

A RETROSPECTIVE STUDY OF THE EFFICACY OF CHEMOIRRADIATION IN LOCALLY ADVANCED URINARY BLADDER CANCERB. Nehru¹, R. Bala Sankar²**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: BACKGROUND: Radical cystectomy with pelvic lymph node dissection is the standard method used to treat patients with locally advanced carcinoma of urinary bladder. Furthermore, a significant proportion of patients are deemed unsuitable for surgery due to inoperability, advanced age, and/or comorbid conditions. Because of disappointing results with radical cystectomy in terms of survival, as well as the morbidity and decreased quality of life associated with the surgery, bladder-conserving therapies like trimodality (TURBT, concurrent chemoradiation) therapy have been gained popularity as the survival rates are nearly equal with radical cystectomy along with functioning bladder. **AIM OF STUDY:** To study retrospectively the effectiveness of chemoradiation therapy in bladder preservation approach in the management of patients with locally advanced (Invasive) bladder cancer in medically unfit and unwilling patients for radical cystectomy and those who cannot tolerate combination chemotherapy drugs. **METHODS AND MATERIAL:** The data was collected from the patient's records between 2004 -2010 who were treated in our Regional cancer hospital. All were biopsy/CT scan proven muscle invasive urinary bladder tumors with T2-3, N0, M0 lesions. Post TURBT status. Medically unfit and Unwillingness for surgery and underwent concurrent Radiotherapy with weekly cisplatin therapy. And men and / women with age between 45 -70 years were included in the study. **RESULTS:** Out of 28 patients 4(14.29%) patients who had good TURP procedure showed complete response, 20(71.43%) patients had partial response and 4(14.29%) patients showed stable disease. 71.43% patient showed symptomatic response to treatment. **CONCLUSION:** Being a single agent chemotherapy with radiation and it is feasible without major toxicity and offers a potentially usefulness in locoregional control and symptomatic relief in unfavorable population with invasive bladder cancer. Moreover it demonstrates high rate of response in relation to the completion of TURBT and size of initial tumor.

KEYWORDS: Muscle invasive bladder TURBT, Bladder preservation, Concurrent chemo radiation.

INTRODUCTION: Carcinoma of the urinary bladder is the second most common malignancy of the urinary tract. The published report from National cancer Registry Programme by ICMR projected an age adjusted incidence rate of 0.9 to 5.5 /100,000 population in India.¹ In USA² the number of new cases of bladder cancer was 20.5 per 100,000 men and women per year. The number of deaths was 4.4 per 100,000 men and women per year. These rates are age-adjusted and based on 2007-2011 cases and deaths.

The tumors of the urinary bladder can arise from the epithelium, muscles, lymphatics, nerves, etc. Of all, epithelial tumors are the most frequent neoplasms, the transitional cell carcinoma (TCC) accounts for 90% of the epithelial. The others are squamous carcinoma, adenocarcinoma and other rare variants.^{3,4}

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Majority of patients show muscle invasion at the time of presentation. The infiltrative tumors are usually solid and can have vascular and lymphatic invasion. 10%-30% of the superficial tumors may actually have muscle invasion. Locally advanced tumors are patients with muscle-invasive disease (T2, T3, T4) tend to progress locally, with increasing tumor size and increasing depth of invasion. The incidence of lymphadenopathy correlates well with the depth of the tumor invasion in the bladder wall.^{3,4}

Radical cystectomy with pelvic lymph node dissection is the standard method used to treat patients with locally advanced carcinoma of urinary bladder. Some reports suggest that nearly 50% of patients treated locally for invasive bladder tumors develop metastatic disease within 2 years of therapy.³

Because of disappointing results with radical cystectomy in terms of survival, as well as the morbidity and decreased quality of life associated with the surgery, bladder-conserving therapies have been gained popularity as the survival rates are nearly equal with radical cystectomy along with functioning bladder.

Urothelial tumors of the bladder are moderately sensitive to radiotherapy⁴. In situations where patients are old and inoperable they are managed with External Beam Radiotherapy (EBRT) alone. A review of the world literature on treatment outcomes in EBRT-treated patients showed the following incidence of 5-year survival: T1, 35% to 71%; T2, 10% to 59%; T3, 10% to 38%; and T4, 0% to 16%.³

It is of importance to note that the addition of chemotherapy to EBRT has increased disease-free survival but has not improved the overall survival and failed to reduce the incidence of distant metastasis, while the median time to local recurrence was 18 months. Currently induction chemotherapy followed by radical RT has shown improved local control and cure rates.

Various groups study reports revealed that the addition of chemotherapy to EBRT results in an increase in CR from about a 40% to 65% to 80% range in post TURBT cases.³

In addition more than three-fourths of patients with CR are expected to be free of recurrence of an invasive tumor. 50% are expected to be 5 year survival with nearly the same number with an intact bladder with 54% to 67% of patients surviving with a tumor free, normally functioning bladder.^{3,5,6,7,8} Concurrent CT and RT approach is more suitable and beneficial to the patients who are unfit to the radical surgical procedure, unwillingness to the surgery, and with compromised general condition. With this background our aim of study is to analyze the outcome for patients with muscle invasive urinary bladder carcinomas who were treated with combined modality bladder-sparing treatment technique in our institute.

AIM & OBJECTIVES OF THE STUDY: To study retrospectively the effectiveness of chemoradiation therapy with bladder preservation approach in the management of patients with locally advanced (invasive) bladder cancer in medically unfit and unwilling for radical cystectomy and those who could not tolerate combination of chemotherapy drugs. And to assess its effectiveness to improve quality of life, the local tumor control, decrease the distant metastasis and improve the survival.

MATERIAL AND METHOD: The data was collected from the patient's records between 2004 -2010 who were treated in our Regional cancer hospital. Men and women with age between 45 -70 years. All were biopsy/CT scan proven muscle invasive urinary bladder tumors with T2 -T3, N0, M0 lesions. Post TURBT status. Medically unfit and unwilling for radical cystectomy, underwent concurrent Radiotherapy with injection cisplatin.

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All were treated with Concurrent External Beam Radiotherapy (EBRT) and Chemotherapy with inj. Cisplatin.

Technique: External beam Radiotherapy (EBRT): it is observed that all cases were planned (2D) under Xemitron simulator. Treatment given with Megavoltage Telecobalt and linac (DHX) treatment unit.

Initial large pelvic volume Includes: Urinary Bladder, proximal urethra and in male patients the prostate and prostatic urethra. The regional lymphatics - (Hypogastric, external iliac and obturator lymph nodes). Included in both sexes.

Target Localization: 10ml of Renograffin was inserted in the bulb of the Foley catheter and 60ml of dye diluted (50/50) in saline was inserted into the bladder along with about 10ml of air. The purpose of air, which will rise to the top, is to define the anterior extension of the bladder.

PHASE I: 44GY -Primary tumor and lymph node drainage areas. Four field box technique with full bladder and followed the standard protocol for field arrangement.^{3,4}

Dose: 44 Gy/22# -Anterio posterior field: 60cgy.

Posterioroanterior field: 60cgy.

Right lateral field: 40cgy.

Left lateral field: 40cgy

PHASE II: Boost field: The fields was reduced to include the empty bladder contrast with a 2-cm margin:

Three field technique-20Gy/10#.

Anterior field - 80cgy.

Right lateral field -60cgy.

Left lateral field -60cgy.

Total radiation dose= 64GY.

32 fractions (200cGy/ fraction).

Over 6 1/2 weeks.

Chemotherapy: Chemotherapy with inj. Cisplatin 100mg /m² divided in Day 1 &Day 2 of EBRT and Day 22 & Day 23 of EBRT. (During boost RT).

The following schedule was Observed:

1. Premedication with ondansetron, Dexamethasone, Ranitidine was given intravenous.
2. The patient was given IV fluids 1000 ml normal saline over 3 to 4 hours before chemotherapy.
3. Inj. Cisplatin was given 2 to 3 hours infusion in normal saline followed by.
4. Inj. Lasix 20mg IV push.
5. Inj. MgSO₄ 1amp + 1amp KCL in 500ml of 5%Dextrose.
6. IV fluid- 1000ml of NS.

OBSERVATION AND RESULTS:

1. The male to female ratio in this study is 26: 2.
2. Median age at the diagnosis is 58years (range 45 to 70years).

3. The percentage of tobacco smokers 75%.
4. Commonest symptoms:
 - Haematuria - 4 (14.29%).
 - Dysuria & frequency - 20 (71.4%).
 - Dysuria & haematuria - 4 (14.29%).
5. Percentages of Location of tumor:
 - Poster lateral wall - 20 (71.43%).
 - Posterior wall - 4 (14.29%).
 - All walls involved - 4 (14.29%).
 - Anterior wall - 0.
6. Histological types:
 - Transitional Cell Carcinoma - 26 (92.8%)
 - Squamous cell carcinoma - 2 (7.14%).
7. Histological Grading of tumor:
 - Grade I - 8 (29.57%).
 - Grade II - 12 (42.86%).
 - Grade III & IV - 8 (29.57%).
8. Stage distribution:
 - Stage II: 24 (85.71%).
 - Stage III: 4 (14.29%).
9. Symptomatic Response to the treatment:
 - Symptoms free patients-20 (71.43%).
 - Partially responded patients - 8 (28.57%).

Four patients underwent repeat TURBT after 6 months of treatment for hematuria & frequency of micturition.
10. Toxicity & complications during treatment and in follow-up:

Organ tissue	Grade 0	Grade -I	Grade-II	Grade-III	Grade-IV
Skin reactions	4(14.29%)	16(57.14%)	8(28.57%)	-	-
Lower GIT including pelvis	8(28.57%)	16(57.14%)	4(14.29%)	-	-
Upper GIT	6(21.43%)	20(71.4%)	2(7.14%)	-	-
Genitourinary	4(14.29%)	14(50%)	8(28.57%)	2(7.14%)	-

Table 1.1: Acute toxicity⁹

Late complications:^{3,10} – After 3 months of treatment:

1. Bladder – Hematuria: 4 (14.29%).
 - Dysuria & frequency: 4 (14.29%).
2. Bowel complications: Nil.
3. Haematological: Anaemia: 4 (required blood transfusion).
4. Kidney toxicity: Nil.

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11. Patient follow –up:

Out of 28 patients, 4 patients came for follow up upto 24 months, 20 patients came for average up to 12 months and 4 patients lost follow up after 6 months.

Assessment was done with help of CT scan reports obtained during follow up.

The following Response criteria observed to asses¹¹

Complete response: Complete disappearance of all clinical Evidence of tumor for at least one Month.

Partial response: A reduction in at least 50% in the Sum of the product of two greatest Perpendicular diameters of all Measurable lesions and the absence of Progression of disease elsewhere for at least one month.

Stable disease: A reduction of less than 50% or on Increase of less than 20% in sum of the product of two greatest Perpendicular diameters of all Measurable lesions.

Progressive disease: unequivocal increase in size of any Lesion by more than 20% of the product of the two largest diameters or any new disease.

Tumor status	Total no. of patients	Complete response	Partial response	Stable disease
T2	24(85.71%)	4(14.29%)	20(71.43%)	-
T3	4(14.29%)	-	-	4(14.29%)

Table 1.2: Response in relation to the primary tumor status (T)

Tumor location	Total no. of patients	Complete response	Partial response	Stable disease
Posterolateral wall	20(71.43%)	2(7.14%)	16(57.14%)	2(7.14%)
Posterior wall	4(14.29%)	2(7.14%)	2(7.14%)	-
All walls	4(14.29%)	-	2(7.14%)	2(7.14%)

Table 1.3: Response in relation to the location of the tumor

Post TURBT Status of disease	No. of patients	Complete response	Partial response	Stable disease
No mass lesion	4	4	-	-
Residual disease	24	-	20	4

Table 1.4: Treatment response in relation to post TURBT status - radiological

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Complete response	4(14.29%)
Partial response	20(71.43%)
Stable disease	4(14.29%)

Table 1.5: DISEASE RESPONSE

All patients (28) completely received EBRT and two courses of chemotherapy with inj. Cisplatin on day 1 and day 22. It was observed that during follow up period loco regional control rate was good and there was considerable subjective improvement and quality of life.

DISCUSSION: The standard treatment for locally advanced muscle invasive bladder tumor is Radical cystectomy.³ The acceptable alternate to facilitate bladder preservation is TURBT followed by concurrent chemoradiation preferably using cisplatin as radio-sensitizer.

The present study which was taken up for bladder preservation included patients with T2-T3 lesions without any nodal involvement, patients with all histologies, medically unfit for surgery and unwilling for surgery.

The study collected the data from December 2004 to Dec. 2010. Observed that minimum follow up period was 6 months and maximum follow up was 24months. out of 28 patients collected for study, 4(14.29%) patients showed complete response with 24 months follow up, 20(71.43%) patients showed partial response and observed average 12 months of follow up and 4(14.29%) patients showed stable disease and observed average 6 months of follow up. all cases were confirmed by CT scan study. Clinically 20(71.43%) patients had symptoms free and 8(28.57%) patients persisted with haematuria & dysuria.

Post TURBT is critical for better out come and even in this study 4 patients with no mass lesion in post TURBT had complete response. The other 24patients with residual disease responded to the treatment according to the size of the residual disease left. Those who had minimal residual disease responded to treatment partially with good symptomatic improvement and the patients who had stable disease and unwilling for cystectomy were subjected to repeat TURBT. These patients had partial relief.

The study comparable to the other studies, Chuvet et al^{9,3} as all the 24(85.71%) patients with T2- lesions had better response compared to 4patients (14.29%) withT3- lesions, and when compared to complete clinical response of other studies.^{3,6,7,8,9} Tester et al (66%), Sauer et al (85%), the present study showed partial response 71.43% and symptoms free response 71.43%. all the above prominent studies had been conducted after optimal TURB, in comparable to these studies in our study those who (4 patients) underwent optimal TURB showed complete clinical response (100%) As per the toxicity concern only two patients had grade III toxicity of genitourinary tract. The toxicity profile was better compared to Chenwc et al.^{12,3} who used concurrent RT+ Cisplatin along with 5FU. They observed 4 patients out of 23, who had grade III toxicity and only 74% (17/23) completed the concurrent CT+RT protocol. Whereas by using cisplatin alone all the 28 patients completed concurrent CT+RT in the present study observed.

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CONCLUSION: Concurrent cisplatin and radiation therapy was a feasible and promising treatment even in relatively old patients with muscle invasive bladder cancer and who were unfit for or unwilling to receive radical cystectomy and particularly those with intravesical stage T2 and T3 tumors.

Being a single agent chemotherapy with radiation and it was feasible without major toxicity and offers a potentially usefulness in locoregional control and symptomatic relief even in unfavorable population with invasive bladder cancer. Moreover it demonstrates high rate of response in relation to initial volume of tumor and the completion of TURBT.

Local control was directly proportionately to the completion of initial TURBT. Those who underwent maximum TURBT had got good response in terms of tumor size regression, symptomatic relief. Initial size of the tumor, general condition of the patient, post TURBT residual disease had played deterrent role in post treatment response.

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