Original Study

Supraclavicular Lymph Node Metastases in Advanced Lung Cancer: Prevalence and Analysis of Demographic, Clinical and Molecular Characteristics

Rocco Trisolini,[1,#] Valeria Cetoretta,[1,2,#] Giovanni Sotgiu,[3] Alessandra Cancellieri,[4] Mariangela Puci,[3] Marta Viscuso,[1,5] Vanina Livi,[1] Massimiliano Cani,[2] Giovanni Scambia,[6] Federico Cappuzzo,[7] Emilio Bria,[8] Silvia Novello[2]

Abstract

This study investigates the prevalence of supraclavicular lymph node metastasis (SNM) in patients with advanced lung cancer and examines the main demographic, clinical, and molecular characteristics of patients with and without SNM. The Findings reveal that SNM is prevalent in this setting and is independently associated with small-cell lung cancer histology and with metastasis to less common sites. This study also suggests that ultrasound-guided biopsy of SNM is a safe, inexpensive and effective tool for diagnosis and molecular profiling.

Background: The prevalence of supraclavicular lymph nodes metastases (SNM) in advanced lung cancer has not been systematically evaluated, nor has then been a comparison of demographic, clinical, or molecular characteristics between patients with and without SNM. **Methods:** In this prospective cohort study, the presence of SNM was evaluated using imaging studies (CT, PET, neck ultrasonography) in patients with suspected advanced lung cancer referred for biopsy aimed at diagnosis and molecular profiling. Ultrasound-guided biopsy confirmed or excluded metastatic involvement when suspicious supraclavicular nodes were identified. We assessed the prevalence of SNM and compared the demographic, clinicopathologic and molecular characteristics of patients with and without SNM. **Results:** Among the 348 patients with advanced lung cancer, 94 (27%) had SMN. SMN was more common in small cell lung cancer (24/48, 50%) and adenocarcinoma (61/248, 24.6%) than in squamous cell carcinoma (4/35, 11.4%). Compared to patients without SMN, those with SMN were more likely to have small-cell lung cancer, N2/3 disease (97.9 vs. 83.9%, $P < .0001$), liver metastases (29.8% vs. 16.1% $P = .006$), and metastases to less common sites (33.7% vs. 14.1%, $P < .0001$). The prevalence of genomic alterations and PD-L1 expression did not differ between biopsy samples obtained from SNM and those from the primary tumor or other metastatic sites. **Conclusion:** SNM is common in patients with advanced small-cell lung cancer and adenocarcinoma. Ultrasound-guided biopsy of SNM is a simple and relatively inexpensive method for obtaining adequate tissue samples for diagnosis and comprehensive molecular profiling.

Clinical Lung Cancer, Vol. 000, No.xxx, 1–9

Keywords: Adenocarcinoma, Next generation sequencing, Programmed cell death ligand-1, Small-cell lung cancer, Ultrasound guided-biopsy

[1]Interventional Pulmonology Division, Fondazione Policlinico Universitario A. Gemelli IRCCS, Catholic University of the Sacred Hearth, Rome, Italy
[2]Department of Oncology, University of Turin, Azienda Ospedaliero-Universitaria San Luigi, Turin, Italy
[3]Clinical Epidemiology and Medical Statistics Unit, Department of Medicine, Surgery and Pharmacy, University of Sassari, Sassari, Italy
[4]Pathology Division, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[5]Pulmonology Division, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[6]Gynecologic Oncology Unit, Department of Woman, Child and Public Health, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[7]Medical Oncology Division, IRCCS Regina Elena National Cancer Institute, Rome, Italy Medical
[8]Oncology Division, Gemelli Isola Hospital, Catholic University of the Sacred Hearth, Rome, Italy

Submitted: Aug 29, 2024; Revised: Jan 29, 2025; Accepted: Feb 7, 2025; Epub: xxx

Address for correspondence: Silvia Novello is MD, PhD, Department of Oncology, San Luigi Hospital, University of Turin, Orbassano (TO), Italy
E-mail contact: silvia.novello@unito.it

[#] The two authors contributed equally.

1525-7304/$ - see front matter
https://doi.org/10.1016/j.cllc.2025.02.003

Please cite this article as: Rocco Trisolini et al, Supraclavicular Lymph Node Metastases in Advanced Lung Cancer: Prevalence and Analysis of Demographic, Clinical and Molecular Characteristics, Clinical Lung Cancer, https://doi.org/10.1016/j.cllc.2025.02.003

Introduction

Lung cancer is one of the most prevalent malignancies and the leading cause of cancer-related mortality worldwide.[1,2] Significant progress has been achieved in the treatment of this disease over the past 2 decades. Targeted therapies for patients with actionable genomic alterations and immune checkpoint inhibitors for those with high levels of PD-L1 have considerably enhanced survival rates and improved quality of life in advanced lung cancer.[3]

Unfortunately, a substantial proportion of patients with advanced nonsquamous non-small cell lung cancer (NSCLC) still do not undergo comprehensive genomic testing at diagnosis, often due to the lack of adequate tissue samples.[4-8] Even in patients eligible for biopsy, advanced diagnostic techniques like endosonography yield sufficient tissue for complete molecular profiling in only about 85% of cases when next-generation sequencing (NGS) is employed,[9] and less than 80% when single-gene testing methods are used.[10]

Enlarged and/or PET positive cervical and supraclavicular lymph nodes represent ideal anatomical sites for minimally invasive diagnosis and molecular profiling of lung cancer via percutaneous ultrasound-guided biopsy.[11-13] However, the specific prevalence of metastatic involvement of supraclavicular lymph nodes among with lung cancer patients has not been thoroughly investigated. Additionally, the potential correlation between supraclavicular lymph node metastasis (SNM) and the molecular profile remains unexplored, unlike other metastatic sites.[14-15]

This study aims to prospectively assess the prevalence of SNM in advanced lung cancer and compare the demographic, clinicopathologic and molecular characteristics in patients with and without SNM.

Methods

Design and Study Population

This single-center, prospective observational study enrolled patients with suspected advanced lung cancer from January 1, 2023, to September 30, 2023. The study received approval from the local Ethics Committee (Prot. n. ID 5394), and all patients provided written informed consent. The study protocol was registered at clinicaltrials.gov (identifier: NCT05706883).

Eligible participants were adults over 18 years with suspected, treatment-naïve advanced lung cancer, as indicated by imaging studies (contrast-enhanced CT and/or PET) and requiring tissue acquisition for histological diagnosis and molecular profiling, where indicated. Exclusion criteria included unwillingness or inability to consent, referral for re-biopsy in previously treated patients, presence of noncorrectable coagulation disorder, and use of antiplatelet (excluding aspirin) or anticoagulant drugs that could not be discontinued.

Procedures

The presence of suspected SNM was assessed using imaging studies. An ultrasound examination of the supraclavicular fossa was performed in all patients with supraclavicular lymph nodes measuring > 5 mm in short axis size on CT and/or PET-avid supraclavicular lymph nodes. Ultrasound-guided biopsy was performed to confirm or exclude SNM if the ultrasound identified a lymph node with a short axis >10 mm or ultrasonographic features suggestive of increased malignancy risk.[16]

In the absence of suspected SNM, tissue samples were obtained from the primary tumor, intrathoracic lymph nodes, or distant metastases using either endoscopic (conventional bronchoscopy, guided bronchoscopy, or endosonography) or percutaneous (ultrasound- or CT-guided) biopsy techniques. Surgical biopsy was reserved for cases where minimally invasive sampling methods were unsuccessful.

Molecular profiling involved immunohistochemistry analysis of PD-L1 expression (tumor proportion score) and the 9 guidelines-recommended genes (EGFR, ALK, ROS1, KRAS, BRAF, MET, RET, NTRK, ERBB2).[26-29] Genotyping primarily utilized next generation sequencing; single gene analysis via real-time PCR and in-situ hybridization was conducted when the tumor sample was insufficient for next generation sequencing.

Study Outcomes

The primary outcome was the relative frequency of SNM in patients with advanced lung cancer. The secondary outcomes included: (1) the prevalence of SNM, overall and by lung cancer histology; (2) the prevalence of genomic alterations in EGFR, ALK, ROS1, BRAF, MET, RET, NTRK, ERBB2 in patients with and without SNM; (3) PD-L1 expression assessed through the tumor proportion score in patients with and without SNM; (4) the correlation between SNM and the following factors: age, sex, smoking habit, tumor histologic type, central versus (vs.) peripheral primary tumor location (central vs. peripheral), primary tumor growth pattern (solid vs nonsolid), intrathoracic lymph node involvement (cN0 vs. cN1 vs. cN2/N3), and molecular profile.

Sample Size Calculation and Statistical Analysis

Literature indicates a KRAS mutation prevalence of 25% to 35% in unselected European patients with advanced NSCLC.[17-19] Assuming an 18% KRAS mutation prevalence difference in patients with and without SNM (12% vs. 30%), and with *alpha* and *beta* errors set at 0.05 and 0.2, a total of 168 patients (84 per group) would be required, considering a 5% dropout rate.

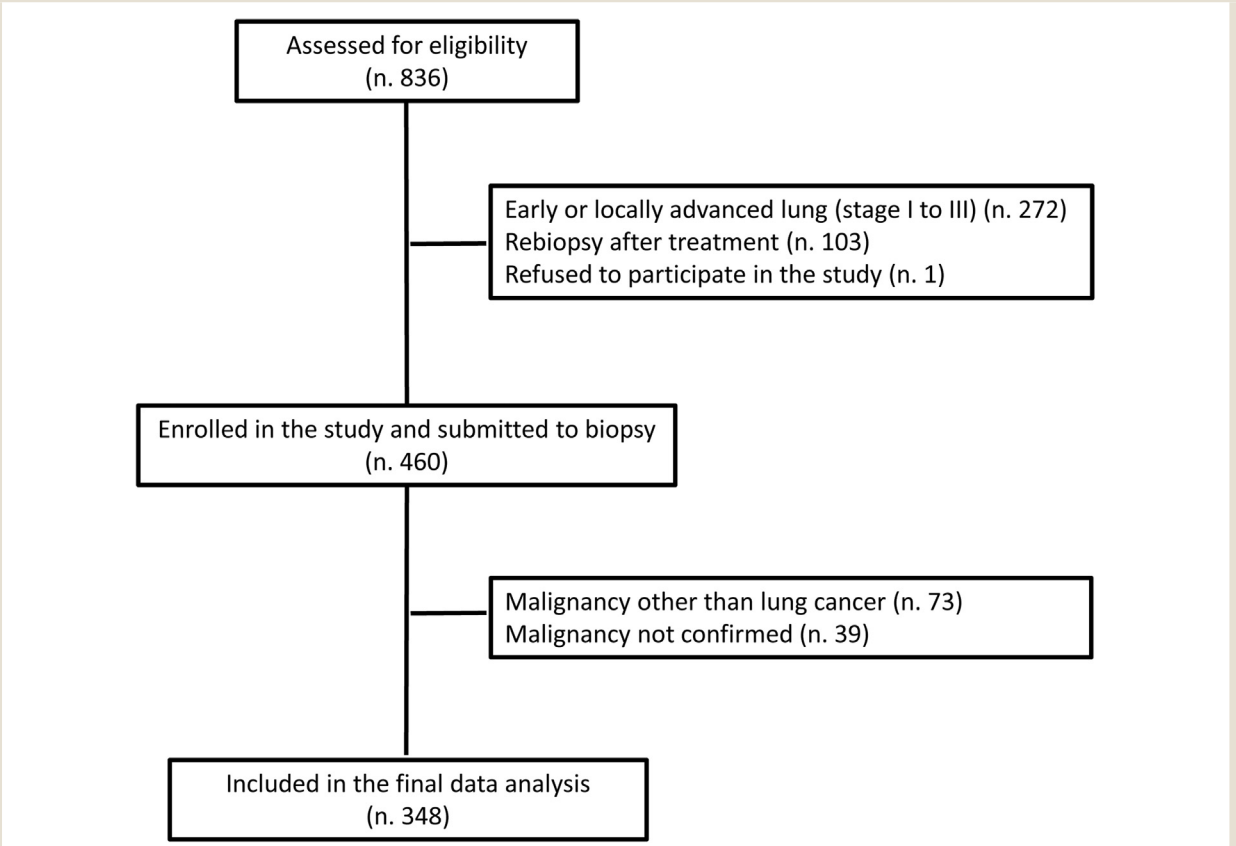
Data were summarized using descriptive statistics. Comparisons between groups utilized Pearson Chi or Fisher exact tests for quantitative variables. Multivariate logistic regression analysis was performed to identify factors associated with SNM: Odds Ratios (ORs) with corresponding 95% Confidence Intervals (95% CI) were adopted. Candidate variables were selected based on clinical and statistical significance at univariate analysis. The Hosmer-Lemeshow (HL) goodness of fit statistic was calculated assess model fit. Statistical significance was set at $P < .05$. All statistical computations were performed using STATA version 17 software.

Results

During the study period, 836 patients were assessed for eligibility, and 348 were included in the final data analysis (Figure 1). The baseline characteristics of the study cohort are summarized in Table 1. Median (IQR) age was 68 (62-75) years, and 56.9% were male. Adenocarcinoma was the most prevalent histology ($n = 248$,

Please cite this article as: Rocco Trisolini et al, Supraclavicular Lymph Node Metastases in Advanced Lung Cancer: Prevalence and Analysis of Demographic, Clinical and Molecular Characteristics, Clinical Lung Cancer, https://doi.org/10.1016/j.cllc.2025.02.003

Figure 1 STROBE diagram.



71.3%), followed by small cell lung cancer (SCLC) ($n = 48$ patients, 13.8%) and squamous cell carcinoma ($n = 35$, 10.1%).

Among the 348 patients enrolled, 94 (27.0%) had SNM. The prevalence of SNM was highest in patients with SCLC and lowest in those with squamous cell carcinoma (Figure 2).

Table 2 compares the main tumor characteristics relative to the T, N, and M descriptors (IASLC, 8th TNM edition) stratified by supraclavicular lymph node involvement. Intrathoracic lymph node metastases (especially cN2/3 metastases), liver metastases, and metastases to less common sites were significantly more common in patients with SNM compared to those without.

Molecular alterations in one or more of the guideline-recommended genes were identified in 172/254 patients (67.7%). There was no significant difference in the overall prevalence of genomic alterations between patients with and without SNM (41/61, 67.2% vs. 131/193, 67.9%, respectively: $P = .92$). The prevalence of individual genomic alterations, including *KRAS* mutations, was not statistically different between patients with and without SNM (Table 3). Similarly, PD-L1 expression, classified into tumor proportion scores of $< 1\%$, 1%-49%, and $\geq 50\%$, did not differ between the 2 groups (Table 4).

Only SCLC histology (OR: 2.1; 95% CI, 1.25-5.01) and metastasis to less common sites (OR: 3.00; 95% CI, 1.64-5.48) were associated with SNM, whereas squamous cell histology was inversely associated with SNM (OR: 0.18; 95% CI, 0.04-0.77) (Table 5).

The diagnostic yield of ultrasound-guided biopsy from supraclavicular lymph nodes was 95.7% (90/94) for detecting of SNM, and 92.6% (87/94) for achieving complete molecular profiling. No complications were observed in patients who underwent ultrasound-guided biopsy of supraclavicular lymph nodes.

Discussion

To the best our knowledge, this is first study to systematically and prospectively assess the prevalence of SNM in patients with advanced lung cancer. Previous studies have evaluated the prevalence of abnormal supraclavicular lymph nodes using imaging criteria (short axis size > 5 mm and/or ultrasonographic features suggestive of malignancy) without systematically confirming their metastatic involvement through biopsy.[20,21] Additionally, other studies focused on stage III lung cancer,[21,22] or included lung cancer patients at various stages without providing detailed information on metastatic disease.[23,24]

SNM was present in approximately one in 4 patients with advanced lung cancer. We also observed significant variation in the prevalence of SNM among different histological types, with the highest prevalence in SCLC and adenocarcinoma, and the

Please cite this article as: Rocco Trisolini et al, Supraclavicular Lymph Node Metastases in Advanced Lung Cancer: Prevalence and Analysis of Demographic, Clinical and Molecular Characteristics, Clinical Lung Cancer, https://doi.org/10.1016/j.cllc.2025.02.003

Table 1 Baseline Characteristics of the Cohort

Variables		Sample ($n = 348$)
Age (Years), Median (IQR)		68 (62-75)
Age (Years), n (%)	≤ 50	24 (6.9)
	51-80	283 (88.7)
	> 80	43 (12.3)
Male Sex, n (%)		199 (57.2)
Smoking, n (%)	Current	146 (42)
	Former	152 (43.4)
	Never	52 (14.6)
Underlying Disease, n (%)	Adenocarcinoma	248 (71.3)
	Squamous cell carcinoma	35 (10.0)
	NSCLC NOS	10 (2.9)
	Small cell lung cancer	48 (13.8)
	Large cell neuroendocrine carcinoma	7 (2.0)
Genomic Profile, n (%)	Successfully completed	245 (70.4)
	Failed, insufficient tissue specimen	2 (0.6)
	Partially completed, suboptimal tissue specimen	9 (2.6)
	Not requested[a]	8 (2.3)
	Not indicated	84 (24.1)
Genomic Assessment, n (%)	Actionable genomic alteration	122 (35.1)
	Wild type	82 (23.5)
	Undruggable genomic alteration	50 (14.4)
	Non assessed[b]	94 (27.0)
PD-L1 Testing, n (%)	Successfully completed	278 (79.9)
	Failed, insufficient tissue specimen	14 (4.0)
	Not requested[a]	1 (0.3)
	Not indicated	55 (15.8)
PD-L1 Tumor Proportion Score, n (%)	<1%	59 (17.0)
	1%-49%	88 (25.3)
	≥ 50%	131 (37.6)
	Not assessed[b]	70 (20.1)

[a] Patient died or was sent for palliative care.
[b] Not indicated or failed for insufficient material.

lowest in squamous cell carcinoma. Identifying SNM as a common site of metastasis has important clinical implications for the diagnostic work-up of patients with advanced lung cancer. Supraclavicular lymph nodes are easily accessible through minimally invasive ultrasound-guided biopsy, which has been shown to provide adequate tissue for both diagnosis and comprehensive molecular testing in the vast majority of patients, with minimal to no complications.[12,13,25] Despite these data, no international guideline currently recommends ultrasound assessment and biopsy of "superficial" metastasis, including SNM, in patients with lung cancer.[26-29] Our findings support the regular assessment of SNM in patients with stage IV disease, as this approach would facilitate personalized treatment approaches. This is particularly important given the challenges in obtaining sufficient tissue from primary lung tumors or deep-seated metastatic sites, as well as the costs and complications associated with advanced bronchoscopic or CT-guided biopsy.[30-33]

We identified several factors related to the T, N and M lung cancer descriptors, with a significantly higher prevalence in patients with SNM compared to those without. Intrathoracic lymph node metastases were significantly more prevalent in patients with SNM, although they were also prevalent in patients without SNM, as typically observed in stage IV disease.[34] This finding is consistent with previous studies,[20-22] and suggests that a systematic ultrasonographic examination of the supraclavicular fossa could be particularly useful in patients exhibiting hilar or mediastinal lymph node involvement on imaging. The observation of a higher prevalence of liver metastases and metastases to less common sites in patients with SNM is more difficult to interpret and requires further confirma-

Please cite this article as: Rocco Trisolini et al, Supraclavicular Lymph Node Metastases in Advanced Lung Cancer: Prevalence and Analysis of Demographic, Clinical and Molecular Characteristics, Clinical Lung Cancer, https://doi.org/10.1016/j.cllc.2025.02.003

Table 2 Key Characteristics of the T, N and M Descriptors in Patients With and Without SNM

T Descriptor, n (%)		SNM + ($n = 94$)	SNM – ($n = 254$)	*P*-Value
Location	Central	67 (71.3)	172 (67.7)	.53
	Peripheral	27 (27.7)	82 (32.3)	
Growth Pattern	Solid	88 (93.6)	224 (88.2)	.14
	Other	6 (6.4)	30 (11.8)	
N Descriptor, n (%)		**SNM + ($n = 94$)**	**SNM – ($n = 254$)**	***P*-Value**
N0	All the values cancelled in this column belong to the SNM + (n = 94) column, on the right. The present column shoulf be left blank. Please check the "word table" in the manuscript	All the values cancelled in this column belong to the SNM - (n = 254) column, on the right	All the values cancelled in this column belong to the P-value columm, on the right	
N1				
N2/3[a]				
M Descriptor, n (%)		**SNM + ($n = 94$)**	**SNM – ($n = 254$)**	***P*-Value**
Lung				
Pleura				
Brain				
Liver				
Bone				
Adrenal Gland				
"Other"[b]				

[a] N3 is referred to lymph nodes contralateral to the primary tumor in the middle mediastinum.
[b] Refers to less common metastatic sites.

Table 3 Prevalence of Main Genomic Alterations in Patients With Advanced Nonsquamous NSCLC With and Without SNM[a]

Genomic Alteration, n (%)		SNM Group ($n = 61$)	Control Group ($n = 193$)	*P*-Value
EGFR	Any mutation	9 (14.8)	21 (10.9)	.49
	Druggable mutations	6 (9.8)	15 (7.7)	.60
	Undruggable mutations	3 (4.9)	6 (3.1)	.46
KRAS	Any mutation	16 (26.2)	59 (30.9)	.49
	G12C	5 (8.2)	31 (16.2)	.14
	Undruggable mutations	11 (18.0)	28 (14.7)	.53
ALK		6 (9.8)	16 (8.4)	.73
ROS1		1 (1.6)	2 (1.1)	.57
BRAF		5 (8.2)	10 (5.3)	.37
MET		6 (9.8)	13 (6.8)	.44
RET		3 (4.9)	5 (2.9)	.44
NTRK		0 (0.0)	0 (0.0)	-
ERBB2		0 (0.0)	8 (4.2)	.21

[a] This table is applicable to the 254 patients who were indicated for cancer genotyping and had tissue specimens suitable for the analysis.

Please cite this article as: Rocco Trisolini et al, Supraclavicular Lymph Node Metastases in Advanced Lung Cancer: Prevalence and Analysis of Demographic, Clinical and Molecular Characteristics, Clinical Lung Cancer, https://doi.org/10.1016/j.cllc.2025.02.003

Figure 2 Prevalence of supraclavicular lymph node metastasis (SNM) stratified by lung cancer histotype.

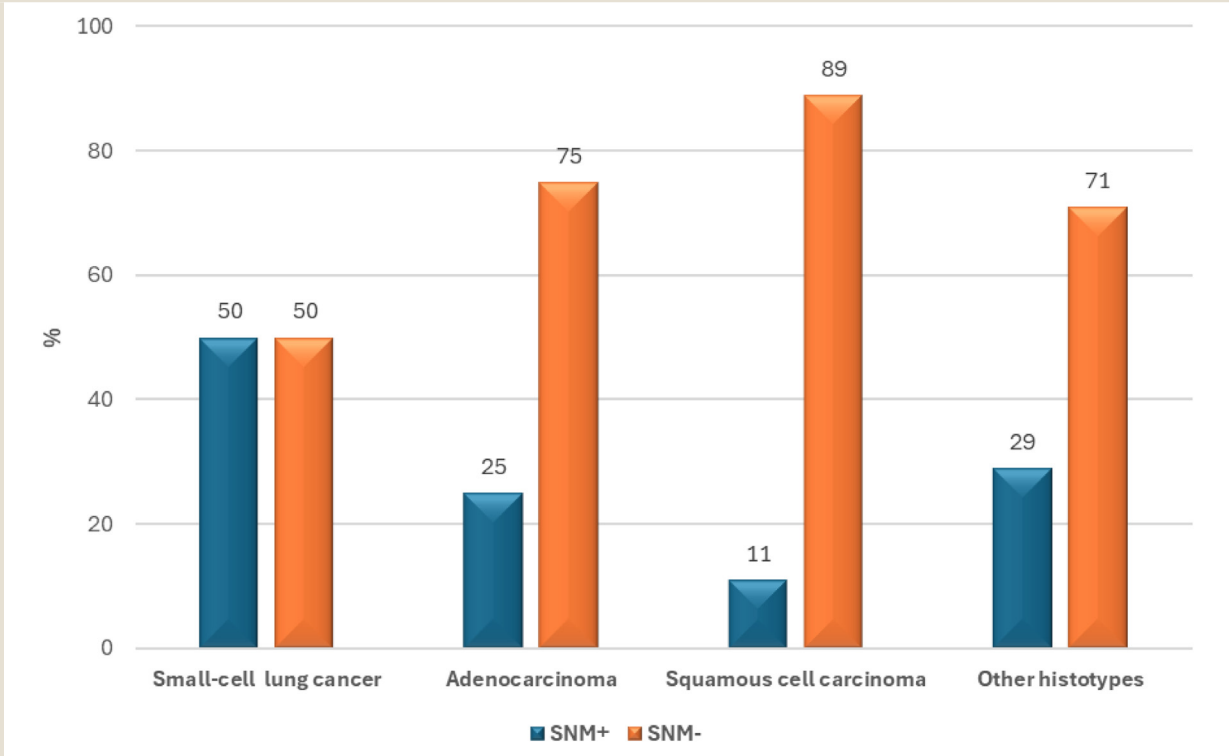


Table 4 Prevalence of PD-L1 TPS Classes in Patients With and Without CSLS Metastasis[a]

PD-L1 TPS	SNM Group ($n = 67$)	Control Group ($n = 211$)	*P*-Value
< 1%	10 (14.9)	49 (23.2)	.35
1%-49%	23 (34.3)	65 (30.8)	
> 50%	34 (50.7)	97 (46.0)	

[a] This table is applicable to the 278 patients who were indicated for PD-L1 testing and had tissue specimens suitable for the analysis.

tion. However, metastases to less common sites were independently associated with SNM, along with SCLC histology.

Evidence from the literature suggests that oncogene status may predict patterns of metastatic spread in patients with treatment-naïve NSCLC.[35-38] Contrary to our hypothesis, that was based on the results of a retrospective case-control analysis, we did not observe significant differences in the prevalence of genomic alterations, including KRAS mutations, between patients with and without SNM. This finding highlights the limitations of retrospective studies and suggests that SNM might not be directly associated with specific molecular profiles but rather reflects the overall metastatic tumor spread.

Similarly, PD-L1 expression did not differ significantly between the 2 groups. This finding is noteworthy, as conflicting and somewhat confusing results were published regarding the role of metastatic lymph nodes in evaluating PD-L1 expression and predicting response to immune checkpoint inhibitor treatment in NSCLC.[39-41] Some studies have shown that PD-L1 expression is higher in patients with lymph node metastasis.[42,43] However, there is no clear evidence that PD-L1 expression is higher in samples obtained from lymph nodes compared to those from the primary tumor or other distant metastatic sites in the same patient.[40] Although a direct comparison of PD-L1 expression levels in SNM and paired primary tumor or other distant metastatic site samples would be necessary to confirm this, the similar prevalence of PD-L1 levels in SMN compared to other biopsy sites found in the present study may indirectly suggest that SNM is a reliable indicator of PDL1 expression.

While our study provides valuable insights, it has limitations that need to be acknowledged. The study was conducted at a single institution, which may limit the generalizability of the findings to other settings or populations. Although we enrolled a substan-

Please cite this article as: Rocco Trisolini et al, Supraclavicular Lymph Node Metastases in Advanced Lung Cancer: Prevalence and Analysis of Demographic, Clinical and Molecular Characteristics, Clinical Lung Cancer, https://doi.org/10.1016/j.cllc.2025.02.003

Table 5 Logistic Regression Analysis to Assess the Relationship Between Demographic, Clinical, Molecular Characteristics, and Cervical/Supraclavicular Lymph Node Involvement

Variables		Univariate Analysis		Multivariate Analysis	
		OR (95%CI)	*P*-Value	OR (95%CI)	*P*-Value
Age, Years		1.00 (0.98-1.03)	.79	1.02 (0.99-1.04)	.21
Male Sex		0.90 (0.56-1.45)	.67	0.84 (0.50-1.42)	.51
Smoking Habit	Never	Ref.	Ref.	Ref.	Ref.
	Former	0.91 (0.43-1.93)	.80	-	-
	Current	1.64 (0.79-3.41)	.16	-	-
Histologic Subtype	Adenocarcinoma	Ref.	Ref.	Ref.	Ref.
	SQCC	0.40 (0.13-1.17)	.09	0.18 (0.04-0.77)	**.02**
	SCLC	3.07 (1.62-5.79)	.001	2.10 (1.25-5.01)	**.009**
	Other	1.28 (0.43-3.77)	.66	1.16 (0.33-4.05)	.82
Primary Tumor Location	Central	Ref.	Ref.	Ref.	Ref.
	Peripheral	0.85 (0.50-1.42)	.53	-	-
Primary Tumor Growth Pattern	Solid	Ref.	Ref.	Ref.	Ref.
	Other	0.51 (0.21-1.26)	.15	-	-
[a]Lymph Node Involvement N0 (vs N1)		0.12 (0.02-0.90)	.04	-	-
Lymph node involvement N1		4.8 (1.11-20.7)	.04	4.72 (1.04-21.53)	.05
[a]Lymph Node Involvement N2/3		8.86 (2.10-37.38)	.003	-	-
Lung Metastases		0.87 (0.54-1.42)	.60	-	-
Pleural Metastases		1.46 (0.89-2.41)	.14	-	-
Bone Metastases		1.15 (0.83-1.88)	.56	-	-
Liver Metastases		2.31 (1.33-4.05)	.003	1.77 (0.96-3.28)	.07
Adrenal Gland Metastases		1.38 (0.75-2.52)	.28	-	-
Brain Metastases		1.75 (0.99-3.09)	.05	-	-
Other Metastases		2.90 (1.65-5.08)	< .0001	3.00 (1.64-5.48)	**< .0001**
EGFR Mutation		1.42 (0.61-3.28)	.42	-	-
KRAS Mutation		0.80 (0.42-1.52)	.49	-	-
ALK Fusion		1.19 (0.45-3.20)	.73	-	-
ROS-1 Fusion		1.58 (0.15-17.68)	.71	-	-
BRAF Mutation		1.67 (0.53-4.90)	.40	-	-
RET Fusion		2.2 (0.51-9.53)	.29	-	-
MET Mutation/Amplification		1.68 (0.60-4.65)	.32	-	-
PD-L1 TPS	< 1%	Ref.	Ref.	Ref.	Ref.
	1%-49%	1.71 (0.75-3.91)	.21	-	-
	≥50%	1.7 (0.78-3.72)	.19	-	-

[a] Omitted because of collinearity. HL, *P*-value = .63.

tial number of patients, the sample size may still be insufficient to detect smaller differences in molecular characteristics between subgroups. Patients included in the study were typically referred to our Interventional Pulmonology Unit for an endoscopic biopsy; therefore, this sample may not be representative of all patients with advanced lung cancer, possibly introducing selection bias. Finally, the study did not perform a direct comparison of PD-L1 expression levels or molecular characteristics between SNM and paired primary tumor or other metastatic site samples within the same patient.

Conclusion

This study demonstrates that SNM is prevalent in patients with stage IV lung cancer, with a higher occurrence in SCLC and adenocarcinoma. Ultrasound-guided biopsy of SNM is a simple and relatively inexpensive method for obtaining adequate tissue samples for diagnosis and comprehensive molecular profiling. These findings underscore the importance of incorporating SNM assessment into the diagnostic work-up of advanced lung cancer in patients with abnormalities in the supraclavicular fossa on imaging studies (CT and/or PET).

Please cite this article as: Rocco Trisolini et al, Supraclavicular Lymph Node Metastases in Advanced Lung Cancer: Prevalence and Analysis of Demographic, Clinical and Molecular Characteristics, Clinical Lung Cancer, https://doi.org/10.1016/j.cllc.2025.02.003

Disclosure

None of the authors has financial or nonfinancial interests that are directly or indirectly related to the work submitted for publication.

CRediT authorship contribution statement

Rocco Trisolini: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. **Valeria Cetoretta:** Writing – review & editing, Supervision, Investigation, Data curation. **Giovanni Sotgiu:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Alessandra Cancellieri:** Writing – review & editing, Investigation. **Mariangela Puci:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Marta Viscuso:** Writing – review & editing, Investigation, Data curation. **Vanina Livi:** Writing – review & editing, Investigation, Data curation. **Massimiliano Cani:** Writing – review & editing, Methodology. **Giovanni Scambia:** Writing – review & editing, Supervision, Conceptualization. **Federico Cappuzzo:** Writing – review & editing, Investigation. **Emilio Bria:** Writing – review & editing, Investigation. **Silvia Novello:** Writing – review & editing, Investigation, Conceptualization.

Acknowledgments

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660.
2. GBD 2019 Respiratory Tract Cancers CollaboratorsGlobal, regional, and national burden of respiratory tract cancers and associated risk factors from 1990 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Respir Med*. 2021;9(9):1030–1049. doi:10.1016/S2213-2600(21)00164-8.
3. Reck M, Rabe KF. Precision diagnosis and treatment for advanced non-small-cell lung cancer. *N Engl J Med*. 2017;377(9):849–861. doi:10.1056/NEJMra1703413.
4. Paz-Ares L, Gondos A, Saldana D, et al. Genomic testing among patients with newly diagnosed advanced non-small cell lung cancer in the United States: a contemporary clinical practice patterns study. *Lung Cancer*. 2022;167:41–48. doi:10.1016/j.lungcan.2022.01.021.
5. Hess LM, Krein PM, Haldane D, Han Y, Sireci AN. Biomarker testing for patients with advanced/metastatic nonsquamous NSCLC in the United States of America, 2015 to 2021. *JTO Clin Res Rep*. 2022;3(6):100336. doi:10.1016/j.jtocrr.2022.100336.
6. Griesinger F, Eberhardt W, Nusch A, et al. Biomarker testing in non-small cell lung cancer in routine care: analysis of the first 3,717 patients in the German prospective, observational, nation-wide CRISP Registry (AIO-TRK-0315). *Lung Cancer*. 2021;152:174–184. doi:10.1016/j.lungcan.2020.10.012.
7. Kerr KM, Bibeau F, Thunnissen E, et al. The evolving landscape of biomarker testing for non-small cell lung cancer in Europe. *Lung Cancer.*. 2021;154:161–175. doi:10.1016/j.lungcan.2021.02.026.
8. Schilsky RL, Longo DL. Closing the gap in cancer genomic testing. *N Engl J Med*. 2022;387(23):2107–2110. doi:10.1056/NEJMp2210638.
9. Zhao JJ, Chan HP, Soon YY, Huang Y, Soo RA, Kee ACL. A systematic review and meta-analysis of the adequacy of endobronchial ultrasound transbronchial needle aspiration for next-generation sequencing in patients with non-small cell lung cancer. *Lung Cancer*. 2022;166:17–26. doi:10.1016/j.lungcan.2022.01.018.
10. Centeno C, Serra Mitja P, Avila M, et al. Molecular analysis in cytological samples obtained by endobronchial or oesophageal ultrasound guided needle aspiration in non-small cell lung cancer. *Pulmonology*. 2022;28(1):28–33. doi:10.1016/j.pulmoe.2020.05.001.
11. Stigt JA, Oostdijk AH, Boers JE, van den Berg JW, Groen HJ. Percutaneous ultrasound-guided biopsies in the evaluation of thoracic tumours after PET-CT: a prospective diagnostic study. *Respiration*. 2012;83(1):45–52. doi:10.1159/000330018.
12. Livi V, Paioli D, Cancellieri A, et al. Diagnosis and molecular profiling of lung cancer by percutaneous ultrasound-guided biopsy of superficial metastatic sites is safe and highly effective. *Respiration*. 2021;100(6):515–522. doi:10.1159/000514316.
13. Livi V, Sotgiu G, Cancellieri A, et al. Ultrasound-guided needle aspiration biopsy of superficial metastasis of lung cancer with and without rapid on-site evaluation: a randomized trial. *Cancers (Basel)*. 2022;14(20):5156. doi:10.3390/cancers14205156.
14. Kuijpers CCHJ, Hendriks LEL, Derks JL, et al. Association of molecular status and metastatic organs at diagnosis in patients with stage IV non-squamous non-small cell lung cancer. *Lung Cancer*. 2018;121:76–81. doi:10.1016/j.lungcan.2018.05.006.
15. Doebele RC, Lu X, Sumey C, et al. Oncogene status predicts patterns of metastatic spread in treatment-naive nonsmall cell lung cancer. *Cancer*. 2012;118(18):4502–4511. doi:10.1002/cncr.27409.
16. Vassallo P, Wernecke K, Roos N, Peters PE. Differentiation of benign from malignant superficial lymphadenopathy: the role of high-resolution US. *Radiology*. 1992;183(1):215–220. doi:10.1148/radiology.183.1.1549675.
17. Garcia BNC, van Kempen LC, Kuijpers CCHJ, Schuuring E, Willems SM, van der Wekken AJ. Prevalence of KRAS p.(G12C) in stage IV NSCLC patients in the Netherlands; a nation-wide retrospective cohort study. *Lung Cancer*. 2022;167:1–7. doi:10.1016/j.lungcan.2022.03.
18. Grosse A, Grosse C, Rechsteiner M, Soltermann A. Analysis of the frequency of oncogenic driver mutations and correlation with clinicopathological characteristics in patients with lung adenocarcinoma from northeastern Switzerland. *Diagn Pathol*. 2019;14(1):18. doi:10.1186/s13000-019-0789-1.
19. Lim TKH, Skoulidis F, Kerr KM, et al. KRAS G12C in advanced NSCLC: prevalence, co-mutations, and testing. *Lung Cancer*. 2023;184:107293. doi:10.1016/j.lungcan.2023.107293.
20. Prosch H, Strasser G, Sonka C, et al. Cervical ultrasound (US) and US-guided lymph node biopsy as a routine procedure for staging of lung cancer. *Ultraschall Med*. 2007;28(6):598–603. doi:10.1055/s-2007-963215.
21. El-Shaarawy B, Gharraf HS, El-Hefny A, Hassan M. Prospective study of focused neck US by Respiratory physicians in patients with pulmonary disease and intrathoracic lymphadenopathy. *Chest*. 2023;163(4):994–996. doi:10.1016/j.chest.2022.10.005.
22. Ahmed M, Daneshvar C, Breen D. Routine neck ultrasound by respiratory physicians in the diagnosis and staging of patients with lung cancer and mediastinal lymphadenopathy: a prospective pilot study. *ERJ Open Res*. 2020;6(1):00180–02019. doi:10.1183/23120541.00180-2019.
23. Kumaran M, Benamore RE, Vaidhyanath R, et al. Ultrasound guided cytological aspiration of supraclavicular lymph nodes in patients with suspected lung cancer. *Thorax*. 2005;60(3):229–233. doi:10.1136/thx.2004.029223.
24. Kendirlinan R, Ozkan G, Bayram M, et al. Ultrasound guided fine-needle aspiration biopsy of metastases in nonpalpable supraclavicular lymph nodes in lung cancer patients. *Multidiscip Respir Med*. 2011;6(4):220–225. doi:10.1186/2049-6958-6-4-220.
25. Duguay S, Wagner JM, Zheng W, et al. Ultrasound-guided needle biopsy of neck lymph nodes in patients with suspected lung cancer: are the specimens sufficient for complete pathologic evaluation to guide patient management? *Ultrasound Q*. 2017;33(2):133–138. doi:10.1097/RUQ.0000000000000270.
26. Riely GJ, Wood DE, Ettinger DS, et al. Non-small cell lung Cancer, version 4.2024. *J Natl Compr Canc Netw*. 2024;22(4):249–274. doi:10.6004/jnccn.2204.0023.
27. Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(4):339–357. doi:10.1016/j.annonc.2022.12.009.
28. Hendriks LE, Kerr KM, Menis J, et al. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(4):358–376. doi:10.1016/j.annonc.2022.12.013.
29. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.*. 2013;143(5 Suppl):e142S–e165S. doi:10.1378/chest.12-2353.
30. Magnini D, Sotgiu G, Bello G, et al. Thirty-day complications, unplanned hospital encounters, and mortality after endosonography and/or guided bronchoscopy: a prospective study. *Cancers (Basel)*. 2023;15(18):4531. doi:10.3390/cancers15184531.
31. Heerink WJ, de Bock GH, de Jonge GJ, Groen HJ, Vliegenthart R, Oudkerk M. Complication rates of CT-guided transthoracic lung biopsy: meta-analysis. *Eur Radiol*. 2017;27(1):138–148. doi:10.1007/s00330-016-4357-8.
32. Wiener RS, Schwartz LM, Woloshin S, Welch HG. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: an analysis of discharge records. *Ann Intern Med*. 2011;155(3):137–144. doi:10.7326/0003-4819-155-3-201108020-00003.
33. Chiu YW, Kao YH, Simoff MJ, et al. Costs of biopsy and complications in patients with lung cancer. *Clinicoecon Outcomes Res*. 2021;13:191–200. doi:10.2147/CEOR.S295494.
34. Lin Z, Li Y, Tang S, Deng Q, Jiang J, Zhou C. Comparative analysis of genomic profiles between tissue-based and plasma-based next-generation sequencing in patients with non-small cell lung cancer. *Lung Cancer*. 2023;182:107282. doi:10.1016/j.lungcan.2023.107282.

Please cite this article as: Rocco Trisolini et al, Supraclavicular Lymph Node Metastases in Advanced Lung Cancer: Prevalence and Analysis of Demographic, Clinical and Molecular Characteristics, Clinical Lung Cancer, https://doi.org/10.1016/j.cllc.2025.02.003

35. Kuijpers CCHJ, Hendriks LEL, Derks JL, et al. Association of molecular status and metastatic organs at diagnosis in patients with stage IV non-squamous non-small cell lung cancer. *Lung Cancer*. 2018;121:76–81. doi:10.1016/j.lungcan.2018.05.006.
36. Doebele RC, Lu X, Sumey C, et al. Oncogene status predicts patterns of metastatic spread in treatment-naive nonsmall cell lung cancer. *Cancer*. 2012;118(18):4502–4511. doi:10.1002/cncr.27409.
37. Gillespie CS, Mustafa MA, Richardson GE, et al. Genomic alterations and the incidence of brain metastases in advanced and metastatic NSCLC: a systematic review and meta-analysis. *J Thorac Oncol*. 2023;18(12):1703–1713. doi:10.1016/j.jtho.2023.06.017.
38. Mogenet A, Barlesi F, Besse B, et al. Molecular profiling of non-small-cell lung cancer patients with or without brain metastases included in the randomized SAFIR02-LUNG trial and association with intracranial outcome. *Lung Cancer*. 2022;169:31–39. doi:10.1016/j.lungcan.2022.05.004.
39. Yang H, Hall SRR, Yao F. The value of PD-L1 expression in metastatic lymph nodes of advanced non-small cell lung cancer. *Chest*. 2020;158(4):1785–1787. doi:10.1016/j.chest.2020.06.077.
40. Hong L, Negrao MV, Dibaj SS, et al. Programmed death-ligand 1 heterogeneity and its impact on benefit from immune checkpoint inhibitors in NSCLC. *J Thorac Oncol*. 2020;15(9):1449–1459. doi:10.1016/j.jtho.2020.04.026.
41. Hu Y, Zhang Y, Lu Y, et al. Heterogeneity in PD-L1 expression between primary and metastatic lymph nodes: a predictor of EGFR-TKI therapy response in non-small cell lung cancer. *Respir Res*. 2024;25(1):233. doi:10.1186/s12931-024-02858-3.
42. Zhang M, Li G, Wang Y, et al. PD-L1 expression in lung cancer and its correlation with driver mutations: a meta-analysis. *Sci Rep*. 2017;7(1):10255. doi:10.1038/s41598-017-10925-7.
43. Perrotta F, Nankivell M, Adizie JB, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for PD-L1 testing in non-small cell lung cancer. *Chest*. 2020;158(3):1230–1239. doi:10.1016/j.chest.2020.04.059.

Please cite this article as: Rocco Trisolini et al, Supraclavicular Lymph Node Metastases in Advanced Lung Cancer: Prevalence and Analysis of Demographic, Clinical and Molecular Characteristics, Clinical Lung Cancer, https://doi.org/10.1016/j.cllc.2025.02.003