

Diagnostic value of NSE factor combined with ultrasound hemodynamic indexes in cervical lymph node metastasis of lung cancer

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Abstract. Value of neuron-specific enolase (NSE) factor combined with ultrasound hemodynamic parameters in the diagnosis of cervical lymph node metastasis of lung cancer was explored. The clinical data of 85 patients with lung cancer, admitted to Qingdao Municipal Hospital (Group) from January 2015 to December 2016, were retrospectively analyzed. According to the results of pathological examination, 47 patients with cervical lymph node metastasis were enrolled in the metastatic group and 38 patients without lymph node metastasis were enrolled in the non-metastatic group. The expression level of NSE in serum and the hemodynamic indicators of blood flow resistance index (RI) and pulsatility index (PI) were compared between the two groups. ROC curve analysis was used to analyze the diagnostic efficacy of NSE, RI, PI, and their combination in lymph node metastasis of lung cancer. The NSE, RI and PI indexes in the metastatic group were significantly higher than those in the non-metastatic group ($P < 0.05$). The sensitivity and specificity of NSE in the diagnosis of cervical lymph node metastasis of lung cancer were 73.68 and 72.34%, respectively; the sensitivity and specificity of RI were 78.95 and 80.85%, respectively; the sensitivity and specificity of PI were 81.58 and 68.09%, respectively. Also, the sensitivity and specificity of NSE combined with RI were 89.47 and 61.70%, respectively, and the diagnostic AUC was 0.881. The sensitivity and specificity of NSE combined with PI were 92.11 and 74.47%, respectively, and the diagnostic AUC was 0.905. NSE, RI, and PI have certain diagnostic value for cervical lymph node metastasis of lung cancer, however, the combined diagnosis is more valuable,

and can be used as the auxiliary diagnosis of cervical lymph node metastasis of lung cancer.

Introduction

Lung cancer is one of the most common malignant tumors in clinic, and because its early symptoms are not obvious, a number of patients are diagnosed at late stages, which is one of the reasons leading to a low survival rate within 5 years. Numerous related investigations have shown that lung cancer has the highest clinical mortality rate at present (1,2). Besides, the metastasis and recurrence of lung cancer is also one of the main causes of poor prognosis and low survival rate in patients with lung cancer (3). Lymph node metastasis is one of the most common diffusion pathways in lung cancer, and one of the main causes of death among patients with lung cancer (4). Therefore, the accurate diagnosis of lymph node metastasis in patients with lung cancer has an important clinical significance for the timely and effective treatment, and the improvement of survival rate of patients with lung cancer.

Serum tumor markers play an important role in the diagnosis of lung cancer. Neuron-specific enolase (NSE) is one of the most important tumor markers in the clinical diagnosis of lung cancer (5). NSE is a substance of the acidic protease-containing neuronal tissues, such as the neuroendocrine and the peripheral nerve tissues. Since 80% of lung cancers are tumors of neuroendocrine origin, NSE is also one of the tumor markers with high sensitivity to the diagnosis of lung cancer (6). However, its single detection has some limitations to the detection of lymph node recurrence and metastasis in lung cancer patients. Therefore, in the present study, its combination with other indexes was investigated. According to some scholars (7,8), angiogenesis and lymph node metastasis have a close relationship, and cancer patients with active angiogenesis are more likely to develop lymph node metastasis. Another study (9) has suggested that tumor angiogenesis can promote the contact of active tumor cells and lymphatic channels, thus allowing more tumor cells to enter the lymphoid system. In the present study, the value of hemodynamic parameters in the diagnosis of lymph node metastasis in patients with lung cancer was investigated.

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Previous studies (10) have shown that ultrasound hemodynamic indexes and the lymph node metastasis of breast cancer have a close relationship. However, the diagnostic value of ultrasound hemodynamic parameters in patients with cervical lymph node metastasis of lung cancer has not been evaluated. Therefore, the value of NSE and ultrasound hemodynamic indexes for the individual and joint detection of the lymph node metastasis of lung cancer was assessed, so as to provide a more suitable scheme for the diagnosis of the patients with the cervical lymph node metastasis of lung cancer.

Patients and methods

General information. The clinical data of 85 patients with lung cancer, admitted to the Qingdao Municipal Hospital (Group) (Qingdao, China) from January 2015 to December 2016, were retrospectively analyzed. There were 51 male and 34 female patients. The average age of the patients was 49.26 ± 5.45 years. According to the results of pathological examination, 47 patients with cervical lymph node metastasis were enrolled in the metastatic group, and 38 patients without lymph node metastasis were enrolled in the non-metastatic group. There was no significant difference in sex, age, BMI, smoking history, pathological type of cancer, family medical history, and the stage of cancer between the two groups ($P > 0.05$) (Table I).

Inclusion and exclusion criteria. Inclusion criteria: Patients diagnosed with lung cancer by pathology. The metastatic group included patients diagnosed with lymph node metastasis by pathology and patients who underwent ultrasound hemodynamic examination. Exclusion criteria: Patients who had undergone anticancer treatment, such as radiotherapy and chemotherapy; patients with severe hepatic and renal dysfunction; patients with other malignant tumors; patients with communication and cognitive impairment; patients who did not cooperate with the examination. All patients and their families agreed to participate in the research and signed an informed consent form. The study was approved by the Ethics Committee of Qingdao Municipal Hospital (Group).

Treatment method. Three milliliters of fasting venous blood were collected from the patients in the morning after they were admitted to the hospital. Serum was separated via centrifugation at $2,600 \times g$ at 4°C for 20 min, after the collection of venous blood. Then, the content of NSE in the serum of patients was detected by electrochemiluminescence. The normal reference range of NSE was $0-16.3 \mu\text{g/l}$. Color ultrasound hemodynamic examination was performed on all patients. Voluson 730 color Doppler ultrasonic imaging instrument (GE Healthcare) with a probe frequency of 7-12 MHz was used. The examined part of the patients' neck was fully exposed and examined by color Doppler flow imaging (CDFI). The blood flow resistance index (RI) and pulsatility index (PI) were measured.

Observation indexes and evaluation criteria. The expression level of NSE in serum and the hemodynamic indexes RI and PI were compared between the two groups. The diagnostic efficacy of NSE, RI, PI, and their combination in lymph node metastasis of lung cancer were analyzed by ROC curve analysis.

Statistical analysis. SPSS 19.0 software (Shanghai Yuchuang Network Technology Co., Ltd.) was used for the statistical analysis of experimental data. Chi-square test was used for counting data. Measurement data were expressed as the mean \pm standard deviation, and t-test was used for their analysis between two groups. The experimental graphs were generated using GraphPad Prism 6 software (GraphPad Software, Inc.). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Expression of NSE in serum, and the hemodynamic indexes RI and PI in patients of both groups. In the metastatic group, the serum NSE and the indexes RI and PI were $41.24 \pm 11.34 \mu\text{g/l}$, 0.81 ± 0.08 , and 2.02 ± 0.54 , respectively, while those in the non-metastatic group were $33.56 \pm 12.46 \mu\text{g/l}$, 0.65 ± 0.09 , and 1.23 ± 0.35 , respectively. NSE expression, RI and PI in the metastatic group were significantly higher than those in the non-metastatic group ($P < 0.05$) (Table II).

Diagnostic value of NSE, RI and PI indexes in cervical lymph node metastasis of lung cancer. The sensitivity and specificity of NSE in the diagnosis of cervical lymph node metastasis of lung cancer were 73.68 and 72.34%, respectively, the diagnostic AUC was 0.783, and the diagnostic critical value was $38.58 \mu\text{g/l}$. The sensitivity and specificity of RI in the diagnosis of cervical lymph node metastasis of lung cancer were 78.95 and 80.85%, respectively, the diagnostic AUC was 0.820, and the diagnostic critical value was 0.745. The sensitivity and specificity of PI in the diagnosis of cervical lymph node metastasis of lung cancer was 81.58 and 68.09%, respectively, the diagnostic AUC was 0.844, and the diagnostic critical value was 1.564. There was no significant difference in sensitivity and AUC between NSE, RI, and PI in detecting cervical lymph node metastasis of lung cancer (Table III and Fig. 1).

Diagnostic value of NSE combined with RI or PI, and their combination in cervical lymph node metastasis of lung cancer. The sensitivity and specificity of NSE combined with RI were 89.47 and 61.70%, respectively, and the diagnostic AUC was 0.881. The sensitivity and specificity of NSE combined with PI were 92.11 and 74.47%, respectively, and the diagnostic AUC was 0.905. The sensitivity and specificity of the combination of NSE, RI, and PI were 97.37 and 57.45%, respectively, and the diagnostic AUC was 0.939. The combination of NSE with RI or PI had good diagnostic value, however, the combination of the three had the highest diagnostic value (Table IV and Fig. 2).

Discussion

As a malignant tumor with the highest mortality in clinical practice, lung cancer has no obvious early symptoms and is easy to be ignored by patients. Most patients have advanced lung cancer or metastasis at the time of lung cancer detection (11,12). Cervical lymph node metastasis is common in lung cancer patients and one of the main causes of death in lung cancer patients (13). Therefore, timely diagnosis and detection of lymph node metastasis in patients with lung cancer have important clinical significance for effective treatment and

Table I. General information [n (%)].

Factors	Metastatic group (n=47)	Non-metastatic group (n=38)	χ^2	P-value
Sex			0.008	0.929
Male	28 (59.57)	23 (60.53)		
Female	19 (40.43)	15 (39.47)		
Age (years)			0.004	0.949
≤49	30 (63.83)	24 (63.16)		
>49	17 (36.17)	14 (36.84)		
BMI (kg/m ²)			0.024	0.876
≤22	28 (59.57)	22 (57.89)		
>22	19 (40.43)	16 (42.11)		
Smoking history			0.007	0.935
Yes	35 (74.47)	28 (73.68)		
No	12 (25.53)	10 (26.32)		
Pathological type			0.053	0.974
Lung adenocarcinoma	13 (27.66)	10 (26.32)		
Large cell carcinoma	25 (53.19)	20 (52.63)		
Squamous cell carcinoma	9 (19.15)	8 (21.05)		
Family medical history			0.010	0.922
Yes	24 (51.06)	19 (50.00)		
No	23 (48.94)	19 (50.00)		
Stages			0.018	0.999
I	15 (31.91)	12 (31.58)		
II	16 (34.04)	13 (34.21)		
III	9 (19.15)	7 (18.42)		
IV	7 (14.89)	6 (15.79)		

Table II. Expression of serum NSE, and the hemodynamic indexes RI and PI in the two groups.

Factors	Metastatic group (n=47)	Non-metastatic group (n=38)	t	P-value
NSE (μ g/l)	41.24±11.34	33.56±12.46	2.970	<0.050
RI	0.81±0.08	0.68±0.09	7.043	<0.001
PI	2.02±0.54	1.23±0.35	7.788	<0.001

NSE, neuron-specific enolase; RI, resistance index; PI, pulsatility index.

improvement of survival time of patients with lung cancer. However, the current diagnosis of lymph node metastasis in patients with lung cancer is mainly pathological examination, which is traumatic and may cause pain to the patient (14). The main non-invasive diagnostic method is enhanced CT and PDG-PET, however, they both involve radiation exposure that some patients are unwilling to accept (15). In recent years, with the development of molecular biology, the application of serum tumor markers in the auxiliary diagnosis of lung cancer and the monitoring of recurrence and metastasis has achieved good results (16,17). NSE is recognized as a highly sensitive tumor marker in lung cancer. It is not only expressed in nerve tissue, but also a specific marker of neuroendocrine

tumors (18). However, the application of NSE in the diagnosis of cervical lymph node metastasis of lung cancer is relatively rare. Studies (19) have explored the mechanism of lymph node metastasis in lung cancer, suggesting that the condition for lung cancer metastasis is the continuous survival of neovascularization. In the present study, the value of ultrasound hemodynamics in the diagnosis of cervical lymph node metastasis of lung cancer is investigated. Ultrasound hemodynamics is a non-invasive method, which has achieved good results as assistant in the diagnosis of cervical lymph node metastasis of thyroid cancer in recent years. PI and RI, as important indexes of hemodynamics, can effectively reflect the status of blood flow (20).

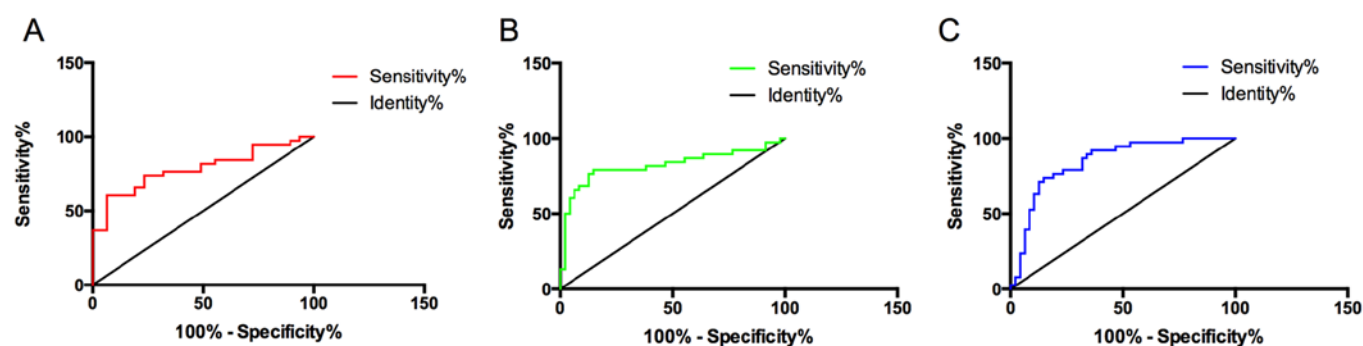


Figure 1. Diagnostic value of NSE, RI, and PI in cervical lymph node metastasis of lung cancer. (A) The sensitivity of NSE in the diagnosis of cervical lymph node metastasis of lung cancer was 73.68%, the specificity was 72.34%, the diagnostic AUC was 0.783, and the diagnostic threshold was 38.58 $\mu\text{g/l}$. (B) The sensitivity of RI in the diagnosis of cervical lymph node metastasis of lung cancer was 78.95%, the specificity was 80.85%, the diagnostic AUC was 0.820, and the diagnostic threshold was 0.745. (C) The sensitivity of PI in the diagnosis of cervical lymph node metastasis was 81.58%, the specificity was 68.09%, the diagnostic AUC was 0.844, and the diagnostic threshold was 1.564. NSE, neuron-specific enolase; RI, resistance index; PI, pulsatility index.

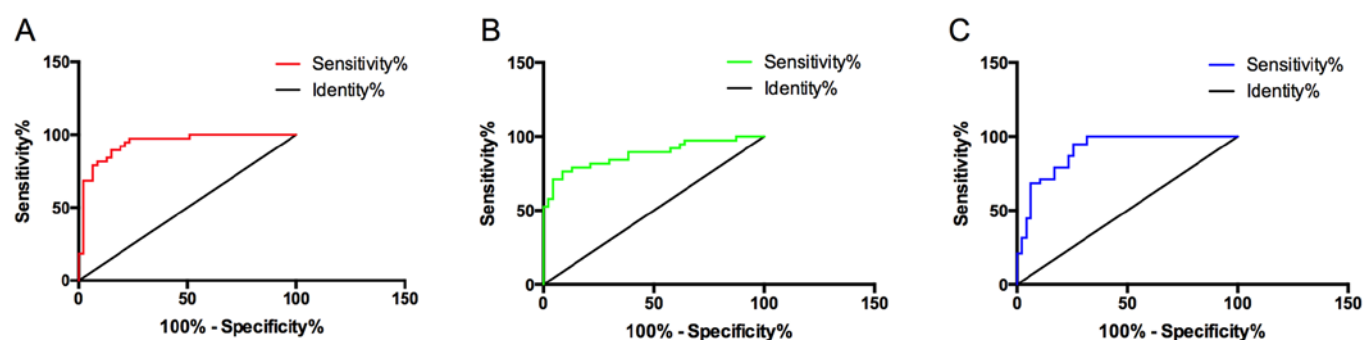


Figure 2. Diagnostic value of NSE combined with RI or PI, and their combination in lymph node metastasis of lung cancer. (A) The sensitivity of NSE combined with RI was 89.47%, the specificity was 61.70%, and the diagnostic AUC was 0.881. (B) The sensitivity of NSE combined with PI was 92.11%, the specificity was 74.47%, and the diagnostic AUC was 0.905. (C) The sensitivity of the combination of NSE, RI, and PI in the diagnosis of cervical lymph node metastasis was 97.37%, the specificity was 57.45%, and the diagnostic AUC was 0.939. NSE, neuron-specific enolase; RI, resistance index; PI, pulsatility index.

Table III. Diagnostic value of NSE, RI, and PI alone, and of their combination in cervical lymph node metastasis of lung cancer.

Diagnostic method	Sensitivity (%)	Specificity (%)	AUC
NSE	73.68	72.34	0.783
RI	78.95	80.85	0.820
PI	81.58	68.09	0.844

NSE, neuron-specific enolase; RI, resistance index; PI, pulsatility index.

Table IV. Diagnostic value of NSE combined with RI or PI, and of their combination in cervical lymph node metastasis of lung cancer.

Diagnosis method	Sensitivity (%)	Specificity (%)	AUC
NSE combined with RI	89.47	61.70	0.881
NSE combined with PI	92.11	74.47	0.905
NSE, RI, and PI combined diagnosis	97.37	57.45	0.939

NSE, neuron-specific enolase; RI, resistance index; PI, pulsatility index.

Therefore, the value of serum tumor marker NSE and hemodynamic indexes RI and PI individually and jointly in the diagnosis of cervical lymph node metastasis of lung cancer were analyzed. NSE in serum of metastatic and non-metastatic patients was detected by pathology diagnosis. Then, the hemodynamic parameters of the cervical lymph nodes in the two groups were measured by ultrasound. The results revealed that NSE, RI and PI indexes in the metastatic group were significantly higher than those in the non-metastatic group ($P < 0.05$). These results suggest that a large amount of NSE is secreted by tumor cells when cervical lymph node metastasis occurs in patients with lung cancer. A previous study (21) has explored

the relationship between NSE and prognosis of patients with lung cancer, indicating that the expression of NSE in serum of patients with lymph node metastasis is significantly higher than that of patients without metastasis, which is consistent with our conclusion. A previous study (22) has also found that the RI and PI indexes of patients with lymph node metastasis are significantly higher than those of patients without lymph node metastasis when examining the hemodynamics of cervical lymph node metastasis of thyroid cancer. Although this is not a diagnostic study for cervical lymph node metastasis of lung cancer, it also confirms our conclusion. At present, there are

numerous clinical methods for the diagnosis of lymph node metastasis, such as CT (23), cell biopsy (24) and pathological diagnosis (25). However, there is still radiation in the detection by CT. Both cellular biopsy and pathology are traumatic and can cause more pain to the patient besides the pain caused by the disease. The value of serum tumor marker NSE and the hemodynamic indexes RI and PI individually and jointly were analyzed in the diagnosis of cervical lymph node metastasis of lung cancer. The results showed that there was no significant difference between the sensitivity and AUC of NSE, RI and PI indexes in detecting cervical lymph node metastasis of lung cancer ($P>0.05$). However, AUC and the sensitivity of the combination of NSE, RI, and PI were significantly higher than those of NSE, RI, and PI alone ($P<0.05$). The specificity of the combined diagnosis was shown to be lower than that of each single diagnosis, which may be a defect of joint diagnosis. These results suggest that NSE, RI, and PI are valuable for the diagnosis of cervical lymph node metastasis of lung cancer, however, their combined diagnosis is more valuable. Up to our knowledge, there are no relevant studies on the diagnostic value of NSE and hemodynamic indexes RI and PI in the diagnosis of cervical lymph node metastasis of lung cancer, and therefore further research is needed.

In conclusion, the serum NSE and hemodynamic indexes RI and PI in patients with cervical lymph node metastasis of lung cancer are higher than those without metastasis, which has certain diagnostic value for cervical lymph node metastasis of lung cancer. However, the diagnostic value of their combination is higher. Thus, it can be used as an auxiliary diagnostic method for cervical lymph node metastasis of lung cancer. In the present study, the combined diagnostic value of more serum tumor markers and hemodynamics was not explored, and there are relatively few reports to confirm our conclusions at present. Therefore, our conclusions still need to be further verified.

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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

YK wrote the manuscript. YK and YJ analyzed and interpreted the patient data. YL performed the experiments and designed the study. SB was responsible for the analysis and discussion of the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Qingdao Municipal Hospital (Group) (Qingdao, China). Patients who

participated in this research had complete clinical data. Signed informed consents were obtained from the patients or their guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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