



# A Dream Comes True: Trimodal Therapy is a Valid Option for Patients with Muscle Invasive Bladder Cancer

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## Abstract

In many centers, radical cystectomy is the standard treatment of non-metastatic muscle invasive bladder cancer. In most series, 5-year pelvic control rates of 80% to 90% and 5-year overall and disease-specific survival rates of 59% to 60% and 55% to 65% respectively, are achieved. The major drawback is the associated incontinence and impotence, occurring in 15%–50% and 40%–60% of cases, respectively. Trimodal therapy with cystoscopy resection and chemo-radiation has an evolving role, with privilege of bladder preservation. Recently, a comparable outcome to radical cystectomy can be achieved with this modality; thanks to the evident survival benefit of adding neoadjuvant chemotherapy and the advances in radiation therapy techniques. Image guided and intensity modulated radiation therapy offer the opportunity to enhance the therapeutic ratio by reducing the irradiated volume of organs at risk and escalating the dose to the planned clinical target volume. Also, it facilitates salvage cystectomy with accepted levels of morbidity and mortality. In conclusion, trimodal therapy is a valid treatment option that can be discussed with all patients with non-metastatic muscle invasive bladder cancer.

**Keywords:** Muscle invasive bladder; Radical cystectomy; Neo adjuvant chemotherapy; Trimodal therapy; Bladder preservation

## Introduction

Bladder Cancer (BC) is a worldwide health problem. It is the 7<sup>th</sup> most commonly diagnosed cancer in male population worldwide, whilst it drops to 11<sup>th</sup> for both sexes. Approximately 25% of newly diagnosed patients have muscle-invasive disease. Despite potentially curative radical surgery, approximately 50% of muscle invasive cases develop relapse within 2 years, and most of them die [1].

Organ preservation has been the main goal of cancer care in the last two decades, yet it is not generally adopted for the cure of non-metastatic muscle invasive bladder cancer. The aim of this article is to elaborate the evolving role of “trimodal therapy”, cystoscopy resection and chemo-radiation therapy, for bladder preservation and capability to reach the goal of cure with better quality of life, compared to radical cystectomy.

## Risk Factors

Tobacco smoking is the most well-established risk factor for BC, causing 50–65% of male cases and 20–30% of female cases. Also, there is a well established relationship between schistosomiasis and urothelial carcinoma of the bladder, which can develop towards Squamous Cell Carcinoma (SCC), although a better control of schistosomiasis is decreasing the incidence of SCC of the bladder in endemic zones such as Egypt [2].

## Radical Cystectomy

For muscle-invasive tumours (p T2–T4N0M0), Radical Cystectomy (RC) with pelvic lymphadenectomy has been the gold standard for the past several decades. Contemporary series show impressive 5-year pelvic control rates of 80% to 90% and 5-year overall and Disease-Specific Survival (DSS) rates of 59% to 60% and 55% to 65%, respectively, for radical cystectomy. Complication and perioperative mortality rates have been declining, with reported rates as low as 17%–32% and 2%–3%, respectively. Other voiced concerns with surgery were incontinence and impotence. With an orthotopic ileal neobladder, daytime and nocturnal continence rates as high as 85%–90% and 50%–90%, respectively, can be achieved. Also, with unilateral and bilateral nerve-sparing cystectomy, potency rates of 33%–60% can be achieved [3,4].

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Received Date: 29 Jun 2017

Accepted Date: 31 Jul 2017

Published Date: 10 Aug 2017

### Citation:

Hamdy HK. A Dream Comes True: Trimodal Therapy is a Valid Option for Patients with Muscle Invasive Bladder Cancer. *J Surg Tech Proced.* 2017; 1(1): 1004.

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## Neoadjuvant Chemotherapy

Cisplatin based neoadjuvant chemotherapy has become the standard of care in muscle invasive bladder cancer. Giving chemotherapy prior to radical cystectomy may improve cancer specific survival, presumably by treating micrometastatic disease and pathologic downstaging. A meta-analysis of 11 trials showed an overall survival rate benefit of 5% in patients who received neoadjuvant chemotherapy [5]. Of interest, a group of 63 patients were evaluated, as they declined to undergo a planned cystectomy, because they achieved a complete clinical response to neoadjuvant cisplatin-based chemotherapy. The median follow-up was 86 months and all patients were followed for more than 5 years. Forty patients (64%) survived, with 54% of them having an intact functioning bladder. Consequently, complete response to neoadjuvant chemotherapy can be considered as an important prognostic factor for survival and bladder preservation [6].

## Trimodal Therapy

With the advancement of cystoscopiesurgery, radiation therapy and chemotherapy, TriModal Treatment (TMT) evolved as an alternative to RC. TMT entails maximal trans-urethral resection of the bladder tumour, and radical radiation therapy with concurrent cisplatin based chemotherapy. TMT can achieve complete response rates of 60%- 80%, 5-year survival rates of 50%-60% and survival rates with an intact bladder of 40%-45% [7].

## Advances in Radiation Therapy

When 3-Dimensional conformal radiation therapy is utilized, with shrinkage field technique, a dose of 40 GY–45 GY is prescribed to the bladder and pelvic nodes, with dose escalation to 60 GY–64 GY to the bladder in conventional fractionation. The rates of significant late pelvic toxicity for patients completing TMT and retaining their native bladder are low. Within a median follow-up period of 5.4 years (range, 2 to 13.2 years), 7% of patients' experienced late grade 3 pelvic toxicity: 5.7% GU and 1.9% GI. Notably there were no late grade 4 toxicities and no treatment-related deaths [8]. The pivotal problem in radiotherapy for bladder is the organ motion. Therefore, a margin for internal movement of the Urinary Bladder (UB) has to be taken for calculating the Internal Target Volumes (ITV). The proposed internal margins (IMs) for these movements range from 2 cm to 3 cm with 3-dimensional radiotherapy. When these margins are applied to the contoured UB especially in the cranio-caudal direction, it can end up including a substantial amount of bowel within the target volumes. With the use of Image-Guided Radiation Therapy (IGRT) that margin can isotropically reduced to 10 mm to 12 mm [9]. Also the use of Intensity Modulated Radiation Therapy (IMRT) can potentially escalate the radiation dose to the tumour primary site within the bladder, which is the most frequent site of disease local relapse. An increment in dose of 10GY would yield a 1.44–1.47 increase in the odds of local control. Such dose level can be safely administered to the tumour primary site, as the estimated tolerance for two-thirds of the bladder is around 80 GY [10,11].

## Radical Cystectomy versus Trimodal Therapy

Many centers advocate TMT for patients denying, or unfit for RC. Although TMT seems to be inferior to RC in terms of disease control, yet no available reliable complete randomized controlled trials to support this concept. It is difficult to compare trials using either

modality due to discrepancies in clinico-pathologic variables, using different chemotherapy regimens, and different radiation therapy techniques and dose levels. Also, TMT is usually prescribed for old unfit patients, with negative impact on tolerance to chemoradiation and subsequent treatment irregularity and lowered dose intensity [12-15]. To overcome these limitations of published non-comparative studies, recently a study used propensity score matching with patients who underwent either RC or TMT, to generate comparable groups using stringent criteria. For a total of 112 patients (56 treated with TMT and 56 underwent RC) the data showed that TMT provides midterm survival outcomes comparable to RC. At a median follow-up of 4.51 years, there were 20 deaths (35.7%) in the RC group (13 as a result of BC) and 22 deaths (39.3%) in the TMT group (13 as a result of BC). The 5-year disease specific survival rate was 73.2% and 76.6% in the RC and TMT groups, respectively ( $P = .49$ ). Salvage cystectomy was performed in 10.7% of patients who received TMT [16].

## Quality of Life

Another issue to be considered is the quality of life. A study from the Massachusetts General Hospital reported on the QOL and urodynamics of 49 patients who had completed trimodality bladder preservation therapy a median of 6.3 years earlier. In this study, 75% of patients had normally functioning bladders. The majority of men retained sexual function, with only 8% reporting dissatisfaction [17].

## Salvage Radical Cystectomy

Earlier studies considering salvage RC for local relapse after TMT, showed that ileal neobladders become much more challenging following pelvic irradiation, with complication rates as high as 33% including prolonged urinary leakage, ureteral stenosis, fistulas, and urinary retention with a re-operation rate of 17% at 28 months and significant day and night incontinence rates of 33% and 44%, respectively [18]. However, more recently with advent of radiation therapy techniques, peri-operative morbidity and mortality rates in almost 100 patients who underwent salvage cystectomy at Massachusetts General Hospital were remarkably similar to rates for immediate cystectomy without radiation [19].

## Conclusion

In conclusion, TMT is a valid treatment option that can be discussed with non-metastatic muscle invasive bladder cancer patients, considering their social and intellectual status, to realize this treatment modality. It can achieve comparable survival and disease specific survival to RC, without mortality and better QOL. Maximal TURBT, and complete response to neoadjuvant cisplatin based chemotherapy, encourage the implementation of TMT. Patients not amenable for maximal TURBT, or with residual disease after neoadjuvant chemotherapy, can be challenged with escalated dose of radiation therapy, implementing modern radiation therapy techniques (IMRT and IGRT), if the patient still desires to preserve his native bladder. In the era of modern radiation therapy, salvage RC can be safely implemented, but ileo-bladder reconstruction is still a challenge to the surgeon, and the radiotherapist to pursue the utmost effort to lower the radiation dose to the intestine that will be implemented as the future urinary reservoir.

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