# **Original Paper**

# Urinary Bladder Tumors Clinical and Statistical Retrospective Study

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**ABSTRACT:** Nowadays, urinary bladder cancer represents a major health problem, due to very high medical and social costs. This disease affects mainly the elderly. We performed a study on 1073 patients admitted to the Urology Clinic within the Emergency Clinical Hospital of Craiova, between 2013-2015 with bladder cancer. Of the 1073 cases, 741(69.06%) were diagnosed in men, and 332 (30.94%) were found in women, the men/ women ratio being of 2.23/1. The highest incidence of bladder tumors was recorded in individuals aged between 60 and 79 years old. In this age group, there were admitted 734 patients with bladder cancer, representing 68.44%. Regarding the tumor recurrence, out of 1073 bladder tumors, a number of 608 (56.66%) patients were diagnosed with primary tumors, while a number of 465 (43.34%) patients presented recurrent tumors. Of the symptoms presented by the patients, the most frequent were haematuria (present in about 87% of the patients), pollakiuria (present in 64% of the patients), dysuria (present in 55% of the patients) and urinary infections (present in about 23% of the patients).

**KEYWORDS:** bladder cancer, invasive cancer, age, gender, recurrence

## Introduction

In the last decades, urinary bladder cancer has become a serious social problem, due to its ever-growing incidence and to a great recurrence rate [1,2].

Statistical data show that between 2002 and 2012, worldwide, the number of bladder cancers increased from 375.000 to about 430.000 [3,4], while the mortality increased from 145.000 patients in 2002 up to 165.000 patients in 2012 [5-7].

The distribution of bladder cancer cases is quite variate around the world. According to some data, two thirds of bladder cancers appear in developing countries [8,9].

In Europe, in 2012, the estimated incidence of bladder cancer was about 151 300 cases, of which 118 400 (78.26%) were diagnosed in men and 32 900 were diagnosed in women (21.74%) [5,10]. With all these data, most clinical and statistical studies admit that there are major differences between various countries regarding the incidence of bladder cancer, generated not only by the etiopathogenic factors, but also by the deficiencies of some cancer-related records, which do not present a real situation of this condition all the time.

In the present study, we proposed to study the clinical and statistical aspects of bladder cancer in the patients admitted to the Urology Clinic within the Emergency Clinical Hospital of Craiova, between 2013-2015.

# **Material and Methods**

The study was intended as a retrospective survey analysis, assessing the clinical and statistical features of bladder cancer during a 3-year period (2013-2015).

In order to perform the study, we analyzed the patients' medical transcript records of the Urology Clinic within the Emergency Clinical Hospital of Craiova, the medical transcripts of the admitted patients, the histopathological records of the excised tumoral lesions, as well as the laboratory data and imaging investigations performed for the patients with bladder cancer admitted during this period of time.

Each patient or, depending on the case, his/her caregiver gave a written informed consent for using the material for both research and diagnostic purposes.

#### Results

Between 2013-2015, in the Urology Clinic, there were admitted 1073 patients with bladder tumors. The yearly distribution was relatively

proportional. Thus, in 2013, there were admitted 369 patients (34.39%), in 2014 there were admitted 381 patients (35.51%), and in 2015 there were admitted 323 patients (30.10%) with this diagnostic (Fig.1).

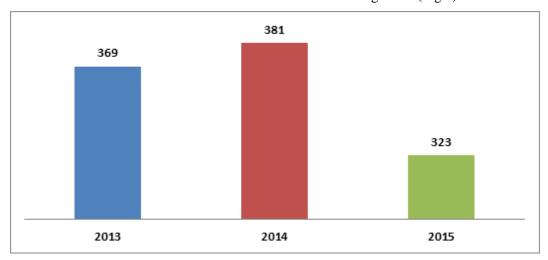


Fig.1. Yearly distribution of patients with urinary bladder tumors

Regarding the gender distribution, similar to other studies, we observed that the bladder tumors were much more frequent in men. Thus, of a total of 1073 bladder cancers, 741 (69.06%)

were diagnosed in men, while 332 (30.94%) were found in women, the men/ women ratio being of 2.23/1 (Fig.2).

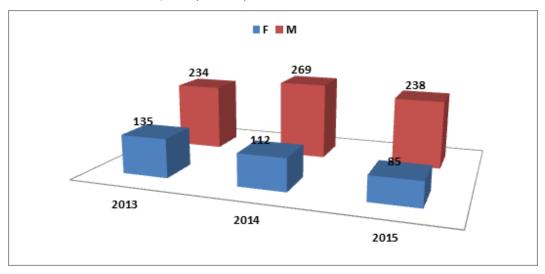


Fig.2. Sex distribution of urinary bladder tumors

We questioned if this ratio presented any high variations in the three year period of investigation. In 2013, there were recorded 369 patients with bladder tumors, 234 (63.42%) men and 135 women (36,58%), the men/ women ratio being 1.73/1; in 2014, of 381 patients, 269 (70.60%) were men and 112 (29.49%) women, the men/ women ratio being 2.4/1; in 2015, of 323 patients, 238 (73.68%) were males, and 85 (26.32%) were females, the men/ women ratio being 2.8/1. Thus, in the whole studied

group, the men/ women ratio varied between 1.73/1 and 2.8/1.

By analyzing the distribution of bladder cancer cases according to the social environment, there was observed that from the 1073 cases, 709 (66.08%) cases were recorded in the rural area, and only 364 (33.92%) cases in the urban area. In the studied period, we observed a decreasing trend of the number of bladder tumors in the rural area and an increasing trend in the urban area (Fig.3).

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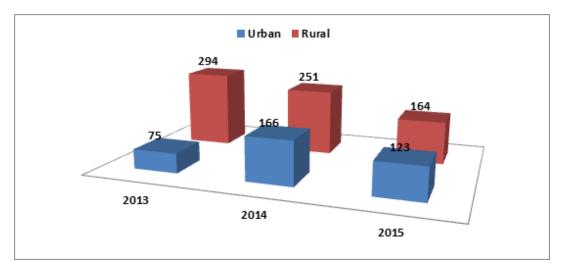


Fig.3. The patients' social environment distribution of bladder tumors

By analyzing the distribution of bladder tumor cases according to the age groups, we observed that the incidence of bladder cancer increased with the patient age (Fig.4).

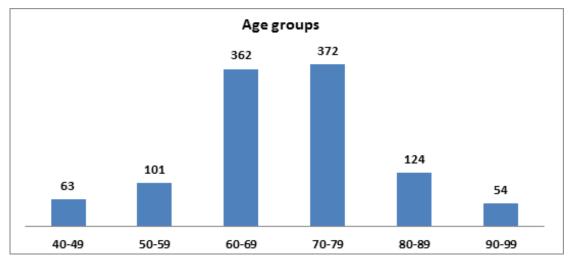


Fig.4. Distribution of urinary bladder tumors according to the patients' age

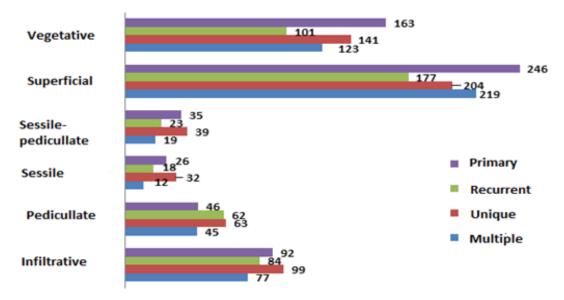


Fig.5. Diagram of urinary bladder tumors according to the macroscopic aspect

Thus, in the 40-49 years old group, there were recorded only 63 (5.87%) patients; in the 50-59 years old group there were admitted 101 (9.41%) patients; in the 60-69 years old group there were recorded 362 (33.74%) patients; in the 70-79 years old group there were recorded 372 (34.70%) patients; in the 80-89 years old group, 124 (11.54%) patients, and in the age group over 90 years old, there were recorded 51 (4.74%) patients. As observed, the highest incidence of bladder tumors was recorded in the patients aged between 60 and 79 years old, there were admitted 734 patients, representing about 68.44%.

The macroscopic aspect of bladder tumors, observed in cystoscopy or during surgery, was variable. There were recorded the following macroscopic variants of bladder tumors:

- the superficial form was found in 423 (39.42%) cases, of which 246 were primary tumors and 177 were recurrent ones;
- the vegetative form was diagnosed in 264 (24.60%) patients; of these, 163 tumors were primary and 101 recurrent ones;

- the infiltrative form was diagnosed in 176 (16.40%) patients, of which 92 were primary tumors and 84 recurrent ones.
- the pedicultate form was found in 108 (10.07%), of which 46 were primary tumors and 62 recurrent ones;
- the sessile form was identified in 44 (4.10%) patients, of which 26 presented primary tumors and 18 recurrent ones;
- the sessile-pedicultate form was diagnosed in 58 (5.41%) patients, of which 35 presented primary tumors and 23 recurrent ones.

Histopathology showed that non-infiltrative papillary urothelial neoplasm of low malignant (PUNLMP) were mostly potential vegetative and pediculate-sessile types, low papillary carcinomas grade were macroscopically vegetative, superficial, pediculate and sessile-pedicullate, while high grade papillary carcinomas came especially from sessile and sessile-pedicullate tumors (Fig.6).

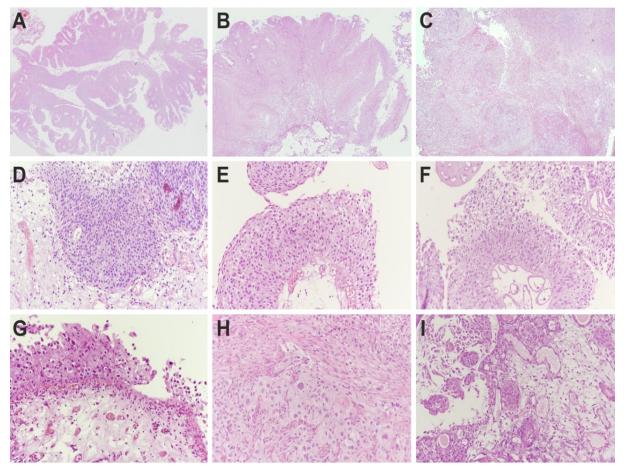


Fig.6. The main microscopic features of bladder urothelial carcinoma. At low power view the prototype of the lesions are papillary (A), flat (B) and overt infiltrative (C) profiles. High power view typical aspects of PUNLMP (D), non-invasive low-grade papillary carcinoma (E), non-invasive high-grade papillary carcinoma (F), carcinoma in situ (G) and different extensions of infiltration in invasive tumors (H-I).

A-C, 0.5x; D-I, 20x, Hematoxylin Eosin staining

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The cases with carcinoma in situ came from macroscopically superficial tumors, but also from sessile tumors. Infiltrative carcinomas were macroscopically with diffuse growth, but also papillary and sessile-pedicullate. Urothelial hyperplasia, dysplasia and urothelial papillomas have not been considered in this case series. Regarding tumor recurrence, of 1073 bladder tumors, 608 (56.66%) patients were diagnosed with primary tumors, and 465 (43.34%) patients presented recurrent tumors. Of 1073 tumors, 578 were unique, and 495 were multiple.

Of the symptoms presented by the patients, the most frequent were haematuria (present in about 87% of the patients), pollakiuria (present in 64% of the patients), dysuria (present in 55% of the patients) and urinary infections (present in about 23% of the patients).

### **Discussion**

At present, cancer is a major health problem worldwide, both due to its ever growing incidence and to the very high medical and social costs [1]. Urinary bladder cancer is the 7th most frequent cancer form in men and the 17th most frequent cancer form in women, all over the world [2].

Between 1988 and 2008, the number of patients diagnosed in the USA every year has increased by more than 50%, having a diagnostic rate higher than 25% in men than in women [11].

In our study, during the investigated three years, in the Urology Clinic within the Emergency Clinical Hospital of Craiova, there were admitted 1073 patients with bladder cancer, with an average value of 353 patients per year. Overall, in our study, we observed an increase of bladder cancers. Most bladder tumors (69.06%) were recorded in males, the men/ women ratio being of 2.23/1. Other studies found a higher ratio of bladder tumors between men and women (around 4/1) [12,13].

The data we obtained are similar to the ones found by other studies, showing that bladder tumors are more frequent in men due to smoking [14,15], alcohol intake and exposure to professional fumes (aromatic amines, chloride hydrocarbures and polycyclic aromatic hydrocarbures) [16-19].

According to some studies, although men present a higher risk than women for developing urinary bladder cancer, women are diagnosed in a more advanced stage compared to men.

Another aspect investigated by us was the age of the patients found with a form of bladder

cancer. Thus, we observed that the patients admitted to the Urology Clinic in Craiova between 2013-2015 were aged between 40 and 94 years old. As shown above, the tumor distribution according to age increased with the patient's age.

Most cases were recorded in the age group between 60 and 79 years old (734 patients, representing about 68.44%); after the age of 80 years old the incidence of bladder tumors decreased, but this decrease was due to the fact that the individuals over 80 years old represent a lower percent of the general population, as there is an increased mortality in this segment due to other conditions.

Other epidemiological studies have also shown that the incidence and prevalence of bladder cancer increases with age, having an incidence peak in the seventh and eight life decade [6].

According to population studies, age represents a strong and independent risk factor for developing cancer in general [20,21] and bladder cancer in particular. There was shown that individuals aged over 65 years old have a much higher incidence of cancer in general (approximatively 11 times higher) and a cancer mortality rate 15 times higher than individuals aged under 65 years old [22].

The incidence of bladder cancer increases from about 142 in 100.000 men and 33 in 100.000 women aged between 65-69 years old, to 296 in 100.000 men and 74 in 100.000 women aged over 85 years old [15].

The increase of incidence in the elderly may be explained by the diminished response of the immune system to various antigens, including tumor antigens, and the onset of some abnormal inflammatory responses [23-25].

It is documented that the immune system plays an important part in the onset and development of cancer [26]. After the age of 60 years old, the number and functions of T lymphocytes present a significant drop, being one of the characteristics of the aging immune system [27,28].

The deterioration of the immune system with age includes a decrease of the volume and lymphocyte parenchyma of the thymus, with a simultaneous decrease of T lymphocytes subpopulations, a reduction of the specific hormones and cytokines and an overall diminished defense capacity, which favors the development and progression of cancer [29].

Another mechanism that connects aging with cancer is the oxidative stress, a process by which

the production of reactive oxygen species and free radicals may activate the transcription of the genes involved in the inflammatory processes. Oxidative stress may also cause alterations of the DNA and of various proteins associated with aging and malignity [30].

Regarding the macroscopic aspect of bladder tumors in the patients of our group, we observed that these cases presented under various forms, the most frequent one being the superficial form.

Another particular aspect of bladder tumors, in our study, was the case of patients with recurrent tumors; of 1073 patients with bladder tumors, 465 (43.34%) presented recurrent tumors. Other studies found that the recurrence rate for these tumors is between 50-70%, while 10-15% progress towards developing muscular invasion over a period of 5 years [31,32].

The disease recurrence may be local or in the upper urinary tract even after a few years, thus requiring lifetime monitoring. Approx. 30% of the patients have a muscular invasive tumor at initial diagnosis; from this group, half of the cases develop farther metastases in the following 2 years and 60% die in the next 5 years, despite the applied treatment [33,34].

#### Conclusion

The study was performed on 1073 patients admitted with bladder tumors to the Urology Clinic within the Emergency Clinical Hospital of Craiova, between 2013-2015, and highlighted 741(69.06%) tumors diagnosed in men, and 332 (30.94%) in women, the men/women ratio being 2.23/1.

Bladder tumors were diagnosed in the patients aged between 40 and 94 years old. The highest incidence of bladder tumors was recorded in the individuals aged between 60 and 79 years old. In this age group, there were admitted 734 patients with bladder tumors, representing about 68.44%.

A particular aspect of this case series, most probably related to the local specific epidemiologic factors, was the relative high incidence of tumor recurrences, respectively for 465 (43.34%) patients.

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\* M.L. Ştefănescu And M.C. Forţofoiu contributed equally to the paper.

#### References

- Keyghobadi N, Rafiemanesh H, Mohammadian-Hafshejani A, Enayatrad M, Salehiniya H. Epidemiologyand trend of cancers in the province of Kerman: southeast of Iran. Asian Pac J Cancer Prev, 2015, 16(4):1409-1413.
- Pakzad R, Mohammadian-Hafshejani A, Mohammadian M, Pakzad I, Safiri S, Khazaei S, Salehiniya H. Incidence and Mortality of Bladder Cancer and their Relationship with Development in Asia. Asian Pac J Cancer Prev, 2015, 16(16):7365-7374.
- Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin, 2005, 55(2):74-108.
- Murta-Nascimento C, Schmitz-Drager BJ, Zeegers MP, Steineck G, Kogevinas M, Real FX, Malats N. Epidemiology of urinary bladder cancer: from tumor development to patient's death. World Jo Urol, 2007, 25:285-295.
- Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer, 2015, 1;136(5):E359-386.
- Malats N, Real FX. Epidemiology of bladder cancer. Hematol Oncol Clin North Am, 2015, 29(2):177-189.
- Zhao M, He XL, Teng XD. Understanding the molecular pathogenesis and prognostics of bladder cancer: an overview. Chin J Cancer Res, 2016, 28(1):92-98.
- Ploeg M, Aben KK, Kiemeney LA. The present and future burden of urinary bladder cancer in the world. World J Urol, 2009, 27(3):289-293.
- Yavari P, Sadrolhefazi B, Mohagheghi MA, Mehrazin R. A descriptive retrospective study of bladder cancer at a hospital in Iran (1973-2003). Asian Pacific Journal of Cancer Prevention, 2009, 10(4):681-684.
- Benhamou S, Bonastre J, Groussard K, Radvanyi F, Allory Y, Lebret T. A prospective multicenter study on bladder cancer: the COBLAnCE cohort. BMC Cancer, 2016, 16(1):837.
- Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. CA Cancer J Clin, 2008, 58(2):71-96.
- Mungan NA, Aben KK, Schoenberg MP, Visser O, Coebergh JW, Witjes JA, Kiemeney LA. Gender differences in stage-adjusted bladder cancer survival. Urology, 2000, 55(6):876-880.
- Mungan NA, Kiemeney LA, van Dijck JA, van der Poel HG, Witjes JA. Gender differences in stage distribution of bladder cancer. Urology, 2000, 55(3):368-371.
- 14. Zeegers MP, Tan FE, Dorant E, van Den Brandt PA. The impact of characteristics of cigarette smoking on urinary tract cancer risk: a metaanalysis of epidemiologic studies. Cancer, 2000, 89(3):630-639.
- 15. Shariat SF, Sfakianos JP, Droller MJ, Karakiewicz PI, Meryn S, Bochner BH. The effect of age and gender on bladder cancer: a critical review of the literature. BJU Int, 2010, 105(3):300-308.

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- 16. Colombel M, Soloway M, Hideyuki A, Böhle A, Palou J, Buckley R, Lamm D, Brausi M, Witjes AJ, Persad R. Epidemiology, staging, grading, and risk stratification of bladder cancer. European Urology Supplements, 2008, 7:618-626.
- Brown T, Slack R, Rushton L. Occupational cancer in Britain. Urinary tract cancers: bladder and kidney. Br J Cancer, 2012, 107(Suppl 1):S76-S84.
- Latifovic L, Villeneuve PJ, Parent ME, Johnson KC, Kachuri L. The Canadian Cancer Registries Epidemiology Group, Harris SA. Bladder cancer and occupational exposure to diesel and gasoline engine emissions among Canadian men. Cancer Med, 2015, 4(12):1948-1962.
- Andreassen BK, Aagnes B, Gislefoss R, Andreassen M, Wahlqvist R. Incidence and Survival of urothelial carcinoma of the urinary bladder in Norway 1981-2014. BMC Cancer, 2016, 16(1):799.
- Hewitt M, Rowland JH, Yancik R. Cancer survivors in the United States: age, health, and disability. The Journals of Gerontology: Series A, 2003, 58(1):M82-M91.
- Yancik R, Ries LA. Cancer in older persons: an international issue in an aging world. Semin Oncol, 2004, 31(2):128-136.
- 22. Messing EM. Urothelial tumors of the bladder. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA (Eds): Campbell-Walsh Urology, Ninth Edition, Chapter 75. Philadelphia: Saunders-Elsevier, 2008, 2407-2446.
- Sawhney R, Sehl M, Naeim A. Physiologic aspects of aging: impact on cancer management and decision making, part I. Cancer J, 2005, 11(6):449-460.
- 24. Sehl M, Sawhney R, Naeim A. Physiologic aspects of aging: impact on cancer management and decision making, part II. Cancer J, 2005, 11:461-473.
- Wu D, Meydani SN. Age-associated changes in immune and inflammatory responses: impact of vitamin E intervention. J Leukoc Biol, 2008, 84(4):900-914.

- 26. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. Clin Interv Aging, 2006, 1(3):253-260.
- 27. Bălăşoiu M, Bălăşoiu AT, Mogoantă SŞ, Bărbălan A, Stepan AE, Ciurea RN, Alexandru DO, Enescu A, Mogoantă L. Serum and tumor microenvironment IL-8 values in different stages of colorectal cancer. Romanian Journal of Morphology and Embryology, 2014, 55(2 Suppl):575-578.
- Weinberger B, Herndler-Brandstetter D, Schwanninger A, et al. Biology of immune responses to vaccines in elderly persons. Clin Infect Dis, 2008, 46(7):1078-1084.
- Kumar R, Burns EA. Age-related decline in immunity: implications for vaccine responsiveness. Expert Rev Vaccines, 2008, 7(4):467-479.
- 30. Langen RC, Korn SH, Wouters EF. ROS in the local and systemic pathogenesis of COPD. Free Radic Biol Med, 2003, 35(3):226-235.
- 31. Pagano F, Bassi P, Galetti TP, Meneghini A, Milani C, Artibani W, Garbeglio A. Results of contemporary radical cystectomy for invasive bladder cancer: a clinicopathological study with an emphasis on the inadequacy of the tumor, nodes and metastases classification. J Urol, 1991, 145(1):45-50.
- Prout GR Jr, Barton BA, Griffin PP, Friedell GH. Treated history of noninvasive grade 1 transitional cell carcinoma. The National Bladder Cancer Group. J Urol, 1992, 148(5):1413-1419.
- Madersbacher S, Hochreiter W, Burkhard F, Thalmann GN, Danuser H, Markwalder R, Studer UE. Radical cystectomy for bladder cancer today-a homogeneous series without neoadjuvanttherapy. J Clin Oncol, 2003, 21(4):690-696.
- 34. Shariat SF, Karakiewicz PI, Palapattu GS, Lotan Y, Rogers CG, Amiel GE, Vazina A, Gupta A, Bastian PJ, Sagalowsky AI, Schoenberg MP, Lerner SP. Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporaryseries from the Bladder Cancer Research Consortium. J Urol, 2006, 176(6 Pt 1):2414-2422.

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