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ORIGINAL ARTICLE

How to improve patient selection for neoadjuvant chemotherapy in bladder cancer patients candidate for radical cystectomy and pelvic lymph node dissection

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Abstract

Purpose To improve patient selection for neoadjuvant chemotherapy (NAC) before radical cystectomy (RC) in bladder cancer patients (BCa).

Methods Retrospective evaluation of 1057 patients with cT2–4N0M0 BCa treated with RC and pelvic lymph node dissection between 1990 and 2018 at 3 referral centers. Adverse pathologic features (APF) were defined as pT3–pT4/pN + disease at RC. A regression tree model (CART) was used to assess preoperative risk group classes. A multivariable logistic regression (MVA) was performed to identify predictors of APF at RC.

Results Median age was 70 years and most of the patients were men (83%). Of the 1057 patients included in our study, 688 (65%) had APF. CART analysis was able to stratify patients into 3 risk groups: low (cT2 and single disease, odds ratio [OR] 0.62), intermediate (cT2 and multiple disease, OR 1.08), and high (cT3–cT4, OR 1.28). On MVA APF were associated with variant histology (odds ratio [OR] 3.97, 95% confidence interval [CI] 1.46–10.83, $p = 0.007$), multifocality at TUR (OR 2.56, CI 1.27–5.17, $p = 0.09$), completeness of resection (OR 0.47, CI 0.23–0.96, $p = 0.04$) and clinical extravesical disease (OR 3.42, CI 1.63–7.14, $p = 0.001$).

Conclusion We defined three pre-operative risk classes. Our results indicate that patients with a cT3–T4 disease are those who might benefit more from NAC whereas those with T2 single disease should be those to whom NAC probably shouldn't be proposed. Given the high rate of understaging in BCa patients, NAC can be proposed in selected cases of cT2/multifocal disease.

Keywords Bladder cancer · Radical cystectomy · Neoadjuvant chemotherapy

Introduction

Bladder cancer (BCa) is the second most common genitourinary malignancy with 81,190 estimated new diagnosis in 2018 in the United States only [1]. About 25% of patients with BCa, presents at first diagnosis a muscle-invasive disease, whose gold standard treatment is radical cystectomy (RC) with bilateral pelvic lymph node dissection (PLND) [2]; however, RC alone, provides an overall 5-year survival in approximately half of the patients, probably as a result of the presence of radiologically non-detectable micrometastasis. Cisplatinum-based neoadjuvant chemotherapy (NAC) confers an overall survival benefit of 8% at 5 years [3] in patients with a cT2–T4a non-metastatic disease and its use is recommended by international guidelines [2, 4]. Unfortunately, although there is a documented benefit in survival, this treatment is underutilized worldwide with some series reporting that from 1.4 to 20.9% only of eligible patients are effectively treated with NAC [5–8]. Several reasons are probably the cause of this under-use such as

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numerous patients' comorbidities, low performance status, poor renal function [9], the concern of delay of RC [10] and of an increase in surgical morbidities, even if Grossman et al. [11] reported no difference between patients treated with RC alone and with RC preceded by NAC. For all these reasons, an accurate selection of patients who can benefit more from NAC is very important. Therefore, the aim of our study was to analyze a cohort of patients treated with RC alone, defining preoperative risk-groups to help urologists to identify best candidates for NAC.

Materials and methods

We retrospectively investigated 1057 patients who underwent RC without NAC for clinical T2–4N0 non-metastatic BCa between 1990 and 2018 at three tertiary referral centers. All data regarding demographics characteristics, last transurethral resection (TUR) before RC and RC characteristics were collected in prospectively maintained institutional databases. Patients with a suspicion of BCa were valuated with a TUR and staged preoperatively with pelvic/abdominal computerized tomography (CT), bone scan when indicated and chest X-ray or thoracic CT scan. Dedicated pathologists examined all TUR and RC specimens: tumor grade was evaluated according 1973 WHO grading system for all patients who underwent TUR or RC between 2001 and 2004 and, for patients submitted to surgery later, according grading WHO 2004 [12]. Concomitant carcinoma in situ (CIS) was defined as the presence of CIS at TUR specimens in association with another pathological stage and variant histology any presence of urothelial or nonurothelial variants at the pathological report [13]. Multifocality was visually evaluated and defined as the presence of more than one macroscopic disease; complete resection was visually evaluated and defined as the absence of macroscopic residual tumor at the end of the TUR.

Adverse pathological features (APF) were defined as the presence of a pT3–pT4 stage and/or positive pathologic node stage disease at RC which correspond to the preoperative inclusion criteria for adjuvant chemotherapy. Bladder cancer staging was assessed according to VI edition TNM classification [14]. Follow-up consisted of a visit every 3–4 months for the first year after surgery, biannual during the second year and annual successively: examinations included radiological imaging with a chest-abdominal CT scan in all patients. In addition to physical examination laboratory testing, intravenous pyelography, endoscopic view of the neobladder, urine cytology, urethral washings and bone scan were carried out if indicated.

Primary and secondary endpoint

Primary endpoint was to assess pre-operative risk classes to find which categories of patients can benefit more from NAC before RC. Secondary endpoint was to assess pre-operative predictors of APF after RC.

Statistical analyses

Descriptive statistics of categorical variables focused on frequencies and proportions. Means, medians, and interquartile ranges (IQR) were reported for continuously coded variables. The Kruskal–Wallis test and Chi square test were used to compare the statistical significance of differences in medians and proportions, respectively. Univariable and multivariable logistic regression analyses were used to assess predictors of APF. Multivariable models were adjusted for all available preoperative features: age, gender, presence of pre-operative hydronephrosis, concomitant CIS at TUR, presence of histological variants, multifocality, completeness of TUR, clinical T stage and clinical nodal stage. A regression tree model (CART) was used to assess preoperative risk group classes. Statistical significance was considered at $p < 0.05$. Statistical analyses were performed using STATA 14.0® (Stata Corp., College Station, TX, USA).

Results

We evaluated 1057 patients with clinical non-metastatic BCa treated with RC between 1990 and 2018. Baseline pre-operative characteristic are reported in Table 1. Median age was 70 (63–76) years and most of the patients were men ($n = 874$, 83%). At post-operative evaluation 688 (65%) had APF.

A decision tree generated by CART analyses was tested for its ability to stratify patients according to risk of presenting APF. This tree was able to stratify patients into 3 risk groups: low (cT2 and single disease, OR 0.62), intermediate (cT2 and multiple disease, OR 1.08), and high (cT3–cT4, OR 1.28) (Fig. 1). Univariable and multivariable logistic regression analyses predicting APF are reported in Table 2. On univariable analyses age (odds ratio [OR] 1.01, 95% confidence interval [CI] 1.00–1.02, $p = 0.02$), presence of hydronephrosis (OR 2.29, CI 1.49–3.53, $p < 0.001$), concomitant CIS at TUR (OR 0.45, CI 0.29–0.71, $p = 0.001$, multifocality at TUR (OR 1.50, CI 1.07–2.09, $p = 0.01$), completeness of resection (OR 0.62, CI 0.43–0.90, $p = 0.01$), cT3–4 vs cT = 2 (OR 1.92, CI 1.27–2.90, $p = 0.02$) were associated with an increased risk of APF at RC.

On multivariable logistic regression analyses APF were associated with variant histology at TUR (OR 3.97, CI

Table 1 Baseline pre-operative characteristic of patients treated with radical cystectomy (RC) and pelvic lymph node dissection for bladder cancer (BCa) stratified according the presence of adverse pathologic features (AFP, defined as the presence of a pT3–pT4 stage and/or positive pathologic node stage disease at RC and/or the occurrence of an early recurrence after RC)

Variables	Overall ($n=1057$, 100%)	No APF ($n=364$, 35%)	APF ($n=688$, 65%)	p value
Age, years				
Mean	69	68	69	0.01
Median (IQR)	70 (63–76)	69 (62–75)	70 (63–77)	
Gender				
Male	874 (83%)	309 (85%)	561 (82%)	0.2
Female	182 (17%)	55 (15%)	127 (18%)	
Hydronephrosis				
No	352 (74%)	186 (82%)	166 (67%)	< 0.001
Yes	124 (26%)	40 (18%)	82 (33%)	
CIS at TUR				
No	841 (91%)	272 (86%)	566 (93%)	< 0.001
Yes	88 (9.0%)	45 (14%)	43 (7.0%)	
Variant histology at TUR				
No	630 (86%)	234 (89%)	395 (84%)	0.06
Yes	103 (14%)	28 (11%)	74 (16%)	
Unifocality at TUR				
No	282 (47%)	95 (41%)	186 (51%)	0.01
Yes	314 (53%)	136 (59%)	177 (49%)	
Complete TUR				
No	304 (60%)	110 (54%)	194 (65%)	0.01
Yes	201 (40%)	95 (46%)	105 (35%)	
cT stage				
cT2	312 (64%)	125 (74%)	187 (60%)	0.002
cT3–4	173 (36%)	44 (26%)	127 (40%)	

APF adverse pathological features, *IQR* interquartile range, *CIS* carcinoma in situ, *TUR* transurethral resection of bladder

1.46–10.83, $p=0.007$), multifocality at TUR (OR 2.56, CI 1.27–5.17, $p=0.009$), completeness of resection (OR 0.47, CI 0.23–0.96, $p=0.04$) and cT3–4 vs cT = 2 (OR 3.42, CI 1.63–7.14, $p=0.001$).

Discussion

Although the administration of NAC is recommended in patients with cT2–T4 BCa, this treatment is underutilized worldwide, especially in Europe [8]. Moreover, the role of NAC in patients with T2 diseases remains controversial, since these patients have a 5-year survival of approximately 80% when treated with RC alone [15]. This consideration could lead to an "a priori" decision to exclude all patients with a clinical T2 diseases from NAC, even if it has been largely demonstrated that current techniques of staging are inaccurate for BCa-patients, with some series reporting more than 40% of understaging [16, 17]. That would then translate in the omission of NAC in patients classified as "T2", who are found to have an extravesical disease at RC specimen and consequently, would have probably benefit from NAC. The presence of APF and in particular, extravesical disease and positive nodes at RC specimens, has been reported associated with worse survival outcomes and, therefore, patients with these pathological characteristics are those who might benefit more from chemotherapy pre-surgery. Considering all these issues our main objective was to detect pre-surgical characteristics associated with APF to improve selection for NAC. To make this possible, we applied the CART regression tree analysis, which is a statistical approach able to detect interactions between variables similarly to multivariable logistic regression analysis, but additionally is able to build a decision tree.

We made several findings: first and foremost, in our study the CART method identified two pre-operative variables

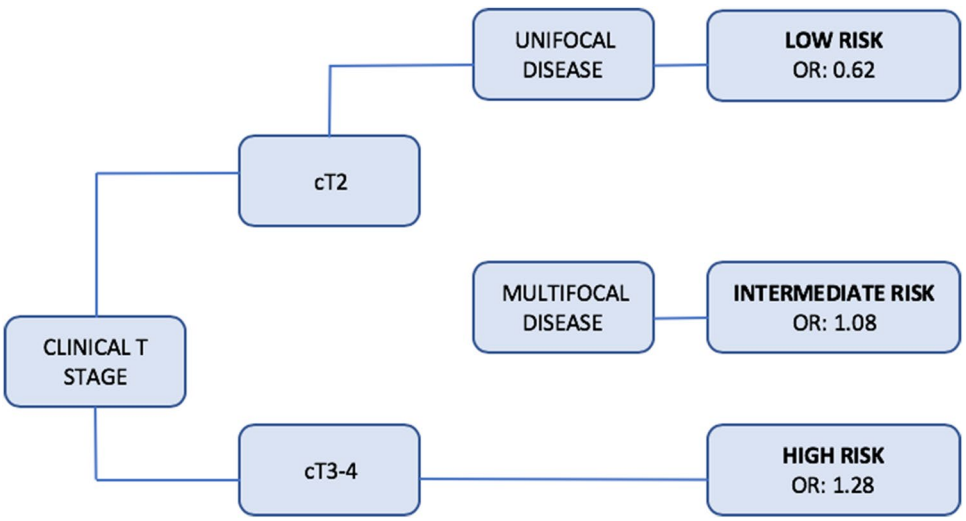

Fig. 1 Decision tree generated by CART analyses, stratifying patients with clinical non-metastatic bladder cancer (BCa) treated with radical cystectomy (RC) and pelvic lymph node dissection (PLND) according to risk of presenting APF after RC

Table 2 Univariable and multivariable logistic regression analyses predicting adverse pathological feature (APF) after radical cystectomy (RC) and pelvic lymph node dissection

Variables	Univariable analyses		Multivariable analyses	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age, years	1.01 (1.00–1.02)	0.02	1.02 (0.99–1.07)	0.1
Gender				
Male	Ref	Ref	Ref	Ref
Female	0.78 (0.55–1.11)	0.2	1.01 (0.42–2.42)	0.9
Hydronephrosis yes vs. no	2.29 (1.49–3.53)	< 0.001	1.42 (0.66–3.07)	0.4
CIS at TUR yes vs. no	0.45 (0.29–0.71)	0.001	0.51 (0.18–1.43)	0.2
Variant histology yes vs. no	1.56 (0.98–2.48)	0.06	3.97 (1.46–10.83)	0.007
Multifocality yes vs. no	1.50 (1.07–2.09)	0.01	2.56 (1.27–5.17)	0.009
Complete TUR yes vs. no	0.62 (0.43–0.90)	0.01	0.47 (0.23–0.96)	0.04
cT stage				
cT = 2	Ref	Ref	Ref	Ref
cT3–4	1.92 (1.27–2.90)	0.002	3.42 (1.63–7.14)	0.001

OR odds ratio, *CI* confidence interval, *CIS* carcinoma in situ, *TUR* transurethral resection

(clinical T stage and number of tumors) as significant predictors of APF. These two variables permitted a stratification of patients in 3 risks groups according ORs: the low-risk group includes patients with a clinical T2 unifocal disease who are probably those who don't benefit from NAC and to whom NAC shouldn't be proposed; high-risk group includes patients with clinical T3–4 stage (unifocal or multifocal) and are those who can benefit more from NAC and to whom NAC should be always proposed; lastly, the intermediate-risk group which includes patients with a clinical T2 multifocal disease who can probably benefit from NAC, but less compared to the high-risk group and to whom NAC should be proposed in selected cases. In particular, since NAC is recommended in all guidelines [2, 4] in T2–T4a non-metastatic disease, our finding can improve decision-making in patients with clinical T2 diseases which, as previously mentioned, are one of the categories in which administration of NAC remains controversial.

Clinical T staging, but not organ confined disease, was also a predictor of worse survival in Culp et al. study [18, 19]: risk groups were found according to survival analyses in patients who underwent NAC and RC and the high-risk group included patients with pre-operative hydroureteronephrosis, cT3b–T4a disease, and/or histological evidence of lymphovascular invasion, micropapillary or neuroendocrine features at transurethral resection. Even if Culp et al. study [18] reported an association between histological variants and worse survival outcomes, in our study the CART analysis didn't include it in the decision tree. Anyway, in our study variant histology at TUR was associated to APF after RC at multivariable logistic regression analyses ($p = 0.007$). Our results are in accordance with Abufaraj et al. [20], who reported a significant relationship ($p = 0.04$) between variant histology at TUR and APF (such as lymph node metastasis and advanced pathological T stage). All these findings support results reported in several previous studies, which have underlined the importance of variant histology as prognostic factor in patients affected by BCa in term of higher risk of APF, worse survival outcomes [21] and also higher risk of progression in patients with non-muscle invasive bladder disease [22] compared to patients affected by standard urothelial histology.

Our study is not without limitation. First of all, our study is limited by its retrospective design and inherent biases. While data were recorded prospectively and were adequately transferred to institutional databases, all the analyses were retrospective. Second, in the present cohort, clinical evaluation was performed by different radiologist and we did not perform a central review of all CT scans. This aspect might have impact on the results of clinical T stage. Same was for all pathological TUR and RC specimens, which have not been submitted to a central review although were all analyzed by dedicated uro-pathologists. Third, all patients included in our cohort underwent TUR and RC at high-volume referral centers, therefore our findings might not be applicable to other non-referral centers. Fourth, data regarding presence of lymphovascular, which is a well-known prognostic factors for lymph nodes invasion and upstaging, and data regarding presence of variant histology were not available in our dataset.

Conclusion

We found three pre-operative risk classes to help urologist to identify patients who can benefit more from NAC before RC. Our results suggest that patients with a clinical T3–T4 disease are those who might benefit more from NAC whereas patients with a cT2 unifocal disease might be those who don't benefit from this treatment. Moreover, given

the high rate of understaging in BCa patients and the result of our regression tree, we suggest to propose NAC also in selected cases of clinical cT2 disease with multifocal BCa (intermediate group). Nonetheless, more studies are needed to confirm our results in order to facilitate patient selection for NAC.

Author contributions SZ: manuscript writing, statistical analyses, data collection; MM: project development, data collection, drafting of the manuscript; AA: critical revision of the manuscript; CS: critical revision of the manuscript; SB: drafting of the manuscript; LC: drafting of the manuscript; FM: critical revision of the manuscript; AB: critical revision of the manuscript; AG: critical revision of the manuscript; AS: critical revision of the manuscript; LM: critical revision of the manuscript; AM: critical revision of the manuscript; PB: project development, supervision, critical revision of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All person gave their informed consent to use their data for this retrospective study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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