Evaluation of secondary cancers, synchronous and metachronous with bladder cancer

Seyed Jalal Eshagh Hoseini1, Mohammad Heidari2, Hassan Fatemi Manesh3

DOI. 10.21931/RB/2022.07.01.6

Abstract: The number of bladder cancer survivors worldwide is increasing due to the advancement of diagnostic methods and bladder cancer treatment. Besides, bladder cancer is the sixth most common cancer in Iran. Nowadays, many secondary cancers have been proven with bladder cancer. This study focused on synchronous and metachronous cancers with bladder cancer. This study was performed retrospectively. A total of 276 patients with a definitive diagnosis of bladder cancer were included in the study. Tumors were diagnosed using ultrasound and cystoscopy. Out of 276 patients with bladder tumor, 240 underwent resection, 25 underwent radical cystectomy, and 31 underwent chemotherapy in addition to resection. The mean age of patients was 65±3.9 years. Among the patients, 184 were male (67%), and 92 were female (33%). Smoking was the most common known risk factor. There were 165 smokers, 135 of whom were male and 30 female. Sixty-nine patients had no known risk factor (P <0.05). Gastric cancer was the most common secondary cancer with bladder cancer in all individuals (5.7%). Prostate cancer (20%) in men and cervical cancer (11.9%) in women was the most common secondary cancer simultaneous with bladder cancer. Given the importance of SPC as a cause of cancer death, early detection and screening of primary cancer survivors will increase patients’ life expectancy and quality of life.

Key words: Secondary cancers, synchronous, metachronous, bladder cancer.

Introduction

Bladder cancer is the most common malignancy of the urinary system and the 11th most common cancer in people. The prevalence of this cancer is increasing in different countries of the world. This cancer’s mortality rate and incidence vary in different countries and regions. This difference depends on epidemiological data, social, cultural, and economic characteristics1-2. Bladder cancer is the sixth most common cancer in Iran. The prevalence of this cancer in Iran’s population is 33.2 patients per 100,000 people3. Statistics indicate that this cancer has an increasing prevalence in Iran4 and registers more than 70,000 new cases and 30,000 deaths annually5. In general, 7.04% of cancers in Iran are associated with bladder cancer6. Bladder cancer’s leading risk factor is smoking, accounting for 50-65% of all cases. Occupational or environmental toxins also play a significant role in causing this disease. In general, the risk factors for bladder cancer can be classified into three subtypes: genetic and molecular abnormalities, chemical or environmental exposure, and chronic irritation.

The bladder is an empty organ that stores urine in the lower abdomen. The urothelial cells of the bladder’s lining are exposed to mutagenic substances secreted by the kidneys. These substances cause metaplasia and dysplasia changes and eventually bladder cancer. Most bladder tumors are transitional. In studies, bladder tumors have been synchronous and metachronous with other tumors. 90% of bladder cancers are diagnosed at 55 and above, and the disease is four times more common in men than women7-10. In general, the treatment approach in bladder cancer is determined after determining the type of cancerous tissue. Treatments include bladder tumor resection, radical cystectomy, and complementary therapies such as single-dose intravesical immunotherapy with bacillus Calmette-Guérin (BCG) or intravesical chemotherapy11. This study aimed to evaluate secondary tumors synchronous and metachronous with bladder tumors that, if diagnosed and treated in time, the disease will have a better prognosis, and the person will achieve better recovery.

Materials and methods

Ethics

This study was performed in the Center of Shohada Ashayer Khorramabad and Kamkar-Arabiia Hospital in Qom from 2006 to 2019. Written consent was obtained from all participants in the study. The personal information of patients included in the study was kept secret.

Study population and inclusion and exclusion criteria

In this study, 276 patients were included in the study. The inclusion criteria were those patients with significant bladder tumors. All types of bladder tumors were considered. These patients then underwent bladder tumor resection surgery based on a specialist diagnosis or, if necessary, radical cystec-
tomy or additional treatments were considered for them. Suspected patients to bladder cancer, which were referred to the hospital for cystoscopy and had consented to participate in the study were included in this survey. Patients without bladder tumors and those who don’t have access to a definitive diagnosis were excluded from the survey.

**Tumors diagnosis**

Tumors were diagnosed using ultrasound and cystoscopy. Ultrasound was carried out with GE Voluson 730 using a convex probe with 5.3 Hz for all patients. A single individual carried out all ultrasounds. Afterward, the patients underwent cystoscopy conducted by a urologist who was not aware of the patients’ ultrasound results. Afterward, tissue samples were prepared and sent to a pathology laboratory for pathological examinations. Olympus flexible fiberoptic cystourethroscopy was used for cystoscopy diagnosis of bladder tumors.

**Study procedure**

This study was performed retrospectively. The patients’ information in the study was evaluated at intervals of about one year and five years after the diagnosis of bladder tumor in reading files, telephone calls, self-reports, and door-to-door visits for underlying diseases and secondary cancers. In case of the patient’s presence and declaration of secondary cancer, the inclusion criteria were pathology reports, biopsy, endoscopy, and cancer-appropriate imaging in their medical records in the hospital. The subjects’ underlying disease information in the study was recorded as a reading of hospital information.

**Statistical analysis**

According to the chi-square test, all data were then analyzed using SPSS software (version 22). P-value <0.05 was considered a significant level.

**Results**

**Demographic characters**

Out of 276 patients with bladder tumor, 240 underwent resection, 25 underwent radical cystectomy, and 31 underwent chemotherapy in addition to resection. The mean age of patients was 65±3.9 (69 years). The youngest was 24 years old, and the oldest was 105 years old. Among the patients, 184 were male (67%), and 92 were female (33%). Men’s ratio to women was 2, and men 61-80 years old had the highest prevalence (P <0.05). Smoking was the most common known risk factor. There were 165 smokers, 135 of whom were male and 30 female. Sixty-nine patients had no known risk factor (P <0.05).

**Bladder tumors frequency**

Table 1 shows the frequency of bladder tumors amongst included patients. Findings showed that Transitional cell cancer (TCC) was the most frequently detected tumor amongst studied samples (88.60%) (P <0.05). However, adenocarcinoma was the less frequently detected tumor.

**Job frequency**

Table 2 shows the job frequency of included patients. Teachers (26.44%), farmers (23.18%), and workers (17.75%) were the most frequently determined jobs amongst the study population.

**Age distribution**

Table 3 shows the age distribution of examined patients. The majority of patients (30.79%) had 61-80 years old. Frequency of 0-30 and 101< years old patients were 3.26% and 8.33%, respectively.

**Frequency of underlying diseases**

Table 4 shows the frequency of underlying diseases amongst the studied patients. The most commonly identified underlying diseases amongst the studied patients were skeletal (35.14%), diabetes (18.47%), blood pressure (14.85%), and digestive (14.49%). Only 1.81% of examined patients had thyroid disorders. Additionally, only 2.53% of patients had pulmonary disease.

**Other cancer distribution**

Table 5 shows the frequency of other cancer types amongst the studied patients. In clinical, self-report and confirmed pathology examination, synchronous tumors, five years and if alive ten years after bladder tumor, diverse cancers were obtained. The most frequently detected cancer types were prostate (13.40%), stomach (5.79%), colon (4.34%), and cervix (3.98%). 63.40% of patients had no other cancers 5 years after the bladder tumor. No testicular tumor was clinically observed in the urogenital tract. Laryngeal and pancreatic tumors were also not observed in this study.

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Distribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transitional cell cancer (TCC)</td>
<td>244 (88.40)</td>
</tr>
<tr>
<td>Squamous cell carcinoma (SCC)</td>
<td>21 (7.60)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>5 (1.81)</td>
</tr>
<tr>
<td>Mix</td>
<td>6 (2.17)</td>
</tr>
<tr>
<td>Total</td>
<td>276</td>
</tr>
</tbody>
</table>

Table 1. Frequency of bladder tumors amongst included patients.
Discussion

Despite high advances in the medical sciences\textsuperscript{19-24}, some diseases remain health-threatening\textsuperscript{25-30}. The bladder is a hollow organ lined with mucous epithelial cells that stores urine for several hours. Mutagenic substances such as phenethylamines and benzene compounds and synthetic substances, chronic infection and inflammation cause metaplasia, dysplasia and eventually cancer and invasion to the underlying muscle tissue. According to the latest GLOBOCAN data, bladder tumors have 3% prevalence among tumors and increase in developed and developing countries. In the United States, bladder tumors are the sixth most common, mostly 55 years old, and are 2 to 4 times more common in men than women. In tumors with lower stage, the 5-year lifespan is 77%, and in metastatic cases, it is 5%. Cigarette tobacco is the most potent risk factor. Occupational and environmental factors contribute to about 20% of cases. Only about 7% of bladder tumors are inherited. In many cases, no specific exposure is found\textsuperscript{7}.

Kotake et al.\textsuperscript{31} found that 376 patients with bladder tumors were analyzed for clinical cases. In their study, 299 patients were male, and 77 were female. The mean age of the subjects was 65.7 years. The most common synchronous tumors with bladder cancer in men were first gastric cancer (27.4%) and then prostate (15.3%), and in women, first cervical cancer (27.9%) and then gastric cancer (16.2%). Of the 119 cases, 58 were synchronous tumors, and 61 were metachronous tumors. Bladder tumors in 85% of cases coincided with other urological tumors. Also, the ratio of secondary cancers to total cancers was 5.2%, and the ratio of secondary cancers with bladder cancer to total cancers was 15.9\%\textsuperscript{32}. In another study, multiple tumors were associated with prostate cancer in 93 patients (15.2%), and the organ most associated with prostate cancer was gastric cancer, followed by bladder, colon, and lung cancer. The mean age of the first, second, and third cancers was 72, 74 and 75 years. In 37 cases of death (71.4%) due to prostate cancer, the first and second cancers were about 20 months and about 8 months for third cancer. The primary stage in primary prostate tumors was lower than in secondary tumors. Survival rates were also reported to be better in this group. For this reason, it is recommended to consider the possibility of secondary cancers in primary ones\textsuperscript{32}.

In a study in Taiwan conducted by Wu et al.\textsuperscript{33} from 1987 to 2002 on 2109 patients, 99 patients were diagnosed with multiple secondary cancers with gastric tumors (4.7%). Secondary cancer (77.8\%) was diagnosed 5 years before and after gastric cancer. 34.3\% of patients were diagnosed with the synchronous tumor within one year. 77 male patients, prostate cancer, was the most common (19.5\%), followed by colon cancers (18.2\%) and liver (14.3\%). In 22 female patients, colon cancer (31.9\%) first followed by breast and cervical cancers (22.7\%) had the highest prevalence rate\textsuperscript{33}. In another study in
Hypertension, 77,504 autopsy cases were examined, of which 385 (4.2%) had double multiple primary malignant tumors. There was no significant difference in gender. Thyroid tumors were more commonly associated with lung, breast, and gastrointestinal tumors. In another study, secondary cancer was seen in 16.8% of kidney cancers, 12.5% of bladder cancers, and 21.8% of prostate cancers. The cause of recurrent tumor connections can be explained somewhat by the high average age (72 years). Uroepoetic cancer was associated with lung cancer (the role of tobacco), gastrointestinal tumors (genetic or dietary factors), prostate cancer, bladder cancer, and hematologic malignancies. In this study, no association was found between testicular cancer and other malignancies.

In the study of Özdamar et al., On 147 patients with genitourinary tumors, 8 patients had another tumor, 2 of which were concomitant and 4 of which were asynchronous. Cancer patients are at higher risk of secondary cancer than the general population. Secondary cancer may be diagnosed in long-term follow-up of cancer patients, or etiological factors may cause pleiotropic effects, or it may be due to treatments for first cancer. In a study in France, from 1989 to 2004, 10047 patients with bladder cancer were evaluated for secondary cancer. This study showed that the risk of new cancer among cancer survivors is 60% higher than the general population. Male patients also had a higher risk of prostate, head, neck, and lung cancers.

In another study by T Fukagai et al. from Japan on October 1980 to December 1994, 392 patients were treated for malignant neoplasms. 42 patients (10.6%) had multiple neoplasms, their mean age was 72.2 years, and 83% were male. Malignant neoplasms of the bladder, prostate, and kidney were observed in 19 (35%), 19 (35%), and 10 cases (11%), respectively. The incidence of prostate cancer was more associated with genitourinary organs than other primary malignant neoplasms. Other organs which had malignant neoplasms along with the genitourinary tract organs were the stomach (39%), lungs (12%), esophagus (9%), and pancreas (9%). Only 16 patients (35%) simultaneously had multiple malignancies neoplasms.

In a study by Whi-An Kwon et al. in South Korea from 1993 to 2013, 48,875 people were investigated with an early diagnosis of bladder cancer. Bladder cancer survivors were at increased risk for some secondary cancers, particularly prostate and kidney, squamous cell carcinoma of the lung, and the lung’s adenocarcinoma. In the cohort study by Eric Adjei Boake et al., 2930241 cancer patients were identified, of which 259685 (8.9%) developed secondary cancer (7.6% female and 10.3% male). Patients with smoking-related cancers had a higher risk of developing SPC than patients with non-smoking-related cancers. Besides, considering the infection of 30–80% of different communities with H. pylori and proving its role in the development of various cancers, including gastric cancer and its concurrence with bladder cancer in most studies, it seems that the prevalence of this infection also plays a role in the development of multiple secondary cancers.

However, specific research should assess other aspects and epidemiological properties of bladder cancer among the population. The study was limited to follow small samples and low frequencies of studied groups.

**Conclusions**

Due to the increasing trend of bladder cancer worldwide and the evidence of concurrence or subsequent secondary cancers, identifying the causative agents and related risk factors can improve the prognosis of the disease and increase the life expectancy and quality of life of patients with this cancer. Therefore, it is essential to continuously monitor the risk of secondary cancer among bladder cancer survivors. On the other hand, owing to the growing number of cancer survivors cases and the SPC importance as a cancer death reason, there is a need to upsurge SPC screening and prevention.

**Bibliographic references**


