Upsala J Med Sci 113 (2): 193–200, 2008

Multiple Primary Malignancies Involving Lung: An Analysis of 40 Cases

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Abstract

We aimed to assess the incidence of multiple primary malignancies in primary lung cancer patients. We retrospectively evaluated the clinical files of 1038 primary lung cancer patients diagnosed in 2004. Forty patients (3.9 %) had multiple primary malignancies. There were 34 men (85 %) and 6 women (15 %). Their mean age was 62.4 ± 8.6 years. While 35 cases were smokers, 5 cases were nonsmokers. Tumour pathology of the lung was squamous cell carcinoma in 15 cases, adenocarcinoma in 10 cases, small cell carcinoma in 3 cases and non-small cell carcinoma in 12 cases. There were 2 primary tumours in 37 cases and 3 primary tumours in 3 cases. The first detected tumour was located in larynx in 11 cases, in genitourinary system in 9 cases, in intestine in 5 cases, in lung in 3 cases and in other organs in 12 cases. The mean interval between the first and the second tumour was 77 months with a range of 1 months to 32 years. This interval was shorter than 6 months in 4 cases. Treatment modality for the first detected tumour was surgery in 35 cases. The last primary tumour was treated with surgery in 12 cases. In conclusion, the development of multiple primary tumours is not a rare phenomenon. Patients with a malignancy should be followed for development of a second primary malignancy. The treatment of lung cancer in patients with a previous malignancy should be the same as for lung cancers presenting as the first cancer.

Introduction

Multiple primary malignancies are defined as the occurrence of two or more primary malignancies, where each cancer originates in a separate primary site and is neither an extension, recurrence or metastasis (1,2). In 1889 Billroth, quoted by Hui and associates (2), first described a patient in whom cancer of the stomach was found after the removal of an epithelioma of the external ear. In 1932 Warren and Gates identified 1259 verified cases of multiple malignancies either reported in the literature or encountered in their own postmortem examinations (3). While observations of multiple primary malignancies were previously considered isolated and exceptional cases, as a result of the improvement in the diagnostic tools, treatment modalities and supportive care, survival time for cancer patients has been prolonged and the number of multiple primary cancers has continued to grow (4). Up to 10 % of cancer patients have been

Key words: primary malignancy, multiple, lung cancer

Received 3 March 2008
Accepted 13 March 2008

reported to acquire multiple primary cancers of separate organ sites in the 10 years following the diagnosis of their first cancer (5).

Lung cancer is one of the most common cancers worldwide. The risk of developing a second lung cancer in patients with non-small cell lung cancer is approximately 1 % to 2 % per patient per year. For small cell lung cancer, it is approximately 6 % per patient per year (6). It was reported that 193 patients with multiple primary cancers involving lung cancer were found among 22,405 cancer cases (7). In this study, we aimed to assess the incidence of multiple primary malignancies in primary lung cancer patients.

Materials and methods

The present study was conducted at Sureyyapasa Thoracic and Cardiovascular Diseases Training and Investigation Hospital, located in Istanbul. The clinical files of 1038 primary lung cancer patients diagnosed in our center in 2004 were retrospectively evaluated to determine previous malignancies. Information recorded at the time of developing last primary cancer included patient characteristics, histology and anatomic localization of the primary cancers, interval between the first and the second primary malignancy, and treatment modalities.

Multiple primary malignancies were defined as multiple autonomously originating malignancies in an individual patient. Each tumour had to be clearly malignant histologically, each had to be geographically distinct, and the possibility that one tumour represented a metastasis had to be excluded (3). In cases of index tumour in lung, the criteria of Martini and Melamed (8) were used for the diagnosis of second primary cancer. All last tumours had been staged according to TNM staging system (9). The index tumour was defined as the first detected tumour. Synchronous primaries include any second malignancy occurring within 6 months of the diagnosis of the index tumour and metachronous primaries are diagnosed after 6 months.

Results

Of the 1038 patients with primary lung cancer, 40 (3.9 %) patients had multiple primary malignancies. There were 34 men (85 %) and 6 women (15 %). Their mean age at the time of diagnosis of the last tumour was 62.4 ± 8.6 years. While 35 cases were smokers, 5 cases were nonsmokers. The incidence of the patients with multiple primary malignancies was 4.8 % (35/724) among smokers and was 7.7 % (5/65) among nonsmokers ($p>0.05$). Four patients had history of alcohol and 6 patients had positive family history of malignancy. Thirty-seven patients (3.6 %) had double primary malignancies and 3 (0.3 %) had triple primary malignancies. The first and the second tumours were synchronous in 4 patients. Results are summarized in table 1.

Index tumour was located in larynx in 11 patients, in genitourinary system in 9

Table 1. Distribution of multiple primary malignancies

Patients	n	%
with lung cancer reviewed	1038	100
with multiple primary malignancies	40	3.9
with double primary malignancies	37	3.6
with triple primary malignancies	3	0.3
with synchronous multiple primary malignancies	4	0.4
with metachronous multiple primary malignancies	36	3.5

patients, in intestine in 5 patients, in lung in 3 cases and in other organs in 12 cases. While the index primary tumour was treated with surgery in 35 patients, treatment modality was radiotherapy and/or chemotherapy in 5 patients. The mean interval between the first and the second tumour was 77 months with a range of 1 months to 32 years. This interval was shorter than 6 months in 4 cases. The interval between the second and the third tumour in three patients with the triple tumours were 5, 24 and 72 months (table 2 and table 3).

The last primary tumour was lung cancer in all patients. Tumour type of the lung was squamous cell carcinoma in 15 cases, adenocarcinoma in 10 cases, small cell carcinoma in 3 cases and non-small cell carcinoma in 12 cases. Among patients with non-small cell carcinoma, the stage was 6 stage IA, 7 stage IB, 3 stage IIB, 3 stage IIIA, 12 stage IIIB, and 6 stage IV. All patients with stage IA were treated with surgical resection. While 4 patients with stage IB were treated with surgery, 1 patient rejected surgery. There were 2 medically inoperable patients in this group. While 1 patient with stage IIB was subjected to surgical resection, 2 patients rejected surgery. Among patients with stage IIIA, 1 patient was treated with surgery. One patient rejected surgical treatment. Because the other had multiple N2 disease, he was treated with radiotherapy. There were 6 patients with stage IV in this series. They were given chemotherapy.

Discussion

The incidence of multiple primary malignancies has increased in recent decades (7,10). The American Cancer Society, quoted by Mydlo and associates (11), has reported that one out of 5 Americans will develop cancer in his or her lifetime. Furthermore, there is one out of three chances of developing a synchronous, antecedent or subsequent tumour in these patients' lifetime. According to two previous reports, the incidence of multiple primary malignancies has ranged from 0.4 % to 11.8 % (2,12). This incidence was 2.4 % in Buiatti's report (13), was 2.5 % in Cheng's series (14) and was 11 % in Brock's study (15).

In our series, 3.9 % of the patients with primary lung cancer had multiple primary

Table 2. Features of the patients with double primary malignancies

Case No	Age (years)	Sex	Index tumour	Treatment of index tumour	Interval	Cell type of last tumour
1	60	M	Colon	Surgery	6 years	Squamous
2	72	F	Kidney	Surgery	4 years	Adeno
3	58	M	Larynx	Surgery	26 years	Non-small
4	63	M	Hodgkin	RT* and CT**	5 years	Squamous
5	49	M	Pancreas	Surgery and RT	5 years	Non-small
6	68	M	Larynx	Surgery	2 years	Adeno
7	54	M	Larynx	Surgery	18 months	Squamous
8	66	F	Breast	Surgery and CT	5 months	Adeno
9	72	M	Colon	Surgery	6 years	Adeno
10	71	M	Prostate	CT	5 years	Non-small
11	65	M	Larynx	Surgery	17 years	Small cell
12	54	M	Lung	Surgery	30 months	Squamous
13	62	F	Uterus	Surgery	10 months	Non-small
14	61	M	Lip	Surgery	1 year	Squamous
15	75	M	Thyroid	Surgery	9 years	Squamous
16	40	F	Breast	Surgery	4 years	Small cell
17	77	M	Larynx	Surgery	7 years	Non-small
18	62	M	Bladder	Surgery	23 months	Small cell
19	50	F	Colon	Surgery	11 years	Adeno
20	69	M	Skin	Surgery	9 years	Non-small
21	66	M	Lung	Surgery	8 months	Squamous
22	51	M	Larynx	Surgery	4 years	Squamous
23	49	M	Small bowel	Surgery	25 months	Non-small
24	64	M	Bladder	Surgery	1 months	Non-small
25	66	M	Lung	Surgery	20 months	Adeno
26	77	M	Testicular	Surgery and RT	32 years	Adeno
27	55	M	Rectum	Surgery	12 years	Squamous
28	62	M	Larynx	Surgery	35 months	Squamous
29	69	M	Bladder	Surgery	14 years	Adeno
30	67	M	Larynx	Surgery	10 years	Non-small
31	64	M	Prostate	CT	5 years	Non-small
32	59	F	Uterus	CT	1 months	Squamous
33	59	M	Larynx	RT and CT	1 months	Non-small
34	56	M	Muscle	Surgery and CT	25 months	Squamous
35	72	M	Parotid	Surgery	2 years	Non-small
36	62	M	Lip	Surgery	13 years	Squamous
37	60	M	Larynx	Surgery	17 months	Squamous

*RT: Radiotherapy **CT: Chemotherapy

Table 3. Features of the patients with triple primary malignancies

Case No	Age (years)	Sex	Index tumour	Treatment of index tumour	Interval	Second tumour	Treatment of second tumour	Interval	Third tumour	Cell type of last tumour
38	59	M	Left cord vocal	Surgery	42 months	Right cord vocal	Surgery	5 months	Lung	Adeno
39	77	M	Larynx	Surgery	18 years	Penis	Surgery and RT*	2 years	Lung	Squamous
40	58	M	Thyroid	Surgery	8 years	Bone	Surgery and CT**	6 years	Lung	Adeno

* RT: Radiotherapy **CT: Chemotherapy

malignancies. In the present series, the last tumour was lung cancer in all patients. Utsumi et al (12) reported that 37 of 313 primary lung cancer patients had a history of previous malignancy. Hui et al (2) found that there were multiple primary malignancies in 2.1 % of the patients. In their series, apart from the 5 patients with simultaneous tumour, lung cancer was the index tumour in 8 patients and the second tumour was in 8 patients. It was reported that a total of 193 patients with multiple primary cancers involving lung cancer were detected among 22,405 cancer patients. Of these 193 patients, 51 had lung cancer diagnosed before the occurrence of the other cancers and the remaining 142 had other cancers occurring ahead of the lung cancer (7). Index tumour was lung cancer in three patients in our series. In this series, the most frequent index tumour was larynx carcinoma, followed by malignancy of genitourinary and digestive systems. Laryngeal index tumours have the highest percentage of pulmonary second primaries (16,17). Jones et al (14) reported that 47 per cent of 110 laryngeal index tumours have second primaries in lung. There were 37 lung cancer patients with a history of previous malignancy in a previous report. The previous malignancies included 13 gastric cancers and 6 colorectal cancers (12). According to a previous report, the mean interval between the first and the second tumour was 6 years and 8 months with a range of 2–20 years. The interval between the second and the third tumour in 2 patients with the triple tumours were 2 and 6 months (2). In our series, the mean interval between the first and the second tumour was 77 months with a range of 1 month to 32 years. The interval between the second and the third tumour in 3 patients with the triple tumours were 5, 24 and 72 months.

The development of multiple primary malignancies may be associated with several factors such as genetic factors, hormones, environmental carcinogens, dietary factors, previous therapy, alcohol and smoking (7,11,12,14,18). Liu et al (10) pointed out that smoker patients had a significantly higher risk for the development of multiple primary malignancies involving lung cancer. Two previous reports supported that there was a causal association between cigarette smoking and cancer of

the aerodigestive system, lungs, stomach, liver, kidney, uterine cervix, and bladder (19,20). Oral cavity, orohypopharynx and larynx were locations related to smoking and alcohol (18). In our study, most of the index tumours were tumours related to smoking. It was showed that risk of lung cancer was significantly increased in patients treated for Hodgkin's lymphoma and breast cancer (21,22). The risk of developing a second lung cancer in patients who survived resection of a non-small cell lung cancer is approximately 1 % to 2 % per patient per year (6). It is known that genetic factors play an important role in the development of multiple primary malignancies (11,12,15,23). In our series, there were 35 smoker patients. Four of 35 patients also drunk alcohol. Six patients had a family history of malignancy. One of 6 patients was nonsmoker. Among nonsmoker patients, one patient received chemotherapy for breast cancer and one patient was treated with radiotherapy for uterine cancer.

Treatment of lung cancer in patients with previous malignancies should be the same as for lung cancer presenting as the first cancer (12). Surgery should always be the treatment of choice in these patients if the tumour is operable (24,25). We considered surgical treatment in 20 patients. Because the patients rejected surgery or they were medically inoperable in 8 cases, resection was performed in only 12 patients.

In conclusion, the development of multiple primary tumours is not a rare phenomenon. Patients with a malignancy should be followed for development of a second primary malignancy. Treatment of lung cancer in patients with a previous malignancy should be the same as for lung cancer presenting as the first cancer.

References

1. Watanabe S, Kodama T, Shimosato Y, Arimoto H, Sugimura T, Suemasu K, Shiraishi M (1984). Multiple primary cancers in 5,456 autopsy cases in the National Cancer Center of Japan J Natl Cancer Inst 72: 1021–7.
2. Hui LI, Zhangyu Z, Liqun S, Xuechang LI, Tiangui W (2000). Carcinoma of the lung and multiple primary tumours. Chin Med J 113: 799–801.
3. Warren S, Gates O (1932). Multiple primary malignant tumours. Am J Cancer 10: 1358–1414.
4. Filali K, Hedelin G, Schaffer P, Estève J, Arveux P, Bouchardy C, Exbrayat C, Faivre J, Lévi F, Macé-Lesech J, Pottier D, Torhorst J (1996). Multiple primary cancers and estimation of the incidence rates and trends. Eur J Cancer 32A: 683–90.
5. Horii A, Han HJ, Shimada M, Yanagisawa A, Kato Y, Ohta H, Yasui W, Tahara E, Nakamura Y (1994). Frequent replication errors microsatellite loci in tumours of patients with multiple primary cancers. Cancer Res 54: 3373–5.
6. Jhonson BE (1998). Second lung cancers in patients after treatment for an initial lung cancer. J Natl Cancer Inst 90: 1335–45.
7. Salminen ES, Pukkala E, Teppo L, Pyrhönen S (1994). Subsequent primary cancers following bladder cancer. Eur J Cancer 30A: 303–7.
8. Martini N, Melamed MR (1975). Multiple primary lung cancers. J Thorac Cardiovasc Surg 70: 606–12.
9. Mountain C (1997). Revisions in the International System for Staging Lung Cancer. Chest 11: 1710–7.
10. Liu YY, Chen YM, Yen SH, Tsai CM, Perng RP (2002). Multiple primary malignancies involving lung cancer-clinical characteristics and prognosis. Lung Cancer 35: 189–94.

11. Mydlo JH, Agins JA, Donohoe J, Grob BM (2001). A review of urologic cancer patients with multiple primary malignancies. World J Urol 19: 240–3.
12. Utsumi T, Fujii Y, Takeda S, Minami M, Yoon HE, Okumura M, Matsuda H (1998). Clinical study on lung cancer as a second primary cancer. Surg Today 28: 487–91.
13. Buiatti E, Crocetti E, Acciai S, Gafà L, Falcini F, Milandri C, La Rosa M (1997). Incidence of second primary cancers in three Italian population-based cancer registries. Eur J Cancer 33: 1829-34.
14. Cheng HY, Chu CH, Chang WH, Hsu TC, Lin SC, Liu CC, Yang AM, Shih SC (2005). Clinical analysis of multiple primary malignancies in the digestive system: A hospital-based study. World J Gastroenterol 11: 4215–9.
15. Brock MV, Alberg AJ, Hooker CM, Kammer AL, Xu L, Roig CM, Yang SC. Kammer AL, Xu L, Roig CM, Yang SC (2004). Risk of subsequent primary neoplasms developing in lung cancer patients with prior malignancies. J Thorac Cardiovasc Surg 127: 1119–25.
16. Jones AS, Morar P, Phillips DE, Field JK, Husband D, Helliwel TR (1994). Second primary tumours in patients with head and neck suamous cell carcinoma. Cancer 75: 1343–52.
17. Haughey BH, Gates GA, Arfken CL, Harvey J (1992). Meta-analysis of second malignant tumours in head and neck cancer: The case of an endoscopic screening protocol. Ann Otol Rhinol Laryngol 101: 105–12.
18. Leon X, Quer M, Diez S, Orus C, Lopez-Pousa A, Burgues J (1999). Second neoplasm in patients with head and neck cancer. Head and Neck 21: 204–10.
19. Sasco AJ, Secretan MB, Straif K (2004). Tobacco smoking and cancer: a brief review of recent epidemiological evidence. Lung Cancer (45 Suppl 2): s3–9.
20. Otrock ZK, Mahfouz AR, Salem ZM (2005). Four primary tumours of lung, bladder, prostate, and breast in a male patient. South Med J 98: 945–8.
21. Lorigan P, Radford J, Howell A, Thatcher N (2005). Lung cancer after treatment for Hodgkin's lymphoma: a systematic review. Lancet Oncol 6: 773–9.
22. Darby SC, McGale P, Taylor CW, Peto R (2005). Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300 000 women in US SEER cancer registries. Lancet Oncol 6: 557–65.
23. Heard A, Roder D, Luke C (2005). Multiple primary cancers of separate organ sites: implications for research and cancer control (Australia). Cancer Causes Control 16: 475–81.
24. Ferguson MK, DeMeester TR, DesLauriers J, Little AG, Piraux M, Golomb H (1985). Diagnosis and management of synchronous lung cancers. J Thorac Cardiovasc Surg 89: 378–85.
25. Mathisen DJ, Jensik RJ, Faber LP, Kittle CF (1984). Survival following resection for second and third primary lung cancer. J Thorac Cardiovasc Surg 88: 502–10

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