

## Stage of bladder cancer in Central Europe – Polish perspective

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Mortality rate from bladder cancer in Europe is the highest in its Central Region. This study is an attempt to find underlying factors by proper characterisation of large cohort of Polish patients with bladder cancer.

This is a multicentre study enrolling 1360 consecutive patients diagnosed with primary urothelial carcinoma of the bladder in years 2012-2013 in Poland. All patients underwent transurethral resection of the bladder tumor. Data on staging and grading of all cancers were collected, as well as several demographic and clinical factors were tested for the association with muscle invasiveness of the cancer.

Mean age of the cohort was 69.6 years, male to female ratio was 3:1. Bladder cancer stage Ta, T1 and muscle-invasive (MIBC) was diagnosed in 533 (39.2%), 516 (37.9%) and 296 (21.8%) patients, respectively. Patients with MIBC were older (73 vs. 68 years,  $p < 0.05$ ), had lower body mass index (25.4 vs. 26.5 kg/m<sup>2</sup>,  $p < 0.05$ ), lower haemoglobin concentration (12.2 vs. 13.4 mg/l,  $p < 0.05$ ), longer history of haematuria (86.2 vs. 74.4 days) and longer time interval from first symptom to diagnosis (118.0 vs. 88.2 days), compared to patients with Ta and T1 tumors.

High mortality rate from bladder cancer in Central Europe can result from very high incidence of high-risk T1 tumors and high prevalence of prognostic factors of poor survival.

*Key words: bladder cancer, diagnosis, cancer stage, prognosis, Central Europe*

Bladder cancer is the most common malignancy occurring within the urinary tract. According to GLOBOCAN data, the incidence in Central and Eastern Europe is 14.6 and 2.6 new cases per 100000 inhabitants per year among men and women, respectively [1]. Despite the progress in treatment protocols, mortality from bladder cancer in Poland, Romania and Bulgaria did not decline over last 15 years [2]. Simultaneously, the mortality rate from bladder cancer in Poland, Spain, Latvia and Lithuania are the highest in Europe, as reported by Bosetti et al. in European analysis [2]. The spectrum of the disease covers cases of non muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). They differ in terms of biology, potential of progression, prognosis and treatment

modes. Due to these facts, MIBC requires special attention among clinicians. Recently Dybowski et al. outlined relatively poor survival after radical cystectomy in Poland [3]. This leads to open discussion about factors that can be modified in order to improve treatment outcomes in Central Europe. Probably the first rational step in the process is proper characterisation of bladder cancer cases in the region. Unfortunately, detailed and reliable epidemiological data regarding Central Europe, including Poland are not available. While trends in incidence, potential exposure to risk factors of carcinogenesis in urothelium, lifestyle and health systems may vary between regions, the extrapolation of Western European data into Central Europe could be confusing. The aim of this study was to present

oncological characteristics of large cohort of Polish patients with primary urothelial carcinoma of the bladder.

## Patients and methods

**Material.** All patients with primary urothelial carcinoma of the bladder diagnosed in years 2012-2013 in 14 Polish urological centers participating in the project were retrospectively enrolled into the study. All patients underwent transurethral resection of the bladder tumor (TURBT). No exclusion criteria were adopted.

**Methods.** Data on staging and grading of all cancers were collected. Additionally several demographic and clinical factors were tested for the association with muscle invasiveness of the cancer. Microscopic examinations of TURBT specimens were performed by dedicated uropathologists. No central or local reviewing of pathological reports was done. For staging 2009 TNM classification was implemented. For grading 1973 WHO and / or 2004 WHO/ISUP classification was used depending on pathologist's personal experience and preference. For 1973 WHO classification no exact criteria of grading were established in this study, while for 2004 WHO/ISUP classification the criteria proposed by International Society of Urological Pathology were respected.

**Statistical analysis.** Statistical calculations were done with Statistica 12.0 Software (StatSoft, USA). Results are presented as absolute values in case of parametric variables and mean or median values in case of non-parametric variables. Normal distribution was confirmed by the Shapiro-Wilk test, while the equality of variances was assessed using Levene's test. For comparison of quantitative variables between study subgroups (men vs. women or NMIBC patients vs. MIBC patients) unpaired t-test or U-Mann Whitney test were adopted. In case of qualitative variables, Chi2 test with McNemar formula was implemented. Differences were considered statistically significant when p value was <0.05.

## Results

1360 patients were diagnosed with bladder cancer within the analysed time frame. Basic data on study population is presented in table 1.

**Table 1. Basic characteristics of the study group**

Number of patients	Total	1360
	Men	75.4% (n=1025)
	Women	24.6% (n=335)
Age of patients (mean value)	Total	69.6 ± 11.3years
	Men	69.6 ± 11.1 years
	Women	69.8 ± 11.9 years
History of cigarette smoking *	Total	57.0% (604/1059 pts)
	Men	60.2% (483/802 pts)
	Women	47.1% (121/257 pts)
History of haematuria *	Total	77.8% (1021/1312 pts)
	Men	76.1% (245/322 pts)
	Women	78.4% (776/990 pts)
Time from first symptom to TUR * (median value)	Total	30 ± 181days (in 1012 pts)
	Men	30 ± 173 days (in 756 pts)
	Women	30 ± 204 days (in 256 pts)

Results are presented as absolute or mean or median values or percentage.

\* Reliable data was not available in all patients, given numbers present actual number of patients in whom appropriate information was collected.

Staging and grading of diagnosed cancers is presented in table 2. MIBC was diagnosed in 21.8% of cases. Patients with MIBC were significantly older and more frequently they reported incidences of haematuria comparing to patients with NMIBC. Advanced stage of the disease was associated with significantly lower BMI values and significantly lower haemoglobin concentrations. Also significantly longer time interval between first symptom and TUR was observed in MIBC group. Table 3 presents the comparison of patients diagnosed with NMIBC and MIBC.

## Discussion

The data on European patients with bladder cancer come mainly from Western European countries. With latest papers presenting delay in radical cystectomy in over 20% of Central European patients and a 5-year survival following the surgery of 31.7% [3-5], one can think about differences in culture, lifestyle and health policy between the region of Central and Western Europe. As a consequence, we decided to perform

**Table 2. Oncological characteristics of the study group**

T stage	Total number	Total %	G1	G2	G3	1973 WHO classification used	PUNLMP	LG	HG	2004 WHO/ISUP classification used
a	533	39.2%	208	186	6	75.0%	50	267	24	64.0%
1	516	37.9%	89	246	60	76.6%	13	191	143	67.2%
2 or higher	296	21.8%	2	76	155	78.7%	-	15	168	61.8%
Cis alone	2	0.1%								
x	13	1.0%	1	2	9	76.9%	-	1	4	38.5%
Total	1360	100%	300	510	230	76.5%	63	474	339	64.4%

Ta – Non-invasive papillary carcinoma; T1 – Tumor invades subepithelial connective tissue; T2 – Tumor invades muscle; Cis – carcinoma *in situ*, 'flat tumor'; x – Primary tumor cannot be assessed; G1-3 – grade 1-3; WHO – World Health Organisation grading classification; PUNLMP – papillaryurothelial neoplasm of low malignant potential; LG – low grade cancer, HG – high grade cancer; ISUP – International Society of Urological Pathology grading classification

**Table 3. Comparison of patients diagnosed with NMIBC and MIBC**

Parameter	NMIBC	MIBC	P value
Number of patients	1051	296	
Median age	68 ± 11.6 yrs	73 ± 9.9 yrs	0.000
Percentage of women	24.7% (n=260)	24.0% (n=71)	>0.05
Height	170.2 ± 7.8cm	170.2 ± 7.9 cm	>0.05
BMI	26.5 ± 4.2kg/m <sup>2</sup>	25.4 ± 4.0 kg/m <sup>2</sup>	0.000
Haemoglobin serum concentration	13.4 ± 2.0 mg/l	12.2 ± 2.4 mg/l	0.000
History of haematuria	74.4% (n=760/1022)	86.2% (n=250/290)	0.000
History of nicotine use	55.4% (n=456/824)	63.0% (n=145/230)	>0.05
Mean time from first symptom to TUR	88.2 ± 182.5 days	118.0 ± 179.7 days	0.03

a study aimed at basic clinical characterisation of Polish patients diagnosed with bladder cancer with the special focus on oncological data.

The main finding of our study is that the stage of primary bladder cancer in Poland differs from literature data. As the incidence of MIBC is similar to European data, the percentage of T1 tumors in the group of NMIBC patients is very high (table 2). The incidence of T1 tumors among patients with primary NMIBC in large contemporary international series is reported to be 36.8–39.0% [6, 7]. In our study, in the group of 1049 NMIBC cases, T1 tumors are noticed in 49.2% and hence these patients are qualified as high-risk patients based only on this sole criterion [8]. While the vast majority of these cases are also high-grade tumors, based on EORTC tables we can calculate the 5-year risk of progression of 17% [9]. What is more, according to European Association of Urology guidelines all these patients should be submitted to restaging TURBT with the risk of upstaging to MIBC of 4–25% [8]. These numbers may be even higher, as Fritsche et al. noticed the presence of MIBC after radical cystectomy in 49.7% of 1136 patients submitted to surgery due to T1 tumors [10].

In our cohort low grade or G1 and G2 tumors are most commonly observed. G3 and high-grade cancers consist 8.3% and 24.3% of NMIBC cases, respectively (table 2). In the series of 1400 patients published by van der Meijden the G3 tumors were diagnosed in 11.9% of patients, however, agreement of local and review pathologist on grade in G3 tumors was observed only in 61.3% [11]. In more recent analysis considering 2004 WHO/ISUP classification and covering 327 patients, Schned et al. diagnosed high-grade tumors in 22.6% of cases with the agreement rate between pathologists of 83% [12]. The problem of discrepancies between pathologists opinion on tumor grade is both well known and unsolved, recently confirmed also in representative cohort of Polish population [13]. Simultaneously, the differences between the incidence of G3 and high-grade tumors outlines the core differences between 1973 WHO and 2004 WHO/ISUP classifications. May et al. found that high-grade tumors are diagnosed even five times more frequently than G3 tumors [14]. Due to this fact, we assessed also the preferences of pathologists in selecting the grading

classification. While 1973 WHO classification is more popular than 2004 WHO/ISUP one, in the majority of cases grading is presented according to both classifications (table 2). As the evidence of the better prognostic value of 2004 WHO/ISUP classification is still lacking, only 51% pathologists use it in clinical practice [15], while European Association of Urology experts advise to use both 1973 WHO and 2004 WHO/ISUP classifications [8].

In present study the overall incidence of tobacco use is 57%, significantly lower among women than among men (table 1). Two facts are worth mentioning at this point. First, the cigarette-related risk of bladder cancer development seems to have increasing trend in last years and this phenomenon can be explained by the decrease in nicotine concentration associated with the increase in carcinogens concentration in cigarettes [16]. Nowadays, the risk of bladder cancer is 2.0 to 2.6-fold higher in former smokers and 3.8 to 5.5-fold higher in current smokers, when compared to never smokers [17–19]. Second, some authors outline particularly increased risk of bladder cancer development in female smokers. Freedman et al. reported 4.7-fold and 3.9-fold higher risk in female and male current smokers, respectively [17].

In our cohort MIBC is diagnosed in significantly older patients than NMIBC. Prout et al. first highlighted that 75-year old and older patients with MIBC are less likely to undergo radical cystectomy when compared to younger patients, independently of physical status [20]. However, the general patient condition, including nutrition status and comorbidities seem to be more important prognostic factors than age alone [21–23]. Simultaneously, data on the influence of age on survival after radical cystectomy are not consistent [24–29], although there is no doubt that the risk of severe surgical complications increases with patient age [24, 30, 31]. On the other hand, renal function and performance status diminish with increasing age and progression of oncological disease, what reduces the chance of qualification for cisplatin-based chemotherapy in advanced or metastatic disease.

Additionally, we observe longer time interval between the first symptom (mainly haematuria) and TUR in MIBC versus NMIBC patients. There is no data on the influence of TUR timing on treatment outcomes. However, one can assume, that

delay in TUR lead to delay in radical cystectomy in patients with operable MIBC and fit for surgery. As a consequence, shorter survival can be expected [32-36].

We also report lower haemoglobin concentration and lower body mass index (BMI) in MIBC versus NMIBC group. Both facts can be associated with increased cancer-related catabolism. In bladder cancer patients low haemoglobin concentration can be attributed to anaemia of chronic disease, commonly seen in malignancy, as well as it can result from macro- or microhaematuria. Two recent research groups have independently reported that low haemoglobin concentration (defined as lower than 10.5 or 12.6 g/dL) is associated with shorter survival after radical cystectomy, especially in patients aged over 75 years [24, 37]. The impact of BMI on the risk of carcinogenesis in bladder is controversial. Population studies present conflicting results [38, 39]. It is well known that abnormal (low or high) BMI increases the risk of surgical complications of radical cystectomy [30, 40-42]. However, previously published studies on the obesity did not find any association between high BMI and survival after radical cystectomy, nor increased costs [40, 43, 44]. On the other hand, the malnutrition, which can be indirectly assessed also by low BMI, significantly decreases the survival after radical cystectomy [45].

Our study is not free of limitations. The most important is a bias related to the retrospective nature of the study. Second, slides were not re-assessed, so the staging and grading was based on subjective opinion of experienced but single pathologist. The risk of misdiagnosis is then considerable as discussed before. Finally, while the study presents representative population, it is not a national database. Every year over 6500 cases of bladder cancer are reported to Polish National Cancer Registry [46]. However, this number covers primary, as well as recurrent tumors, while the exact number of new cases is unfortunately not known.

## Conclusions

Basic demographic data of Polish patients with primary bladder cancer does not differ from Western European population. Also the NMIBC to MIBC rate is comparable. However, the incidence of high-risk NMIBC is significantly higher. Additionally, in the group of MIBC several prognostic factors of poor survival are present at the time of initial diagnosis in substantial portion of patients. These facts can independently and directly lead to worse treatment outcomes in the region of Central Europe.

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