Medicine

NON-MUSCLE INVASIVE BLADDER CANCER RECURRENCE RISK FACTORS

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ABSTRACT:
TO ESTABLISH THE RISK OF TUMORAL RECURRENCE FOR NON-MUSCLE INVASIVE BLADDER CANCER (NMIBC) DEPENDING ON HISTOLOGICAL OR ENVIRONMENTAL FACTORS. THE AIM OF THIS PAPER IS TO IMPROVE THE STANDARD CLINICAL CARE IN NMIBC PATIENTS FOLLOW-UP.WE INITIALLY EVALUATED 987 PATIENTS DIAGNOSED WITH BLADDER CANCER BETWEEN JANUARY 2005 AND DECEMBER 2014. MUSCLE-INVASIVE BLADDER CANCER (MIBC) WAS DIAGNOSED FOR 309 PATIENTS (31.3%) WHILE 678 (68.7%) HAD NMBIC. A TOTAL OF 540 PATIENTS WITH NMIBC WERE ANALYZED IN THE STUDY, WHILE THE OTHER 138 (20.4%) WERE EXCLUDED DUE TO INCOMPLETE CLINICAL DATA OR FOLLOW-UP. THE RETROSPECTIVE STUDY ANALYZED PATIENTS' CHARTS, DISCHARGE NOTES, ONCOLOGY REPORTS. PATIENTS WITH AT LEAST 3 YEARS COMPLETE FOLLOW-UP DATA WERE ENROLLED.THE AVERAGE AGE OF DIAGNOSED PATIENTS WITH NMIBC WAS 65.3 YEARS. THE MAJORITY OF PATIENTS WERE DIAGNOSED WITH SINGLE TUMORS (68.5%). NMIBC WAS PREDOMINANT IN MALES, WITH A SEX RATIO 3.25:1 FOR MALES. BLADDER TRIGON IS THE MAIN LOCATION FOR BLADDER TUMORS. SMOKING WAS THE MAIN RISK FACTOR ACCORDING TO OUR RESULTS. SMOKERS HAD A 4 TIMES HIGHER RISK FOR NMIBC DEVELOPMENT. PATIENTS WITH MULTIPLE BLADDER TUMORS HAD 2.28 HIGHER RISK OF RECURRENCE. OVERALL RECURRENCE FOR NMIBC WAS 49.1%.SMOKING IS THE MOST IMPORTANT RISK FACTOR AND THE RECURRENCE RATE IS HIGHER IN SMOKING-PATIENTS.ALSO, PATIENTS WITH MULTIPLE TUMOURS HAVE BEEN DIAGNOSED WITH HIGHER RISK FOR TUMOR RECURRENCE ($P<0.05$). LARGE TUMORS AND PATIENTS WITH ASSOCIATED UROLOGICAL CONDITIONS HAVE HIGHER RISK OF TUMORAL RECURRENCE (OR =2.2).

KEY WORDS: RECURRENCE, BLADDER CANCER, PROGRESSION, RISK FACTORS

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INTRODUCTION

Bladder cancer is the most frequent tumor of the urinary tract and second among urogenital tract tumors. This high frequency and the relapsing nature of bladder cancer, means that this poses an enormous burden on health care systems. Approximately 75% of newly diagnosed bladder cancers are non-invasive and have a high rate of recurrence and progression, despite adequate therapy. The remaining 25% of bladder cancer diagnosed with muscle-invasion require either radical surgery or radiotherapy. Often this therapy has poor outcome, despite association with systemic adjuvant therapy[8].

Gender differences exist in the timeliness and completeness of hematuria evaluation, women experiencing a significantly greater delay in urologic referral and undergoing guideline-concordant imaging less frequently. Correspondingly, women have more advanced tumors at the time of bladder cancer diagnosis[9].

The incidence of bladder cancer has decreased in some reports possibly reflecting the decreased impact of causative agents, mainly smoking and occupational exposures [2]. Tobacco smoking is the most important risk factor for bladder cancer, accounting for approximately 50% of cases[10].

Smoking is associated with an advanced histological grade and with higher T grade, suggesting that smoking favors tumor progression[11].

The most important environmental risk factor for development of bladder cancer is occupational exposure to aromatic amines which can be found in chemical products, dyes and rubber industries as well in hair dyes, paints, fungicides, cigarette smoke, plastics, metals and motor vehicle exhaust gases[12].

According to the TNM classification system, tumors confined to the mucosa are classified as Ta while those confined to the mucosa with flat appearance are classified as CIS. Tumors that have invaded the lamina propria are classified as T1. They are all grouped within the NMIBC group[13].

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NMIBC evolution is marked by tumor progression and tumor recurrence. These are the most debated aspects to establish standard clinical care.

MAIN TEXT

OBJECTIVE

Although primary bladder cancer risk factors are well known, there is little evidence regarding tumor recurrence risk factors. This study aims at establishing the incidence of tumoral recurrence depending on each histological or environmental studied factors and to increase the standard clinical care of surveillance for NMIBC.

PATIENTS AND METHODS

We analyzed 987 patients diagnosed with bladder cancer between January 2002 and December 2011.

We found in the database 309 (31.3%) patients diagnosed with MIBC and 678 (68.7%) diagnosed with NMBIC and 540 (79.6%) patients with primary NMIBC, diagnosed between January 2005 and December 2014, at the Craiova Urology Department and with at least 3 years of documented follow-up were included in the study while 138 patients (20.4%) with poor clinical and paraclinical data, tumoral progression, non-oncological deaths or incomplete follow-up have been excluded.

For all patients we used the same diagnostic protocol, surgical treatment (TUR-V) and oncological treatment. The cystoscopic evaluation was performed according to EAU Guidelines depending on risk group stratification every: 3 months in the first 2 years, every 6 months until 5 years and then yearly for high-grade risk tumors. Mean postoperatory follow-up was 47.1±12.3 months (range 36-72 months).

Evaluated bladder cancer recurrence risk factors were: age, sex, smoking habit, toxic environment, significant urological history (with significant post-voiding residual urine volume) as well as tumor factors (number, size, location, depth of invasion - T and differentiation – G). The analysis endpoint was the presence of tumor recurrence after 3 years of cystoscopic follow-up.

Statistical data analysis was performed using the MS Excel and MedCalc 10.2 software.

RESULTS

Mean patients age was 65.3±10.1 years, with a sex ratio 3.25:1 for males.We also have found that in the 8 th decade the sex ratio is 1.7:1 for males, probably because life expectancy is higher for females.

Only 142 (26%) patients were non-smokers while 398 (74%) were active smokers. Risk factors such as petroleum products or painting workers were found for 30 patients only (5%).

Most of the patients were diagnosed with single tumors (68.5%) and only 31.5% had more than 2 tumors at the time of initial diagnosis. One patient was diagnosed with 22 tumors.

Mean tumor size was 21.3±13.6 mm, with limits between 3 – 60 mm. The majority of patients were diagnosed with small tumors, <3 cm (77.2%). According to European Guidelines we stratified bladder tumors in two categories depending on the tumor size: <3cm and >3cm. We found that the majority of patients was diagnosed with tumor size <3cm (77.2%).

Predominant location of bladder tumors was at the level of bladder trigone (167 cases - 30.9%), right lateral wall (21.5%) and left lateral wall (19.4%). For multiple tumors, the location of the largest tumors was recorded.

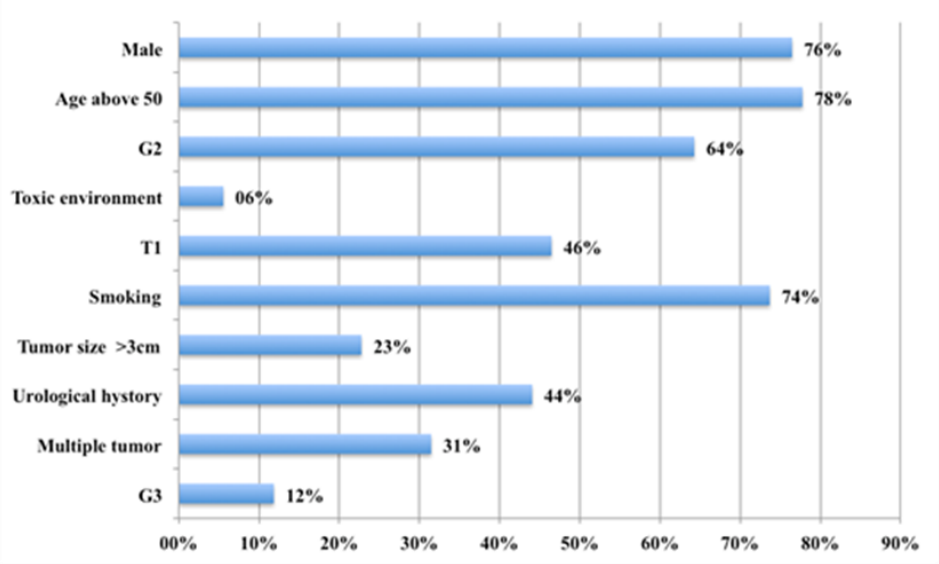

Fig. 1. NMIBC recurrence risk factors incidence

Analizing the pathological reports, we found that 528 (97.8%) were diagnosed with urothelial carcinoma and 12 (2.2%) were diagnosed with other rare forms of bladder carcinoma. According to TNM classification, Ta was the most frequent stage (53.5%), followed by T1.We could not appreciate the incidence of CIS frequency because of incomplete data. Moderate differentiated form (G2) was the most frequent form (56.9%), followed by G1 (35.2%) and G3 (12.2%).

At recurrence analysis we identified 265 patients with at least one tumour recurrence during the first 3 years of follow-up. Overall recurrence rate was 49.1%. Males, older patients, smokers and those with urological history have a higher recurrence rate. Regarding tumor characteristics, patients with large, multiple tumors, T1, G2, G3 have also a higher recurrence rate. Highest recurrence rate (63-64%) was found for patients with multiple or poorly differentiated tumors (G3).

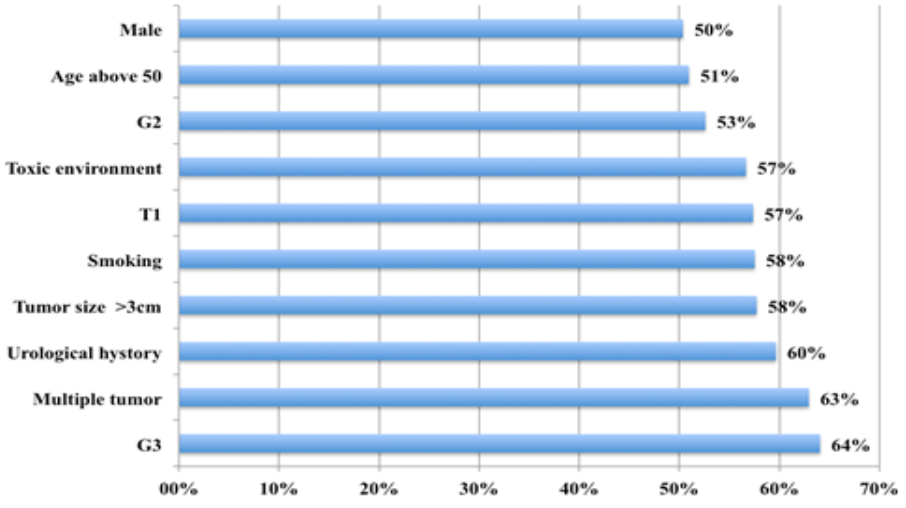

Fig. 2. NMIBC recurrence rate depending on the risk factors

Smoking was identified as the main risk factor. It was found in 398 (73.7%) patients. From all smoking patients, 229 were diagnosed with recurrence (58%) while only 36 non-smoking patients had recurrence (25%).

Recurrence risk analysis was performed by calculating the odds ratio (OR) for tumor recurrence for each of the risk factors. As expected, highly significant tumor recurrence risk ($p < 0.0001$) was identified for smokers with a 4 fold higher probability of developing recurrences than non-smokers (OR=3.99, 95%CI=2.60-6.12) followed by patients with multiple tumors (OR=2.28, 95%CI=1.57-3.31) and those with significant urological history (OR=2.15, 95%CI=1.32-3.04). Significant risk ($p < 0.05$) was also found for patients with G3 poorly differentiated carcinomas (OR=2.10, 95%CI=1.86-3.23), T1 invasive tumors (OR= 1.87, 95%CI=1.33-2.63) and tumors larger than 3 cm (OR= 1.57, 95%CI=1.05-2.37), while non-significant risk was shown for the other evaluated factors (age, sex, environmental factors). Due to the many possible tumor locations and the existence of multiple tumors the risk analysis for tumor location was not possible. Noticeably the highest recurrence rate was found for tumors located at the bladder trigone (58.1%).

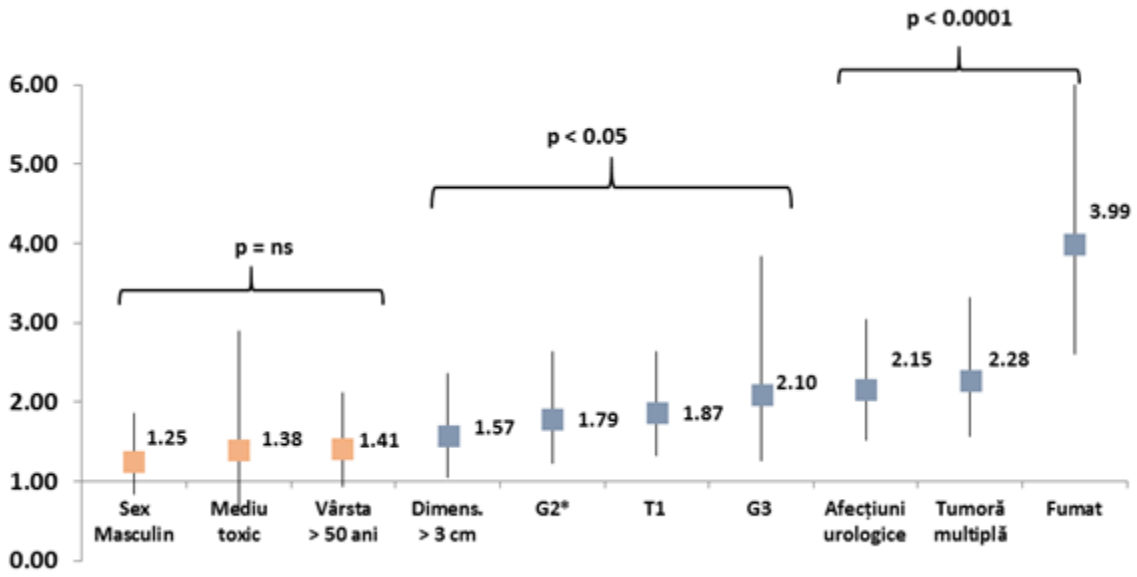

Fig. 3. Odds Ratio for tumor recurrence (OR ±95%CI.; red - insignificant risk, blue significant risk – p<0.05).

DISCUSIONS

The mean age of patients with NMIBC was 65.3 years. Most patients had single tumors mainly located at the bladder trigone. Overall recurrence rate after 3 years of follow-up is around 50%. Smoking was proven to be the most important recurrence risk factor. Also, patients with large, multiple or undifferentiated tumours have a higher risk for tumor recurrence as well as those with associated urological conditions. No significant recurrence risk was identified for patients exposed to toxic environment.

Smoking remains the main risk factor for recurrence (4X risk increase) while histological factors such as number of tumors and histological differentiation have a lower impact for bladder cancer recurrence..

Smokers have a higher rate of progression. Patients exposed to toxic environment have a high rate of recurrence. Considering our data, patients with T1, G3 tumors have highest rate of recurrence.

The most debated aspect considering bladder cancer is tumor recurrence, that was identified for a long time, but with all efforts that include adjuvant treatment, periodic endoscopic follow up, stil remains a pathology that is affecting healthcare system and patients quality of life.

Patient category	n =	(%)	Recidive	%	OR±95%CI	p =
Patients no.	540	100%	265	49.1%	-	-
> 50 years	420	77.8%	214	51.0%	1.41 (0.93-2.12)	0.103
< 50 years	120	22.2%	51	42.5%		
Males	413	76.5%	208	50.4%	1.25 (0.84-1.86)	0.2803
Females	127	23.5%	57	44.9%		
Smokers	398	73.7%	229	57.5%	3.99 (2.60-6.12)	<0.0001
Non-smokers	142	26.3%	36	25.4%		
Toxic environment	30	5.6%	17	56.7%	1.38 (0.66-2.90)	0.3937
No toxic environment	510	94.4%	248	48.6%		
Urological conditions	238	44.1%	142	59.7%	2.15(1.32-3.04)	<0.0001
No patological conditions	302	55.9%	123	40.7%		
Tumor						
Single tumor	370	68.5%	158	62.9%	2.28 (1.57-3.31)	<0.0001
Multiple tumors	170	31.5%	107	42.7%		
> 3 cm	123	22.8%	71	57.7%	1.57 (1.05-2.37)	0.02960
< 3 cm	417	77.2%	194	46.5%		
Trigon	167	30.9%	97	58.1%	-	-
Posterior wall	88	16.3%	47	53.4%		
Anterior wall	64	11.9%	31	48.4%		
Right lateral wall	113	20.9%	51	44.0%		
Left lateral wall	108	20.0%	39	37.1%		
Ta	289	53.5%	121	41.9%	1.87 (1.33-2.63)	0.0003
T1	251	46.5%	144	57.4%		
G1	167	35.2%	63	37.7%	1.79 (1.22-2.63)	0.0030
G2	307	56.9%	161	52.4%		
G3	66	12.2%	41	62.1%	2.10 (1.86-3.23)	0.0055
G1,G2						

Table 1. Risk factors incidence, specific recurrence rates, and OR (significant risk if p <0.05)

CONCLUSIONS

Despite standardized treatment and follow-up protocols, NMIBC still has a high recurrence rate as proven by our study. Highest risk is for smokers, multiple and G3 tumors, while lowest risk is for non-smokers, Ta, G1tumors.

A better follow-up for associated urological conditions and quitting smoking could improve the risk of recurrence for patients diagnosed with bladder cancer. An improved adjuvant treatment and follow-up schedule according to tumoral risk grade will be necessary to further reduce the recurrence risk and facilitate timely diagnosis

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