Medical & Surgical Urology
ISSN: 2168-9857
OPEN ACCESS Freely available online
Review Article

Treatment of Muscle Invasive Urothelial Bladder Cancer- A Review of the Literature

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ABSTRACT

Carcinoma of the bladder is the fourth and fifth most frequently diagnosed cancer in the United States and Europe respectively. Muscle-Invasive Urothelial Bladder Cancer (MIBC) (cT2-T4) is an aggressive disease with poor 5-year Overall Survival (OS) of 50%. Epidemiological studies are unavailable in most African countries; however, Africa was found to have a lower incidence. Current optimal management is based on Radical Cystectomy (RC) and pelvic Lymph Node Dissection (LND), generally associated with pre-operative cisplatin-based chemotherapy. Adjuvant chemotherapy may be necessary in patients who did not benefit from neoadjuvant chemotherapy. A selected few patients who desire bladder preservation may benefit from bladder sparing procedures but should be cautioned about the risk of recurrence. The African literature lacks structured prospective studies on the management of urothelial muscle invasive bladder cancer and much of the clinical data are extrapolated from current evidence-based guidelines.

Keywords: Adjuvant Chemotherapy; Muscle Invasive Urothelial Bladder Cancer; Neoadjuvant; Pelvic Lymph Node Dissection; Radical Cystectomy

INTRODUCTION

Carcinoma of the bladder is the fourth and fifth most frequently diagnosed cancer in the United States and Europe respectively [1]. An estimated 74,690 cases of urinary bladder cancer were diagnosed in the United States in 2014, of which approximately 30% was muscle-invasive [2]. Cigarette smoking remains the strongest risk factor of bladder cancer in America and Europe where Urothelial Carcinoma (UC) represents the most common histologic form [3]. Besides smoking, occupational exposure to carcinogens, namely aromatic amines, polycyclic aromatic, hydrocarbons, and chlorinated hydrocarbons is considered as the second most important risk factor for urothelial BC [4]. Epidemiological studies are unavailable in most African countries; however, Africa was found to have low incidence of around 22,053 cases with Sub Saharan Africa having 45.5% (10,042) of cases [5].

About 30%–40% of patients with non-muscle invasive tumor will eventually progress to muscle-invasive disease [6]. Muscle-Invasive Urothelial Bladder Cancer (MIBC) (cT2-T4) is an aggressive disease with poor 5-year Overall Survival (OS) of 50% [7]. Current optimal management is based on Radical Cystectomy (RC) and pelvic Lymph Node Dissection (LND), generally associated with pre-operative cisplatin-based chemotherapy [7]. For highly selected patients, surgical bladder preservation approaches including radical Trans-Urethral Resection (TUR) and Partial Cystectomy (PC) with or without bilateral PLND may be reasonable alternatives to RC/PLND [8]. Certainly, high-risk patients (extravesical and/or node-positive disease) who did not receive neoadjuvant chemotherapy may benefit most from adjuvant chemotherapy though there is limited evidence on the routine use of adjuvant chemotherapy [4].

The 5-year mortality rate of patients with MIBC is approximately 50%–70% even after radical cystectomy [9-12]. With the high rate of treatment failure for patients with MIBC, a new multidisciplinary approach integrating surgery, medical oncology, and radiation oncology is encouraged to improve clinical outcomes for patients with MIBC [9,12]. Therefore, the aim of this study is to provide evidence-based literature review of the current management of muscle invasive non-metastatic urothelial bladder cancer in both developed and developing settings.

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Received: April 03, 2019, **Accepted:** April 25, 2019, **Published:** May 02, 2019

Citation: Cassell A, Yunusa B, Mbodji MM, Jalloh M, Diallo A, Diallo Y, et al. (2019) Treatment of Muscle Invasive Urothelial Bladder Cancer- A Review of the Literature. Med Sur Urol 8:223.

METHODOLOGY

A literature review was conducted from March 1, 2000 to March 10, 2019 using Medline, African Journals online and PubMed electronic databases. The Search strategies included the following terms (management of muscle invasive bladder cancer) and (Urothelial bladder cancer in Africa). Only studies written in English were included. The study included 28 articles comprising retrospective, prospective, randomized trials, systemic reviews and meta-analyses on the search topic. Both the abstract and full text of these studies were retrieved and reviewed for neoadjuvant chemotherapy therapy, radical cystectomy, urinary diversion, adjuvant radiotherapy and chemotherapy. Studies on non-muscle invasive bladder cancer, case reports and Case Series were excluded from the study (Table 1).

RESULT AND DISCUSSION

Perioperative therapies

Patients with clinical stage T2-T4aN0M0 MIBC who are candidates for RC or definitive radiotherapy have been shown to benefit from neoadjuvant chemotherapy [4]. The basis for neoadjuvant chemotherapy is to treat micro metastases present at diagnosis, because within two years about 50% of patients diagnosed with MIBC will progress to metastatic disease (Figures 1 and 2) [4].

Neoadjuvant radiation muscle-invasive urothelial carcinoma of the bladder

Several small studies have evaluated radiotherapy in the neoadjuvant setting showing disparate results. Randomized trials have not shown any benefit in overall survival of radiotherapy as a monotherapy in the neoadjuvant setting compared to radical cystectomy [3]. A prospective study by Mourad et al. in Egypt involving 56 patients receiving neoadjuvant radiotherapy for T2-T4aN0M0 MIBC at dose of 45 Gy for 3 weeks before radical cystectomy showed a marginally insignificant improvement in disease free survival in those that showed tumor regression following a univariate analysis [10]. The African Literature lacks published data on neoadjuvant radiotherapy. Neoadjuvant radiotherapy is not currently recommended however, radiotherapy has been incorporated into various multimodal bladder-sparing approaches [3].

Neoadjuvant chemotherapy for muscle-invasive urothelial carcinoma of the bladder

In the neoadjuvant setting, randomized controlled trials have consistently shown that cisplatin-based multi-agent chemotherapy prior to surgery improves overall survival by 5%–10% [11]. These results are supported by three subsequent meta-analyses, the most recent of which included 3285 patients from 15 randomized trials [11]. The SWOG randomized phase III study revealed that three cycles of MVAC chemotherapy can achieved pathologic T0 rates

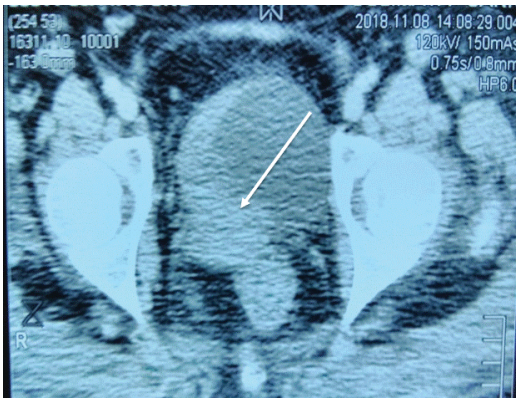

Figure 1: Axial excretory phase CT Urography showing a focal irregular thickening along right posterolateral wall of bladder.

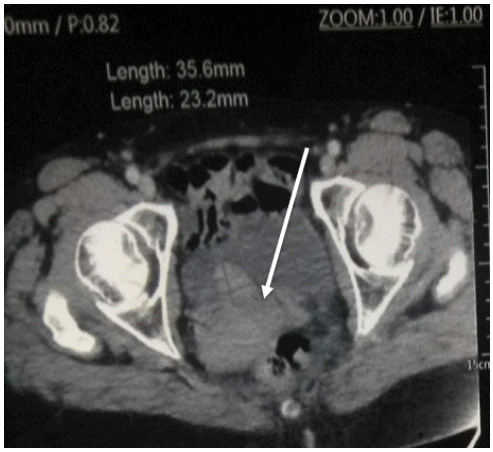

Figure 2: Axial excretory phase CT urography showing diffuse irregular mural thickening along right posterolateral wall of bladder (T2-T4aN0M0 MIBC). Courtesy of Hopital General de Grand Yoff.

Types of Studies	Neoadjvant chemotherapy radiatherapy (MVAC/GC)	Radical cystectomy/urinary diversion	Adjuvant chemotherapy MVAC/GC	Bladder sparing approach/ Trimodal approach
Guidelines Review Articles, Systemic Reviews and Meta-analysis	Dall'Era et al. [3]	Tang et al. [1]	Dall'Era et al. [3]	Premo et al. [2]
	La´zaro et al. [4]	Dall'Era et al. [3]	La´zaro et al. [4]	Cha et al. [8]
	Mourad et al. [10]	La´zaro et al. [4]	Park et al. [12]	Park et al. [12]
	Raphael et al. [11]	Chang et al. [13]	Chang et al. [13]	Chang et al. [13]
	Park et al. [12]	Roth et al. [20]	Leow et al. [24]	Fahmy et al [25]
Randomized Controlled Trials	Grossman et al. [9]	Grossman et al. [9]		
	Plimack et al. [27]			
	Sternberg et al. [28]			
Prospective and Retrospective Studies	Orrea et al. [7]; Stein et al. [17]; Madersbacher et al. [18]; Herr et al. [19]; Donat et al. [23]; Sternberg et al. [24]; Van de Putte et al. [26]			
African Studies	Ngowi et al. [5]; Ikuerowo et al. [6]; Mapulanga et al. [14]; Shelbaia et al. [15]; Biluts et al. [16]; Heyns et al. [21]			

Table 1: Citations of 28 articles used to review the literature on muscle invasive urothelial bladder cancer considering neoadjuvant therapy, radical cystectomy/urinary diversion, adjuvant chemotherapy and bladder sparing approach. No randomized trials were found in the African Literature on muscle invasive urothelial cancer.

of 38% compared to 9% in the surgery-alone group (p<0.001) without altering a patient's benefit of radical cystectomy [12]. Two large studies including the advanced bladder cancer meta-analysis collaboration and the meta-analysis by Winquist et al. have shown an overall survival benefit using cisplatin-based combination regimens [12].

30%-50% of patients with MIBC may not be amenable to safe receipt of cisplastin-based chemotherapy due to associated toxicities including diminished cardiac function, nephrotoxicity, neurotoxicity, and hearing loss [13] however, Gemcitabine and Cisplatin (GC) as an alternative two-drug regimen have been widely accepted for neoadjuvant use [12]. Nevertheless, the efficacy of both regimens (MVAC and GC) has not been compared in a prospective study [14-25].

Dose-dense regimens: several retrospective studies and phase II randomized trial have shown that dose-dense regimen can achieve higher response rates and reduce the duration of therapy [12,26,27]. In the EORTC study by Sternberg et al., involving patients with advanced metastatic bladder cancer showed that dose-dense MVAC given every two weeks with growth-factor support resulted in a higher response rate and better safety profile as compared to the standard protocol of MVAC given over four weeks [12,28].

The African literature is sparse on the use of neoadjuvant chemotherapy for muscle invasive bladder cancer. Most of these studies are descriptive or retrospective highlighting epidemiological profile of bladder cancer and outcome of surgery [14-16]. Further research and randomized studies are much needed to provide a more evidence-based perspective as most African literatures on bladder cancer are on squamous cell carcinoma.

Radical cystectomy

The gold standard for surgical treatment of MIBC is Radical Cystectomy (RC) with extended lymphadenectomy, often preceded by neoadjuvant cisplatin-based chemotherapy, and urinary diversion which involves removal of the bladder, prostate, seminal vesicles, proximal vas deferens and proximal urethra in men, and bladder, uterus, ovaries, fallopian tubes, urethra and part of vagina in women [4]. Current series have projected a 5-year overall survival rates of 59%–66% with radical cystectomy alone with recurrence-free survival ranging from 62% to 68% [3,17,18].

Lymph node dissection: Multivariate analyses of a randomized trial showed that negative surgical margin status along with greater than 10 lymph nodes removed were associated with improved survival in both treatment arms [3,19]. Extended dissection with radical cystectomy provides more accurate pathologic staging for determining prognosis or the need for adjuvant treatment and appears to correlate with improved survival after surgery although it remains to be shown if the role of lymph node dissection in bladder cancer is more diagnostic or therapeutic [3].

Urinary diversion: A surgically constructed urinary diversion can reliably establish urine drainage after radical cystectomy [12]. The bowel segments from the stomach, small bowel, or colon are used to construct these urinary drainages as continent or incontinent diversions [12]. The various forms of urinary diversion include orthotopic bladder replacement and uretero-ileourethrostomy (Studer and Padovana neobladder) or an incontinent external ostomy with cutaneous ureteroileostomy (Bricker diversion) [4]. Since the kidneys must compensate the metabolic acidosis following the integration of bowel in the urinary tract, a glomerular filtration rate of at least 50 mL/min is obligatory for continent reservoirs [4,20]. A normal liver function is obligatory for candidates requiring continent urinary diversion (risk of hyperammonemia if the reservoir becomes infected) and should not have undergone any previous major bowel resection in the ileocecal area (risk of vitamin B12 deficiency) [4,20].

A retrospective study done at Cairo University Hospital by Shelbaia et al. showed that long term follow-up for patients with radical cystectomy and orthotopic diversion is associated with high complication rate. Unfortunately, many patients in Africa still present with advanced and inoperable bladder cancer, and many do not have access to healthcare facilities that can provide a cure and a good quality of life by means of radical cystectomy and neobladder construction [21].

Adjuvant chemotherapy muscle-invasive urothelial carcinoma of the bladder

Certainly, high-risk patients (extravesical and/or node-positive disease) who did not receive neoadjuvant chemotherapy may benefit most from adjuvant chemotherapy though there is limited evidence on the routine use of adjuvant chemotherapy [4]. The evidence was based on the results of an updated meta-analysis of nine randomized trials, including 945 patients who received cisplastin-based adjuvant chemotherapy revealed an Overall Survival (OS) and Disease-Free Survival (DFS) benefit [4,22]. Nevertheless, the high complication rate radical cystectomy may prevent timely administration of adjuvant therapy [9,12]. In a retrospective analysis of 1142 patients (Memorial Sloan-Kettering) who underwent radical cystectomy, 64% had one or more complications within 90 days of radical cystectomy, making 30% not fit to receive adjuvant chemotherapy [12,23]. African Studies on adjuvant chemotherapy for muscle invasive bladder cancer is sparse and most of the clinical decisions and data are extrapolated from American and European guidelines.

Bladder sparing approach

Sternberg et al. assessed the possibility of patient selection for definitive partial cystectomy or TURBT based on response to neoadjuvant chemotherapy and the study showed that the five-year survival rate was 67% in the TURBT group and 69% in the partial cystectomy group [12,24]. Fahmy et al. a systematic review and meta-analysis on the oncological long-term outcomes after trimodality therapy and radical cystectomy with or without neoadjuvant chemotherapy for muscle-invasive bladder cancer showed a comparable outcome with a mean 10-year OS was 30.9% for TMT and 35.1% for RC (p= 0.32) [25]. Therefore, more stringent criteria are warranted for appropriate selection of candidates for this nonstandard, bladder-preserving approach [12,25].

Studies has shown that single modality bladder preservation approach has been suboptimal therefore, a more integrated approach involving surgery, radiation, and chemotherapy has evolved, with the goal of improving both local and distant disease control [12]. Several approaches involving definitive TURBT in combination with chemotherapy and radiation for maximum local and systemic control in selected patients with MIBC have shown reassuring clinical outcomes with a reasonable rate of bladder-preservation [12]. Significantly, a patient's ability to tolerate chemoradiotherapy must also be assessed before considering this approach [12].

Follow up

The American Urological Association (AUA), the American Society of Clinical Oncology (ASCO), the American Society for Radiation Oncology (ASTRO), and the Society of Urologic Oncology (SUO) guidelines recommend that Clinicians should obtain chest imaging and cross-sectional imaging of the abdomen and pelvis with CT or MRI at 6-12-month intervals for 2-3 years and then may continue annually [13]. Following cystectomy and urinary diversion, all patients should undergo assessment of electrolytes and renal function [13].

CONCLUSION

The standard management of muscle invasive non-metastatic urothelial bladder cancer is neoadjuvant chemotherapy followed by radical cystectomy and bilateral pelvic lymph node dissection. Adjuvant chemotherapy may be necessary in patients who did not benefit from neoadjuvant chemotherapy. A selected few patients who desire bladder preservation may benefit from bladder sparing procedures but should be cautioned about the risk of recurrence. The African literature lacks structured prospective studies on the management of Urothelial muscle invasive bladder cancer and much of the clinical data are extrapolated from current evidence-based guidelines.

CONFLICT OF INTEREST

The authors declare no conflict of interest towards this publication.

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