OPERATIVE APPROACH FOR MULTIPLE PRIMARY LUNG CARCINOMAS

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Of 908 patients who underwent operation for primary lung cancer between January 1985 and June 1996, we considered 57 (6.3%) to have a second primary lung cancer, which was synchronous in 28 cases (3.1%) and metachronous in 29 cases (3.2%). Five-year survival for patients with synchronous and metachronous disease from initial treatment of cancer was 70.3% and 66.0%, respectively. Survival after the development of a metachronous lesion was 32.9% at 5 years. Sixteen of the synchronous second tumors (57%) were detected on preoperative radiography or bronchoscopy and 11 (39%) at the time of operation. Survival of patients at stage I or II from treatment of a synchronous lesion ($p = 0.002$) and of a metachronous second lesion ($p = 0.028$) was significantly better compared with those at stage III or IV. Therefore it is important to carefully examine a synchronous lesion before and during the operation of a primary lung cancer and to perform close follow-up surveillance for early detection of a metachronous lesion. In treating multiple lung carcinomas consideration should always be given to performing precise staging, aggressive operative approach for early stage, and oncologically sound parenchymal sparing procedures. (J Thorac Cardiovasc Surg 1998;115:836-40)

Although the idea of multiple primary lung carcinomas, which was first described by Beyreuther¹ in 1924, has been generally accepted, the prevalence remains unclear and varies from 1% to 10% for synchronous and metachronous cancers together.²⁻⁹ Despite a recently reported increase, most reports of large series of patients with multiple primary lung cancers did not use developed radiographic technique, such as computed tomography, in the past. If they did it, they probably would have found a higher prevalence of synchronous cancers in the preoperative workup and of metachronous cancers during follow-up. In addition, we followed the policy that lung-saving procedures, such as bronchoplasty for a primary lesion, must always be kept in mind. This article summarizes our experience of evaluation and operative treatment of patients in whom multiple

primary lung carcinomas were suspected over the past 11 years.

Patients and methods

The medical records of all patients who underwent operation for primary lung cancer at our center between January 1985 and June 1996 were reviewed. All charts of patients with a probable diagnosis of multiple primary lung cancer were available for analysis. The following criteria, based on and modified from those of Martini and Melamed,⁴ have been used for designation of multiple primary lung cancers: (1) The tumors were anatomically separate (different lobes or lungs). (2) The tumors were histologically different. If the tumors were histologically the same, they must have no systemic metastases or mediastinal spread. Where all the lesions were squamous cell carcinomas, a classification was accepted if a separate origin from an area of carcinoma in situ could be identified for each. In case of the metachronous tumors with the same histologic findings, tumor-free interval was at least 2 years. Patients who did not meet these criteria were excluded. All cancers were staged using the criteria of the New International Staging System for Lung Cancer,¹⁰ and staging was based on data obtained from imaging, bronchoscopy, invasive diagnostic techniques, operative findings, and pathologic findings. Careful intraoperative staging at the time of operative resection was done by dissecting intrapulmonary, hilar, and mediastinal nodes. Histologic typing was done according to the World Health Organization classification.¹¹ All cases of bronchioloalveolar carcinoma were excluded just because of the question of multicentricity of those primary cancers. A syn-

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Table I. Histologic classification of multiple primary lung carcinomas

Classification	Synchronous	Metachronous
Squamous cell carcinoma		
Squamous cell carcinoma	6 (21)	14 (48)
Adenocarcinoma	12 (43)	2 (6)
Small cell carcinoma	0	2 (6)
Carcinoid	1 (4)	0
Adenosquamous carcinoma	1 (4)	0
Large cell carcinoma	0	1 (3)
Adenocarcinoma		
Adenocarcinoma	6 (21)	5 (17)
Small cell carcinoma	1 (4)	3 (10)
Large cell carcinoma	1 (4)	1 (3)
Small cell carcinoma		
Large cell carcinoma	0	1 (3)
Total	28 (100)	29 (100)

Numbers in parentheses are percentages.

chronous multiple primary lung cancer was identified if there was radiographic evidence of a second primary tumor before the first operation or if a second primary tumor was discovered incidentally during operation or in the resected specimen. The larger of two synchronous tumors was considered the first primary cancer for the purpose of analysis. All patients who underwent resection for a primary lung cancer had a chest roentgenogram, a history, and a physical examination at the follow-up visit, which took place at least twice a year.

Cumulative survivals were calculated by the Kaplan-Meier estimation, and differences in survival were determined by log-rank analysis.

Results

From January 1985 to June 1996, 908 patients underwent operation for a primary lung cancer at our center. Fifty-seven (6.3%) patients were found to have a second primary lung cancer, three of these also had a third cancer.¹² Synchronous tumors comprised 28 of 908 (3.1%) and metachronous tumors 29 of 908 (3.2%). Overall follow-up ranged from 6 to 144 months, with a median of 51 months.

Synchronous carcinoma. The average age at initial treatment was 64.3 ± 7.7 years (mean $\pm$ standard error), with an age range of 47 to 76 years. There were 24 male and 4 female patients. Squamous cell carcinoma constituted 14 of 28 (50%) of the first tumors and 12 of 28 (43%) of the second tumors. Adenocarcinoma was seen in 11 of 28 (39%) of the first tumors and 15 of 28 (54%) of the second tumors. The histologic findings of the synchronous second tumor were the same as those of the synchronous first tumor in 12 (43%) patients and equally consisted of squamous cell carcinoma and adenocarcinoma (Table I). Sixteen of the sec-

Table II. Staging of multiple primary lung carcinomas

Stage	Synchronous	Metachronous	
	Most advanced tumor	First tumor	Second tumor
I	11 (39)	15 (52)	17 (59)
II	5 (18)	6 (21)	1 (3)
IIIA	5 (18)	8 (28)	11 (38)
IIIB	3 (11)	0	0
IV	4 (14)	0	0
Total	28 (100)	29 (100)	29 (100)

Numbers in parentheses are percentages.

ond tumors (57%) were detected on preoperative radiography or bronchoscopy, and 11 (39%) were discovered during operation. In the other remaining patient (4%), the second lesion was diagnosed incidentally by histologic examination of the resected specimen. The second tumor was on the same side as the first tumor in 21 cases (75%). Stage I, II, IIIA, or IIIB disease was noted in 11 (39%), 5 (18%), 5 (18%), or 3 tumors (11%), respectively (Table II). The four remaining patients (14%) had double tumors that were histologically different, and postoperative pathologic examination showed additional lesions that were diagnosed with pulmonary metastasis. Staged resection was performed on 18% of synchronous lesions (5 of 28) because they were contralateral to the first tumor. Resection was performed in all patients except for one with extended disease. Lobectomy was by far the most common procedure and was performed in 23 patients (82%), including seven combined sleeve resections of the bronchus. Two pneumonectomies including sleeve technique for the bronchus and two segmentectomies were carried out. Resection of the tumors was possible in all patients, but two patients had pleural dissemination. No postoperative deaths occurred within 30 days after resection.

Overall 5-year survival was 70.3% for all patients having a synchronous cancer (Fig. 1). The 5-year survival of patients with stage I or II and stage III or IV was 79.0% and 41.0%, respectively. Survival for patients with stage I or II was significantly better ($p = 0.002$) compared with stage III or IV (Fig. 1).

Metachronous carcinoma. The average age at the time of treatment for the first and second tumor was 62.6 ± 8.6 years (mean $\pm$ standard error) with an age range of 32 to 73 years, and 66.7 ± 9.3 years with an age range of 33 to 79 years, respectively. All patients except one were men. The mean interval between the initial treatment and the second was

Fig. 1. Actuarial survival curves of patients in whom synchronous multiple primary lung cancers developed. Middle curve indicates survival for all patients with synchronous disease. Top and bottom curves indicate the survival of patients with stage I or II and stage III or IV, respectively. Survival of patients with stage I or II was significantly better ($p = 0.002$) compared with stage III or IV.

4.1 $\pm$ 2.3 years. The longest interval was 10 years and 8 months, and the shortest only 8 months. Every case whose interval was less than 2 years had a histologically different tumor. More than 5 years after the first tumor, metachronous primary tumors appeared in 13 patients (45%). Squamous cell carcinoma was the most common histologic type, making up 17 (59%) of 29 patients as the first tumor and 16 (55%) patients as the second tumor. The next most common histologic type was adenocarcinoma, occurring in 8 (28%) and 8 (28%) of the first and second tumors, respectively. The first and second tumors shared the same histologic findings in 19 (63%) patients (Table I). The same histologic type was more likely to occur if the first tumor was a squamous cell carcinoma as opposed to an adenocarcinoma (14 of 17 patients, 82% and 5 of 8, 63%, respectively). Stage I in first and second tumors constituted 52% (15 of 29) and 59% (17 of 29), respectively. No tumors were more advanced than stage IIIA (Table II). Resection of the tumors was possible in all patients. Obviously, more patients underwent segmentectomy or wedge resection at reoperation for the second disease compared with initial operation. No postoperative deaths occurred within 30 days after resection.

The 5-year actuarial survival after the initial and the second resection was 66.0% and 32.9%, respectively, for all patients with a metachronous cancer

Fig. 2. Actuarial survival curves of patients in whom metachronous multiple primary lung cancers developed. Top and bottom curves indicate the survival from treatment of the first and the second tumor, respectively.

(Fig. 2). Survival for patients with metachronous disease determined from treatment of first tumors was not significantly different from that of patients with synchronous disease. Survival curves from treatment of the first tumor indicated no significant difference between patients with stage I or II and stage III (Fig. 3). Patients with stage I or II and stage III of the second tumor had survival rates of 49.8% and 24.0% for 5 years, respectively. Survival from treatment of the second tumor was significantly better ($p = 0.028$) for patients with stage I or II compared with stage III (Fig. 4).

Discussion

Clinically, it is difficult to distinguish a second primary carcinoma from a metastatic lesion arising from a first tumor. Martini and Melamed⁴ in 1975 outlined the criteria for differentiation between the two, which have been used by most subsequent authors, including us. Pairolero and associates¹³ using criteria similar to ours, reported a 52% 2-year survival for metachronous primary tumors compared with 23% and 9% 2-year survival for local and distant recurrent disease, respectively. These data suggest that patients with multiple primary tumors have a more favorable prognosis than patients with locally recurrent or metastatic disease.^{14, 15} Therefore an appropriate identification of multiple primary lung cancers is critical. In addition to the application of stringent criteria for the diagnosis of multiple primary lung cancers, incidence of this disease may be affected by several factors, including

Fig. 3. Actuarial survival curves of patients in whom metachronous multiple primary lung cancers developed from treatment of the first tumor. *Solid and dashed lines* indicate the survival in patients with stage I or II and stage III of the first tumor, respectively. No significant differences in survival probability were found between stage I or II and stage III.

the sensitivity of diagnostic procedures, the pathologist's skill, the efficacy of the treatment used, and the length of the patient's survival. These latter factors, in particular the development of radiography, would contribute to an increase in the incidence of these multiple tumors, and therefore standardized criteria for the diagnosis of this disease should be developed. In contrast to recent years, most studies in the past did not use computed tomography. If they did it preoperatively, they could have found a higher prevalence of synchronous tumors in the same way they might have found a higher prevalence of metachronous cancers or might have detected them earlier should they have used it during follow-up. The developed radiographic technique in this series probably accounted for the increased incidence of multiple primary tumors and a high proportion of synchronous lesions.

The result that 57% of synchronous second lesions were discovered preoperatively and 39% intraoperatively indicated the role of careful detection of second lesions before and during the procedure for a primary lung cancer. The inferior survival of metachronous second lesions compared with first lesions might be related to underestimating because of technical difficulties during the second procedure and to resorting to lesser resections because of limited pulmonary reserve. The survival advantage of metachronous lesions compared with synchro-

Fig. 4. Actuarial survival curves of patients in whom metachronous multiple primary lung cancers developed from treatment of the second tumor. *Solid and dashed lines* indicate the survival in patients with stage I or II and stage III of the second tumor, respectively. Survival of patients with stage I or II was significantly better ($p = 0.028$) than that of patients with stage III disease.

nous ones has been reported by others^{14, 16, 17} and does not agree with our study. The possibility that some patients with recurrent or metastatic disease have also been included as subjects cannot be ruled out for other published literature. We believe that the difference between synchronous and metachronous cancers is just an arbitrary one because it refers to the moment of diagnosis and not to the moment of development.

The question of whether a newly discovered lung lesion after resection is actually a second primary tumor or a recurrence remains a theoretical one. We follow the policy of thoroughly restaging all such lesions and operating with the intention to cure whenever possible. Therefore, although patients with unilateral lesions found in separate lobes should be treated by pneumonectomy or bilobectomy, lobectomy with additional wedge resection may be done in patients with limited pulmonary function. In patients with bilateral lesions a curative resection should be done on the side that initially appears to be more advanced. However, lung tissue should not be sacrificed for expediency in these patients. If a lung-saving procedure such as a sleeve lobectomy for the first lesion is done and sufficient pulmonary function is preserved, a second radical operation is possible. Otherwise, there is no choice except to perform conservative treatment, including wedge resection, chemotherapy, radiation therapy

or all three. A curative yet limited extent of operation allowing for maximum preservation of pulmonary function should be of prime consideration. This strategy may allow subsequent treatment of the second lesion by operation. Bronchoplasty, including sleeve resection, has been used frequently at this center not only for patients with limited pulmonary reserve but also for those with sufficient reserve.¹⁸ Bronchoplasty on the first occasion would leave the patient with more lung tissue to resect should a second primary tumor develop later. This principle of conservation is very important because the loss of pulmonary function from more radical procedures for the first lesion may be extensive or may prevent a second operation. Re-resection can almost be performed safely, as indicated by our series with no operative deaths and others' operative mortality rates.^{2, 16}

Survival for patients with early-stage multiple primary tumors was significantly better than those with advanced tumors, as has been reported by us and others.² These data highlight the need for careful lifelong screening for a second lesion to improve overall survival. We obtained very poor results in the whole group of stage III or IV synchronous tumors and of stage III metachronous second tumors. The advance of staging and the presence of a second primary tumor could influence survival. Therefore, when a new primary lung tumor has been found, precise staging is necessary and an aggressive operative approach is indicated, especially for earlier second tumors.

We recommend that the resection be tissue-sparing whenever it is reasonable to do so whether it is the first or any subsequent operation. Therefore we should avoid pneumonectomy and instead try to use bronchoplasty as much as possible.

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