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Effect of Micropapillary Pattern and Spread through Air Space in Patients with Lung Adenocarcinoma ≤ 2 cm

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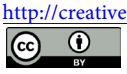


Abstract

Objective: To analyze the relationship between micropapillary pattern (MIP) and tumor spread through air space (STAS) and postoperative survival rate in patients with lung adenocarcinoma ≤ 2 cm. **Methods:** Retrospective analyses were performed on clinical data of 575 patients with lung adenocarcinoma ≤ 2 cm, which were resected from 2009 to 2011. We analyzed the pathological findings on the resected specimens, with special reference to the presence/absence MIP and STAS, which have been reported to be a marker of poor prognosis of lung adenocarcinoma. Patients were divided into three according to the presence/absence of MIP and STAS: low-risk (MIP− STAS−), medium-risk (either MIP or STAS + (one plus)) and high-risk group (+/+: double plus). Endpoint was postoperative survival rate, which was compared among three groups. **Results:** There was no statistical difference in age, sex, and serum CEA level among three groups. In lobectomized patients, there was no statistical difference in prognosis among three groups; however, in sub-lobectomy group, patients with double + (+/+ for MIP and STAS) showed a lower survival rate than others ($P < 0.001$). **Conclusion:** The presence of MIP and STAS reduced the survival rate in sub-lobectomized patients.

Keywords

Micropapillary, Spread through Air Space, Lobectomy, Sub-Lobectomy, Prognosis

*Contributed equally to this work.

1. Introduction

Lung cancer is a malignant tumor with the highest incidence and death rate in the world. The main pathology type is non-small cell lung cancer (NSCLC), and the incidence of lung adenocarcinoma has surpassed squamous cell carcinoma [1], endanger people's health. In treatment, thoracoscopic lung cancer surgery has become the primary treatment of early lung cancer [2] [3] [4], sub-lobectomy in the treatment of early lung cancer can not only achieve similar safety as lobectomy, but also have the advantage of better protection of pulmonary function [5] [6] [7].

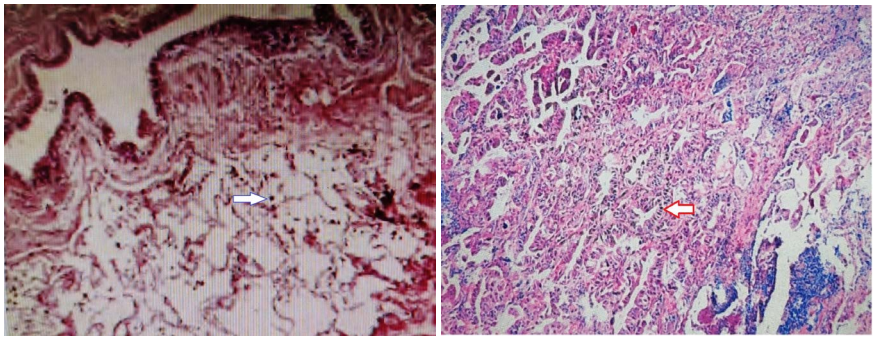
However, the presence of micropapillary pattern (MIP) and tumor spread through air space (STAS) in lung adenocarcinoma has a higher risk of invasion and recurrence [8] [9] [10]. MIP was first identified in breast cancer, and has been classified as a new histological subtype in lung cancer since 2011, The histological morphology of micropapillary is a cluster of infiltrating cells without fibrous vascular axis [11] [12]. And STAS is the diffusion of cancer cells through the alveolar and capillary bronchials to the surrounding lung parenchyma (**Figure 1**). This data is the reconfirmation of the preceding data and research provides reference for clinical surgical treatment of early lung adenocarcinoma, by analyzing and comparing the postoperative survival status of patients with lung adenocarcinoma including MIP and STAS, data analysis of 575 patients from multiple centers is reported as follows. This research has been approved by The Third Affiliated Hospital of Soochow University Ethics Committee, abide by the "Declaration of Helsinki".

2. Methods

According to the international lung cancer research association (IASLC) in September 2015, the 8th edition of lung cancer TNM staging [13], Patients with stage IA ≤ 2 cm lung adenocarcinoma treated in 7 medical centers (including The second affiliated of Zhejiang University, Shanghai Pulmonary Hospital, Zhejiang Cancer Hospital, Jiangsu Cancer Hospital, Jiangsu Provence hospital Hospital, Affiliated Hospital of Nantong University and The First People's Hospital of Changzhou in Chian) between 2009 to 2011 were included. Inclusion criteria: lung adenocarcinoma ≤ 2 cm with negative lymph node and surgical margin. Exclusion criteria: 1) neoadjuvant therapy or adjuvant therapy. 2) adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA). 3) presence of multiple nodules. 4) presence of tumors with positive margin. 5) concurrent progressive diseases or accidental death. 6) incomplete follow-up information. Ultimately a total of 575 patients were included in this study. gender, age, CEA, surgical procedure, tumor diameter and patient survival were collected, progression free survival (PFS) was the time of the patients without tumor recurrence and progression after surgery.

Re-observed the postoperative pathological sections of the patients, according to the 2011 International Association for the Study of Lung Cancer/American

Thoracic Society /European Respiratory Society, IASLC/ATS/ERS standard [14], MIP was considered present if it made up ≥5% of the tumor, STAS was recorded as micropapillary cell clusters, solid carcinoma nests or single tumor cells ≥ 1 alveolar [15]. Patients were divided into three according to the presence/absence of MIP and STAS: low risk (MIP− STAS−), medium risk (either MIP or STAS + (one plus)) and high risk group (+/+: double plus). Clinical information and analysis of patients in the three groups are shown in (Table 1).



(a) (b)

Figure 1. Morphologic features of micropapillary pattern and STAS pattern (original magnification: ×100). (a) infiltrating lung adenocarcinoma with a micropapillary growth. (b) STAS (arrows) identified within air spaces in the lung parenchyma beyond the edge.

Table 1. Characteristic of patients.

Characteristic	Low-risk	Middle-risk	High-risk
Age	59.2 ± 8.8	59.4 ± 9.3	60.3 ± 10.6
Sex			
Male	108	98	45
Female	171	118	35
Surgical procedure			
Lobectomy	233	173	66
Sub-lobectomy	46	43	14
Tumor size, cm			
<1 cm	84	35	18
≥1 cm	195	181	62
Predominant histologic subtype			
Lepidic	157	35	13
Acinar	86	116	39
Papillary	31	44	14
Solid	5	19	12
MIP	0	2	2
CEA			
<10 ng/ml	266	187	69
≥10 ng/ml	13	29	11

3. Follow-Up Policy

All patients received a physical examination, interval history, and chest computed tomography (CT) scan every six to twelve months during the first two years after resection and yearly thereafter. Follow-up visits were made until October 2018, Tumor locoregional recurrence or distant metastasis was diagnosed using chest CT, brainmagnetic resonance imaging (MRI), and bone scintigraphy as well as ultrasound and/or abdominal CT.

4. Statistical Analysis

Use SPSS 19.0 (SPSS, Chicago, IL) for statistical analysis, the patient characteristics between the three groups were compared using univariate and multivariate analysis of variance, survival analyses for lobectomy and sub-lobectomy were performed by means of the Kaplan-Meier approach. All P-values were based on analysis and P-value less than 0.05 was considered statistically significant.

5. Results

There was no statistical difference in age, sex, tumor size and serum CEA level among three groups (P > 0.05) (Table 2). The survival rate of the low-risk group was significantly higher than that of the high-risk group (P < 0.001) (Figure 2). In lobectomized patients, there was no statistical difference in prognosis among three groups; (P = 0.132) (Figure 3). However, in sub-lobectomy group, patients with double + (+/+ for MIP and STAS) showed a lower survival rate than others (P < 0.001) (Figure 4).

Table 2. Data analysis of patients' general conditions.

Factors	Univariate analysis		Multivariate analysis	
	HR	P	HR	P
Age	0.983	0.584	0.970	0.354
Sex	0.490	0.129	0.761	0.715
Tumor size	1.848	0.272	0.535	0.396
CEA	4.181	0.002	1.294	0.748
Risk group	6.967	<0.001	10.971	<0.001

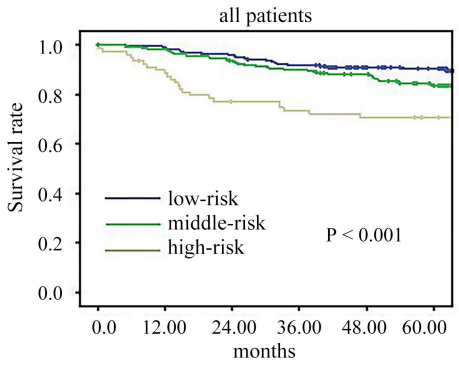


Figure 2. PFS of all patients. (P < 0.001 low-risk group compare with high-risk group).

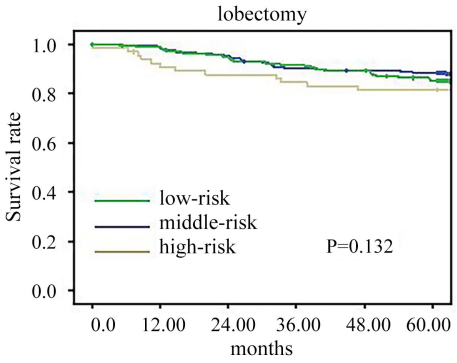


Figure 3. PFS of lobectomy patients. (P = 0.132 low-risk group compare with high-risk group).

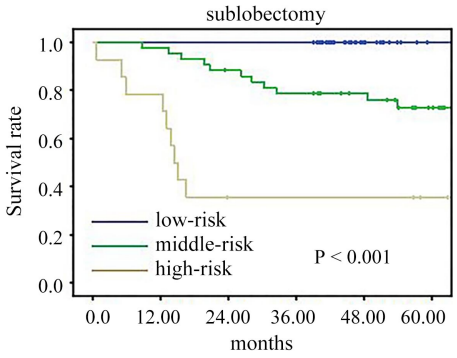


Figure 4. PFS of sub-lobectomy patients. (P < 0.001 three risk groups compare with each other).

6. Discussion

In 2011, MIP was redefined as a new histological subtype, after which researchers gradually had a comprehensive understanding to MIP [16]. Existing studies proved that: the recurrence rate of lung adenocarcinoma patients experiencing sub-lobectomy was higher, and the postoperative survival rate was much lower than that of patients who were given lobectomy [17]. In terms of patients who obtain wedge-shaped lung resection, their postoperative pathology displays micropapillary structure or solid structure. At this time, another pulmonary segment or lobectomy is recommended, because the two operations can avoid recurrence of tumor. In this present research, MIP and STAS significantly reduced the survival rate of postoperative patients (P < 0.001). However, the survival status of patients suffering from stage IA lung adenocarcinoma, MIP and STAS and experiencing pulmonary segmental resection was not compared with that of patients with lobectomy. Whether pulmonary segmental resection can reduce the risk of postoperative recurrence is still under discussions.

During the infiltration of lung adenocarcinoma, the appearance of micropapillary structure and solid structure are the histological basis of STAS [18] [19], revealing that the presence of STAS increases the risk of tumor recurrence after surgery [20], may be considered a parameter in lung cancer staging, especially lung adenocarcinoma [21]. However, the accuracy of the diagnosis of STAS is

still a difficult problem. During the process of pathological examination, lung tumors need to experience continuous dissection, thus inevitably leading to the shedding of tumor cells and false positive of STAS [22]. It was reported that various complications of lung cancer, including pulmonary interstitial fibrosis, may have potential effects on tumor STAS [23]. Therefore, accurate diagnosis of STAS is significantly important.

At present, thoracic surgeon has a good knowledge of thoracoscopic lobectomy and sub-lobectomy. Meanwhile, in intraoperative rapid freezing section, it is remarkably difficult to know whether tumors involve MIP and STAS. At the same time, the presence of rapid intraoperative pathology also increases the operative time, and the risk of surgery as well. Therefore, in intraoperative rapid pathology, rapid and accurate diagnosis of MIP and STAS is of guiding significance for patients' choice of surgical mode and the need to change surgical mode.

In conclusion, for patients obtaining sub-lobectomy, MIP and STAS can increase recurrence and progression of tumor, and the choice and change of operation mode need the support of rapid pathology. In terms of patients with lung adenocarcinoma MIP and STAS, the resection range can be appropriately expanded, so as to reduce the risk of post-operative recurrence and improve the survival rate of patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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