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Evaluation and Surgical Treatment Strategies for Solitary Pulmonary Nodules

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Abstract

Background: The origin of solitary pulmonary nodules (SPN) is difficult to determine because they do not exhibit distinct imaging features; further, it is not easy to determine if the lesions are benign or malignant, which may lead to misdiagnosis and delayed treatment. Caution should be taken during intraoperative diagnosis and surgical treatment of SPN to avoid the use of invasive diagnosis methods and excessive treatment. In this study, we investigated the diagnosis and treatment strategies for patients with SPNs.

Methods: The clinical data of 167 patients who underwent surgical removal of SPNs between January 2010 and December 2015 was collected for retrospective analysis.

Results: Tumor removal was achieved by conventional incision or video-assisted small-incision surgery. Malignant lesions were confirmed in 69 patients (41.32%) by performing pathological examination after operation. Different degrees of hilus pulmonis and mediastinum lymph node metastases were observed in 11 patients. The preoperative diagnostic accordance rates and diagnostic specificity of chest computed tomography (CT), CT-guided percutaneous aspiration biopsy, and positron emission tomography (PET)/CT examinations were significant difference. The diagnostic accordance rates were 70.77%, 85.96%, and 91.67%, respectively (P=0.002), diagnostic sensitivities were 86.06%, 77.78%, 95.83%, respectively (P=0.165), diagnostic specificities were 68.18%, 100%, 87.50%, respectively (P=0.003).

Conclusion: Preoperative chest CT, CT-guided percutaneous lung biopsy, and PET/CT examinations could be used for the diagnosis of SPNs. Surgical resection has both diagnostic and therapeutic implications for SPNs. Surgical treatment should be personalized according to the patient's condition. Excessive or conservative surgery must be avoided as far as possible to avoid pathological misdiagnosis.

Keywords: Solitary pulmonary nodule; Diagnosis; Pulmonary resection

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Introduction

The origin of solitary pulmonary nodules (SPNs) is not known; on chest X-ray (CXR) scans, SPNs appear as a well-defined opaque lesion of 3cm or less in diameter surrounded by normal lung without any associated atelectasis or adenopathy [1]. Developments in radiology have enabled the detection of SPNs that are important indicators of early-stage lung cancers; this aspect has attracted the attention of scientists and is under investigation [2]. In mass screening studies, SPNs were identified in 0.09%-0.2% CXR examinations. This percentage has increased with the increasing use of chest computed tomography (CT) techniques. In the past 20 years, the introduction of modern imaging techniques, fine-needle aspiration (FNA) [3], and positron emission tomography (PET) [4] has improved the scope of diagnostic modalities; however, no technique can provide a definitive diagnosis of SPNs [5].

Due to the complex nature of SPNs and the clinical difficulties associated with the definitive diagnosis of benign and malignant lesions, the treatment of these tumors is often delayed. Qualitative diagnosis and surgical strategies for the treatment of SPNs have been the challenges for contemporary lung surgery. Accurate determination of the nature of SPN plays a crucial role in guiding the treatment of the disease. In clinical practice, malignant lesions should be resected as early as possible to avoid the spread of the disease, and unnecessary thoracotomy should be avoided for benign lesions. Therefore, it is crucial for both radiologists and lung surgeons to determine if an SPN is benign or malignant [6]. However, surgery is the only option if definitive diagnosis cannot be established [7].

Table 1: Chest CT, CT-guided transthoracic needle biopsy, PET/CT examinations before operation and the diagnostic accordance rates.

	CT diagnosis		CT-guided TNB		PET/CT diagnosis		*P* value
	Malignancy	Benign	Malignancy	Benign	Malignancy	Benign	
Preoperative diagnosis (case)	96	71	28	29	26	22	
Postoperative pathology (case)	58	60	28	21	23	21	
Diagnostic accordance rate (%)	60.41	84.51	100.00	72.41	88.46	95.45	
Total diagnostic accordance rate (%)	70.77		85.96		91.67		0.002
Diagnostic sensitivity (%)	84.06		77.78		95.83		0.165
Diagnostic specificity (%)	68.18		100		87.50		0.003

Table 2: Benign and malignant pathological status of SPN with different diameters after operation.

SPN diameter(cm)	Postoperative pathology		Total	*P*
	Malignancy(case)	Benign(case)		
≤1.0	11(6.59%)	18(10.78%)	29(17.37%)	0.769
1.1-2.0	26(15.57%)	40(23.95%)	66(39.52%)	
2.1-3.0	32(19.16%)	40(23.95%)	72(43.11%)	
Total	69(41.32%)	98(58.68%)	167(100%)	

In this study, we report our experience with minimal invasive surgery for the treatment of SPNs and our analysis of the evolution of diagnostic-therapeutic techniques developed in the recent 10 years.

Methods

Between January 2010 and December 2015, 167 patients underwent surgical removal of SPNs at the Department of Cardiothoracic Surgery, Changzheng Hospital, and Second Military Medical University. We performed a retrospective analysis of the data of these patients. Our study was approved by The Institutional Review Board of Changzheng Hospital, Second Military Medical University, Shanghai, China. Among the 167 patients, 116 (69.46%) were males and 51 (30.54%) were females, and their age was in the range of 30-79 years (average, 52.4 years). Eighty-eight (52.69%) non-symptomatic patients were incidentally diagnosed during physical fitness examinations; 45 (26.95%) were diagnosed when they presented at a hospital with different degrees of respiratory symptoms such as cough, bloody sputum, and chest pain; and 34 (20.36%) were diagnosed during CXR examination or CT scanning for detection of other diseases, among which 7 (4.19%) patients had a history of malignant tumors. All patients underwent preoperative CXR examination and 64-slice spiral CT (SCT) enhanced scanning (GE Discovery CT 750 HD 64-slice, detector collimation 64×0.6mm, pitch 0.9, rotation time 0.4 sec, scan time ~5sec. reconstruction slice thickness 2.5mm, interval 2.5mm, Window Wide 400 Hu, Window Level 40Hu).

After completing preoperative examinations, all 167 patients underwent endotracheal intubation with a double-lumen catheter and were operated under balanced general anesthesia. For patients in whom malignant tumors were confirmed preoperatively, standard lobectomy plus lymph node dissection was performed by making a conventional incision or by a video-assisted small thoracic incision. For patients in whom peripheral nodules could not be confirmed preoperatively, wedge excision of tumor-containing lung tissues was performed by making a small incision or by using a video-assisted thoracoscope to ensure adequate resection and no residual tumor. Finally, frozen tumors sections were sent for pathological examination. The specimens of nodules located near the hilus pulmonis were obtained while ensuring safety during surgery. If it was indeed difficult to obtain a specimen of a lesion or if preoperative examination suggested that the lesion was highly malignant, a lung lobe or lung segment was resected to determine whether to perform an extended resection and lymph node dissection. For patients who were diagnosed with malignant lesions by rapid pathological examination and whose pulmonary function can tolerate, standard lung resection plus lymph node dissection were performed; further, for patients whose pulmonary function cannot tolerate, wedge resection of the lung segment or the lung was performed. For patients with benign lesions, the lung edge was sutured to complete the surgical procedure. If active proliferation was not suggested or confirmed by rapid pathological examination, the scope of resection was extended up to the extent to which pulmonary function allowed lobectomy. After surgery, the patients received combined therapy for lung cancer and preventive treatment for tuberculosis and fungal infection.

Statistical analysis

Descriptive statistics and crosstabs were used to determine the correlation between benign or malignant SPNs and respiratory symptoms. Kruskal-Wallis one-way Analysis of Variance (ANOVA) was used to determine the correlation between the size of SPN and their benign or malignant nature. The nonparametric Chi-square test was applied to determine the diagnostic accordance rate of preoperative chest CT, CT-guided percutaneous lung biopsy, and PET/CT examinations. A value of $P< 0.05$ was considered statistically significant. Statistical analysis and data processing were performed using SPSS 12.0 software.

Results

The CT images of lung nodules obtained using the standard lung window revealed that the nodules were ≤3 cm in diameter; the nodules of 96 (57.49%) patients showed the signs of malignancy and those of remaining 71 (42.51%) patients showed benign features. Peripheral pulmonary nodules were observed in all patients. Preoperative CT-guided percutaneous lung biopsy examination was performed in 57 (34.13%) patients and PET or PET/CT scanning were performed for 48 (28.74%) patients. According to economic conditions for patients and diagnostic uncertainty for doctors, 28 (29.17%) cases of 96 patients CT images showed the signs of malignancy and 20 (28.17%) cases of 71 patients showed benign features were underwent PET or PET/CT scanning. The standard uptake value (SUV) ≥2.5 was considered as the diagnostic standard of malignant pulmonary nodules.

Out of the 167 patients, 104 (62.28%) underwent wedge resection, 36 (21.56%) underwent upper lobe resection, 19 (11.38%) underwent lower lobe resection, and 8 (4.79%) underwent middle lobe resection. Rapid examination of the frozen biopsy specimens was performed intraoperatively. Benign lesions were confirmed in 98

patients (58.68%); pneumonic nodules were detected in 30 (17.96%) patients, inflammatory pseudotumors in 19 (11.38%) patients, pulmonary hamartoma in 17 (10.18%) patients, tuberculosis in 13 (7.78%) patients, fibrous nodules in 9 (5.39%) patients, sclerosing hemangioma in 5 (2.99%) patients, and cryptococcal granuloma in 5 (2.99%) patients. Malignant lesions were confirmed in 69 patients (41.32%); adenocarcinoma was detected in 35 (20.96%) patients, squamous cell carcinoma in 18 (10.78%) patients, and adenosquamous carcinoma in 5 (2.99%) patients, small cell carcinoma in 4 (2.40%) patients, lung metastasis from breast cancer in 4 (2.40%) patients, and lung metastasis from rectal cancer in 3 (1.80%) patients. Out of the 88 patients in whom SPNs were detected during physical fitness examination, 32 (36.36%) patients had malignant tumors; of the 45 patients with respiratory symptoms, 27 (60.0%) patients had malignant tumors; and out of the 34 patients who underwent CXR or CT examinations for other diseases, 10 (29.41%) patients had malignant tumors. The diagnosis rate of malignant SPN was significantly higher in the group with respiratory symptoms than in the groups who had undergone physical fitness examination (P = 0.009) or CXR and CT examination for other diseases (P = 0.007). Postoperatively, non-small cell lung lesions (58 patients) were staged on the basis of the 2009 International Staging System for lung cancer; 34 (58.62%) patients were stage Ia (T1N0M0), 13 (22.41%) were stage Ib (T2aN0M0), 5 (8.62%) were stage IIa (T1N1M0 and T2aN1M0), and 3 (5.17%) each were stage IIb (T3N0M0) and stage IIIa (T1N2M0 and T2aN2M0). The number of patients who underwent preoperative chest CT, CT-guided percutaneous lung biopsy, and PET/CT examinations, and their diagnostic accordance rates diagnostic sensitivity and specificity are listed in Table 1. There were significant difference in the diagnostic accordance rates and diagnostic specificity among the 3 detection methods. The accuracy of PET/CT examination was higher than that of chest CT and CT-guided percutaneous needle aspiration biopsy examination of the lung. Diagnostic specificity of CT-guided Transthoracic Needle Biopsy (TNB) was higher than PET/CT and CT. But there was no significant difference in the diagnostic sensitivity. The nature of SPNs, whether benign or malignant, with different diameters as determined by postoperative pathological examination is shown in Table 2. Statistical analysis of the grouped information of the 3 groups using Kruskal-Wallis one-way ANOVA test indicated that the size of the SPNs in our study group was not related to the benign or malignant nature of the nodules (P = 0.769; P > 0.05). Out of the 69 patients with malignant lesions, 11 (15.94%) had hilar or mediastinal lymph node metastases. Sixty-four patients were followed up 1~72 months postoperatively (average, 39.8 months), and the follow-up rate was 92.75%, 3 (4.69%) patients died during follow period, 2 (3.13%) patients received.

Discussion

SPNs are mostly located in the peripheral lung; however, imaging examination of peripheral lungs reveals clinically asymptomatic pulmonary nodules with no typical characteristics [2]. Due to the rapid development of CT and PET/CT techniques and people's awareness of community physical fitness examinations, the diagnosis rate of SPNs and the opportunities for early detection of lung cancer have increased significantly. Reported data and increasing incidences of lung cancer indicate that malignant tumors account for about 60%-70% of SPNs and benign lesions account for only 30%–40% of SPNs [6,7]. Out of the 167 examined patients, malignant lesions were detected in about 41.32% patients. But there were limitations; the findings of this paper could not be applied to all SPNs. Since there are patients with a solitary nodule which has benign features and demonstrates no growth over time, which would not be referred for surgery but followed by the treating physician [8-10]. The size of pulmonary nodules in these patients was not associated with the benign or malignant nature of the lesion. Out of the 167 patients with SPN, primary lung cancer ranked the first in single disease, followed by pneumonic nodules, inflammatory pseudotumors, pulmonary hamartomas, fibrous nodules, tuberculosis, sclerosing hemangiomas, cryptococcal granulomas, and lung metastases. Adenocarcinoma was the most predominant form of primary lung cancer, possibly because adenocarcinoma mainly affected the peripheral lung [11].

Radiological diagnosis of the SPN

The complex origin of SPNs and their unremarkable imaging features complicate the diagnosis of benign and malignant SPNs, which often leads to misdiagnosis and delayed treatment. Caution should be taken during intraoperative diagnosis and treatment of SPNs to avoid using unnecessary methods of invasive diagnosis and excessive treatment. Majority of SPN patients are asymptomatic and are diagnosed during physical fitness examinations. CXR examination is generally used for the diagnosis of chest disease, and this method is commonly used for general survey and screening purposes. The use of CT, particularly, SCT and high-resolution CT (HRCT), should be advocated for the detection and diagnosis of SPN. According to the CT characteristics of lesions, correct diagnosis can be made for most nodules, with a reported diagnostic rate of 86.0% [12]. In our study group, all patients underwent enhanced SCT examination, with diagnostic accordance rate of 70.77%, thereby indicating that this technique has a very good diagnostic value. PET detects tumors based on the metabolism of tumor cells, i.e., it evaluates the physiological rather than anatomical characteristics and is therefore considered to have higher accordance rate, sensitivity and specificity than CT. One limitation of PET is that it fails to identify false positive and false negative cases. Because fludeoxyglucose (FDG) is not a tumor-specific imaging agent, tuberculosis, proliferative granuloma, inflammation, sarcoidosis, and other benign nodules may lead to false-positive PET findings. In our study group, 3 patients for whom pneumonic nodular and tuberculosis were confirmed in pathological examination showed false-positive findings on PET. PET diagnosis yielded relatively low false negative results, with cell types and differentiation degree of lung cancers being the key factors of false negative findings. The integration of functional imaging and anatomical structures is achieved in PET/CT. For pulmonary nodules that are difficult to identify by CT, non-invasive examination by PET/CT should be preferred. However, since PET/CT is costly, its widespread clinical application is limited [13], and for solitary pure ground-glass nodules >5mm, PET/CT is of limited value, potentially misleading, and PET/CT is considered for solitary part-solid nodules >10mm [7]. CT-guided percutaneous aspiration biopsy examination of lung nodules is a common preoperative detection method used in recent years; this method is reported to detect malignancy with a sensitivity of 60%-90%. However, because of the small size of the majority of pulmonary nodules and differences in the imaging and paracentesis techniques, the diagnostic rate of this CT-guided technique varies greatly. This technique was performed in 57 patients, and the diagnostic accordance rate was 85.96%, and the diagnostic specificity was 100%. Since this is an invasive examination method, it may result in pneumothorax, hemothorax, and other complications after the operation and is not cost efficient. Therefore, CT-guided percutaneous aspiration

biopsy of lung nodules is also subject to certain limitations. Patients with negative aspiration biopsy results and high risk of lung cancer suspected by CT should immediately undergo surgical treatment [14]. Patients with no diagnostic evidence of SPN or lung cancer in CT or not willing to undergo aspiration biopsy should be periodically followed up for a short term. The size of majority of peripheral lung lesions may change within 1-3 months. During the follow up period, anti-inflammatory or anti-tuberculosis treatment may be given, but if no improvement is observed or the lesions increase in size, surgical treatment should be proactively performed [15]. Sixteen patients underwent surgery and were followed up for 20–60 days, which was invalid, and 8 were confirmed as lung cancers.

Surgical treatment and pathological examination of SPN

SPNs can be confirmed intraoperatively and also treated thereafter. The degree of surgical trauma can be reduced by introducing a small incision or performing video-assisted thoracoscopic surgery for tumor resection; the nature of the tumor can be confirmed before deciding the type of surgery by performing pathological examination of the intraoperatively obtained frozen sections [16]. We advocate the pathological examination of frozen tumor sections obtained after surgical resection of SPN, regardless of whether preoperative pathological examination has been performed, especially when preoperative pathological examination suggests benign lesions. Excessive or conservative surgery due to pathological misdiagnosis should be avoided as far as possible.

The results of postoperative pathological staging suggest that not all types of lung cancers with SPN are early-stage lung cancers. Pathological examination revealed 11 cases (18.97%) with different degrees of hilar and mediastinal lymph node metastases. In addition, past history of malignant nodules also indicates the possibility that the nodules were malignant tumors. In our study group, there were 7 patients with history of breast cancer and rectal cancer, which were confirmed to be metastasised by postoperative pathological examination. The 5-year survival rate of the patients after early surgical resection of SPN lung cancer was up to 80% or high, while the 5-year survival rate of advanced lung cancer that could be operated was only 30%–40%; these findings suggest the significance of early diagnosis and treatment of SPN lung cancer. Complete surgical excision of the lesions will help relieve the patient's psychological pressure and prevent malignant transformation [17]. Video-assisted thoracoscopy is currently developing rapidly; this technique has the advantages of being minimal invasive, fully revealed vision, clear images, and few postoperative complications, and it appears to be gradually accepted by several patients. However, thoracoscopy has certain limitations because it is expensive, technically demanding, and has less scope. Sixty-three patients with SPN underwent surgery at our hospital via a small axillary incision and some patients underwent routine lobectomy incision through extended incisions; all patients showed good postoperative recovery and no patient developed serious perioperative complications. Therefore, presently, this is a good treatment method that can be adopted by primary hospitals at the present stage.

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