Research Article

Concurrent chemoradiotherapy for muscle-invasive bladder carcinoma for organ preservation: A feasibility study from tertiary care center

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ABSTRACT

Background: The primary goal of treatment in oncology is cure but efforts should be made to preserve quality of life. The gold standard for treatment of muscle-invasive bladder cancer is radical cystectomy. However, radical cystectomy cannot be performed without risk of complications and often the outcome for the patient is a mediocre quality of life as the patient has to live with an artificial bladder or ileal conduit. Even after radical cystectomy, 40–50% of patients will succumb to distant metastases within 5 years. As in the case of several other malignancies, increasing efforts have been made over the last few decades to adopt organ sparing treatment. Bladder-sparing monotherapies lead to disappointing results, local disease control may be maximized using a trimodal approach based on complete transurethral tumor resection of bladder (TURB), followed by concurrent chemoradiotherapy and cisplatin-based systemic chemotherapy. **Objectives:** The aim of our study is feasibility of concurrent cisplatin with radiation in bladder preservation in our hospital. **Materials and Methods:** Thirty-two previously untreated patients of histologically proven transitional cell carcinoma of urinary bladder received concurrent chemoradiation (60 Gy) with cisplatin. All patients received concurrent chemotherapy with cisplatin infusion in a dose of 20 mg/m^2/day on consecutive 5 days from Day1 to Day5 in 1st and 5th week of radiotherapy. Detailed clinical examination along with cystoscopy, TURB along with biopsy, and computed tomography scan of abdomen pelvis were done before treatment and to assess response toxicity, and disease-free survival (DFS) during follow-up period. **Results:** Median follows up period was 36 months. Local disease control was seen in 71% patients. Five years DFS is 58%. Five years overall survival is 64%. **Conclusions:** Concurrent chemoradiation in carcinoma of urinary bladder is feasible in our hospital and results in good local control, survival with acceptable toxicity.

KEY WORDS: Bladder Cancer; Chemoradiotherapy; Cispaltin

INTRODUCTION

The gold standard for treatment of muscle-invasive bladder cancer is radical cystectomy. This procedure is associated with good local control.[1-3] However, radical cystectomy cannot be performed without risk of complications and often the outcome for the patient is a mediocre quality of life as the patient has to live with an artificial bladder or ileal conduit.[4-6] Moreover, although recent years have witnessed the development of continent urinary diversions, there is still no substitute for the patient's own fully functional bladder. Even after radical cystectomy, 40–50% of patients will succumb to distant metastases within 5 years. Exclusive radiation therapy controls local disease in only 30–40% of patients.[7] Cisplatin is one of the most active chemotherapy agents in this disease and when given concurrently with radiation has the added advantage of acting as a radiation sensitizer without significantly increasing late normal tissue toxicity. Concurrent chemotherapy is used primarily to potentiate the effects of radiation (radiosensitization) employing lower total doses and

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limited number of cycles. Concurrent chemoradiation may decrease the shoulder or increase the slope of the radiation dose–response curve through mechanisms such as direct tumor cytotoxicity, tumor cell synchronization, and inhibition of sublethal radiation repair. Concurrent chemotherapy, unlike neoadjuvant chemotherapy, does not delay the commencement of radiotherapy (XRT), which is a proven effective treatment in bladder cancer. These chemoradiation schedules increase both local and systemic control compared to radiation alone. One of the most potent chemotherapeutic agents in carcinoma urinary bladder is cisplatin. All the other chemotherapeutic agents have significantly lower response rates as compared to cisplatin. Once the concept of effective radiosensitization by these agents was established, it became logical to synchronize the two modalities, based on drug pharmacokinetics.[8] The adoption of induction chemotherapy before concurrent chemoradiotherapy (CRT) does not improve clinical outcomes.[9] A number of studies of cisplatin-based concurrent chemoradiation[10,11] using a variety of schedules has suggested that this approach is better than radiation alone with survival rates almost similar to those seen with radical cystectomy. In addition, the majority of surviving patients have been able to maintain a functioning bladder. Patients treated with cisplatin or gemcitabine had less toxicity and improved tolerability.

Due to bladder-sparing monotherapies lead to disappointing results, local disease control may be maximized using a trimodal approach based on complete transurethral tumor resection of bladder (TURB), followed by concurrent XRT and cisplatin-based systemic chemotherapy.[12] Although concurrent administration exploits the radiosensitizing property of cisplatin but the effect of chemotherapy is not by radiosensitization alone but also by systemic effect by elimination of micrometastases.[13] We wanted to determine if primary chemoradiation for bladder preservation is feasible or not in our hospital.

MATERIALS AND METHODS

Treatment Protocol Depicted in Following Chart

Thirty-two previously untreated patients of histologically proven transitional cell carcinoma of urinary bladder registered in Nil Ratan Sircar Medical College and Hospital from January 2012 to December 2016, entered in the treatment protocol after fulfilling the following criteria: (1) Good Karnofsky performance score >70, (2) Stage T2–T3, N_0M_0, and (3) no prior chemotherapy or XRT. All patients enrolled into protocol for the study were initially evaluated with full medical history and physical examination. The investigative workup include: Baseline hematological profile and blood biochemistry, chest X-ray posteroanterior view, intravenous pyelography, transurethral resection, histopathological examination report for confirmation of diagnosis and to determine depth of tumor invasion, computed tomography (CT) scan (non-contrast and contrast enhanced) of pelvis and abdomen, and bone scan in indicated cases.

Radiotherapy*(XRT)*

XRT was initiated 4–6 weeks after transurethral resection of bladder tumor. Initially, whole pelvis treated using rectangular portals. Field border was L5-S1 interspace superiorly, 1.5–2 cm beyond pelvic bone laterally, and inferior border of obturator foramen caudaly. A dose of 40 Gy/4 weeks/20#/4 weeks delivered to this field by conventional 2 Gy/#. Treatment executed in cobalt 60 (THERATRON-780) or 6 MV linear accelerator. After completion of 40 Gy, consolidation XRT initiated and another dose of 20 Gy in 2 weeks was delivered to the bladder.

Chemotherapy

All patients received concurrent chemotherapy with cisplatinum infusion in a dose of 20 mg/m^2/day on consecutive 5 days from D_1 to D_5 in 1st and 5th week of XRT. Cisplatinum infusion started 3 h before XRT. Proper hydration (l L NS infusion in 1 h – cisplatinum in 500 ml NS in ½ h – mannitol 20% 100 ml infusion in 10 min – 1 L NS infusion in 1 h) and antiemetic prophylaxis with 4 mg ondansetron used in all patients. Acute treatment-related toxicity noted every weekly and graded using Common Terminology Criteria for Adverse Events v4.0.

Post treatment follow-up

After completion of treatment, patients were followed up as out lined: (1) Patients were evaluated with cystoscopy, 12 weeks after completion of XRT, (2) complete responder was evaluated with cystoscopy every 3 monthly, (3) patients, who do not achieve complete response after completion of XRT, were offered to undergo salvage cystectomy, (4) CT scan pelvis and abdomen every 3 monthly, and (5) during follow-up period patients were receive supplementary vitamins, iron, and symptomatic treatment.

Urinary bladder has two functions; first, storage of urine and second, expulsion urine through urethra. Storage function can be assessed clinically by noting frequency of micturation, pre voiding bladder volume (bladder capacity). Second function can be assessed by noting post voiding bladder volume by ultrasound.

RESULTS

Patient's Characteristics

The age of patients ranged from 34 to 85 years with median of 64 years. A total of 16 patients have age >65 years. Patients specific variable are depicted in Table 1. Stage and histology depicted Table 2.

Disease Control

A total of 32 patients were treated and median follows up period 36 months. Median age is 64 years with ranges from 34 to 85 years. Local disease control is seen in 71%. Disease status, at last, follow-up depicted in Table 3.

Survival

Disease free survival (DFS) and overall survival (OS) were computed using Kaplan–Meier survival analysis. Five years DFS is 58%. Five years OS is 64%. DFS for stage, grade was analyzed and none was statistically significant.

Functional Results

Urinary bladder has two functions; first, storage of urine and second, expulsion urine through urethra. Storage function was assessed clinically by noting frequency of micturition. At 3 months follow-up, all patients had Grade I increased frequency of micturition. At subsequent visit frequency of micturition subsided and did not experience frequency of micturition at all. Nine patients reported Grade II dysuria and responded well to symptomatic management. None of the patients experienced difficulty in emptying bladder or incontinence**.**

Table 1: Patient's demographic characteristics

Variable and measure	Number of patients (*n*) (%)
Sex	
Male	31 (97)
Female	1 (3)
Family history	
Absent	0
Addiction history	
Present	12 (38)
Absent	20 (62)
Comorbidities	
Absent	0
KPS	
90	15 (47)
80	9 (28)
70	8 (25)

Table 2: Distribution of the patients' according to histology and grading of tumor

Histology and grade	Number of patients (*n*) (%)
Transitional cell	32 (100)
Low grade (Gr.−1)	7 (22)
Intermediate grade (Gr.−2)	9 (28)
High grade (Gr.−3)	16 (50)
T stage	
T2	20 (63)
T3	12 (37)
N stage	
N0	32 (100)

Table 3: Disease status at last follow up

Disease status	Numbers of patients (*n*) (%)
NED	23/32 (72)
Local failure	6/32 (19)
Nodal failure/distant metastasis	3 (9)

DISCUSSION

In our study, six patients had local failure and underwent salvage cystectomy. Three had distant failure at the time of last follow-up. Local control was achieved in 23 of 32 (71%) patients and in these patients bladder function preserved with acceptable toxicity. Five years DFS was 58% and 5 years OS 65%. The acute toxicity profile in our study was comparable and similar to what has been observed in other cisplatin-based chemoradiation trials.[11-13]

Rödel *et al*.[14] reported initial results of an intensified protocol of transurethral surgery and radiation therapy plus concurrent cisplatin and 5-fluorouracil for organ preservation in patients with invasive bladder cancer (*n* - 45). Hematologic Grade 3/4 toxicity occurred in 10% and 4%, respectively; Grade 3 diarrhea occurred in 9%. Thirty-four patients (76%) completed the protocol as scheduled or with only minor deviations. The 5 years survival rate reported by different authors using concurrent chemoradiation for organ preservation, varies from 49% to 63% and 5 years survival with intact ladder varied from 42% to 48%.[14-16] DFS, OS, and toxicity profile in our study were comparable and similar to what has been observed in other cisplatin-based chemoradiation trials. Unfortunately, comparing the results of any non-randomized trial of chemoradiation therapy with contemporary cystectomy series is not easy to judge, which is superior than others. Differences in survival are explained in part by inherent selection bias. Patients recruited for bladder-preserving treatment tend to be older, with significant comorbidity, compared with those selected for radical surgery. Furthermore, outcome is confounded by discrepancies between clinical (bladder-preserving regimens) and pathological (cystectomy) staging. It has been shown that clinical staging is more likely to under stage disease with regard to depth of muscle-invasion when compared with pathological staging. Any outcome bias is therefore in favor of the radical cystectomy series. The variety of treatment protocols and chemotherapeutic regimens being used further limit comparison of outcomes between CRT series.

However, in our study, small number patients and short period of follow-up are major limitation for conclusions.

CONCLUSIONS

Chemoradiation is effective, feasible, and without any increase in acute morbidity. This modality could be offered in patients who refuse radical cystectomy or medically inoperable, however, to validate the findings of our study and

for determining long-term benefit, i.e., improvement in OS, longer follow-up, and more sample size is required.

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