Bladder cancer in patients under 40 years. A French experience and a review of the recent literature.

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Abstract

Introduction

Bladder cancer is a disease of people around the 60ies. Here we describe a large series of bladder cancers in patients under 40 years. Only patients treated in France were taken into consideration

Materials and Methods

This retrospective study includes 156 patients treated between 1992 and 2013 with less than 40 years at the time of diagnosis. Tumours were classified according to the 8th TNM edition and WHO 2016 edition.

Results

156 patients were included. Hundred fourty-four were urothelial carcinomas, 12 had other patterns. PUNLMP was a frequent finding (28%), 128 had non muscle invasive tumours. Fourteen patients displayed lymphnode metastasis, 10 had distant metastasis. Thirty seven patients displayed recurrence and 12 patients died of disease.

Conclusion

PUNLMP is a frequent finding in young patients under 40 with bladder cancer. Nevertheless muscle invasive bladder cancer is also present and often a very aggressive disease. Patients should be treated according to the guidelines.

Key words: Bladder cancer, urothelium, papillary urothelial neoplasm of low malignant potential, young patients, urothelial carcinoma, low grade
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Introduction

Urothelial bladder cancer (UBC) is the 5th most common malignancy with a peak of incidence during the 6th decade of life. There is a debate in the literature regarding the specific clinical behavior and histological lesions of UBC in young patients. In this population, frequency of UBC is low, as bladder cancer depends mostly on expositions, such as smoking or professional exposure. Therefore bladder cancer in young patients remains an exception. Furthermore only very few cases of inheritance have been described, which is another reason, why we encounter only few cases in young patients (1).

When regarding the frequency of these tumours, an incidence of 1.35 to 1.6% has been reported in patients < 40, whereas in patients less than 20 years the frequency is even less with 0.003% (2,3). Less than 50 cases of UBC have been described in the international literature in patients under 10 years (4-6). One of the major problems remains the limited data, only small series have been reported, although during these last years increasing numbers of cases have been collected (4,7-11). A recent paper described several new cases in very young patients (5). Information retrieved from the SEER (Surveillance, Epidemiology and End results) database between 1973 and 2003 in the United States of America showed papillary urothelial neoplasms of low malignant potential (PUNLMP) as the predominant bladder tumor in patients under 18 years with higher incidence in the late teenage years (10). Noninvasive low grade papillary urothelial tumors are also one of the most important findings. Like in other UBC of older patients, a male predominance has been described; the sex ratio in the literature is three boys to one girl (6).

Material and methods

Study design

This retrospective multicenter study included patients between 1992 and 2013. The authors collected data of patients diagnosed with UBC less than 40 years at first diagnosis from different academic centers in France. After approval by institutional review boards at all of the centres, surgical and pathological data were collected and analyzed.

All patients were followed from diagnosis until death or until data were censored (and the patient considered as alive).

Pathological assessment:

Specimens were examined by genitourinary pathologists according to standard pathological procedures with assessment of carcinoma in situ and vascular embolism status.

The tumors were classified according to the 8th edition of pTNM (12) and the WHO 2016 classification (13).

Results

Characteristics of the bladder study population

We identified 155 patients, including 115 males and 40 females, with a mean follow up of 86 month (median 49 months). Mean age was 34.2 years (range 16-40). One patient was under 20 years, all the others belonged to the group 20-40 years. In 17 cases (11%) bladder cancer was diagnosed in patients less than 30 years.

History of cigarette smoking was observed in 66 patients (42%), familiar history of smoking in 3 (2%), professional exposure was reported in 9 (6%) cases.
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Four patients had a prior history of schistosomiasis; all of them were of African origin (Table 1).

**Initial pathological features**

At the time of the first trans-urethral resection of the bladder (TURB), 131 were unifocal (85%), 24 (15%) multifocal. No link could be found between smoking exposure and uni- or multifocality of the bladder tumor (p=NS).

Results of pathological findings are reported in Table 2. Most cases (92%) were pure urothelial carcinomas. Initially, forty-four (28%) were PUNLMP (papillary urothelial neoplasm of low malignant potential) (Fig. 1a and b), 99 (64%) low grade lesions and 57 (36%) high grade urothelial carcinomas according to different stages (pTa-pT4). When dividing patients into groups of <30 years and > 30, we could observe predominant presence of PUNLMPs in the group of under 30 years with 47% of cases. In the group > 30 years, the percentage decreased to 26%. In cross checking stage and grade data, 55 patients (36%) displayed pTa low grade (LG), 5 (2%) pTa high grade, 23 (14%) pT1. In one case stage could not be precisely be given, because of inflammatory and desmoplastic underlying stroma. This tumor was counted as pT1 as detrusor muscle invasion could not be given with certitude. Twenty-eight (18%) had HG muscle-invasive UBC. Among those, 14 patients displayed invaded lymphnodes (9%) and 10 (6%) presented metastasis at the time of discovery.

Regarding the presence of carcinoma in situ (Cis) only 9 (6%) had an association with Cis, no patient had primary Cis without any other tumoral lesion.

Twelve cases displayed other histological features: 4 squamous carcinomas, 3 adenocarcinoma, 1 carcinoma with signet ring cells, 1 leiomyosarcoma, 1 paraganglioma and 2 pseudoinflammatory myofibroblastic tumors.

Within the 4 patients with prior history of schistosomiasis, all had infiltrating urothelial carcinomas at time of first diagnosis (2 pT1, 1 pT2 and 1pT3).

**Subsequent treatment**

After initial TURB, 10 (6.4%) underwent immediate cystectomy, 7 (6%) received systemic chemotherapy, 1 had radiation therapy. Three patients (2%) underwent a supplementary nephroureterectomy as they presented synchronous diffuse lesions of the upper urinary tract.

**Discussion**

One of the major problems encountered in this kind of study is that the definition of “young” is not the same for everyone, although most authors agree of the age under 40 years. Nevertheless, many authors make a difference between <20 years and < 40 years, knowing that the group 30-40 years approaches to the patients diagnosed with UBC in older age (14). The second problem are the cases observed in children or young adults, mostly under 15 years, frequently first treated in pediatric structures, and later followed-up in adults hospitals, those patients might get lost in studies. This probably explains partially the lack of young patients < 15 years in many studies.

Several reasons of low incidence in young people have been exposed. First, UBC risk is directly related to age. Major environmental risk factors are smoking or professional exposure during several years (probably around 20 years) (15). Male predominance is noted in most studies, similar to that reported in older patients, but also similar to studies in very young patients under 20 years (9). Interestingly female gender does not show any significant results concerning the overall
survival neither in uni- nor multivariate analysis on the contrary to results in older patients, where it is well known, that female patients with the same stage and grade have worse outcome (14,16).

Up to date, only one original study with more than 150 cases for UBC in young patients has been published and another with more than 100 cases (11,14). In the largest study with more than 150 patients, the authors show that most patients displayed not invasive urothelial carcinomas; carcinoma in situ was a rare finding. A vast majority had PUNLMP (40.3%) in the group under 30 years, and in the group between 30 and 40 years (27.2%) still had the same kind of tumours. Nevertheless this study also highlighted the fact that some of these UBC are highly aggressive with 18% high grade muscle invasive bladder cancers. In these cases lymph node and distant metastasis are not rare. In our study we could show that muscle invasive bladder cancer shows sometimes aberrant variants such as signet cell variant or squamous/sarcomatoid aspects.

Another recent paper published data from 2 urology referral centers. In their group of patients younger than 30 years, they identified 5 patients with 12 years or younger, 7 in the group from 13-19 and 6 with less than 30 years. Interestingly they had a female predominance, but the global histology findings were like those in other studies, with a predominance of PUNLMP and low grade pTa tumours. Like in other studies, high grade lesions were rare, but nevertheless occurred in 22% (5).

Wang et al. also showed that the NMIBC was more frequent in younger patients, furthermore they demonstrated that in this group the 5 years survival was better (93.8%) than in elder patients (85.1%) (17).

Recent data try to understand on a molecular level why young patients had more often low grade pTa tumours. A link to the FGFR3 pathway, known to be overexpressed in the NMIBC pathway, seems to exist. These findings were especially true for patients under 25 years (18).

A paper from Gunlsoy et al. included also a large series of 91 patients with UBC. In their series 91.2% of patients displayed NMIBC. Unluckily they reported the grades according to the WHO 1973 classification, which makes the comparison with other studies difficult. Nevertheless 43.9% were pTa lesions and 47.2% pT1 tumours. They report a progression rate of 10.9%, they underline that the progression rate increases with the number of relapses.

In our study, we decided to report our results according to the grading of the WHO 2016 classification. This grading and staging system is recommended worldwide and easy to employ. Furthermore it improves considerably prior classifications schemas by providing detailed histological description for each entity. At least the WHO 2016 classification includes the definition of PUNLMP, which is a relatively frequent histological finding in young patients with bladder tumors. It is known that PUNLMPs have a low biological risk of progression and recurrence. In the current study more than 44 of the cases corresponded at the first incidence to PUNLMP. This entity remains controversial, although there is less discussion compared to the first description in the WHO 2004 classification, when PUNLMP was employed for the first time (3). French uropathologists rarely employ PUNLMP, nevertheless a high number with nearly 30% was reported in this study. Therefore one might suggest that urothelial lesions in young patients have a particular aspect and behavior. The definition of PUNLMPs is very strict; only simple papillar structures lined by a thickened urothelium, but with normal cytology and preserved architecture are
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admitted (3). In a recent study Fine et al reported predominant aspects of PUNLMPs in a cohort of young patients between 4-20 years (9). Although patients in our series were older, we observed globally the same histological profile as in the above mentioned study. We also report a predominance of PUNLMPs in the group under 30 years, which decreases in the population over 30 years. In the younger population we objective together with low grade pTa lesions an overall of 65%. These findings confirm the findings in Paner’s paper, where they report three different groups of patients according to the results of the SEER database: those under 20, those between 20 and 30 and those over 30 (6). The group with the youngest patients included 73% of PUNLMPs the second group 33% and the third 27% respectively. Therefore it is reasonable to conclude that PUNLMPs are obviously predominant in younger age (<30 years), and their number obviously decreases over the decades.

For several reasons it is important to recognize PUNLMPs, even if they may recur in up to 36%, but are known to have a low rate of progression (3.7%) (19,20). Our data confirmed these findings with 7% of recurrence and 10% of progression only to low grade pTa lesions and underlined the importance of this entity, which avoids the “cancer” diagnosis to these very young patients, who mostly have favorable outcome.

Our results clearly demonstrate in uni- and multivariate analysis the importance of grading and staging. The histological grade was one of the most important predictive factor (p=0.0009). The second important variable was stage (p=0.0002). Both factors taken together suggest a good oversight on the overall survival of patients. Furthermore multifocality was a strong predictor of recurrence, our data confirmed that the presence of multifocal tumors has a major impact on recurrence free survival (p=0.025).

Although the majority of patients had low grade lesions (PUNLMPs and pTa), only 13.8% had pT1 tumors and 18% had aggressive high grade muscle invasive urothelial carcinomas, on the other hand association of carcinoma in situ was rare (6%). Similar findings were reported by Yossepowitch, older patients displayed higher stage, more frequent recurrence and lower disease free survival (7). In our cohort 45% of patients were smokers or had a prior history of cigarette smoking, which is close to the data of the literature. Exposure and dose were supposed to be shorter than in older patients, and probably therefore no correlationship between smoking and survival without recurrence was found (p=NS). This might also explain the high number of PUNLMPs and low grade UBC. Cigarette smoking, increases the risk of developing a UBC approximatively 3 fold compared to non-smokers, nevertheless an exposure of several years is required (21). In different series the smoking incidence was variable (22,23).

A particularity of our study was the presence of 4 patients with schistosomiasis, who all had invasive UBC at the time of diagnosis. It clearly shows that schistosomiasis is an important factor of bladder carcinogenesis even in young patients and underlines the high aggressivity already in young age.

In contrast with series including older patients, no intermittent mortality was observed. Interestingly, even in young patients urothelial carcinoma seems to show the same behavior of recurrence and progression as in series with older patients (24). Patients who relapsed had a tendency to develop several recurrences as we know in older patients; some of them relapsed up to 5 times. Among the patients who relapsed, 15 had multiple recurrences and 8 progressed towards higher grade and stage.
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Histological grade and stage are still the gold standard in predicting patients’ outcome. Furthermore our results underline the necessity to keep the PUNLMP entity, which is especially useful in young patients avoiding the diagnosis of cancer. The important number of cases gives a good insight into the behavior and histology. Our clincopathological study, which is the largest original contribution in the literature of UBC in patients under 40 years, confirms the necessity to employ the WHO2016 classification. This study underlines the importance of the PUNLMP entity, although pathologists get more and more used to this entity.
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**Tables**

Table 1: Patient characteristics at diagnosis and at first recurrence

<table>
<thead>
<tr>
<th></th>
<th>At Diagnosis</th>
<th>At Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>156 (100%)</td>
<td>37 (24.3%)</td>
</tr>
<tr>
<td><strong>Age in years (min-max) ± SD</strong></td>
<td>33.2 (10-40) ± 5.8</td>
<td>37.3 (26-46) ± 4.6</td>
</tr>
<tr>
<td><strong>Sex Ratio</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Male</td>
<td>116 (74.4%)</td>
<td>27 (73.0%)</td>
</tr>
<tr>
<td>- Female</td>
<td>40 (25.6%)</td>
<td>10 (27.0%)</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Tabaco Exposure</td>
<td>64 (42.1%)</td>
<td>14 (37.8%)</td>
</tr>
<tr>
<td>- Professional Exposure</td>
<td>9 (5.9%)</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>- Schistosomiasis Exposure</td>
<td>4 (2.6%)</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>- Family History of urothelial bladder cancer</td>
<td>3 (2.0%)</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td><strong>Histological Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Urothelial Cell Carcinoma</td>
<td>143 (92%)</td>
<td>37 (100%)</td>
</tr>
<tr>
<td>- Adenocarcinoma</td>
<td>3 (2.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>- Squamous cell carcinoma</td>
<td>3 (2.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>- Others</td>
<td>6 (2.6%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Table 2: Pathological findings at diagnosis

<table>
<thead>
<tr>
<th>Type</th>
<th>At diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Uca</td>
<td>143 (92%)</td>
</tr>
<tr>
<td>Uca + other pattern</td>
<td>12 (8%)</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
</tr>
<tr>
<td>PUNLMP</td>
<td>44 (28%)</td>
</tr>
<tr>
<td>LG UCa</td>
<td>99 (64%)</td>
</tr>
<tr>
<td>HG UCa</td>
<td>57 (36%)</td>
</tr>
<tr>
<td>n=143*</td>
<td></td>
</tr>
<tr>
<td>NIMBC</td>
<td>123 (82%)</td>
</tr>
<tr>
<td>MIBC</td>
<td>20 (18%)</td>
</tr>
<tr>
<td>pTa</td>
<td>103</td>
</tr>
<tr>
<td>pT1</td>
<td>20</td>
</tr>
<tr>
<td>pTis primary</td>
<td>0</td>
</tr>
<tr>
<td>pT2-4</td>
<td>20</td>
</tr>
<tr>
<td>N+</td>
<td>14 (9%)</td>
</tr>
<tr>
<td>M+</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Cis</td>
<td>9 (6%)</td>
</tr>
</tbody>
</table>

*excluding variants and non urothelial carcinomas
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References


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23. Fitzpatrick JM, Reda M. Bladder carcinoma in patients 40 years old or less. J Urol. 1986 Jan;135(1):53-4

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Patients Tenon:


2. Homme 33 ans, pT2N2 (08/2005), cell bague à chaton, M+, décédé à 6 mois (03/2006)  
   possible primitif gastrique (biopsie gastrique : ADK cell indp)
