Histological subtypes of solitary pulmonary nodules of adenocarcinoma and their clinical relevance

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ABSTRACT

Objective: To explore the histological subtypes of solitary pulmonary nodules (SPNs) of invasive adenocarcinoma and their clinical relevance.

Methods: A total of 188 patients with pathologically confirmed invasive adenocarcinoma in our hospital from January 2007 to December 2011 were enrolled in this study. In accordance with the new classification of lung adenocarcinoma, all the histological sections were reviewed and classified, and the clinical data were collected and analyzed.

Results: Of these 188 patients who had been initially diagnosed as SPNs of adenocarcinoma, there were 6 cases of lepidic predominant adenocarcinoma (LPA), 71 cases of acinar predominant adenocarcinoma (APA), 74 cases of papillary predominant adenocarcinoma (PPA), 15 cases of micorpapillary predominant adenocarcinoma (MPA), and 22 cases of solid predominant adenocarcinoma (SPA) with mucin production. The incidence of lymph node metastasis was 80.0% and 81.8% in MPA and SPA, respectively, which was significantly higher than those in LPA, APA, and PPA (all $P<0.01$). The incidence of LPA was 83.3% (5/6) in women, which was significantly higher than that in men ($P=0.037$).

Conclusions: According to the new classification, MPA and SPA have high incidence of lymph node metastasis. LPA is more likely to occur in women. Sub-typing of the lung adenocarcinoma based on the newest international classification criteria is helpful to identify the clinical features of this disease.

KEY WORDS Adenocarcinoma solitary pulmonary nodule (SPNs); histological subtype; clinical manifestations

J Thorac Dis 2013;5(6):841-846. doi: 10.3978/j.issn.2072-1439.2013.12.16

Solitary pulmonary nodules (SPNs) are a group of single, opaque, and small (diameter ≤3 cm) lesions, characterized by dense shadows in the pulmonary X-ray picture. They are usually surrounded by the air-containing lung tissue but without obstructive pneumonia, atelectasis, pulmonary hilar enlargement, or pleural effusion (1,2). The causes of SPNs are diverse but mainly include granulomatous disease and bronchopulmonary cancer; in rare cases, they can also be resulted from carcinoids or the single lung metastasis of other tumors. Once SPNs are confirmed to be lung cancer, they are often still in stage 1, and the patients often can be cured or have a long survival after proper treatment (3). Compared with the squamous cell carcinoma, the lung adenocarcinoma, with a rapid metastasis and short clinical course, is often not sensitive to radiotherapy or chemotherapy. In 2011, the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) released an international muhidisciplinary classification of lung adenocarcinoma (4). The new classification is still morphology-based but also incorporated the new advances in oncology, imaging, thoracic surgery, molecular biology, and many other relevant fields, providing a new multidisciplinary classification protocol for lung adenocarcinoma. However, it has been proposed that the prognoses significantly differed when different pathological typing was applied, and the new classification-based grading/scoring system was remarkably superior in predicting the relapse/metastasis of stage 1 lung adenocarcinoma (5). Therefore, a strict subtyping of the adenocarcinoma in accordance with the new classification criteria will be clinically valuable to determine the clinical characteristics of the adenocarcinoma.

In our current study, we retrospectively analyzed the clinical data of 188 patients with pathologically confirmed SPN of adenocarcinoma (ASPN). According to the 2011 new

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Submitted Nov 19, 2013. Accepted for publication Dec 10, 2013.
Available at www.jthoracdis.com

ISSN: 2072-1439

classification protocol of lung adenocarcinoma, we subtyped all the histological sections and compared the clinicopathological features of different ASPN types.

Subjects and methods

Subjects

A total of 188 patients with pathologically confirmed invasive adenocarcinoma in our hospital from January 2007 to December 2011 were enrolled in this study. The pathologic data of these patients were reviewed, and meanwhile the clinical data including age, gender, smoking status, lymph node metastasis, as well as the sites and diameters of ASPN were collected and analyzed.

Methods

The specimens were obtained by biopsy or surgical resection, and then fixed in 10% neutral-buffer formalin solution, embedded in parafin wax, sectioned, and stained with hematoxylin and eosin (HE). The morphological and microscopic findings were described. All the histological sections were reviewed and subtyped in accordance with the 2011 lung cancer classification. All the sectioned were independently read by two experienced pathologists. If the results differed, these two pathologists jointly discussed the sections under a multi-head microscope.

Statistical analysis

The statistical analysis was performed using the SPSS 19.0 software package. Parameters were compared using chi square test, whereas the comparison of the tumor diameter was performed using univariate analysis of variance. $P<0.05$ was considered significantly different.

Results

Clinical features

Of these 188 patients with invasive ASPN, there were 73 men (38.8%) and 115 women (61.2%) aged 32-67 years (mean: 57 years). Seventy-eight patients (41.5%) had a history of smoking. Cancer was confirmed in the left lung in 73 cases (38.8%) and in the right lung in 115 cases (61.2%). Lymph node metastasis was detected in 69 patients (36.7%). The mean diameter of these nodules was 2.87±0.36 cm.

Histopathological findings

According to the new classification, there were 6 cases of lepidic predominant adenocarcinoma (LPA), 71 cases of acinar predominant adenocarcinoma (APA), 74 cases of papillary predominant adenocarcinoma (PPA), 15 cases of micorpapillary predominant adenocarcinoma (MPA), and 22 cases of solid predominant adenocarcinoma with mucin production (SPA), accounting for 3.2%, 37.8%, 39.4%, 7.9%, and 11.7%, respectively. The LPA was featured by the cancer cells with lepidic growth but without stroma, vessel, or papillary/micropapillary structures; also, there was no cancer cell aggregation inside the alveolar cavity. The APA had round or oval glands with central lumen. The PPA was mainly composed of fibrovascular cores covered by ramified papillae. In the MPA, the tumor cells formed papillary cell clusters without fibrovascular cores. For the SPA, the tumors were mainly formed by sheet-like polygonal cells (Figure 1).

Relationship between histological subtypes and clinical features

The diameters of tumors were relatively small in LPA (mean: 1.47 cm) and PPA (mean: 1.89 cm) but were relatively large in SPA (mean: 2.54 cm), APA (mean: 2.83 cm), and MPA (mean: 2.90 cm) ($P<0.05$).

The LPA was more common in women ($P<0.05$), but was not significantly associated with age, smoking status, and sites ($P>0.05$).

The lymph node metastasis rate differed among different histological subtypes. It was remarkably high in SPA (81.0%) and MPA (80.0%), but was relatively low in PPA (22.9%), LPA (33.3%), and APA (28.2%) (Table 1).

Relationship between lung adenocarcinoma histologic subtypes and clinical prognoses in literature

In 2011, the IASLC/ATS/ERS jointly released the new pathological classification criteria of lung adenocarcinoma. Since then, many clinical studies have described the new pathological classification of lung adenocarcinoma; however, the proportions of different subtypes of invasive lung adenocarcinoma as well as their prognostic relevances varied among these studies. Therefore, we searched all the clinical studies on the new pathological classification of lung adenocarcinoma and made a brief summary in Table 2. A total of 16 articles (6-21) entered the final analysis, involving the populations mainly in the United States, China, Japan, Australia, the United Kingdom, and Germany. Seven articles were focused on stage I adenocarcinoma, whereas the remaining studies were on stage I-IIIa tumors. The sample sizes of these studies ranged 64-949. Of these 16 studies, the proportions of the different subtypes of invasive lung adenocarcinoma remarkably differed: LPA, 0-31.4%; APA, 12-56.8%; PPA, 5.8-48.6%; MPA, 0-29.3%; and SPA, 8.1-20%. Obviously, APA and PPA are common subtypes, whereas LPA and MPA are less common. Thirteen

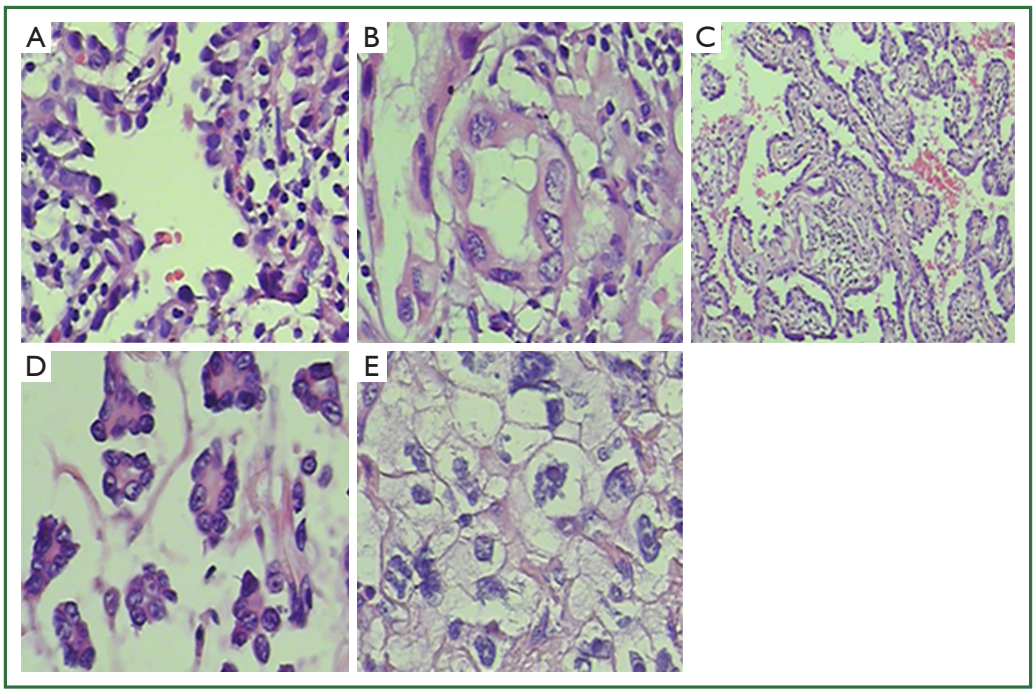

Figure 1. (A) lepidic predominant adenocarcinoma, HE ×400; (B) acinar predominant adenocarcinoma, HE ×400; (C) papillary predominant adenocarcinoma, HE ×400; (D) micorpapillary predominant adenocarcinoma, HE ×400; and (E) solid predominant adenocarcinoma with mucin production, HE ×400.

Table 1. Relationship between histological subtypes and clinical features of lung adenocarcinoma.

Clinical features	n	LPA	APA	PPA	MPA	SPA	P
Gender							0.037
Men	73	1	23	30	6	12	
Women	115	5	48	44	9	10	
Age							0.939
≥60	106	2	43	40	8	13	
<60	82	4	28	34	7	9	
Smoking status							0.659
Yes	78	3	37	18	10	10	
No	110	3	34	56	5	12	
Site							0.921
Right lung	115	5	44	40	12	14	
Left lung	73	1	27	34	3	8	
Lymph node metastasis							0.001
Yes	69	2	20	17	12	18	
No	119	4	51	57	3	4	
Tumor size							0.044
<2 cm	74	5	27	26	8	8	
2-3 cm	114	1	44	48	7	14	

Abbreviations: LPA, lepidic predominant adenocarcinoma; APA, acinar predominant adenocarcinoma; PPA, papillary predominant adenocarcinoma; MPA, micorpapillary predominant adenocarcinoma; SPA, solid predominant adenocarcinoma.

Table 2. Histologic subtypes of invasive lung adenocarcinoma and their clinical relevance in literature.

Study-year	Source	Stage	N	Proportion for new classification of invasive adenocarcinoma (%)					Independent prognostic factor
				LPA	APA	PPA	MPA	SPA	
Ding-2012	China	I	125	3.2	29.6	38.4	5.6	17.6	New grading and scoring system
Xu-2013	USA	NA	125	7.2	56.8	8.8	NA	18.4	NA
Hung-2013	China	I	283	10.9	31.1	34.6	29.3	8.1	MPA and SPA
Kadota-2012	USA	I	270	5.2	43.7	41.8	1.1	8.1	NA
Song-2013	China	I	251	7.6	30.3	31.9	16.7	13.5	MPA and SPA
Warth-2012	Germany	I-IV	487	8.4	42.5	4.7	6.8	37.6	Survival analysis[a]
Russell-2011	Australia	I-IIIa	183	5.5	45.9	14.2	7.7	26.8	Survival analysis[b]
Woo-2012	Japan	I	137	31.4	43.1	11.7	0.7	8.8	NA
Yoshizawa-2013	Japan	I-IIIa	373	9.7	16.4	48.0	5.1	21.0	Survival analysis[c]
Russell-2013	Australia	III N2	64	0	36.0	6.3	20.2	37.5	Survival analysis[d]
Yanagawa-2013	Japan	I	163	31.3	24.5	31.9	0	12.3	SPA, survival analysis[e]
Zhang-2013	China	Ia	148	9.5	27.0	48.6	6.8	8.1	New grading indicator, survival analysis[f]
Gu-2013	China	I-III	261	11.9	42.9	13.8	11.5	20.0	New grading indicator
Tsuta-2013	Japan	I-IV	757	18.0	12.9	44.6	8.1	16.4	New grading indicator, survival analysis[g]
Kadota-2013	USA	I	949	10.9	43.3	25.2	6.3	14.3	APA, survival analysis[h]
von der Thüsen JH-2013	UK	I-III	223	24.2	48.0	5.8	4.0	17.9	new classification
This study	China	I-III	188	3.2	37.8	39.4	7.9	11.7	NA

NA, not applicable; [a], overall survival differed significantly between LPA (78.5 months), APA (67.3 months), SPA (58.1 months), PPA (48.9 months), and MPA (44.9 months) predominant ADCs; [b], five-year survival of LPA, APA, PPA, MPA and SPA was 86%, 68%,71%, 38% and 39%, respectively; [c], MPA and SPA showed the worst prognoses, with a 43.3% DFS at five years and a 0% DFS at three years, respectively. APA (5-year DFS rate =69.7%) and PPA (5-year DFS rate =66.7%) were identified; [d], APA was significantly improved overall survival compared with those with non-acinar predominant tumors (HR: 0.45; 95% CI: 0.22-0.91; P=0.026); [e], five-year survival of LPA, APA, PPA and SPA was 94.9%, 89.7%, 85.4% and 54%; [f], five-year survival of LPA, APA, PPA, MPA and SPA was 100%, 85%, 85%, 80% and 66%, respectively; [g], five-year OS rates of LPA, APA, PPA, MPA and SPA was 93%, 67%, 74%, 62%, and 58%, respectively; [h], five-year OS rates of LPA, APA, PPA, MPA and SPA was 92%, 87%, 83%, 62%, and 70%, respectively.

studies reported the prognostic significances of different lung adenocarcinoma subtypes. Hung *et al.* (8) and Song *et al.* (10) suggested MPA and SPA are independent poor prognostic factors for lung cancer, and Kadota *et al.* (20) argued that APA is an independent indicator of poor prognosis for lung cancer. Ding *et al.* (6), Zhang *et al.* (17), Tsuta *et al.* (19), and von der Thüsen *et al.* (21) reported that the new classification system and the score are independent prognostic factors for lung cancer. Most studies agreed that MPA and SPA were associated with poor prognosis while LPA and APA with relatively better prognosis.

Discussion

SPNs are commonly seen in clinical practice. In a normal population census conducted by Comstock *et al.* (22), the incidence of SPNs reached up to 0.2%. Along with the wide application of computed tomography (CT), the detection rate of SPNs has remarkably increased. The proportions of malignant SPNs (mainly lung adenocarcinoma) varied among different articles, ranging from 5-69% (23-25). A study has confirmed that the prognoses of different lung adenocarcinoma subtypes remarkably differ. Adenocarcinoma in situ, microinvasive

adenocarcinoma, and LPA tend to have "good" prognosis, PPA and APA have "relatively good" prognosis, whereas invasive mucinous adenocarcinoma, colloid carcinoma, SPA, and MPA often have "relatively poor" prognosis (5). In their study, Kadota *et al*. (20) enrolled 949 patients with stage I lung adenocarcinoma, and the prognostic analysis of the different subtypes showed that the 5-year survival of LPA, APA, PPA, MPA, and SPA was 100%, 85 %, 85%, 80%, and 66%, respectively. Therefore, determination of the histological subtype of a lung adenocarcinoma is helpful for predicting the prognosis.

Warth *et al*. demonstrated that the different histological subtype of lung adenocarcinoma is a stage-independent prognostic factor; survival differences according to patterns were influenced by adjuvant chemoradiotherapy; in particular, solid-predominant tumors had an improved prognosis with adjuvant radiotherapy. The predominant pattern was tightly linked to the risk of developing nodal metastases. As shown in our current study, the lymph node metastasis rates were high in SPA and MPA; therefore, for SPA or MPA patients who have undergone lobe resection or VATS, systematic lymph node dissection should be considered.

The prognosis of lung cancer patients (particularly those with adenocarcinoma) may differ even after receiving the same treatment, suggesting that many intrinsic biological characteristics of these tumors may also have prognostic significance. The histological heterogeneity of different subtypes is characteristic for lung adenocarcinoma. Morphological heterogeneity may exist among different lung adenocarcinomas and even within the same type, and different histological subtypes of lung adenocarcinoma also have different response to treatment (26-28). In our current study, the LPA was predominantly seen in female patients. Interestingly, women are also more likely to develop lung adenocarcinoma with epidermal growth factor receptor (EGFR) mutations, which histologically is seen to be tumors with lepidic growth. Therefore, LPA is the predominant histologic subtype that is suitable for targeted therapies.

Sakurai *et al*. (29) retrospective analyzed the clinical data of 380 patients with adenocarcinomas sized ≤2 cm; among the 91 patients with tumors sized <0.6 cm, only 3.3% experienced tumor relapse. More importantly, all the patients survived for more than seven years. Martini *et al*. (30) retrospectively analyzed 498 cases of stage IA non-small cell lung cancer and found that the survival of patients with tumors sized <1 cm was significantly superior to those with tumors sized 1-3 cm. Therefore, tumor size can be a prognostic factor. As shown in our study, LPA had relatively small diameter, whereas the diameters of SPA, APA, and MPA were relatively large, which is consistent with a previous study (5).

Among the 188 cases of invasive lung adenocarcinoma, APA and PPA accounted for 77%, while LPA and MPA only accounted for 11.1%. The proportions of the different subtypes of invasive lung adenocarcinoma in our study are basically similar to the results of the other 16 articles (6-21). Our current study was also limited by its retrospective design, and no detection result of the EGFR gene mutation lung in tissue was available. An ongoing follow-up study among these patients will provide more evidences.

In summary, the histological subtypes of lung adenocarcinoma have their unique clinicopathological features. Strict subtyping of the lung adenocarcinoma based on the new international classification criteria is of great clinical importance.

Acknowledgements

The study was supported by a grant from "Twelve-Five Plan", the Major Program of Nanjing Medical Science and Technique Development Foundation (Molecular Mechanism Study on Metastasis and Clinical Efficacy Prediction of Non-small Cell Lung Cancer) and Third Level Training Program of Young Talent Project of Nanjing Health, Nanjing Medical Science and Technology Development Project (QRX11226), and Young Professionals Foundation of Nanjing Chest Hospital.
Disclosure: The authors declare no conflict of interest.

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Cite this article as: Hu HD, Wan MY, Xu CH, Zhan P, Zou J, Zhang QQ, Zhang YQ. Histological subtypes of solitary pulmonary nodules of adenocarcinoma and their clinical relevance. J Thorac Dis 2013;5(6):841-846. doi: 10.3978/j.issn.2072-1439.2013.12.16