



Urothelial Bladder Cancer in Young Patients

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Abstract

Introduction: Bladder cancer is the 2nd urological cancer, most known in people over 50 years old. It starts being seen more and more in subjects under 40 years of age mostly due to several factors. The purpose of our study is to specific those risk factors, to study the characteristics of these tumors and also to appreciate their evolutionary profile.

Methodology: Retrospective, descriptive study, on 17 patients, within the urology department A of the University Hospital of Rabat (Center A) and Urology department of CHIC Alençon in France (Center B).

From March 1st, 2010 to March 1st, 2020.

Results: This study concerns 17 patients hospitalized in center A and B with an average age of 35 years, sharing the same risk factor. The pathology was revealed by its main symptom. Our patients benefited from an initial TUR-V resection; the follow-up was then based on the results of Anatomic Pathology. These tumors were preferentially localized on the lateral face and retro-trigone with average size of 3 cm in both centers. The most common histological type was urothelial carcinoma Ta Low Grade in both centers.

Conclusion: Bladder tumors in young people are unusual, favored by the presence of risk factors. However, these factors cannot be incriminated due to the short exposure time.

From an evolutionary point of view, superficial bladder tumors seem to have a good prognosis with little recurrence unlike infiltrating tumors.

Keywords: Urothelial carcinoma; Young subject; Progressive profile; Characteristic of tumors

Introduction

Bladder cancer is a common pathology, clearly increasing, with greater incidence beyond 50 years. It represents the 2nd urological cancer and the 5th cancer in the world. However, we are witnessing the frequency of young subjects with bladder cancer progressively increasing, whereas considered rare in patients less than 40 years of age and it represents only for 0.4% to 1% of urothelial tumors [1-4].

The onset growth of these bladder tumors is linked to the influence of the environment and changes in our way of living. Smoking is an important factor in the genesis of these tumors and there are other factors that can intervene, such as industrial carcinogens or genetics.

Purpose:

- Specify the risk factors involved in the occurrence of bladder tumors in young.
- Study the characteristics of these bladder tumors.
- Appreciate the evolutionary profile of these bladder tumors after treatment.

Methodology

Retrospective, descriptive study, on 17 patients, within the urology department A of the University Hospital of Rabat (Center A) and Urology department of CHIC Alençon in France (Center B).

From March 1st, 2010 to March 1st, 2020.

Over a period of 10 years, 17 patients were hospitalized in the two departments for a bladder

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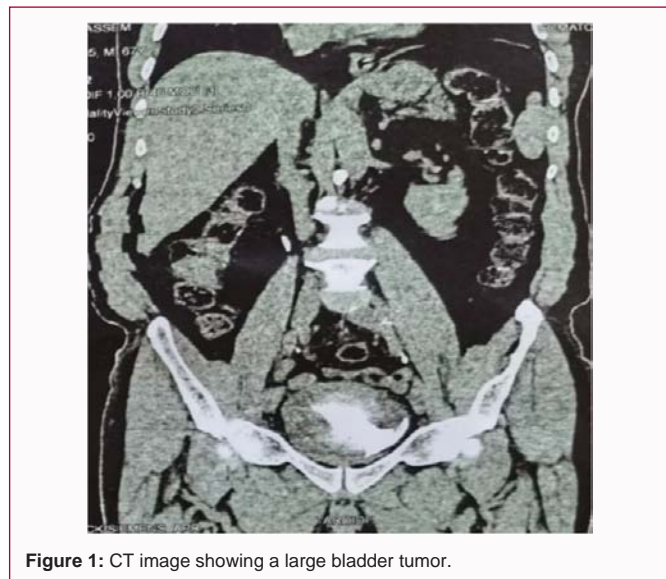
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Table 1: The histological type was urothelial carcinoma.

Histological type		Center A	Center B
pTa	Low grade	3	3
	High grade	2	0
pT1	Low grade	1	1
	High grade	4	0
pT2		2	1

**Figure 1:** CT image showing a large bladder tumor.

tumor with an age less than 40 years, 12 patients in Center A and 5 patients in Center B.

An operating sheet has been prepared specifying the identity, risk factors, circumstances of discovery, tumor characteristics, treatment and follow-up (Figure 1).

This study includes all patients with a bladder tumor with an age less than or equal to 40 years. All patients with an age greater than 40 years or with incomplete file were excluded.

Results

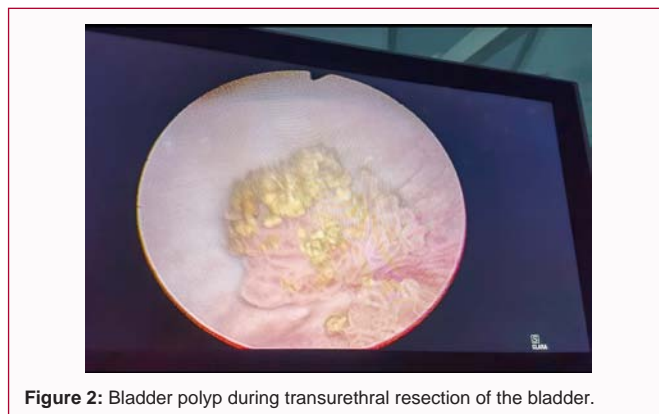
Over a period of 10 years, 17 patients were hospitalized in our departments for a bladder tumor with an age less than 40 years; 12 and 5 in Center A and B respectively.

Patients in Center A had an average age of 34 years (26-39) and 35.6 years (31-40) in Center B, they were predominant males and two women, one for each center.

All patients, in both Centers, shared the same smoking risk factor with an average of 10 pack/year. Two patients in Center A had a professional exposure, one working as a painter, the second in a textile factory. No professional exposure was detected in Center B.

The main symptom, revealing, was hematuria in the 17 patients, 8 of them had, in addition, an irritant syndrome of the lower urinary tract.

In Center A, the average size of these bladder tumors was 3.2 cm with extremes ranging from 1 cm to 5 cm and localized on the lateral face in 5 patients, and in decreasing order, retro-trigone then anterior face. For Center B, the average size was 2.3 cm (from 1 cm to 4 cm)

**Figure 2:** Bladder polyp during transurethral resection of the bladder.

and the lateral face was the preferential localization (Figure 1).

The histological type was urothelial carcinoma.

The anatomopathology study had also revealed in Center A's patients, a case of in situ carcinoma and an extensive squamous inflection in another one. For Center B, we found a case of associated undifferentiated carcinoma.

All patients initially had transurethral resection of the bladder (monopolar for Center A and both bipolar or monopolar for Center B), for diagnostic and therapeutic purposes (Figure 2). In Center A, the transurethral resection was curative in 8 patients, two of whom benefited from intravesical β CG therapy (according to the protocol of 6 cures). Three of them underwent a radical cystoprostatectomy with a urinary diversion type Studer enterocystoplasty or Bricker for having a pT2 or for endoscopically uncontrollable tumor. The last one had a palliative surgery with cutaneous ureterostomy due to the intraoperative discovery of an inextricable tumor with peritoneal carcinosis. Four patients in Center B, benefited from a curative TUR-V resection and one of whom had a BCG intravesical therapy. The last patient had radical cystoprostatectomy with a urinary diversion type Bricker for having a pT2 tumor.

In Center A, the monitoring consisted in carrying out control cystoscopy every 3 to 6 months in patients with superficial tumors, while patients with a high-risk tumor, they systematically had a second look after the 1st resection. Two patients recurred after an interval of 4 months. For patients benefiting from radical gestures a quarterly check of renal function and a check scanner was carried out at 6 months of the intervention as well, also the appreciation of the tolerance of the type of diversion. Ten of the 12 patients, could be contacted, 9 are still alive ensuring regular follow-up as mentioned above. As for the last one, he died due to the evolution of his illness.

For Center B, the follow-up protocol consisted of regular cystoscopies every 3, 6, 12 months according to the risk group. Of the 5 patients in Center B, 3 are still alive ensuring regular follow-up. Of the 3 patients with a pTa low grade tumor, one had its first follow up cystoscopy only recently and no recurrence has been detected, another had a recurrence detected 10 months after the initial resection and will be re-operated shortly. The last one died 18 months after the initial resection because of his severe comorbidities. No recurrence has been detected in the meanwhile. The patient with the pT1 tumor has an ongoing follow up for 5 years, the second look showing no residual tumor and no recurrence having been detected during the subsequent cystoscopies. The patient with the pT2 tumor died 1 month after the cystectomy due to a meningeal carcinomatosis

despite a neo adjuvant chemotherapy.

Discussion

Several studies show that bladder tumors are very rare before the age of 40 and represent only 0.4% to 1% of bladder tumors [1-4] and this from the 1st case which has been reported by Smythe in 1872 [5].

In the literature, we observe a clear male predominance, variously appreciated by the authors, with a sex ratio of 3.6 to 9 men for a woman [1-4,6] as in our study, from all 17, males were 15. It should be kept in mind that bladder tumors can express themselves with an atypical clinical form with signs of bladder irritation. Nevertheless, hematuria remains the telltale sign of the pathology. Smoking is defined as a recognized risk factor for urothelial tumor, this risk increases with the number of pack/year and the degree of smoke inhalation. However, it is difficult to assert the harmful role of smoking in young subjects because of the short duration of exposure in our series. Although the 2007 WHO report shows that 15.5% of smokers are between the ages of 13 and 15 and 24% of young smokers started before the age of 10. We found in our series that two patients were exposed to chemicals products, the 1st patient worked as a painter and the 2nd in a textile factory. These professional risk factors have been demonstrated in a study by Benton and Henderson [7] with an exposure duration varying between 3 years and 11 years.

In addition to these risk factors, the genetic predisposition to bladder neoplasia was mentioned in several retrospective studies and for the first time by Fraumeni in 1967 [8]. For Sidransky [9], a mutation in the gene coding for the protein p53 (chromosome 17p), seems to be a bad factor of prognosis and tumor progression. Iori [10] and Linn [11] find a high mutation rate on these 2 chromosomes in their population of young subjects.

So, in the presence of any patient under 40 years of age with a bladder tumor, a genetic predisposition must be evoked by investigating family history, in order to screen the risk requiring close urological monitoring.

From the histological point of view, in all the articles published in the French and English journals, there is a clear predominance of superficial tumors as it has been demonstrated by the series of Kutarski [12] who was interested in the variation of the histological stage and age with a pTa tumor rate of 77% between 40 and 50, and a rate that reaches 94% before 20 years of age. Regarding invasive tumors, the results are again very variable depending on the series. For example, Javadpour [2] and Kutarski [12] did not find any infiltrating tumor in their study. Conversely, Aboutaieb [13] isolates 14 cases of infiltrating tumors out of 25 urothelial tumors.

The evolution of bladder tumors is more favorable for superficial tumors as shown by the series of Aboutaieb [13] in subjects less than 30 years who did not find any recurrence or progression in this age group. As for patients over 30 years old, healing was noted in 3 cases, recurrence in 3 cases and progression in one case for a high-risk tumor.

Bladder tumors in young subjects seem to have a variable and heterogeneous prognosis, it seems to be more favorable for superficial tumors developed before 30 years, which are most often papillary, unifocal and not very progressive, as demonstrated by the series of McGuire [14] on 62 subjects or by Javadpour and Mostofi [2] who noted 40 cases of primary epithelial tumors of the bladder in young

people before 20 years of age. Conversely, infiltrating tumors in this group of age seem to be very aggressive with a bad prognosis which has been observed by Johnson and Hillis [3] who found 6 cases of infiltrating tumor in their 22 patients, all died within 2 years. The series of Cherrie [1] counted 11 tumors showing signs of aggression on 27 cases and from the 11 patients, 8 died from their disease.

A genomic study identified mutations of the P53 (TP53)/RB1 tumor suppressor pathway in 93% of tumors, activation of the PTEN/PI3KCA oncogene pathway in 72%, with frequent loss of function of histone modifying enzymes (MLL2, MLL3, UTX and ARID1a) in 89% described by the Cancer Genome Atlas project (TCGA) [15]. Different stage tumors have different mutation rate (Genomic profile analysis showed a similar frequency of mutations in TERT, TP53, RB1, PTEN, PIK3CA, KMT2D and ARID1A at presentation among progresses and non-progresses) which is associated to relatively high neoantigen burden and response to checkpoint inhibitors as has been demonstrated in melanoma and lung cancers, where response to the immunotherapeutic agents nivolumab and pembrolizumab are directly correlated with Total Mutational Burden (TMB) [16-18].

The surveillance of this tumor bladder requires regular cystoscopies, making this one expensive on cost per patient and uncomfortable. Nowadays, some non-invasive methods are seeing the light as liquid biopsies able to identify and quantify in urine, proteins that can detect and classify bladder tumors and even show a significant difference between urinary proteome in patients with different bladder cancer stages as shown by Falcão et al. [19].

Conclusion

Bladder tumors in young people are rare, favored by the presence of the described risk factors. However, our study could not objectify the entire action of its factors due to the short exposure time and a family investigation is required if a significant family history.

From an evolutionary point of view, superficial bladder tumors seem to have a good prognosis with little recurrence; whereas infiltrating tumors have a bad prognosis with particular aggressive potential.

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