Original Article

Factors related to upstaging of clinical stage T2 organ-confined bladder cancer following radical cystectomy: A multicenter study

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Abstract

Aims: This study aimed to detect possible risk factors related to upstaging of clinical stage T2 organ-confined (OC) to non-OC (nOC) bladder cancer (BC) following radical cystectomy (RC).

Settings and Design: This was a prospective multicenter study.

Subjects and Methods: This is a multicenter prospective study including 196 Egyptian BC patients undergoing RC from January 2017 to February 2019 at Cairo University, Fayoum University, and Menoufia University. Only patients with muscle invasive BC (T2) were included in the study. Patients' characteristics, preoperative clinical data (including Hydronephrosis), cystoscopy data, and biopsy pathological data were recorded. Preoperative clinical staging is compared to postoperative pathological staging, to determine upstaged cases. The occurrence of upstaging in correspondence to each preoperative factor is recorded and statistically analyzed.

Results: Among 196 BC patients of our study, upstaging from OC T2 to nOC occurred in 88 (44.9%) patients. Statistical analysis showed that the factors related to upstaging are older age ($P \leq 0.001$), large tumor size ($P = 0.048$), lymphovascular invasion (LVI) ($P \leq 0.001$), and multifocal tumor ($P \leq 0.001$). On the other hand, the following factors were not related to upstaging: gender ($P = 0.159$), smoking ($P = 0.286$), preoperative hydronephrosis ($P = 0.242$), and presence of carcinoma *in situ* ($P = 0.349$).

Conclusions: The difference between clinical and pathological staging of BC patients following RC is a frequent problem with no clear guidelines to overcome it. Several factors including age of the patient, large tumor size, LVI, and multifocal tumor are predictors of upstaging in OC BC. A good concern must be taken in these patients to achieve an optimum treatment plan for them.

Keywords: Bladder cancer, nonorgan confined, Organ confined, Radical cystectomy, upstaging

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INTRODUCTION

The ninth most commonly diagnosed cancer worldwide is urinary bladder cancer (BC) with an estimated incidence of 430,000 patients in 2012 alone.[1]

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Transitional cell carcinoma (TCC) is nowadays known to be the most prevalent replacement histopathology of squamous cell carcinoma (SCC). This is may be attributed

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to the reduction in schistosoma infection and increase in cigarette smoking and chemical exposure.[2]

Clinical staging is a very important step, both in treatment planning and when counseling patients with BC. Clinical staging depends on the pathological examination of transurethral resection of bladder tumor (TURBT) specimens, bimanual physical examination under anesthesia, and imaging (computed tomography [CT], magnetic resonance imaging [MRI]).[3] There is a distinction between clinical and pathological staging (based on radical cystectomy [RC] pathology). Clinical staging remains inaccurate with about 40% being upstaged from organ-confined (OC) to non-OC (nOC) disease at the time of RC.[4]

Although the treatment of OC cancer with RC alone can lead to good results,[5] early dissemination of occult micrometastases is a notable source of failure.

The rates of 5-year recurrence after surgery vary from 20% to 30% in pT1 and pT2 disease to 50%–90% in pT3–4 disease. The incidence of loco-regional recurrence (5%–15%) is less than distant recurrence (20%–50%) which may rise the importance of the perioperative systemic therapy in high-risk patients to potentially treat micrometastasis.[6,7]

Neoadjuvant chemotherapy has been shown to improve the survival rates in patients with cT2–4a disease. This is particularly relevant with respect to the upstage of OC to nOC disease (T3 or N+) since some studies indicate that patients with nOC disease benefit the most from neoadjuvant chemotherapy.[8,9]

A prominent issue about preoperative chemotherapy administration is toxicity and latency of RC.[10]

The purpose of our study was to analyze the details of BC staging in a large combined RC database from three academic centers. In addition, in our research, we aimed to examine the upstage risk factors.

SUBJECTS AND METHODS

This is a multicenter prospective study where 196 Egyptian BC patients undergoing RC were included from January 2017 to February 2019 at Cairo University, Fayoum University, and Menoufia University.

Informed consent was signed in each case after explaining the nature of the disease, the risks, and potential benefits of the study.

Only patients with OC BC (T2) were included. All 196 consecutive patients suffering from urothelial BC are undergoing RC and lymphadenectomy.

Excluded from this study were patients with nonmuscle invasive BC who were candidates for RC and patients with nOC BC diagnosed by imaging.

Full history with detailed medical history, laboratory investigations in the form of complete blood count, renal function tests, and liver function tests, and radiological investigations in the form of abdominal and pelvic CT with intravenous contrast and chest radiography (in patients with elevated renal functions, MRI of the abdomen and pelvis was done instead of CT) were done for every patient included in the study.

The following clinical and pathological data were analyzed: age, gender, initial BC presentation (date, grade, and stage), intravesical therapies, date of surgery, extent of lymphadenectomy, pre-RC clinical stage, concomitant carcinoma *in situ* (CIS), and post-RC pathology. Tumor grade was reported as in the 2004 classifications of the International Society of Urologic Pathology (ISUP) and the 2002 Tumor, Nodes, and Metastases (TNM) classification was used to record the stage.[6] The study included only urothelial cancers (UCs).

During TURBT, bimanual examination was performed before resection under general anesthesia. Both specimens of TURBT and RC have been examined by genitourinary pathologists. When the TUR was performed at an outside institution, either TURBT slides were reviewed or rebiopsy was performed at the study institutions.

RC included removal of the bladder, seminal vesicles, and the prostate in males, while the uterus, ovaries, and anterior vaginal wall were included in females.

Extended pelvic lymph node dissection was performed in all patients, the cranial boundary of dissection was the crossing of ureters across the common iliac vessels.

For upstaging, two definitions were used: (1) any increase in T- and/or N-stage, i.e., clinical stages were compared with that following cystectomy, i.e., pathological stage and (2) upstaging from OC to nOC tumor (any cT ≤2, cN0 tumor being upstaged to pT ≥3 or pathologically confirmed node-positive disease).

The data were coded and entered using the Statistical Package for the Social SciencesStatistical Package for

the Social Sciences version 23 (IBM corp., Armonk, NY, USA). Data were compiled using mean, standard deviation, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data.

Correlations were done using Spearman correlation coefficient between quantitative variables. $P < 0.05$ was considered statistically significant.

This study was approved by the local ethical committee.

RESULTS

One hundred ninety-six patients with OC BC were included in this study.

The mean age of the studied population is 58.16 ± 7.83. Patients' demographics are listed in Table 1.

The criteria of the bladder masses diagnosed are listed in Table 2.

Different factors related to upstaging of the bladder masses. Among 196 patients, upstaging from OC T2 to non-OC occurred in 88 (44.9%) patients. Statistical analysis showed that the following factors are related to upstaging: older age ($P < 0.001$), larger tumor size ($P = 0.048$), multifocal tumor ($P < 0.001$), and lymphovascular invasion (LVI) ($P < 0.001$).

Table 1: Patients' demographics

	Count (%)
Sex	
Female	28 (14.3)
Male	168 (85.7)
Smoking	
Yes	158 (80.6)
No	38 (19.4)

Table 2: Criteria of bladder masses

	Count (%)
Size large>3 cm	
Yes	152 (77.6)
No	44 (22.4)
Multiplicity	
Yes	44 (22.4)
No	152 (77.6)
CIS (yes/no)	
Yes	10 (5.1)
No	186 (94.9)
HN (yes/no)	
Yes	50 (25.5)
No	146 (74.5)
Upstage (yes/no)	
Yes	88 (44.9)
No	108 (55.1)

CIS: Carcinoma *in situ*, HN: Hydronephrosis

On the other hand, the following factors were not related to upstaging: gender ($P = 0.159$), smoking history ($P = 0.286$), preoperative hydronephrosis ($P = 0.242$), and presence of CIS ($P = 0.349$).

Comparison between preoperative factors in relation to the occurrence of postoperative pathological upstaging is illustrated in Table 3.

DISCUSSION

Physical examination, transurethral resection pathology, and imaging are the mainstay of clinical staging that predict patient outcome and the treatment plan, but the ability to predict pathological stage from clinical stage in BC remains unfortunately limited.[11]

In this study, we tried to evaluate different factors that affect upstaging from OC T2 to nOC T2 BC where we found that older age, larger tumor size, multifocal tumor, and LVI are related to upstaging of the disease, while gender, smoking history, preoperative hydronephrosis, and presence of CIS are not related to upstaging of the disease.

Several studies approached the upstaging of pathological examination of BC. In 2012, Turker *et al*. stated that upstaging was found in tumors with LVI was in agreement with our study, but in contrast, tthey found that female gender was associated with increased upstaging.[11]

In 2013, Mitra *et al*. agreed with our study where they stated that age, LVI, and tumor growth count were significantly associated with upstaging. In contrary, they found that the presence of hydronephrosis was significantly associated with upstaging.[12]

In our study, we studied only the TCC variant of BC without studying other histologic variants, while other studies[11,13] identified the role of histological variants in upstaging of the disease and this is attributed to the paradigm shift in histological variants in Egypt from SCC to TCC which is the most common pathology found in pathological specimens.[2]

Further studies are needed to study the role of combined treatment (neoadjuvant chemotherapy and RC) in cases with the presence of any factor that may increase the rate of upstaging from OC to nOC disease.

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Table 3: Comparison between preoperative factors in relation to occurrence of postoperative pathological upstaging

	Upstage (yes/no)		*P*
	Yes, count (%)	No, count (%)	
Age, mean±SD	60.80±8.30	56.02±6.74	<0.001
Sex			
Female	16 (18.2)	12 (11.1)	0.159
Male	72 (81.8)	96 (88.9)	
Smoking			
Yes	68 (77.3)	90 (83.3)	0.286
No	20 (22.7)	18 (16.7)	
HN (yes/no)			
Yes	26 (29.5)	24 (22.2)	0.242
No	62 (70.5)	84 (77.8)	
Size large >3 cm			
Yes	74 (84.1)	78 (72.2)	0.048
No	14 (15.9)	30 (27.8)	
Multiplicity			
Yes	30 (34.1)	14 (13.0)	<0.001
No	58 (65.9)	94 (87.0)	
CIS (yes/no)			
Yes	6 (6.8)	4 (3.7)	0.349
No	82 (93.2)	104 (96.3)	
Lymphovascular invasion			
Yes	70 (79.5)	10 (9.3)	<0.001

CIS: Carcinoma *in situ*, HN: Hydronephrosis, SD: Standard deviation

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder cancer incidence and mortality: A global overview and recent trends. Eur Urol 2017;71:96-108.
2. Felix AS, Soliman AS, Khaled H, Zaghloul MS, Banerjee M, El-Baradie M, *et al*. The changing patterns of bladder cancer in Egypt over the past 26 years. Cancer Causes Control 2008;19:421-9.
3. Bostrom P, Rhijn B, Fleshner N, Finelli A, Jewett M, Thoms J, *et al*. Staging and staging errors in bladder cancer. Eur Urol Suppl 2010;9:7.
4. Shariat SF, Palapattu GS, Karakiewicz PI, Rogers CG, Vazina A, Bastian PJ, *et al*. Discrepancy between clinical and path logic stage: Impact on prognosis after radical cystectomy. Eur Urol 2007;51:137-51.
5. Herr HW, Dotan Z, Donat SM, Bajorin DF. Defining optimal therapy for muscle invasive bladder cancer. J Urol 2007;177:437-43.
6. Dalbagni G, Genega E, Hashibe M, Zhang ZF, Russo P, Herr H, *et al*. Cystectomy for bladder cancer: A contemporary series. J Urol 2001;165:1111-6.
7. Madersbacher S, Hochreiter W, Burkhard F, Thalmann GN, Danuser H, Markwalder R, *et al*. Radical cystectomy for bladder cancer today – A homogeneous series without neoadjuvant therapy. J Clin Oncol 2003;21:690-6.
8. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, *et al*. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859-66.
9. Clark PE. Neoadjuvant versus adjuvant chemotherapy for muscle-invasive bladder cancer. Expert Rev Anticancer Ther 2009;9:821-30.
10. Sonpavde G, Sternberg CN. Neoadjuvant systemic therapy for urological malignancies. BJU Int 2010;106:6-22.
11. Turker P, Bostrom PJ, Wroclawski ML, Rhijn BV, Kortekangas H, Kuk C, *et al*. Upstaging of urothelial cancer at the time of radical cystectomy: Factors associated with upstaging and its effect on outcome. BJU Int 2012;110:804-11.
12. Mitra AP, Skinner EC, Miranda G, Daneshmand S. A precystectomy decision model to predict pathological upstaging and oncological outcomes in clinical stage T2 bladder cancer. BJU Int 2013;111:240-8.
13. Cohen AJ, Packiam V, Nottingham C, Steinberg G, Smith ND, Patel S. Upstaging of nonurothelial histology in bladder cancer at the time of surgical treatment in the National cancer data base. Urol Oncol 2017;35:34.e1-34.e8.