developed distant metastases. Of those, three (3·8%) were discovered to have both local and distant recurrences on re-evaluation. Of the 62 Arm 2 patients who had CR, four (6·5%) patients experienced superficial bladder relapse, 15 (24·2%) patients developed muscle-invasive relapse and 10 (16%) patients developed distant metastases. Of those, three (4·8%) were discovered to have developed both local and distant recurrences on re-evaluation. There were no significant differences regarding the incidence of local recurrences (excluding non-invasive recurrence), distant metastasis and deaths from

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bladder cancer among the two arms ($p = 0{\cdot}20$, 0·17, 0·50, respectively).

Patients with superficial bladder relapse were treated conservatively with TURBT and intravesical therapy. During follow-up, two of them developed invasive recurrence and underwent salvage cystectomy. Of the patients who developed muscle-invasive relapse, 11 were treated with salvage cystectomy, whereas radical surgery could not be performed in the other four patients because of poor PS or patient refusal.

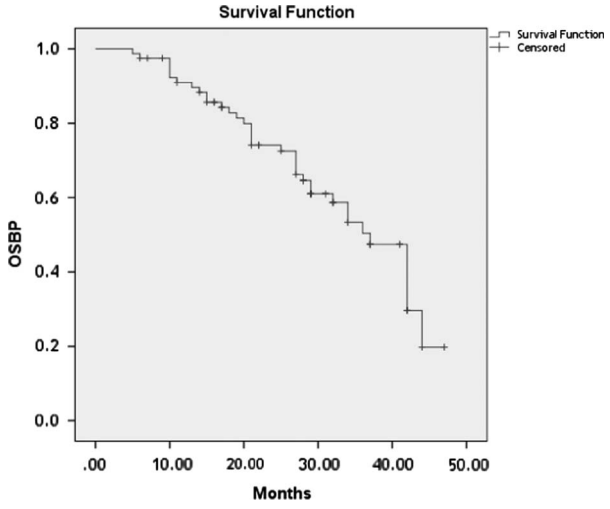

Figure 3. The overall survival with bladder preservation curve for Arm 2 patients.

Multivariate analysis (MVA) was performed for the whole series to assess potential prognostic factors for OS and DSS (Table 2). The results of MVA showed that the tumour stage and PS were the only factors independently associated with DSS, whereas PS was the only factor independently associated with OS. In addition, residual disease after TURBT in Arm 2 patients was independently associated with both DSS and OS (Table 2).

Toxicity

Regarding Arm 2 patients, post-operative complications were mild and transient and included haematuria in eight patients (relieved by medical treatment and bladder wash) and urinary tract infections in five patients treated by antibiotics.

The acute reactions, attributable to chemotherapy combined with radiotherapy of different grades included bladder irritation in 32% of the patients, diarrhoea in 26%, fatigue in 21% and leucopenia in 8%. None of these patients had incontinence. Grade 3 cystitis and proctitis were recorded in 7·5 and 2·5%, respectively.

Table 2. *Multivariate analysis of potential prognostic factors affecting disease-specific survival and overall survival*

			95·0% CI for OR	
	Significance	**OR**	**Lower**	**Upper**
Factors affecting disease-specific survival				
Sex	0·09	1·31	0·71	2·4
Age	0·06	0·99	0·97	1·02
PS	0·003	2·13	1·1	4·1
Stage	0·005	0·49	0·26	0·94
Grade	0·06	1·29	0·75	2·23
Hydronephrosis	0·08	1·33	0·68	2·95
Residual disease after TURBT (Arm 2 only)	0·04	0·29	0·09	0·96
Factors affecting overall survival				
Sex	0·087	1·66	0·62	3·6
Age	0·064	0·02	0·01	0·21
PS	0·007	8·04	3·6	12·4
Stage	0·054	1·19	0·63	2·29
Grade	0·059	0·01	0·001	12·29
Hydronephrosis	0·07	1·33	0·68	2·95
Residual disease after TURBT (Arm 2 only)	0·02	0·2	0·05	0·77

Abbreviations: OR, Odd's ratio; CI, confidence interval; PS, performance status; transurethral resection of the bladder tumour.

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Haematologically, grade 3 neutropenia occurred in three patients (3·75%), whereas grade 3 thrombocytopenia and anaemia were encountered each in one patient. No grade 4 toxicities were recorded.

When questioned at the follow-up examinations after the completion of treatment, all patients reported that their bladder function had remained satisfactory.

Regarding Arm 1 patients, intra-operative complications included injury of a major vessel in two patients and rectal tears in three patients that were controlled by surgical repair. Immediate post-operative complications included acute gastric dilatations in four patients and hypovolemic shock in three patients. Early complications included hypokalaemia in five patients, wound adhesions in two patients and urinary tract infections in six patients. All were well managed by appropriate measures.

The main late complications that developed during follow-up of Arm 1 patients included adhesive intestinal obstructions in three patients and hyperchloremic acidosis in three patients.

Of the 62 Arm 2 patients, six patients (9·7%) experienced late gastrointestinal toxicity (grade $\geq$2) in the form of chronic diarrhoea and tenesmus, whereas 11 (17·7%) patients developed late urinary toxicity (grade $\geq$2) in the form of reduced bladder capacity, with less-than-voiding intervals $<$2 hours; however, none required cystectomy for bladder contraction. There was no grade 4 toxicity and no treatment-related deaths.

DISCUSSION

In this study, we aimed to compare the outcome among patients with invasive bladder cancer treated with cystectomy alone, with outcome among those treated with trimodality approach in a randomised phase III trial. On the basis of our results, we found no evidence that survival is compromised by the bladder-sparing technique we used.

The similarity in survival rates between cystectomy arm and selective bladder-preserving arm is likely due, in part, to the prompt use of salvage cystectomy when necessary in Arm 2 (26 (32·5%) of all entered patients). This underscores the need in selective bladder-preserving approaches for close cystoscopic evaluation and prompt removal of the bladder for an incomplete response or invasive recurrence.[14]

The 3-year OS rate of 61%, DSS rate of 69% and 3-year survival rate with a preserved native bladder of 50% plus CR achieved in 77·5% of our Arm 2 patients are approaching the results of other recently reported combined-modality series using transurethral surgery plus concurrent chemotherapy and radiotherapy.[15–23] The current 5-year OS rates range from 50 to 67% with trimodality treatment, and ~75% of the surviving patients maintain their bladder. After trimodality treatment complete response is obtained in more than 70% of patients with muscle-invasive bladder cancer.[24] The 3-year survival rate with bladder preservation of our patients was in accordance with that (52·1%) reported by Tunio et al.[25] who conducted a similar study on 116 Pakistani patients with muscle-invasive bladder cancer (MIBC). Using a similar protocol with the addition of adjuvant chemotherapy in one-third of their cases, Ibrahim et al.[26] reported post-induction CR in 24 (60%) patients, with 2-year actuarial survival and progression-free survival rates of 67% (95% CI 52·2–82·7%) and 58% (95% CI 42·3–74·0%), respectively.

The Radiation Therapy Oncology Group (RTOG) and the Massachusetts General Hospital (MGH) have great experience in this field.[23] During the years 1985–2001, the RTOG conducted six trials, of which five were phase I and II, and the 6th one a phase III trial, which tested the role of adjuvant chemotherapy with trimodality treatment. A total of 415 patients were enrolled in these trials. The 5-year OS was ~50%, with 75% of surviving patients retaining a functionally preserved bladder.[27,28] The MGH's experience with 348 MIBC patients, who were entered on successive prospective trimodality protocols from 1986 to 2006, has recently been recently updated.[29] With a median follow-up for all surviving patients of 7·7 years, the 5, 10 and 15-year OS rates were

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52, 35 and 22%, respectively. The 5, 10 and 15-year DSS was 64, 59 and 57%, respectively.[30]

Long-term outcomes of 473 patients with muscle-invasive bladder cancer treated with TURBT and radiochemotherapy or radiotherapy with curative intent between 1982 and 2007 in the AKH (Allgemeines Krankenhaus der Stadt Wien) General Hospital was reported by Krause et al.[31] in 2011. A total of 99·4% of the patients received a platinum-based chemotherapy: 143 cisplatin, 97 carboplatin, 67 cisplatin/5-FU, six carboplatin/5-FU, nine cisplatin/carboplatin, four cisplatin/carboplatin/5-FU, two 5-FU and three cisplatin/gemcitabine. Complete remission (CR) was achieved in 70·4% of the patients. Focusing on the subgroup of 331 patients treated with TURBT and radiochemotherapy, a median survival of 70 months was found with overall 5, 10 and 15-year survival rates of 54, 36 and 24%, respectively.[31]

Our results of cystectomised patients (Arm 1) are also approaching those reported in prospective cystectomy series for patients with muscle-invasive bladder cancer. Contemporary series shows 5-year overall and DSS rates of 55–60% and 59–65%, respectively, for RC.[32–34]

In cases with initial CR, muscle-invasive recurrences were detected in 15 (24·2%) of our cases during their follow-up. This was found to be worse than the results of Rödel et al.,[7] Perdona et al.[20] and Weiss et al.[10] who reported invasive recurrences in 18, 17·6 and 11·1%, respectively, in their studies. This can be explained by higher percentage of multifocality and Bilharziasis in our series, in addition to poor compliance of some of our patients to be regularly followed by cystoscopy, resulting in failure to detect recurrences earlier at superficial stage. Only 6·5% of our CR cases were diagnosed as superficial recurrences during follow-up. In studies by Rödel et al.,[7] Perdona et al.[20] and Weiss et al.,[10] the superficial recurrences were reported in 14, 16·7 and 13·1%, respectively.

Again, salvage cystectomy was recommended for muscle-invasive recurrences (but only performed for non-metastatic cases with good general conditions), whereas superficial recurrences were treated by TURBT and intravesical immunotherapy (Bacillus–Calmette–Guérin). Intravesical immunotherapy was well tolerated by the previously irradiated bladders, and no patient required treatment breaks.

In the Arm 2 patients, distant metastases were reported in 13 cases (21%) after the initial CR matching with other series. Ten of these cases were having completely disease free bladders. In the study by Rödel et al.,[7] the authors demonstrated that distant metastases were evident in 21% of cases after the initial CR with 10 years of follow-up.

Several factors have been correlated with survival and bladder preservation rates in organ-preservation treatments for muscle-invasive bladder cancer. On MVA, the completeness of TURBT, tumour stage, tumour size, and in some studies, the presence of hydronephrosis or ureteral obstruction at diagnosis were found to be correlated with OS and local recurrence.[24] For the whole series of our study, MVA showed that tumour stage and PS were the only factors independently associated with DSS, although PS was the only factor independently associated with OS. In addition, residual disease after TURBT in Arm 2 patients was independently associated with both DSS and OS.

To be a reasonable bladder-preserving alternative, a bladder-preserving approach should also have good bladder-sparing capacities.[35] The 3-year OSBP for Arm 2 patients was 50%. Most of the long-term surviving patients in Arm 2 preserved their functioning native bladders, which is similar to other studies.[15–23] Acute toxicity was moderate and most of the late toxicities were grade 2 with no grade 4 toxicity and no treatment-related deaths.

However, it is important to realise that the patient numbers are relatively small. Therefore, large multi-institutional well-controlled randomised trials are needed to confirm these results.

CONCLUSION

This randomised phase III study demonstrates that trimodality bladder-preserving approach and represents a valid alternative for suitable patients.

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The OS and DSS rates of patients treated with trimodality bladder-preserving protocol are comparable to the results reported on patients treated with immediate RC. Although one-third of the patients treated on this protocol ultimately require cystectomy, this approach with bladder preservation is safe and results in a majority of the long-term survivors retaining functional bladders. The close collaboration of urologists, radiation oncologists and medical oncologists is of paramount importance in succeeding in bladder preservation.

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Conflicts of Interest

Authors certify that there is no actual or potential conflict of interest in relation to this article.

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