Letter to the Editor
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Algorithm using Neuron-Specific Enolase and Pro-Gastrin-Releasing Peptide to Increase the Diagnostic Accuracy for Small Cell Lung Cancer

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Dear Editor,

Small cell lung cancer (SCLC) is an aggressive neuroendocrine tumor that accounts for approximately 15% of all lung cancers [1]. Because cancer cells in SCLC grow rapidly, the cancer likely has invaded other organs by the time symptoms present, which frequently delays initial treatment [2]. Therefore, early detection of SCLC is essential for improving the prognosis.

Chest X-ray and computed tomography (CT) are the diagnostic methods of choice in lung cancer. Although low-dose CT is recommended for lung cancer screening in high-risk populations, issues concerning its efficacy, high false-positive rates, overdiagnosis, significant costs, and radiation risk have been raised [3]. Therefore, it is important to focus on harmless biomarkers, and neuron-specific enolase (NSE) has been acknowledged as the most reliable tumor marker for SCLC [4].

Pro-gastrin-releasing peptide (ProGRP) has been used for SCLC screening in Korea since the fully automated ARCHITECT ProGRP immunoassay (Abbott Laboratories, Abbott Park, USA) was introduced in 2012. While ProGRP is a better SCLC marker than NSE [5], it is not as commonly used in clinical practice as NSE. This is likely because of the low serum stability of ProGRP [6]. In the Elecsys ProGRP assay (Roche Diagnostics International, Rotkreuz, Switzerland) that was developed later, the ProGRP-stability issue was solved, and the assay showed clear benefits over the ARCHITECT ProGRP assay [7].

Although numerous studies have compared the validity of various tumor markers in SCLC diagnosis [8-10], no study has presented a practically available tool that uses NSE and ProGRP to increase the diagnostic accuracy. The goal of our study was to create an algorithm to differentiate SCLC from non-small cell lung cancer (NSCLC) using NSE and ProGRP. We prospectively analyzed serum samples from 100 lung cancer patients (age=67.8±1.0 years, male/female ratio=2.85), including 24 SCLC and 76 NSCLC patients (adenocarcinoma [N=47], squamous cell carcinoma [N=25], large-cell carcinoma [N=3], and adenosquamous carcinoma [N=1]), for NSE and ProGRP. The Institutional Review Board of Kosin University Gospel Hospital, Busan, Korea, approved the study protocol (KUGH 2015-06-106). Informed consent was obtained from the patients. NSE (Elecsys NSE, Roche Diagnostics International) and ProGRP (Elecsys ProGRP, Roche Diagnostics International) levels were analyzed using the Cobas e601 module (Roche Diagnostics International).

The area under the receiver operating characteristic (ROC)

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curve, sensitivity, specificity, and diagnostic accuracy results are presented in Table 1. ProGRP level showed excellent performance in differentiating between SCLC and NSCLC at a cutoff value of 85.70 pg/mL but had a relatively weak sensitivity, whereas NSE level showed excellent sensitivity but very low specificity at a cutoff value of 17.30 ng/mL. This indicates that NSE level alone may lead to false-positive results at a cutoff value of 17.30 ng/mL and that it cannot accurately differentiate between SCLC and NSCLC.

We created an algorithm using NSE and ProGRP to increase the diagnostic accuracy for SCLC (Fig. 1). When ProGRP and NSE results differed, the final result was decided by the algorithm. If the NSE level was greater than 14.24 ng/mL (the cutoff value for 100% sensitivity based on ROC curve analysis) in the ProGRP (+)/NSE (–) group or 83.97 ng/mL (mean plus three times the SD of NSE level in the NSCLC group) in the ProGRP (–)/NSE (+) group, a positive result was reported. By applying this algorithm, we could improve the relatively low sensitivity of ProGRP level from 75% to 87.5%, with a specificity of 94.7%. The accuracy improved to 93% from 90% for ProGRP level and 49% for NSE level.

The algorithm was created considering the limited number of lung cancer patients and is based on the NSE and ProGRP levels from our hospital. The cutoff values of NSE and ProGRP levels could vary in each institution. We did not evaluate the NSE and ProGRP levels in normal control or other cancer groups; these need to be further studied.

In conclusion, an elevated NSE level is observed in many NSCLC patients. NSE level alone is not sufficient to accurately differentiate between SCLC and NSCLC. To improve the diagnostic power and accuracy for SCLC, ProGRP level needs to be additionally tested. Sequential testing of NSE and ProGRP levels and application of a diagnostic algorithm could increase the ac-

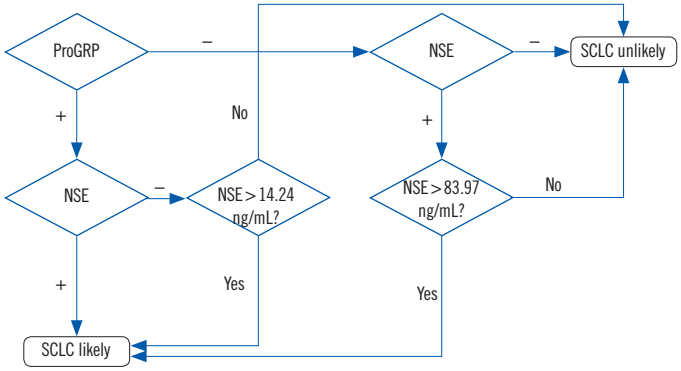

Fig. 1. Algorithm for differentiating between SCLC and NSCLC. The cutoff value for ProGRP is 85.70 pg/mL, and that for NSE is 17.30 ng/mL. When a discordant result is observed between ProGRP and NSE, two cutoff values are used. One of the values is 14.24 ng/mL, which is the cutoff value for 100% sensitivity of NSE based on the ROC curve analysis, and the other is 83.97 ng/mL, which is the mean value plus 3SD of NSE in the NSCLC patient group. We calculated these values based on the test results of 100 patients. Therefore, these values could be adjusted based on the evaluated patient groups in each institution.
Abbreviations: NSE, neuron-specific enolase; ProGRP, pro-gastrin- releasing peptide; SCLC, small cell lung cancer.

Table 1. Sensitivity, specificity, accuracy, and AUC of NSE, ProGRP, and the proposed algorithm for SCLC

Test		SCLC (N)			Sn (%)	Sp (%)	Ac (%)	Cut-off	Mean (SD)	AUC (95% CI)	*P*
		+	–	Total							
NSE	+	23	50	73	95.8	34.2	49.0	17.30 ng/mL	38.27 (37.84) ng/mL	0.847 (0.760-0.935)	<0.001
	–	1	26	27							
	Total	24	76	100							
ProGRP	+	18	4	22	75.0	94.7	90.0	85.70 pg/mL	374.59 (1,279.93) pg/mL	0.867 (0.766-0.969)	<0.001
	–	6	72	78							
	Total	24	76	100							
Algorithm	+	21	4	25	87.5	94.7	93.0	14.24 ng/mL	-	-	-
	–	3	72	75				83.97 ng/mL			
	Total	24	76	100							

The percentage of positive results for NSE was 68.06% (49/72) in NSCLC and 31.94% (23/72) in SCLC. The mean±SD of NSE level in SCLC was significantly greater than that in NSCLC (76.1±54.7 vs. 26.3±19.2; $P<0.001$); this explains the low specificity for NSE. When the 2-by-2 table for estimating the diagnostic accuracy of NSE, ProGRP, and algorithm test results was prepared, the positive test results were categorized into true positives and false positives, and negative results into true negatives and false negatives. Diagnostic accuracy was defined as the fraction of true positives and true negatives derived from all classifications.
Abbreviations: SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; NSE, neuron-specific enolase; ProGRP, pro-gastrin-releasing peptide; Sn, sensitivity; Sp, specificity; Ac, diagnostic accuracy; SD, standard deviation; AUC, the area under the receiver operating characteristic curve; CI, confidence interval.

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curacy of SCLC diagnosis. Further studies assessing the clinical usefulness of this algorithm by comparing routine diagnostic processes using radiological and histological methods with the present algorithm are warranted.

AUTHOR CONTRIBUTIONS

Conceptualization: Hwang H and Lee H; data curation: Choi H and Lee H; methodology: Jang TW, Park SD, and Kim T; validation: Hwang H; writing-original draft: Lee H; writing-review & editing: Hwang H.

CONFLICTS OF INTEREST

None declared.

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