Original Article

Feasibility of organ preservation in muscle-invasive transitional cell carcinoma bladder: A single institutional approach

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ABSTRACT

Background: Trimodality treatment initial transurethral resection of the bladder tumor [TURBT] followed by concurrent chemotherapy and radiation and organ preservation have been gradually replacing the radical cystectomy in muscle-invasive transitional cell carcinoma (TCC) of bladder. **Aims:** The aims of this study is to determine the clinical effectiveness, safety and protocol completion rate of trimodality treatment in muscle-invasive TCC of the bladder. **Settings and Design:** Prospective randomized and open-labeled study. **Subjects and Methods:** Patients with TCC of bladder, American Joint Committee on Cancer tumor node metastasis (TNM) Bladder Cancer Staging (2002) T2-3, N0, M0. Were underwent TURBT followed by three cycles of neoadjuvant chemotherapy with methotrexate, vinblastine, adriamycin, and cisplatin regimen. The patients were then randomized to receive either concurrent cisplatin 75 mg/m^2 in week 1 and 4 (arm-A) or no cisplatin (arm-B) along with external beam radiation therapy (EBRT) 45 Gy, in 25 fractions over 5 weeks. 4 weeks after completion of the initial phase of treatment, all patients were re-evaluated with TURBT. Those with complete remission (CR) received additional 15 Gy of EBRT in 8 fractions, while patients with residual disease were recommended for immediate radical cystectomy. All the patients of arm-B received boost dose of 15 Gy of EBRT. **Statistical Analysis Used:** The major statistical endpoints of this study were the CR rate at 8 weeks post-concurrent chemoradiotherapy (CCRT) and only radiotherapy. Statistical significance was accepted at the $P < 0.05$ (two-sided) level. Statistical analysis was performed entirely using the Statistical Package for the Social Sciences for Windows, version 17 (SPSS Inc., Chicago, IL, U.S.A.). **Results:** 8 weeks after completion of treatment 13/16 (81%) patients were in CR in CCRT arm (arm-A) compare to 6/15 (40%) patients receiving radiation only (arm-B). **Conclusions:** Patients, after TURBT receiving CCRT, had a better chance of organ preservation (81%) than those receiving radiation only.

Key words: Concurrent cisplatin, transitional cell carcinoma bladder, trimodality treatment

INTRODUCTION

Bladder cancer is the 9th most common cancer worldwide, with around 429,800 new cases diagnosed in 2012 (3% of the total). Bladder cancer incidence rates are the highest in Southern Europe and the lowest in Western Africa, but this partly reflects varying data quality worldwide.[1] Bladder cancer is a disease of elderly but more and more young people are being detected with this. Median age at presentation is 60 years (range: 18–90 years). Male to female ratio in world literature describes as 4:1 but in Indian it is predominantly a disease of the male population with male to female ratio of 8.6:1.[2,3] Bladder cancer may develop along a continuum of preneoplastic and preinvasive disease of the bladder, and may be categorized as superficial, muscle-invasive or metastatic disease.[4] At presentation, 75% of patients are diagnosed with superficial disease and ~20% have muscle-invasive disease. Transitional cell carcinoma (TCC) is the most common histologic subtype accounting for approximately 95% of the case.[5] More than 90% of the TCC throughout the lining of the urinary tract occur in the urinary bladder.[6]

With a superficial tumor, the goal is to prevent a superficial relapses and progression to an incurable stage and is curable in most cases with transurethral resection (TUR) and intravesical therapy. For a metastatic tumor, the

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main clinical issue is how to choose the most effective palliation and radical cystectomy remains the standard for organ-confined muscle-invasive disease. However, about 50% of patients will progress to metastatic disease and untreated patients die within 2 years.[5] Local failure rate also was disappointingly high with conventional radiotherapy alone and this approach as monotherapy has largely been abandoned. A previous Southwest Oncology Group study demonstrated that radiation therapy before radical cystectomy did not improve the outcome.[7]

The recent advances in surgical techniques with the introduction of urinary diversion have improved postoperative quality of life. However, even the construction of a neo-bladder with continent urinary diversion, cannot substitute for the original bladder. The trend in the 1990s has changed towards organ preservation using combined chemotherapy and radiation, with or without conservative local surgery, for patients with cancer of the breast, esophagus, anus, larynx and limb sarcoma.[8] Based on the experience and result that a combination regimen of radiation therapy and platinum-containing chemotherapy yielded far better local control result than expected trimodality treatment, with transurethral resection of the bladder tumor (TURBT) and concurrent chemoradiotherapy (CCRT) has been suggested as a bladder-preserving therapy in muscle-invasive bladder cancer over the past two decades.[9-11] To determine the clinical effectiveness, safety and the protocol completion rate of this trimodality treatment, we designed the present study of CCRT incorporating cisplatin following TURBT for the treatment of muscle-invasive TCC.

SUBJECTS AND METHODS

It was a prospective interventional randomized open labeled study done from April 2011 to March 2013. Inclusion criteria for the study were:

- Patients with histopathologically proved muscle invading TCC, American Joint Committee on Cancer TNM Bladder Cancer Staging (2002) T2-3, N0, M0
- Patients having Karnofsky performance scale 100–60
- Initial evaluations with chest radiograph, computed tomographic (CT) scan of abdomen and pelvis revealed no evidence of metastases
- Serum chemistry within normal limits
- TURBT is as complete as possible followed by histopathological confirmation.

Patients were ineligible with

- Age >60 years.
- Karnofsky performance scale of <60
- Evidence of metastases to lymph nodes or distant areas.
- Abnormal liver function test, a serum creatinine >1.5 mg/dl, a creatinine clearance <60 ml/min, a white count <4000/mm^3, an absolute neutrophil count (ANC) <1800/mm^3, a platelet count < 100,000/mm^3
- Hydronephrosis
- Refusal to sign a consent form and
- Prior pelvic irradiation or cisplatin chemotherapy.

Signed study-specific informed consent, in agreement with Helsinki declaration 1996, prior to study entry were mandatory.

All patients underwent TURBT as complete as possible, prior to randomization. Completeness of TURBT was assessed according to residual tumor status. Complete TURBT was defined as microscopic no residual tumor, whereas incomplete TURBT was defined as microscopic or macroscopic residual tumor. All post-TURBT patients received three cycles of induction chemotherapy (IC), every 28 days followed by induction phase of external beam radiation therapy (EBRT), initiated 4–6 weeks after completion of IC. Patients in arm-A (study arm) received concurrent chemotherapy on weeks 1 and 4 of EBRT.

Chemotherapy was administered intravenous and the regimen used for IC was, methotrexate, vinblastine, adriamycin, and cisplatin (M-VAC) (methotrexate - 30 mg/m^2, day 1,15,22; vinblastine - 3 mg/m^2 day 2,15,22; doxorubicin - 30 mg/m^2 day 2; and cisplatin - 70 mg/m^2 day 2) every 28 days. Patients in arm-A received concurrent chemotherapy with cisplatin 75mg/m^2, on week 1 and 4 of radiations. The radiation was given between 1 and 2 h following the completion of the concurrent chemotherapy in arm-A. If a grade-3 hematologic toxicity developed (platelet < 50,000/mm^3 or ANC < 1800/mm^3), both the chemotherapy and radiation therapy were discontinued for 1 week and resumed when the ANC returned to ≥ 1800/mm^3 and the platelet count to ≥ 100,000/mm^3 periodic blood transfusions were given if the HB% levels become <10 g%.

EBRT was given using megavoltage equipment, cobalt-60 ATC-C9, with a source skin distance of 80 cm. During the induction phase, the radiation was given to the whole bladder, bladder tumor volume and the pelvic nodes, using one anterior and opposing lateral wedged fields with dose prescription at the center of the fields. All the fields were treated daily. The total dose was 45 Gy in 25 fractions, 1.8 Gy of daily fraction over 5 weeks. Complete responders of arm-A underwent consolidation therapy that began 1–2 weeks after the response evaluation. All the patients of the arm-B received a boost dose of EBRT. For the consolidation phase and the boost, the dose was delivered 15 Gy in 8 fraction, 1.8 Gy of daily fraction over 2 weeks to the whole bladder and the bladder tumor volume using one anterior and two posterior oblique fields with dose

prescription at the center of the fields. All the fields were treated daily. Thus, at end of the consolidation phase and the boost dose, the total dose delivered to the whole bladder and the bladder tumor volume was 60 Gy in 33fractions and the pelvic lymph nodes had received 45 Gy in 25 fractions.

After 4 weeks completing CCRT (post-CCRT), the initial response was evaluated by cystoscopy, biopsy of the tumor site, and urine cytology. Complete remission (CR) was considered, when there was no visible tumor on cystoscopy, the tumor-site biopsy was negative, and a negative urine cytology. Complete responders underwent consolidation EBRT. In the case of persistent invasive cancer at initial evaluation after CCRT, salvage cystectomy was preferentially recommended.

On completion of therapy, patients were assessed at 8 weeks, by urine cytology and cystoscopic biopsy. The acute hematologic and nonhematologic toxicities were assessed weekly during CCRT. Subsequent assessment was done three monthly for the 1st year and then every six monthly with cystoscopy, biopsy of the tumor site, bimanual examination under anesthesia, and urine cytology. Median follow-up was 12 months (range 9–15). Accrual to this trial was completed in 15 months. Acute radiation toxicity was assessed using Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) acute radiation morbidity scoring during treatment and follow-up (up to 90 days post-EBRT) period.

RESULT

The study was a prospective interventional randomized open labeled study done from April 2011 to March 2013. A total of 31 patients with histopathologically proved TCC bladder were randomized after fulfilling the eligibility criteria, with 16 patients in arm-A, and 15 patients in arm-B. One patient of arm-A was lost to follow-up.

The pretreatment characteristics [Table 1] were comparable in both the arms of the study, with number of patients being 16 and 15 in arm-A (CCRT) and arm-B (radiation) respectively. Patient who suffered from treatment-related toxicities were offered gap in treatment, but all of them completed treatment within 30 weeks. Median follow-up was 12 months ranging from 9 to 15 months. Within 12 months of median follow-up 5 of 13 patients amongst complete responders of the CCRT arm (arm-A) developed bladder recurrence (one invasive and four superficial tumors), which was three of six in arm-B (two invasive and one superficial). The superficial recurrence have been treated, successfully with conservative method. Radical cystectomy had been recommended for the invasive recurrence, which was refused by all except one and was treated with cisplatin-based chemotherapy. Metastases had developed in 2 of 19 patients, one from each arm. One patient died of disease, and the other one received further cisplatin-based chemotherapy. One patient of arm-A was lost to follow-up.

At 8 weeks after completion of the treatment protocol 81% (13/16) in arm-A received CCRT had CR unlike 40% (6/15) in arm-B received radiation only, which was statistically significant (P ~ 0.02). The odds ratio of CCRT versus RT alone was 6.500 (95% confidence interval, 1.279–33.034) [Table 2a and b and Figure 1].

Table 1: Pretreatment characteristics, no statistical difference between the treatment arms

Pretreatment characteristics	Arm-A chemo-radiation (*n*=16) (%)	Arm-B radiation (*n*=15) (%)
Sex		
Male	14 (88)	13 (87)
Female	2 (12)	2 (13)
Age (in years)		
Range	49-65	45-64
Average	58.25	57.33
Karnofsky score		
60-70	7	6
80-100	9	9
TNM staging - (T)		
T2a	4	4
T2b	5	6
T3a	3	2
T3b	4	3
Creatinine clearance (ml/min)		
Range	63	64
Average	60-72	60-70
Grade of tumour		
II	3 (19)	3 (20)
III	11 (69)	11 (73)
IV	1 (6)	0
Unknown	1 (6)	1 (7)
Completeness of TURBT		
Yes	3 (19)	3 (20)
No	13 (81)	12 (80)

TNM: Tumor node metastasis, TURBT: Trans urethral resection of the bladder tumor

Table 2a: Assessment of response 8 weeks after chemoradiation/radiation

Residual disease	Arm-A (*n*=16) chemoradiation (%)	Arm-B (*n*=15) radiation (%)
Residual disease absent	13 (81)	6 (40)
Residual disease present	3 (19)	9 (60)

P~0.02. Significant

Table 2b: Risk estimate

Odds ratio for response (no residual/residual)	Value	95% confidence interval	
		Lower	Upper
	6.500	1.279	33.034

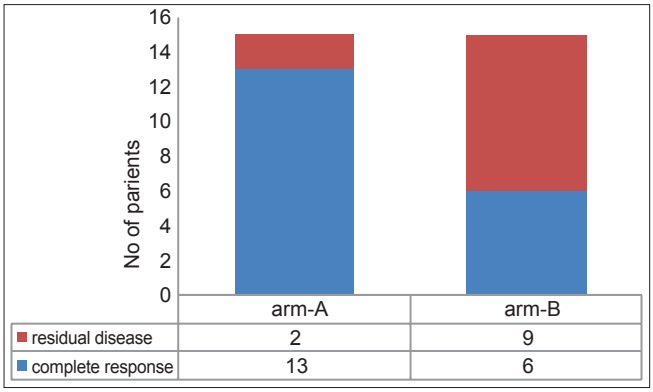

Figure 1: Bar diagram showing response 8 weeks after chemoradiation/radiation

The overall toxicity profiles in both arms were comparable with no statistical difference detected by Chi-square test. No patient had toxicity of grade 5 [Table 3 and Figure 2a and b].

Table 3: The toxicity profiles were compared in both the arms using RTOG/EORTC acute radiation morbidity scores

Toxicity evaluation-acute	Arm-A (*n*=16) chemoradiation (%)	Arm-B (*n*=15) radiation (%)	*P*
Hematological			
Grade 1	4 (25)	7 (47)	0.444 (NS**)
Grade 2	8 (50)	5 (33)	
Grade 3	4 (25)	3 (20)	
Grade 4	0	0	
GI			
Grade 1	4 (25)	8 (53)	0.226 (NS**)
Grade 2	6 (37)	4 (27)	
Grade 3	5 (32)	3 (20)	
Grade 4	1 (6)	0	
Bladder			
Grade 1	4 (25)	5 (33.3)	0.846 (NS**)
Grade 2	10 (62)	8 (53.33)	
Grade 3	2 (13)	2 (13.33)	
Grade 4	0	0	

**NS: Nonsignificant statistical difference. Chi-square test was used for analysis. GI: Gastrointestinal, RTOG: Radiation Therapy Oncology Group, EORTC: European Organization for Research and Treatment of Cancer

DISCUSSION

Broadly, the treatment options of muscle-invasive bladder carcinoma are either bladder-sparing or nonsparing. In the United States, the standard method is radical cystectomy and pelvic lymph node dissection. Organ preservation is now the standard method of care in numerous malignancies that including the breast, the anus, and the head and neck. Any bladder conserving treatment approach which have a high likelihood of eradicating the primary tumor, preserve good bladder function and not result in compromised patient survival, must be accepted, because various population-based studies comparing symptoms experienced by patients who had cystectomy to those who received radiotherapy showed satisfactory urinary, rectal and sexual function in patients treated without cystectomy.[12] In a number of published reports, it has been documented that the use of radiotherapy alone, for an unselected population of patients with muscle-invasive bladder cancer is unsatisfactory.[13]

The key to the success of bladder preservation is to reserve only those patients for it, who show a clinical CR to CCRT. Prompt cystectomy is recommended to partial responders and who subsequently develop invasive bladder cancer. All the protocols developed at the Massachusetts General Hospital (MGH) or within the RTOG, since 1986, at the earliest sign of local failure discontinued bladder-preserving effort and recommended radical cystectomy. They observed that one-third of the patients of those protocols requires radical cystectomy. In this study, we also preferentially recommended cystectomy, but the majority of patients with a persistent tumor at initial evaluation after CCRT refused a salvage operation.

Some studies have been undertaken to identify clinical factors that help distinguish candidates for trimodality treatment. Rödel *et al*. concluded that the completeness of TURBT is one of the most potent factors of survival after CCRT for patients with invasive bladder cancer.[14] Other clinical factors that have been considered when choosing patients for bladder-preserving surgery include; small tumor size (<5 cm), early tumor stage, absence of ureteral obstruction, and no evidence of pelvic lymph node metastases.[15]

Shipley *et al*. showed that local control and chance of bladder preservation is best in patients with T2-T3 or tumors <5 cm in diameter, not close to the dome of the bladder, and without associated diffuse carcinoma *in situ*.[16]

During the last two decades, different successful bladder-preserving approach has been evolved. Following TUR, the use of concurrent radiotherapy and cisplatin have been shown to improve local control in muscle-invasive bladder cancer in carefully selected patients.[17] Cisplatin concurrently with radiation was used for the 1st time by the National Bladder Cancer Group from 1981 to 1985 in 68 patients with muscularis-propria invading bladder cancer that was unsuitable for cystectomy and in a multicenter protocol this approach was proved safe and feasible with a long-term survival of 64% and 22% with stage T2 and T3 to T4 tumors.[18] This early result was validated by the National Institute-Canada randomized trial of radiation with or without concurrent cisplatin for T3 bladder cancer, which showed a significant (67% vs. 47%) improvement in pelvic tumor control with concurrent cisplatin.[19]

The rationale for CCRT after TURBT is twofold. First, certain cytotoxic agents like cisplatin act as a radiosensitizer and inhibit repopulation during radiotherapy. Second, systemic therapy is necessary to eradicate rates of occult

metastases that have already developed in as many as 50% of muscle-invasive cancer.[15]

The selection of optimal regimens is another concern, but optimal regimens have not been established. Many investigators are still recommending cisplatin and 5-fluorouracil because both agents have been shown to have radiosensitizing activities and acceptable toxicities.[20] Newer chemotherapeutic agents, particularly gemcitabine and taxanes, have also been shown to be potent radiation sensitizers, especially in urinary balder cancer and in head and neck cancer.[21] Furthermore, recent studies have established that gemcitabine in combination with radiotherapy is a feasible regimen for bladder-sparing treatments, and other series have shown that CCRT using platinum and paclitaxel or docetaxel was also an effective regimen.[22,23]

For almost two decades, the MGH and the RTOG have evaluated in phase II and III protocols concurrent radio-chemotherapy and neoadjuvant or adjuvant chemotherapy using various radiosensitizing agent, either singly or in combination. The comparative analysis of these studies is illustrated in Table 4. All these results strongly suggest that CCRT is superior to RT alone.[24]

Shipley *et al*. reports a complete response of 63% using concurrent cisplatin containing chemotherapy and radiotherapy after rigorous TUR of the muscle-invasive bladder cancer.[16] Kaufman *et al*. in RTOG 95–06 trial showed a complete response of 67% (22/33) following induction therapy and 90% (18/20) following consolidation therapy.[25] The rate of CR showed by Housset *et al*. is 74%,[9] and by Rödel *et al*. it is 72%[14] using trimodality therapy. Efstathiou *et al*. showed that 72% of all patients (78% with T2 disease) achieved CR to induction chemoradiation.[26] Koga *et al*. found a 41/97 (42%) a CR, 29/97 (30%) partial response, 24/97 (25%) stable disease, and 3/97 (4%) progressive disease with the same treatment.[27] Joung *et al*. showed a 75% (15/20) CR rate.[28] In our study, 81% (13/16) patients in arm-A receiving CCRT had CR unlike 40% (6/15) in arm-B.

Of concern is that, in our study, within 12 months of median follow-up 8 of the 19 (42%) of the complete responding patients who completed the protocol, have had local recurrence (3 invasive and 5 superficial). For 33 patients, Kaufman *et al*. in RTOG 95–06 trial showed that, within 29 months of median follow-up, 9 of 20 (45%) complete responding patients had local recurrence (three invasive and six superficial).[25] Shipley *et al*. reported a long-term follow-up data for 190 patients on conservative treatment of muscle-invasive bladder cancer at MGH which showed a bladder recurrence rate of 40% (24% superficial and 16% invasive) amongst complete responders.[8] Housset *et al*. report a bladder recurrence rate of 17% (12/71) amongst complete responders.[9] Joung *et al*. showed that, of 15 patients with CR, tumor recurrence (both local and distant) occurred in 7 patients. Two patients showed invasive tumor recurrence at the preserved bladder 6 months and 52 months post-CRT. The patient with later

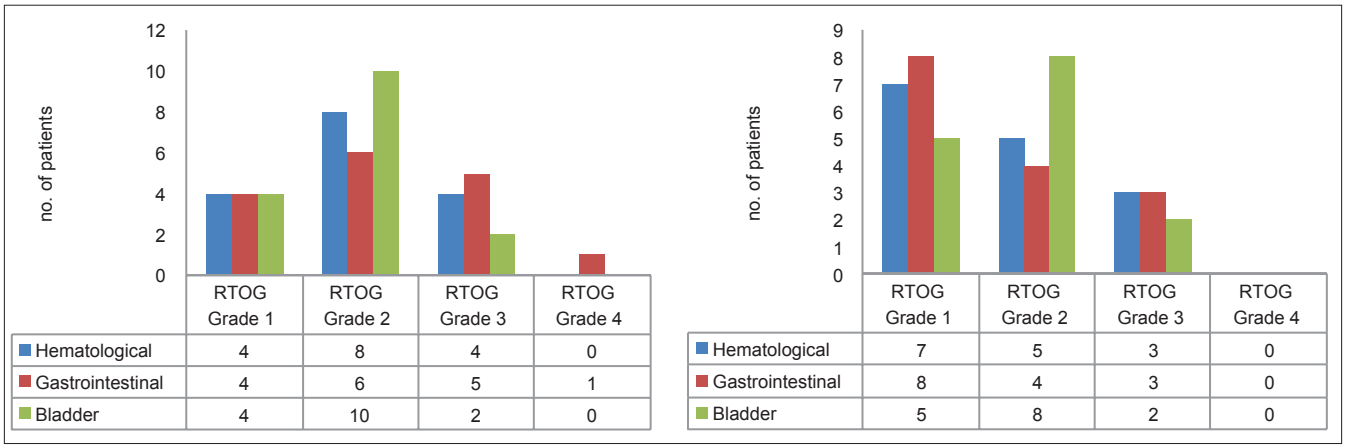

Figure 2: (a) Bar diagram showing acute toxicity arm-A, (b) Bar diagram showing acute toxicity arm-B

Table 4: Results of multimodality treatment for muscle-invading bladder cancer

Series (references)	Multimodality therapy used	Number of patients	5-year overall survival (%)	5-year survival with intact bladder (%)
RTOG 8512 (1993)	External-beam radiation+cisplatin	42	52	42
RTOG 8802 (1996)	TURB, MCV, external-beam radiation+cisplatin	91	51	44 (4 years)
RTOG 8903 (1998)	TURBT±MCV, external-beam radiation+cisplatin	123	49	38
MGH (2003)	TURBT±MCV, external-beam radiation+cisplatin	190	54	45

RTOG: Radiation Therapy Oncology Group, TURBT: Transurethral resection of bladder tumor, MCV: Methotrexate, cisplatin, vinblastine, MGH: Massachusetts General Hospital

recurrence developed a recurrent superficial cancer before an invasive cancer. For salvage treatment of invasive cancer, both patients requested chemotherapy rather than salvage cystectomy, and they remained in a locally controlled state with no evidence of distant metastasis by cystoscopy or CT scan at 6 months after chemotherapy using M-VAC regimen. On the other hand, isolated superficial recurrences were found in another 2 patients. Of these, one patient experienced superficial recurrences on three occasions, which were managed by TUR and intravesical chemotherapy. The other patient showed experienced a single recurrence at 48 months post-CRT. In another 3 patients, isolated distant metastases to brain, lung and liver developed at 6, 10 and 24 months post-CRT, and underwent M-VAC for the treatment of distant metastasis. Subsequently, they died of progression to bladder cancer.[28]

Regarding survival, Kaufman *et al*. showed an overall 3 years survival of 83% after consolidation phase of trimodality therapy.[25] Shipley *et al*. reported a 5 years and 10 years actuarial overall survival rate of 54% and 36% respectively (stage T2, 62 and 41%; stage T3-T4a, 47 and 31% respectively) after consolidation phase of trimodality therapy.[18] In our study because of the limited accrual of patients, and also of the short period of median follow-up, it is inappropriate to conclude the survival advantage.

In our study, the overall toxicity profiles in both the arms were same with patients of arm-A suffering from more grade 2/3 RTOG/EORTC lower gastrointestinal-toxicity (11/16) than in patients of arm-B (7/15). The common acute side effects with CCRT are transient diarrhea and voiding symptoms (frequency and urgency), which were easily managed with supportive treatment. Moreover, these symptoms usually resolved within 2 or 3 weeks of completing treatment. The morbidity of this protocol was documented, and it was found that no patients required modification of induction or concurrent chemotherapy or radiotherapy doses or discontinuation of the treatment due to acute toxicity. Shipley *et al*. in RTOG 89–03 trial, showed that the toxicity was mostly severe leucopenia and sepsis, which resulted in 3 of 174 treatment-related death.[18] Kaufman *et al*. in RTOG 95–06 trial showed that 7 of 34 patients (21%) developed Grade 3 or 4 hematologic toxicity with trimodality therapy.[25] In our study 4 of 16 patients (25%) in chemoradiation arm and 3 of 15 (20%) in radiation arm developed Grade 3 hematological toxicity and there is no Grade 4 hematological toxicity in both the arms. Jung *et al*. showed that, in their study, in terms of hematologic toxicities, neutropenia, leukopenia, thrombocytopenia, and anemia were reported in 1 (5%), 5 (25%), 2 (10%), and 2 (10%) patients, respectively. Only one patient (5%) required a dose reduction due to neutropenia and recovered within 2 weeks. In terms of nonhematologic toxicities, diarrhea was most frequently reported and occurred in 7 (35%) patients. No case of grade 3–4 nonhematologic toxicity was encountered. All patients who experienced a nonhematologic toxicity recovered with conservative treatment. In terms of bladder function, mild dysuria, urgency, and nocturia were registered in 20–55% of patients, but these were temporary and improved 3 months post-CRT. No remarkable late complication occurred though one patient complained of nocturnal frequency due to a decreased functional bladder capacity.[28]

The present study is limited by small number of patients recruited, and shorter median follow-up. Moreover, this study did not include advanced T4 tumors and those with hydronephrosis. So it is difficult to compare these results with other published bladder-sparing results. Study with more accrual of patients and longer median follow-up is required to identify factors that distinguish candidates for bladder-preserving treatment, and the efficacy of the treatment. The protocol completion rate of both the arms of this study is same and 100%, and so also the rate of complete responders after induction phase of the treatment in chemoradiation arm which might also be different in case of greater accrual of patients. The protocol completion rate of Kaufman *et al*. was 76%[25] and that of Joung *et al*. is 91%.[28]

In our study, majority of patients with a persistent tumor after CCRT refused salvage cystectomy. The number of patients with incomplete TURBT was too small to reach the conclusion of the survival difference with respect to the completeness of TURBT. Radiotherapy as a sole treatment for muscle-invasive bladder cancer did not prove to be a good alternative to radical cystectomy. However, the adoption of trimodality treatment seems to be an equally effective alternative management for such patients. The value of this trimodality treatment depends upon the extent and adequacy of TURBT, the use of effective chemotherapeutic agents as sensitizing agents for radiotherapy and more importantly, upon the precise technique of irradiation to achieve the desired results. Ensuring target coverage may improve the tumor control probability by ensuring the target receives the intended dose. Furthermore, the use of this technology could allow researchers to reduce treatment toxicity in two-way; first, the use of smaller margins than those traditionally used could reduce the volume of small bowel and rectum irradiated; second, bladder toxicity may be reduced by using improved localization techniques, reduced margins and full-bladder protocols to deliver a partial bladder boost. If we can more precisely target the bladder tumor, this could allow larger doses to be given with further improvement in tumor control without an increase in normal tissue complication probability.

CONCLUSION

This neoadjuvant chemoradiotherapy is easy to implement and well tolerated even in elderly patients, provides a high complete response rate. The trimodality therapy with selective bladder preservation is not designed to replace radical cystectomy but can be offered as a reasonable alternative to appropriately selected patients with invasive bladder cancer who are not willing to undergo radical cystectomy and urinary diversion. Radical cystectomy is an available option in those who fail combined radiation and chemotherapy, with no diminution in survival related to the delay in cystectomy. Close follow-up of patients after CCRT is mandatory even in those patients who achieved CR at initial response evaluations.

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