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Correlation between HRCT signs and levels of CA125, SCCA, and NSE for different pathological types of lung cancer

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Abstract. – OBJECTIVE: The aim of this study was to investigate the correlation between high-resolution CT (HRCT) signs and serum tumor markers, to improve the diagnostic level and identify different pathological types of lung cancer.

PATIENTS AND METHODS: 102 patients with pathologically confirmed lung cancer were selected as the observation group. HRCT scan and serum tumor markers [cancer antigen 125 (CA125), squamous cell carcinoma antigen (SCCA), and neuron-specific enolase (NSE)] were performed to analyze the correlation.

RESULTS: Among the 102 cases of lung cancer, 88 cases were of lobulation sign, 78 cases of speculation sign, 45 cases of pleural indentation sign, 35 cases of vessel tracking sign, and 34 cases of vacuole sign. CA125 had the highest concentration in lung adenocarcinoma (55.74±14.18) ng/ml, and SCCA had the highest concentration in lung squamous cell carcinoma (18.98±6.37) ng/ml. The concentration of NSE in small cell lung cancer was the highest (48.12±16.19) ng/ml.

CONCLUSIONS: Pleural indentation sign and vacuole sign were more likely to happen in lung adenocarcinoma and lung squamous cell carcinoma, respectively. The significant increase of CA125, SCCA, and NSE concentrations suggested that lung cancer patients were more likely to suffer from lung adenocarcinoma, lung squamous cell carcinoma, and small cell lung cancer, respectively.

Key Words:
Tomography, X-ray computer, Tumor markers, Lung tumor, Pathology.

Introduction

Lung cancer has become one of the most dangerous malignancies to human health and life because of its high morbidity and mortality. Latest research[1] information showed that the incidence and mortality of male lung cancer ranked first among all malignant tumors, accounting for 21.9% and 26.4% of all cancers respectively. The incidence of female lung cancer ranks the second among all malignant tumors, accounting for 13.3% of the total number of cancer cases, while the mortality rate has risen to the first place, accounting for 20.3% of the total number of cancers deaths[1-5]. Due to the lack of specific clinical symptoms, it is easy to be ignored, and most patients have reached the middle and late stage when diagnosed, thus losing the chance of cure. Therefore, the early diagnosis is essential.

CT has high accuracy in the diagnosis and differential diagnosis due to its imaging features for lung cancer. However, there are no obvious imaging features for some cases. Therefore, the differential role of tumor markers is needed[6]. Serum tumor markers have the advantages of easy specimen acquisition, little trauma, and high reproducibility, and are of great value in the early screening, pathological classification, and prognosis of tumors.

Cancer antigen 125 (CA125) is commonly found in the serum of patients with ovarian tumors. In addition, elevated levels of serum CA125 can also be observed[7] under other physiological or pathological conditions (such as menstruation, pregnancy, endometriosis, and peritoneal inflammatory disease). Squamous cell carcinoma antigen (SCCA) is a glycoprotein that regulates protein decomposition during normal and malignant transformation of cells[8]. It is a member of serine/cysteine with inhibitory effect, and the components of SCCA are relatively large in the cytoplasm of squamous cell[9,10]. At the beginning, serum SCCA was obtained from female cervical squamous cell carcinoma tissues. Later, more sampling sites were found not only in the reproductive system, but also in other sites such as pharynx and larynx, but the increased of these cancers was not as significant as that of cervical cancer. Detection of SCCA expression levels can

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provide insight into the disease stage of non-small cell lung cancer (NSCLC) patients.

Nowadays, CA125 has been widely used in the diagnosis of ovarian cancer, and its auxiliary role in the diagnosis of lung cancer is also attracting increasingly attention. SCCA was initially isolated from the squamous epithelium of the cervix and is closely related to the occurrence and development of squamous cell carcinoma. In addition, it has been reported[11] that neuron specific enolase (NSE) is associated with lung cancer with higher diagnostic positive rate.

High-resolution CT (HRCT) scan of the chest is the primary imaging method for screening and diagnosis, which can track and record the process of its growth and change into visible and recognizable images with higher spatial resolution. At present, relevant studies[12-14] have evaluated the diagnostic value of HRCT in pulmonary diseases. HRCT can provide better image quality than conventional CT examination for pulmonary nodules with a diameter of less than 8 mm. HRCT has also a characteristic significance in the differential diagnosis of pulmonary lymphangiolleiomyomatosis.

This paper aims to study the correlation between HRCT signs and serum tumor markers in lung cancer, and to improve lung cancer diagnosis and treatment.

Patients and Methods

Participants

A total of 321 patients with suspected pulmonary nodules or masses were enrolled. They underwent chest HRCT scanning and serum tumor markers examination. At last, they underwent CT-guided percutaneous lung puncture biopsy. There were 285 cases with definite pathological diagnosis and 38 cases without definite diagnosis. Among the 285 cases with definite pathological diagnosis, 102 cases with complete data such as clinical imaging, serum tumor marker detection, and definite pathological diagnosis. Among them, 62 were males and 40 were females. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The present study was approved by the Ethics Committee of Affiliated Suzhou Hospital of Nanjing Medical University.

Imaging Examination

CT examination was performed by Toshiba TSX-101A 64 slice spiral CT (Ichibuku Shiura, Tokyo, Japan), tube voltage 135 kV, automatic tube current, pitch 0.9, matrix 512×512, field of view 320 mm×320 mm, layer thickness 5.0-6.0 mm, layer interval 1 mm. The scan was carried out continuously from the tip to the bottom. After the scan, the conventional lung window of 5 mm and a thin lung window of 1 mm were reconstructed, and the postprocessing such as multi-planner reconstruction (MPR) was performed on the postprocessing workstation.

Detection of Serum Tumor Markers

Peripheral bloods of all patients were collected in an empty stomach for detection of serum tumor markers. Normal reference range: CA125: 0-35 U/ml; SCCA: 0-2.5 ng/ml; NSE: 0-6 ng/ml. Positive judgment criteria: a ≥1 index beyond the normal reference value range is judged as a positive test result.

Puncture Biopsy Pathological Examination

All 111 cases underwent CT-guided percutaneous needle biopsy, and 18-21 G needle aspiration with needle core or 18-20 G bullet biopsy needles were used for lung lesion puncture biopsy. Needle biopsy has a requirement for the length of the sample (>1 cm). Hematoxylin-eosin staining and tissue sections were stained by immunohistochemical acid fast staining and silver hexamine staining was used for histopathological diagnosis if necessary.

Statistical Analysis

The data were statistically analyzed using SPSS 22.0 (IBM Corp., Armonk, NY, USA) software package. The data of the study were expressed as $\bar{x}\pm s$. The rates were compared by χ^2 test. Student-Newman-Keuls (SNK) test was used for pairwise comparison of multiple samples. The $p<0.05$ should be considered to be significant difference.

Results

HRCT Signs

Table I showed the whole characteristics of patients with lung cancer. Among the 102 patients, 77 lesions were ≥3 cm in diameter and 25 lesions were <3 cm in diameter. Among 102 were nodular lesions, 108 were lobulated sign (Figure 1), 65 were burr sign (Figure 2), and 45 were pleural indentation sign (Figure 3), 35 cases were cluster sign (Figure 4), and 34 cases were cavitation sign (Figure 5). Among the 102

Table I. The whole characteristics of patients with lung cancer.

Characteristics	Lung cancer patients (n=102)
Gender	
Male	56 (54.9%)
Female	46 (45.1%)
Age	61.3±12.1
Histopathological type	
Adenocarcinoma	61 (59.8%)
Squamous cell carcinoma	27 (26.5%)
small cell carcinoma	14 (13.7%)
Treatment	
Surgery	12 (11.8%)
Chemotherapy	56 (54.9%)
Radiotherapy	10 (9.8%)
Symptomatic treatment	18 (17.6%)
Others	6 (5.9%)

patients, 61 cases were lung adenocarcinoma, 27 cases were squamous cell carcinoma, and 14 cases were small cell carcinoma pathologically confirmed. The relationship between CT findings and pathological types of lung cancer are shown in Table II.

Detection of Serum Tumor Markers

Serum tumor marker detection results showed that CA125 had the highest concentration in lung adenocarcinoma, SCCA had the highest concentration in squamous cell carcinoma, and NSE had the highest concentration in small cell carcinoma. The level of NSE in small cell carcinoma was higher than that in adenocarcinoma and squamous cell carcinoma ($p<0.05$). The comparison between pathological types and serum tumor markers was shown in Table III.

Discussion

In recent years, the incidence and mortality of lung cancer have increased significantly[15-17]. The examination of lung cancer includes fibro bronchoscopy, pathological examination, imaging

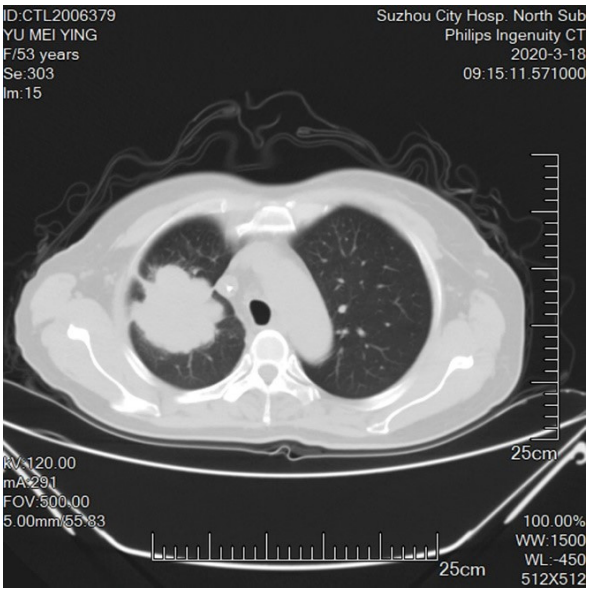

Figure 1. 102 were nodular lesions which were indicated by CT.

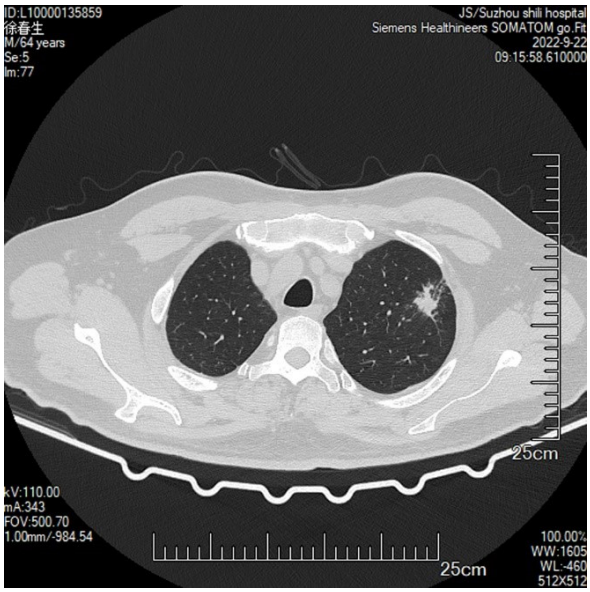

Figure 2. 65 were lobulated signs which were indicated by CT.

Table II. Relationship between CT findings and pathological types of lung cancer.

Signs	Types of lung cancer Adenocarcinoma	Squamous cell carcinoma	Small cell carcinoma	p
Lobulated	53 (86.9)	23 (85.2)	12 (85.7)	0.874
Speculation	42 (68.9)	18 (66.7)	8 (57.1)	0.652
Pleural indentation	40 (65.6)	4 (14.8)	1 (7.1)	0.024
Vessel tracking	17 (27.9)	11 (40.7)	7 (50.0)	0.095
Vacuole	11 (18.0)	22 (81.5)	1 (7.1)	0.014

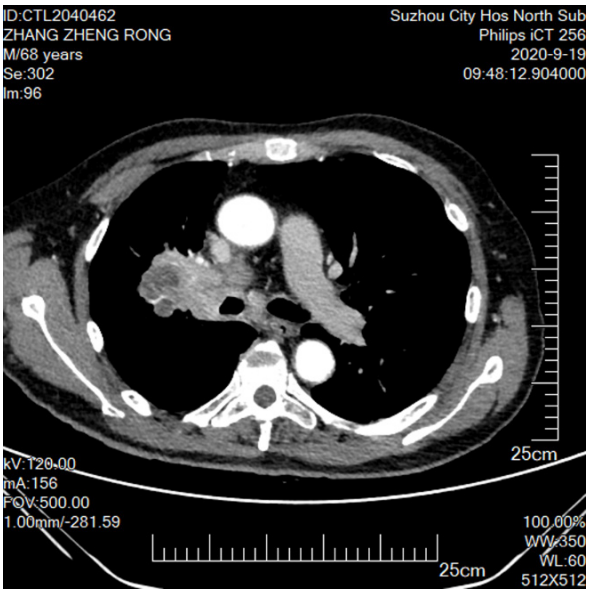

Figure 3. 45 were pleural indentation signs which were indicated by CT.

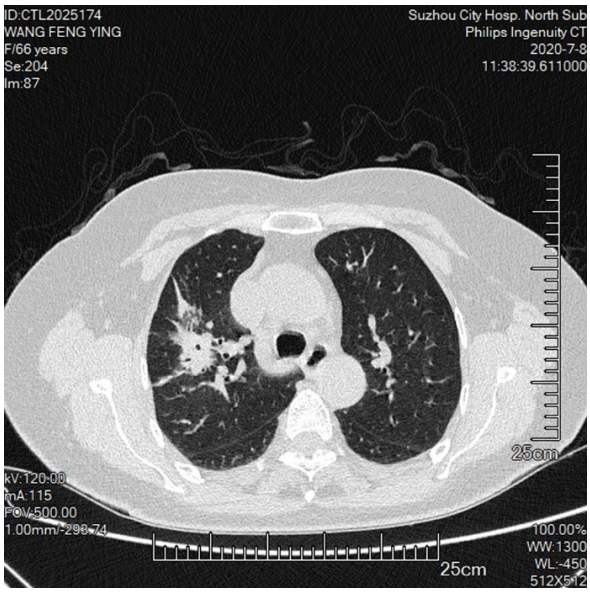

Figure 5. 34 cases were cavitation signs which were indicated by CT.

examination, and molecular biological examination. Serum tumor marker examination is also one of the important means for its diagnosis. For the early diagnosis of lung cancer, the currently accepted diagnostic method is low-dose CT screening, which is helpful to some extent, but still has problems including high cost, radiation exposure, and false positives. Pathological examination is the gold standard, but this method is a traumatic examination, which is not suitable for all patients. What's worse, the operation is complicated and the waiting time for results is long. Therefore, more minimally invasive and efficient diagnostic methods are needed clinically. Tumor markers are biological substances synthesized and released by tumor cells or substances produced by the body's response to tumor tissue. In the process of tumor occurrence and growth, the level of tumor markers will change abnormally due to the gene expression of tumor cells. Tumors can be identified and identified through the immune characteristics of tumor markers, and the activity of tumor occurrence and growth can be reflected.

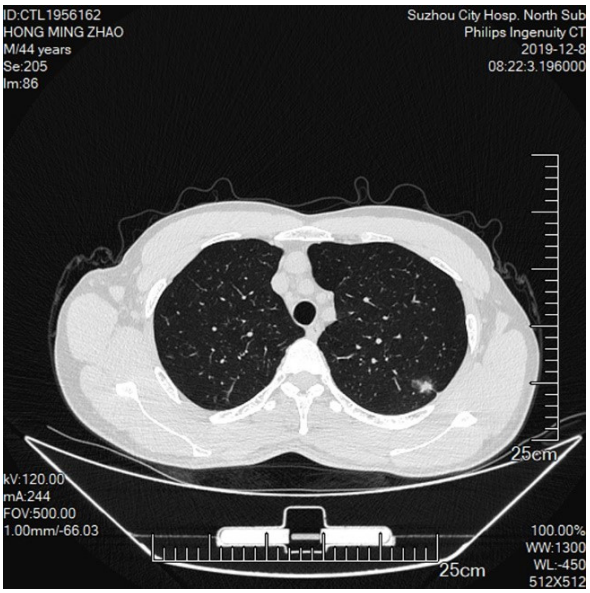

Figure 4. 35 cases were cluster signs which were indicated by CT.

In the era of precision diagnosis and treatment, with the deepening of clinical application of tumor markers, tumor marker detection has become increasingly important in the diagnosis and treatment of lung cancer. Tumor marker detection has the advantages of non-invasive, simple operation, and rapid results. It can dynamically monitor or fully reflect the actual situation of tumors. It can not only provide more information on medical reference for the diagnosis and treatment of lung cancer, but also effectively make up for the many limitations of CT, histology, sputum cytology, and other methods.

CT is widely used in the diagnosis of lung cancer, but some early lung cancer and other lung lesions cannot be effectively identified by CT imaging. During the occurrence and development of lung cancer, some glycoproteins, lipoproteins, and other substances will be expressed, which can reflect some characteristics of the tumor.

Table III. Comparison between pathological types and serum tumor markers.

Tumor markers	Types of lung cancer Adenocarcinoma	Squamous cell carcinoma	Small cell carcinoma	*p*
CA125	55.74±14.18	47.98±12.18	38.93±11.34	0.365
SCCA	9.91±3.58	18.98±6.37	4.18±2.17	0.098
NSE	22.65±7.37	20.39±6.83	48.12±16.19	0.022
CA153	57.39±9.83	62.84±10.84	61.51±10.34	0.982
CA199	104.15±19.13	102.28±18.20	101.51±18.83	0.830

These tumor markers are commonly used in the clinical diagnosis of lung cancer. This paper aims to study the correlation between HRCT signs and serum tumor markers in lung cancer, and to improve the lung cancer diagnosis and treatment.

CA125 is a glycoprotein that can be naturally secreted by the human body. Normally, when abnormal malignant changes occur in the body tissues due to various physiological and pathological factors or invasive tumors damage, the tissue structure, CA125 will be released into the blood and its level will rise. If CA125 level continues to rise after treatment, it indicates latent metastasis or residual tumor, indicating a poor treatment effect. SCC, also known as squamous cell carcinoma antigen, mainly exists in human serum in free forms such as SCCA1 and SCCA2. Different forms of squamous cell carcinoma antigen have different roles in preventing apoptosis of tumor cells. Squamous cell carcinoma antigen was first detected in the serum of patients with cervical squamous cell carcinoma and squamous cell carcinoma cells. Further studies[18,19] found that the concentration of squamous cell carcinoma antigen was higher than normal in the serum of patients with lung squamous cell carcinoma, head and neck malignancies, and other tumors. It was also found that the SCC value of patients with squamous cell carcinoma changed with the development of the disease. Therefore, SCC is used as a standard in the diagnosis of squamous cell carcinoma. SCCA, a member of the serine/cysteine inhibitory family, is highly concentrated in the cytoplasm of squamous epithelial cells and is involved in the regulation of protein breakdown during normal and malignant degeneration.

As far as we know, this is the first article which investigates the association between CT signs and CA125, SCCA and NSE concentrations. Our results and conclusions may contribute to the diagnosis of lung cancer, especially identifying different pathological types of lung cancer. Currently, bioinformatics plays a crucial role in multiple disciplines, including medicine[20-22]. Additionally, bioinformatics has been always contributing to predict and understand genetic variation, genetic expression, and even genetic function[24-26]. The entire advance is helpful in disease diagnosis and prognosis. We would like to cite more technology and knowledge of bioinformatics for lung cancer in the near future.

Limitations

We have to admit that this study has some limitations. Firstly, we do not have data about the presence of pleural effusion. Secondly, we do not have any data about the survival and the serum value of CA125, SCC, and NSE. We do think that investigating the relationship between the survival and serum value of CA125, SCC, and NSE is a meaningful and important topic, which may contribute to the diagnosis, prognosis and treatment for patients with lung cancer. However, follow-up of lung cancer patients is a long process. Unfortunately, we did not get enough follow-up data of patients, so we could not provide enough reliable data in this study. At present, we are collecting this important information and data, and in future studies we will analyze these data to get more important results.

Conclusions

Pleural indentation sign and vacuole sign were more likely to happen in lung adenocarcinoma and lung squamous cell carcinoma, respectively. The significant increase of CA125, SCCA, and NSE concentrations suggested that lung cancer patients were more likely to suffer from lung adenocarcinoma, lung squamous cell carcinoma, and small cell lung cancer, respectively.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Ethics Approval
The present study was approved by the Ethics Committee of Affiliated Suzhou Hospital of Nanjing Medical University (approve number: 2018021). The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Informed Consent
The written informed consent was obtained from all patients prior to the study.

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Authors' Contributions
Y.-T. Wang and L.-H. Wu conceived and designed the manuscript. L.-H. Wu and L. Chen wrote the manuscript. L. Chen and Q.-Y. Wang collected and analyzed the references. L.-H. Wu, L. Chen, Q.-Y. Wang and Y.-T. Wang checked, proofread, and polished the manuscript.

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Conflict of Interest
The authors declare that they have no competing interests.

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