ORIGINAL ARTICLE

Continuous chemoradiation following complete response to neo-adjuvant chemotherapy provides improved outcomes in muscle invasive urothelial carcinoma

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Received: April 13, 2015 **Accepted:** May 12, 2015 **Online Published:** June 3, 2015
DOI: 10.5430/jst.v5n2p59 **URL:** http://dx.doi.org/10.5430/jst.v5n2p59

Abstract

Purpose: To evaluate the outcomes of patients with localized muscle invasive bladder cancer (MIBC) treated with neo-adjuvant chemotherapy followed by continuous chemo-radiation (cCRT). To evaluate the prognostic significance of clinical complete response to neo-adjuvant chemotherapy in the setting of bladder preservation.

Materials/Methods: From 2002 to 2012, twenty-two patients with cT2-4 N0-2 M0 MIBC were treated using cCRT for bladder preservation. All patients were felt to be medically inoperable and/or refused cystectomy. They were treated with maximal transurethral tumor resection (TURBT) and multiple cycles of platinum-doublet-based neoadjuvant chemotherapy, followed by definitive cCRT. Tumor response was evaluated with an abdomino-pelvic CT scan and cystoscopy 4 weeks after neoadjuvant chemotherapy and 3 months after completion of all therapy. Radiation therapy was delivered using 3DCRT or IMRT to a median dose of 45 Gy to the pelvis and 63 Gy to the bladder (range 41.4 Gy to 71.4 Gy). Three-year local control (LC) and disease-free survival (DFS) estimates were determined by the Kaplan-Meier method and log rank analysis.

Results: The median age was 67.5 years. Median follow-up was 24 months (range 6 to 86). Clinical stage was T2 in 12 patients, T3 in 8, and T4 in 2. Fourteen patients were node-negative while 8 were node-positive. Actuarial 3-year OS, DFS, LC for the entire cohort were 62.2%, 62% and 78.3%, respectively. Furthermore, the 3-year OS and DFS for patients achieving a CR on cystoscopy following neo-adjuvant chemotherapy was 64.6% *vs.* 57.1% without CR (p=.046), and 64.3% *vs.* 57.1% without CR (p=.03). The 3-year LC was 90.9% in patients showing complete response to neo-adjuvant chemotherapy. When stratified by T stage, 3-year LC was 90.9% for T2, 87.5% for T3 and 0% for T4 (p=.007). Local failure was associated with distant metastases in 4 out of 5 patients. Two patients had non-invasive local recurrences and both were successfully treated with intra-vesical BCG.

Conclusions: Maximal TURBT followed by neo-adjuvant platinum based chemotherapy and definitive cCRT offers good rates of OS, DFS and LC in MIBC at three-years of follow-up. Complete response to neo-adjuvant chemotherapy is a favorable prognostic factor, achieving LC rates >90% at 3 years.

Key words

Bladder cancer, Chemo-radiation, Neo-adjuvant chemotherapy, Bladder preservation

1 Introduction

Muscle Invasive Bladder Cancer (MIBC) typically occurs in the elderly population with a significant history of smoking. Radical cystectomy is the treatment of choice, though many patients are not good candidates for radical cystectomy due to advanced age and co-morbidities. Despite improved surgical techniques, cystectomy with pelvic lymph node dissection and urinary diversion is associated with considerable peri-operative morbidity as well as long term-complications [1]. Significant interest in bladder preservation has led to the increasing use of trimodality therapy (TMT) with maximal transurethral resection of the bladder tumor (TURBT) and chemoradiation (CRT) as an alternative treatment option. Contemporary series of TMT have shown 3-year survival rates of 61%-75% [2-9], comparable to large cystectomy series [10, 11]. The safety and efficacy of CRT has been established by two randomized trials [12, 13].

Most bladder preservation studies have used a split-course radiation protocol, with response assessment at 40Gy. Patients with complete response to this initial treatment continue on protocol to full dose; those with less than complete responses undergo cystectomy. Successive RTOG protocols examining altered fractionation, neo-adjuvant or adjuvant chemo-therapy have all been modifications of this primary design [2, 7, 14-16].

For patients with high-risk, localized disease who have no contra-indications to cystectomy, the current standard of care is a maximal trans-urethral resection of tumor (TURBT), followed by multiple cycles of cisplatin-based combination chemotherapy and then cystectomy [17-21]. Though neo-adjuvant pre-operative cisplatin-based chemotherapy has shown to prolong both disease-free survival and overall survival [17-21], this strategy has yet to be the standard of care in patients treated with definitive CRT. At our institution, we have followed a strategy of maximal TURBT, multiple cycles of cisplatin-doublet neo-adjuvant chemotherapy and definitive continuous chemoradiation (cCRT) as a bladder preservation protocol.

2 Methods and materials

From 2002 to 2012, 22 patients with cT2-4 N0-2 M0 MIBC were evaluated and treated with curative intent in the Department of Radiation Oncology. All patients were treated with maximal TURBT and platinum-based neoadjuvant chemotherapy followed by definitive cCRT.

2.1 Initial evaluation

All patients were evaluated in the multidisciplinary Urologic Oncology clinic by an urologist, medical oncologist and radiation oncologist. Baseline evaluation included complete blood counts, comprehensive metabolic profile and physical examination. All patients had to have a creatinine less than 1.5 and an ECOG performance status of 1 or better prior to the initiation of therapy. The study cohort included nine patients who refused cystectomy, and 13 considered unfit for bladder resection (medical inoperable) as determined by a team consisting of the anesthesiologist and urologist. All patients underwent cystoscopic evaluation and maximal TURBT prior to the start of neo-adjuvant chemotherapy. Pathological confirmation of muscle invasive transitional cell carcinoma was available in all patients. For patients referred from other medical facilities, the pathology slides and/or blocks were reviewed at our institution. Relevant radiological studies included contrast enhanced CT scans of the chest abdomen and pelvis.

2.2 Neoadjuvant chemotherapy

All patients received cisplatin- based neo-adjuvant chemotherapy (see Table 1). The most common regimen was cisplatin 100 mg/m^2 on Day 1, and gemcitabine 1,000 mg/m^2 on Days 1 and 8, on a 21-day cycle, used in fourteen cases. Other

neo-adjuvant chemotherapy combinations included the following: carboplatin (AUC 5), and paclitaxel 170 mg/m^2 on day 1 of a 21-day cycle, used in 4 cases; carboplatin (AUC 5) on Day 1, and gemcitabine 1,000 mg/m^2 on Days 1 and 8, on a 21-day cycle, used in 3 cases; and cisplatin 100 mg/m^2 on Day 1, and etoposide 100 mg/m^2 on days 1, 2, 3 of a 21-day cycle used in 1 case, due to presence of small cell components in the biopsy. It was our standard practice to administer pegylated G-CSF (Neulasta) on day 1 of each cycle of chemotherapy. Tumor response was evaluated 4 weeks after completion of neo-adjuvant chemotherapy with an abdomino-pelvic CT scan and cystoscopy. Repeat TURBT was performed in patients with organ confined persistent papillary tumor as noted on the diagnostic cystoscopy, and without evidence of peri-vesicular tumor extension on abdominopelvic CT scan. For patients with larger residual tumor, with peri-vesicular extension, a biopsy was performed to confirm persistent disease. We did not routinely obtain a biopsy to confirm pathologic complete response in patients with a clinical complete response.

Table 1. Patient Characteristics

Characteristic	Patients (n, %)
Age	Median = 67.5 yrs (45 - 83)
Histology	
Transitional Cell	21 (95)
Transitional Cell / Small Cell	1 (5)
T-Stage	
T2	12 (55)
T3	8 (36)
T4	2 (9)
Neo-Adjuvant Chemotherapy	
Platinum based	(100%)
Cisplatin + Gemcitabine	14/22 (64)
Carboplatin + Gemcitabine	3/22 (14)
Carboplatin + Taxol	4/22 (18)
Cisplatin + Etoposide	1/22 (5)
Concurrent Chemotherapy	
Platinum based	14/22 (64)
Cisplatin	11/22 (50)
Carboplatin	3/22 (14)
Gemcitabine	7/22 (32)
Capecitabine	1/22 (5)
Radiation Therapy	Median Dose = 63 Gy

2.3 Radiation therapy

The exact procedure of RT simulation for bladder cancer evolved over the period during which the patients were treated. However, generally all patients underwent CT simulation in the supine position, following immobilization using alpha-cradle™ device. Patients were administered oral contrast prior to scanning for visualization of small bowel and intravenous contrast was administered during simulation. Patients were scanned with full and empty bladder. Radiotherapy planning was performed on Varian™ Eclipse workstation. Treatment fields were designed (for 3DCRT) or Planning Target Volumes (PTV) constructed for intensity modulated radiotherapy (IMRT) such that the pelvic lymphatics were treated to a median dose of 45 Gy. The whole bladder was treated to an additional 10.4 Gy (to 55.4 Gy), followed by a final boost to the bladder tumor to 63 Gy (range 41.4 Gy to 71.4 Gy). The dose per fraction was 1.8 Gy. One patient opted to stop cCRT at 41.4 Gy and elected to undergo partial cystectomy; all others received >60 Gy to the bladder tumor. Image guidance was performed using weekly megavoltage EPID or daily kilo-voltage imaging, in accordance with the departmental policy at that time. All patients were evaluated in clinic on a weekly basis and toxicities recorded prospectively. The toxicity of radiation therapy was graded using the NCI - Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

2.4 Concurrent chemotherapy

Platinum-based concurrent chemotherapy was used in 14 patients (see Table 1). The most common regimen was weekly cisplatin 30 mg/m^2 used in 11 patients. Concurrent gemcitabine at 27 mg/m^2 twice per week was used in 7 patients. Weekly carboplatin + paclitaxel at 50 mg/m^2 was used in 3 patients and capecitabine 825 mg/m^2 BID, Monday through Friday, was used in 1 patient. The toxicity of chemotherapy was graded using the NCI - Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

2.5 Follow-up

After completion of all therapies, patients were followed every 3 months for 2 years and at every 4 months thereafter. Follow up was performed whenever possible in the multidisciplinary clinic or separately by the concerned specialists. In addition to a physical examination at every visit, patients had an abdomino-pelvic CT and cystoscopy at three months for initial response assessment and at six-month intervals thereafter during the first 2 years of follow up. Beyond this time period, CT was performed every six months, but cystoscopy was performed only when clinically or radiologically indicated.

2.6 Statistical analysis

Three-year local control (LC) and overall survival (OS) estimates were determined utilizing the Kaplan-Meier method. Disease-related outcomes were then stratified by variables of interest, and the log rank test was employed to test for significance. All statistical tests were completed utilizing SPSS software version 22 (IBM Armonk, NY).

3 Results

From 2002 to 2012, a total of 93 patients with bladder cancer were evaluated for treatment in the Department of Radiation Oncology. Of these, 40 were treated with palliative intent due to advanced stage of their cancer or poor performance status. A total of 53 patients with cT2-4 N0-2 M0 MIBC were evaluated and treated with curative intent. Of these 22 patients were treated after maximal TURBT with platinum-doublet-based neoadjuvant chemotherapy followed by definitive cCRT (see Figure 1). Twenty patients were male, and 2 were female. The median (inter-quartile range) age at the time of treatment was 67.5 (55-71) years. Twenty-one patients had transitional cell histology and one showed elements of both transitional cell carcinoma and small cell components. Clinical stage was T2 in 12 patients, T3 in 8, and T4 in 2 patients. Fourteen patients had N0 status while 8 were node-positive. The American Joint Committee on Cancer (AJCC) TNM classification version 7 was used for staging.

All patient received cisplatin based neo–adjuvant chemotherapy. Cisplatin-Gemcitabine combination was used in 14 patients (64%) and Carboplatin-Gemcitabine in 3 patients (14%) (see Table 1). All but 3 patients received 4 cycles of chemotherapy, while the remainder received 3 cycles. Toxicities were modest and treatable. Only 1 patient required hospitalization for neutropenic fever (grade 4 toxicity), with recovery. Three patients missed one dose of chemotherapy; full doses were administered in all other patients. Cisplatin was switched to carboplatin in 4 patients during treatment because of nephrotoxicity, but all these patients ultimately received 4 cycles of treatment. Peripheral neuropathy and hearing loss was non-existent or mild in all patients (Grades 1 or 2) and usually resolved with time.

When assessed for response, 15 patients (68%) showed complete response (CR) to systemic chemotherapy on cystoscopic evaluation, while 6 had partial response and 1 patient showed stable disease. CT of the abdomen and pelvis confirmed no evidence of disease progression in all patients. Since the decision to proceed to cCRT was not based on response to neo-adjuvant chemotherapy, biopsy was not routinely done to confirm pCR if clinical CR was suspected. However, maximal safe TURBT was performed in 3 patients with organ confined residual papillary tumor as determined by a diagnostic cystoscopy and abdominopelvic CT scan. In the other 4 patients with residual tumors that extended beyond the

 ISSN 1925-4067 E-ISSN 1925-4075

bladder (cT3-T4), a biopsy was performed to confirm partial response. Repeat maximal TURBT was not attempted in these patients. One additional patient had a biopsy proven complete response.

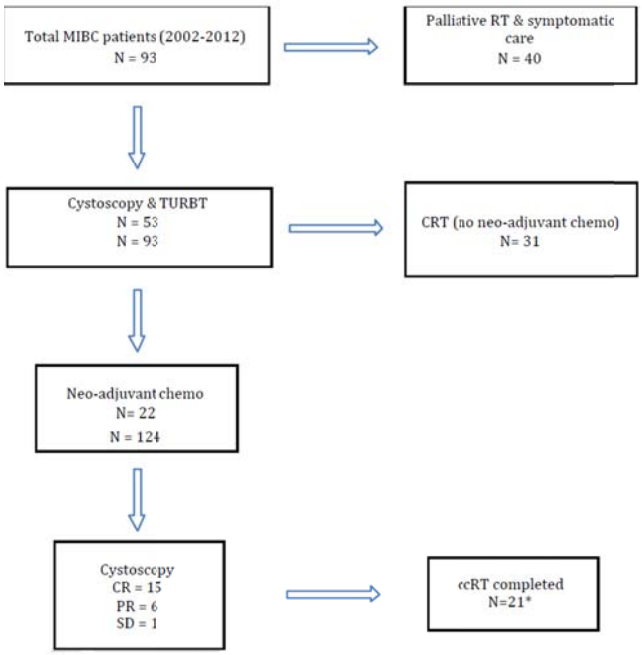

Figure 1. Treatment Schema: Bladder Preservation Protocol using Continuous Chemoradiation (cCRT)

* 1 patient discontinued cCRT at 41.4 Gy

After neoadjuvant chemotherapy, all patients received cCRT. One patient who opted to abort cCRT at 41.4 Gy underwent partial cystectomy and remained alive without evidence of disease at 64 months of follow up. All other patients received >60 Gy to the bladder tumor. Overall, cCRT was tolerated very well, with most patients having grade 1-2 genitourinary toxicity. Two patients had radiation cystitis with hematuria requiring blood transfusion and hospitalization (grade 3 GU toxicity). Cystoscopic evaluation at the end of all treatment revealed 17 patients (77%) with complete response. All patients with CR after neoadjuvant chemotherapy remained without evidence of disease after cCRT. Two additional patients were converted from PR after chemotherapy to CR after completion of cCRT. These two patients had a repeat maximal TURBT after completion of neoadjuvant chemotherapy and prior to the start of cCRT.

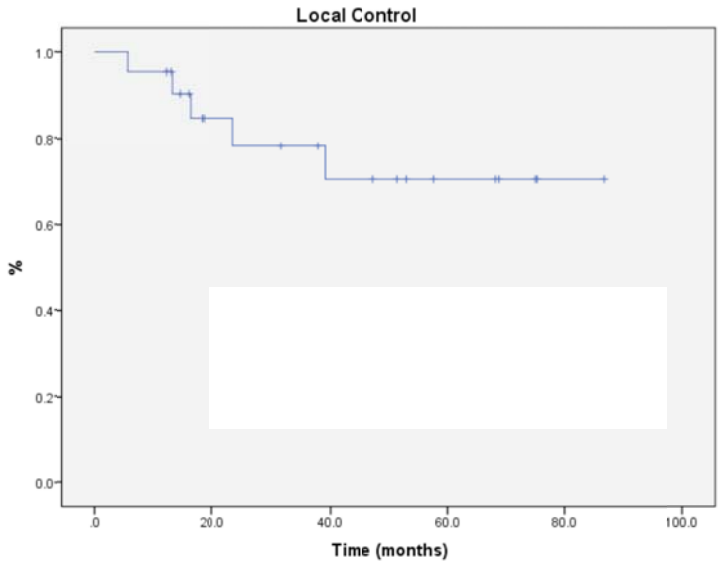

Figure 2. Kaplan-Meier Curve for Local Control (LC)

The median follow-up was 24 months (range 6 to 86). At the time of analysis 8 of 22 patients were alive without evidence of cancer, all with intact bladders. The actuarial 3-year DFS and LC for the entire cohort were 62% and 78.3% (see Figure 2). Three-year overall survival was 62.2% with median survival 53.2 months (95% CI: 41.6-64.8) (see Figure 3).

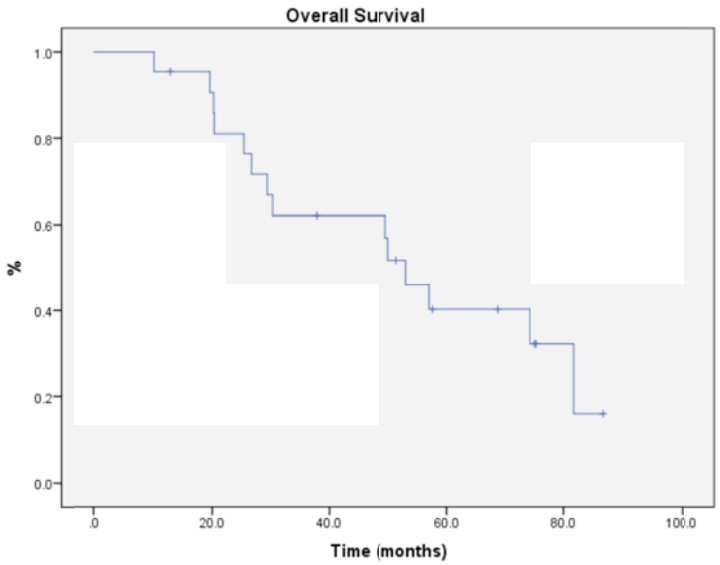

Figure 3. Kaplan-Meier Curve for Overall Survival (OS)

When stratified by T and N stage, 3-year DFS was 81.8% for T2, 50% for T3 and 0% for T4 (p = .006); and 77.4% for N0 *vs.* 37.5% for N1-2 (p = .195). The 3-year LC was 90.9% for T2, 87.5% for T3 and 0% for T4 (p = .007); and 92.9% for N0 *vs.* 51.4% for N1-2 (p = .199) (see Table 2).

Table 2. Three year LC, DFS and OS estimates, stratified by variables of interest

Variable	% LC (p-value)	% DFS (p-value)	% OS (p-value)
Age			
> 60 years	73.4%	57.1%	57.1%
< 60 years	87.5% (.834)	72.9% (.532)	72.9% (.575)
T Stage			
T2	90.9%	81.8%	81.8%
T3	87.5%	50%	50%
T4	0% (.007)	0% (.006)	0% (.012)
N Stage			
+	51.4%	37.5%	37.5%
-	92.9% (.199)	77.4% (.195)	77.4% (.274)
Response to NAC			
CR	90.9%	64.3%	64.6%
PR	57.1% (.024)	57.1% (.03)	57.1% (.046)

For patients with CR on cystoscopy following neo-adjuvant chemotherapy the 3-year LC was 90.9% *vs.* 57.1% without CR (p = .024) (see Table 2 and Figure 4). Local recurrence was associated with distant metastases in 4 out of 5 patients. Two patients had non-invasive bladder cancer local recurrence and both underwent successful treatment with intra-vesical BCG. The 3-year DFS and OS for patients achieving CR on cystoscopy following neo-adjuvant chemotherapy was 64.3% *vs.* 57.1% without CR (p=.03), and 64.6% *vs.* 57.1% without CR (p=.046), respectively (see Table 2).

 ISSN 1925-4067 E-ISSN 1925-4075

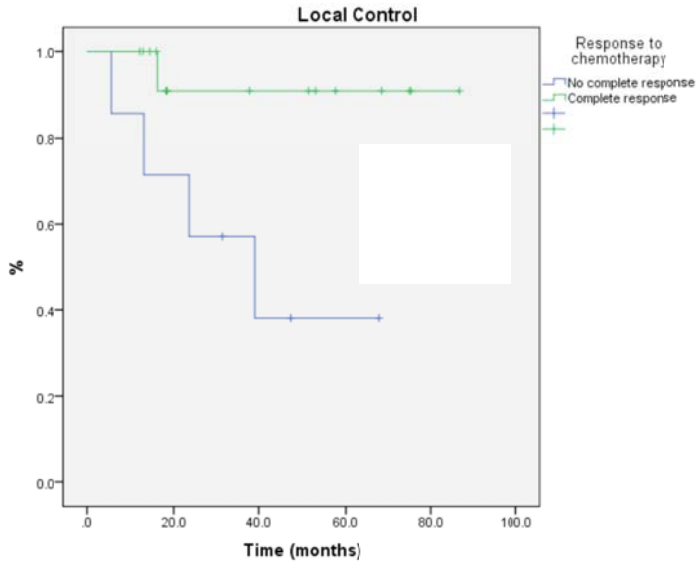

Figure 4. Kaplan-Meier curves for Local Control (LC) for patients with complete response *vs.* no complete response at the time of cystoscopy evaluation following neo-adjuvant chemotherapy

4 Discussion

Chemoradiation (CRT) has emerged as a viable option for bladder preservation in muscle invasive urothelial carcinoma. Contemporary series of bladder preservation using CRT as definitive treatment have shown complete response rates of 53%-88% and projected 3-year survival rates ranging between 61% and 75% [2-9]. All CRT studies also report high rates of bladder preservation, ranging between 42%-66% at 5 years among patients completing the treatment [2-9]. In the present study, maximal TURBT followed by neoadjuvant platinum based chemotherapy resulted in a complete response rate of 68%, and 77% after completion of cCRT. Despite having an elderly cohort of patients with significant comorbidities our 3-year DFS of 62% and LC of 78.3% compare favorably with contemporary bladder preservation series [2-9] as well as large cystectomy series [10, 11].

Numerous Phase II studies [2-9, 15, 22-25] have demonstrated that concurrent chemotherapy improves radiation response in MIBC and a recent Phase III study demonstrated survival advantage with this approach [13]. In addition, successive RTOG protocols have proven the safety of concurrent chemotherapy with reported low rates of grade 3 late GU and GI toxicities at 5.7% and 1.9% respectively [25]. Urodynamic and Quality of Life studies also confirm that a high percentage of retained bladders demonstrated normal capacity and flow parameters [26].

However, the doses of concomitant chemotherapy in all these studies, as well as in the present study, are significantly lower than those used in the neoadjuvant pre-cystectomy setting. We were concerned that concomitant chemotherapy, if used as the sole systemic modality, would have markedly less activity against micro-metastatic disease than the regimens used in the pre-cystectomy setting. Therefore, we adopted a regimen used in the pre-cystectomy, neoadjuvant setting to the pre-radiation therapy setting. Our experience shows that such a regimen is well tolerated.

Despite these encouraging results, definitive CRT continues to be underused. Gray et al. analyzed the treatments of 28,691 patients with MIBC treated between 2004-2008 from the United States National Cancer Database which excluded those with cT4b and metastatic disease. This study showed that >25% of patients between ages 70-79 years and nearly 40% for those aged 80-89 years were treated with observation alone [27]. Although many of these patients were likely to have limited functional status and associated comorbidities that limited their therapeutic options, many contemporary CRT studies including our experience have demonstrated the feasibility of treating this subgroup of elderly patients [28].

The RTOG investigated the role of neoadjuvant CMV chemotherapy prior to CRT in MIBC stage T2-T4aNxM0 on a randomized trial. In this study, 126 patients received 2 cycles of neoadjuvant chemotherapy (CMV) followed by CRT *vs.*

CRT alone. Cystectomy was reserved for patients who did not achieve CR on mid-treatment cystoscopy. This trial which was closed early due to an unexpected high rate of hematologic toxicity and neutropenic sepsis during induction chemotherapy, showed no improvement in survival with neoadjuvant chemotherapy [16]. In contrast, all but 3 patients in our study received 4 cycles of chemotherapy while the remainder received 3 cycles. Full doses were administered in all but 3 patients. One patient was hospitalized due to neutropenic fever (grade 4 toxicity), with recovery. All other toxicities were modest and treatable.

Our approach of administering cisplatin-based neoadjuvant chemotherapy [17, 20, 21] was adopted following the publication of several Phase III studies demonstrating the value of neoadjuvant chemotherapy in patients undergoing cystectomy. This has been further substantiated by pooled studies and meta-analyses [18, 19, 29]. The SWOG study, which showed the greatest survival improvement with neoadjuvant chemotherapy, employed the classic MVAC regimen [21]. However, data from a subsequent Phase III trial in the metastatic setting comparing MVAC to cisplatin plus gemcitabine (GC) showed that GC had lower toxicity and equivalent efficacy [30]. A retrospective, non-randomized study comparing MVAC to GC in the pre-cystectomy, neoadjuvant setting showed that GC had similar efficacy and lower toxicity [31]. These data have led most medical oncologists to prefer cisplatin and gemcitabine in the pre-cystectomy neoadjuvant setting. The majority of these studies also demonstrate that neoadjuvant pre-cystectomy chemotherapy increases the proportion of patients who are T0 at the time of surgery [21, 32, 33] and that patients who are rendered T0 at the time of surgery [17, 19, 21, 33, 34] have improved long-term survival. Finally, the number of patients who progressed while receiving neoadjuvant pre-cystectomy chemotherapy has been shown to be very low (less than 10%). These considerations provided a rationale for the use of a similar regimen in the pre-radiation therapy setting. Therefore, in the present study, we adopted the practice of administering multiple cycles of cisplatin-based doublet therapy (with GC as the preferred regimen), to be followed by re-staging and subsequent cCRT. In our cohort of patients, all completed neo-adjuvant chemotherapy and went on to receive definitive cCRT.

Our study also shows that patients who achieve a complete response to neoadjuvant chemotherapy had excellent 3-year LC of 90.9% *vs.* 57.1% (p=.024) and improved DFS and OS. In a recent meta-analysis of 13 neo-adjuvant chemotherapy and cystectomy trials, complete pathologic response was found to be a strong predictor of improved DFS and OS [35]. Response to neo-adjuvant chemotherapy could aid the multidisciplinary team select patients who are good candidates for bladder preserving treatment.

5 Conclusion

Maximal TURBT followed by neo-adjuvant platinum based chemotherapy and definitive cCRT offers excellent bladder preservation rates in MIBC. Complete response to neo-adjuvant chemotherapy is a favorable prognostic factor, achieving LC rates >90% at 3 years. Validation of these results would require a prospective randomized trial.

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