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Multiple primary malignancies in patients with lung cancer

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Background. *To evaluate the incidence of multiple primary malignancies in lung cancer patients, we summarized our experience in lung cancer patients with multiple primary malignancies.*

Methods. *A total of 1194 consecutive lung cancer patients, who were admitted to our division over a 29-year period up to August 2004, were retrospectively analyzed.*

Results. *Ninety-eight (8.2%) of 1194 lung cancer patients had multiple primary malignancies. Metachronous malignant disease comprised 77.6% and synchronous 21.4%. Multiple primary tumours in our patients were detected more frequent in the advanced stage of lung cancer (IIIA-IV 67.3%) than in the early stage (IA-IIB 32.7%). The histological examination of lung cancer revealed a preponderance of squamous cell carcinoma (40 patients, 40.8%). First primary tumours developed most commonly in gastrointestinal tract, followed by lung and uterus. Fifty-seven (85.1%) of 67 patients with aerogastrointestinal and head and neck cancers had a smoking habit. In 98 patients with multiple primary cancers, forty (40.8%) patients had stage IA-IIIA lung cancer, however, 26 (26.5%) had a surgical resection.*

Conclusions. *Existing metachronous primary tumours proved to be a worse prognostic factor in non-small cell lung cancer patients (p=0.0480), while synchronous primary tumours were not, as well as there was not proven that multiple primary tumours were worse prognostic factors in patients with small cell lung cancer.*

Key words: lung neoplasms; neoplasms, multiple primary

Introduction

Nearly one hundred years ago, Billroth[1] first reported on synchronous cancers in various organs. About 40 years later, Warren and Gated established the criteria for the diagnosis of multiple primary tumours.[2] According to the criteria, such tumours occurring at different locations must be histologically malignant and separated by normal mucosa, and one tumour must not be a metastasis of another. Thereafter, a greater awareness, improved diagnostic techniques and facilities account for the observed increase in the incidence of metachronous and synchronous malignancies. Of patients with lung cancer, 3.2 -

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9.7% are considered to have a metachronous or synchronous malignancy in various sites at presentation.[3-5] This article summarizes our experience in lung cancer patients with metachronous or synchronous malignancies at various sites.

Methods

A total of 1194 consecutive lung cancer patients, who were admitted to our division over a 29-year period up to August 2004, were retrospectively analyzed. In all patients, the diagnosis of lung cancer was confirmed pathologically. Patients were classified using the International System for Staging Lung Cancer.[6] The following criteria have been used for the designation of synchronous cancers: (1) the tumours were anatomically separate; (2) the tumours were histologically different. If the tumours were histologically the same ones, the gross appearance of each tumour was strongly suggestive of the primary cancer.[7]

The criteria that we have used to determine metachronous cancers were related: (1) the tumours were anatomically separated; (2) tumour-free interval was at least 2 years.

At the time of admission, the past medical history including malignancies was taken from all patients. Staging procedures including physical examination, brain magnetic resonance imaging (MRI), chest computed tomographic (CT) scan, abdominal CT scan or ultrasonography, and bone scintigraphy were performed in all patients.

A Cox's proportional hazard model[8] was used for the multivariate regression analysis to clarify the independent prognostic importance of the following variables: gender, age, stage, performance status (PS), resectability at surgery, and existing multiple primary tumours.

Table 1. Characteristics of lung cancer patients with multiple primary malignancies (n=98)

	Number of patients
Gender	
Male	78
Female	20
Age in years	
Range; median	45-85; 70
Histology	
Adenocarcinoma	35
Squamous cell carcinoma	40
Small cell carcinoma	19
Large cell carcinoma	3
Others	1
Performance status (ECOG)	
0-1 / 2-3 / 4	76/20/1
Clinical stage	
IA-B/IIA-B/IIIA/IIIB/IV	20/12/8/24/34
Malignant diseases	
Synchronous/matachronous/both	21/76/1
Gastrointestinal	49
Urogenital	15
Lung	9
Head and neck	9
Others	19
Treatment	
Chemotherapy	37
Surgery	26
Radiation	20
Best supportive care	15

Results

Among the 1194 patients with lung cancer, 98 (8.2%) patients were diagnosed as having metachronous and synchronous malignancies. All relevant data relating to the patients who had metachronous and synchronous malignancies are shown in Table 1. The mean age at presentation of lung cancer was 70 years (range 45-85). Eighty-six (87.8%) of patients were 60 years of age or more. There were 78 men and 20 women. Among 98 patients, 76 had metachronous malignancies, 21 had synchronous malignancies, and 1 had both. As metachronous or synchronous ma-

lignancy, gastric cancer found in 32 patients, colon and rectal cancers in 10, lung cancer in 9, uterus cancer in 6, and prostate cancer in 5, respectively.

A histological examination of lung cancer revealed a preponderance of squamous cell carcinoma (40 patients, 40.8%). There were 35 patients (35.7%) with adenocarcinoma, 19 patients (19.4%) with small cell carcinoma and 3 patients (3.1%) with large cell carcinoma. This distribution of pathologic types is in striking contrast to that found in patients without multiple primary tumours, in whom there was a lower frequency of squamous cell carcinomas (29.5%) and a higher frequency of adenocarcinomas (47.1%).

With regard to tobacco smoking, 77.6% of patients with multiple primary tumours were habitual smokers including 68 patients (69.4%) with 30 pack year or more history of smoking. Fifty-seven (85.1%) of 67 patients with aerogastrointestinal and head and neck cancers were smokers. On the other hand, 76.3% of patients without multiple primary tumours were smokers including 65.1% of patients with 30-pack year or more history of smoking. There was no significant difference in smoking habit between the two groups (p = 0.3510). However, there was a significant difference in 30 pack year or more history of smoking in the two groups (p=0.0005).

In 98 patients with multiple primary cancers, forty (40.8%) patients had stage IA-IIIA lung cancer, however, 26 (26.5%) had a surgical resection. Twenty (20.4%) received chest irradiation, and 15 (15.3%) had only the best supportive care.

A Cox's proportional hazard model was used for the multivariate regression analysis to clarify the independent prognostic importance of the following variables: gender, age, stage, PS, resectability at surgery, and existing multiple primary tumours. For each variable, the proportional hazard assumption was examined graphically. In 1194 patients with lung cancer, gender ($p<0.0001$), stage ($p<0.0001$), PS ($p<0.0001$), and resectability at surgery ($p<0.0001$) were significantly related to the survival. In these patients, the existing multiple primary tumours were not proved to be a worse prognostic factor for the survival ($p=0.1919$). However, in 1018 patients with non-small cell lung cancer, the existing metachronous primary tumours were a significant prognostic factor for survival ($p=0.0480$) (Table 2).

Discussion

The criteria of double primary cancers enunciated by Warren and Gates[2] are now generally accepted. Of patients with lung cancer, an incidence for multiple primary tumours of 3.2 - 9.7% has been reported in the literature.[3-5] Cahan reported the incidence of second malignancies was 3.2% of patients with lung cancer.[3] Antakli *et al*[4] demonstrated 4.1% incidence of the second primary lung cancer in 1572 cases of cancer patients, the metachronous cancer comprised 60% and the synchronous are 40%. Reynolds *et al*[5] found an unusually high association of another primary cancer (9.7%) in cases of lung cancer,

Table 2. Prognostic factors in 1018 patients with non-small cell lung cancer determined by the Cox proportional hazard model

Variables	Coefficient	Standard error	p-value
Age	- 0.095	0.236	0.6884
Performance status	0. 752	0.100	<0.0001
Stage	- 0.633	0.122	<0.0001
Existing metachronous primary tumours	- 0.381	0.193	0.0480
Resectability at surgery	1.019	0.122	<0.0001

and the analysis by the stage of lung cancer as the second primary cancer showed a higher incidence of associated malignancies in the early stage lung cancer than in the advanced stage. In our 1194 lung cancer patients, 98 (8.2%) of them had multiple primary malignancies; the metachronous malignant disease comprised 77.6% and the synchronous one 21.4%. Inconsistent with the report by Reynolds *et al*,[5] more multiple primary tumours in our patients were detected in the advanced stage of lung cancer (in stage IIIA-IV 67.3%) than in the early stage(in IA-IIB 32.7%). We cannot explain the reason why the difference in incidence with regard to the stage was derived from. The precise incidence varies from series to series and might also be related to the length of the follow-up. Moreover, greater awareness and improved diagnostic techniques account for the apparent increase in incidence.

All retrospective studies published so far have revealed that multiple primary tumours occur more frequently than it would be expected by chance in patients who have primary lung cancer. Several environmental factors are thought to play a role in the development of primary and second malignancies. The role of tobacco and/or alcohol use in susceptible tissues of the upper aerodigestive tract is of major importance in multiple primary tumours including lung cancer. In our patients, 85.1% of patients with aerogastrointestinal and head and neck cancers had a smoking habit. The possible roles of immunity, heredity, nutrition are not completely known. The development of the second primary cancer has been well known following the chemotherapy,[9-11] but in this series no patients received chemotherapy for the first primary cancers.

There have been reported that a grater percentage of multiple primary cancers occur in the same organ or in the organs of the same system than in the unrelated organs.[12] The association between unrelated organs, such as lung, stomach and kidney may indicate the circulation of carcinogenic metabolites.[13] Our study showed that the first primary tumours occurred most commonly in gastrointestinal tract, followed by lung and uterus. Our results also revealed that the existing multiple primary tumours were not proved to be a worse prognostic factor for the survival in 1194 patients with lung cancer. However, in 1018 patients with non-small cell lung cancer, the existing metachronous primary tumours were a significant prognostic factor for the survival.

The second primary cancers may develop as much as 30 years later, and therefore, the possibility of a second cancer should be kept in mind in all cancer cases although the concept of a 5-year cure may be valid for the first cancer in most cases.[14] Recognizing that the incidence of the development of the second malignant tumour depends on the exactitude of evaluation, length of follow-up, curability of the first primary tumour, and patterns of tobacco and alcohol use, we should approach the problem of the second malignancies in lung cancer from several angles in the future. When a second primary cancer appears, a careful search for the metastatic disease should be made and a consideration for the curative intervention should be given. An aggressive curative approach conserving as much organ function as possible still offers the greatest chance for the long-term survival.

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