

Radical Cystectomy Versus Tri-Modal Therapy For Treatment Of cT2N0M0 Urinary Bladder Transitional Cell Carcinoma

Protocol of a Thesis for partial fulfillment of MD in Urology

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1.What is already known on this subject?

Radical cystectomy with lymphadenectomy is classically performed in patients with muscle invasive transitional cell carcinoma of urinary bladder cT2N0M0.

Bladder-preserving, trimodality therapy (TMT) was suggested for patients with muscle-invasive urothelial bladder cancer who are not surgical candidates due to medical comorbidities and for those who desire to retain their native bladder.

2. AIM / OBJECTIVES

The aim of this study is to compare the oncological outcome of trimodal therapy (TMT) with bladder preservation versus radical cystectomy with pelvic lymph node dissection (PLND) for treatment of muscle invasive transitional cell carcinoma of urinary bladder cT2N0M0.

3. INTRODUCTION / REVIEW

Bladder cancer is the 11th most commonly diagnosed cancer worldwide. For localized muscle-invasive bladder (MIBC), treatment includes induction chemotherapy (CT). followed by radical cystectomy [1,2].

Advances in the surgical technique and perioperative care, significantly reduced complication rates. On the other hand, orthotopic neobladder may have a positive impact on quality of life but has the potential of increasing short and long-term complication rates, compared to standard urinary diversion [3,4].

However, Hautmann's study shows that among 923 patients (pts) having had an orthotopic neobladder, 40% had late complications [5]. More than one-third of pts develop metastasis within 3 years after surgery, particularly pts with pT3 stages. In this context, alternative conservative strategies have been developed during the last decade, following approaches similar to the anal canal or laryngeal cancer treatments. (5)

The usual conservative approach in localized MIBC is a trimodal therapy (TMT). It consists of a transurethral resection of the bladder tumor (TURBT) as complete as possible, followed by concomitant radiotherapy (RT) and chemotherapy.

Response to (RT) and chemotherapy is then assessed by cystoscopy and biopsies. Planned surgery is proposed to non-responder patients and additional chemotherapy and RT with careful regular endoscopic examination is performed in responders [6].

Except for the incomplete selective bladder preservation against radical excision (SPARE) trial, there is no large and meaningful randomized trial comparing radical cystectomy and TMT [7].

Several single-institution series and prospective trials conducted by radiation therapy oncology group (RTOG) have shown that the conservative approach can achieve high rates of complete histologic response, bladder conservation in many patients, and survival rates similar to recent surgery series [8–10].



4. Description of the study:

▫ **Type of Study:**

This is a randomized controlled clinical trial comparing radical cystectomy and trimodal therapy, included adult patients with cT2N0M0 muscle invasive localized urinary bladder TCC presented to our urology clinic.

Date of study: we started recruitment of the patients from April 2021 to April 2022 and then followed up for three years.

Venue of study: Ain Shams University hospitals.

All patients underwent a proper preoperative assessment including history taking and appropriate clinical assessment. All patients underwent cystoscopy and biopsy of bladder tumor.

Ethical Considerations: -

Permission was received from the ethical committee of Ain Shams University after accepting our study protocol with approval number (FMASU MD 183/2022) to start our study. No personal identifiers were abstracted from the medical records.

The patients were counselled and signed an informed consent to be included in our study. They received detailed information about both ways of management, advantages, disadvantages, and possible adverse effects.

Any participant does not have to take part in or continue this research if he or she wanted. Patients were allowed to stop participating at any time.

Inclusion and exclusion criteria:**A) Inclusion Criteria:**

- 1) Adults of any gender, older than 18 years.
- 2) Urinary bladder TCC cT2N0M0 that was proven by imaging (CT, MRI), cystoscopy and histopathologic examination of biopsied tumor tissue.

B) Exclusion Criteria: -

- 1) Suspected significant nodal involvement on imaging.
- 2) Carcinoma in situ (CIS).
- 3) Hydronephrosis caused by bladder tumor.
- 4) Urinary bladder carcinoma other than TCC
- 5) Bladder TCC with atypical variants (e.g. micropapillary, plasmacytoid, anaplastic and sarcomatoid variants)
- 6) High grade non muscle invasive bladder cancer (NMIBC).
- 7) Patients not fit for surgery.
- 8) Patients not fit for chemotherapy or radiotherapy.
- 9) Patients who refused randomization.
- 10) Patients who received prior chemotherapy or prior radiation For treating the bladder tumor.

The Sample size was calculated according to (PASS 11) program after reviewing results from the previous relevant study (*Chamie et al., 2017*). We assumed an effect size difference = 0.8 between the two treatment groups regarding the oncologic outcome. Based on this assumption and after 10% adjustment for dropout rate, a sample size of 30 patients per group achieves 80% power to reject the null hypothesis of zero effect size when the population effect size is 0.8 and the significant level (alpha) is 0.05 using a two-sided z test.

Randomization:

Selected patients were randomized by simple 1:1 randomization by using sealed envelopes method ,into two main groups:

- **Group (A):** underwent radical cystectomy with lymphadenectomy.
- **Group (B):** underwent trimodal therapy (TMT).

CONSORT Flow Diagram

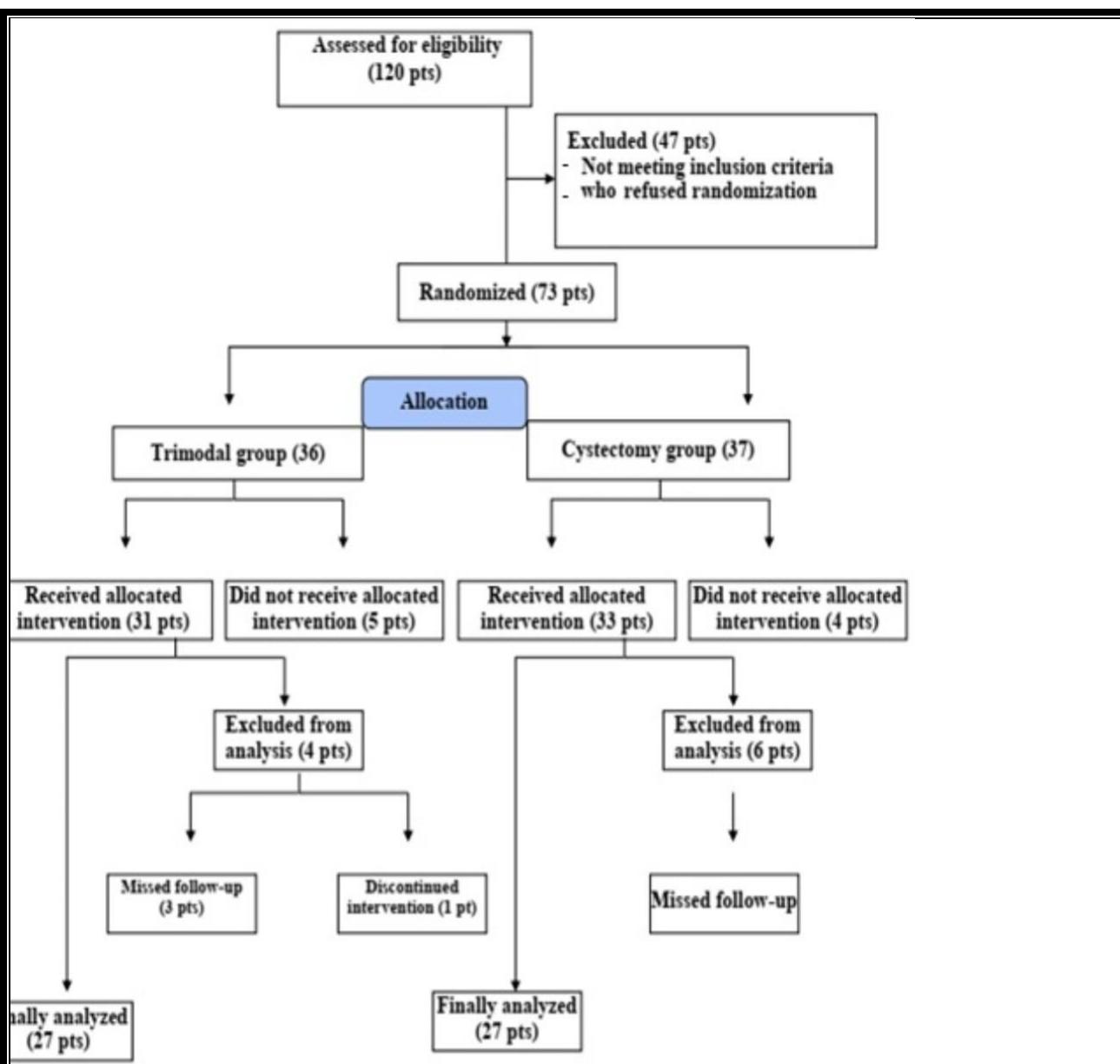


Figure (9): CONSORT Flow Diagram.

Preoperative work-up:

a) *Laboratory investigations:*

All the patients were examined for complete blood count, serum biochemistry, coagulation tests, urine culture and routine viral markers before operation. All Patients in both arms received preoperative prophylactic antibiotic.

b) Radiological investigations:

Pelviabdominal ultrasound.

-Chest, Pelviabdominal CT or pelviabdominal MRI were done for assessment of local staging, nodal involvement, and distant metastasis.

Radical cystectomy group (group A):

a) Surgical procedure:

RC included surgical removal of the bladder, adjacent organs, and regional lymph nodes. In males, it included removal of urinary bladder, prostate, and seminal vesicles whereas in females, it included removal of urinary bladder and reproductive organs (ovaries, fallopian tubes, uterus, and anterior vagina).

Standard pelvic lymph node dissection was performed to all patients in this group.

The boundaries of lymphadenectomy: extended proximally to the bifurcation of the common iliac artery, extended laterally to the genitofemoral nerve, medially to the bladder and internal iliac vessels and distally by the circumflex iliac vein.

This was followed by urinary diversion. we have utilized only two types of urinary diversion procedures:

- 18 patients underwent ileal conduit, and 9 patients underwent orthotopic diversion (ileal neo-bladder).
- Choosing the type of diversion and reconstruction was decided according to :

1- Patient-related factors:

-Performance status and life expectancy.

- Body built
- Renal and liver functions.
- Debilitating diseases and dexterity.

2- Oncologic factors:

- Location of the bladder tumor.
- Positivity of the urethral margin on frozen section.

3- Surgeon's preference.

b) Early postoperative events were recorded.

c) Follow up visits:

Initially after one month then every 3 months for 1 year then every 6 months for 2 years:

1) Early postoperative visit:

After 1 month, included proper assessment of overall health including general, local examination and assessment of stoma. Blood test for renal, liver functions and electrolytes + CBC.

2) 3-month visit:

As before + pelviabdominal ultrasound. Proper functional assessment including potency and urinary continence.

3) 6-month visit:

- Clinical examination, renal functions, CBC

-Chest, Pelviabdominal CT with contrast to detect any local or distant metastasis.

4) Imaging repeated every 6 months for 2 years then at 3 years.

Trimodal therapy group (group B):

- a) In this group, the patients underwent maximal TURBT, where as much tumor as possible was completely resected using bipolar resectoscope. The goal was to remove all visible tumor including the underlying muscle layer and tumor edges.
- b) This is followed by radio-sensitizing chemotherapy and RT.

Chemotherapy consisted of weekly administration of iv infusion of cisplatin (40mg/m²) + 500 ml normal saline. This was administered weekly on day 1 or 2 of each week of radiation therapy. If renal function got impaired, cisplatin was replaced by weekly administration of carboplatin or gemcitabine with adjusted doses according to creatinine clearance.

RT was delivered as external beam radiotherapy (EBRT). aimed at delivering approximately 44– 46 Gy to the urinary bladder and pelvic lymph followed by additional boost to the bladder 54 GY and a final boost to the tumor 64-65 GY. Radiation therapy delivered in daily fractions (5 days per week) over a period of 5 to 7 weeks.

c) Follow up visits:

One week postoperative then every 3 months for 2 years then every 6months at the third year.

1) Early postoperative visit, one week after tumor resection:

This included proper history taking, patient asked about any hematuria or storage symptoms, with review of the histopathology report.

Proper clinical assessment included general and local examination. Follow up CBC, renal functions.

Patients were referred to the clinical oncology and radiation units for proper assessment, and to start the chemo-radiation protocol.

5) 3-month visits:

- Proper clinical assessment, physical examination
- Diagnostic cystoscopy (with or without biopsies) every 3 months for 2 years.
- Computed tomography (CT) or magnetic resonance imaging (MRI) scans for the chest, abdomen, and pelvis was performed at 6-month intervals for 2 years then at 3 years.
- Salvage radical cystectomy was offered for any invasive tumor recurrence during follow up.

Data analysis:

All previously mentioned data were collected and analyzed. This included the preoperative, postoperative data and oncological outcome of both groups. The main focus was to compare the oncological outcome of the two treatment modalities.

- **Group A:** Radical cystectomy with pelvic lymphadenectomy.
- **Group B:** Trimodal therapy.

Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter-quartile range (IQR) when data found non-parametric. Also qualitative variables were presented as number and percentages.

The comparison between groups regarding qualitative data was done by using ***Chi-square test*** and/or ***Fisher exact test*** when the expected count in any cell found less than 5.

The comparison between two groups regarding quantitative data and parametric distribution was done by using ***Independent t-test*** while with non parametric distribution was done by using ***Mann-Whitney test***.

Kaplan-Meier analysis using ***Log Rank test*** was used to compare between the two studied groups regarding overall and disease free survival (months).

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:

P-value > 0.05: Non-significant (NS)

P-value < 0.05: Significant (S)

P-value < 0.01: Highly significant (HS).

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