CA-62 and Combined Biomarker Performance in Pulmonary Lesions: Prospective Confirmation

Authors: Antonio K. Chekini[1], Janneta R. Tcherkassova[2], Konstantin S. Titov[1], Sergei S. Lebedev[1], Dmitry N. Grekov[1], Sergei A . Tsurkan[2], Evgueni Klinski[2*], and Ricardo Moro[3]

[1] Moscow Botkin Multidisciplinary Scientific-Clinical Center, Moscow, Russia, [2] UCM Technologies Inc., Toronto, ON, Canada, [3] Pacific Biosciences Research Center, Vancouver, BC, Canada
*Corresponding author: Evgueni Klinski, UCM Technologies Inc., Toronto, Ontario, Canada, Tel: +1 (514) 898-2931, E-mail: evgueni.k@ucmtechnologies.com

Background: Lung cancer remains the leading cause of cancer mortality worldwide, accounting for approximately 2.5 million new cases and 1.8 million deaths in 2022 [1]. Prognosis is strongly stage-dependent: only 23.7% of lung cancers are diagnosed while localized, whereas 51% are detected after distant spread; five-year relative survival decreases from 65.5% to 10.5%, respectively [2]. Although targeted and immune therapies have improved outcomes in advanced disease, they have also increased the duration, complexity, and cumulative cost of treatment, further strengthening the clinical and economic rationale for earlier detection [3].CA-62 is measured in serum using a competitive flash chemiluminescence immunoassay. The assay recognizes a shared N-glycan determinant carried by circulating glycoproteins associated with poorly differentiated and developmentally active cellular states. CA-62 is therefore better considered a cell-state-associated biological signal than a tissue-of-origin marker. Altered N-glycosylation and release of membrane and soluble glycoproteins may generate a detectable circulating signal before substantial tumor burden develops, providing a rationale for early sensitivity but limited organ specificity [4–7].Previous blinded studies demonstrated high CA-62 sensitivity in early-stage NSCLC, while a predefined score combining CA-62, CEA, and CYFRA 21-1 improved discrimination compared with CA-62 alone [5,6]. The present study prospectively applied this score without refitting to a heterogeneous cohort of patients with CT-detected pulmonary lesions.

Aim: To prospectively assess CA-62 signal characteristics across stages and malignant phenotypes of CT-detected pulmonary lesions and to determine whether the predefined CA-62, CEA, and CYFRA 21-1 score retains incremental discriminatory value without refitting.

Materials and methods: A prospective, single-center pilot clinical study was conducted using serum from 267 patients with focal lung neoplasms detected by computed tomography scans. The study was carried out at the S.P. Botkin Medical Scientific and Clinical Center from May 2025 to April 2026. To evaluate suspicious lesions and accurately stage cancer, all 267 patients in the Oncosurgical Department No. 72 of the S.P. Botkin MS Clinical Center underwent computed tomography-guided, robot-assisted transthoracic biopsies for morphological verification of lung nodules and to compare CA-62 tumor marker levels with histological examination results. Quantitative measurements of tumor markers were performed using commercial immunoassays. The obtained results for CA-62, CEA, and CYFRA 21-1 tumor marker levels were compared with the results of immunohistochemistry (IHC) and the established diagnosis, as well as with a preliminary CT scan - based diagnosis. The study results were evaluated, algorithms were identified, and recommendations for the use of combined CA-62 testing in patients with focal lung lesions suspicious for malignancy were developed. Inclusion criteria for patients to participate in the pilot study: patients (men and women aged 18 years and older) with suspected lung malignancies based on chest CT scans, with a satisfactory general condition, and without contraindications to TTNB. Robot-assisted TTNB were performed using a PERFINT MAXIO robotic navigation system (Italy) under the guidance of a Canon Aquilion Prime SP multisided CT scanner (160 slices). CT scanning was performed with the following parameters: 120 kV, 28.5–150 mA, 0.5 s/rev, and 39.37 mm/rev. CT data were reconstructed into images with a 512 × 512 matrix and a slice thickness of 3.75 mm. The surgeon selected the biopsy trajectory and final target on the Perfint Maxio robotic console to perform a biopsy using the robotic arm. After the biopsy, all patients underwent a follow-up chest CT scan to assess for complications.

Results: The cohort included 267 patients with CT-detected pulmonary lesions: 123 with primary lung cancer, 65 with pulmonary metastases or malignancies of other origins, and 79 with non-malignant lesions.CA-62 was above 5,000 U/mL in 105/123 primary lung cancers (85.4%), including 41/47 stage I–II cases (87.2%). In early-stage disease, CEA and CYFRA 21-1 were elevated in only 23.4% and 12.8% of cases, respectively. Across all malignant diagnoses, CA-62 was positive in 158/188 cases (84.0%). Signal frequency was similar across primary lung cancer, pulmonary metastases, and malignancies of other origins, and between adenocarcinoma and squamous-cell carcinoma, although median CA-62 concentration was higher in squamous-cell carcinoma. Detailed subgroup data are presented in Table 1.The predefined three-marker score consistently improved discrimination compared with CA-62 alone across all evaluated endpoints. AUC increased from 0.706 to 0.828 for primary lung cancer versus non-malignant lesions and from 0.627 to 0.765 for primary lung cancer versus all alternative diagnoses. Complete comparative results are shown in Table 2.

Table 1. CA-62 signal frequency and serum concentrations across malignant phenotypes, stages, and histological types in CT-detected pulmonary lesions

	Clinical or pathological subgroup	n	CA-62 ≥5,000 U/mL, n (Sens %)	Median CA-62, U/mL	IQR, U/mL
Diagnostic groups	**All malignancies**	**188**	**158 (84.0%)**	**6,910**	5,404–9,258
	Primary lung cancer	123	**105 (85.4%)**	6,888	5,528–9,304
	Pulmonary metastases	44	**36 (81.8%)**	7,111	5,341–8,100
	Malignancies of other origin	21	**17 (81.0%)**	6,475	5,642–9,401
	Non-malignant pulmonary lesions	79	38 (48.1%)	4,707	2,623–6,665
Primary LC	Stage I–II	47	**41 (87.2%)**	6,759	—
	Stage III–IV	69	**57 (82.6%)**	6,888	—
Primary LC by histological type	Adenocarcinoma	81	**69 (85.2%)**	6,707	5,388–8,477
	Squamous-cell carcinoma	13	**11 (84.6%)**	**10,834**	7,465–14,201
	Small-cell lung cancer*	6	4 (66.7%)	7,250	5,193–8,513
	Large-cell carcinoma*	4	3 (75.0%)	6,466	5,762–7,523
	Other neuroendocrine tumors*	3	2 (66.7%)	12,440	8,320–13,644

**Rare histological subgroups are presented descriptively and should be interpreted as exploratory because of their small sample sizes.*
Stage was documented in 116 of 123 primary lung cancer cases.

Table 2. Prospective performance of CA-62 and the predefined combined biomarker score across clinically relevant endpoints $TM = \frac{CEA+(CA\text{-}62/1000)+2\times CYFRA\ 21\text{-}1}{3}$

Clinical endpoint	CA-62 AUC	3TM AUC	ΔAUC
Stage I–II primary lung cancer versus non-malignant lesions	0,719	**0,799**	+0,080
All malignancies versus non-malignant lesions	0,694	**0,779**	+0,085
Primary lung cancer versus non-malignant lesions	0,706	**0,828**	+0,122
Primary lung cancer versus all alternative diagnoses	0,627	**0,765**	+0,138

Discussion:

CA-62 retained a high signal frequency in stage I–II primary lung cancer, with positivity and median concentrations comparable to those observed in advanced disease. In contrast, CEA and CYFRA 21-1 were less frequently elevated at early stages.

These findings are consistent with previous blinded studies and support the interpretation of CA-62 as an early cell-state- and N-glycosylation-associated signal rather than a marker determined primarily by tumor burden [4–6].

The similar CA-62 positivity observed in primary lung cancer, pulmonary metastases, and malignancies of other origins supports its broad malignancy-associated character. In a pre-biopsy pathway, detection of a metastatic or non-pulmonary malignancy should not be considered an oncologic false-positive result, although this biological breadth limits the ability of CA-62 alone to determine tissue of origin.

CA-62 positivity was nearly identical in adenocarcinoma and squamous-cell carcinoma, whereas median serum concentration was significantly higher in squamous-cell carcinoma than in adenocarcinoma (10,834 vs 6,707 U/mL; p=0.025). This suggests that threshold crossing and signal magnitude represent distinct characteristics. Differences in tumor-cell glycoprotein biology and tissue or inflammatory response may contribute to this finding, which remains exploratory because of the small squamous-cell subgroup.

The predefined three-marker score improved discrimination across all evaluated endpoints without coefficient refitting. This supports a complementary biomarker architecture in which CA-62 provides the broad early-sensitive component, while CEA and CYFRA 21-1 add information related to lung-cancer phenotype and tumor burden [4,5]. The findings support prospective transportability of the combined approach, but not population-screening validation or replacement of imaging and morphological verification.

Conclusions:

- CA-62 retained a high signal frequency in stage I–II primary lung cancer, supporting its potential role as an accessible biological signal for earlier diagnostic routing.
- The similar frequency and concentration of CA-62 across primary lung cancer, pulmonary metastases, and malignancies of other origins confirm that the marker reflects a broad malignancy-associated cellular phenotype rather than tissue of origin.
- The higher median CA-62 concentration in squamous-cell carcinoma compared with adenocarcinoma, despite nearly identical positivity rates, indicates that signal intensity may contain additional information related to histological phenotype.
- The predefined three-marker score combining CA-62, CEA, and CYFRA 21-1 consistently improved discrimination compared with CA-62 alone. Its application without refitting supports the prospective transportability of the combined biomarker approach to a heterogeneous pre-biopsy clinical cohort.

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