Epidemiological and Morphological Characteristics of Urothelial Bladder Cancer in a Bulgarian and a French Sample of Patients

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Abstract
Bladder carcinoma (BC) is one of the most common malignancies of the urinary system in developed countries, and it is also characterized by a high number of recurrences and progression rates despite multimodal treatment. BC is a biological and clinically heterogeneous tumor with a great propensity of divergent differentiation. Around the world, bladder cancer is responsible for 549,000 new cases and 200,000 deaths each year. In Bulgaria, bladder carcinoma is the 18th most common neoplasia. Our results on 105 proven bladder carcinoma cases confirmed that this tumor arises at 70 years on average (60-90 years), it affects men predominantly and there was no difference regarding the nationality of patients. In conclusion, it remains a diagnostic challenge.

Keywords: Bladder Cancer, Urothelial Carcinoma, Urinary Tract.

1. Introduction
Urothelial bladder cancer is a common disease that takes the 9th rank in worldwide cancer incidence (Ploeg et al., 2009). The incidence of bladder cancer is three times greater in males than in females (Hartge et al., 1990). These differences in gender prevalence explained largely by differences in exposure to certain risk factors. In the developed country, the major risk factor is smoking (Aydin et al., 2017; Battista Di Pierro et al., 2012; Gilbert et al., 2004). In Western countries, smoking is responsible for around 50% of urothelial bladder cancer in males and 35% in females (Ploeg et al., 2009). On the other hand, in countries where the infection caused by Schistosoma haematobium is endemic, like Egypt, primary squamous cell carcinoma of the bladder is the dominant histological type. The third most important risk factor for bladder cancer development is occupational exposure, as chronic exposure to arsenic.

Carcinoma of the bladder is a 7th most common malignant disease in men and 17th in women. The majority of bladder cancer is composed of urothelial carcinoma (90%), where the remaining less common types include primary bladder’s adenocarcinoma, squamous cell carcinoma, and neuroendocrine carcinomas (small cell carcinoma) (Carneiro et al., 2015).

Urothelial carcinoma of the bladder is usually admixed with other morphologically recognizable differentiations (Beltran et al., 2017). In recent years, the spectrum of microscopic forms of urothelial carcinoma has been expanded to include several histological variants. Most of them are described in the World Health Organization (WHO2016) book (Moch et al., 2016). The recognition of histological variants in urothelial neoplasia is essential for a pathologist and oncologist because different
histology subtypes of urothelial cancer of the bladder may be associated with different clinical outcomes and have a different therapeutic approach.

2. Materials and Methods

We examined 105 cases of urothelial carcinoma from tissue database of University Hospital “St. George “Plovdiv, Bulgaria and Grand Hospital de l’Esté Francilien, Jossigny, France, and reviewed the period from 2016 to 2020. All analyzed patients in this study have been diagnosed with invasive or non-invasive high-grade (HG) and low-grade (LG) urothelial carcinomas of the bladder.

Histological analysis of the tissues was performed using automatic tissue processor „DIAPATH EN ISO 9001:2000“ and 4-5 μm formalin-fixed paraffin-embedded tissue sections underwent routine staining with hematoxylin-eosin (HE) and hematoxylin-eosin-safran (HES) to determine the presence of individual histological features.

Statistical analysis was performed with the software package for statistical analysis (SPSS®, 92 IBM 2009, version 19) using descriptive statistics and dispersion analysis (ANOVA). We considered the results for significant if p<0.05.

3. Results

The analyzed 105 patients in our study were diagnosed with proven urothelial carcinoma. Still, we must clarify that we included a few cases of urothelial carcinoma of renal pelvis and ureter. The patients only with urothelial carcinoma of bladder were 95.2%. Nevertheless, all analyzed patients were characterized and separated by two features: 1) by localization and 2) by age and gender.

The most common site of urothelial carcinoma was in the bladder, presented by 100 (95.2%) cases. Second by frequency urothelial carcinoma was in the distal part of the ureter, observed in 3(2.9%) cases. The least of the urothelial carcinoma included in our study were 3(1.9%) cases in the renal pelvis. These results are presented in Table 1.

Table 1. Number and percentage of patients with urothelial carcinoma according to its location

|                  | Bladder | Renal pelvis | Ureter | Total |
|------------------|---------|--------------|--------|-------|
| Number of patients | 100     | 2            | 3      | 105   |
| Percentages of patients | 95.2    | 1.9          | 2.9    | 100   |

Although we analyzed our result according to the average age, the mean age of our patients was 70±10.98 years, as the youngest patient was 42 years old, while the oldest was 93 years old. Because of that heterogeneity of the age, we separated all patients in our study into six decades, as it is shown in Figure 2. The majority of our patients fit in the 60-89 years of age.

![Figure 2. The number and % of patients with urothelial carcinoma according to age divided into decades](image)

In regards to the age and nationality of our patients with urothelial carcinoma of the bladder, we did not find a significant difference between them. The median age of the patients from Bulgaria was 70.14 ±11.16 years, and from France was 69.62 ±10.09 years, p=0.873. This is graphically presented in Figure 3.

![Figure 3](image)
We have obtained the following results according to the gender of the patients form cohort comprised of 105 patients with urothelial carcinoma: 72.4% (76/105) were males, and 27.6% (29/105) were females. The data are graphically presented in Figure 4.

Figure 3. Differences in the average age of patients according to the nationality

Figure 4. Distribution of patients according to the gender
Figure 5. Distribution of the patients according to their nationality

Figures 4 and 5 show the distribution of urothelial carcinoma of bladder by gender, in Bulgarian and French samples of patients with a significant difference between male and female, for both countries. In essence, 65/92 (70.7%) for Bulgarian patients and 11/13 (84.6%) for France were males, and 27/92 (29.3%) in Bulgaria and 2/13 (15.4%) in France were females. Descriptive statistical methods showed no significant differences in patient’s samples for both countries, p=0.292.

4. Discussion
Bladder carcinoma still presents a diagnostic challenge, and it remains the 7th most common malignant disease and the 2nd most common neoplasia of the excretory system right after prostatic carcinoma. It is also characterized by a high tendency for recurrence, necessitating expensive life-long clinical surveillance with repeated surgical interventions. Even in highly developed countries where standards of medical care and treatment are high, outcomes remain unchanged from 20 years ago. Urothelial carcinoma of the bladder is a significant public health problem in South Europe (especially in Greece, Spain, and Italy) and the most common cause for the lethal outcome of malignancies in males, and in Lebanon - in females (Bray et al., 2018).

This study demonstrated that the urothelial carcinoma of the bladder is a high-risk tumor. Moreover, among men, this is the most commonly diagnosed malignancy in Bulgaria and France, which is in correspondence with the data from other studies. According to literature, Bulgaria is the only country where males had a significant increase in both incidence and mortality (Wong et al., 2018). In our study, we also established the ratio between man and women was 3.2:1, and the average age of the patients with urothelial carcinoma of the bladder is 70.14 years on average, which is similar to the results of almost all published studies (Horstmann et al., 2008; Gandomani et al., 2017).

5. Conclusion
This study demonstrated that bladder carcinoma is not a “simple” pathology but a common and aggressive malignant disease. It remains a diagnostic challenge. As we described in the interdiction, many factors affect its epidemiology. Still, most of them might be controlled with all common forces for one purpose only – reduces its incidence and mortality.

Conflict of interests
The authors state no conflict of interest.

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