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The Predictive Value of Spectral CT Combined with Serum Biomarkers for Lymph Node Metastasis in Non-Small Cell Lung Cancer

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Abstract: ***Objective:*** ***To investigate the clinical value of combining spectral CT multi-parameter imaging with pulmonary serum markers for predicting lymph node metastasis in non-small cell lung cancer (NSCLC).*** ***Methods:*** ***A retrospective analysis was conducted on patients who underwent dual-source CT (DSCT) chest enhancement examinations at our hospital. All patients were diagnosed with NSCLC via surgery or pathology and presented with lymphadenopathy. The nature of all lymph nodes was confirmed by pathology or cytology. Multiple parameters were obtained using the Syngo. via workstation. The levels of pulmonary serum markers and the spectral imaging features were compared between NSCLC patients with and without lymph node metastasis. Correlation analysis and statistical methods were applied to draw conclusions.*** ***Results:*** ***This study found that the effective atomic number (Z-effective) demonstrated excellent performance in predicting metastasis. Its predictive efficacy became more significant when combined with serum tumor markers such as procalcitonin and cytokeratin fragments. This finding is consistent with the application of spectral CT in oncology research.*** ***Conclusion:*** ***This study confirms the significant value of a multimodal parameter (imaging + serum) combined analysis in diagnosing tumor metastasis. It provides a new approach for the early warning and precise assessment of tumor metastasis.***

Keywords: Dual-layer detector spectral CT, Effective atomic number (Z-effective), Serum tumor markers, Non-small cell lung cancer (NSCLC).

1. Introduction

Global cancer statistics reports indicate that lung cancer is the leading cause of cancer-related mortality worldwide. In China, lung cancer is also the most common type of cancer, and its incidence is increasing annually [8]. Non-small cell lung cancer (NSCLC) accounts for over 80% of all lung cancer cases [12]. Lymph node metastasis is a common mode of metastasis in NSCLC. Pathological biopsy via lymph node puncture remains the gold standard for diagnosing lymph node nature. However, its invasive nature and the often-limited sample size restrict its widespread clinical application [7]. Conventional CT is currently the most commonly used non-invasive imaging modality for evaluating mediastinal lymph nodes in lung cancer. As it primarily relies on morphological and density-based assessments, its diagnostic accuracy is limited. The advent of spectral CT enables the differentiation between benign and malignant tumors, allowing for quantitative, qualitative, and graded analysis of tumor tissues [5]. It reveals significant differences between metastatic and non-metastatic lymph nodes, elevating lung cancer assessment from a morphological to a functional level. This advancement represents a crucial tool for enhancing the precision of lung cancer diagnosis and treatment. Serological lung cancer markers can provide clues regarding pathological subtypes and, more importantly, are used to assess treatment efficacy and predict recurrence. Therefore, this study investigates the value of combining spectral CT with serum lung cancer markers for mediastinal lymph node metastasis in NSCLC.

2. Materials and Methods

2.1 Study Subjects

A retrospective analysis was planned for patient cases who underwent dual-source CT (DSCT) chest enhancement examinations, were diagnosed with non-small cell lung cancer (NSCLC), and presented with lymphadenopathy. Inclusion Criteria:(1) Patients with a confirmed pathological diagnosis of NSCLC;(2) Presence of lymphadenopathy involving locations such as bilateral supraclavicular, mediastinal, and inguinal regions, with the nature of all lymph nodes confirmed by pathology or cytology; (3) Completion of immunodetection for pulmonary serum markers.

2.2 CT Scanning Protocol and Parameters

Patients underwent dual-phase (arterial and venous) chest enhancement scans on a dual-layer detector spectral CT system (IQon Spectral CT, Philips Healthcare). The scanning position was supine, head-first. Scanning parameters included: automatic tube current, tube voltage 120 kVp [16], collimator width 64×0.625 mm, matrix 512×512, pitch 1.234, rotation time 0.4 s/rotation, slice interval and thickness both 5.0 mm.

2.3 Data Processing and Image Analysis

The acquired data were transferred to the Syngo.via workstation (abbreviated as ISP). Regions of interest (ROIs) were delineated on conventional CT enhancement images. Subsequently, the system was switched to spectral imaging modes (effective atomic number [Z-effective] maps, iodine density maps, and spectral CT monoenergetic [MonoE] images at 40 keV) to obtain relevant spectral parameters for the arterial phase.

2.4 Statistical Methods

Multivariate logistic regression analysis was employed to identify influencing factors for lymph node metastasis in NSCLC and to establish a predictive scoring model [14]. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive value of the scoring model—based on spectral CT examination combined with pulmonary serum markers—for lymph node metastasis in NSCLC [11].

3. Results and Analysis

3.1 Analysis of Patient General and Clinical Data

This study included 76 patients with non-small cell lung cancer (NSCLC), who were divided into a metastasis group and a non-metastasis group. The metastasis group comprised 51 patients, including 28 male and 33 female patients. Within the metastasis group, 36 patients had a history of smoking, and 12 had a history of alcohol consumption. The non-metastasis group comprised 25 patients, including 16 male and 9 female patients. The average age in the non-metastasis group was 63.84 ± 10.10 years. Within the non-metastasis group, 19 patients had a history of smoking, and 3 had a history of alcohol consumption.

3.2 Multi-parameter Analysis of Spectral CT

All 76 cases underwent lymph node biopsy at our hospital. Based on pathological results, they were categorized into a metastatic lymph node group and a non-metastatic lymph node group. Among the 76 patients, 51 were pathologically diagnosed with lymph node metastasis, and 25 were diagnosed without lymph node metastasis. The following table presents the differences in values measured at two distinct sites (lung lesions and lymph node lesions) between the non-metastasis and metastasis groups, utilizing four different measurement parameters: effective atomic number, iodine concentration, CT value, and CT value on 40 keV monoenergetic images. The key finding is that the values in the metastasis group were significantly higher than those in the non-metastasis group. This indicates that, for both pulmonary and lymph node lesions, the imaging features of the metastasis group were more "active" or "dense" compared to the non-metastasis group.

The statistical results are shown in Table 1:

Table 1: Comparison of Test Results at Different Sites Between Two Groups

	Non - metastasis Group (N = 25)	Metastasis Group (N = 51)	t	*P*
Effective Atomic Number				
Pulmonary Lesion	7.98±0.29	8.46±0.56	-4.836	0.000
Lymph Node Lesion	8.06±0.49	8.65±0.51	-4.799	0.000
Iodine Concentration				
Pulmonary Lesion	1.18±0.62	1.75±0.95	-3.160	0.002
Lymph Node Lesion	1.14±0.57	1.84±0.90	-3.513	0.000
CT				
Pulmonary Lesion	47.73±15.43	68.37±27.94	-4.142	0.000
Lymph Node Lesion	64.74±21.21	83.33±31.74	-3.026	0.004
40KevHounsfield Unit (HU)				
Pulmonary Lesion	101.07±38.67	163.93±81.07	-4.576	0.000
Lymph Node Lesion	109.03±43.70	185.00±81.41	-5.289	0.000

Clinical Significance Interpretation: The effective atomic number (Z-eff) and iodine concentration are two metrics typically associated with tumor vascularity and metabolic activity. The significantly elevated values in the metastasis group suggest that metastatic lesions may exhibit richer angiogenesis (higher degree of vascularization) or greater metabolic demands. The iodine concentration value, in particular, more strongly indicates either enhanced angiogenesis or a higher degree of inflammation within the lesions, leading to increased iodine uptake. Consequently, these features manifest more prominently on the images.

In summary, the value of multi-parameter combined assessment: The effective atomic number, iodine concentration, and 40 keV enhanced CT values of both lung lesions and lymph node lesions in the metastasis group were significantly higher than those in the non-metastasis group. Notably, the changes in lymph node lesion parameters were particularly pronounced, suggesting a close association between elevated imaging parameters and tumor metastasis. This finding indicates that the imaging characteristics of primary and metastatic lesions produce a "resonance" (correlation), underscoring the synergistic value of multi-parameter spectral CT evaluation in identifying metastatic potential.

3.3 Analysis of Tumor Markers in NSCLC Patients with and without LNM

Common tumor markers were collected and compared between the NSCLC patient groups without lymph node metastasis (non-LNM group) and with lymph node metastasis (LNM group). The specific markers analyzed included: carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), neuron-specific enolase (NSE), progastrin-releasing peptide (ProGRP), cytokeratin 19 fragment (CYFRA 21-1), procalcitonin (PCT), and interleukin-6 (IL-6)—totaling seven indicators. The differences between the two groups for these markers are presented in Table 2:

Table 2: Comparison of Tumor Markers Between Two Groups

	Non - metastasis Group (N = 25)	Metastasis Group (N = 51)	χ2	*P*
NSE			11.193	0.000
No	20(80.00)	20(39.22)		
Yes	5(20.00)	31(60.78)		
CEA			5.606	0.018
No	18(72.00)	22(43.14)		
Yes	7(28.00)	29(56.86)		
CA125			9.221	0.002
No	20(80.00)	22(43.14)		
Yes	5(20.00)	29(56.86)		
Cytokeratin 19			15.930	0.000
No	21(84.00)	18(35.29)		
Yes	4(16.00)	33(64.71)		
Progastrin releasing Peptide Precursor			3.591	0.058
No	21(84.00)	32(62.75)		
Yes	4(16.00)	19(37.25)		
Procalcitonin			23.566	0.000
No	24(96.00)	19(37.25)		
Yes	1(4.00)	32(62.75)		
Interleukin - 6			11.562	0.000
No	25(100.00)	33(64.71)		
Yes	0(0.00)	18(35.29)		

Note: In the table, "No" and "Yes" correspond to the negative and positive test results of the tumor markers, respectively; "χ^2" denotes the Chi-square value, and "P" indicates the statistical significance level.

The high positivity rates of these classic tumor markers in the metastatic group align with expectations, suggesting increased tumor burden or disease progression. While procalcitonin (PCT) is typically used for diagnosing bacterial infections, this study found that PCT levels were significantly elevated in the metastatic group. This may indicate a higher susceptibility to concurrent infections in patients with metastasis, or that the tumor itself triggers activation of the inflammatory response.

3.4 Combined Analysis of Effective Atomic Number (Z-eff) in Lung Lesions and Tumor Markers

Table 3: Logistic Regression Analysis of Effective Atomic Number of Pulmonary Lesions and Tumor Markers

	B	SE	Wald	P	OR(95%CI)
Model 1					
Effective Atomic Number of Pulmonary Lesions	2.428	0.709	11.727	0.000	11.335(2.825-45.492)
NSE	2.289	0.671	11.643	0.000	9.866(2.649-36.742)
Model 2					
Effective Atomic Number of Pulmonary Lesions	2.339	0.746	9.824	0.002	10.374(2.402-44.798)
CEA	1.211	0.583	4.318	0.038	3.357(1.071-10.523)
Model 3					
Effective Atomic Number of Pulmonary Lesions	2.003	0.741	7.302	0.007	7.414(1.734-31.703)
CA125	1.160	0.613	3.574	0.059	3.189(0.958-10.615)
Model 4					
Effective Atomic Number of Pulmonary Lesions	2.552	0.797	10.257	0.001	12.829(2.691-61.151)
Cytokeratin 19	2.594	0.700	13.719	0.000	13.390(3.393-52.847)
Model 5					
Effective Atomic Number of Pulmonary Lesions	2.051	0.820	6.251	0.012	7.773(1.558-38.796)
Procalcitonin	3.537	1.087	10.591	0.001	34.361(4.083-289.195)
Model 6					
Effective Atomic Number of Pulmonary Lesions	1.087	0.389	7.806	0.005	2.965(1.383-6.356)
Interleukin - 6	20.545	9031.886	0.000	0.998	0.000(-)

Table 4: ROC Analysis of Effective Atomic Number of Pulmonary Lesions and Tumor Markers

	AUC (95%CI)	Sensitivity	Specificity	Youden Index	Cut-off Value
Effective Atomic Number of Pulmonary Lesions					
+ NSE	0.861 (0.773-0.950)	0.882	0.760	0.642	0.53575
+ CEA	0.838 (0.747-0.929)	0.784	0.800	0.584	0.66425
+Cytokeratin 19	0.898 (0.824-0.973)	0.902	0.800	0.702	0.53463
+Procalcitonin	0.906 (0.834-0.979)	0.843	0.920	0.763	0.55410

Tables 3 and 4 present the results of the combined analysis of the effective atomic number (Z-eff) in lung lesions with different tumor markers. This indicates that the Z-eff value of the lung lesion itself is a very strong independent risk factor; the higher the value, the greater the risk of metastasis.

Combined Indicators Significantly Enhance Predictive Performance: When imaging parameters (Z-eff) are combined with serological indicators (such as NSE, CYFRA 21-1, PCT), the Odds Ratio (OR) for predicting metastasis increases significantly.

In summary: Relying solely on imaging or solely on serological markers has its respective limitations. This study confirms that combining the two can yield a synergistic effect ("1+1>2"), significantly improving the accuracy of predicting tumor metastasis. Based on the data, the combination of "Z-eff in lung lesions + Procalcitonin (Z-eff + PCT)" demonstrated the best performance. In the logistic regression analysis, it achieved the highest OR value (34.361), indicating the strongest risk prediction capability. In the ROC analysis, it achieved the highest AUC value (0.906) with a specificity as high as 0.920, demonstrating its high precision in correctly identifying non-metastatic patients.

4. Discussion

Metastatic lymph nodes in non-small cell lung cancer (NSCLC) exhibit a greater abundance of abnormal neovascularization. The alteration of tumor-associated vascular patterns within metastatic lymph nodes may lead to changes in parameters such as the effective atomic number (Z-eff) and iodine concentration during enhanced scans. This study compared the imaging characteristics and serological markers between the non-metastasis group (N=25) and the metastasis group (N=51), aiming to identify effective biomarkers and imaging parameters for predicting or diagnosing tumor metastasis. The data revealed that in both lung lesions and lymph node lesions, the Z-eff, iodine concentration, CT value, and Hounsfield unit (HU) value in the metastasis group were significantly higher than those in the non-metastasis group (all $P < 0.05$). This indicates that metastatic lesions exhibit higher density and stronger vascularization features on imaging. Notably, the increases in all measured parameters within lymph node lesions were particularly pronounced in the metastasis group, suggesting that lymph nodes may serve as a sensitive window reflecting the metastatic status.

Early Warning Signals from Serological Markers: Significantly elevated markers: Table 4 shows that the positive rates of NSE, CEA, CA125, CYFRA 21-1, procalcitonin (PCT), and interleukin-6 (IL-6) in the metastasis group were significantly higher than those in the non-metastasis group ($P < 0.05$). Although PCT is commonly used for infection diagnosis, its positive rate in the metastasis group reached 62.75%, suggesting that metastasis may be accompanied by a significant inflammatory response or alterations in the immune microenvironment.

Imaging Parameters as Key Indicators: The effective atomic number (Z-eff) demonstrated excellent performance in predicting metastasis, which aligns with the application of dual-energy CT (DECT) in oncology research. Z-eff reflects the chemical composition of tissue; a high Z-eff is typically associated with calcification, hemorrhage, or retention of high-concentration contrast agents. In tumor metastasis, this may indicate richer angiogenesis or a more active metabolic state within the metastatic foci. This study, through logistic regression and ROC analysis, confirmed that the combined model of “imaging parameter (Z-eff) + serological indicator (PCT/CYFRA 21-1)” significantly outperformed any single indicator. This multimodal diagnostic strategy is consistent with the current trend towards precision medicine, offering a more comprehensive assessment of the disease state.

5. Conclusion

Based on the aforementioned analysis, this study draws the following detailed conclusions:

1) Metastatic lesions exhibit distinct imaging characteristics: The effective atomic number (Z-eff), iodine concentration, CT value, and Hounsfield unit (HU) value of both pulmonary lesions and lymph node lesions in the metastasis group were significantly higher than those in the non-metastasis group.

2) Serological indicators reveal metastasis-associated inflammatory status: The levels of procalcitonin (PCT) and interleukin-6 (IL-6) were significantly elevated in the metastasis group, suggesting that tumor metastasis may be accompanied by a significant systemic inflammatory response or alterations in the immune microenvironment.

3) The combined diagnostic model demonstrates optimal efficacy: Single indicator: The effective atomic number (Z-eff) was the single most effective imaging parameter for predicting metastasis (AUC ≈ 0.80). Combined indicator: The combination of “effective atomic number in lung lesions (Z-eff) + procalcitonin (PCT)” was the most effective predictive model.

This study also acknowledges certain limitations. The sample size, particularly that of the control group, was relatively small [3], which may have affected the statistical power. Future research should focus on expanding the sample size, optimizing measurement methodologies, and integrating multidisciplinary approaches to obtain more precise and reliable results.

In summary, this study confirms the significant value of a multimodal parameter (imaging + serum) combined analysis in diagnosing tumor metastasis. Specifically, the combined application of the effective atomic number and procalcitonin provides a new approach for the early warning and precise assessment of tumor metastasis.

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