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Serum tumor markers: potential indicators for occult lymph node metastasis in clinical $T_{1-2}N_0M_0$ small cell lung cancer patients

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Abstract

In their letter-to-the-editor entitled "Letter to the Editor: Incidence rate of occult lymph node metastasis in clinical $T_{1-2}N_0M_0$ small cell lung cancer patients and radiomic prediction based on contrast-enhanced CT imaging: a multicenter study", Prof. Chen et al. provided insightful comments and suggestions on our original study. We appreciate the authors' feedback and have conducted a preliminary exploration of the predictive value of serum tumor markers (TMs) for occult lymph node metastasis (OLM) in clinical $T_{1-2}N_0M_0$ ($cT_{1-2}N_0M_0$) small cell lung cancer (SCLC) patients. The results indicate that neuron-specific enolase (NSE), carbohydrate antigen 125 (CA125), and squamous cell carcinoma antigen (SCC) have potential predictive value for detecting OLM in $cT_{1-2}N_0M_0$ SCLC patients. Additionally, further exploration and confirmation through prospective, large-scale studies with robust external validation are needed.

Keywords Small cell lung cancer, Occult lymph node metastasis, Serum tumor markers, Neuron-specific enolase, Carbohydrate antigen 125, Squamous cell carcinoma antigen

We thank Prof. Chen et al. for their letter and appreciate their excellent comments on our study. Our group published a study in *Respiratory Research* that explored the incidence rate (33.9%, 82/242) of occult lymph node metastasis (OLM) in clinical $T_{1-2}N_0M_0$ ($cT_{1-2}N_0M_0$) small cell lung cancer (SCLC) patients and developed a noninvasive method to predict OLM in patients with $cT_{1-2}N_0M_0$ SCLC preoperatively. This retrospective multicenter study, which included 242 patients, was rigorously screened and quality controlled. The combined model including clinical features and intratumoral and peritumoral radiomic data demonstrated stable predictive performance for preoperative OLM status in the external validation group (area under the curve: 0.772; sensitivity: 67.9%; specificity: 80.4%) [1]. According to the latest SCLC treatment guidelines, surgery is only recommended for certain patients with clinical stage I-IIA ($T_{1-2}N_0M_0$) SCLC diseases [2]. The accurate preoperative prediction of OLM in $cT_{1-2}N_0M_0$ SCLC patients could help selecte the candidates who would benefit most from surgery and avoid unnecessary surgical procedures, which is critical for personalized treatment strategies.

SCLC is characterized by high malignancy and an early propensity for lymph node metastasis [3]. Determining whether early-stage $cT_{1-2}N_0M_0$ SCLC patients have

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OLM preoperatively remains challenging, especially when using noninvasive methods. Our innovative model, which includes smoking status, tumor shape, and combined intratumoral and peritumoral radiomic features, offers significant predictive value for OLM. Although our study incorporated clinical factors, conventional imaging features, and radiomics, it lacked laboratory indicators, as described by Prof. Chen et al.

Serum tumor markers (TMs), as laboratory indicators, are known to reflect the differentiation and malignancy of lung cancer. They are correlated with tumor metastasis and have predictive significance for diagnosis, staging, prognosis, and treatment efficacy [4–7]. Common TMs associated with lung cancer are carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), neuron-specific enolase (NSE), cytokeratin-19 fragment (CYFRA 21-1), progastrin-releasing peptide (ProGRP), and squamous cell carcinoma antigen (SCC). TMs are also widely used in SCLC. For instance, NSE is one of the most extensively studied biomarkers in SCLC, playing a significant role in diagnosis and treatment monitoring [8, 9], and it is superior to ProGRP in prognostic prediction [10]. However, ProGRP, known for its sensitivity and specificity in SCLC [11, 12], is particularly effective in diagnosis and differential diagnosis [10]. We reviewed recent literature from the past five years on the application of TMs in SCLC and summarized the relevant information in Table 1. Overall, TMs are correlated with the diagnosis, treatment efficacy, and prognosis of SCLC, although findings vary significantly across studies. Unfortunately, only one study has mentioned lymph node metastasis specifically within pulmonary neuroendocrine tumors (PNETs). In this study, Zhang et al. [13] conducted a retrospective analysis of 266 patients with PNETs, including 219 patients with SCLC, and found that pretreatment CEA level (CEA > 5 ng/ml: OR, 3.084; $P=0.014$) was an independent risk factor for lymph node metastasis in PNETs. Additionally, pretreatment CEA (OR, 2.260; $P=0.007$) was also an independent risk factor for distant metastasis in PNETs.

Given the limited number of studies on TMs in patients with lymph node metastasis in SCLC, we conducted a preliminary exploration of TMs based on the suggestions of Prof. Chen et al. Due to variations in tumor marker types across hospitals, different negative reference values of laboratory indicators, and measurement errors, we collected only preoperative TM data from 158 patients at the main center (National Cancer Center/Cancer Hospital). This center commonly uses six lung cancer TMs: CA125, CYFRA21-1, NSE, SCC, CEA, and ProGRP. Ultimately, patients with incomplete preoperative TM data were excluded, resulting in a final sample of 88 patients. To determine the potential predictive value of the TMs, an exhaustive analysis was performed to identify the optimal cut-off points for these indices. The following cut-off values were identified: CA125 at 8.39 U/ml, NSE at 10.79 ng/ml, SCC at 1.1 ng/ml, CYFRA21-1 at 8.22 ng/ml, CEA at 1.4 ng/ml, and ProGRP at 460.55 ng/ml. Based on these cut-off values, categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Table 2 shows the comparison of various TMs with the presence (OLM+) or absence (OLM-) of OLM in $cT_{1-2}N_0M_0$ SCLC patients.

In this study, all patients with OLM had NSE levels above the cut-off value of 10.79 ng/ml ($p=0.014$), demonstrating a strong correlation between higher NSE levels and the presence of OLM. For CA125, a greater proportion of patients with OLM had CA125 levels above the cut-off value of 8.39 U/ml ($p=0.039$), indicating its potential predictive value for OLM. Conversely, a lower proportion of OLM positive patients had SCC levels above the cut-off value of 1.1 ng/ml ($p=0.008$), suggesting an inverse relationship between SCC levels and OLM. Among the three TMs, NSE demonstrated the highest sensitivity at 100% (30/30), while its specificity was low at 17.2% (10/58). CA125 had a sensitivity of 73.33% (22/30) and a specificity of 50% (29/58), and SCC had a sensitivity of 6.67% (2/30) and a specificity of 67.2% (39/58). However, there is insufficient evidence to suggest that CYFRA21-1 ($p=0.341$), CEA ($p=0.263$), or ProGRP ($p=0.295$) can predict the presence of OLM in $cT_{1-2}N_0M_0$ SCLC patients. This suggests that NSE, CA125, and SCC have potential predictive value for OLM in $cT_{1-2}N_0M_0$ SCLC patients. Previous studies have shown that NSE is most highly expressed in SCLC [7, 10], while CA125 and SCC are most highly expressed in non-small cell lung cancer [7, 14–16]. These findings indicate that these three tumor markers are widely used in lung cancer diagnostics, particularly NSE in SCLC. Although this study identified three potentially meaningful indicators, the small sample size may limit the generalizability of their clinical predictive value for OLM in SCLC. Further exploration and confirmation through prospective, large-scale studies with robust external validation are needed. Furthermore, it is well known that elevated TMs are more evident in mid- to late-stage SCLC [7, 17]. We speculate that the relationship between various TMs and OLM status might be less pronounced in $cT_{1-2}N_0M_0$ SCLC patients, which increases the difficulty of the research.

In conclusion, NSE, CA125, and SCC have potential predictive value for detecting OLM in $cT_{1-2}N_0M_0$ SCLC patients. We believe that TMs remain a promising research direction, as highlighted by Prof. Chen et al.'s comments. We are keen to closely monitor the TMs of the included patients and further explore the correlation. In future studies, we aim to expand our sample size, establish standardized prospective quality

Table 1 Recent literatures from the past five years on the application of various TMs in SCLC

Author, year	Cases	TM	Study endpoints	Performance of TMs				
				OR/HR (95% CI)	*P* value	AUC (95% CI)	Sensitivity	Specificity
Zhu C et al., 2024 [18]	97 SCLC with platinum-based chemotherapy	NSE	OS	2.676(1.3777,5.200)	0.004	NA	NA	NA
Li W et al.,2023 [19]	737 SCLC	CEA	Brain metastasis	1.788(0.918–3.381)	0.079	NA	NA	NA
		NSE		0.378(0.211,0.680)	0.001	NA	NA	NA
Li L et al.,2023 [20]	102 SCLC, 60 BLD, and 90 healthy controls	TuM2-PK	Diagnosis	NA	NA	0.816(0.731.0.901)	0.8235	0.9111
		NSE		NA	NA	0.642(0.529,0.755)	0.6078	0.8111
		ProGRP		NA	NA	0.759(0.662,0.856)	0.7745	0.8667
	102 SCLC	TuM2-PK	OS	3.278(1.486,7.231)	0.003	NA	NA	NA
Ueki K et al.,2022 [21]	62 LS-SCLC underwent TRT and received platinum-based chemotherapy	ProGRP	Brain metastasis	7.96(1.68,37.80)	0.0091	NA	NA	NA
Li L et al.,2021 [22]	102 SCLC treated with first-line PD-1/PD-L1 inhibitors	NSE	PFS	1.93(1.18,3.17)	0.009	NA	NA	NA
			OS	2.41(1.14,5.10)	0.021	NA	NA	NA
			PFS	8.4 vs. 4.5 months*	0.002	NA	NA	NA
			OS	23.3 vs. 7.4 months*	< 0.0001	NA	NA	NA
Chen Z et al.,2021 [23]	1505 NSCLC and 101 SCLC	CEA	Diagnosis	NA	0.033	0.563(0.511, 0.615)	0.455	0.595
		SCC		NA	0.029	0.438(0.382, 0.494)	0.059	0.876
		CYFRA 21-1		NA	0.196	0.538(0.484, 0.593)	0.505	0.581
		NSE		NA	< 0.001	0.794(0.739, 0.849)	0.683	0.817
		TPA		NA	< 0.001	0.614(0.56, 0.667)	0.307	0.766
		ProGRP		NA	< 0.001	0.844(0.789, 0.898)	0.723	0.912
Wang C et al.,2021 [24]	301 SCLC platinum-based chemotherapy and TRT was performed in 112 patients	NSE	OS	1.514(1.003, 2.284)	0.048	NA	NA	NA
		CEA		1.009(0.757, 1.344)	0.953	NA	NA	NA
Huang LL et al.,2021 [25]	358 ES-SCLC	Cyfra21-1	OS	1.21(1.04, 1.40)	0.01	NA	NA	NA
		CA125		1.18(1.02, 1.36)	0.02	NA	NA	NA
		NSE		1.19(0.99, 1.43)	0.06	NA	NA	NA
		Cyfra21-1	PFS	1.22(1.06, 1.40)	0.006	NA	NA	NA
Du J et al.,2020 [17]	118 SCLC, 166 NSCLC, 33 BLD, and 200 healthy controls	NSE	Diagnosis	NA	NA	0.855(0.810, 0.901)	0.407	NA
		ProGRP		NA	NA	0.905(0.912, 0.973)	0.678	0.995
Li M et al.,2020 [26]	120 SCLC treated with chemotherapy	ProGRP	PFS	0.714 (0.475-1.073)	0.105	NA	NA	NA
		NSE		0.567(0.384-0.837)	0.004	NA	NA	NA
Dong A et al.,2019 [27]	827 SCLC, 56 LCNEC, 29 PC, 659 BLD, 6368 NSCLC	ProGRP	Diagnosis	NA	NA	0.943	0.865	0.965
		NSE		NA	NA	0.894	0.788	0.863

If there are multivariate analysis in the original study, this table extracts the results of multivariate analysis. Otherwise, the results of univariate analysis are extracted in the table

*No HR or OR of NSE at 3 weeks was reported in the study

Abbreviations: OS, overall survival; PFS, progression-free survival; BLD, benign lung disease; PC, pulmonary carcinoid; AC, atypical carcinoid; TC, typical carcinoid; TM, tumor markers; TPA, tissue polypeptide antigen; TRT, thoracic radiotherapy; TuM2-PK, tumor M2-pyruvate kinase; EA, carcinoembryonic antigen; CA125, carbohydrate antigen 125; NSE, neuron-specific enolase; CYFRA 21-1, cytokeratin-19 fragments; ProGRP, progastrin-releasing peptide; SCC, squamous cell carcinoma antigen; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; LS-SCLC, limited-stage small cell lung cancer; ES-SCLC, extensive-stage small cell lung cancer; AUC, area under curve; OR, odds ratio; HR, hazard ratio

control measures, and conduct multicenter studies. This approach will allow us to comprehensively collect TM data and explore their predictive significance with a larger sample size, paving the way for improved performance of the prediction model for OLM in $cT_{1-2}N_0M_0$ SCLC.

Table 2 The comparison of various TMs with the presence (OLM+) or absence (OLM-) of OLM

TM	OLM+	OLM-	X^2	*P* value
CA125			4.418	0.036*
≤8.39(U/ml)	8(26.7%)	29(50%)		
>8.39(U/ml)	22(73.3%)	29(50%)		
Cyfra21-1				0.341
≤8.22(ng/ml)	29(96.7%)	58(100%)		
>8.22(ng/ml)	1(3.3%)	0(0%)		
SCC				0.008*
≤1.1(ng/ml)	28(93.3%)	39(67.2%)		
>1.1(ng/ml)	2(6.7%)	19(32.8%)		
NSE				0.014*
≤10.79(ng/ml)	0(0%)	10(17.2%)		
>10.79(ng/ml)	30(100%)	48(82.8%)		
CEA				0.263
≤1.4(ng/ml)	5(16.7%)	4(6.9%)		
>1.4(ng/ml)	25(83.3%)	54(93.1%)		
ProGRP				0.295
≤460.55(ng/ml)	30(100%)	54(93.1%)		
>460.55(ng/ml)	0(0%)	4(6.9%)		

*Significant difference ($p<0.05$). Abbreviations: TM, tumor marker; CEA, carcinoembryonic antigen;

CA125, carbohydrate antigen 125; NSE, neuron-specific enolase; CYFRA 21-1, cytokeratin-19 fragment;

ProGRP, progastrin-releasing peptide; SCC, squamous cell carcinoma antigen

Abbreviations

SCLC	Small cell lung cancer
OLM	Occult lymph node metastasis
TMs	Tumor markers
CEA	Carcinoembryonic antigen
CA125	Carbohydrate antigen 125
NSE	Neuron-specific enolase
CYFRA 21-1	Cytokeratin-19 fragment
ProGRP	Progastrin-releasing peptide
SCC	Squamous cell carcinoma antigen
PNETs	Pulmonary neuroendocrine tumors

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Author contributions
L.Y., L.Z. and M.L: Study design. Z.L. and X.J.: data analysis. X.J.: manuscript writing. J.X. and JM.J.: data collection. L.M. and L.Z.: study supervision. L.M., MW.L. and L.Z.: manuscript revision. All the authors have read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Consent for publication
Not applicable.
Informed consent was waived due to the retrospective nature of the study.

Competing interests
The authors declare no competing interests.

Ethical approval
The study was approved by the Cancer Hospital, Chinese Academy of Medical Sciences Ethics Commission (NCC2021C-213).

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