Multiple Primary Lung Cancers*

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From November 1957 to June 1984 at Shanghai Chest Hospital, 30 cases of multiple primary lung cancers were confirmed, based on clinical characteristics, diagnostic process, histologic type, treatment, and prognosis. Out of 3,815 cases of resected primary lung cancer, the incidence of multiple primary lung cancers was 0.8 percent. There were ten synchronous cases and 20 metachronous cases. Seventeen cases were unilateral, and 13 cases were bilateral, of which only one case was synchronous, and the remaining 12 cases were postoperative resection of an opposite lesion. Among the ten synchronous cases, four cases of multiple primary lung cancers were definitely diagnosed before surgery by chest x-ray films or fiberoptic bronchoscopy. Among the 20 metachronous cases, 11 cases were definitely diagnosed before surgery as the second primary lesion by chest x-ray films taken during periodic follow-ups after the initial resection, while nine cases were proven by thoracotomy. All of the 15 cases definitely diagnosed before surgery as multiple primary lung cancers were according to our criteria. Histologically, adenocarcinoma was relatively scarce, at a rate of 13 percent (4/30); but epidermoid carcinoma was predominant, at a rate of 87 percent (26/30), of which 11 cases were accompanied by adenocarcinoma or large-cell undifferentiated carcinoma. The average postoperative survival in the ten synchronous cases was 29 months and in the 20 metachronous cases was 26.2 months, counting from the time of the second operation. The criteria of clinicopathologic findings, early diagnostic procedure, and surgery for multiple primary lung cancers were also discussed.

In recent years, as a result of improvement in the diagnostic methods and the therapy for primary lung cancer, the number of patients suffering from multiple primary lung cancers is increasing. Those suffering from two or more tumors found at the same time are called synchronous, while those suffering from a second primary lung cancer found after the initial resection are called metachronous. Such tumors could be found in different parts of the lung, either unilaterally or bilaterally, and could be of the same or different histologic types. From November 1957 to June 1984, out of 3,815 cases of resected primary lung cancer, there were 30 cases (0.8 percent) of multiple primary lung cancers confirmed by histopathologic examination at the Shanghai Chest Hospital. In this report, we are dealing in retrospect with the criteria for diagnosis, the method of treatment, and the prognosis.

Materials and Methods

Criteria for Diagnosis

Referring to the criteria presented by Warren and Gates in 1953 and by Martini and Melamed in 1975, we drew up the following criteria for the diagnosis of multiple primary lung cancers: (1) Each tumor must be malignant. (2) The two tumors must be anatomicallv distinct and separate. (3) The tumors must be histologically different. (4) If the tumor's histology is of the same type, then for synchronous tumors, each should have its own original site (eg, origin from carcinoma in situ or with invasion of mucosa or scar cancer), and there should be no carcinoma in lymphatic vessels common to both; and for metachronous tumors, the initial primary lung cancer should be resected completely without stump involvement or lymphatic metastasis, the original site of the second primary cancer can be found, and if the original site cannot be found, the interval between the two tumors must be at least three years. (5) Each tumor has its own metastasis. (6) No extrapulmonary metastasis is found.

Clinical Material

Based on the previously mentioned criteria for diagnosis, we have confirmed 30 cases of multiple primary lung cancers. All were male patients, with the age ranging from 41 to 76 years old (average age, 59 years). The average age of the synchronous group was 56 years, while that of the metachronous group was 56 years at initial resection and 60 years at the second resection.

Among the 30 cases, 27 had symptoms of cough, hemoptysis, or chest pain. Three cases were discovered by physical examination. Out of the 27 patients who smoked cigarettes, 23 (85 percent) had smoked more than 400 on the Brinkmann Index.

Ten patients had synchronous lesions, and the other 20 patients had metachronous lesions. The average interval between the two tumors was four years and four months (Fig 1).

*From Shanghai Chest Hospital, Shanghai, People's Republic of China.
Table 1—Surgical Procedures Performed on Ten Synchronous Patients

<table>
<thead>
<tr>
<th>Multiple Cancer Site</th>
<th>Lobectomy</th>
<th>Middle</th>
<th>Lower</th>
<th>Pneumonecotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right lung</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Left lung</td>
<td>3*</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

*In one of three cases, one cancer in situ was removed under fiberoptic bronchoscopy three months before resection of left upper lobe.

Diagnosis

All of the 30 cases were confirmed by histologic or cytologic examination. Out of the ten synchronous cases, four cases of two tumors were found by preoperative chest x-ray films or fiberoptic bronchoscopy and were confirmed by postoperative pathologic examination. The rate of correct preoperative diagnosis was 40 percent (4/10). One case was suspected to be tuberculosis before surgery, but it turned out to be two tumors on thoracotomy. The other five cases were confirmed by pathologic examination of resected lungs. Out of the 20 metachronous cases, 11 were found from chest x-ray films on periodic follow-ups after the initial resection. Seven patients had symptoms after surgery, with positive findings on cytologic examination of the sputum and a mass on chest x-ray films. Two cases had symptoms with positive sputum but normal chest x-ray films; the new tumor was discovered by fiberoptic bronchoscopy. All of the new primary tumors of the 20 cases were confirmed by pathologic examination of resected lungs. Tables 1 and 2 detail the surgical procedures.

Pathologic Characteristics

There were 61 tumors in the 30 cases. Twenty-nine cases had two masses, and only one case had two masses at the left upper lobe and one primary cancer at the opening of the right upper bronchus synchronously.

The diameter of the resected tumors ranged from 0.3 to 8 cm. Eleven cases had tumors in the right lung and six in the left; one case had tumors bilaterally. Twelve cases of second primary tumors were found in the opposite lung after initial resection (60 percent of the metachronous group). Nineteen cases were found in the upper lobe (63 percent), of which eight were synchronous (42 percent) and 11 were metachronous (58 percent) (Table 3).

From Table 4, we can see that 19 cases had two tumors of the same histologic type, in which 15 cases were epidermoid carcinoma. Among them, there were five synchronous cases, all having tumors in different segments of the same lobe. Out of the ten metachronous cases, three were in contralateral lungs, and the other seven were cases of a peripheral mass located in different lobes. The interval between the two tumors was over three years. Two of four cases of adenocarcinoma were sar cancer. In 11 cases with tumors of two different histologic types, nine had epidermoid carcinoma combined with adenocarcinoma, and the other two cases had epidermoid carcinoma combined with large-cell undifferentiated carcinoma.

Outcome

In our study, one patient died of respiratory failure after the second resection of the right upper lobe. Surgical mortality in this study was 3 percent (1/30). The other 29 cases were followed after surgery until May 31, 1985. The rate of follow-up was 100 percent (29/29). The survival rate was as shown in Table 5.

The period of postoperative survival in the ten synchronous cases ranged from half a year to seven years, and the average length of survival was 29 months; while that in the 20 metachronous cases ranged from half a year to five years and four months, counting from the second operation, and the average length of survival was 26.2 months. If the whole course, including two resections, is considered, 11 patients survived more than four years after the initial resection, ten patients more than five years, and four patients more than ten years. The longest period of survival was 14 years. Fifty percent of the postoperative deaths during follow-up were due to recurrence or metastases.

Discussion

Incidence

Early in the year 1924, Beureuther found a bilateral primary lung cancer in postmortem studies. After Lindburg reported a dual cancer in a resected lung in 1935, clinical reports on this subject were scarce. This subject did not arouse attention until Auerbach et al reported in 1967 that the incidence of multiple primary lung cancers reached as high as 3.5 to 14.5 percent in postmortem studies.

In the last 20 years, more than 20 authors have reported 341 cases of multiple primary lung cancers out of 21,381 cases of primary lung cancer all over the

Table 2—Surgical Procedures Performed on 20 Metachronous Patients

<table>
<thead>
<tr>
<th>Location of Second Tumor and Lobe Involved</th>
<th>Initial Lobectomy</th>
<th>Second Resection</th>
<th>Complete Lobectomy</th>
<th>Pneumonecotomy</th>
<th>Sleeve Lobectomy</th>
<th>Segmentectomy</th>
<th>Wedge</th>
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<tbody>
<tr>
<td>Ipsilateral</td>
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<td>Left upper</td>
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<td>...</td>
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<tr>
<td>Left lower</td>
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<td>...</td>
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<tr>
<td>Right upper</td>
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<td>...</td>
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<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Right middle</td>
<td>...</td>
<td>2</td>
<td>3</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1</td>
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<tr>
<td>Right lower</td>
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<td>...</td>
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<td>...</td>
</tr>
<tr>
<td>Contralateral</td>
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<tr>
<td>Left upper</td>
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<td>...</td>
<td>...</td>
<td>1</td>
<td>...</td>
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<td>...</td>
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<td>Left lower</td>
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<td>Right upper</td>
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<tr>
<td>Right middle</td>
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<td>Right lower</td>
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<td>...</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>11</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
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</table>
world. The incidence ranged from 0.5 to 3.9 percent. The average incidence was 1.6 percent. The 30 cases mentioned in this study comprise 0.8 percent of the number of resected primary lung cancers in the same period of time. This percentage is lower than that reported abroad but is similar to that of the reports by Shen and by Wang and Liu in Beijing, China. This low incidence probably resulted from inadequate recognition of this disease, inconsistency in the criteria for diagnosis, and giving up aggressive therapy through erroneous diagnosis, mistaking the second tumor found after the initial resection for a recurrence or metastasis. As the interval between the two tumors in the metachronous group was four years and four months, some patients with new primary cancer did not have enough time to be definitely diagnosed during their period of survival. Furthermore, 60 percent of the specimens in the synchronous group were found by pathologic examination of consecutive histologic sections. All six cases except one were found to have lesions by the naked eye before pathologic sectioning. Thus, it seems possible that an erroneous diagnosis of this disease was easily made by histologic examination only of the lesions found by the naked eye. In recent years the number of multiple primary lung cancers is increasing because of the universal recognition of this disease and the increasing number of second resections on those patients who have a mass after resection of the initial primary lung cancer.

**Etiology and Pathogenesis**

Like the other paired organs, such as the breasts and ovaries, the lungs may have multicentric, systemic, dually located primary cancers. Five cases of epidermoid carcinoma in the synchronous group all had two tumors located in different parts of the lungs, which suggested multiple foci of this disease and different degrees of squamous metaplasia throughout the bronchial tree of patients with lung cancer. The fact that 90 percent of the patients in this study had cigarette smoking habits and 85 percent of them smoked more than 20 packages per year has something to do with the epidermoid carcinoma of many patients in this study. Long-term smoking and stimulation of carcinogen on the epithelium of the whole respiratory tract resulted in the generation of the second or the third primary tumor on the involved mucosal epithelium after the initial resection. After the initial resection of the tumor in four cases of epidermoid carcinoma in this study, the second primary tumor was adenocarcinoma. The fact that two cases of these originated from scar cancer suggested that through the weakening of self immunity, another specific adenocarcinoma could generate from scar tissue of old tuberculosis, pneumonia, or pulmonary infarction. This is another factor resulting in multiple primary lung cancers.

**Criteria for Diagnosis**

It is difficult to give a definition for dual primary cancers or the second primary lung cancer. It could now be considered as multiple primary cancers when two tumors located in different segments or lobes of lungs have varying histologic or cytologic patterns and...
no involvement in lymphatic vessels common to both. There were 19 cases (63 percent) in this study in which two tumors had the same histologic type. It is difficult to establish with absolute certainty whether the second tumor is a metastasis, a recurrence, or indeed a new primary lesion. In our study, there were five cases of the synchronous isolateral type with the two tumors being epidermoid carcinoma; among the five cases, there were four cases in which two tumors were separated in different segments of the same lobe, with three cancers in situ of the eight foci, while the origin of the carcinogenic foci of the other five tumors could be found in the mucosa of a bronchus. In another synchronous case, there were two cancers in the left upper lobe and one more carcinoma in situ located in the opening of the bronchus of the right upper lobe. Thus, all of the 11 tumors were primary lung cancers according to the previously mentioned criteria for diagnosis. Fourteen cases of the metachronous group had the same histologic type; all of their initial primary lung cancers were of the stage-I group and were completely resected. There were five cases in which the second tumors were located in different parts of the isolateral lung, and the other nine cases were located in the contralateral lung. All of the original sites of these second tumors could be found. The average interval between the two tumors was four years and four months. If the period of survival after an initial resected lung cancer is longer than three or more years, there is an expectation of cure, so any tumor detected on chest x-ray films after that period may well represent the second primary lung cancer, rather than a metastasis. Although the interval between two resections presented by Martini and Melamed in 1975 was two years, they considered that the histologic confirmation was more important, especially in the synchronous group. Our criteria for diagnosis of metachronous primary lung cancers includes that the initial tumor has been completely resected without stump involvement and that the original site of the second primary cancer could be found by histologic examination. If the apparent original site of the second cancer cannot be found, then the free interval between the two tumors should be more than three years. Of course, the longer the interval, the less the probability of metastasis or recurrence will be, and the greater the probability of a primary cancer will be.

**How to Diagnose Multiple Primary Lung Cancers**

First, it is necessary to have sufficient understanding of this disease. Secondly, detailed physical checkups and continual follow-ups should be carried out of those patients with respiratory-tract disease who have heavy chronic smoking habits or are exposed to carcinogens, especially those who have undergone resection of a primary lung cancer. Thirdly, chest x-ray films, cytologic examination, and fiberoptic bronchoscopy could be used as routine diagnostic means for this disease. The preoperative diagnosis of 40 percent (4/10) for synchronous patients in this study was in conformity with the postoperative results and was similar to that of Tanimora et al. Fifty-five percent (11/20) of the metachronous patients were found by postoperative routine roentgenograms and were confirmed by histologic examination of resected specimens. We found that 25 percent of the cases were considered before surgery as a recurrence or metastasis for several isolated masses on chest x-ray films or as another tumor developed after the initial resection, but they were confirmed as multiple primary lung cancers after thoracotomy or a second resection. This fact suggests that making an exploratory thoracotomy as early as possible is not only the most reliable means to identify a recurrence, metastasis, or multiple primary lung cancers, but also an aggressive management of this disease.

**Procedures**

Multiple methods of management, mainly resection combined with chemotherapy or radiotherapy, should be adopted according to the histologic types and biologic characters of the tumors (synchronous or metachronous; located unilaterally or bilaterally). As conservative resection does not predispose the patient to local recurrences more frequently than standard lobectomy or pneumonectomy and the probability of survival with the former is similar to that of the latter, it is considered that a conservative resection

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**Table 6—Postoperative Survival Rate in Multiple Primary Lung Cancers**

<table>
<thead>
<tr>
<th>Year</th>
<th>Jensik et al (Cumulative Survival; Metachronous)</th>
<th>Tanimora et al (Kaplan-Meier Method; Synchronous)</th>
<th>Present Study (Life-Table Analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>70</td>
<td>Synchronous</td>
</tr>
<tr>
<td>2</td>
<td>.</td>
<td>48</td>
<td>Metachronous</td>
</tr>
<tr>
<td>3</td>
<td>.</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>22</td>
<td></td>
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<tr>
<td>15</td>
<td>13</td>
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</tbody>
</table>

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which permits a more favorable functional result is preferable, so that if the patient develops a second primary tumor, there is a chance of an appropriate second resection.\textsuperscript{14,13} Because many synchronous tumors were scattered in different parts of the lung, because the number of metachronous patients was twice that of synchronous, and because 60 percent of the metachronous tumors were located in the opposite lung from the initial primary cancer, we think that it is necessary to resect tumor and involved lymph nodes but, more importantly to preserve pulmonary function at the same time. It must be carefully considered whether segmentectomy, sleeve lobectomy, or wedge resection is to be applied in order to resect the second primary tumor. This all depends upon the patient's physiologic condition and the resected fields of the initial cancer.\textsuperscript{14,13} While resecting the second tumor, if there is close pulmonary adhesion and the tumor has involved lymph nodes and blood vessels, it would be easier and safer to isolate and cut off the bronchus first, and then to manage the blood vessels.

**Prognosis**

The average survival of 30 cases in this study was 27.6 months; that in the synchronous group was 29 months, and that in the metachronous group was 26.2 months. Worth mentioning are the two cases in which the patients were over 70 years old. One patient had his left upper lobe resected at the age of 72 years and had his right middle lobe resected 30 months later. Both were primary epidermoid cancers. This patient survived for 4.5 years after resection. The other patient had his epidermoid cancer accompanied by adenocarcinoma on the left lower lobe resected when he was 64 years old. Twelve years later (ie, when he was 76 years old), he had his large-cell undifferentiated tumor in the right lower lobe resected. He has survived one year since then and is still living well. The five-year survival period of this group is similar to that reported by Jensik et al\textsuperscript{15} and Tanimora et al\textsuperscript{16} in 1981 and 1982, respectively (Table 6).

**Conclusion**

In conclusion, it is considered necessary to draw up criteria for diagnosis of this disease. The key to early diagnosis of multiple primary lung cancers lies in detailed examination of the respiratory tract and continual follow-ups on those who have undergone initial resection of a primary lung cancer. A conservative resection with the aim of preserving pulmonary function is not only in conformity with the pathophysiologic characteristics of multiple primary lung cancers, but also is an important factor affecting the length of survival after resection or the second resection.

**References**