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UPPER URINARY TRACT TUMORS AFTER PRIMARY SUPERFICIAL BLADDER TUMORS: PROGNOSTIC FACTORS AND RISK GROUPS

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ABSTRACT

Purpose: We evaluated the prognostic factors of primary superficial bladder cancer that may predict a metachronous upper urinary tract tumor. We also determined whether the incidence of upper urinary tract disease varies according to risk group based on primary superficial bladder tumor classification.

Materials and Methods: We studied disease evolution in a cohort of 1,529 patients with a primary superficial bladder tumor. To determine the prognostic factors of upper urinary tract cancer we performed multivariate analysis using Cox regression. Independent variables were grade, T stage, multiplicity, tumor size, carcinoma in situ association, previous or synchronous upper urinary tract tumor and intravesical instillation. We also performed the chi-square test and Kaplan-Meier survival analysis to assess the variable incidence of upper urinary tract tumors according to primary superficial bladder tumor risk group classification.

Results: The incidence of upper urinary tract cancer was 2.6%. The only factor prognostic for an upper urinary tract tumor was multiplicity (relative risk 2.7, 95% confidence interval [CI] 1.06 to 6.84). All patients with an upper urinary tract tumor had a previously recurrent primary superficial bladder tumor. In the low, intermediate and high risk groups the incidence of upper urinary tract cancer was 0.6% (relative risk 1), 1.8% (relative risk 3.1, 95% CI 0.4 to 23.9) and 4.1% (relative risk 8.3, 95% CI 1.1 to 61.6), respectively (chi-square and log rank tests $p = 0.007$ and $p < 0.05$, respectively).

Conclusions: A higher risk of upper urinary tract cancer must be expected in cases of multiple primary superficial bladder tumors. This finding supports the multicentricity theory of transitional cell carcinoma. Primary superficial bladder tumor classification by risk group is also useful for predicting the various risks of metachronous upper urinary tract cancer.

KEY WORDS: bladder, bladder neoplasms, urologic neoplasms, urothelium, proportional hazards models

An important characteristic of urothelial carcinoma is its tendency toward multifocal sites. Thus, the development of upper urinary tract tumors after the initial diagnosis of superficial bladder cancer has been studied by many groups for a long time.[1–15] This incidence was 1.7% to 6% in previous studies.[1, 2, 6, 8, 9, 13–15] These series focused on the etiology of the upper urinary tract tumor, as explained by multicentricity[1, 6] or by cancer cell migration from a refluxing bladder,[12, 13] and on the necessity of routine excretory urography (IVP) for diagnosing the upper urinary tract tumor early.[3, 7, 9–11, 14]

On the other hand, these studies were performed in patients with various conditions, including primary bladder cancer only,[1, 13] any type of epithelial bladder tumor,[2, 11] superficial and invasive bladder cancer,[2, 7, 9, 11, 15] bladder cancer treated with bacillus Calmette-Guerin (BCG),[4] high risk superficial bladder cancer[5] and bladder cancer associated with carcinoma in situ.[6] In these studies 82[6] to 680[9] cases were evaluated. Although Hurle et al defined some risk groups,[8] we found no studies that assessed any factor prognostic for upper urinary tract cancer by multivariate analysis.

For these reasons we performed multivariate analysis to determine factors prognostic for primary superficial bladder tumors that may predict an upper urinary tract tumor. Also, as in the study of Hurle et al,[8] we determined whether the incidence of upper urinary tract cancer varies according to a previously established classification of bladder tumor risk groups.[16] To achieve these 2 objectives we evaluated a cohort of 1,529 patients with primary superficial bladder cancer[17] who were homogeneously treated and followed.

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MATERIALS AND METHODS

We studied 1,529 patients treated with transurethral resection and random bladder biopsy from November 1968 to December 1996 for primary superficial transitional cell carcinoma of the bladder. Patient characteristics, technique and followup have been described previously.[17] We established 3 risk groups according to progression, mortality and recurrence by combining the main prognostic factors,[16] including low risk—stage Ta grade 1 disease or a single stage T1 grade 1 tumor, intermediate risk—multiple stage T1 grade 1 or stage Ta grade 2 tumors, or a single stage T1 grade 2 tumor and high risk—multiple stage T1 grade 2, stage Ta grade 3 or stage T1 grade 3 tumors, or carcinoma in situ association. Of the 1,529 cases 35 and 21 involved a previous or synchronous upper urinary tract tumor, respectively. IVP was initially performed at the initial diagnosis of bladder cancer and every 2 years thereafter at followup.

We prepared a descriptive study of the main characteristics of upper urinary tract cancer, and compared grade and T stage of the previous primary superficial bladder tumor with those of the upper urinary tract tumor. Factors prognostic for upper urinary tract cancer were analyzed by a Cox proportional hazards model with stepwise forward selection. Independent variables were determined by the previous bladder tumor, including grade, T stage, multiplicity, size, carcinoma

in situ association, previous or synchronous upper urinary tract tumor and intravesical instillation. The dependent variable was subsequent development of an upper urinary tract tumor. The study period began at the date of initial resection and ended at the date of upper urinary tract tumor diagnosis.

In addition, we assessed the incidence of later upper urinary tract tumors according to previously defined, primary superficial bladder tumor risk groups by the chi-square test and Kaplan-Meier survival analysis. The end point was the subsequent development of an upper urinary tract tumor. Censored from analysis were patients who died, were lost to followup and did not have subsequent upper urinary tract cancer. Time was calculated from the date of initial resection to the date of the diagnosis of upper urinary tract cancer in uncensored patients and to the date of death or the last followup in those who were censored. Cumulative distribution of the upper urinary tract tumor-free interval was evaluated by group according to the previously defined bladder cancer risk groups. We also determined relative risk in each bladder risk group by Cox regression. All p values are 2-sided and relative risk is presented with the 95% confidence interval (CI).

RESULTS

After primary superficial bladder cancer was diagnosed an upper urinary tract tumor developed in 40 of the 1,529 cases (2.6%) (table 1). The incidence increased according to previously established bladder cancer risk groups, including 1 case (0.6%) in the low, 12 (1.8%) in the intermediate and 27 (4.1%) in the high risk group. Table 1 lists the main descriptive characteristics of the upper urinary tract tumors. These lesions were slightly more common on the right than on the left side (56.1% versus 41.5%) and nearly 18% were multiple. There was the same incidence of pyelocaliceal and ureteral tumors (41%). On the other hand, the rate associated with less invasive surgery was similar to that of the open approach (37.8% and 43.2%, respectively). A combined approach was used in nearly 20% of patients. The most common treatments were nephroureterectomy in 57.6% of cases and ureterectomy with ureteral reimplantation in 6.1%. Endoscopic resection was done in 21.2% of the patients with upper urinary tract cancer and only 15.2% were treated with biopsy and coagulation.

Disease grade and T stage were not available in 2.6% and 19.4% of cases, respectively (table 2). Grades 2 and 3 upper urinary tract cancer were present in 60.5% and 28.9% of cases, while disease was superficial and invasive in almost 50% and 33.4%, respectively (table 2). Tables 3 and 4 show the correlation of previous primary superficial bladder and subsequent upper urinary tract cancer by grade and T stage. Except for grade 1 disease the correlation was higher for grade than for T stage, including 76%, 54.5%, 18.2% and 20% for grades 2 and 3, and stages Ta and T1, respectively. On the other hand, all patients had bladder tumor recurrence more than once before upper urinary tract cancer developed (table 5).

The only prognostic factor of primary superficial bladder cancer that predicted subsequent upper urinary tract tumor development was multiplicity (relative risk 2.7, 95% CI 1.06 to 6.84). Cox regression multivariate analysis revealed that neither grade, T stage, tumor size, carcinoma in situ association, a previous or synchronous upper urinary tract tumor nor intravesical instillation was significant (table 6). In addition, Kaplan-Meier analysis showed that the risk of a subsequent upper urinary tract tumor varied in the 3 bladder tumor risk groups (log rank $p < 0.05$, see figure). This finding agreed with that of the chi-square test (table 7).

Table 7 shows the median time from bladder tumor resection to the development of an upper urinary tract tumor in the 3 risk groups. In the low risk group only 1 upper urinary tract tumor developed at year 10 of followup, while half of all upper urinary tract cancer was evident at years 4 and 3 in the intermediate and high risk groups, respectively. Also, 25% of upper urinary tract disease in the high risk group appeared in the initial 10 months. Table 7 also shows the relative risk and 95% CI of upper urinary tract cancer in the 3 risk groups. An intermediate risk bladder tumor was associated with a risk of subsequent upper urinary tract disease 3-fold that of a low risk bladder tumor, and the risk associated with a high risk bladder tumor was 8-fold greater. Nevertheless, risk was only statistically significant in the high risk group.

TABLE 1. *Upper urinary tract tumor characteristics*

Characteristic	%
Overall incidence	2.6
Side:	
Rt.	56.1
Lt.	41.5
Bilat.	2.4
Location:	
Calix	5.1
Renal pelvis	35.9
Lumbar ureter	5.1
Pelvic ureter	10.3
Intramural ureter	25.6
Multiple	17.9
Surgical approach:	
Ureteroscopy	29.7
Percutaneous	8.1
Open surgery	43.2
Combined	18.9
Treatment:	
Endoscopic resection	21.2
Ureterectomy + reimplantation	6.1
Biopsy + coagulation	15.2
Nephroureterectomy	57.6

TABLE 2. *Pathological findings*

	%
Grade:	
1	2.6
2	60.5
3	28.9
Nondifferentiated	5.3
X	2.6
T stage:	
Ta	22.2
T1	22.2
Ca in situ	2.8
T2	11.1
T3	16.7
T4	5.6
Tx	19.4

TABLE 3. *Concordance of previous bladder tumor with upper urinary tract tumor grade*

Bladder Tumor Grade	% Upper Urinary Tract Tumor Grade				
	1	2	3	Undifferentiated	X
1	0	50	50	0	0
2	4	76	16	0	4
3	0	27.3	54.5	18.2	0

TABLE 4. *Concordance of previous bladder tumor with upper urinary tract tumor stage*

Bladder Tumor Stage	% Upper Urinary Tract Tumor Stage						
	Ta	T1	Ca in Situ	T2	T3	T4	Tx
Ta	18.2	27.3	0	18.2	18.2	9.1	9.1
T1	24	20	4	8	16	4	24

DISCUSSION

In our series the incidence of upper urinary tract cancer after a primary superficial bladder tumor was 2.6%, similar to that in

TABLE 5. *Bladder cancer recurrence before development of upper urinary tract tumor according to bladder cancer risk group*

Risk Group	No. Recurrences (%)					Total No.
	1	2	3	4	5	
Low	0	1 (100)	0	0	0	1
Intermediate	5 (41.7)	1 (8.3)	1 (8.3)	2 (16.7)	3 (25)	12
High	10 (37)	5 (18.5)	3 (11.1)	3 (11.1)	6 (22.2)	27
Totals	15 (36.6)	7 (17)	4 (9.75)	5 (12.2)	9 (24.4)	40

TABLE 6. *Cox regression multivariate analysis of prognostic factors*

Prognostic Factor	p Value	Relative Risk (95% CI)
Multiplicity	0.0365	2.7 (1.06–6.84)
Ca in situ	0.1595	Not significant
Grade	0.2799	Not significant
Previous or synchronous upper urinary tract tumor	0.4977	Not significant
Tumor size	0.5423	Not significant
T stage	0.7334	Not significant
Intravesical instillation	0.94	Not significant

previous studies (1.7% to 6%).[1,2,6,8,9,13–15] However, others noted a higher incidence (table 8).[1,2,4–6,8,10,12,13] The explanation for this discrepancy may be the various characteristics of the patients studied. In the series of Miller[4] and Herr[5,10] et al high risk patients were treated with several BCG cycles. Consequently more aggressive evolution with a higher incidence of multifocal disease would be expected. This hypothesis was confirmed by our results and those of Hurle et al,[8] in which there was a greater risk of upper urinary tract cancer in the high risk bladder tumor group (9.8% and 4.1%, respectively).

The characteristics of the 40 patients with upper urinary tract cancer in our study indicate that there is no preferred site because there were multiple tumors in almost 18% and distribution was the same for pyelocaliceal and ureteral disease (41%) (tables 1 and 8). Others also noted a similar distribution[5,9] but in some series it was different (table 8).[1,2,8] Of the cases 36.4% were managed by less invasive techniques, such as endoscopic resection or biopsy with coagulation (table 1). In previous studies the application of less invasive techniques was not homogeneous because some patients only underwent open surgery,[1,8] while less invasive techniques were used in 25%[6,9] and 39%.[5] Although conservative management was more comfortable for patients, the disadvantage is that data on grade and T stage were not available in 2.6% and 19.4%, respectively (table 2).

Furthermore, although previous bladder tumors were superficial, at least 33.4% of upper urinary tract lesions were not superficial. Table 3 shows that upper urinary tract tumor grade was the same or higher than that of the previous primary superficial bladder tumor. Table 4 shows the same trend toward an increase in the previous bladder T stage. Some groups reported increased grade as well as increased T stage,[1,4,8] while others observed that grade and T stage were similar for previous bladder and subsequent upper urinary tract cancer.[2,9,13] In addition, another interesting finding is that all patients had recurrent bladder neoplasms once (36.6%) or more than once (63.4%) before the upper urinary tract tumor developed (table 5). Shinka et al noted this result in 83.3% of patients.[1] Furthermore, Hurle et al observed a higher incidence of upper urinary tract disease in cases of recurrent than primary bladder lesions.[8] These findings imply that there is a greater probability of an upper urinary tract tumor developing after bladder cancer recurrence than after no recurrence.

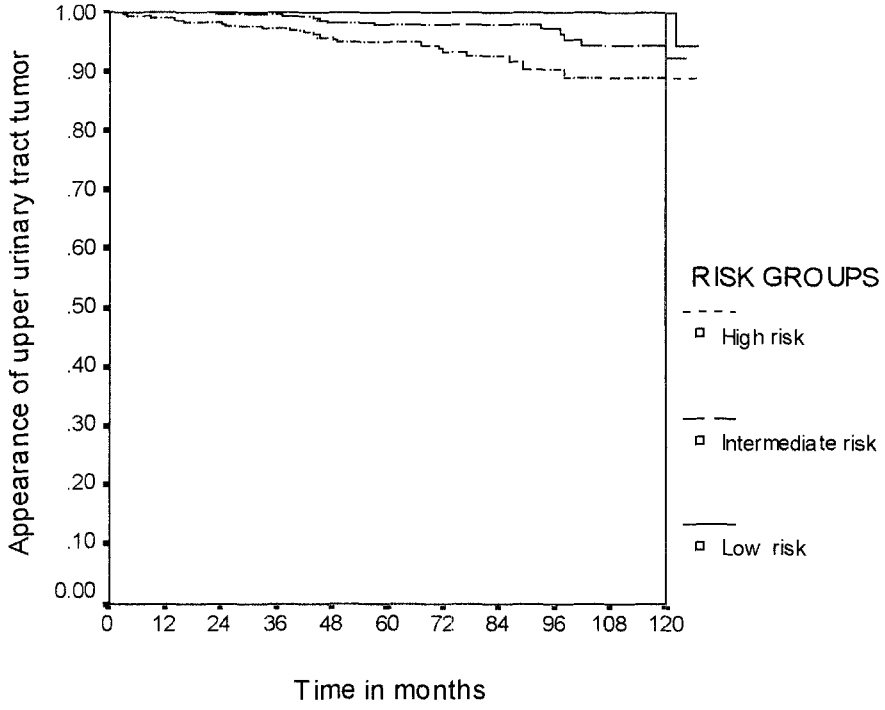
Previous bladder tumor characteristics were analyzed by multivariate analysis, including grade, T stage, multiplicity, size, carcinoma in situ association, previous or synchronous upper urinary tract cancer and treatment with intravesical instillation. Multiplicity was the only prognostic factor (relative risk 2.7, 95% CI 1.06 to 6.84, table 6). Thus, the risk of future upper urinary tract cancer is 3-fold higher for a multiple than for a single bladder tumor. This fact and the finding that all upper urinary tract lesions were associated with previous bladder tumor recurrence strongly support the theory of multicentricity of transitional cell cancer of the urinary tract, which concurs with the opinions of Herr[5] and Solsona[6] et al (table 8). They also noted a significant difference in the risk of upper urinary tract cancer in patients with and without associated bladder carcinoma in situ (21.2% versus 2.3%).[6] This finding disagrees with ours that carcinoma in situ association is not a factor prognostic for an upper urinary tract tumor (table 6).

On the other hand, previous intravesical instillation did not influence upper urinary tract tumor development. However, Miller et al concluded that patients treated with BCG instillation were at higher risk (13.4%) for a metachronous upper urinary tract tumor.[4] In our opinion this conclusion may be accepted tentatively. BCG is always given to high risk patients, and so there may have been a selection bias.

Moreover, others insist that the main factor in the development of a metachronous upper urinary tract tumor is vesicoureteral reflux (table 8).[12,13] We have no opinion on the role of vesicoureteral reflux because it was not the objective of the study. To assess the veracity of this theory systematic voiding cystourethrography must be performed in each patient. This information was not available, and so we did not include this variable in our multivariate analysis. An interesting study of the etiology of upper urinary tract cancer is that of Shinka et al, who observed a higher incidence of upper urinary tract disease in patients with previous occupational bladder cancer.[1] These results support the hypothesis that biological carcinogenesis is the main factor in upper urinary tract tumor development after bladder cancer.

We also determined whether the incidence of upper urinary tract cancer varied by bladder tumor risk group classification. Our study shows that a higher bladder risk group was associated with a higher risk of a future upper urinary tract tumor (see figure and table 7). Hurle et al observed the same trend in a similar study that compared risk groups by the chi-square test but not by survival analysis.[8] The slightly higher incidence may be due to the fact that they also included recurrent bladder neoplasms and those in which intravesical chemotherapy failed (table 8). However, each series supports the idea that the risk of upper urinary tract cancer is higher in patients with previous high risk bladder cancer.

Another interesting point is the long interval from bladder cancer to the development of a secondary upper urinary tract tumor. The median interval in the low, intermediate and high bladder risk groups was 10, 4 and 3 years, respectively (table 7). This finding was also noted by others (median 2.5 to 7.3 years).[2,4,5,8–10] Thus, we may assume that the development of upper urinary tract cancer may correlate with the time factor and if followup with routine IVP is planned to diagnose an upper urinary tract tumor, it must be performed in the long term. However, some groups question the usefulness of routine followup IVP.[7,9,11,14] They argue that the incidence of secondary upper urinary tract cancer is low and early diagnosis by IVP does not improve the prognosis. It is difficult to prove this conclusion. In contrast, others recommend routine IVP even yearly, mainly for cases of high risk bladder cancer.[3–5,8,10] In our patients IVP was performed



Kaplan-Meier plot of upper urinary tract tumor appearance comparing low, intermediate and high risk bladder tumor groups (log rank test $p < 0.05$).

TABLE 7. *Upper urinary tract tumor risk according to superficial primary bladder cancer risk group*

Risk Group	% Frequency	Cox Regression Relative Risk (95% CI)	Median Mos. (95% CI)
Low	0.6	1	122
Intermediate	1.8	3.1 (0.4–23.9)	47 (27–67)
High	4.1	8.3 (1.1–61.6)	39 (10–68)
p Value	0.007	0.001	

TABLE 8. *Characteristics of published studies*

References	No. Pts.	Risk Factor	% Upper Urinary Tract Tumors	Location
Amar and Das[12]	629	Vesicoureteral reflux	0.44–6.4	—
De Torres Mateos et al[13]	288	Vesicoureteral reflux	6–26	—
Shinka et al[1]	519	Occupational bladder Ca	2.3	8 Ureteral, 2 renal pelvic + 2 multiple
Oldbring et al[2]	463	—	1.7	5 Ureteral, 3 renal pelvic + 3 multiple
Miller et al[4]	82	BCG	13.4	—
Herr et al[5]	86	Intact bladder, multifocality + recurrent tumors	21	9 Ureteral + 9 renal pelvic
Solsona et al[6]	138	Prostate + panurothelial involvement	24.6	—
Hurle et al[8]	591	High risk group, Ca in situ, grade 3 + intravesical chemotherapy failure	4	9 Ureteral, 12 renal pelvic + 4 multiple
Herr[10]	307	High risk group	25	—
Present study	1,529	Multiplicity + high risk group	2.6	16 Ureteral, 16 renal pelvic + 8 multiple

routinely every 2 years.[3, 17] According to our current results it appears reasonable not to perform IVP in the low risk bladder tumor group and to perform it before 2 years in the high risk bladder tumor group when tumors are multiple and recurrent.

CONCLUSIONS

Although there is a low incidence of secondary upper urinary tract cancer developing after the diagnosis of a primary superficial bladder tumor, such lesions may appear late. Thus, it is reasonable to consider this possibility when following bladder cancer. The main characteristic of bladder tumors that may predict a higher risk of upper urinary tract cancer is multiplicity. This finding and the fact that all patients had recurrent bladder tumors before the upper urinary tract tumor developed support the theory of multicentricity of transitional cell carcinoma of the urinary tract. Furthermore, we noted that the risk of upper urinary tract cancer varies by bladder tumor risk group, which may be useful for designing strategies to follow these cases.

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EDITORIAL COMMENT

The authors present a large series of patients with nonmuscle invasive urothelial carcinoma treated with transurethral resection and then followed for an upper urinary tract tumor. Upper tract imaging consisted of IVP at the initial diagnosis and every 2 years thereafter. The overall incidence of an upper tract tumor was 2.6%. The risk of an upper tract tumor increased with increasing aggressiveness of the primary bladder tumor. Of the traditional risk factors assessed in patients with nonmuscle invasive urothelial carcinoma tumor multiplicity increased the risk nearly 3-fold and was the only factor predictive of an upper urinary tract tumor on multivariate analysis.

These data are important. They add additional support to the theory of multicentricity in urothelial carcinoma. More importantly, the data imply that routine followup imaging strategies may be tailored based on primary bladder tumor characteristics. In low risk patients imaging the upper urinary tract may be done at the initial diagnosis and subsequently based on clinical suspicion rather than routine imaging. On the other hand, patients with multiple, recurrent or intermediate risk tumors may undergo imaging every 2 years. Also, patients with high risk factors (grade 3, stage T1 or carcinoma in situ) should likely undergo upper tract imaging annually for the first 5 years and then every other year. I agree with the authors that while it is difficult to prove that routine upper tract imaging results in improved prognosis, a tailored strategy based on risk assessment likely balances the forces of good clinical practice and cost containment.

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