

Original Research Article

Clinical outcome of muscle invasive carcinoma urinary bladder patients treated with bladder preservation protocol

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ABSTRACT

Background: To evaluate the outcome in terms of bladder preservation in muscle invasive urinary bladder patients treated with radical radiotherapy.

Methods: A total of sixty patients with muscle invasive bladder cancer who were treated between 2011 and 2013 with bladder preservation protocol were identified. Thirty-two patients were stage T2 disease, rest were T3 and T4. Initial TURBT was reported complete in 24 of the total 60 patients. All patients received 60 to 64Gy to the whole bladder.

Results: The follow-up range was 3 to 72 months. One year follow-up proportion was 78%. The median progression free survival was 40 months. Early stage (T2) and advanced stage (T3 and T4) had progression free survival of 87.8% and 48.5% respectively at one year follow-up with a p value of 0.001. Thirty-six patients who had an incomplete Transurethral resection of bladder tumor (TURBT) initially had a statistically significant lower PFS compared to those patients who had a complete TURBT with a p value of 0.029. Twenty-nine patients were disease free with an intact bladder during the follow-up period providing a bladder preservation rate of 48%.

Conclusions: A bladder-conserving protocol with radiotherapy provides encouraging results with nearly half of the patients able to retain a disease-free bladder. Proper patient selection with early stage disease and those with complete TURBT may further improve the bladder preservation rates.

Keywords: Muscle invasive bladder cancer, Bladder preservation, Radiotherapy

INTRODUCTION

Urinary bladder cancer accounts for 3% of the total new cancer cases diagnosed worldwide. It ranks 10th in incidence among both sexes and sixth among men worldwide.¹ Neoadjuvant chemotherapy followed by radical cystectomy is the standard treatment for muscle invasive localised bladder cancer. Radiation treatment remains the mainstay of non-surgical management of muscle invasive bladder cancer and provides an opportunity to achieve organ preservation.²

Although radiotherapy is active as a single modality, rates of local control and survival have been disappointing. A major concern with radiation as a single modality for bladder preservation is the relatively high rate of local recurrence or persistence of disease and the need for post-radiotherapy salvage cystectomy.³ As a result, combined modality approach for bladder preservation, incorporating transurethral resection, chemotherapy and radiotherapy have been tried with improved local control.⁴

Here we report the results of a retrospective analysis of muscle invasive bladder cancer patients who were treated at our institution from 2011 to 2013 with a bladder preservation combined modality approach.

METHODS

Patient characteristics

From January 2011 to December 2013, a total of sixty patients with localised muscle invasive bladder cancer patients (T2- T4) who were treated at Regional Cancer Centre Trivandrum with bladder preservation protocol were included in this retrospective analysis. Of the 60 patients, 58 were men and two were women with a median age of 62years (range 43 to 77). Thirty-one patients had history of cigarette smoking. Stage-wise distribution was as follows, thirty-two patients were T2, twenty patients were T3 and eight were T4. The patient characteristics are summarized in (Table 1). During Trans-urethral resection of bladder tumour (TURBT), a histological diagnosis of high grade urothelial carcinoma was documented in all patients.

Treatment details

Initial TURBT was reported complete in 24 of the total 60 patients. Neoadjuvant chemotherapy before radiotherapy was received by 19 out of the total 60 patients. Neoadjuvant chemotherapy administered was platinum-based regimen with majority receiving a combination of Cisplatin and Gemcitabine for 3 cycles. For Cisplatin ineligible patients it was replaced with Carboplatin. Radiotherapy was delivered using 6 or 15 MV photons. All patients were planned using computed tomography images with 25 patients receiving 3D conformal radiotherapy. Thirty-four patients were treated with four field MLC plan while one of the patients received Intensity modulated radiotherapy (IMRT). All the patients received total dose of 60 to 64 Gy. Forty-eight patients received 60 Gy/25 F, seven patients had 60 Gy/30 F while 5 patients received 64 Gy/34 F, all in one fraction per day schedule, five days per week. All patients were treated in a continuous phase without any break for cystoscopy in between. A total of only 8 patients received concurrent chemotherapy with Cisplatin at a dose of 40 mg/m² weekly.

Follow-up

The follow-up evaluation included clinical examination, cystoscopy and ultrasound examination of the pelvis at two months of completion of treatment and three to four months thereafter till two years. After two years, patients were followed up biannually till five years and yearly thereafter. For residual disease in the bladder or in case of invasive local recurrence during follow-up, salvage cystectomy was advised if simultaneous distant metastasis was not evident.

Statistical analysis

Descriptive statistics were reported in frequencies or median values. Progression free survival (PFS) curves were generated using Kaplan- Meier estimates. Differences were tested for statistical significance using the log-rank test. The risk for PFS was done using Cox regression analysis. The analyses were performed using Statistical package for social sciences (SPSS) version 11.0.

RESULTS

The median progression free survival was 40 months. The (Figure 1) shows the progression free survival plot. The follow-up range was three to seventy-two months. One year follow-up proportion was 78%. Of all the clinical factors, stage and completeness of TURBT had significant impact on the survival outcome. Early stage (T2) and advanced stage (T3 and T4) had progression free survival of 87.8% and 48.5% respectively at one year follow-up with a p value of 0.001. Thirty-six patients had an incomplete TURBT initially. They had a statistically significant lower PFS compared to those patients who had a complete TURBT with a p value of 0.029.

The survival plot for stage and completeness of TURBT is shown in (Figure 2) and (Figure 3) respectively. Other factors like smoking, neoadjuvant chemotherapy and technique of radiation had no significant impact on the progression free survival as shown in (Table 2).

Table 1: Patient characteristics.

Entire cohort	Number of subjects n=60 (%)	
Median age (range)	62 years (43-77)	
Men	58 (97)	
Women	2 (3)	
Smoking	Yes	31 (52)
	No	29 (48)
Stages	T2	32 (53)
	T3	20 (33)
	T4	8 (14)
TURBT Complete	24 (40)	
Biopsy only	36 (60)	

Eight patients had residual disease after radiation treatment and further 14 more developed bladder- only invasive recurrence during the course of the follow-up. Twenty-nine patients were disease free with an intact bladder during the follow-up period providing a bladder preservation rate of 48%.

Of the 16 patients who had salvage cystectomy, the median time to cystectomy after treatment was 10months. The

(Figure 4) shows the survival plot for the patients who had salvage cystectomy.

Table 2: Progression-free survival for variables.

Variables	P value, hazard ratio
Smoking (yes versus No)	0.601, 1.266
NACT (yes versus No)	0.249, 1.707
Technique (4F versus 3DCRT)	0.877, 1.071

NACT – Neoadjuvant chemotherapy 4F- Four field 3D- 3 dimensional conformal RT.

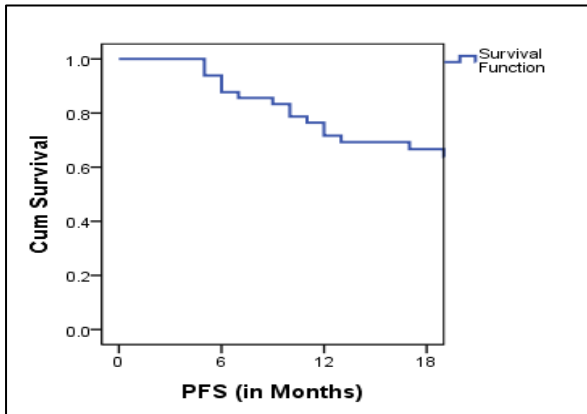


Figure 1: Progression-free survival for the entire cohort.

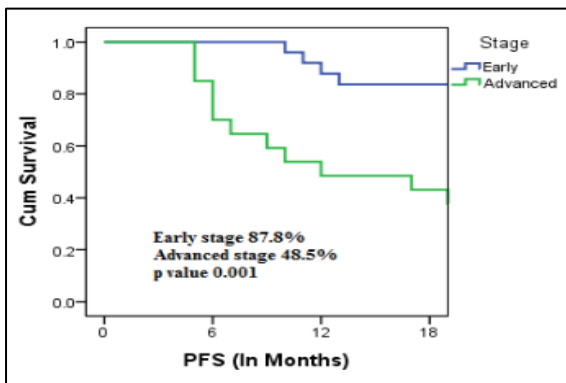


Figure 2: Progression-free survival according to stage.

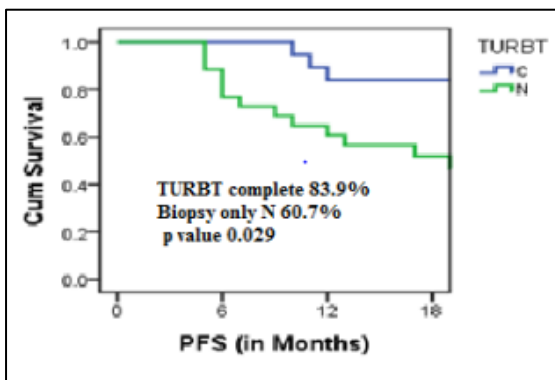


Figure 3: Progression-free survival according to TURBT status.

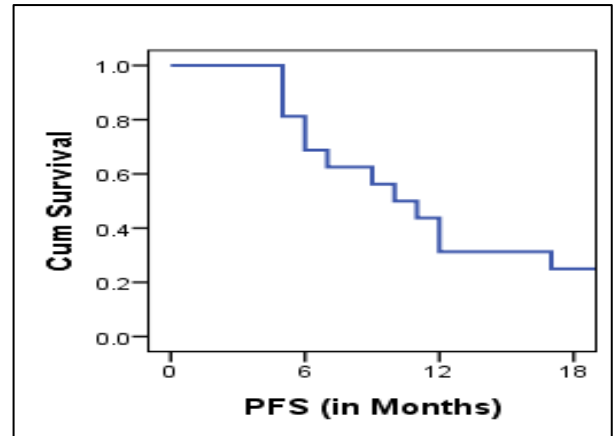


Figure 4: Progression-free survival for salvage cystectomy.

DISCUSSION

Muscle invasive bladder cancer represents a potentially grave disease with long term survival of approximately 50%.^{6,7} Radical cystectomy with urinary diversion has long been considered the standard treatment for muscle invasive bladder cancer. Contemporary series have described five-year overall survival rates of 45-67% and recurrence-free survival of around 62-71%.⁸⁻¹⁰ Radiotherapy is an alternative option with comparatively good results for those who are too frail to undergo cystectomy or for those who refuse surgery.

Multiple institutions and co-operative groups have played a role in developing and refining the modern approach to radiotherapy-based bladder preservation protocol.¹¹ Bladder preservation with aggressive transurethral surgery, systemic chemotherapy and radiotherapy have resulted in 5 year survival rates approximately equivalent to those after cystectomy, with about 50 to 60% of the patients surviving with intact bladder.¹²⁻¹⁴ For radiotherapy of bladder, the regimens commonly used in conventional treatment are 60 to 66 Gy in 30 to 33 fractions to the whole bladder.^{15,16} IMRT has been used for dose escalation with improved results and the organ motion uncertainty being overcome with adaptive radiotherapy techniques.¹⁷

At our institution we have been offering bladder preservation treatment with radiotherapy for patients who are unfit for surgery or for those who are unwilling to undergo surgery. In this study all the patients after initial TURBT, received a dose of minimum 60 Gy to the whole bladder in a single phase. Two main different radiotherapy approaches have been employed following TURBT. In protocols developed at the Massachusetts General Hospital (MGH) and adopted in the Radiation Therapy Oncology Group (RTOG) trials, patients for bladder preservation are selected according to their response to induction dose of 40 Gy, with a cystoscopy assessment of response. In these protocols, the remaining dose of 15 Gy is given only to those having complete resolution of the lesion, whereas all others undergo salvage cystectomy.¹⁸ The second bladder

preservation approach, mainly used in the University of Erlangen and adopted by many European centres, consists of the delivery of an upfront full-dose of radiotherapy as a continuous treatment. In this case, patients with an incomplete response and continuing pelvis confined disease at post-treatment evaluation undergo salvage cystectomy.¹⁹ Since majority of our patients have residual disease after TURBT, we estimated that the chance of sterilization was rather poor at 40 Gy dose and hence do follow the continuous treatment approach.

In this study 60% of patients had an incomplete TURBT initially and they had a statistically significant lower PFS compared to those who had a complete TURBT with a p value of 0.029. Another factor which had an impact on PFS in this study was the initial stage of the disease. Early stage (T2) and advanced stage (T3 and T4) had PFS rates of 87.8% and 48.5% respectively with a significant p value of 0.001. Residual disease after TURBT, advanced stage and presence of hydro-nephrosis have been implicated with poorer outcome in combined modality treatment trials.²⁰ Neoadjuvant chemotherapy prior to local treatment has shown improvement survival rates.²¹ In our study, only very few patients received concurrent and neoadjuvant chemotherapy, as most of the patients were ineligible for platinum-based chemotherapy. As such chemotherapy did not show any impact on progression free survival in this study. Chemotherapy and targeted agents have been used as radio-sensitising agents as part of the bladder preservation protocol. The BC2001 trial used mitomycin and 5flourouracil along with radiation resulting in improved local control rates.¹¹ Trastuzumab as radiation sensitizer was used in the RTOG 05-24 trial.²² Concurrent carbogen and nicotinamide has shown improved recurrence free survival in the phase III BCON study.²³

The limitations of the study are its retrospective nature, single institution-based evaluation and the limited sample size. The whole purpose of bladder preservation protocol is to retain a disease-free bladder. According to the literature, most of the bladder recurrences occur in the first two years after treatment. In this study 48% patients were disease free with intact bladder which is comparable to the international standards. Median time to bladder recurrence in this study was 10 months.

CONCLUSION

A bladder-conserving protocol with radiotherapy may be offered appropriately with encouraging results as an alternative to cystectomy for a group of selected patients who are unwilling or unable to undergo surgery. Nearly half of the patients could retain a disease-free bladder by the bladder preservation approach. Proper patient selection with early stage disease and those with complete TURBT may further improve the bladder preservation rates. Addition of novel radiation sensitising agents may further improve the outcome.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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