



Chemoradiation for organ preservation in the treatment of muscle invasive bladder cancer: Our Institutional Experience

S. Gupta¹, S. De¹, N. Leekha², S.C. Sahay³, P. Chaudhary¹, S. Srinivasan¹, M. Nandy⁴

¹Dept. of Radiation Oncology, ²Dept. of Surgical Oncology, ³Dept. of Urology, ⁴Dept. of Medical Oncology, Max Super Speciality Hospital, Vaishali, Ghaziabad U.P. India

Abstract

Aim

To assess outcome of chemoradiotherapy for organ preservation in muscle invasive bladder cancer.

Material and Methods

41 patients treated between January 2010 to January 2015 were evaluated in the present study. All patients T staged ranging from cT2–T4a and had undergone maximal transurethral resection of bladder tumour (TURBT). After maximum bladder tumour resection patients were treated with Radiotherapy with or without concurrent chemotherapy. 8 weeks after completion of treatment response was assessed by check cystoscopy, urine cytology and CECT scan Abdomen. Data regarding the toxicity profile, initial complete response rates at 3 months, occurrence of loco regional or distant failure and survival was recorded.

Results

Age ranged between 45– 84 years, (mean age 65.44). Radiotherapy dose planned ranged from 60 Gy/30fr to 70.3 Gy/37 fractions to primary target and 59.2 Gy/37fractions to the nodal disease. PTV volume ranged

from 69–548.9 cc. 23 patients received concurrent chemotherapy weekly.

11 patients have cystitis (5 Gr I, 4 Gr II and 2 Gr III). 5 patients have myelosuppression. 10 patients have acute gastrointestinal toxicity (5 Gr–I, 4 Gr–II, 1 Gr–III). At the time of analysis follow up ranged from 3 –42 months (median follow 1 year).The DFS at 42 months was 54%. Out of 39 patients 3 were lost to follow up (2 in partial bladder group and 1 in whole bladder group). Out of 36 patients 24 (66.6%) are disease free, 4 (11.1%) patients had recurrence for which 2 underwent salvage cystectomy whereas 2 patients received palliative chemotherapy. Five patients developed distant metastases (4 bone and 1 brain metastasis).

Conclusion

Bladder–preservation therapy for muscle–invasive bladder cancer is a valid substitute in selected cases with long–term efficacy similar to radical cystectomy, with the additional advantage of preserving excellent bladder function in the majority of long–term survivors.

Keywords

bladder cancer, Radiotherapy, cystectomy

Introduction

Urinary bladder cancer continues to pose a substantial global health challenge. Transitional cell carcinoma is the most predominant pathological subtype and approximately 30% of such cases are muscle–invasive at the time of diagnosis.^(1,2) Locally advanced carcinoma bladder, represents a potentially serious threat, with long–term survival of approximately 50%.^(3,4) Neoadjuvant chemotherapy followed by radical cystectomy is the standard therapy for these patients with an expected 5–year survival of 45–60%.⁽⁵⁾ Another alternative is the

trimodality therapy for bladder preservation, in which maximal transurethral resection of the bladder (TURBT) is followed by definitive chemoradiotherapy. Although good outcomes have been reported in the literature but most these studies have been retrospective and have

Corresponding Author: Dr. Sweety Gupta,
(Consultant, Dept. of Radiation Oncology Max Super Speciality Hospital Vaishali Ghaziabad), B–1 503, Olive County, sector–5, Vasundhara, Ghaziabad (U.P.) India.
Pin code – 201012. Tel. No. (91)–9891981332,
Email: drsg2411@yahoo.co.in

had multiple lacunae. There has been no randomized controlled trials comparing the Gold standard neoadjuvant chemotherapy followed by Radical cystectomy with bladder preservation using the trimodality treatment (TMT). However with time the general acceptability of bladder salvage protocol has increased and has now been accepted as an alternative management for locally advanced bladder cancer in guidelines.⁽⁵⁾ Most of the retrospective studies reported good outcomes with TMT however there has been no consensus on the dose of Radiation and the use of concurrent Chemotherapy. Multiple institutions and cooperative groups have played a role in evolving and refining the contemporary approach to Radiotherapy based bladder preservation. There is, however, a need to assess the quality of bladder conservation and other late effects of this treatment strategy. The present study was done to assess the outcome of patients with MIBC treated by transurethral resection of the bladder and concomitant chemo radiation therapy.

Material and Methods

A retrospective analysis of Muscle Invasive Bladder Cancer who were treated with bladder conservation intent at our institute was done, 41 patients who had undergone treatment between January 2010 to January 2015 were evaluated in the present study. Two patients did not complete the treatment and were excluded from the final analysis. All patients T staged ranging from cT2–T4a and had undergone maximal transurethral resection of bladder tumour (TURBT). Histopathology was invasive transitional cell carcinoma for all the patients. A review of histopathology was done at our centre to ensure the presence of deep muscle in the specimen hence ensuring the adequacy of resection. All patients underwent CECT Chest, CECT Abdomen or MRI Abdomen for staging work up. PET CT scan was done in selected cases. After maximum bladder tumour resection patients were treated with Radiotherapy with or without concurrent chemotherapy. Planning CT scan was done with 200 ml of bladder volume for day to day reproducibility and empty rectum. Target volume included the TURBT resected region, remaining bladder with margins and pelvic nodes. Planning was done on Eclipse 8.6.23. Technique used was IG–IMRT (Image guided intensity modulated Radiotherapy). Radiotherapy treatment was done on Clinac iX with MMLC 120.

Concurrent chemotherapy included Cisplatin weekly. 8 weeks after completion of treatment response was assessed by check cystoscopy, urine cytology and CECT scan Abdomen. Complete responders were followed by 3 monthly clinical examination and 6 monthly check

S. No	Variable	Categories	Number	Percentage
1	Sex	Males	36	92.3
		Females	3	7.6
2	T stage	T2	15	38.46
		T3	22	56.4
		T4	2	5.1
3	N Stage	N0	35	89.74
		N1	3	7.60
		N2	1	2.56
4	Stage of cancer	II	15	38.4
		III	20	51.2
		IV	4	10.2
5	Concurrent Chemotherapy given	Yes	23	59
6	Radiation	Whole bladder	9	23
		Partial bladder	30	77

Table 1: Showing characteristics of study participants

cystoscopy, urine cytology and CECT scan Abdomen for the first 2 years. Patients with residual disease were offered to undergo salvage cystectomy and those who denied or developed metastases were considered for palliative chemotherapy. However this protocol of treatment has been revised in accordance with the widely accepted bladder salvage protocol where as a check cystoscopy for response evaluation is now being done after 45 Gray of radiation dose in all patients. Responders are being treated with radical radiotherapy and non responders are offered salvage cystectomy.

Data regarding the toxicity profile, initial complete response rates at 3 months, occurrence of loco regional or distant failure and survival was recorded.

Results and Observation

Age ranged between 45– 84 years, (mean age 65.44). Tumour stage, according to the 2010 7th edition International Union against Cancer classification, was based on TUR findings. Detailed patient characteristics in terms of sex, stage, concurrent chemotherapy given or not and partial versus whole bladder irradiation are described in Table 1.

S. No	Toxicity	Frequency (%)
1	No toxicity	12 (30.7)
2	Bladder	11 (28.2)
	Grade I	4
	Grade II	6
	Grade III	1
3	GI	8 (20.51)
	Grade I	2
	Grade II	5
4	Grade III	1
	Myelosuppression	6 (15.4)

Table 2: Toxicity Profile of study participants

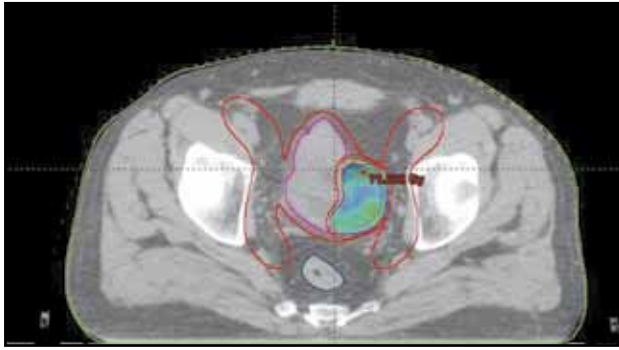


Figure 1: Axial view of Partial bladder radiation volume

Radiotherapy dose planned ranged from 60 Gy/30 fractions to 70.3 Gy/37 fractions to primary target and 59.2 Gy/37 fractions to the nodal disease. (See Fig.1)

PTV volume ranged from 69–548.9 cc. 23 patients received concurrent chemotherapy weekly (Inj Cisplatin 40 mg/m²). The National Cancer Institute Common Toxicity Criteria version 2.0 was used to score acute radiation and chemotherapy toxicity (≤ 90 days from the start of radiation therapy). 12 patients did not experience any acute toxicity. 11 patients had cystitis (5 Gr I, 4 Gr II and 2 Gr III). 5 patients had myelosuppression. 10 patients had acute gastrointestinal toxicity (5 Gr-I, 4 Gr-II, 1 Gr-III). See Table 2.

At the time of analysis follow up ranged from 3–42 months (median follow 1 year). The median survival could not be calculated as the survival did not drop below 50% within the follow up period. The DFS at 42 months (end of follow up) was 54% (Figure 2).

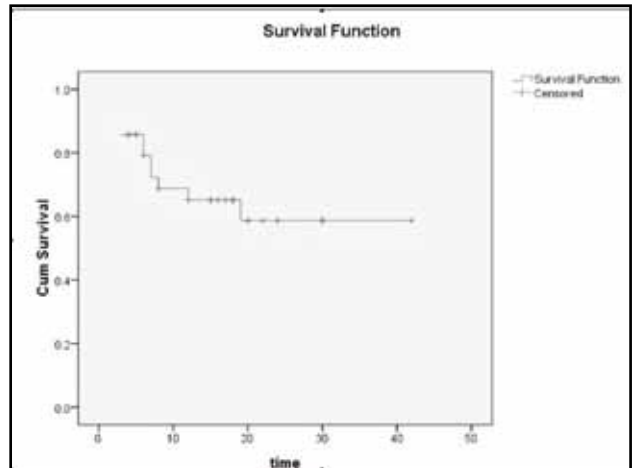


Figure 2: Kaplan Meier survival function curve depicting Disease free survival

Out of 39 patients 3 were lost to follow up (2 in partial bladder group and 1 in whole bladder group). Out of 36 patients 24 (66.6%) are disease free, 4 (11.1%) patients had recurrence for which 2 underwent salvage cystectomy and are disease free whereas 2 patients received palliative chemotherapy. Five patients developed distant metastases (4 bone and 1 brain metastasis). Two patients developed second primary lung with bone metastases. One patient died due to liver cirrhosis (See Table 3).

Discussion

Genitourinary tumors are commonly encountered in clinical practice. In an Indian study, genitourinary

S. No	Factor	Death	NED	Residual	LR	DM
1	Radiation					
	Partial	1(3.5)	17(60.7)	0	2(7.14)	5(17.8)
	Whole	0	6 (75)	0	2 (25)	0
2	CCT					
	Yes	0	14(60.9)	4(17.4)	1(4.3)	1(4.3)
	No	1(5.9)	9(52.9)	1(5.9)	0	4(23.5)
3	Stage					
	II	0	11(78.6)	2(14.3)	0	1(7.1)
	III	1(5)	11(55)	2(10)	1(5)	3(15)
	IV	0	1(16.7)	1(16.7)	0	1(16.7)
	Total	1(2.5)	23(57.5)	5(12.5)	1(2.5)	5(12.5)

Table 3: Comparison of outcome of patients based on stage of cancer, radiation and concurrent chemotherapy (NED: No evidence of disease, LR: local recurrence, DM: distant metastases)

cancers (20.79%) were the most common cancers in both sexes. 17.48% of all the malignancies were constituted by genitourinary cancers in males out of which urinary bladder were 30.40%.⁽¹⁾ Majority of these patients are males and are the bread earners of the family. Traditionally, radical cystectomy has been offered to them for treatment of muscle–invasive bladder cancer. Although radical cystectomy has been considered as gold standard in the treatment of bladder cancer, yet it fails to cure more than 50% of patients who would finally develop distant metastatic disease. Radical cystectomy also results to decreased quality of life (QoL) and is associated with complications like hemorrhage, infection, urinary leaks, pelvic lymphoceles, intestinal obstruction, and peritonitis.⁽²⁾ Apart from these there are long term impact on the lifestyle and psyche of patients who seldom get accustomed to wearing urine bags. Sadly most of these patients belong to lower socioeconomic strata of society and are ground level workers who find it difficult to work post surgery. India is a tropical country and temperature gets quite high during summers in north India resulting in sweating and fluid loss, diarrhea coupled with malnutrition aggravates the problem and frequently patients presents to emergency rooms with electrolyte imbalance.

An effective bladder salvage protocol in form of trimodality treatment (maximal TURBT, chemotherapy, and radiation therapy) has been adopted by many centers as a standard option for a bladder preserving strategy. Centres like Massachusetts General Hospital (MGH), the University of Erlangen and the University of Paris have considerable experience in bladder preservation strategies with tri modality approach.^(3,4) Published data from such institutions indicate that, a complete response to an initial treatment consisting of TURBT followed by chemoradiation, selects patients whose tumor is likely to be controlled by a bladder sparing approach. If interval cystoscopy after 4–6 weeks shows evidence of residual disease, the intent of bladder preservation is aborted and only complete responders is considered for consolidation chemoradiation. In the Erlangen series, interval cystoscopy was not done and re–evaluation was done after completion of concurrent chemoradiotherapy with restaging TURBT. Complete responders were kept on follow up and patients with persistent or recurrent disease were considered for re–TURBT + intravesical treatment or cystectomy depending on depth of invasion.^(5,6,7) In our study patients were also advised for check cystoscopy after 8 weeks of completion of treatment.

A considerable number of studies have shown that in terms of disease–specific survival radical radiotherapy results are comparable to those for radical surgery at 5 years and 8 years.^(8,9,10) In terms of oncological safety of

bladder conservation the present study reports a DFS of 54% and a follow up of 42 months. Khadar et.al reported that after bladder conservation protocol at a median follow–up of 18.5 months 5 of 8 (62.5%) patients with complete response were alive.⁽¹¹⁾

Several Phase II trials have been performed to assess the option of conservative treatment for muscle–invasive bladder cancer using concurrent chemoradiotherapy, in both Europe and the United States. These studies have shown that concurrent chemoradiotherapy is more effective than radiotherapy alone and concurrent chemoradiotherapy offers a conservative alternative for more than two thirds of selected patients with probabilities of survival similar to surgical series i.e., 50–60% at 5 years.⁽⁹⁾ In our study there was no significant difference in survival of patients with or without chemotherapy ($p=0.525$). 14 (60.9%) patients were disease free, residual disease was present in 4 (17.4%) patients, local recurrence was seen in 1 patient in chemotherapy arm. Distant metastases 4 (23.5%) patients was more common in radiation alone arm.

The benefit of chemoradiation was demonstrated in the Bladder Cancer 2001 (BC2001) phase III trial that enrolled 360 patients with muscle–invasive bladder cancer. Following cystoscopic resection of tumor and biopsy, patients were randomly assigned treatment with RT alone or RT plus chemotherapy. After a median follow up of 70 months chemoradiation resulted in better two–year locoregional control compared to radiation alone (67% vs 54%), improvement in 5 year overall survival (48% vs 35%), lower rate of cystectomy at two years (11% vs 17%) but increased rate of gastro intestinal toxicity (10% vs 3%).⁽¹⁰⁾ The RTOG 0233 trial compared paclitaxel with cisplatin with 5–FU with cisplatin with concurrent radiation in patients with mostly T2 disease (95%).^(10,11) Following TMT, patients received adjuvant gemcitabine, cisplatin, and paclitaxel. Both regimens showed similar rates of CR (62%–72%), 5–year OS (71%–75%), and 5–year survival with an intact bladder with moderate toxicity.

At the radiobiological level, chemotherapy appears to act synergistically with radiotherapy by targeting cells in the radio–resistant phases of the growth cycle, leaving a population of synchronized, more radiosensitive cells.⁽¹²⁾ Cisplatin has been widely investigated for its interaction with ionizing radiation. Cisplatin exerts its cytotoxic effects by chelating guanine residues, yielding monofunctional adducts and intrastrand or inter–strand crosslinks. The first phase II study reporting the concurrent use of cisplatin with pelvic radiotherapy in bladder cancer was published in 1982.⁽¹³⁾ In the present study patients received Cisplatin

as chemotherapy and one patient received Carboplatin in view of deranged renal function test. Conventionally, a four-field box technique has been used to encompass the tumor volume, bladder, and pelvic lymph nodes followed by cone-down boost. The optimal volume of irradiation is an area of controversy. In most North American trials, treatment includes an initial course of Radiotherapy to a total dose of 39.6 to 45 Gy directed at the pelvic lymph nodes below the bifurcation of the common iliac vessels, the prostate in men, and the whole bladder. A margin surrounding the bladder is included to account for daily variation in bladder filling, visceral organ motion, and setup error. To increase the reproducibility of daily treatment, patients are simulated and treated with an empty bladder. In our study the patients were trained to bladder volume to optimal volume (250 cc) on a daily basis. The rationale for including pelvic lymph nodes in the initial portion of the radiation treatment field relates to the high rate of occult lymph node involvement in regions typically targeted with pelvic RT⁽¹⁴⁾ the finding that extensive lymphadenectomy at the time of radical cystectomy improves survival, suggesting that treatment of these lymph nodes have therapeutic efficacy. The rationale for not specifically targeting pelvic lymph nodes includes good tolerance to treatment by excluding more normal tissues from the treatment volume. In our study also the dose ranged from 60Gy–70.3 Gy. Patients who had suboptimal bladder filling were considered for whole bladder radiotherapy. Target volume included pelvic nodes (common iliac, internal iliac and external iliac) in all the patients. Data supporting a more limited boost include the BC2001 trial, in which 219 patients were randomized to receive full-dose radiation to the bladder alone versus 80% of the dose to the bladder with full dose to the tumor bed. Cowan et al compared whole bladder and partial bladder irradiation techniques for bladder cancer patients. They reported in-bladder recurrence rates of 16.7% and 25.3% in whole bladder and partial bladder irradiation respectively and partial bladder irradiation resulted in a reduction of PTV by >60%⁽¹³⁾. Subsequent to maximal TURBT, definitive treatment with concurrent chemoradiation leads to a complete response in approximately 70% of patients⁽¹⁵⁾. In a series of prospective RTOG trials the 5-year overall survival and disease-specific survival with TMT (trimodality therapy) were 57% and 71%, respectively. An intact bladder was preserved in approximately 80% of patients alive at 5 years after TMT.^(16,17) A series of 112 patients treated with TMT-based bladder preservation reported that 79% of survivors with an intact bladder were charmed or satisfied with urinary function. The need for cystectomy ranges from 0% to 2% in several series to deal with complications of Radiotherapy. Other possible complications of TMT include gastrointestinal

complaints and sexual dysfunction. Single-institution series using patient questionnaires have described gastrointestinal complaints of any severity (10%–32% of patients) and sexual dysfunction (8%–38%) in a larger number of patients.^(18,19,20) In the present study acute gastrointestinal toxicity was seen in 28.2% of patients and 20.51% patients experienced acute genitourinary toxicity with only one patient each having grade 3 toxicity. Myelosuppression (neutropenia) was seen in 15.4% patients. Thus, the use of bladder-preservation therapy for muscle-invasive bladder cancer is a valid substitute in selected cases with long-term efficacy similar to radical cystectomy, with the additional advantage of preserving excellent bladder function in the majority of long-term survivors. Prospective studies have reported encouraging quality of life evaluations for such patients.

Conclusion

Patient selection for organ preservation is important. The ideal patient is the one with good urinary function, is healthy enough to tolerate radio-sensitizing chemotherapy concurrent with radiotherapy, and is one for whom radical cystectomy is a salvage option. The ideal setting is one in which care is judiciously harmonized by the surgical oncologist, medical oncologist, radiation oncologist and pathologist in order to adhere to what is an fundamentally multifaceted management algorithm.

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