Can we identify those patients who will benefit from prostate-sparing surgery? Predictive factors for invasive prostatic involvement by transitional cell carcinoma

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ARCE J, GAYA JM, HUGUET J, RODRIGUEZ O, PALOU J, VILLAVICENCIO H. Can we identify those patients who will benefit from prostate-sparing surgery? Predictive factors for invasive prostatic involvement by transitional cell carcinoma. The Canadian Journal of Urology. 2011;18(1):5529-5536.

Objectives: *To determine which patients may benefit from prostate-sparing surgery and which factors are predictive of invasive prostatic involvement.*
Materials and methods: *A total of 717 men underwent radical cystoprostatectomy (RC) for bladder transitional cell carcinoma (TCC) between 1978 and 2002. Analysis of prostatic urethral involvement by transitional cell carcinoma (pTCC) and of invasive prostatic involvement by TCC was performed according to recurrence, presence of carcinoma in situ (CIS) and multifocality, previous intravesical chemotherapy, grade, stage and location of bladder tumor, presence of CIS in precystectomy transurethral resection (TUR) and indication for RC.*
Results: *pTCC was present in specimens from 140 patients (19.5%), of whom 83 (59.3%) showed invasive prostatic involvement. Tumor location at the trigone or bladder neck (p = 0.011, OR 2.29, 95% CI 1.21-4.33) and a history of CIS (p = 0.003, OR 2.03, 95% CI 1.27-3.22) were independent predictors of pTCC. Presence of a solitary T2-T3 bladder tumor was a predictive factor for invasive prostatic involvement (p = 0.001, OR 3.73, 95% CI 1.70-8.16). Neither solitary tumors nor T2-T3 bladder tumors showed significant differences in 5 year specific survival (p = 0.277 and p = 0.618 respectively) when comparing patients according to the presence of superficial or invasive prostatic involvement. Bladder tumor stage in precystectomy TUR was a predictor of disease-specific survival (p = 0.018, OR 1.62, 95% CI 1.08-2.44).*
Conclusions: *Patients with a history of CIS and bladder tumor location at the trigone or bladder neck are not candidates for prostate-sparing surgery. The only variables that can predict invasive prostatic involvement are the presence of a solitary T2-T3 bladder tumor at the trigone or bladder neck.*

Key Words: transitional cell carcinoma, prostatic urethra neoplasm, cystectomy, carcinoma in situ, recurrence, multifocality

Introduction

Prostatic urethral involvement by transitional cell carcinoma (pTCC) in patients with bladder cancer is defined as pT4a in the 2002 TNM Classification. Based on whether the mucosa, ducts or stroma is involved, pTCC may be subcategorized into superficial involvement (tumor confined to mucosa or ducts) or invasive (tumor involving prostatic stroma).[1] Prostatic stromal involvement directly impacts on prognosis, survival and treatment decisions. Thus, patients with stromal involvement have a poor prognosis despite radical treatment, their 5 year overall survival being 22%-65% as compared with 50%-100% in patients with mucosa and duct involvement.[1-7] In light of the above, it is evident that care needs to be taken to avoid progression due to undetected invasive prostatic involvement.[1,3]

While some have suggested that prostate-sparing cystectomy may be appropriate in selected men to improve postoperative sexual and urinary function,[8,9] concerns have been raised about that it may entail the risk of neglecting pTCC. Several authors have reported that high risk non-muscle-invasive bladder cancer [high-grade Ta, T1 and carcinoma in situ (CIS)]

Accepted for publication November 2010

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is associated with an increased incidence of pTCC, which rises from 10%-15% within 5 years to 20%-40% within 15 years.[1,10-12] With increasing use of intravesical therapy for high risk patients, the number of patients at risk of developing pTCC will rise. In view of these considerations, efforts have been made to determine clinical variables that could predict the best candidates for prostate-sparing surgery.[13,14]

Reported risk factors for pTCC include carcinoma in situ (CIS) of the bladder, multifocal disease, previous intravesical chemotherapy, and tumor location in the trigone or bladder neck.[1,12,15-18] Patients with any pTCC have a high risk of urethral recurrence, with invasive prostatic involvement demonstrating the highest risk.[19-22] However, no studies have evaluated which factors are predictive of invasive prostatic involvement.

The aim of the present study was to determine which bladder tumor characteristics and clinical-pathological variables are predictive of invasive pTCC involvement in radical cystoprostatectomy (RC) specimens, and thereby to determine which patients may benefit from prostate-sparing surgery.

Materials and methods

We reviewed, from our computerized cystectomy database, the records of 717 consecutive male patients who underwent RC for bladder transitional cell carcinoma (TCC) between 1978 and 2002. Median age was 63.4 years (SD 9.06). Patients had no previous history of either treatment of bladder TCC in another center or radical surgery for prostate cancer.

The following clinical and pathological variables were extracted for all patient records: age at RC, recurrent tumor (more than one relapse of bladder TCC), the presence of CIS in previous transurethral resection of bladder tumor (TURBT) or multiple random biopsy (MRB) specimens, a history of multifocality (presence of more than one bladder TCC during a TURBT), previous intravesical chemotherapy, the grade, stage and location of bladder tumor, presence of CIS in precystectomy TURBT and MRB specimens, pathology of the prostatic urethra in RC, last follow up and causes of death.

Endoscopic staging prior to cystectomy was performed by means of cystoscopy, TURBT and six cold cup biopsies of normal-looking mucosa, one of which included the prostatic urethra near the verumontanum. If there was any macroscopic tumor in the prostatic urethra, we performed TUR and a histological study was carried out separately from that of the bladder. Bladder TCC location was classified as either (1) the trigone and bladder neck or (2) the rest of the bladder.

Pathological assessment of RC specimens with special attention to the prostate was performed by two expert pathologists using routine step sectioning. Complete transverse sections of the prostatic urethra, with a thickness of 4mm-5 mm, were obtained at the bladder neck, verumontanum and apex for pathological examination. Bladder tumor stage was assessed according to the 2002 TNM classification. TIS, Ta and T1 bladder tumors were considered to be non-muscle-invasive bladder cancer (NMIBC) and ≥ T2 tumors, muscle-invasive bladder cancer (MIBC). The extent of pTCC in RC specimens was classified as superficial (papillary tumor or CIS confined to prostatic urethral mucosa or paraurethral ducts) or invasive (tumor involving prostatic stroma).

We analyzed the incidence and extent of pTCC in RC specimens by univariate and multivariate analyses according to all clinical and pathological factors. We also analyzed pTCC in relation to the indications for radical surgery. For this purpose we considered three indications for RC: (1) persistence or recurrence of NMIBC and/or CIS after TURBT and intravesical therapy, (2) progression of NMIBC to MIBC and (3) primary MIBC. In addition, the extent of pTCC was analyzed with respect to two indications for RC, namely: (1) persistence or recurrence of NMIBC and/or CIS after TURBT and intravesical therapy and (2) presence of muscle-invasive disease (progression of NMIBC and primary MIBC). Instances of missing data in some clinical records were excluded from analysis.

Patients were followed up for a median of 42.11 months (SD 48.49). Disease-specific survival was calculated from the time of RC to last follow up or death from bladder cancer. Patients who died owing to other causes or who were alive at last follow up were censored.

Mean and standard deviation were used for quantitative variables and absolute frequency and percentage for qualitative variables. The chi-square test was used to compare categorical variables. The odds ratio values with 95% confidence intervals (CI) were also obtained for these variables. The chi-square test was performed for univariate analysis in order to assess risk factors. The most significant variables in univariate analysis were incorporated into a multivariate study using a forward stepwise binary logistic regression model in order to analyze predictive factors. A p value of < 0.05 was considered statistically significant. Survival analysis was performed with the Kaplan-Meier test. The log rank test was used to compare groups of patients. The Cox regression model was performed for multivariate survival analysis with forward selection of variables. The statistical analysis was carried out with the SPSS statistical package, v. 14.0.

Results

A total of 140 patients (19.5%) had pTCC in RC specimens. Invasive prostatic involvement was present in 83 of these patients (59.3%). Table 1 shows the frequency of clinical and pathological variables extracted for all patient records.

Factors related to pTCC were CIS in precystectomy TURBT (p = 0.001, OR 2.03, 95% CI 1.35-3.07), history of multifocality (p = 0.036, OR 1.50, 95% CI 1.02-2.21), the presence of CIS in previous TURBT and MRB specimens (p < 0.001, OR 2.21, 95% CI 1.45-3.35) and tumor location at the trigone or bladder neck (p = 0.005, OR 2.24, 95% CI 1.26-3.97), Table 2. Frequency of pTCC was also higher in patients with progression of NMIBC (23.8%) but there were no significant statistical differences in pTCC between the indications for RC (p = 0.552). In multivariate analysis, tumor location at the trigone or bladder neck (p = 0.011, OR 2.29, 95% CI 1.21-4.33) and history of CIS (p = 0.003, OR 2.03, 95% CI 1.27-3.22) were independent predictors of pTCC, Table 3. The 5 year disease-specific survival rate was significantly lower in patients with bladder tumor at the trigone or bladder neck (46.2% versus 69.2%, p < 0.0001) and a history of CIS (44.2% versus 70.4%, p < 0.0001) when the prostatic urethra was involved as compared to those without such involvement, Figure 1. Neither tumor at the trigone or bladder neck nor a history of CIS showed any superiority over the other factors as a predictor of disease-specific survival (p = 0.856 and 0.441 respectively).

In our series, bladder tumor stage in precystectomy TURBT was related to the extent of pTCC, Table 2. Patients with T2-T3 bladder tumors had an increased risk of invasive

TABLE 1. **Clinical and pathological characteristics of 717 male patients undergoing radical cystectomy for bladder transitional cell carcinoma**

Characteristics	n (%)
Indications for RC	
Primary MIBC	481 (67.1)
Recurrent NMIBC	152 (21.2)
Progression of NMIBC	84 (11.7)
Prostate involvement (RC specimen)	140 (19.5)
Superficial (CIS, papillary, ducts)	57 (40.7)
Invasive (stroma)	83 (59.3)
Tumor stage (precystectomy TURBT)	
Ta, T1, Tis	166 (23.2)
T2, T3	551 (76.8)
Tumor grade	
Low/moderate	79 (11.4)
High (G3)	611 (88.6)
Number of tumors	
1	404 (62.1)
2 or more	247 (37.9)
Associated CIS	284 (44.7)
Tumor location	
Trigone and bladder neck	63 (9.8)
Rest of the bladder	582 (90.2)
History of recurrence	295 (41.1)
History of multifocality	304 (44.8)
History of CIS	346 (52.9)
Previous intravesical chemotherapy	171 (23.8)

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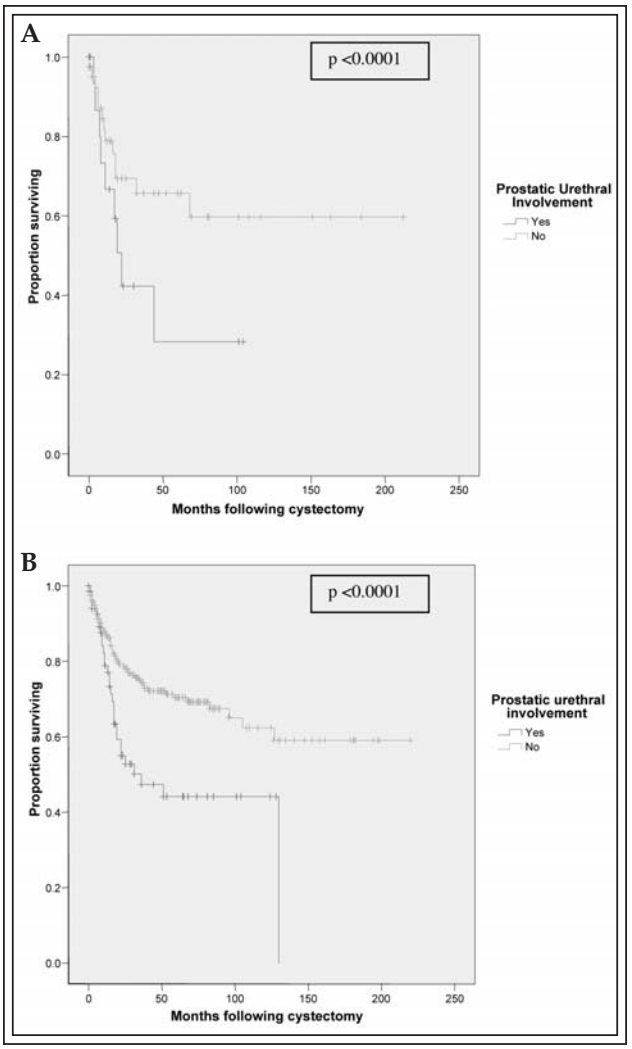

Figure 1. Disease-specific survival in patients with tumor at trigone or bladder neck (A) and history of carcinoma in situ (B) stratified by whether RC specimen had pTCC or not.

TABLE 2. **Analysis for risk factors of pTCC and invasive prostatic involvement in RC specimens**

Characteristics at precystectomy TURBT	n	pTCC n (%)	p	Superficial n (%)	Invasive n (%)	p
Tumor stage			0.896			0.008
Ta,T1,Tis	166	33 (19.9)		20 (60.6)	13 (39.4)	
T2, T3	551	107 (19.4)		37 (34.6)	70 (65.4)	
Tumor grade			0.113			0.599
Low/moderate	79	10 (12.7)		5 (50)	5 (50)	
High (G3)	611	123 (20.1)		51 (41.5)	72 (58.5)	
Number of tumors			0.152			0.002
1	404	67 (16.6)		19 (28.4)	48 (71.6)	
2 or more	247	52 (21.1)		29 (55.8)	23 (44.2)	
Associated CIS			0.001			0.314
Yes	284	68 (23.9)		31 (45.6)	37 (54.4)	
No	351	47 (13.4)		17 (36.2)	30 (63.8)	
Tumor location			0.005			0.317
Trigone or bladder neck	63	20 (31.7)		6 (30)	14 (70)	
Rest of the bladder	582	100 (17.2)		42 (42)	58 (58)	
History of recurrence			0.108			0.014
Yes	295	66 (22.4)		34 (51.5)	32 (48.5)	
No	422	74 (17.5)		23 (31.1)	51 (68.9)	
History of multifocality			0.036			0.003
Yes	304	68 (22.4)		36 (52.9)	32 (47.1)	
No	374	60 (16)		16 (26.7)	44 (73.3)	
History of CIS			< 0.001			0.645
Yes	346	84 (24.3)		36 (42.9)	48 (57.1)	
No	308	39 (12.7)		15 (38.5)	24 (61.5)	
Previous intravesical chemotherapy			0.932			0.850
Yes	171	33 (19.3)		14 (42.4)	19 (57.6)	
No	541	106 (19.6)		43 (40.6)	63 (59.4)	
Indication for RC			0.552			0.053
Primary MIBC	481	90 (18.7)		32 (35.6)	58 (64.4)	
Recurrent NMIBC	152	30 (19.7)		18 (60)	12 (40)	
Progression of NMIBC	84	20 (23.8)		7 (35)	13 (65)	

TABLE 3. **Multivariate analysis of clinical pathological factors related to pTCC and prostatic invasive involvement in RC specimens**

Prostatic urethral involvement by transitional cell carcinoma (pTCC)	**p**
CIS associated	0.491
Tumor location at bladder neck	0.011
History of multifocality	0.123
History of CIS	0.003
Prostatic invasive involvement	**p**
T2-T3 bladder tumor at precystectomy TURBT	0.048
Non-recurrent tumor	0.143
History of solitary tumor	0.965
Solitary tumor at precystectomy TURBT	0.009

prostatic involvement (p = 0.008, OR 2.91, 95% CI 1.30-6.50). Other factors related to invasive prostatic involvement were a history of non-recurrent tumors (p = 0.014, OR 2.35, 95% CI 1.18-4.69), a history of solitary tumors (p = 0.003, OR 3.02, 95% CI 1.43-6.37) and the presence of a solitary tumor at precystectomy TURBT (p = 0.002, OR 3.18, 95% CI 1.48-6.83), Table 2. Invasive prostatic involvement was also seen more often in 13 of 20 patients with progression of NIMBC (65%) and in 58 of 90 with primary MIBC (64.4%) (p = 0.053). Overall, invasive prostatic involvement was present in 71 patients (64.5%) with muscle-invasive disease (progression of NMIBC and primary MIBC). This incidence was statistically significantly higher than that observed in 12 patients (40%) with RC due to persistence or recurrence of NMIBC and/or CIS (p = 0.021, OR 2.73, 95% CI 1.19-6.25). Multivariate analysis showed that presence of a solitary bladder tumor at precystectomy TURBT (p = 0.009, OR 2.84, 95% CI 1.30-6.21) and presence of a T2-T3 bladder tumor at precystectomy TURBT (p = 0.048, OR 2.55, 95% CI 1.008-6.49) were both independent predictive factors for invasive prostatic involvement, Table 3. When these factors were combined, it was found that presence of a solitary T2-T3 bladder tumor at precystectomy TURBT was a strongly significant predictive factor for invasive prostatic involvement (p = 0.001, OR 3.73, 95% CI 1.70-8.16).

In survival analysis, patients with invasive prostatic involvement had a lower 5 year disease-specific survival rate than those with superficial prostatic involvement (29.7% versus 49% respectively). However, this difference in survival was not statistically significant

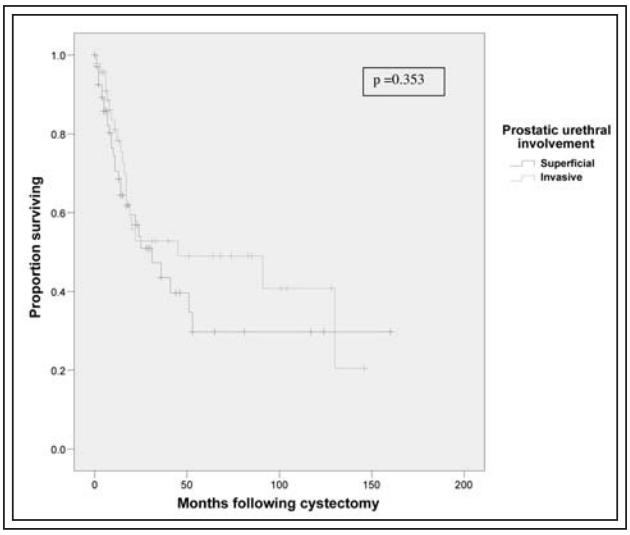

Figure 2. Kaplan-Meier curves comparing survival in patients with prostatic superficial or invasive involvement.

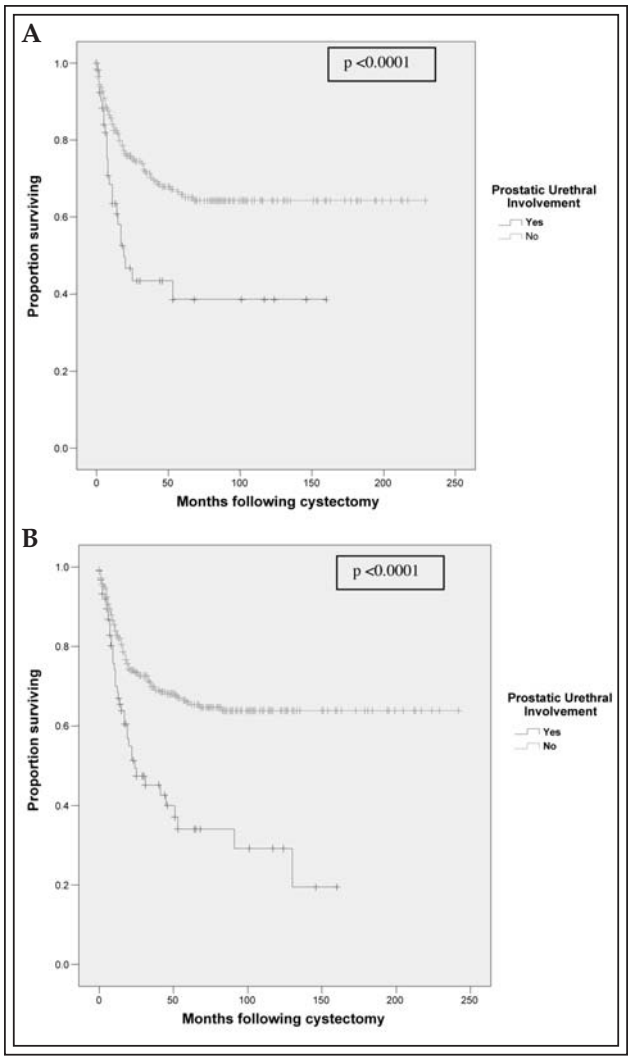

Figure 3. Kaplan-Meier curves comparing survival in patients with solitary tumors (A) and T2-T3 bladder tumors at precystectomy TURBT (B) stratified by whether RC specimen had PTCC or not.

(p = 0.353, Figure 2). Patients with solitary bladder tumors and pTCC had a lower 5 year disease-specific survival rate than those without pTCC (38.6% verus 65.8% respectively) (p < 0.0001, Figure 3). Similarly, in patients with T2-T3 bladder tumors the 5 year disease-specific survival rate was lower in those who had pTCC (34% verus 65.9% respectively) (p < 0.001, Figure 3). However, only bladder tumor stage at precystectomy TURBT was a predictor of disease-specific survival (p = 0.018, OR 1.62, 95% CI 1.08-2.44). Neither solitary tumors nor T2-T3 bladder tumors showed significant differences in 5-year specific survival (p = 0.277 and p = 0.618 respectively) when comparing patients according to the presence of superficial or invasive prostatic involvement.

Discussion

We observed a 19% incidence of pTCC, which is within the range of 13%-48% described in other series.[1,3-5,12,18,23-25] Patient selection criteria could explain the differences in incidence. For example, Herr and Donat[1] reported an incidence of 39% in patients with high risk NMIBC (72% of them with associated CIS treated with BCG). The high incidences of 43%-48% reported by Wood et al[18] and Revelo et al[25] are attributable to a detailed pathological assessment of the prostate with cross-sections of the entire prostatic urethra rather than routine selective sections of the prostate.

The 59.3% incidence of invasive prostatic involvement observed among patients with pTCC in our series is similar to the 29%-64% reported in other RC series.[2-4,6,12,13,18,23-25] Differences in the incidence of invasive prostatic involvement may be explained by differences in study design, patient population and sample size. In the series in which a larger number of specimens were reviewed, the incidence of invasive prostatic involvement was found to be much higher, with a range of 57%-64%.[5,6,15,26]

When we analyzed the precystectomy clinical and pathological factors and their relation with the incidence of pTCC, we found CIS of the bladder, a history of multifocality but not multifocality in precystectomy TURBT, and tumor location at the trigone or bladder neck to be risk factors for pTCC.[1,12,13,15-18] Further factors reported to be related to pTCC in other series (bladder tumor stage and grade, history of recurrence and previous intravesical chemotherapy treatments)[12,16,18] did not influence prostatic urethral involvement in our analysis. Pettus et al[13] have also evaluated bladder tumor stage and previous intravesical chemotherapy as factors potentially related to pTCC; however, they found only CIS of the bladder and tumor location at the trigone or bladder neck to be predictive factors. In our series, tumor location at the trigone or bladder neck and a history of CIS of the bladder were independent risk factors, but the presence of CIS in the precystectomy TURBT or MRB specimens was not.

Patients with CIS of the bladder are defined as high risk patients owing to the high risk of recurrence and progression.[26] Most patients elect to undergo intravesical therapy after detection of CIS in TUR or MRB, with few choosing to undergo early RC. An increased incidence of pTCC has been reported in the follow up of these patients.[1,10-12] As an increasing number of patients are receiving intravesical therapy, the proportion of patients at risk of pTCC will increase. In our center we perform MRB including the prostatic urethra near the verumontanum prior to TURBT to rule out pTCC or CIS and we have previously found the incidence of CIS in cases of primary NMIBC to be 19%.[26] In this study we have observed that a history of bladder CIS is better predictor of pTCC than presence of CIS in the precystectomy TURBT or MRB specimens. Most patients with diagnosis of CIS (including those with CIS in prostatic urethra) undergo intravesical BCG treatment. The fact that most patients with a history of CIS in our series have received previous intravesical BCG treatment may select those who have failed with the highest risk for pTCC, explaining the association between pTCC and History of CIS. The retrospective analysis of our data is a limitation of our study.

Tumor involvement of prostatic urethra at endoscopic staging in high risk patients who fail to respond to intravesical therapy has been associated with understaging and shorter survival.[27,28] In the current series, patients with history of CIS and pTCC also had a shorter 5 year survival, with a reduction of 26% in the 5 year disease-specific survival. Against this background, patients with a history of CIS should not be considered suitable for prostate-sparing cystectomy.

Patients with multifocal bladder tumors are included in the high risk group since multifocality has been reported to be a risk factor for recurrence and progression.[26] In our series, patients with a history of bladder tumor multifocality had a significantly higher frequency of pTCC. Several authors[12,16] have described an independent association between multifocality and pTCC. However, in our series multifocality was not significant in the presence of other predictive variables in multivariate analysis. The inclusion of bladder tumor location at the trigone or bladder neck in the analysis may explain this difference in the results. In the context of panurothelial disease, the prostatic urethra may be involved by TCC, but in patients with multifocal disease the location of the bladder tumor at the trigone or bladder neck is a better predictor of the risk of pTCC.

Most recent series[1,13,18] also identify bladder tumor location at the trigone or bladder neck as an independent risk factor for pTCC. In the present study, tumor location at the trigone or bladder neck was associated with a statistically significant 23% reduction in the 5 year disease-specific survival. Reported risk factors for urethral recurrence after RC also include tumor location at the trigone or bladder neck[29] and any prostate involvement[20-22] by TCC. Therefore, care should be taken in patients with a bladder tumor at this location owing to the high chance of pTCC in prostate-sparing cystectomy and also the risk of a positive urethral margin during RC.[30]

While other studies have focused on the development of pTCC and the identification of predictive factors for

that development, no previous articles have evaluated the risk and predictive factors for invasive prostatic involvement. In our series, patients with pTCC and without recurrent tumors, with solitary tumors and with T2-T3 bladder tumors had an increased risk of invasive prostatic involvement. However, only the presence of a solitary T2-T3 bladder tumor in a patient with pTCC in the precystectomy TURBT was a predictive factor for invasive prostatic involvement. Nixon et al[12] and Mungan et al[16] have previously reported that multifocality and CIS are related to superficial prostatic involvement by TCC, but invasive prostatic involvement was not addressed. Our results showed neither multifocality nor CIS to be related to invasive prostatic involvement. Interestingly, multifocality and Ta-T1 bladder tumors in our series were independent risk factors for superficial prostatic involvement as reported by Mungan et al.[16]

Prostatic urethral involvement by transitional cell carcinoma is a contraindication for prostate-sparing cystectomy. We have found CIS and bladder tumors at the trigone or bladder neck to be predictive factors for pTCC, while the presence of a solitary T2-T3 tumor is associated with invasive prostatic involvement. From our results, we may conclude that patients with MIBC at any location except the trigone or bladder neck are candidates for prostate-sparing surgery. Patients with invasive prostatic involvement have a poor prognosis despite radical treatment. Our 5 year survival rate was 29.7%, which is within the reported range of 22%-65%;[1-4,6,7] however, this low survival was not related to the extent of pTCC. According to some studies,[3,5,24] the stage of the primary bladder tumor affects the prognosis in patients with pTCC; in our series, patients with T2-T3 tumors and pTCC had a worse prognosis irrespective of whether they had superficial or invasive prostatic involvement.

Conclusions

Patients with a history of CIS and bladder tumor location at the trigone or bladder neck at precystectomy TURBT are not candidates for prostate-sparing surgery. The only clinical variables that can predict invasive prostatic involvement, are the presence of a solitary T2-T3 bladder tumor at trigone or bladder neck. □

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EDITORIAL COMMENT

Re: Can we identify those patients who will benefit from prostate-sparing surgery? Predictive factors for invasive prostatic involvement by transitional cell carcinoma

Radical cystectomy is currently following the path of radical prostatectomy in the sense that an increasing number of patients with bladder cancer and planned radical cystectomy are asking and even requesting nerve sparing/potency sparing options. Obviously, despite our efforts in better dissection techniques, success rates remain low and the majority still harbor erectile dysfunction. In recent years, under the guidance of the French school, prostate-sparing techniques have been introduced to achieve higher potency rates and thus increase quality of life following cystectomy. Two different approaches were presented; 1) Enucleation of the prostatic adenoma and 2) Transurethral resection of the prostatic gland (TURP) prior to radical cystectomy. This would not only offer an easier way to preserve the nerves but also facilitate the anastomosis of the neobladder to the distal urethra/prostatic fossa.

The current study crucial in the sense that it investigates the accurate patient selection for prostate-sparing radical cystectomy. The authors reported a 19% incidence of pTCC, which is within the range of 13%-48% described in the literature. Indeed, as accurately quoted by the authors, Herr and Donat reported an incidence of 39% in patients with high risk NMIBC (72% of them with associated CIS treated with BCG). More specifically, fifty-eight of 90 patients (64.4%) with primary MIBC and pTCC had invasive prostatic involvement; and also 13 of 20 patients (65%) with progression of NMIBC and pTCC.

Thus, a significant number of patients will harbor prostatic involvement and an even more significant number of these will harbor invasive prostatic involvement that was shown by the authors to have a significant worse outcome. The question whether it is wise after all to perform prostate-sparing surgery needs to be addressed. Although the authors concluded that patients with a history of CIS and bladder tumor location at the trigone or bladder neck at precystectomy TURBT were not candidates for prostate-sparing surgery, it remains questionable whether we are successful in identifying accurately the risk groups. The rate of accuracy remains the most important piece of information. Positive and negative predictive values need to be evaluated in prospective trials that still need to be performed. The only clinical variables that were predictive of invasive prostatic involvement in the current study, were the presence of a solitary T2-T3 bladder tumor at trigone or bladder neck. In conclusion, prostate involvement remains a critical issue and is not a rare finding. Prostate-sparing radical cystectomy should be offered in highly selected cases only and the patient counseled adequately. Prospective trials are urgently needed evaluating the validity of predictive factors as presented herein.

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