ORIGINAL ARTICLE
Turkish Respiratory Journal 2007; 8(1): 10-14
Lung and Pleural Malignancies

Long-term Survival Following Lung Resection for Metachronous Lung Cancer in Patients with Bladder Cancer

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Abstract

Objectives: Separate primary cancer is defined as an independent new primary malignant tumor arising simultaneously or after the diagnosis of another neoplasm . We analyzed our results in patients with separate primary bladder and lung cancers. **Design:** Retrospective data review. **Setting:** University Hospital. **Patients:** Files of patients who were previously operated on for bladder cancer and subsequently underwent lung cancer resection were identified. Patient characteristics, clinical, radiologic presentation, surgical management and survival were recorded. Histologic and immunohistochemical analysis were performed. **Results:** 5 patients (4 male) were identified. Four had metachronous (17, 29, 84, 162 months) and 1 had synchronous cancer . Superficial bladder cancers were identified in 4 patients . One patient had advanced stage bladder cancer . All were transitional cell carcinomas. All lung lesions were identified on a chest X-ray. 3 patients received neoadjuvant treatment . Pathologic stages were T1N0 (n=1), T2N0 (n=2), T2N1 (n=1) and T3N2 (n=1). Histologic diagnosis was squamous cell (n=3), large cell (n=1) and adenocarcinoma (n=1). Cytokeratin 20 was negative in 4 and thrombomodulin was negative in all patients, suggestive of primary lung cancer. Four patients are alive at 14, 24, 34 and 80 months after lung resection . One patient is alive with lung cancer recurrence and one patient died due to lung cancer at 17 months. **Conclusions:** Treatment strategy of separate primary cancers should rely on clinical, radiologic and pathologic correlation. Aggressive multimodal treatment leads to a favorable outcome in these patients.

Keywords: Lung cancer, Bladder cancer, Metachronous, Synchronous, Surgical resection, Multimodal treatment.

Received: Oct 27, 2006 Accepted: Mar 14, 2007

INTRODUCTION

Separate primary cancer is defined as an independent new primary malignant tumor arising simultaneously or after the diagnosis of another neoplasm [1]. Separate primary cancers develop with increasing frequency due to the success in the treatment of certain types of cancers . Patients with superficial bladder cancer have a survival expectancy of more than 90% at 10 years [2]. Most of these patients are heavy smokers and therefore are at increased risk of developing second primary malignancies associated with smoking . The incidence of second primary cancers following a urologic malignancy was reported to be around 6% [3, 4]. 30% of the metachronous primary cancers following bladder cancer were identified as lung cancers [4].

As the survival following bladder cancer treatment is high, it is likely to encounter more patients with primary lung cancer following bladder cancer [5]. It is debatable whether these patients should be followed with close intervals using a chest CT or a chest X-ray.

Histologic diagnosis of the lung lesion as a primary lung cancer is crucial, as it determines the approach and the extent of surgery. Non-small cell carcinoma of the lung is histologically difficult to distinguish from the lung metastasis of the transitional cell carcinoma of the bladder [6]. Urothelial markers such as uroplakin III, thrombomodulin, cytokeratin 20 can be used to differentiate between urologic and other malignancies [7]. However, clinical, radiologic and pathologic correlation is still needed for definitive diagnosis.

Management of these patients generally presents a challenge to the physician. Most of the patients with bladder cancer are over 60 years of age and the second primary lung cancer emerges at even older age groups.

In this report, we have analyzed the results and discussed our approach in patients with separate primary bladder and lung cancer.

MATERIAL AND METHODS

Files of patients who were operated on for lung cancer in the Department of Thoracic surgery at Marmara University Hospital during 1997-2003, were reviewed. This study was approved by the ethical council of Marmara University, Faculty of Medicine. Patients who were previously treated for bladder cancer were matched with surgically resected lung cancer patients.

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Table 1. Characteristics and pathologic stages of patients with synchronous/metachronous lung cancer. (LCC, Large cell carcinoma; Adeno, Adenocarcinoma; SCC, Squamous cell carcinoma)

Patient	Age	Time Between Bladder and Lung Cancer (months)	Type of Surgery (Same session)	Histology and Size‡ (cm)	Pathologic Stage γ	Current Status
1†	60	Metachronous, 29	Bronchoscopy, right upper lobectomy	LCC, 5	T2N0	Alive without recurrence (80 mo)
2	69	Metachronous, 84	Bronchoscopy, mediastinoscopy, right upper lobectomy	Adeno, 6	T2N1	Alive with recurrence (14 mo)
3	63	Synchronous	Bronchoscopy, left upper lobectomy, left lower lobe superior segment wedge excision	SCC, 3	T2N0	Alive without recurrence (24 mo)
4†	69	Metachronous, 17	Bronchoscopy, left upper lobectomy	SCC, 0.3	T1N0	Alive without recurrence (34 mo)
5*†	78	Metachronous, 162	Bronchoscopy, right upper lobectomy, en-bloc chest wall resection (3rd, 4th, 5th ribs), radical lymph node dissection	SCC, 6.2	T3N2	Dead from lung cancer (17 mo)

* Patient underwent mediastinoscopy initially at a separate session prior to neoadjuvant treatment and was found to have multistation mediastinal lymph node involvement (Right lower paratracheal and subcarinal).
† These patients received neoadjuvant treatment prior to final surgical resection. Pre-treatment tumor sizes were 7, 3.5 and 8cm respectively.
‡ Sizes of the tumors are post-surgical measurements in the pathology specimens.
γ TNM classification of lung cancer, The American Joint Committee on Cancer and Union Internationale Contre Le cancer (9).

The smoking habits and current status, the method of identification of the lung cancer, the management and stage of the bladder cancer, interval between bladder and lung cancer, clinical picture, radiologic appearance were recorded. Histologic analysis of the lung lesion with conventional hematoxylin-eosin staining and immunohistochemical panel of thrombomodulin, cytokeratin 7 and 20 were performed. Survival of these patients was calculated. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder was used for staging. Similarly, lung cancer patients were staged according to the TNM classification using the guidelines of the American Joint Committee on Cancer and Union Internationale Contre le Cancer in 1997 [8]. Metastatic screening for lung cancer included brain CT with contrast or MRI, bone scinthigraphy and upper abdominal ultrasound.

RESULTS

During 1997-2003, 171 patients were operated on for lung cancer in our department. A total of 5 (%2.9) patients with primary bladder and lung cancer were identified. These patients were included in this study.

Patients in this group were initially treated for their bladder cancer. During the same period, one patient underwent metastasectomy for lung metastasis of the transitional cell carcinoma of the bladder. Two patients underwent lung resection for primary lung cancer following prostate and renal cancer. Two additional patients, one included in our series (Patient 1), developed subsequent primary bladder cancer following lung cancer resection. Both were treated with transurethral resection. All of these patients were excluded from this group.

In 4 patients, bladder cancer was superficial and one patient had advanced stage disease. The average age at the time of bladder cancer was 62.8 (58-67) years. Complete surgical resection was done in all patients and no recurrences were detected in their control cystoscopies.

Lung lesions were initially noticed on a chest X-ray and subsequent chest CT scans were obtained. The characteristics, surgical procedures and pathology of the lung lesions are depicted in Table 1. All patients underwent systematic lymph node sampling during their lung resection. Patients who received neoadjuvant treatment underwent radical lymph node dissection. The average age at the time of lung cancer was 67.8 (60-78) years. Three patients were asymptomatic at the time of diagnosis and the lung lesions were incidentally discovered on chest X-ray. In one patient, chest X-ray was taken for suspected cardiac disease due to swelling of the feet and for malaise in the second patient.

Our 3rd patient with synchronous tumors had widespread intrathoracic calcifications attributed to previous tuberculosis infection. The suspicious lung nodule was on the edge of a calcification (Figure 1a), so we observed the patient for two months to follow the nature of the nodule. During this period, the nodule doubled its size and there was no change in the remaining lung lesions (Figure 1b). In 4 of the patients, lung lesions were described as a mass. Histologic diagnosis was obtained with transthoracic fine needle aspiration biopsy in 4 and with bronchoscopic biopsy in 1 patient.

All patients were current (n=3) or ex-smokers (n=2). The average duration of cigarette smoking was 60 pack-years (45-80). The two ex-smokers stopped smoking before their operation for bladder cancer.

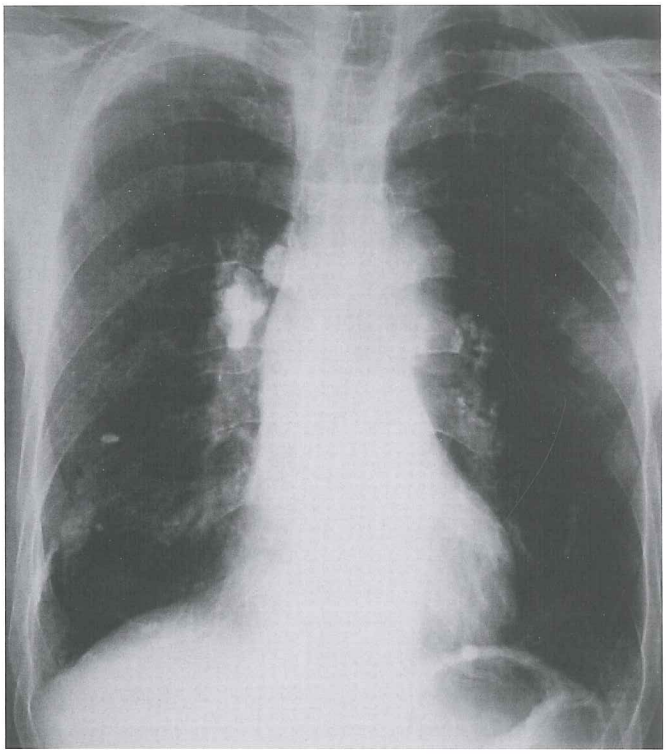

Figure 1a: Initial chest X-ray of the patient with synchronous bladder and lung primary cancers shows widespread intrathoracic calcifications and right apical scarring. A peripheral nodule can be seen on the left middle zone (arrow).

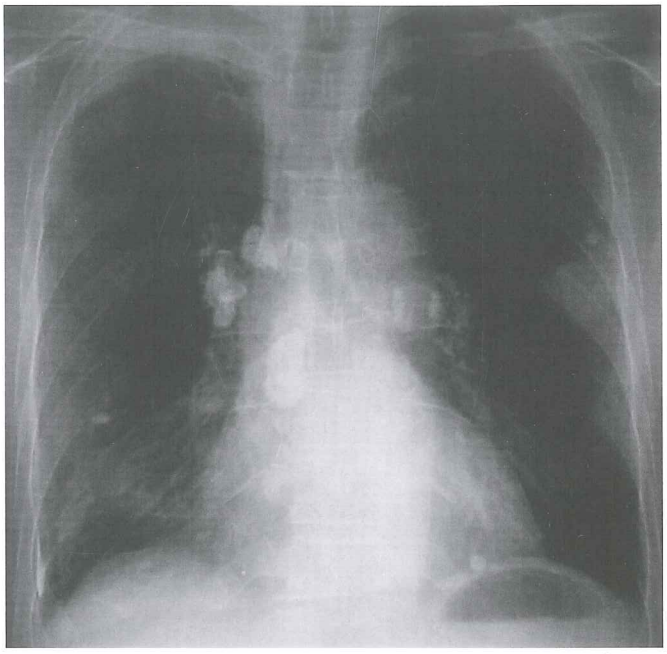

Figure 1b: The peripheral nodule on the left side is significantly enlarged on the chest X-ray at two months follow-up (arrow).

Neoadjuvant treatment was used in 3 patients. In one patient, mediastinoscopy revealed multistation mediastinal (right lower paratracheal and subcarinal) lymph node involvement (Figure 2a) and the tumor was resected after significant shrinkage following 3 cycles of gemcitabine and carboplatin chemotherapy. Second patient received 3 cycles of paclitaxel and carboplatin chemotherapy for possible pulmonary artery and subaortic lymph node involvement (Figure 2b). Third patient received 40 Gy radiation therapy and 4 cycles of paclitaxel and carboplatin for a large right upper lobe tumor. All three patients had significant response to neoadjuvant treatment.

There was no in-hospital mortality. Morbidity occurred in 3 patients. One patient had postoperative delirium, one had atrial fibrillation and subsequently needed temporary non-invasive mechanical ventilation for respiratory failure

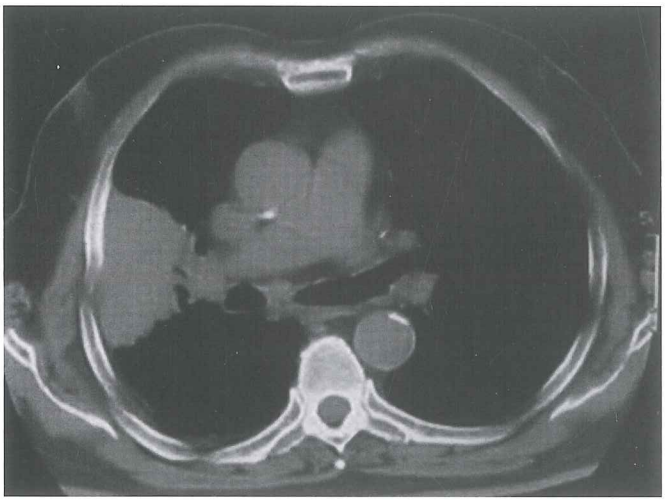

Figure 2a: Chest CT scan shows right sided hilar tumor and associated atelectasis. This patient had multi-station N2 disease and was administered neoadjuvant treatment prior to surgical resection.

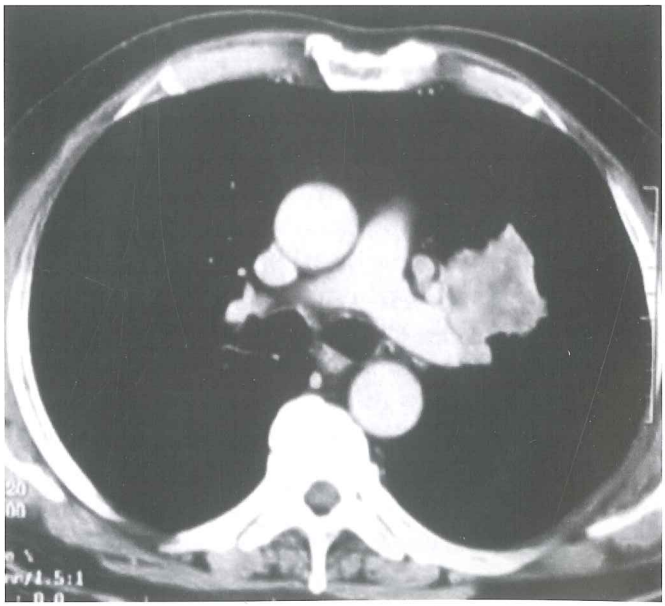

Figure 2b: Left sided hilar mass in close proximity with the left main pulmonary artery and subaortic lymph nodes can be seen. Patient received neoadjuvant treatment and the tumor was downstaged to T1N0.

and one had prolonged air leak. Average hospital stay was 8 days (6-10) and all patients were discharged from the hospital without any problems.

Histologic diagnosis was squamous cell (n=3), large cell (n=1) and adenocarcinoma (n=1) with standard hematoxylin-eosin staining. Squamous cell carcinomas were well differentiated. Immunohistochemical staining for thrombomodulin, cytokeratin 7 and 20 was performed. All patients were negative for thrombomodulin. Cytokeratin 20 was negative in 4 patients, suggestive of a pulmonary malignacy. Cytokeratin 20 positivity was focal in one patient with less than 1% of all tumor cells. Cytokeratin 7 was positive in 4 patients with 2 patients showing strong positivity and 2 with focal staining.

Four patients are currently alive. The patient with multistation N2 disease recurred locally at the subcarinal region and interlobar fissure and distantly with multiple bone metastasis and died 17 months after surgery. The patient with N1 disease had local and distant recurrence (bone metastasis) 8 months after surgery. Three patients are alive without any recurrence (Table 2).

DISCUSSION

Approach to separate primary cancers is always challenging and needs patient based evaluation. Smoking is a common risk factor for many types of cancers, but urologic and tracheobronchial malignancies are very strongly correlated. Expression of cyclooxygenase-2 (COX-2) was accused of early cellular changes leading to the development of both lung and bladder cancer [9]. COX-2 was shown to be induced by a variety of stimuli, especially tobacco related carcinogens [9]. It has been shown that the risk of developing a second primary urologic malignancy after an initial urologic malignancy is higher than any other type of cancer [10]. But for bladder cancer, development of a second primary lung cancer is also common [4].

Chest CT has been shown to be more sensitive than standard chest X-rays for detecting lung cancers at an earlier stage in several studies [11-13]. In the early lung cancer action project, 85% of the lung cancers detected with a low dose spiral CT were Stage I [11]. Other screening studies, also demonstrated similar findings with 60-92% of the lung cancers being detected at an early stage. The size of the lesions in screening studies was between 13 and 20mm [12, 13]. In our patients, size of the tumors during pathologic analysis was over 3cm in four patients and in one patient with significant response to neoadjuvant treatment, a small focus was left from the original tumor (Table 2). Three of our patients continued smoking, even after their bladder cancer operation, which increases the risk for bladder cancer recurrence and a second lung primary. It may be worthwhile to obtain a yearly chest CT scan in those patients with resected bladder cancer, as these patients are invariably at high risk for developing a second primary lung cancer.

In low-grade bladder cancers or superficial bladder cancer, risk of distant metastasis is extremely low (<2%), however local recurrences are common (60%) [14]. Therefore, lung lesions arising in patients with superficial bladder cancer should be accepted as primary lung cancers unless proven otherwise. In 4 of our patients, the lung lesion was a mass, which is generally contrary to the nodular characteristics of a metastasis. Four of the tumors were metachronous with two of them arising beyond five years after bladder cancer resection.

Prior to lung resection, we assess mediastinal lymph node involvement and distant metastasis using radiologic and invasive surgical techniques (mediastinoscopy, mediastinotomy). We also perform an extensive evaluation of the cardiopulmonary reserve of those patients, using pulmonary function tests, ventilation-perfusion scanning, echocardiography and exercise stress test whenever needed. We use neoadjuvant treatment in patients with large hilar tumors and/or positive mediastinal lymph nodes. Persistence of tumor cells in mediastinal lymph nodes following neoadjuvant treatment is a poor prognostic sign as seen in our fifth patient. Patients can be assessed with a PET scan to evaluate the response to neoadjuvant treatment and hence identify those who will benefit from surgery [15]. Currently, in histologically proven multi-station N2 disease or persistent N2 disease following neoadjuvan treatment our approach is mainly non-surgical.

In conclusion, in this small group of patients, it can be clearly seen that separate primary bladder and lung cancer patients share the same risk factors. Initiation of a malignant process in bladder should alert the physician for similar malignant epithelial changes in other organs, especially the bronchopulmonary tree. Routine screening of patients operated on for bladder cancer with a yearly low-dose chest CT should be considered. In borderline cases, treatment strategy should rely on clinical, radiologic and pathologic correlation. Aggressive multimodal treatment of the second primary lung cancers should be performed and have a favorable outcome and acceptable survival.

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