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Original Research Article

Surgery after neoadjuvant chemotherapy for muscle invasive bladder cancer: clinicopathological and surgical outcomes

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ABSTRACT

Background: Neoadjuvant chemotherapy (NAC) before radical cystectomy (RC) is the standard of care for muscle-invasive bladder cancer (MIBC) owing to the survival advantage, which has correlated with down-staging of the cancer to pT0. This approach is underused because it may be associated with increased perioperative morbidity and mortality rates. This study was designed to evaluate NAC plus RC regarding pathological response, perioperative morbidity and mortality outcomes.
Methods: This is a prospective study that was carried out from August 2015 till July 2017 for patients with bladder carcinoma. We enrolled all cases with ≥ T2 bladder receiving NAC. Patients with metastatic disease, poor performance were excluded from this study.
Results: pathological response rate and Complications occurred within 30 and 90 d after surgery. Heterologous blood transfusions, length of stay, readmission, and perioperative morbidity, and mortality were compared.
Conclusions: Our results suggest that non-urothelial tumor showed no response to Platinum based combination chemotherapeutic regimens. NAC followed by RC gives no more perioperative complications.

Keywords: Muscle invasive bladder cancer, Neoadjuvant chemotherapy, Urinary diversion

INTRODUCTION

In the United States, bladder cancer (BC) accounts for about 5% of newly diagnosed cancer cases. It is reported to be the 4th most common cancer in men and the 9th in women. It has the fifth highest incidence of all malignancies, with more than 74,000 newly diagnosed cases and 15,000 deaths in 2014.[1] In Egypt, BC is considered the 2nd most common cancer in men (12.7%) after hepatocellular carcinoma (18.7%), and one of the most common cancers in women after breast cancer (38.8%), lymphoma, leukemia and ovarian cancer.[2]

At the time of first presentation, about 30% of BC patients present with muscle-invasive bladder cancer (MIBC). It is an aggressive malignant disease of

significant morbidity and mortality and associated with high rate of early systemic spread.[3-5] Radical cystectomy (RC) is the cornerstone of management of MIBC. However, there is a 55% rate of recurrence most commonly as distant micro-metastases which cannot be detected by standard imaging studies at the time of cystectomy. So, RC only provides five-year survival in about 50% of patients denoting that surgery is not sufficient treatment alone in a large number of patients with MIBC.[6-11] Neoadjuvant chemotherapy (NAC) has been introduced to eradicate these occult metastasis outside the surgical field early in the disease process and improves overall survival results especially for patients who showed pathologic complete response (pCR) pT0 N0.[12,13] Despite being recommended by all clinical guidelines, NAC is still underused. Not more than 16% of patients receive NAC before surgery even at tertiary care centers with MDT programs.[14] Few data on the role of NAC in treatment of MIBC exist. This study was undertaken to preliminary assess the experience of Oncology Center, Mansoura University regarding clinical, radiological, pathological response of patients with MIBC and perioperative complications related surgery after NAC.

METHODS

Twenty-two patients with MIBC received NAC and underwent surgery 4-6 weeks after their last chemotherapy cycle were enrolled in a prospective study from August 2015 till July 2017 in Oncology Center, Mansoura University (OCMU). All clinical procedures were conducted in accordance with guidelines of the ethical committee of Faculty of Medicine, Mansoura University and after obtaining the written informed consent from the patients. Patients with non-metastatic MIBC (T2-T4a, N0-N2) with good performance status and anaesthetic fitness were selected for this analysis. Patients with metastatic disease, history of previous malignancy, history of pelvic radiation therapy, renal dysfunction, hearing loss, and patient preference were excluded.

After diagnosis and staging of MIBC, all patients were referred to medical oncology unit according to multidisciplinary team decisions. Toxicity was estimated as defined by Good Clinical Practice (GCP). When, NAC course has finished, patients were referred back to surgical oncology unit and submitted to cystoscopic and imaging reevaluation for clinical staging after NAC using criteria of revised RECIST guideline (version 1.1). Then patients were subjected to different surgical procedures. A pathomorphologic assessment of the therapeutic response of the residual tumor volumes and estimation of tumor control were performed using histopathologic tumor regression grades (TRGs) which were defined as follows: TRG1: complete tumor regression (pCR); TRG2: >50% tumor regression; TRG3: 50% or less American Joint Committee on Cancer 2010 TNM staging 7th edition (AJCC)tumor regression. Separate TRGs were assigned for primary tumors and corresponding lymph nodes. All patients were followed up postoperatively with imaging and cystoscopy every 3 months for 2 years with widening of surveillance interval after.

RESULTS

Patients demographics and tumors' characteristics

The present cohort of patients represents all consecutive MIBC patients presenting to our service. Baseline criteria are summarized in Table 1.

Table1: Summary of patient's demographics and tumor' characteristics (n=22).

Characteristics	Value (%)
Age	
Range	51-71 years
Mean±SD	60.95 (±5.38)
Gender	
Male	16 (73%)
Female	6 (27%)
BMI	
Range:	21.2-44.5 kg/m^2
Mean±SD	30.4±7
Smoking	
Smoker	14 (63.6%)
Non-smoker	8 (36.4%)
Comorbidities	
None	11 (50%)
Diabetes	3 (13.6%)
Hypertension	2 (9%)
Chronic liver disease	2 (9%)
2 or more comorbidities	4 (18.2%)
Clinical presentation	
Haematuria	21 (95.5%)
Dysuria	11 (50%)
Urgency and frequency	1 (4.5%)
Urine retention	1 (4.5%)
Clinical and nodal staging (According to AJCC)	
T Tumor	
T2	11 (50%)
T3	10 (45.5%)
T4a	1 (4.5%)
N Node	
N0	18 (81.8%)
N+	4 (18.2 %)
Histopathologic type	
Urothelial carcinoma	17 (77.3%)
Squamous cell carcinoma	4 (18.2%)
Mixed urothelial and adenocarcinoma	1 (4.5%)
Grade	
I	2 (9.1%)
II	7 (31.8%)
III	13 (59.1%)

American Joint Committee on Cancer 2010 TNM staging 7th edition (AJCC)

Table 2: summary of toxicity and undesirable effects related to nac (n=22).

NAC Regimen	Total number of patients	Toxicity
M-VAC	10 (45.5%)	Neutropenia (4 cases)
		Neurotoxicity (1 case)
		Mucositis (3 cases)
		Gastritis (1 case)
GC	8 (36.4%)	Neutropenia (2 cases)
		Ototoxicity (1 case)
G/carbo	4 (18.2%)	Nephrotoxicity (2 cases)
		Skin eruption (1 case)

Methotrexate-vinblastine-doxorubicin-cisplatinum (M-VAC); Gemcitabine and cisplatin combination (GC); Gemcitabine and carboplatin combination (G/C)

Neoadjuvant data

Platinum based combination chemotherapeutic protocols 3 cycles with 3 weeks interval were recommended by the medical oncologists.

The choice of drug therapy is based on its availability at our institute. Nine patients (40.1%) had no symptoms or signs of toxicity while thirteen patients (59.9%) developed toxicity manifestations. Toxicity and undesirable effects related to NAC were collected in Table 2.

Clinical and imaging outcomes

Seven cases showed stationary course, ten cases showed regressive course and four cases showed near complete resolution. One patient clinically staged T3N0 was excluded; he received only 1 cycle G/carbo then developed nephrotoxicity and referred back for surgery. Clinical and imaging outcomes were assessed in Table 3.

Table 3: clinical and imaging outcomes (n=21).

Clinical stage prior to chemotherapy	Number of patients	Clinical stage after chemotherapy						
T Tumor		To	Tis	Ta	T1	T2	T3	T4a
cT2	11	3	3	0	2	3	0	0
cT3	9	1	1	0	1	3	3	0
cT4a	1	0	0	0	0	0	0	1
N Node								
N0	17	21						
N+	4	0						

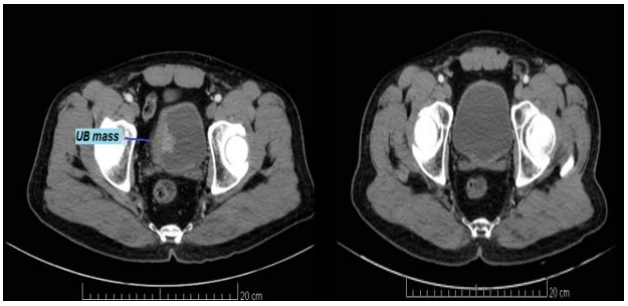

Figure 1: Post contrast CT before NAC and after post contrast CT after NAC revealing good response to neo adjuvant chemotherapy.

Pathological response:

After histopathologic examination of the specimens, the frequency of TRGs 1, 2, and 3 in the primary tumors were n=3, n=4, and n=15; corresponding data from the lymph nodes were n=19, n=1, and n=2. Seven specimens showed non-muscle invasive disease (31.8%) from which three showed pCR (13.6%) (Figures 2, 3) and fifteen showed muscle invasive disease (68.2%) (Table 4). Nineteen showed negative nodes (86.4%) while three showed positive nodal disease (13.6%). Urethral margins were free in all cases. Patients with SCC have no response to NAC

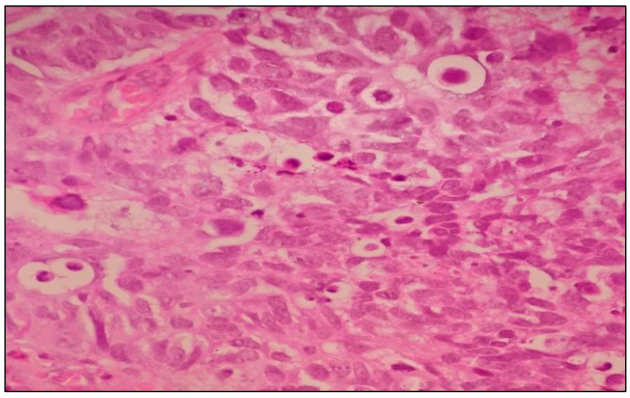

Figure 2: cystoscopic bladder biopsy (pre-neoadjuvant chemotherapy), H&E (40x) section shows atypical mitotic figures (arrows).

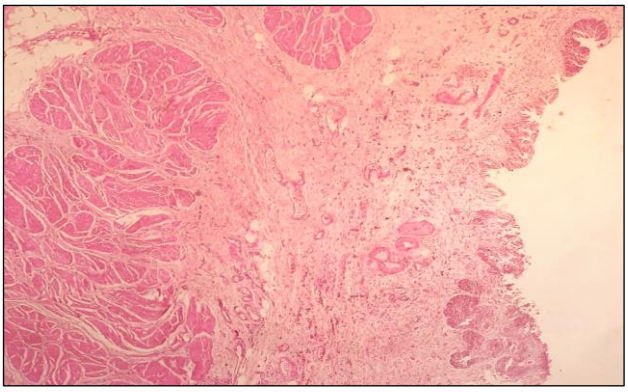

Figure 3: Radical cystectomy specimen (post neoadjuvant chemotherapy), H&E low power section shows thick muscle bundles & partially ulcerated urothelium and no residual tumor tissue (complete pathological response).

Surgical outcome:

Nineteen patients (86.4%) underwent radical cystectomy, bilateral pelvic lymphadenectomy (figure 4) and suitable urinary diversion, and three patients (13.6%) preserved their bladders (one patient (4.5%) underwent partial cystectomy and two patients (9%) underwent TURBT) with maintaining bladder and sexual functions.

One patient died in early postoperative period (0-30 days) after RC due to massive pneumonia. Table 5, 6 shows summary of operative data and perioperative complications of RC

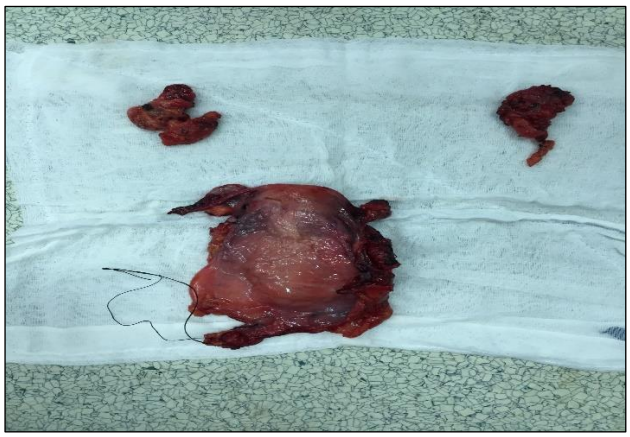

Figure 4: Female patient 61 years old presented by T2 N0 urothelial carcinoma received 3 cycles gem/cis underwent radical cystectomy.

Table 4: pathologic response to NAC (n=22)

Tumor type	Clinical stage prior to chemotherapy	Number of patients	Pathological stage after surgery						
	T Tumor		**To**	**Tis**	**Ta**	**T1**	**T2**	**T3**	**T4a**
Tumor TCC	cT2	9	3	1	0	2	2	1	0
	cT3	9	0	0	0	1	7	1	0
	cT4a	0	0	0	0	0	0	0	0
SCC	cT2	2	-	-	-	-	2	-	-
	cT3	1	-	-	-	-	-	1	-
	cT4a	1	-	-	-	-	-	-	0

Table 5: Summary of operative data after RC (n=19).

Variant	Value
Operative duration	
Range	250-450 minutes
Mean±SD	349.7±67
Estimated blood loss (EBL)	
Range	50-2000 ml
Mean±SD	670±605.6
Blood transfusion	15 patients
Type of urinary diversion	
Ileal loop conduit	11 (57.9%)
Orthotopic neobladder	7 (36.8%)
Rectosigmoid pouch	1 (5.3%)
Hospital stay	
Range	11-31 days
Mean±SD	17.4±6.47

Table 6: summary of perioperative complications after RC (N=19).

Complications	Number of patients
Intraoperative complications	
Genito-femoral nerve injury	1 (5.3%)
External iliac vein injury	2 (10.5%)
Bleeding	2 (10.5%)
Delayed recovery	1 (5.3%)
Early postoperative complications	
(1-30 days)	2 (10.5%)
Prolonged ileus	2 (10.5%)
Pneumonia	1 (5.3%)
Burst abdomen	1 (5.3%)
Pelvic collection wound sepsis	1 (5.3%)
Complications required hospital	
readmission	1 (5.3%)
DVT and PE	3
Metabolic abnormalities	1 (5.3%)
Pouch-cutaneous fistula	
Late postoperative complications	
Parastomal hernia	1 (5.3%)
Night incontinence	1 (5.3%)
Day incontinence	1 (5.3%)
Refluxing pyelonephritis	1 (5.3%)
Incisional hernia	2 (10.5%)
Recurrent DVT and PE	1 (5.3%)

Follow up and survival outcomes

Twenty-one patients were followed up within period ranged from 3 months to 22 months (10.58±4.15). One patient lost follow up 4 months after surgery. Two patients developed distant metastases after surgery, one of them received palliative chemotherapy and died 10 months later and the other was not fit for chemotherapy and died one month later. Both cases were urothelial locally advanced (T3N0, T4N0) and show no response with neoadjuvant therapy. Pathologically, both cases showed nodal invasion after surgery. Eighteen patients were with no evidence of disease (NED) after median follow-up of 22 months

DISCUSSION

The use of NAC has improved 5-year survival those patients and provided about 5 to 6.5% absolute overall survival benefit compared with cystectomy alone. Because of this effect on survival, guidelines from expert institutes recommend platinum-based chemotherapy for T2 clinical disease stage or higher.[15]

The disease population in the present study was roughly comparable to that described in other studies. In a Japanese report of a total number of 29 patients, thirteen (44.8%) of them had T2 disease, thirteen (44.8%) had T3 disease and three (10.3%) with T4a disease. All 29 patients, however were node negative (100%).[16]

In this study, MVAC regimen was used in ten patients (45.5%), GC protocol in eight patients (36.3%) and G/carbo in four patients (18.2%). While in American study, among 106 patients, they used MVAC in 11 patients (10%) and GC in 95 patients (90%).[17]

After NAC, residual local disease, persistent nodal disease and status of surgical margins are the most powerful prognostic factors for patients who underwent RC.[18]

Pathologic complete response (pCR) in the form of pT0N0M0 stage is clearly associated with a 55% lower risk of death and an 80% lower risk of recurrence compared with patients with any residual disease.[19]

Among total number of 59 patients, pCR was observed in 15 specimens (25.4%), 20 (33.9%) showed pTa, pTis and pT1 disease, six were pT2 (10.2%), twelve were pT3 (20.3%) and six were pT4a (10.2%). Fifty specimens were node negative (84.7%) and nine were N+ (15.3%). Urethral margin was involved in 5 cases (8.5%).[20]

While in the present study, only three patients showed TRG 1, pCR (13.6%), four specimens showed TRG 2, pTis and pT1 (18.2%), and only eleven patients were pT2 (50%) as TRG 3. Three cases had pT3 disease (13.7%) and one patient had pT4a disease (4.5%). Nineteen were pN0 (86.5%) and 3 were N+ (13.5%). Urethral margin was negative in all cases.

This significant discrepancy in pathologic response is attributed to the presence of different histopathologic tumor types in our study other than urothelial carcinoma. In Egypt, squamous cell carcinoma is relatively common due to endemic bilhariziasis. In our study four patients (18.2%) had squamous cell carcinoma. All these patients unfortunately showed no pathologic down-staging. It would be worth mentioning that the situation is not yet investigated.

After exclusion of cases with different histopathologic types, pCR was achieved in 17.6% and non-invasive disease was achieved in 23.5%. These results are more comparable to the worldwide reported results.

In a Japanese phase III randomized study, among 59 patients who received NAC, all patients underwent RC and different forms of urinary diversion were done. Regarding operative data, mean operative time was 456 minutes, average blood loss was 1670 ml and fifty-four (84.4%) patients required intra-operative blood transfusion.[21]

In the group of RC, the type of diversion was not significantly different, however the operative time and average blood loss was significantly lower in our study than that in Kitamura et al. study. This is attributed to presence of highly experienced urology team, and presence of well-equipped operative theatre at out center.

In our study, nineteen patients underwent RC. Ten patients experienced different grades of complications (52.6%), five patients (26.3%) were readmitted after discharge. One death (5.3%) was reported in postoperative period due to massive chest infection and two cases (10.5%) died during follow up because of cancer.

Regarding early postoperative (first 90 days) complications, in the University of North Carolina, seventy-eight patients whom received NAC were enrolled in a study to evaluate early postoperative complications. One case (1.3%) required reoperation, seven cases (9%) exhibited wound infection, no cases were reported to have wound dehiscence, UTI was found in seven patients (9%), pneumonia in two cases (2.6%), DVT and PE in two patients (2.6%), acute renal shutdown in 2 patients (2.6%) and cardiovascular complications were found in two patients (2.6%).[14]

Among our patients, two cases suffered from prolonged ileus (10.5%), one patient required reoperation due to pouch-cutaneous fistula (5.3%), one patient developed wound infection (5.3%), one case had wound dehiscence (5.3%), one patient had UTI (5.3%), two patients developed pneumonia (10.5%), one patient developed DVT and PE (5.3%) and one patient had pelvic collection (5.3%). There were no reported cases with cardiovascular or renal complications.

These conflicting results are due to limited number of patients enrolled in our study and due to presence of significant preoperative comorbidities in our patients.

CONCLUSION

Treatment of MIBC requires coordinated multidisciplinary care that often stretches across practice settings. Aiming to improve survival, neoadjuvant chemotherapy has been used for treatment of MIBC targeting the micro-metastatic deposits and to down-stage the disease.

Present results suggest that non-urothelial tumor showed no response to Platinum based combination chemotherapeutic regimens. NAC followed by RC gives no more perioperative complications.

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