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Analysis of risk factors for stage I lung adenocarcinoma using low-dose high-resolution computed tomography

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Abstract. Risk factors for stage I lung adenocarcinoma were analyzed using low-dose high-resolution computed tomography (CT). The patients were divided into case group (stage I lung adenocarcinoma patients) and control group (benign pulmonary nodules patients). All patients were subjected to low-dose high-resolution CT. Multiple linear regression was performed to analyze the CT imaging features of the two groups. Stage I lung adenocarcinoma patients were significantly associated with nodular site (X_3, upper left lobe) [95% CI (1.796, 54.695), p=0.008], nodule type (X_4) (p<0.001), nodule size (X_5) [95% CI (0.614, 0.803), p<0.001], spicule sign (X_7) [95% CI (0.029, 0.580), p=0.008], lobulation sign (X_8) [95% CI (0.048, 0.673), p=0.011]. The stepwise regression equation is: Logistic (p) = -12.009 + 2.294X_3 - 0.327X_4 - 0.354X_5 - 2.042 X_7 - 1.713X_8. Risk factors of low-dose and high-resolution CT imaging for patients with stage I lung adenocarcinoma are nodular site (upper left lobe), nodule type, nodule size, spicule sign, and lobulation sign.

Introduction

Malignancy is a common and frequently occurring disease that seriously threatens human health. Malignancy is the second leading cause of death worldwide, and is the first leading cause of death in some countries. In the past several decades, morbidity and mortality rate of lung cancer is the highest among all types of malignancies (1). The incidence of lung cancer is expected to be significantly increased not only in developed countries, such as USA, but also in developing countries, such as China (2), exerting enormous pressure on the society (3). According to the lung tumor histological classification established by WHO in 2015, lung cancer originates from epithelial and mesenchymal tissues, and epithelial tissue is the more common origin. Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers (4,5). Pulmonary adenocarcinoma is one of the main types of NSCLC. Among patients with lung cancer, prognosis for patients with different TNM clinical stages is significantly different. Early stage (IA-IIB) NSCLC accounts for only 25-30% of the total number of lung cancers (6). The 5-year survival rate for stage I NSCLC is 73%, whereas for stage IV patients is only 13% (7). Therefore, early diagnosis of lung adenocarcinoma is particularly important.

At present, low-dose spiral computed tomography (CT), liquid biopsy and fiberoptic bronchoscopy are mainly used for early screening of lung cancer. Traditional serum tumor markers in liquid biopsy have shown certain specificity and sensitivity in the diagnosis of lung cancer, and the combination of several markers can significantly improve the accuracy (8,9), such as CEA, CA125, CA153, and Cyfra21-1, which is more sensitive to the diagnosis of middle and advanced-stage lung cancer. Circulating tumor cells (CTCs) refer to the tumor cells in circulating blood from the primary tumor or metastatic lesions formed by passive migration, invasion or interference of external factors after passive shedding (10). CTCs are present in peripheral blood even in patients with early-stage lung cancer even before the formation of minimal lesions. However, the detection of CTCs is not easy. As an observation in patients with chronic obstructive pulmonary disease (COPD), chest CT and CTCs detection results of 5 patients were compared every year to see if there is a shift from COPD to lung cancer. The results showed that when CTCs were found in the peripheral blood, no small pulmonary nodules were detected on the chest CT scan; the nodules were gradually found by chest CT scan in 1-4 years of subsequent follow-up monitoring, and stage I lung cancer was confirmed by postoperative pathology (11). CTCs can also be used as a joint detection method to distinguish between benign and malignant pulmonary nodules, and the detection rate is higher than that of traditional tumor

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markers (12). At the same time, detection of CTCs can also be used to guide clinical medication and prediction of prognosis (13,14). Detection of circulating tumor nucleic acids, including circulating tumor DNA (ctDNA) and circulating tumor RNA (ctRNA), which were released by tumors into peripheral blood in the early stages of tumorigenesis, can also be used to guide the diagnosis. However, different examination methods provide different results (15).

New bronchoscopic techniques, such as electromagnetic navigation bronchoscopy (ENB), autofluorescence bronchoscopy (AFB) and narrow band imaging (NBI) expanded the diagnostic vision to a certain extent and increased the diagnostic rate of lung cancer (especially early-stage lung cancer). However, novel bronchoscopic techniques include invasive procedures and patients' compliance is poor (16).

With the advantages of convenient operation, reasonable cost, no obvious trauma and side-effects, low-dose spiral CT has been widely used in the early diagnosis of lung cancer (17,18). However, this technique also has some limitations. For example, the false positive rate is high (19). Therefore, combined diagnosis is always needed. For now, it has become a hot research field to analyze the risk factors of stage I lung adenocarcinoma by low-dose high-resolution spiral CT.

Materials and methods

Subjects. Patients were selected from June 2014 to June 2017 in Guangxing Hospital Affiliated to Zhejiang Chinese Medical University, the First Affiliated Hospital of Zhejiang University (Hangzhou, China), and Peking University People's Hospital (Beijing, China). Patients without complete clinical records and patients younger than 18 years were excluded. The patients were further diagnosed in the Department of Thoracic Surgery in three hospitals, and patients with stage I lung adenocarcinoma were included to serve as case group. At the same time, benign pulmonary nodule patients with similar age and sex distributions were also included to serve as control group.

Diagnostic criteria. Patients in case group (stage I lung adenocarcinoma patients) were diagnosed according to the diagnostic and treatment guidelines for primary lung cancer clinics (2011 edition) established by the Chinese Society of Clinical Oncology (CSCO) (20). TNM staging was performed according to the criteria established by the International Association for the Study of Lung Cancer (IASLC) in 2009: T1a, greatest diameter of tumor ≤2 cm; T1b, greatest diameter of tumor >2 and ≤3 cm; N0, no regional lymph node metastasis; M0, no distant metastasis (21). Patients in control group were diagnosed as benign pulmonary nodules by pathological examination and CT imaging (22).

Inclusion and exclusion criteria. Inclusion criteria: Patients in case group were diagnosed with stage IA and IB lung adenocarcinoma. Patients without serious cardiovascular, digestive and other diseases, without liver and kidney dysfunction, age >18 years and <80 years, Karnofsky score >80 points, volunteered to participate in the study and could cooperate with the researchers. Exclusion criteria: Patients with a history of malignancy, received lobectomy or pneumonectomy, severe infections, severe heart diseases, complicated by liver, kidney and other serious primary diseases, hematopoietic system, nervous system and mental illness, as well as pregnant women were excluded from both case and control group. Patients in control group diagnosed with malignant pulmonary nodules were also excluded.

Data collection. General demographic information (sex, age, ethnicity, marital status and education level) and self-reports of dietary habits, tobacco and alcohol addiction, exercise habits, past history of related diseases and family disease history were collected. All patients were subjected to low-dose high-resolution (512x512 matrix) 128-row 256 iCT imaging.

Ethics approval. This study was approved by the Ethics Committee (approval no. 2014LL001) of Guangxing Hospital Affiliated to Zhejiang Chinese Medical University (Hangzhou, China). Signed informed consents were obtained from the patients or the guardians.

Statistical analyses. χ^2 test was used to determine the baseline of the two groups of subjects. Continuous variables were compared by using ANOVA; Dunnett's method was used when the variance was homogeneous, and Mann-Whitney U test was used when the variance was not homogeneous in comparison between two groups. Multivariate correlation analysis was performed by using logistic regression analysis. Logistic regression analysis of malignancy probability, nodule size and percentage of solid nodules in patients with stage I lung adenocarcinoma were performed by using R language. ROC curve was drawn and AUC was calculated to evaluate the diagnostic value of the nodular site (X_3), nodule type (X_4), nodule size (X_5), spicule sign (X_7), lobulation sign (X_8) to lung adenocarcinoma status. The sensitivity and specificity were calculated according to the cut-off value.

Results

General information. Case group included 82 males and 112 females, with an average age of 57.54 years. Control group included 44 males and 46 females, with an average age of 56.28 years. After examination, no significant differences in sex, age, ethnicity, marital status and educational level were found between case and control group (Table I).

Logistic regression analysis. Logistic regression analysis was performed by using stage I lung adenocarcinoma (1= stage IA and IB lung adenocarcinoma, 0= benign pulmonary nodules) as dependent variable, and low-dose high-resolution CT imaging features including nodule type, nodule size, vacuolar sign, bronchial inflatable sign, bronchial truncated sign, smooth sign, spicule sign, lobulated sign and pleural indentation as independent variables. Using stepwise regression, equation for the final model showed that stage I lung adenocarcinoma was associated with nodular site (X_3, upper left lobe) [95% CI (1.796, 54.695), p=0.008], nodule type (X_4) (p<0.001), nodule size (X_5) [95% CI (0.614, 0.803), p<0.001], spicule sign (X_7) [95% CI (0.029, 0.580), p=0.008] and lobulation sign (X_8) [95% CI (0.048, 0.673), p=0.011] (Table II). Stepwise regression equation is: Logistic (p) = $-12.009 + 2.294 X_3 - 0.327X_4 - 0.354X_5 - 2.042X_7 - 1.713X_8$. Logistic regression

Table I. Comparison of the basic information between two groups.

Variables	Cases	Case group (n=194)	Control group (n=90)	χ^2 value	P-value
Sex					
Male	126	82	44	1.092	0.296
Female	158	112	46		
Age (years)					
<60	153	101	52	0.808	0.369
≥60	131	93	38		
Ethnicity					
Han nationality	267	183	84	0.108	0.742
Minority	17	11	6		
Marriage status					
Married	258	178	80	0.606	0.436
Unmarried and divorced	26	16	10		
Degree of education					
Junior high school and below	151	104	57	2.482	0.289
High school, technical secondary school and college	74	55	19		
College and above	49	35	14		
Smoking					
Yes	85	56	29	0.330	0.566
No	199	138	61		
Family history of cancer					
Yes	52	35	17	0.030	0.864
No	232	159	73		

Table II. Logistic regression analysis of low-dose high-resolution CT imaging features on stage I lung adenocarcinoma.

Variables	Types	B	SE	Wald	Odd ratio	95% CI	P-value
Smoking (X_1)		0.738	0.560	1.739	2.093	0.698-6.271	0.187
Family history of cancer (X_2)		-1.042	0.736	2.007	0.353	0.083-1.491	0.157
Nodular site (X_3)	Left upper lobe	2.294	0.872	6.925	9.910	1.796-54.695	0.008
	Left lower lobe	0.049	1.166	0.002	1.050	0.107-10.334	0.996
	Right upper lobe	1.240	0.832	2.223	3.455	0.677-17.633	0.136
	Right middle lobe	2.164	0.899	5.794	8.708	1.495-50.726	0.016
Nodule type (X_4)				44.188			<0.001
	Partial solid nodules	24.995	27,265.515	0.001	0.001	0.001	0.999
	Solid nodules	21.016	27,265.515	0.001	0.001	0.001	0.999
Nodule size (X_5)		19.901	27,265.515	0.001	0.001	0.001	0.999
	Purely ground glass-like density nodules	-0.354	0.069	26.443	0.702	0.614-0.803	<0.001
	Bronchial inflatable sign (X_6)	-1.326	0.749	3.129	0.266	0.061-1.154	0.077
	Burr sign (X_7)	-2.042	0.764	7.143	0.130	0.029-0.580	0.008
	Lobulation sign (X_8)	-1.713	0.672	6.495	0.180	0.048-0.673	0.011
Constant		-20.009	-	0.001	0.001		0.999

CT, computed tomography.

Table III. The sensitivity and specificity of CT imaging risk factors in the diagnosis of stage I lung adenocarcinoma in the predictive model.

Test result variables	Area under the curve	SE[a]	Asymptotic sig[b]	95% CI Lower bound	95% CI Upper bound	Sensitivity	1-Sensitivity	Youden index
Nodular site (X_3)	0.678	0.067	0.015	0.545	0.810	0.663	0.316	0.347
Nodule type (X_4)	0.821	0.063	0.001	0.697	0.945	0.926	0.316	0.611
Nodule size (X_5)	0.702	0.063	0.006	0.579	0.825	0.800	0.474	0.326
Spicule sign (X_7)	0.600	0.069	0.170	0.465	0.735	0.463	0.263	0.200
Lobulation sign (X_8)	0.616	0.064	0.112	0.490	0.742	0.337	0.105	0.232

The test result variables: predicted probability, predicted. [a]Under the non-parament assumption; [b]null hypothesis: true area, 0.5. CT, computed tomography.

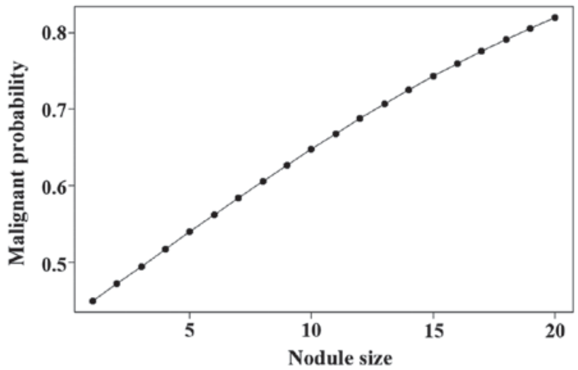

Figure 1. Logistic regression analysis of malignant probability and nodule size in stage I lung adenocarcinoma patients.

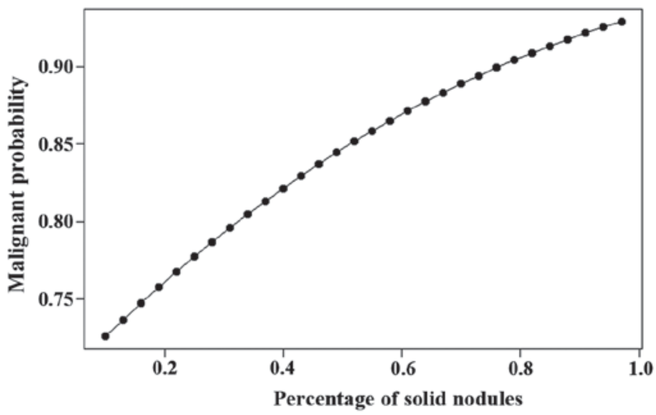

Figure 2. Logistic regression analysis of the percentage of malignant and solid nodules in stage I lung adenocarcinoma patients.

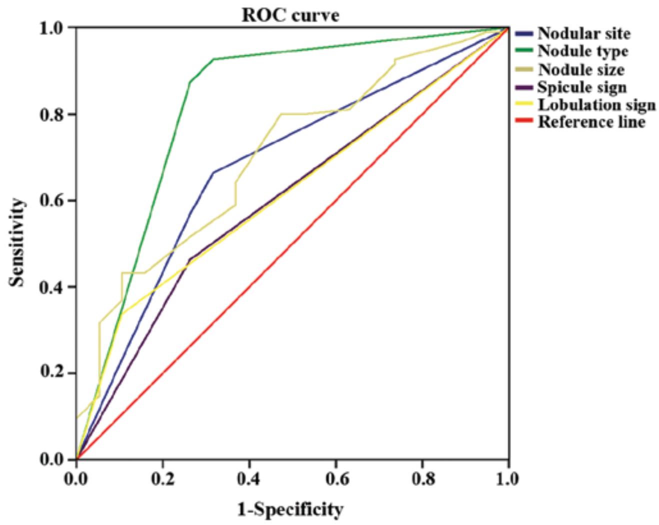

Figure 3. ROC curve of different CT imaging risk factors to stage I lung adenocarcinoma in the predictive model. CT, computed tomography.

analysis of malignant probability, nodule size, and solid nodule percentage in patients with stage I lung adenocarcinoma are shown in Figs. 1 and 2.

The diagnostic value of CT imaging risk factors to stage I lung adenocarcinoma in the predictive model. The AUC of nodular site (X_3), nodule type (X_4), nodule size (X_5), spicule sign (X_7), lobulation sign (X_8) were respectively 0.678 (0.545-0.810), 0.821 (0.697-0.945), 0.702 (0.579-0.825), 0.600 (0.465-0.735) and 0.616 (0.490-0.742). The sensitivity and specificity of nodular site (X_3), nodule type (X_4), nodule size (X_5), spicule sign (X_7), lobulation sign (X_8) in the diagnosis of stage I lung adenocarcinoma were 66.3 and 31.6%, 92.6 and 31.6%, 80 and 47.4%, 46.3 and 26.3%, 33.7 and 10.5%, respectively (Table III and Fig. 3).

Discussion

Early lung cancer usually has no typical symptoms, but it can be detected as pulmonary nodules in imaging. The nodules in CT imaging or chest X-ray are <30 mm in diameter with round or irregular shape and show high density shadow, the border is clear or unclear (23). With the development of imaging technology, low-dose high-resolution CT imaging has gradually become the primary means of early screening of lung cancer, and different screening guidelines, such as National Comprehensive Cancer Network (NCCN) and the American College of Chest Physicians (ACCP) (24,25), have been established by different academic organizations. Based on the characteristics of Asian people, guidelines for the assessment of patients with pulmonary nodules were established in February 2016 (26). Subsequently, guidelines for the classification, diagnosis and treatment of pulmonary nodules has also been updated (2016 edition) in China (27). Those guidelines all suggest that the characteristics of lung CT and risk factors of the patients shall be screened. Age and smoking history were mentioned as a potential factor for lung cancer, however, the morbidity prediction model and the follow-up were different in these guidelines.

Studies on the lung cancer prediction model have a history of >20 years, and the earliest model was the Mayo model proposed in 1997. The area under the ROC curve (>0.75) in Mayo model has been verified by multiple external verifications, this model is currently the most widely used prediction model (28). In recent years, many scholars have put forward relevant prediction models based on the results of their own clinical studies, such as the VA model, and the Brock University model (29,30). Among them, the accuracy of Brock University model is the highest due to the large data included, and the area under the ROC curve can reach at least 0.94. For Chinese population, the relatively mature model is Peking University model (31). Because the sample size and risk factors included in each model are different, reported accuracy is not the same. Therefore, it is important to combine the epidemiological characteristics of lung cancer in various regions, establish a corresponding prediction model for the guidance of local lung cancer treatment.

According to their internal density, pulmonary nodules are simply divided into solid, partial solid and ground glass density nodules. Solid nodules are nodules with uniform soft tissue density, the density is uniform, and the blood vessel and bronchial images are covered during the period. Partial solid nodules refer to the nodules that contain both ground glass density and solid soft tissue density. Ground glass density nodules refer to vague nodules in the lungs, with nodular density slightly increased compared to the surrounding lung parenchyma, but the profile of the internal blood vessels and bronchi are still visible (32). Ground glass density nodules are non-specific imaging manifestations that can be caused by a variety of pathologies including inflammation, and atypical adenomatous hyperplasia. Highest degree of malignancy was observed in partial solid nodules, followed by ground glass density nodules and solid nodules.

Some researchers believe that the diameter of partial solid nodules is positively correlated with the degree of malignancy. In the 2013 version of ACCP, the recommended treatment path for solid nodules is as follows: For partial solid pulmonary nodules with a diameter ≤8 mm, CT should be routinely performed, and non-surgical biopsy or surgical treatment should be performed immediately in the case of enlargement. For partial solid pulmonary nodules with a diameter >8 mm, CT should be performed at 3 months after the initial examination, and PET scan, non-surgical biopsy and surgical treatment should be performed actively if lesion persists. For partial solid pulmonary nodules with a diameter >15 mm, active treatment should be performed immediately (33). As a result, the greater the partial diameter of partial solid nodules is, the higher the risk of malignancy will be. This study also draws similar conclusions (Fig. 2).

The size of pulmonary nodules and its pathological properties are closely correlated with each other. Some studies even concluded that the size of the diameter is an independent risk factor for the diagnosis of benign and malignant lesions, while the diameter of benign nodules is relatively small, and consistent findings were also found in this study. Occurrence of lung cancer includes a series of stages of tumor growth including hyperplasia, atypical hyperplasia, carcinoma *in situ* and invasive cancer (34). This study shows that the size of the nodules is closely related to the degree of malignancy, the larger the nodules, the higher the degree of malignancy (Fig. 1). This shows that follow-up is crucial, and some guidelines suggest that follow-up is not necessary for nodules with a diameter <6 mm, but the results of this study show that attention should also be paid to some nodules with small diameters.

Characteristics of the pulmonary nodules are also important basis for the judgement of the nature of nodules. Due to differences in the growth rate of various cells in malignant pulmonary nodules, or bronchial and vascular blockage of the growth of cancer cells, CT morphological lobulation symptoms arise (35). Lobulation sign is positively correlated with the growth rate of cells and degree of malignancy (36). Spicule sign is caused by the infiltration of tumor into adjacent bronchus, sheath or local lymph node. Lobulation sign is also a characteristic of malignant pulmonary nodules (31). Bronchial inflatable sign is caused by the growth of tumor cells attached to the wall, and alveolar bronchia is still preserved in lesions; at the same time, the tumor cells and peripheral fibrous tissue proliferate, and the bronchiectasis is formed (37). Bronchial inflatable sign is common in malignant tumors, but can also be observed in benign tumors (38). This study also showed that spicule and lobulation sign were closely correlated with pathological features.

Incidence of lung cancer is different in different sites. In terms of lung adenocarcinoma, most cases were found in upper lung lobes (39). This study also showed that stage I lung adenocarcinoma mainly affected upper left lung, followed by upper right lung. However, the mechanism remains unclear.

In conclusion, in this study, the risk factors of disease were combined with CT imaging characteristics of pulmonary nodules to diagnose stage I lung adenocarcinoma. The subjects were with pulmonary nodules but without obvious symptoms. Therefore, our study achieved early diagnosis and treatment. Results show that the size of nodules is closely correlated with the incidence of stage I lung adenocarcinoma. With the increase of the diameter of pulmonary nodules, the possibility of malignancy increases. For smaller nodules, their own risk factors should be combined for follow-up. The nature inside the nodules is correlated with the degree of malignancy, and highest malignancy was observed in partial solid nodules. Lobulation and spicule signs are typical manifestations of early lung adenocarcinoma, and the probability of malignancy is relatively high for bronchial inflatable sign. In addition, incidence of stage I lung adenocarcinoma also showed predilection in the left upper lung. The sample size in this study is small, and most patients were from local region. Future studies with larger sample size are needed to further confirm the conclusion. Our future study will try to combine liquid biopsy to identify the risk factors for stage I lung adenocarcinoma , and establish a more reliable disease prediction model, so as to improve the diagnosis and treatment of this disease.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

RF, YY, HH, XF and LD conceived and designed the study. BX, WL, CM, FC, JH and JW collected, analyzed and interpreted the patient data. RF and YY wrote the manuscript. BX, JH and JW revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Guangxing Hospital Affiliated to Zhejiang Chinese Medical University (Hangzhou, China). Patients who participated in this research had complete clinical data. Signed informed consents were obtained from the patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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