Surgical Treatment and Prognosis of Synchronous Double Primary Lung Cancer: a Report of 31 Cases

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OBJECTIVE The concept of double primary lung cancer (DPLC) has been generally accepted. Recently, an increasing incidence of synchronous DPLC has been reported, while the diagnostic standard and treatment strategies remain to be improved. This study was conducted to investigate effective surgical treatment and prognosis of synchronous DPLC.

METHODS From January 1983 to April 2004, 31 patients with synchronous DPLC were operated in our department. Clinical data, such as surgical pattern, postoperative complications, and survival status, of all these patients were reviewed retrospectively.

RESULTS The 31 patients with synchronous DPLC accounted for 0.67% of all the 4,649 patients operated for primary lung cancer in our department during the same period. Both tumors of the synchronous DPLC were resected with lobectomy or pneumonectomy in 12 patients, while among the other 19 patients at least 1 tumor was treated with partial pulmonary resection. The postoperative morbidity was 29% (9/31), including 1 case of respiratory insufficiency, 3 cases of atelectasis, 2 cases of atrial fibrillation, 1 case of haemoptysis, 1 case of pleural effusion, and 1 case of wound fat necrosis. No deaths occurred during the operations or within 30 days postoperatively. The postoperative 1-, 3-, and 5-year survival rates were 52%, 29%, and 20%, respectively.

CONCLUSION The incidence of synchronous DPLC is low. An aggressive and reasonable surgical approach can achieve a satisfactory outcome in patients with synchronous DPLC. The postoperative morbidity is low. Some patients might achieve long-term survival.

KEYWORDS: synchronous double primary lung cancer, surgery, prognosis.

The concept of double primary lung cancer (DPLC), which was first described by Beyreuther [1] in 1924, has been generally accepted. Recently, an increasing incidence of synchronous DPLC has been reported,[2-7] partly because of improved radiographic techniques, especially the wide use of high-resolution computed tomography in preoperative workups of lung cancer, and partly because of the improvement in understanding of DPLC. Although there have been many reports concerning the diagnosis and surgical treatment of DPLC,[2-7] several issues, such as diagnostic standards, surgical approach and prognostic factors need further investigation. Here we review the clinical data from 31 patients who underwent an operation for synchronous DPLC in our department over the past 20 years. The results are described as follows.

PATIENTS AND METHODS

From January 1983 to April 2004, 4,649 patients underwent an operation for primary lung cancer in the Department of Thoracic Surgery,

Cancer Hospital/Institute, Chinese Academy of Medical Sciences&Peking Union Medical College. The medical records of all of these patients were reviewed retrospectively, and the clinical data of those with 2 separate pulmonary malignant lesions presenting simultaneously and suspected to be synchronous DPLC were analyzed and summarized.

A synchronous DPLC 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 an operation or in the resected specimen.

The following criteria, based on and modified slightly from those recommended by American College of Chest Physicians (ACCP) in 2003,[8] have been used for designation of synchronous DPLC: (1) two simultaneous tumors were histologically different; (2) if two simultaneous tumors were histologically the same, they must be located in different lobes and without N2 or N3 involvement or systemic metastases; (3) two simultaneous tumors located within the same lobe and with identical histology were excluded; (4) the cases with double tumors of bronchioloalveolar carcinoma were excluded.

Histological classification of lung cancer proposed by Liu et al.[9] was adopted in this study. 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, operative findings, and pathologic findings.

Survival time was defined as the period between operation and death or last follow-up, and the outcomes were compared with those of single primary lung cancer operated in our department.[11]

RESULTS

Thirty-one patients were identified to have synchronous DPLC according to the criteria mentioned above, and accounted for 0.67% of all 4,649 patients operated for primary lung cancer in our department during the same period. There were 19 male and 12 female patients. The median age at initial treatment was 63 years, with an age range of 32 to 83 years. The histological findings of the synchronous second tumor were different from those of the synchronous first tumor in 22 patients, and in the other 9 patients, the tumors were histologically the same but located in different lobes and without N2 or N3 involvement or systemic metastases. The second tumor was within the same lobe as the first tumor in 8 cases, in another lobe of the same side in 16 cases, and on the other side in 7 cases.

Synchronous DPLC within the same lobe

Of the 8 cases with synchronous DPLC located within the same lobe, the numbers of cases with lesions in the right upper lobe, right lower lobe, left upper lobe, or left lower lobe were 1, 4, 2, or 1, respectively. Two wedge resections, lobectomy, or bilobectomy were performed in 2, 4, or 2 patients, respectively. Postoperative pathologic diagnoses of the separate tumors were squamous carcinoma and adenocarcinoma in 2 cases, squamous carcinoma and adenosquamous carcinoma in 3, adenocarcinoma and adenosquamous carcinoma in 1, and adenocarcinoma and bronchioloalveolar carcinoma in 1, adenocarcinoma and large cell carcinoma in 1. Postoperative clinical-pathologic stages were double IA in 1 case, IB and IA in 3, double IB in 2, IIA and IB in 1, double IIIA in 1. Operative resection and complete resection rates were 100% (8/8) and 62.5% (5/8), respectively.

Synchronous DPLC in separate lobes on the same side

Of the 16 cases with synchronous DPLC in separate lobes on the same side, the numbers of cases with lesions in the right upper and lower lobes, right upper and middle lobes, right main bronchus and lower lobe, or left upper and lower lobes were 8, 5, 1, or 2, respectively. Lobectomy and wedge resection, lobectomy and resection of the bronchial wall, sleeve lobectomy and wedge resection, bilobectomy and wedge resection, lobectomy and sleeve lobectomy, or pneumonectomy were performed in 8, 1, 2, 1, 1, or 3 patients, respectively. Postoperative pathologic diagnoses of the separate tumors were squamous carcinoma and adenocarcinoma in 4 cases, squamous carcinoma and bronchioloalveolar carcinoma in 3, adenocarcinoma and bronchioloalveolar carcinoma in 2, adenocarcinoma and carcinoid in 1, bronchioloalveolar carcinoma and small cell carcinoma in 1, bronchioloalveolar carcinoma and large cell carcinoma in 1, double squamous carcinomas in 2, double adenocarcinomas in 2. Postoperative clinical-pathologic stages were IB and IA in 4 cases, double IB in 3, IIA and IB in 1, IIB and IA in 2, IIB and IB in 1, double IIB in 1, IIIA and IA in 1, IIIA and IIB in 1, IIIB and IA in 1, IV and IIB in 1. Operative resection and complete resection rates were 100% (16/16) and 75% (12/16), respectively.

Synchronous DPLC on the opposite side

Of the 7 cases with synchronous DPLC on the opposite

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side, the numbers of cases with lesions in the right and left upper lobes, right upper and left lower lobes, or right lower and left upper lobes were 1, 3, or 3, respectively. Staged resections were performed on all these patients because the tumors were bilateral. Two wedge resections, segmentectomy and wedge resection, lobectomy and wedge resection, or bilobectomy were performed in 1, 1, 3, or 2 patients, respectively. Postoperative pathologic diagnoses of the separate tumors were double squamous carcinomas in 1 case, squamous carcinoma and adenocarcinoma in 1, double adenocarcinomas in 1, adenocarcinoma and bronchioloalveolar carcinoma in 1, adenocarcinoma and large cell carcinoma in 1, double adenoquamous carcinomas in 1, double carcinoids in 1. Postoperative clinical-pathologic stages were IB and IA in 3 cases, double IB in 3, IIA and IA in 1. Both operative resection and complete resection rates were 100% (7/7).

Postoperative morbidity and prognosis

The overall operative resection rate and complete resection rate were 100% (31/31) and 77% (24/31), respectively. The postoperative morbidity was 29% (9/31), including 1 case of respiratory insufficiency, 3 cases of atelectasis, 2 cases of atrial fibrillation, 1 case of haemoptysis, 1 case of pleural effusion, and 1 case of wound fat necrosis. No deaths occurred during operations or within 30 days postoperatively. The postoperative 1-, 3-, and 5-year survival rates were 52%(13/25), 29%(4/14), and 20% (2/10), respectively.

DISCUSSION

Incidence

The synchronous DPLC incidence of 0.67% in this series was lower than those reported by others[5-7] (1.1%~3.1%), indicating a need to improve diagnostic rates. An increase in the incidence of synchronous DPLC was observed over the last 5 years in our series, which can partly be attributed to the improvement of radiography, especially the wide use of high-resolution computed tomography in preoperative workups of lung cancer, and partly to better understanding of synchronous DPLC. It should be emphasized that the possibility of synchronous DPLC must always be kept in mind if 2 separate pulmonary malignant lesions present simultaneously in the same patient. If necessary, a thoracotomy exploration and frozen section examination should be conducted in order to help differentiate synchronous DPLC from intrapulmonary metastases produced by a primary lung cancer, thus enabling the surgeon to choose an appropriate procedure. It is usually difficult to determine whether the histological type of the 2 cancers is the same or different based on a frozen section examination, so an ACCP panel believes it is reasonable to proceed with a resection of each lesion if each appears to be a resectable primary lung cancer, given that the patient has already been exposed to the morbidity of a thoracotomy.[8]

The diagnosis of synchronous DPLC

The diagnosis of synchronous DPLC is relatively easy to make when the 2 tumors are of different histology. However, in the absence of reliable molecular biological techniques, in the case of identical histological findings it is difficult to distinguish synchronous DPLC from intrapulmonary metastases formed from a primary lung cancer. Until recently, most investigators adopted the diagnostic criteria outlined by Martini and Melamed [12] in 1975: If the tumors were histologically the same, they must be located in different segments, lobes, or lungs and (1) originate from carcinoma in situ; (2) no carcinoma in the lymphatics common to both; (3) no extrapulmonary metastases at the time of diagnosis. Zuo et al.[13] proposed that the pathologic stage of the 2 tumors with identical histological findings should both be stage I.

The ACCP proposed new criteria for the diagnosis of synchronous DPLC in 2003:[8] (1) different histological types or different molecular genetic characteristics or arising separately from foci of carcinoma in situ; (2) same histology, anatomically separated cancers in different lobes and no N2,3 involvement and no systemic metastases. Compared with the criteria proposed by Martini and Melamed,[12] in the ACCP criteria, the item of *no carcinoma in lymphatics common to both* was modified to *no N2,3 involvement* for histologically identical synchronous DPLC. Any additional focus of lung cancer of the same histological type within the same lobe as the primary lung cancer, and in the absence of systemic metastases was defined as satellite nodules from the primary tumor. Two tumors of the same histology were considered as hematogenously spread pulmonary metastases if they were with multiple systemic metastases or were located in different lobes and with N2,3 involvement.

The criteria of the present study were based on, and modified slightly, from the ACCP criteria.[8] Because of the lack of reliable molecular biological techniques and the difficulty in determining the separate origin from carcinoma in situ, the 2 indexes had not been adopted. We excluded all cases with double tumors of bronchi-

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oloalveolar carcinoma just because of the question of multicentricity of this subtype.

We suggest further differential approaches to improve the diagnosis of synchronous DPLC with the same histology because restrictions only by stage and location are inadequate. For instance, 2 central cancers found via radiography or bronchoscopy, or 2 peripheral cancers with typical features of primary lung cancer found via radiography or during operation may suggest synchronous DPLC. Ichinose et al.[14] suggested that DNA flow cytometric analysis of tumors may be of value in the diagnosis of synchronous DPLC. In their report the tumors were defined as independent of each other when 1 tumor showed diploidy and the other aneuploidy, or when each DNA index of abnormal clones between 2 aneuploid tumors was different.

Surgical treatment

Synchronous DPLC is a special clinical situation and its biological behavior in comparison with single primary lung cancer is still unclear, thus the option of management remains difficult. Surgical treatment is the management of choice for non-small cell lung cancer, which is theoretically applicable to synchronous DPLC. However, the option of surgical procedures is still controversial. Some surgeons suggest partial pulmonary resection in order to preserve pulmonary function, while others recommend aggressive lobectomy just as for single primary lung cancer. We believe that the following rules should be observed: (1) lobectomy should be attempted when there is adequate pulmonary reserve; (2) the cancer in a relatively advanced stage should be resected first if the lesions are bilateral; (3)lobectomy should be performed on the cancer in a relatively advanced stage and partial pulmonary resection conducted on the other one if the pulmonary reserve can not tolerate 2 lobectomies; double partial pulmonary resections are acceptable if the pulmonary reserve is even worse; (4) no matter which surgical procedure is used, systematic regional lymph node dissecton is necessary for accurate staging and improvement of outcome; (5) the choice of a surgical procedure should follow the basic principle of resecting the tumors to the maximal possible extent while preserving the pulmonary reserve and at the same time decreasing operative risks to a minimally possible extent.

Prognosis

The postoperative 5-year survival rate of patients with synchronous DPLC reported by others varies from 0% to 70%.[2-7] In the present study, the 5-year survival rate was 20%, which is much lower than that of single primary lung cancers operated in our department [11] (38.8%). The following factors may help to explain the poor prognosis in this series: (1) the biological behavior of synchronous DPLC can be different from that of single primary lung cancer; (2) intrapulmonary metastases from primary lung cancer occasionally were misdiagnosed as synchronous DPLC; (3) the surgical procedures were too conservative partly because of our viewpoint of patient management and partly because of the limitation by the cardiopulmonary function of the patients. For example, at least one cancer focus underwent partial pulmonary resection in 19(61%) patients, lymph node dissection was not systematic in 8 (26%), and palliative operations were performed in 7 (23%).

Conclusions

There are no ideal criteria for the diagnosis of synchronous DPLC at present. With the diagnostic approaches and criteria available, limitation of distinguishing synchronous DPLC from intrapulmonary metastases formed from primary lung cancer still exists, especially for those with the same histology, and misdiagnosis remains inevitable. The differential diagnosis between synchronous DPLC and intrapulmonary metastases from primary lung cancer is crucial not only for treatment choice but also for prognosis prediction. We believe that the ACCP criteria [8] are feasible and will be refined with the advancement in molecular biology. With an aggressive and reasonable surgical approach, a satisfactory outcome can be obtained in patients with synchronous DPLC, long-term survival can be achieved in some, and the postoperative morbidity and perioperative mortality are acceptable.

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