ORIGINAL ARTICLE

Surgical treatment for pulmonary pleomorphic carcinoma: A retrospective study of 60 patients

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Keywords

Lung cancer surgery; pulmonary pleomorphic carcinoma; retrospective study; surgical treatment; thoracotomy.

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Abstract

Background: Pleomorphic carcinoma is a rare epithelial malignant tumor. Because the clinical characteristics and behavior of the disease remain unclear, we investigated the clinicopathological findings and prognosis of 60 patients with pleomorphic carcinoma.

Methods: The clinicopathological characteristics of 60 cases of pulmonary pleomorphic carcinoma identified between 1999 and 2011 were studied. Of these, 55 patients had peripheral disease and five had central disease. The tumor size in all patients was 1–9.5 cm (mean, 5.8 ± 4.5 cm), while 30 had lesions with a diameter larger than 5 cm. All patients underwent pulmonary resection.

Results: There were no in-hospital deaths. The three and five year survival rates of all patients were 47.2% and 25.6%, respectively. The three and five year survival rates were 57.3% and 32.5% for N0 patients, and 25.4% and 17.1% for N1-2 patients, respectively. Overall survival was significantly different between the radical resection and incomplete resection groups. Multivariate Cox regression analyses of overall survival for all 60 patients indicated that radical resection ($P = 0.041$), tumor node metastasis (TNM) stage ($P = 0.044$), and nodal status ($P = 0.029$) were significant independent prognostic factors.

Conclusion: Pleomorphic carcinoma is a rare type of lung cancer. In our study, pleomorphic carcinoma of the lung was often found as a peripherally located large mass and was associated with a poor prognosis. Radical resection, TNM stage and nodal status were significant independent prognostic factors.

Introduction

Pulmonary pleomorphic carcinoma is a rare disease that accounts for approximately 0.1–0.4% of all pulmonary carcinomas.¹ Before 1999, pulmonary pleomorphic carcinoma was considered a variant of other types of lung cancer because of its specific clinical manifestations, complex pathological tissues, and clinically indefinite characteristics. Because of the lack of a conclusive definition and the rarity of pulmonary pleomorphic carcinoma, no consensus has been reached regarding its diagnosis and treatment. In 1999, lung cancers containing a sarcomatous component were defined as pleomorphic carcinomas according to the World Health Organization (WHO) classification, and thus, pulmonary pleomorphic carcinoma was defined as a new type of lung cancer. In 2003, according to the WHO classification, pulmonary pleomorphic carcinoma was defined as a cancer containing spindle or giant cell components, such as squamous

cell carcinoma, adenocarcinoma, and large cell carcinoma, or cancers consisting only of spindle or giant cells that accounted for at least 10% of the tumor.²

Compared with other subtypes of non-small cell lung carcinomas, pulmonary pleomorphic carcinoma is highly malignant and is associated with a poor prognosis. Because of its rarity, until now, there are only a few published reports available on its clinicopathological characteristics and prognosis of a relatively large number of such patients. Between 1999 and 2011, a total of 60 patients with pulmonary pleomorphic carcinoma were surgically treated in our hospital. We have summarized our findings in this report.

Materials and methods

The patients comprised 55 men and five women whose ages ranged from 45 to 77 years (mean, 63.4 ± 12.5 years). Among the patients, 53 were current or ex-smokers. Fifteen were

asymptomatic, and their disease was discovered on routine examination. Forty-five patients exhibited clinical symptoms, including bloody sputum in 16 patients, cough in 13 patients, and pain in the chest and back in 10 patients. All 60 patients underwent chest computed tomography (CT), which showed nodules or masses with a diameter of 1–9.5 cm (mean, 5.8 ± 4.5 cm). Among these patients, 30 had lesions with a diameter larger than 5 cm. Four patients presented with a tumor in the central cavitation; 15 with a central low-density tumor or tumor necrosis signs; and seven with tumor invasion of the chest wall or other peripheral tissues.

All patients underwent CT or magnetic resonance imaging (MRI) of the head, B ultrasonic examination of the abdomen, and bone scan, and seven patients underwent positron emission tomography-CT (PET-CT) before surgery to exclude metastases. All five central bronchogenic carcinoma patients underwent biopsy under the guidance of a tracheoscope before surgery, and the pathological findings suggested two cases of non-small cell lung carcinoma and three cases of squamous cell carcinoma. Ten peripheral lung cancer patients underwent CT-guided biopsy before surgery, and four cases of adenocarcinoma, three cases of squamous cell carcinoma, and three cases of non-small cell lung carcinoma were noted.

All patients were followed-up. After surgery, the patients were examined (including standard chest radiographs and CT) at the outpatient clinic generally at three to six month intervals. Follow-up continued until June 2012 and lasted for six to 12 months. The mean follow-up time was 63 months. Survival time was calculated from the definite diagnosis date to the date of last follow-up or death. Data were analyzed using SPSS 17.0, and statistical significance was considered if P was <0.05 . Survival rates were calculated using the Kaplan-Meier method and compared using the log rank test. Multivariate analysis was based on the Cox proportional hazards regression model.

Results

Between 1999 and 2011, 60 patients with pulmonary pleomorphic carcinoma were surgically treated, accounting for about 0.3% (60/20000) of all lung cancer patients who underwent surgery at the Shanghai Chest Hospital. Of these, 55 patients had peripheral lung cancer and five had central bronchogenic carcinoma. The locations of the tumors were as follows: 41 cases located in the upper lobe, with 24 on the right side and 17 on the left; 18 cases located in the lower lobe, with eight on the right side and 10 on the left; and one case located in the left general branch (Table 1).

Two patients received two courses of preoperative neoadjuvant chemotherapy, but their tumors did not show obvious shrinkage. Intraoperative histologic frozen section examination of the lung tumor was routinely performed

Table 1 Sites of pulmonary pleomorphic carcinoma in 60 patients

Sites	Central	Peripheral	Total
Left lung	3	25	28
Upper lobe	1	16	17
Lower lobe	1	9	10
Left general branch	1	0	1
Right lung	2	30	32
Superior lobe	1	23	24
Middle lobe	0	0	0
Inferior lobe	1	7	8

during surgery. Fifty-four patients underwent complete resection (R_0). Six patients had gross radical excision, but microscopically positive surgical margins (R_1), including three patients who were positive in the bronchial stumps, two in the superior vena cava and one in the spine. Fifty-one patients underwent pulmonary lobectomy (including five patients who underwent video-assisted thoracic surgery pulmonary lobectomy). Four patients underwent pulmonary bilobectomy. Two patients received pneumonectomy, and two patients underwent bronchial sleeve lobectomy. One patient underwent segmental resection of the lung. Four patients underwent partial chest wall resection, one patient underwent partial pericardium resection, and one patient underwent azygos vein resection. On the basis of postoperative pathological findings and lymphatic metastasis, five patients with stage Ia disease did not receive postoperative chemotherapy and 55 patients with stage Ib disease and above received postoperative adjuvant chemotherapy. Postoperative adjuvant chemotherapy was a platinum-based regimen; cisplatin plus docetaxel was employed in 20 patients, cisplatin plus paclitaxel in 18, cisplatin plus vinorelbine in 12, and cisplatin plus gemcitabine in five. Subsequently, six patients also underwent R1 resection, and five accepted adjuvant radiation.

According to the WHO histological classification of lung tumors (2004) and the International Union against Cancer (UICC) tumor node metastasis (TNM) staging (1997), postoperative pathological findings indicated pulmonary pleomorphic carcinoma in all patients. Of these patients, five had stage IA disease, 12 had stage IB disease, 16 had stage IIA disease, 15 had stage IIB disease, and 12 had stage IIIA disease. Eighteen patients showed lymphatic metastasis: 12 patients were classified as N1 and six as N2. Detailed compositions of epithelial and sarcomatous elements are shown in Table 2. Information on immunohistochemical staining was available in 55 of the 60 patients in this study. Cytokeratin was positive in 53 specimens (96.4%), vimentin in 52 specimens (94.5%), CK7 in 43 specimens (78.2%), thyroid transcription factor (TTF)1 in 40 specimens (72.7%), P63 in five specimens (9.0%), and CK-56 in four specimens (7.3%).

Table 2 Composition of epithelial and sarcomatous elements in the tumors of 60 patients

Tumor composition	Cases	Percentage (%)
Sarcomatous elements		
Spindle cells	30	50.0
Giant cells	19	31.7
Spindle cells combined with giant cells	11	18.3
Epithelial elements		
Adenocarcinoma	44	73.3
Squamous cell carcinoma	5	8.3
Large cell carcinoma	11	18.3

There were no in-hospital deaths. Four patients experienced postoperative atrial fibrillation, and three had prolonged chest drainage (>5 days) because of postoperative pulmonary air leakage. Two patients acquired a postoperative infection. One patient underwent a second surgery because of hemothorax resulting from bronchial arterial hemorrhage on the day of surgery. One patient experienced hoarseness.

The three and five year survival rates of the 60 patients were 47.2% and 25.6%, respectively (Fig 1). Among these patients, the three and five year survival rates of the 42 patients without lymphatic metastasis were 57.3% and 32.5%. These rates in the 18 patients with lymphatic metastasis were 25.4% and 17.1%. The differences in the three and five year survival rates between patients with and without lymphatic metastasis were statistically significant ($P = 0.017$, Fig 2). The three and five year survival rates were 51.5% and 30.3% in patients who underwent radical excision, and 12.5% and 0% in the patients who underwent incomplete excision. The differences in the three and five year survival rates between patients who underwent radical excision and incomplete excision were statistically significant ($P = 0.0162$, Fig 3).

Figure 1 Kaplan-Meier survival curve for 60 patients with pulmonary pleomorphic carcinoma. **Figure 2** Kaplan-Meier survival curves for patients with (NX) and without (N0) lymphatic metastasis among 60 patients with pulmonary pleomorphic carcinoma. —, N0; —, NX.

During the follow-up period, among the 54 patients who underwent radical surgery, 26 had tumor recurrence or metastasis within 12.5 ± 6.5 months after surgery, and tumors recurred in 20 patients within 18 months after surgery. Eight patients suffered local recurrence: four showed intrapleural spread and four showed lymphatic recurrence. Eighteen patients suffered distant metastasis: seven showed bone metastasis, five showed brain metastasis, four showed intra-pulmonary metastasis, and two showed adrenal metastasis.

Findings of univariate and multivariate analyses based on the Cox proportional hazards regression model are presented in Table 3. The independent prognostic factors were radical resection ($P = 0.041$), TMN stage ($P = 0.044$), and lymphatic metastasis ($P = 0.029$).

Discussion

Pulmonary pleomorphic carcinoma is rare, and patients with pulmonary pleomorphic carcinoma accounted for 0.39%

Figure 3 Kaplan-Meier survival curves for patients who underwent radical excision and incomplete resection among 60 patients with pulmonary pleomorphic carcinoma. —, radical; —, incomplete.

Table 3 Results of multifactorial analysis based on Cox proportional hazards regression model among 60 patients with pulmonary pleomorphic carcinoma

Variable	Hazard ratio	95% confidence interval	P-value
Gender	1.03	0.612–1.358	0.80
Age	1.12	0.598–1.387	0.76
Radical resection or incomplete resection	2.88	1.029–3.231	0.041
Tumor node metastasis stage	2.41	1.125–3.050	0.044
Lymphatic metastasis	2.98	1.064–3.836	0.029
Lesion location	1.62	0.873–1.215	0.59
Tumor size	1.86	0.475–1.272	0.12
Type of sarcomatous element in the tumor	1.72	0.759–1.815	0.43
Type of epithelial element in the tumor	1.56	0.779–1.319	0.63

(60/15249 cases) of all patients treated surgically for lung cancer during 1999 to 2011 in our hospital. As reported by Raveglia *et al.*, the tumors in 14 patients (70%) in a group of pulmonary pleomorphic carcinoma patients consisted only of sarcomatous elements,³ and no similarities in this regard were observed in our group of patients.

As mentioned in the literature,^{4,5} most pulmonary pleomorphic carcinoma patients are elderly male patients with a history of cigarette smoking. Although most pleomorphic carcinomas are peripherally located, bloody phlegm is the distinctive manifestation. Most pleomorphic carcinomas are peripherally located in the superior lobe, with diameters >5 cm.⁶ As reported by Kim *et al.*,⁷ 86% of pulmonary pleomorphic carcinomas containing adenocarcinoma elements and 100% of pulmonary pleomorphic carcinomas containing giant cell elements are peripheral, whereas 100% of pulmonary pleomorphic carcinomas containing squamous cell carcinoma elements are central. The clinical manifestations, lesion sizes, and tumor components in our group of patients are consistent with those reported in the literature.

Preoperative diagnosis of pulmonary pleomorphic carcinoma is difficult. Among 60 patients, 15 underwent preoperative biopsy under the guidance of a tracheoscope or puncture biopsy under the guidance of CT, but a pathologic diagnosis of an epithelial element only, rather than pulmonary pleomorphic carcinoma, was confirmed. Because pleomorphic carcinoma consists of epithelial and sarcomatous elements and puncture biopsy samples contain small amounts of tissue, multiple punctures are needed for a definite diagnosis.

Compared with other subtypes of non-small cell lung carcinoma, pulmonary pleomorphic carcinoma often has a poor prognosis. As reported previously, pulmonary pleomorphic carcinoma is prone to invasion of the chest wall and mediastinal tissues,⁸ and the incidence in our patients was slightly lower than that previously reported. As reported by Ito *et al.*,⁴ because the biological behavior of pulmonary pleomorphic carcinoma is highly malignant and even an early tumor may invade the blood vessels, an early pulmonary pleomorphic

carcinoma without lymphatic metastasis may recur or metastasize. However, as revealed by most studies, the effects of radical resection on pulmonary pleomorphic carcinoma are better than those of palliative resection,⁹ and as revealed in this study, radical surgery is a promising prognostic predictor for pulmonary pleomorphic carcinoma. Therefore, although pulmonary pleomorphic carcinoma is highly malignant, radical resection is recommended.

The effects of lymphatic metastasis on the prognosis of pulmonary pleomorphic carcinoma are controversial.^{1,5} Several previous studies, in which a relatively large number of patients were analyzed, have reported that lymphatic metastasis was associated with a poor prognosis.⁵ This study also indicated that lymphatic metastasis was an important factor that determined the prognosis of pulmonary pleomorphic carcinoma. Pulmonary pleomorphic carcinoma patients with lymphatic metastasis are susceptible to local recurrence and circulatory metastasis. This has led some researchers³ to suggest that surgery is only applicable for pulmonary pleomorphic carcinoma patients with stage N0 disease, and that patients with lymphatic metastasis should be treated with chemotherapy. In the present series, TMN stage was also regarded as a prognosis factor of this disease. Because pulmonary pleomorphic carcinoma is not sensitive to chemotherapy, the treatment modality for pulmonary pleomorphic carcinoma with lymphatic metastasis requires further research. Pathological staging and pleural invasion are also reported to be important prognostic indexes of pulmonary pleomorphic carcinoma.⁶

There is no consensus on the appropriate adjunctive therapy for pulmonary pleomorphic carcinoma. In this study, two patients received preoperative neoadjuvant chemotherapy, but their lesions did not show obvious shrinkage, a finding that is consistent with another study.¹⁰ Whether postoperative adjuvant chemotherapy is effective in the treatment of patients with pulmonary pleomorphic carcinoma is still controversial. In this study, adjuvant chemotherapy was given to each patient with stage >Ia (55 patients). Therefore, comparison between patients with and without postopera-

tive chemotherapy was not possible and, thus, evidence of the effectiveness or non-effectiveness of postoperative chemotherapy is unavailable. Because approximately 20% of pulmonary pleomorphic carcinomas exhibit epidermal growth factor receptor mutations, targeted drugs may increase the survival rate of patients with pulmonary pleomorphic carcinoma.¹¹ However, the effects of chemotherapy on pulmonary pleomorphic carcinoma need to be further confirmed in multi-center, large-scale clinical studies.

The limitation of this study was the potential selection bias, given the retrospective nature of the study. In addition, the regimes of adjuvant therapy were not standardized among all patients. The survival results may be affected by heterogeneity of adjuvant therapy.

Conclusion

In conclusion, pleomorphic carcinoma is a rare type of lung cancer, which is often found as a peripherally located large mass and associated with a poor prognosis. This present study indicated that radical resection, TMN stage, and nodal status were significant independent prognostic factors. Further prospective investigation is needed to elucidate the surgical strategy for pleomorphic carcinoma.

Disclosure

No authors report any conflict of interest.

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