ORIGINAL RESEARCH

Analysis of Clinical and Pathological Features of Malignant Pulmonary Nodules

Yijun Wang, MM, Qiaona Huang, BM; Junde Li, MM

ABSTRACT

Context • Early detection of pulmonary nodules in lung cancer and timely intervention can improve the number of diagnoses at early stages of lung cancer and can reduce mortality. At present, it's not possible to accurately determine the degree of pathological invasion of ground-glass nodules and the probability of regional lymph node metastasis using an imaging examination before surgery.

Objective • The study intended to analyze the clinical, imaging, and pathological characteristics of malignant pulmonary nodules and to explore the high-risk factors for lymph node metastasis, using logistic regression multivariate analysis.

Design • The research team retrospectively analyzed lung-cancer patients' demographic and clinical data.

Setting • The study took place in the Department of Thoracic Surgery at Zhangzhou Municipal Hospital, affiliated with Fujian Medical University, in Zhangzhou, China.

Participants • Participants were 1168 patients with malignant pulmonary nodules at the hospital between January 2018 and December 2020.

Outcome Measures • The research team: (1) collected participant's pulmonary nodules after surgical resection, which the hospital had confirmed were primary lung cancer and (2) analyzed the clinical characteristics of the malignant pulmonary nodules using the World Health Organization's (WHO's) 2021 classification standard for lung-cancer tissue. The research team also collected participants' data, including gender, age, smoking status, nodular size, imaging characteristics, pathological type, degree of invasion, and lymph node metastasis, and analyzed the clinical characteristics of the malignant pulmonary nodules and explored the risk factors for lymph node metastasis.

Results • Participants' average age was 56.79 ± 11.53 years, and the study included 675 females (57.79%) and 493 males (42.21%), 932 of whom didn't smoke (79.8%). Imaging indicated that most participants had nodules in the upper lobes of the lungs, 424 participants in the right lung (36.30%) and 303 in the left (25.94%). Imaging also showed that 400 participants had pure ground-glass nodules (34.25%) and 371 had solid nodules(31.76%), 355 had partial solid nodules (30.39%), the other 42 had cavitary nodules (3.60%) , and 1098 participants had adenocarcinoma (94.00%). Regarding the incidence of lymph node metastasis, 67 participants had N1 metastasis (5.74%) and 34 had N2 metastasis (2.91%). The multivariate logistic regression analysis showed that an increase in the nodular size ($P < .001$); the presence of lower-lobe pulmonary nodules, the nodular site ($P = .025$); and the amount of solid components in the nodule, the nodule's features ($P < .001$), were significant adverse factors for N1 lymph node metastasis, while gender, age, and smoking status didn't affect that outcome.

Conclusions • Adenocarcinoma was the most common pathological type, and the probability of lymph node metastasis was low. N1 lymph node metastasis was associated with increased nodular size and solid components and the presence of lower lobe nodules. (*Altern Ther Health Med.* 2023;29(4):188-193).

Yijun Wang, MM; Qiaona Huang, BM; Junde Li, MM; Department of Oncology, Zhangzhou Municipal Hospital, Affiliated with Fujian Medical University, Zhangzhou, China.

Corresponding author: Yijun Wang, MM
E-mail: wangyijun943@163.com

Lung cancer is a malignant tumor, with the high morbidity and mortality worldwide, and the incidence is increasing year by year.[1] The *2018 Chinese Expert Consensus on the Management of Pulmonary Nodules* defines a pulmonary nodule as a focal, rounded, dense, and solid or subsolid shadow that is ≤3 cm in diameter, either isolated or multiple and without pulmonary atelectasis, hilar enlargement, or pleural effusion.[2] That publication divides

pulmonary nodules into solid or subsolid nodules according to findings from computerized tomography (CT) imaging, and the latter category includes pure ground-class nodules (pGGN) and part solid nodules (PART). The publication also defines isolated pulmonary nodules as isolated when the lesion is solitary and multiple pulmonary nodules as multiple when two or more lesions exist.

Zhang et al found that adenocarcinoma was the pathological type in micro-infiltrating or infiltrating pure ground glass nodules less than 1 cm in diameter, while adenocarcinoma accounted for 98.7% in mixed density ground glass nodules.[3] Ma et al indicated that primary lung cancer is mainly adenocarcinoma, and young individuals primary lung cancer has a high degree of malignancy but a good prognosis.[4]

Indicators

According to the *American College of Chest Physicians (ACCP) Evidence-based Clinical Practice Guidelines,* the probability of pulmonary nodules being located in the upper lobe is high, and guidelines indicate that the location of a tumor in an upper lobe can an independent predictor of outcome. [5]

The *China National Cancer Center* indicates that the incidence of primary lung cancer in men is significantly higher than that in women, the cancer incidence and mortality rates both increased with age, and reached the peak in the age groups of 80 years old.[6]

Wu et al found that smoking history is significantly correlated with the risk of lung cancer, and the earlier, longer, and greater the smoking time, the higher the risk of lung cancer will be.[7]

Low-dose Computed Tomography

In 2011, *National Lung Cancer Screening Trial (NLST)* showed that in high-risk groups, compared with chest x-ray, low-dose spiral CT(*LDCT*) can reduce lung cancer mortality by 20%.[8] Two other studies found that early detection of pulmonary nodules and timely intervention using LDCT can improve the number of diagnoses at early stages of lung cancer and can reduce mortality.[9,10] Gao et al also found that clinicians can detect lung nodules early due to the extensive development of LDCT and can provide accurate qualitative and standardized treatment of lung nodules, which has become the main daily work of thoracic surgeons.[11]

LDCT screening allows clinical experts to determine the nature of lung nodules and the needed time and scope of radical surgery, to optimize the surgical method and reduce the scope of resection while ensuring efficacy as much as possible. With the improvements in the comprehensive diagnosis and treatment of cancer, the five-year survival rate for lung cancer has gradually improved, but radical surgical resection is still the most effective method to cure lung cancer at present.

Surgical Resection

Maximizing tumor resection and preserving lung function is one of the main principles of lung-cancer surgery. According to the *2022 Clinical Diagnosis and Treatment Guidelines for Lung Cancer of the Chinese Medical Association,* the feasibility of voluntary segmentectomy may be indicated in the following conditions:(1) the patient's functional status cannot tolerate lobectomy; (2)Peripheral small nodules with a tumor diameter of ≤ 2 cm and one of the following conditions:a ground glass opacity (GGO) of >50%, for adenocarcinoma in situ or microinfiltrating adenocarcinoma or Long-term follow-up tumor doubling time≥ 400 days.[12]

Some studies have found that segmentectomy can play a therapeutic effect similar to that of lobectomy in early lung cancer.[13,14] Zhang et al indicated that Sublobar resection, especially wedge resection without lymph node dissection, may be the preferred surgical procedure for patients with adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) .[15] However, it is difficult to accurately assess lymph node metastasis by imaging before surgery, so it is impossible to accurately select the best surgical modality by imaging evaluation.

Lymph Node Evaluation

For resectable lung cancer, systematic lymph-node evaluation is necessary and is an important means for accurate staging and treatment guidance. Clinicians should base the selection of the method of lymph node dissection on the pathological type and stage of lung cancer as well as on the basic physical condition of patients. Selective lymph node dissection is feasible for patients with early lung cancer.[16]

Moon et al found that the probability of lymph node metastasis of pulmonary ground-glass nodules was low, especially for the pathological types of atypical adenomatosis, adenocarcinoma in situ, and microinfiltrating adenocarcinoma, and that no significant differences existed in postoperative recurrence rates between patients without lymph node dissection and those who underwent lymph node dissection or sampling.[17]

However, an imaging examination before surgical resection can't accurately determine the degree of pathological infiltration of ground-glass nodules. Bai et al recommended stratification of the degree of lymph node intervention in terms of imaging features.[18] Those researchers indicated that pure ground-glass nodules may not require lymph node intervention and that partial solid nodules might permit lymph node sampling or dissection.

At present, it's not possible to accurately determine the degree of pathological invasion of ground-glass nodules and the probability of regional lymph node metastasis using imaging examination before surgery, and researchers need to explore the risk factors for regional lymph node metastasis.

Current Study

The current study intended to analyzed the clinical, imaging, and pathological characteristics of malignant pulmonary nodules and to explore the high-risk factors for lymph node metastasis, using logistic regression multivariate analysis.

METHODS

Participants

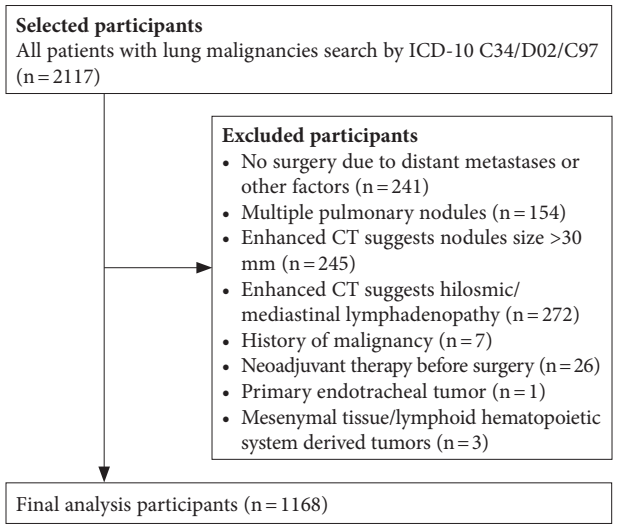
The research team retrospectively analyzed lung-cancer patients' demographic and clinical data. The study took place in the Department of Thoracic Surgery at Zhangzhou Municipal Hospital, affiliated with Fujian Medical University, in Zhangzhou, China. Potential participants were patients with malignant pulmonary nodules at the hospital between January 2018 and December 2020. Data were collected after searching by ICD code on the first page of the medical record.

The study included potential participants if they: (1) were aged ≥18 years, (2) had no previous history of malignant tumors; (3) had a preoperative enhanced CT of their chests that showed single pulmonary nodules of ≤ 30 mm; and (4) had had surgical resection of lung nodules, including but not limited to, thoracoscopic-assisted lobectomy, segmental lung resection or wedge resection of some lung tissue plus sampling, or dissection of hilar or mediastinal lymph nodes.

The study excluded potential participants if they: (1) had multiple pulmonary nodules that an enhanced CT of their chests had found; (2) had had a preoperative enhanced CT of their chests that showed hilar or mediastinal lymph-node enlargement; (3) had had a preoperative imaging examination that suggested distant organ metastases, such as of the liver, adrenal glands, brain, or bones; (4) had received neoadjuvant antitumor therapy, such as chemotherapy, radiotherapy, tumor immunotherapy, or targeted drug therapy before surgical resection; (5) had nodules that were located in the tracheal lumen; or (6) had a pathological examination that suggested that mesenchymal tissue or lymphohematopoietic tissue had originated from a malignant tumor.

The Medical Ethics Committee of the hospital approved the study's protocols. The retrospective collection of medical records didn't affect the formulation of the patient's treatment plan during hospitalization, didn't involve patient privacy, it was complied with the Helsinki Declaration , so we did not require the patient to re-sign the informed consent form. Fig1 shows that flow chart of including and excluding procedure, Final data analysis was performed in 1168 patients.

Figure 1. Flow chart of including and excluding procedure



Procedures

Data collection. Under the authorization of the Hospital Ethics Committee, the research team viewed the inpatient medical records and imaging examination data of discharged patients through the hospital case retrieval system,collected data related to participants' genders, ages, smoking status, nodular sizes within 2 weeks before surgery, imaging characteristics, pathological types, degrees of invasion, and lymph node metastasis,conduct data registration and statistical analysis.

Outcome measures. The research team: (1) through the inpatient medical records collected participant's pulmonary nodules data after surgical resection, which the hospital had confirmed were primary lung cancer and (2) analyzed the clinical characteristics of the malignant pulmonary nodules using the World Health Organization's (WHO's) 2021 Classification of Lung Cancer, the standard for analysis of lung-cancer tissue.[19]

Outcome Measures

athological analysis. After surgical resection,the lung nodule was sent to the Department of Pathology for specimen fixation, material collection and wax block embedding, HE staining, TTF-1, p40, Syn and other immunohistochemical examinations were observed under a light microscope, and the histopathological classification was carried out according to the WHO Classification of Thoracic Tumours (5th Edition) published by the International Agency for Research on Cancer (IARC) in May 2021.[19]

Metastasis. According to TNM staging of lung cancer (2017 AJCC 8th edition), N1 refers to: metastasis to ipsilateral peribronchial lymph and/or ipsilateral hilar and intrapulmonary lymph nodes, including direct invasion of the primary tumor, N2 refers to: metastases to ipsilateral mediastinum and/or subcarinal lymph nodes. Table 1 shows that variables' significance and scoring of factors influencing N1 lymph node metastasis.[20]

Regression analysis. The research team used the presence of N1 lymph node metastasis as the dependent variable, and gender, age, smoking status, nodule size, nodule imaging characteristics, and nodule location as the independent variables. The multivariate logistic regression analysis explored whether the independent variable had an effect on the dependent variable, $P < .05$ indicates a significant effect, and the OR value was compared with 1, the closer to 1, the smaller the degree of influence, and vice versa.

Statistical Analysis

The research team used the SPSS 25.0 software (IBM, Amonk, New York, USA) for statistical analysis. The team: (1) expressed measurement data as means ± standard

Table 1. Variables' Significance and Assignment of Factors Influencing N1 Lymph Node Metastasis

Variables	Meaning	Scoring
N1 Lymph Node	N1 lymph node metastasis	0=No metastasis; 1=N1 lymph node metastasis
Gender	Gender	0=female; 1=male
Age	Patient's age	Continuous variable, in years: 0=<40 years old; 1=≥40 years and <55 years old; 2=≥55 years and <70 years old; 3=≥70 years old
Smoking Status	Smoking or nonsmoking	0=nonsmoking; 1=smoking history
Nodular Size	Length and diameter of pulmonary nodules	0=≤10 mm; 1=>10 mm and ≤20 mm; 2=>20mm
Nodule Feature	Imaging features of nodules	0=pure ground-glass nodule; 1=partial solid nodule; 2=nodule with cavity; 3=solid nodule
Nodular Site	Location of nodules in the lobe of the lung	0=left/right upper lobe; 1=right middle lobe; 2=left/right lower lobe

Table 2. Demographic and Clinical Characteristics of Participants With Malignant Pulmonary Nodules (N = 1168)

Characteristics		n (%) Mean ± SD M
Gender	Male	493 (42.21)
	Female	675 (57.79)
Age	<40 years old	103 (8.82)
	40-55 years old	361 (30.91)
	55-70 years old	571 (48.89)
	≥70 years old	133 (11.38)
	Mean, y	56.79 ± 11.53
	Range, y	24 to 84
Smoking Status	Nonsmoker	932 (79.80)
	<30 package years	134 (11.47)
	30-60 package years	87 (7.45)
	≥60 package years	15 (1.28)
Nodular Site	Upper lobe of right lung	424 (36.30)
	Middle lobe of right lung	96 (8.22)
	Lower lobe of right lung	179 (15.33)
	Left upper lobe of lung	303 (25.94)
	Left lower lobe of lung	166 (14.21)
Nodular Size	≤10mm	326 (27.91)
	10-20mm	631 (54.02)
	> 20mm	211 (18.07)
Nodules' Imaging Features	Ground-glass nodules	400 (34.25)
	Partial solid nodules	355 (30.39)
	Cavitary nodules	42 (3.60)
	solid nodules	371(31.76)

Table 3. Postoperative Pathological Results for Participants With Malignant Pulmonary Nodules (N = 1168)

Postoperative Results		n(%)
Pathological Type	Adenocarcinoma	1098 (94.00)
	Squamous cell carcinoma	34 (2.91)
	Adenosquamous carcinoma	10 (0.86)
	Lymphoepithelioid carcinoma	7 (0.60)
	Large cell neuroendocrine carcinoma	7 (0.60)
	Small cell carcinoma	4 (0.34)
	Large cell carcinoma	3 (0.26)
	Other	5 (0.43)
Degree of Invasion	Carcinoma in situ	114 (9.76)
	Microinfiltration	502 (42.98)
	Invasive carcinoma	552 (47.26)
Lymph Node Metastasis	No metastasis	1067 (91.35)
	N1 lymph node metastasis	67 (5.74)
	N2 mediastinal lymph node metastasis	34 (2.91)

deviations (SDs) and used the independent sample *t* test for comparisons between groups, (2) expressed counting data as numbers and percentages (%) and used the Chi-square test and Fisher's accurate test for comparisons between groups and the Rank sum test for grade data, and (3) conducted multivariate logistic regression analysis to explore the risk factors related to N1 lymph node metastasis. $P < .05$ was considered to be statistically significant.

RESULTS

Participants

Table 2 shows that the study included and analyzed the data of 1168 participants, including 493 males (42.21%) and 675 females (57.79%). Participants were aged from 24 to 84 years old, with an average age of 56.79 ± 11.53 years. Of the 1168 participants, 236 had histories of varying degrees of smoking (20.21%).

The enhanced CT examinations of participants' chests indicated that 424 participants had pulmonary nodules in the upper lobe of the right lung (36.30%), 303 in the left upper lobe (25.94%), 96 in the right middle lobe (8.22%), 179 in the right lower lobe (15.33%), and 166 in the left lower lobe (14.21%). Of the 1168 participants, most, 631 participants, had a nodular diameter of 10-20 mm (54.02%).

Of the 1168 participants, 400 had pure ground-glass nodules (34.25%), 371 had solid nodules(31.76%), 355 had partial solid nodules (30.39%), and 42 had cavitary nodules (3.60%).

Pathological Features

Table 3 shows that out of 1168 participants,1098 had adenocarcinoma (94.00%). The other common pathological types included 34 participants with squamous cell carcinoma (2.91%), 10 with adenosquamous cell carcinoma (0.86%), 7 with lymphoepithelioid carcinoma (0.60%), 7 with large cell neuroendocrine carcinoma (0.60%), 4 with small cell carcinoma (0.34%), 3 with large cell carcinoma (0.26%), and 5 with other types of cancer (0.43%).

Of the 1168 participants, the degree of invasion found 114 participants with carcinoma in situ (9.76%), 502 with

microinfiltration (42.98%), and 552 with invasive carcinoma (47.26%), with the last two representing more than 90% of the cancers.

Of the 1168 participants, 182 underwent pulmonary nodule resection only or wedge resection (15.58%), and the remaining 986 underwent varying degrees of lymph-node sampling or dissection (84.42%), including 807 who underwent mediastinal lymph-node dissection.

Of the 1168 participants, 1067 had no metastasis (91.35%), and 101 had regional lymph node metastasis. Of those 101 participants, 67 only had N1 lymph node metastasis (5.74%), and 34 had N2 lymph node metastasis (2.91%).

Table 4. Multivariate Logistic Regression Analysis of Factors Influencing N1 Lymph Node Metastasis

Influencing Factors	Beta	SE	Wals	*P* value	OR	95%CI Limit	
						Lower	Upper
Gender	-0.09	0.291	0.096	.757	0.914	0.517	1.617
Age	-0.106	0.195	0.293	.588	0.900	0.613	1.319
Smoking Status	-0.421	0.323	1.707	.191	0.656	0.349	1.235
Nodular Size	1.249	0.241	26.922	<.001[a]	3.485	2.175	5.586
Nodule's Feature	1.033	0.174	35.218	<.001[a]	2.810	1.998	3.953
Nodular Site	0.335	0.149	5.049	.025[a]	1.398	1.044	1.872
Constant	-6.424	0.629	104.240	<.001[a]	0.002		

[a]$P < .05$, indicating that an increase in the nodular size; the presence of lower-lobe pulmonary nodules, the nodular site; and the amount of solid components in the nodule, the nodule's features, were significant adverse factors for N1 lymph node metastasis

Risk Factors for Metastasis

The multivariate logistic regression analysis showed that an increase in the nodular size ($P<.001$); the presence of lower-lobe pulmonary nodules, the nodular site ($P = .025$); and the amount of solid components in the nodule, the nodule's features ($P < .001$), were significant adverse factors for N1 lymph node metastasis, while gender, age, and smoking status didn't affect that outcome (Tables 4).

DISCUSSION

The *China National Cancer Center* indicates that the incidence of primary lung cancer in men is significantly higher than that in women, the cancer incidence rates increased with age. However, our study found that the proportion of women in early lung cancer was slightly higher than that of men, and the average age at diagnosis was less than 60 years old, about 4/5 of patients do not smoke,which is considered to be related to the deviation caused by different stages at the time of tumor diagnosis.

The current research team believes that the mechanism of malignant transformation of ground-glass nodules is different from that of solid nodules. Although the screening for lung cancer include high-risk groups, such as older adults and smokers, the team feels that clinicians also need to pay attention to middle-aged people and nonsmokers through regular physical examination and LDCT screening. This screening should include screening for early development of pulmonary nodules, especially ground-glass nodules, as a timely intervention, which could reduce the mortality of lung cancer patients.

Our study found that 62.24% of lung nodules were located in the upper lobes of the lungs, with the upper lobe of the right lung being the most common, which was consistent with other findings. Because the retrospective study was conducted and the team didn't have dynamic follow-up of all lung nodules found by LDCT screening to surgical resection, the research team couldn't determine the probability of malignant lung nodules in different lobes, and couldn't accurately judge the doubling time for the malignant pulmonary nodules for men and women, and the team will explore it in follow-up studies.

The current study found that adenocarcinoma is not only the most common pathological type of primary lung cancer but also a higher incidence of adenocarcinoma occurs in malignant pulmonary nodules. In 9.76% of patients, postoperative pathology suggests carcinoma in situ, in order to avoid premature surgical intervention for non-invasive carcinoma, we will further analyze the clinical and imaging features of carcinoma in situ to avoid overtreatment.

In the study, 986 participants underwent lymph node sampling or dissection to varying degrees, among which 807 patients underwent mediastinal lymph node dissection. The postoperative incidence of N1 and N2 lymph node metastasis was 5.74% and 2.91%, respectively. This shows that a certain amount of lymph node metastasis occurs in malignant pulmonary nodules. Clinicians need to evaluate the risk factors of lymph node metastasis through clinical and imaging characteristics before surgery, to provide a reference for rational selection of surgical methods and lymph node dissection scope.

The multivariate logistic regression analysis showed that nodular size, nodules' features, and nodular location were adverse factors for N1 node metastasis. An increase in nodular length and in solid components increased the probability of N1 node metastasis significantly. Compared with upper-lobe and middle-lobe nodule, lower-lung nodules had a higher risk of N1 node metastasis.

In clinical practice, for pulmonary nodules over 20 mm, especially solid nodules located in the lower lobe or solid nodules with voids, clinicians can use systemic PET/CT examinations to assist in evaluating the probability of regional lymph node metastasis and determine whether to perform lymph node dissection or sampling according to the intraoperative exploration results. This can avoid affecting subsequent antitumor treatment decisions due to inaccurate lymph-node staging.

The evaluation of the high risk factors for lymph node metastasis in the area of pulmonary nodules is helpful for selecting reasonable surgical methods and improving the survival period and quality of life of patients.

CONCLUSIONS

Malignant nodules of the lungs are slightly more common in women, adenocarcinoma was the most common pathological type, and the probability of lymph node metastasis is low. N1 lymph node metastasis was associated with increased nodular size and solid components and the presence of lower-lobe nodules.

AUTHORS' DISCLOSURE STATEMENT

The authors have no potential conflicts of interest to report relevant to this article.

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