

# Urological Implications of Concurrent Bladder and Lung Cancer

Michael Vainrib MD and Ilan Leibovitch MD

Department of Urology, Meir Medical Center, Kfar Saba, Israel  
 Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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## Abstract

**Background:** Multiple primary malignancies are increasingly being detected among cancer patients.

**Objectives:** To investigate the co-occurrence of primary bladder cancer and primary lung cancer, two established smoking-related neoplasms characteristically associated with increased risk of secondary cancers.

**Methods:** A retrospective search of the patient registry in our institution identified 25 patients (23 men and 2 women) who were diagnosed with both bladder cancer and lung cancer during the period 1990–2005. Medical records were reviewed and clinical and pathological data were extracted.

**Results:** In 21 patients (84%) bladder cancer was the first primary tumor and in 4 (16%) the second primary tumor. More than 90% of the patients had a history of smoking. Mean smoking exposure was 62.1 pack years (range 30–120). All bladder cancers were transitional cell carcinomas with the majority being superficial at presentation. Most lung cancers were of the non-small cell type. Second primary lung cancers were significantly more advanced at diagnosis. Overall, mean follow-up was 105.8 months (range 6–288). Seven patients (28%) were alive at the time of evaluation; 68% died of lung cancer, while none died of bladder cancer.

**Conclusions:** Second primary lung cancer may occur in patients with bladder carcinoma and vice versa. In view of the relatively frequent involvement of the genitourinary tract as a site of multiple primary tumors, urologists may have a key role in the detection of second primary tumors arising in the genitourinary tract, or second primary tumors that occur in patients with primary genitourinary tract malignancies.

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Multiple primary malignancies are defined as two or more primary tumors in different organs in the lifetime of a patient. Multiple primary malignancies are being detected increasingly among cancer patients. The estimated rate of detection of multiple primary tumors is 5–8%, 31% higher than the expected occurrence of a malignancy in the general population [1]. The genitourinary system is frequently involved and urological organs are the site of at least one of the primary tumors in 13.5% of the cases presenting with multiple primary malignant tumors [2,3]. Endogenous and exogenous interacting factors may contribute to the phenomenon of multiple primary tumors. Multiple primary tumors in a certain individual may be the result of host-related factors such as genetic diathesis, particular hormonal milieu, and immunological status. Treatments targeted at the first primary tumor (such as radiotherapy, chemotherapy, or their combina-

tion) and certain surgical procedures (for instance construction of ureterosigmoidostomy) may induce second primary neoplasms [3]. The frequent occurrence of multiple primary tumors may be affected by an increased detection rate due to routine use of more accurate diagnostic and imaging modalities during staging, preoperative workup and intensive follow-up of patients with one primary tumor. Additionally, prolonged survival of cancer patients due to improved therapy modalities may facilitate the detection of other synchronous or metachronous primary tumors inside or outside that organ system [4]. Finally, environmental carcinogens, with smoking being the key example, are believed to play a major role in the development of multiple primary tumors [1,3].

The current study focuses on the co-occurrence of primary bladder cancer and primary lung cancer, two established smoking-related neoplasms [5,6] that are characteristically associated with increased risk of second primary cancers [2,3,7].

## Patients and Methods

A retrospective search of the computerized patient registry in our institution between 1990 and 2005 identified 25 patients (23 men and 2 women) who were diagnosed with both bladder cancer and lung cancer, regardless of the sequence of occurrence of these two tumors. The medical records were reviewed and clinical and pathological data were extracted. These included demographic data, sequence of diagnosis of the two malignancies including the time interval between their detection, smoking habits, histological subtypes of tumors, stage of lung cancer and bladder cancer grouped by established TNM classification for each tumor and, finally, follow-up and outcome data.

Statistical analysis was performed using NCSS software (Number Cruncher Statistical System, Kaysville, Utah, USA). The specific tests used included Student's *t*-test, the Mann-Whitney rank-sum test, chi-square test and Fisher's exact test. Survival analysis according to the Kaplan-Meier method and statistical significance were computed using the log-rank test.

## Results

In 21 patients (84%), 19 men and 2 women, bladder cancer was the first primary tumor and lung cancer the second primary tumor. In four patients (16%), all men, bladder cancer was the second primary tumor detected subsequent to the diagnosis of lung cancer.

### Age and time intervals

The mean age at diagnosis of bladder cancer was 66.1 years (range 40–82), and at diagnosis of lung cancer 71 years (56–85). The age at diagnosis of bladder cancer was significantly younger than the age at diagnosis of lung cancer ( $P = 0.003$ ).

Smokers developed bladder cancer or lung cancer at a younger age (65 and 70.3 years old respectively) than non-smokers (68.2 and 72.5 years old respectively); however, this trend was not statistically significant.

Overall, the median time interval between the diagnosis of the two malignancies was 72 months (range 6–276). In patients with known transitional cell carcinomas, the median time interval to the development of a second primary lung cancer was 72 months (range 6–276) in comparison to only 48 months (range 6–192) between the development of a second primary TCC in a patient with primary lung cancer. This trend of a shorter interval to the development of a second primary TCC was not statistically significant. There was also an insignificant trend towards a shorter median interval between the development of the two malignancies in non-smokers in comparison to smokers (60 and 108 months respectively).

### Bladder cancer characteristics

All bladder cancers were transitional cell carcinomas. Among the 21 patients with bladder cancer occurring as the first primary tumor, 16 (76.2%) presented with superficial TCC and 4 (19%) had invasive TCC at the initial presentation. Bladder cancer stage was not known in the remaining patients. In comparison, half of the cases of second primary bladder cancer that were detected in patients with lung cancer presented with invasive disease.

### Lung cancer characteristics

Twenty-three patients (92%) in this study had non-small cell lung cancer, predominantly squamous cell carcinoma. One patient (4%) had small cell lung cancer and another had unclassified carcinoma. Only seven patients (28%) were diagnosed with stage I-II. Sixteen patients (64%) were diagnosed with advanced lung cancer (stages III-IV). The stage was not indicated in 2 of 25 records (8%). It is notable that all patients with first primary lung cancer had relatively early-stage lung cancer (I-II), while second primary lung cancer in patients with known bladder cancer was significantly more advanced at diagnosis, with 16 of 21 patients (76.2%) presenting with stages III-IV ( $P = 0.002$ ).

### Smoking history

Smoking history was available in 23 records. Nineteen patients (90.9%) were current smokers or had quit smoking recently. Mean smoking exposure was 62.1 pack years (range 30–120). Only two patients (9.1%) in this cohort never smoked. The proportion of smokers among patients with bladder cancer as the first primary or bladder cancer as the second primary (84.2% and 75% respectively) did not differ statistically.

### Follow-up

Overall, the mean follow-up period was 105.8 months (range 6–288). The mean follow-up of TCC was 93.2 months (range 6–288) and of lung cancer 32.7 months (range 1–228). Predictably, the overall outcome of the patients was dictated by the outcome of the more aggressive disease, namely lung cancer: 68% (17/25) of the patients died of lung cancer with the majority being cured from bladder cancer at the time of death (from lung cancer). One patient died of another cause. None died of bladder cancer. Only seven patients (28%) were alive at the time the records were being reviewed. All seven developed lung cancer as the second primary malignancy. Three of these seven patients had no evidence of lung cancer or TCC, and the additional four patients were alive with persistent lung cancer but had no evidence of TCC.

In patients who were diagnosed with bladder cancer first, the 5 year survival, calculated from the diagnosis of bladder cancer, was 68%. Once these patients presented with second primary lung cancer, the 5 year survival calculated from the time of diagnosis of the second primary lung cancer was only 23%. The 5 year survival of smokers who presented initially with bladder cancer was 60.6%, while all non-smokers who presented initially with TCC survived at least 5 years.

### Discussion

We identified 25 patients who developed concomitant bladder and lung cancer during the study period. The occurrence of multiple primary tumors in lung cancer patients is not uncommon. The leading single second primary cancer after therapy for lung cancer is a second primary lung cancer, [8], although non-pulmonary second primary cancers are often encountered. Analysis of the Finnish cancer registry identified 1300 second primary cancers among 77,548 lung cancer patients including 140 cases of bladder cancer, nearly twofold higher than the expected rate [9]. In other studies, the overall risk of a second smoking-related malignancy was 10–20% [7,10] and the standardized incidence ratio of bladder cancer was 1.8 [7]. Following intent to curative resection of stage I NSCLC, the average reported incidence of non-pulmonary second primary malignancy is 6.8% (186/2731), including 19 patients with bladder carcinoma (10.2% of all non-pulmonary second primary tumors) [8,11].

Early-stage NSCLC patients who are managed by radiation therapy alone carry a similar risk for developing second cancers [10]. Hypothetically, a history of a non-pulmonary primary malignancy before the diagnosis of lung cancer may increase the risk of subsequent second primary tumors. Interestingly, Brock et al. [12] did not find this risk to be markedly different from the risk of a second primary tumor in patients with lung cancer and no prior malignancies.

Liu and associates [13] reported that among patients with two primary malignancies, the mean and median time interval between the diagnosis of the first cancer and the development of the second malignancy was significantly shorter when the first

TCC = transitional cell carcinoma

NSCLC = non-small cell lung cancer

neoplasm was lung cancer, in comparison to patients whose first cancer was non-pulmonary malignancy. The majority of patients with lung cancer developed the second primary tumor within the first year, shortly after the diagnosis of lung cancer, and only a few patients developed the second tumor later than 5 years. Conversely, lung cancer as the second primary, following non-pulmonary primary neoplasms, tended to develop later than 5 years in the course of disease. On the other hand, El-Hakim and co-authors [14] reported a comparable mean time interval between development of the two primaries regardless of the type of the first diagnosed cancer. In our study, the overall median time interval between the diagnoses of the two malignancies was 6 years. We were able to demonstrate only an insignificant trend towards a shorter time interval between the diagnosis of a second primary TCC in patients with previous lung cancer (4 years) in comparison to the time interval between the development of a second primary lung cancer in patients with former diagnosis of TCC (6 years). Due to the aggressive nature of most lung cancers and the expected relatively shorter survival of lung cancer patients, such a shorter time interval in patients with a previous lung cancer is intuitive, and hence we believe that the 2 years difference in the time interval, as demonstrated in our study, did not show statistical significance only due to the fact that the group of patients who developed second primary TCC subsequent to lung cancer consisted of just four patients.

In the current study, the age at diagnosis of bladder cancer was significantly younger than the age at diagnosis of lung cancer. Although statistically significant, this result has no clinical meaning since this so-called significant age difference is due to the fact that the majority of the patients (84%) were diagnosed first with TCC.

In addition to the time interval between the presentations of the two malignancies, the stage of lung cancer at presentation seems to be another significant factor that affects the likelihood to develop a subsequent second primary malignancy. Advanced lung cancer patients probably will not survive long enough to develop a second primary TCC unless the time interval is very short. However, second primary tumors including bladder cancer may be detected also after successful treatment (resection or chemo-radiotherapy) of stage III primary NSCLC [15,16]. In other studies of multiple primary malignancies involving lung cancer patients, more than half of the patients who were diagnosed with lung cancer first presented with low stage ( $\leq$  stage II), as compared to less than a quarter of the patients who presented with second primary lung cancer following bladder cancer [13,14]. Nevertheless, stage by stage, patients with second primary lung cancers are expected to respond to therapy as well as those who present with lung cancer first [17].

The proportion of patients with low-stage lung cancer at presentation is especially notable among SCLC patients. Unsurprisingly, in small cell carcinoma series, nearly 80% of the patients who survived and developed a second malignancy had presented with low-stage disease [18]. All four patients in our

study who were diagnosed initially with lung cancer had presented with low-stage, surgically curable disease and apparently survived long enough to develop a second primary bladder cancer after a median interval of 4 years. On the other hand, nearly 75% of our patients with second primary lung cancer developing after known bladder cancer presented with advanced stage at diagnosis.

The incidence of second primary cancers is affected also by the histological type of the primary lung cancer, although all histological types are associated with an increased relative risk of developing new primary cancers in general and bladder cancer in particular [9]. Despite the fact that the survival of patients with SCLC is limited, second primary neoplasms are encountered in long-term survivors of SCLC [18-21]. As in most similar studies [13,14], most of the patients in the current study had NSCLC, predominantly squamous cell carcinoma, and only one had SCLC.

The association between cigarette smoking and certain cancers that are generally considered smoking-related cancers is well established [6,22]. The lifelong risk to develop lung cancer in smokers is 20 to 40-fold higher than in non-smokers. Twenty percent of cigarette smokers develop lung cancer and more than 90% of lung cancer patients have a history of smoking [23]. The risk of bladder cancer is related to duration and dose of smoking, with two of every three cases of bladder cancer attributable to smoking [5].

In our study the prevalence of smoking was high and was similar among patients who presented with bladder cancer first and among patients who presented with lung cancer first. Smoking increases the risk of developing multiple primary cancers [1]. Consequently, smoking history and smoking cessation evidently have a major impact on the development of second primary tumors in lung and bladder cancer patients. A significantly higher risk of multiple primary malignancies, mainly smoking-related tumors, is found in lung cancer patients with a history of smoking in comparison to non-smokers [7,13]. A similar effect of smoking on the risk of second primary tumors was shown also in bladder cancer patients [24], with a significantly higher proportion of smokers among patients who presented with lung cancer first than among patients who developed lung cancer as the second primary [13].

Smoking cessation was shown to have a considerable beneficial effect on the risk of developing multiple malignancies. Smoking cessation significantly decreases the known high risk of developing a second primary cancer among SCLC patients who survived beyond 2 years after therapy [18,20,25].

## Conclusions

This retrospective study calls attention to the development of second primary lung cancer in patients with prior diagnosis of bladder cancer or the development of second primary TCC of the bladder in lung cancer patients. We emphasize the importance of close follow-up of patients with bladder or lung cancer – not only to diagnose recurrence or progression of the primary tumor but also to pro-actively detect occurrence of second primary cancers.

SCLS = small cell lung cancer

This is especially crucial in current smokers who are at increased risk as compared to patients who never smoked or those who quit smoking. The probability of a second malignancy associated with tobacco consumption in primary bladder or lung cancer may be definitely diminished by lasting cessation of smoking and possibly by high dose vitamin A adjuvant therapy, at least in successfully resected low-stage NSCLC. In view of the relatively frequent involvement of the genitourinary tract as the site of multiple primary tumors, urologists may have a key role in the detection of second primary tumors arising in the genitourinary tract or second primary tumors that occur in patients with primary genitourinary malignancies.

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**Correspondence:** Dr. I. Leibovitch, Chairman, Dept. of Urology, Meir Medical Center, Kfar Saba 44281, Israel.  
Phone: (972-9) 747-1557, Fax: (972-9) 747-1292  
email: leibovitchi@clalit.org.il