Risk Factors Associated with Bladder Cancer – a Retrospective Study of 391 Radical Cystectomy Patients

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Abstract

Introduction and Objectives. Bladder cancer is one of the most common malignancies in Europe. Many risk factors for bladder cancer have been identify, with tobacco smoking and exposure to environmental and occupational carcinogens being the most important ones. The objective of this study was to identify the risk factors associated with the development of bladder cancer among patients that underwent radical cystectomy.

Materials and Methods. The study included 391 patients that underwent radical cystectomy from January 2017 to December 2018 in our center. According to their smoking status, patients were grouped into non-smokers (patients that didn't smoke any cigarette in the last 10 years), smokers (patients that did smoke in the last 6 months) and ex-smokers (patients that have more than 6 months and less than 10 years since they have quit smoking). Other risk factors analyzed were hereditary factors, history of external beam radiation therapy and exposure to occupational carcinogens.

Results. The median age of the patients was 69 years old with 308 men (78.77%) and 83 women (21.23%) included. 170 patients were classified as smokers (43.48%), while 131 patients were ex-smokers (33.50%) and 90 patients were non-smokers (23.02%). The prevalence of occupational carcinogens exposure was 10.74%. Hereditary risk factors associated with the development of bladder cancer were identified in 17 patients (4.35%). External beam radiation therapy was identified as a risk factor in 27 patients (6.90%). Current smokers were more frequently diagnosed with T3b and T4a, while N1 and N2 lymph node stages were more often diagnosed among smokers and ex-smokers.

Conclusions. Bladder cancer is a common malignancy that has a big impact on health systems and will continue to be so, due to the high prevalence of its most important risk factor, tobacco smoking. In our study, smoking was the most important risk factor, with a prevalence of 77% among patients that were classified as current smokers and ex-smokers. Prevention of smoking needs to be highlighted and cessation programs must be developed in order to lower the incidence of bladder cancer. More measures for increasing safety at work must be taken in order to decrease the exposure to occupational carcinogens.

Key-words: bladder cancer, smoking, occupational exposure, environmental exposure, carcinogens, external beam radiation therapy.

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Introduction and Objectives

Bladder cancer is the fourth most common malignancy in Europe in 2018 with an increasing incidence of 3.924 new cases in Romania, estimated by The International Agency for Research on Cancer. In Europe, males are 4 to 5 times more likely to develop bladder cancer than females, while the mortality rate is 3 to 4 times higher among men comparing to women. [1]

Bladder cancer can be caused by different genetic mutations and by risk factors including tobacco smoking, radiation therapy and occupational or environmental exposure to carcinogens. Smoking is the most important risk factor for developing bladder cancer. Tobacco contains different carcinogenic agents such as aromatic amines that damage DNA. A meta-analysis published in 2016 by Cumberbatch et al. found a relative risk of 3.47 for current smokers and a relative risk of 2.04 for ex-smokers to develop bladder cancer, comparing to non-smokers. [2] Current smoking status is an independent predictor of disease recurrence, cancer-specific mortality and overall survival for patients with bladder cancer. Ex-smokers have an increased risk of bladder cancer recurrence and cancer-specific mortality even 15 years after they have quit cigarette smoking, probably because DNA damage is irreversible and leads to permanent genetic alterations. [3]

Occupational carcinogen exposure can be identified in 5-6% of the bladder cancer cases. Many agents have been identified to play a role as an occupational bladder carcinogen – toluene, metal fluids, diesel exhaust, poly-aromatic hydrocarbons, 4,4'-methylenebis-2-chloroaniline, 2napthylamine, 4-aminobiphenyl, tetrachloroethylene and agents resulting from the combustion and pyrolysis of natural gas. Despite the improvements made in work safety, an increased incidence of bladder cancer was observed in tobacco workers (relative risk – 1.72), dye workers (relative risk – 1.58), chimney sweeps (relative risk – 1.53), nurses (relative risk – 1.49), rubber workers (relative risk – 1.49), waiters (relative risk – 1.43), aluminium workers (relative risk – 1.41), beverage workers (relative risk – 1.35), hairdressers (relative risk – 1.32), printers (relative risk – 1.23), seamen (relative risk – 1.23), oil and petroleum workers (relative risk – 1.20), shoe and leather workers (relative risk – 1.20), plumbers (relative risk – 1.20), iron and metal ware workers (relative risk – 1.18). [4]

Inherited genetic factors can also cause bladder cancer. Slow acetylation of NAT2 and GSTM1 null genotypes can play a role in bladder cancer carcinogenesis by increasing susceptibility to aromatic amines, tobacco smoke or occupational carcinogens. First degree family members of patients with bladder cancer have an increased risk for developing bladder cancer themselves – up to two-fold. [5] Regarding to gender, men have a higher incidence of bladder cancer comparing to women, up to five-fold, but better cancer specific survival, better disease-free and better overall survivor after radical cystectomy. [6]

Exposure to ionizing radiation is associated with an increased risk for bladder cancer. Patients with external beam radiotherapy for prostate cancer or cervical cancer can develop bladder cancer with a latency period of 10 to 30 years and a relative risk of 1.63 in men and 1.74 in women. [7] Recurrent urinary tract infection is also a risk factor for the development of bladder cancer – squamous cell carcinoma, in account of the chronic inflammation of the urothelium that promotes the keratinizing squamous metaplasia. Patients with a history of at least three urinary tract infections have a relative risk of 5.7 for developing bladder cancer. [8] Schistosomiasis, a chronic cystitis based on recurrent infection caused by a trematode that is endemic in northern Africa, is also a risk factor for bladder cancer. The long-term usage of cyclophosphamide, an alkylating agent used in lymphoma and leukemia cases, can increase the incidence of bladder cancer. [5]

The objective of this study is to determine the prevalence of risk factors associated with the development of bladder cancer among patients that underwent radical cystectomy in Fundeni Clinical Institute. Moreover, since tobacco smoking is the most important risk factor of bladder cancer, we are interested in studying the link between the smoking status of the patients and the pathological results of radical cystectomy.

Materials and Methods

The medical records of 391 patients that underwent radical cystectomy from January 2017 to December 2018 in Fundeni Clinical Institute have been retrospectively studied. Risk factors for the development of bladder cancer were identified in the patient's medical record. According to their smoking status, patients were grouped into non-smokers (patients that didn't smoke any cigarette in the last 10 years), smokers (patients that did smoke in the last 6 months) and ex-smokers (patients that have more than 6 months and less than 10 years since they have quit smoking). Other risk factors that we could identify were hereditary factors (patients with first degree family members diagnosed with bladder cancer), history of external beam radiation

therapy and exposure to occupational carcinogens. The smoking status was correlated with the pathological findings (tumor invasion, lymph node staging and tumor grade) in order to analyze the effect smoking has on patients with bladder cancer.

Results

The study included 308 males (78.77%) and 83 females (21.23%), while the median age of the studied patients was 69 years old. Tobacco smoking was identified to be a risk factor for the development of bladder cancer in a total of 301 patients out of 391 (76.98%). 170 of these patients were classified as smokers (43.48%), while 131 patients were ex-smokers (33.50%). The percentage of non-smoker patients that underwent radical cystectomy was 23.02%, while the prevalence of occupational carcinogens exposure was 10.74%. Hereditary risk factors associated with the development of bladder cancer were identified in 17 patients (4.35%) that had first degree relatives diagnosed with bladder cancer. External beam radiation therapy was identified as a risk factor in 27 patients (6.90%) including 18 women and 9 men.

Two different risk factors were identified in 33 patients including 18 patients (smokers or ex-smokers) that were exposed to occupational carcinogens, 9 patients (smokers or ex-smokers) that had a history of external beam radiation therapy, 5 patients (smokers or ex-smokers) with first degree family members diagnosed with bladder cancer and one patient with hereditary risk factor that had been exposed to occupational carcinogens. Two patients had three different risk factors identified – both of them were ex-smokers that were exposed to occupational carcinogens and also had a history of external beam radiation therapy. Finally, 41 patients that underwent radical cystectomy didn't have any identifiable risk factor.

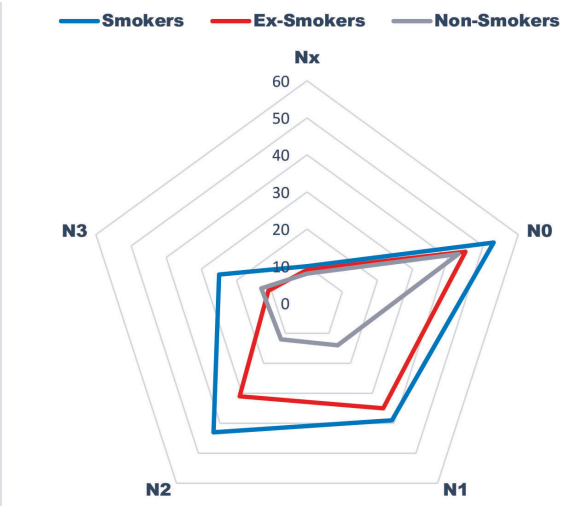


Figure 2.
Distribution of lymph node staging according to smoking status

Since smoking was the most important risk factor identified in our study, in order to obtain significant results, we correlated the pathological reports with the smoking status of every patient, as shown in Figure 1, Figure 2 and Figure 3.

Regarding tumor invasion, there were significantly more smokers diagnosed with T3b and T4a bladder cancer, comparing to ex-smokers or non-smokers, while N1 and N2 staging was significantly more often diagnosed among smokers and ex-smokers than among non-smokers (N1 – 39 smokers, 35 ex-smokers and 14 non-smokers; N2 – 43 smokers, 31 ex-smokers and 12 non-smokers). High-grade bladder cancer was diagnosed in 80.31% of the patients and low-grade bladder cancer was responsible for 19.69% of the cases that underwent radical cystectomy, while significantly more smokers and ex-smokers developed high-grade disease.

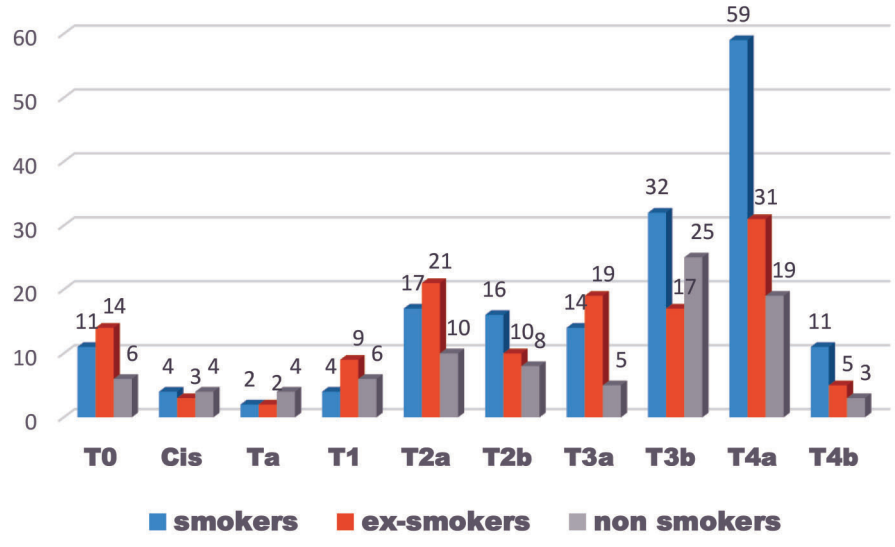


Figure 1.
Distribution of tumor invasion according to smoking status

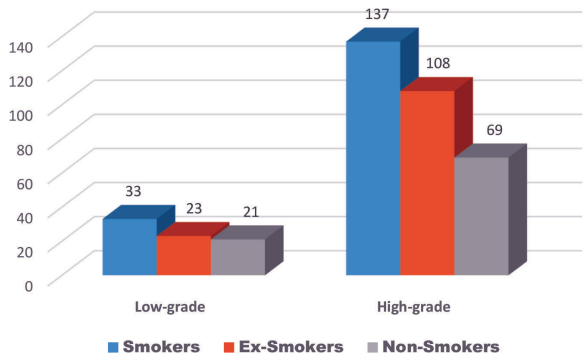


Figure 3.
Distribution of tumor grade according to smoking status

Discussions

Since one of the inclusion criteria of this study was that the patients had to undergo radical cystectomy, our results differ from other studies that also include non-muscle-invasive bladder cancer patients treated with TUR-BT. We expected to identify risk factors with higher prevalence comparing to existing studies. Our findings regarding the patient's smoking status were similar to the ones from a prospective study published in 2012 by Ros et al. which included 421 high grade bladder cancer patients. [9] The same study also found that a greater percentage of patients were exposed to environmental and occupational carcinogens than we did.

Due to non-randomized and retrospective nature of our study, patients may be susceptible to selection bias. Prospective studies that include a large number of patients with a long period of follow-up are required in order to confirm our results. The assessment of the number of cigarettes per day, the age at first exposure and the period of smoking are required in order to obtain statistically significant results. Regarding the exposure to occupational carcinogens, it is important to evaluate the actual period of exposure in order to determine the risk to which the worker is exposed, although this risk has been reduced by taking measures of work-safety in the past years. Molecular profiling of bladder cancer patients can provide us evidence about the genetic pathway of this type of cancer and can lead us to the discovery of new biomarkers.

Regarding pathological findings, all patients with non-muscle-invasive bladder cancer diagnosed on the cystectomy specimen, previously had a TUR-BT sample with clear recommendation for radical cystectomy. For patients with T0 cystectomy result, the TUR-BT pathological finding was considered to establish tumor grade. Unfortunately, 27 patients (10 smokers, 9 ex-smokers and 8 non-smokers) didn't have lymph node dissection, so the pathological report returned Nx. In these cases, the reasons for not doing lymph node dissection were the current status on the patient and his comorbidities and the palliative role of the surgery (in most cases, only for hemostatic purposes). Regarding external beam radiation therapy, 18 out of 83 women (21.68%) that were included in this study had a history of exposure to radiation.

Conclusions

Bladder cancer is a common malignancy that has a big impact on health systems and will continue to be so, due to the high prevalence of its most important risk factor, tobacco smoking. Prevention of smoking needs to be highlighted and cessation programs must be developed in order to lower the incidence of bladder cancer. Smoking cessation is associated with lower risk of development of bladder cancer, lower risk to progress to muscle invasive bladder cancer, lower mortality and lower risk for the patient to underwent radical cystectomy.

Exposure to occupational carcinogens was the second most important risk factor identified in our study. Unfortunately, many industrial workers still have a high risk of developing bladder cancer despite the improvements made in work safety in the last years.

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