



# Age and Sex Do Not Affect First Year Recurrence in Patients with Non-Muscle Invasive Bladder Cancer

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## Abstract

**Introduction:** Although demographic heterogeneity in the management of patients with non-muscle invasive bladder tumor (NMIBT) is an important factor, there are only minimal evidence-based recommendations that adjust for patient age and gender. The relationship and impact of age and gender on the recurrence in NBIMT is poorly investigated and understood.

**Aim:** The aim of the study was to evaluate the impact of age and sex on the recurrence of non-muscle invasive bladder cancer.

**Materials and methods:** Patients treated with transurethral resection (TUR) of primary NMIBT were included in the study. Risk calculation was made according to the European Organization for Research and Treatment of Cancer (EORTC) risk tables. Prognostic factors for predicting tumor recurrence up to 5 years including age and sex were analyzed. The Mann-Whitney U test was used for comparison of non-parametric variables in independent groups. Kaplan-Meier method, with log rank (Mantel-Cox) analyses applied for comparison of mean duration of remission by sex and age, was used to calculate mean duration of remission.

**Results:** A total of 81 patients, 68 males (mean age 59.03 years) and 13 females (mean age 58.13 years) were eligible for final analysis. Mean survival time of patients <60 years old and older was 17.3±2.1 months (13.2–21.3) and 17.9±2.8 months (12.4–23.4), respectively ( $p=0.6$ ). Mean survival time was 17.3±2.1 months for females and 15.4±2.1 months for males ( $p=0.08$ ). However, 1-year tumor-free rate of female patients (53.8%) was not much different from that of males (31%) ( $p=0.11$ ). Although considerable difference was observed between recurrence rates of patients according to sex, it failed to reach statistical significance.

**Conclusions:** The results of the present study suggest that the recurrence of NMIBT is not associated with age or gender.

## Keywords

age, bladder tumor, recurrence, sex, transurethral resection

## INTRODUCTION

Bladder tumor is the 10th most common cancer in the world.<sup>1</sup> World Health Organization estimated 549,000 new cases diagnosed in 2018, and new cases is projected to reach more than 670,000 by 2025.<sup>2</sup> Non-muscle invasive bladder tumor (NMIBT) has a high rate of recurrence

and progression and require frequent cystoscopy, which increases costs and hinders patient compliance. The high risk of recurrences is a cause of high costs which make NMIBT an expensive diseases to treat.<sup>3</sup> In addition, there may be unnecessarily frequent monitoring of low-risk patients and insufficient surveillance of high-risk patients.<sup>4</sup>

Most bladder cancers are transitional cell cancer and 70% of them are disease confined to the mucosa (stage Ta and Tis) or submucosa (stage T1).<sup>5</sup> This patient group is monitored via cystoscopy 2–3 times during the first year.<sup>6</sup> Due to high recurrence rates, intensive control strategies should be performed.<sup>7</sup> The European Organization for Research and Treatment of Cancer (EORTC) created short- and long-term risk tables for recurrence and progression of NMIBT.<sup>8</sup>

Several studies evaluated sex-specific discrepancies in the epidemiology, diagnosis, and clinical outcomes of most of non-gender specific cancers.<sup>9,10</sup> The genders may affect the incidence and severity of diseases.<sup>11</sup> It might be related to differences in carcinogenic exposures, routes of entry, enzymatic processing of environmental substances, and cellular and physiological responses.<sup>11</sup> A sex-related differences were observed in bladder cancer, with about 3-fold higher incidence in men compared to women.<sup>2</sup> Furthermore, Horstmann et al. reported that bladder cancer was diagnosed at a significantly younger age in men than in women (mean age: 62 vs. 67 years).<sup>12</sup>

## AIM

The aim of the study was to examine the impact of age and gender of patients on the recurrence of NMIBT.

## MATERIALS AND METHODS

This study included 81 patients with newly diagnosed NMIBC at the Department of Urology from January 2012 to December 2015. The 5-year follow-up data of 81 patients, 68 males and 13 female were analyzed in this study. The patients were included in the study if they met all the following criteria: presence of primary NMIBC; no previous history of TURBT or bladder intracavitary chemotherapy; had a complete and detailed clinical, pathological, follow-up data record. Patients were excluded if they had metastatic/secondary bladder cancer; patients with Tis stage; any incomplete clinical, pathological, or follow-up data. The medical records of the patients were reviewed retrospectively. The size of tumor was <3 cm and the stages of all tumors were Ta according to the 2017 TNM classification of urinary bladder cancer.<sup>13</sup> Associations between time to recurrence and sex and also age were examined. Follow-up cystoscopies were done every 3 months for the first 2 years, at 6-month intervals in the third year and once per year in the fourth and fifth years in all of the patients.

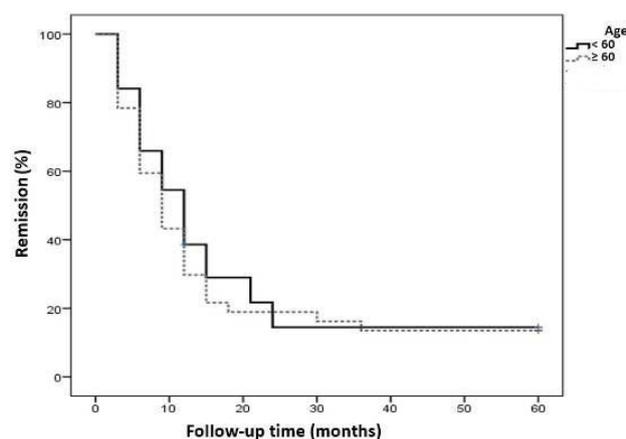
## Statistical analysis

Data were checked for suitability of normal distribution using the Shapiro-Wilk test and expressed as mean (SD) or median [interquartile range (IQR)] values when they did not show normal distribution or percentage for continuous

and categorical variables, respectively. The chi-square test was used for statistical comparisons of categorical data. The Mann-Whitney U test was used for comparison of non-parametric variables in independent groups. Mean duration of remission was calculated using the Kaplan-Meier method, with log rank (Mantel-Cox) analyses applied for comparison of mean duration of remission by sex and age. All analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA). For all statistical analyses,  $p < 0.05$  was considered significant.

## RESULTS

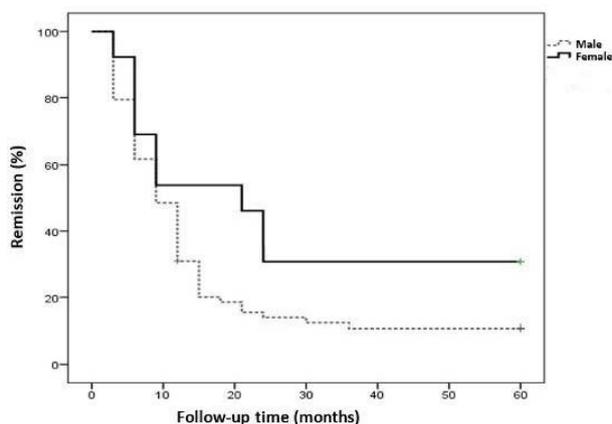
The 1-year tumor-free rate was 38.6% in patients <60 years and 29.7% in those  $\geq 60$  years. The 5-year tumor-free rates were 14.5% in patients <60 years and 13.5% in those  $\geq 60$  years. The mean survival time was  $17.3 \pm 2.1$  months (13.2–21.3) for patients <60 years and  $16.5 \pm 3.1$  months (10.5–22.4) for those  $\geq 60$  years. No statistically significant difference was identified in recurrence status according to age group ( $p = 0.531$ ) (Fig. 1).



**Figure 1.** Recurrence status of patients according to age.

The 1-year tumor-free rate was 53.8% for females and 31% for males ( $p = 0.11$ ). The 5-year tumor-free rate was 31% for females and 11% for males ( $p = 0.06$ ). Mean survival time was  $17.3 \pm 2.1$  months (13.2–21.3 months) for females and  $15.4 \pm 2.1$  months (11.4–19.4) for males (mean  $\pm$  standard error [95% CI]). Although there was a considerable difference between the recurrence statuses of patients by sex, it was not statistically significantly different ( $p = 0.08$ ) (Fig. 2).

According to the EORTC risk classification, there were 60 patients with a recurrence score of 0 and 21 with a score of 2. Those with 0 had 73.33% recurrence observed in the first year and 91.66% by the fifth year. Those with 2 had 71.42% recurrence observed in the first year and 95.24% by the fifth year. In three patients with tumor recurrence in the first year, tumor progression was observed.



**Figure 2.** Recurrence status of patients according to sex.

## DISCUSSION

The results of this study suggested that age and gender of patients was not associated with the recurrence of bladder cancer. Mean survival time of female and male patients was similar. One year tumor free rates of patients <60 and ≥60 years were not statistically significant.

Sylvester et al. created short- and long-term risk tables for recurrence and progression of NMIBT for the EORTC. In this study, patients with a recurrence score of 0 were considered the low-risk group and had predicted recurrence rates of 15.5% in the first year and 31% in the fifth year.<sup>8</sup> For those with a recurrence score of 0, 73.33% recurrence was observed in the first year, and 91.66% by the fifth year. Patients with a recurrence score of 2–4 (moderate risk group) had a predicted recurrence rate of 24% in the first year and 46% by the fifth year. In our study, patients with a recurrence score of 2 had 71.42% recurrence in the first year and 95.24% by the fifth year. A study that included 680 patients monitored for 5 years observed 71% recurrence in patients with low-grade urothelial carcinoma and 73% recurrence in those with high-grade carcinoma.<sup>14</sup> In our study, the low-risk patient group had a recurrence rate of 85%.

In 2014, the American Cancer Society Key Statistics for Bladder Cancer stated that it was the fourth most common cancer in males; however, it was less frequent in females.<sup>15</sup> This explains the higher prevalence of males in our patient group. Bladder cancer occurs most commonly in the elderly and 90% of people with this cancer are >55 years old. Mean age at diagnosis is 73 years old. Therefore, it may be important to study how recurrence may differ by age. Generally, the lifetime chance of developing bladder cancer in males is almost 1 in 27. For females, it is almost 1 in 89. In a previous study, being female was a prognostic factor for developing T1G3 bladder tumors.<sup>16</sup> In our study, the mean age of tumor identification was 59.03 years old for males and 58.13 years old for females. In other studies, the incidence of bladder cancer in males was reported to be four times higher than that of females.<sup>12</sup>

Globally, incidence rates standardized according to age (for every 100,000 people/year) are 9.0 for males and 2.2 for females.<sup>2</sup> The European Union age-standardized incidence rates are 19.1 for males and 4.0 for females. We found similar results in our study with rates of 84% for males and 16% for females. Nonetheless, although males had a higher recurrence rate, the difference was not significant.

Cost is a significant problem for surveillance of bladder tumors, with elderly patients often having problems complying with surveillance. In a previous study, younger patients demonstrated better compliance with surveillance protocols.<sup>17</sup> This would be useful for planning future studies involving patient surveillance success according to age.

The principal limitations of this study are related to its retrospective nature and the risk of selection bias. Another important limitation is the lack of data on several important determinants such as smoking history, performance status, and cardiopulmonary and renal function. Moreover, no patients underwent re-TURBT, immediate single instillation of chemotherapy postoperatively or any maintenance intravesical therapies, all of which may have improved the recurrence rates.

## CONCLUSIONS

The results of the present study suggest that recurrence of low-grade bladder tumors is not associated with age or gender.

## Ethics Committee Permission

Permission was granted by the local clinical research ethics committee. Decision No: 1779, of 12/04/2019.

## Conflict of Interest

The author reports no conflicts of interest. The author is responsible for the content and writing of the paper.

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# Возраст и пол не влияют на рецидив в первый год у пациентов с немышечно-инвазивным раком мочевого пузыря

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## Резюме

**Введение:** Несмотря на то, что демографическое разнообразие в ведении пациентов с немышечно-инвазивной опухолью мочевого пузыря (НИОМП), является важным фактором, существует несколько рекомендаций, основанных на доказательствах, которые относятся к возрасту и полу пациентов. Взаимосвязь и влияние возраста и пола на повторение НИОМП мало изучены и поняты.

**Цель:** Целью исследования было оценить влияние возраста и пола на рецидив немышечно-инвазивного рака мочевого пузыря.

**Материалы и методы:** В исследование были включены пациенты, получавшие трансуретральную резекцию (ТУР) первичного НИОМП. Расчёт риска производился согласно таблицам риска Европейской организации по исследованию и лечению рака (ЕОИЛР). Проанализированы прогностические факторы прогноза рецидива опухоли до 5 лет, включая возраст и пол. U-критерий Манна-Уитни использовался для сравнения непараметрических переменных в независимых группах. Для расчёта средней продолжительности ремиссии использовался метод Каплана-Мейера с логарифмически преобразованным утренним анализом (Mantel-Cox), применяемый для сравнения средней продолжительности ремиссии по полу и возрасту.

**Результаты:** Для окончательного анализа подходили 81 пациент, 68 мужчин (средний возраст 59.03 года) и 13 женщин (средний возраст 58.13 года). Медиана выживаемости пациентов в возрасте 60 лет и старше составила  $17.3 \pm 2.1$  месяца (13.2–21.3) и  $17.9 \pm 2.8$  месяца (12.4–23.4), соответственно ( $p=0.6$ ). Среднее время выживаемости составило  $17.3 \pm 2.1$  месяца для женщин и  $15.4 \pm 2.1$  месяца для мужчин ( $p=0.08$ ). Однако частота отсутствия опухоли в течение года у женщин (53.8%) не отличалась от таковой у мужчин (31%) ( $p=0.11$ ). Хотя наблюдалась значительная разница между частотой рецидивов пациентов по полу, исследование не смогло достичь статистической значимости.

**Заключение:** Результаты настоящего исследования показывают, что рецидив НИОМП не связан с возрастом или полом.

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## Ключевые слова

возраст, опухоль мочевого пузыря, рецидив, пол, трансуретральная резекция

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