Check for updates

Non–Small Cell Lung Cancer With N1 Involvement or Skip Metastases Presents the Same Survival Outcome: Results From a Multicentric Study

Marco Chiappetta,[1,2] Carolina Sassorossi,[1,2] Filippo Lococo,[1,2] Isabella Sperduti,[3] Felice Mucilli,[4] Paraskevas Lyberis,[5] GiovanniBattista Ratto,[6] Lorenzo Spaggiari,[7] Filippo Gallina,[8] Francesco Facciolo,[8] Stefano Margaritora[1,2]

Abstract

The prognostic difference among patients with lung cancer and hilar metastases or mediastinal without hilar involvement is still unclear. We compared these 2 groups of patients and we did not find survival differences. Our results suggest that these patients, despite different staging categories, present the same prognosis and may be managed in the same manner.

Background: The prognostic difference among patients affected by NSCLC with hilar metastases only or mediastinal nodes metastases without hilar involvement (skip metastases) is still unclear. Aim of this study is to analyse if prognostic difference are present or if the two groups present the same survival outcome. **Materials and Methods:** Data on NSCLC patients from 7 high volume centres (2004-2014) were collected and retrospectively reviewed. Histology different from adenocarcinoma(ADC) or squamous cell carcinoma(SCC), patients without data on lymphadenectomy, who underwent neoadjuvant treatment, with distant metastases or incomplete resection were excluded, selecting patients with hilar involvement or with skip metastases. Different prognostic factors such as Tstage, histology, pathological stage, nodal characteristics and adjuvant therapy administration were correlated to overall survival (OS) by the Kaplan–Meier product-limit method. The log-rank test was used to assess differences between subgroups. A multivariable Cox proportional hazard model was developed using stepwise regression to compare the prognostic power of different factors. **Results:** The final analysis was conducted on 480 adenocarcinoma/squamous cell carcinoma patients. Five-year OS (5YOS) resulted 53.9%. No significant differences in OS were detected comparing pN1 vs. pN2 patients or stage IIB vs. stage IIIA-B patients. Univariable confirmed as favourable prognostic factors young age ($P<.001$), T1-2 tumors ($P=.030$), number of resected nodes≥10 ($P=.040$), lymph node ratio ($P=.026$). Multivariable analysis confirmed as independent negative prognostic factors T≥3 (HR:1.385, 95%CI:1.037-1.851, $P=.027$) and age≥68 years (HR1.637, 95%CI:1.245-2.152). **Conclusion:** Patients with N1 involvement or skip metastases present a similar prognosis, suggesting that N2 involvement in these cases may be related to a direct lymphatic drainage to the mediastinal stations.

Clinical Lung Cancer, Vol. 24, No. 7, e275–e281 © 2023 The Authors. Published by Elsevier Inc.
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
Keywords: Adenocarcinoma, Lymph nodes, Squamous cell carcinoma, Surgery, Relapse

The abstract has been presented at the 34th EACTS annual meeting (October 2021, Barcelona)

[1]Università Cattolica del Sacro Cuore, Rome, Italy
[2]Thoracic Surgery, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[3]Biostatistics, IRCCS Regina Elena National Cancer Institute, Rome, Italy
[4]Department of General and Thoracic Surgery, University Hospital "SS. Annunziata", Chieti, Italy
[5]Department of Thoracic Surgery, University of Turin, San Giovanni Battista Hospital, Turin, Italy
[6]Division of Thoracic Surgery, IRCCS AOU "San Martino" IST, Genoa, Italy
[7]Thoracic Surgery Division, European Institute of Oncology, University of Milan, Milan, Italy
[8]Thoracic Surgery, Regina Elena National Cancer Institute, Rome, Italy

Submitted: Mar 29, 2023; Revised: May 17, 2023; Accepted: Jun 12, 2023; Epub: 15 June 2023

Address for correspondence: Filippo Lococo, MD, Thoracic Surgery, Fondazione Policlinico Universitario A. Gemelli IRCCS, LARGO A. Gemelli, 8, 00168, Rome, Italy
E-mail contact: filippo.lococo@policlinicogemellli.it

1525-7304/$ - see front matter © 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
https://doi.org/10.1016/j.cllc.2023.06.007

Introduction

Nodal involvement is one of the most important prognosticator in NSCLC, taken into account for prognosis stratification but also to plan the opportune therapeutic strategies.[1,2]

Indeed, in presence of mediastinal nodal involvement, a multidisciplinary approach, with the chance of different therapeutic strategies, consisting in upfront surgery plus adjuvant therapy, neoadjuvant therapy plus surgery or definitive radiochemotherapy is possible.[1-3] On the other hand, in presence of hilar involvement only, surgery remains the first therapeutic option,[1-3] considering the possibility of adjuvant treatments if needed. However, N2 categorization included a large spectrum of mediastinal involvement, ranging from bulky multistation disease to single metastatic lymph node. In particular, patients with single station involvement or without concomitant hilar metastases (pN0N2, skip metastases) seem to present a better survival rate compared to patients with N1+N2 disease or multiple N2 stations involvement.[4-7] For this reason, the International Association for the Study of Lung Cancer (IASLC) proposed a sub-classification for the N descriptors,[8] separating patients with skip metastases from other kind of N2 involvement. In particular, the proposal categorized patients with hilar involvement if single (N1a) or multiple stations (N1b) were involved, and with N2 single station involvement without (N2a1) or with (N2a2) concomitant hilar involvement. However, analysing the survival curves and comparing this group with patients with hilar involvement, no significant differences were present comparing skip metastases with N1b patients, and also other validation studies reported this limitation considering N1 and skip metastases involvement.[9-11] Moreover, even if not statistically significant, pN0N2 patients presented a slightly better survival compared to pN1 patients, and this survival benefit may be related to adjuvant therapy administration, usually indicated in pN2 patients while its administration in pN1 patients is at physician discretion after multidisciplinary evaluation.[1,2]

However, one of the possible explanation of a similar prognosis in these 2 groups of patients regards the possible lymphatic drainage of the lung, that may variate and in some cases may directly involve the mediastinal stations.[11-13] This is the same concept used in other malignancies such as breast cancer, in which the prognosis and the therapeutic decision is influenced by the lymphatic drainage and the first intercepted node.

Starting from these considerations, it is possible that the pN1 and pN0N2 patients present the same spectrum of disease and may beneficiate from the same therapeutic iter, optimizing the therapeutic pathways without differences in patient management.

Aim of this study are:

- to analyse the prognostic factors in NSCLC patients with N1 involvement or skip metastases;
- to analyse if prognostic differences are present or if the two groups present the same survival outcome.

Methods

Data on 4863 patients affected by NSCLC, who underwent surgical treatment from 01/2002 to 12/2014 among 7 institutions were collected and retrospectively analyzed.

Inclusion criteria were defined as follow:

- Adenocarcinoma or squamous cell carcinoma histology
- Complete anatomical resection (lobectomy, bilobectomy or pneumonectomy)
- Lymphadenectomy
- pN1 or pN2 single station without N1 involvement
- follow-up information

Exclusion criteria:

- Neoadjuvant treatment
- non anatomical resection
- presence of distant metastases
- incomplete pathological data

Preoperative assessment consisted in a whole-body computed tomography with contrast and 18-FDG PET-TC or brain magnetic resonance, when available and appropriate according to available guidelines.[1,2] In case of suspected N2 involvement or in patients with N1 disease, preoperative minimally invasive staging with EBUS or EUS was performed if indicated after multidisciplinary discussion, even if little differences in participated centres might be possible.

Surgery was performed by certified thoracic surgeons via thoracotomy or VATS, and consisted in anatomical resection and lymphadenectomy (sampling or radical mediastinal lymph node dissection) according to the IASLC lymph node map and ESTS guidelines,[14,15] while pathological reports were reviewed and classified according to the 8th TNM edition.[16] In case of lymph node fragmentation, lymph node parts were added to the corresponding node station for the histological analysis.

Patients were categorized according to the 8th TNM proposal as follow[8]:

- N1a: single station hilar involvement
- N1b: multiple stations hilar involvement
- N2a1: single N2 station involvement without hilar metastases.

Adjuvant therapy was indicated and administered in accordance with pathological stage, patients' clinical conditions and clinical guidelines valid during the study period, usually consisting in platinum-based therapy in association with a second chemotherapy drug according to histology and patients' clinical condition.

Despite some inter-institutional variation may be present, follow-up consisted in clinical visit, blood tests and radiological examinations (computed tomography and positron emission tomography when indicated) every 3 to 6 months after surgery for the first 2 years postoperatively and then every 6 months for 5 years.

Age, sex, pathological stage, T dimension, kind of surgery, kind of nodal involvement, number of resected nodes [#RN], number of metastatic nodes [#MN], node ratio [#MN/#RN, NR], were analysed and correlated to overall survival.

Statistical Analysis

Descriptive statistics were used to summarize pertinent study information. Overall survival was calculated by the Kaplan-Meier product-limit method from the date of the surgery until death. If a patient was not dead, survival was censored at the time of the

Table 1 Clinical and Pathological Characteristics

Variable	Number (Rate)
Sex	
Male	360 (75%)
Female	120 (25%)
Age (years)	67 (±8.6)
Histology	
Adenocarcinoma	275 (57.3%)
Squamous cell carcinoma	205 (42.7%)
Surgery	
Lobectomy	342 (71.3%)
Bilo/pneumonectomy	138 (28.7%)
Side	
Right	261 (54.4%)
Left	219 (45.6%)
pT stage	
T1	95(19.8%)
T2	253 (52.7%)
T3	110 (22.9%)
T4	22 (4.6%)
Stage	
II	292 (60.8%)
III	188 (39.2%)
8 TNM p stage	
IIB	293 (61.0%)
IIIA	166 (34.6%)
IIIB	21(4.4%)
Adjuvant therapy	
Yes	270 (56.3%)
No	166 (34.5%)
Missing	44 (9.2%)

Table 2 Lymph Node Characteristics

Variable	
Number of resected nodes (mean)	21±12.7
Number of positive nodes (mean)	2 ±1
Nodal involvement	
N1	373 (77.7%)
N2	107 (22.3%)
Number of resected nodes	
<10	94 (19.6%)
≥ 10	385 (80.2%)
Number of metastatic nodes	
Single	259(54%)
Multiple	221 (46%)
Node ratio	
≤20 %	410 (85.4%)
>20 %	70 (15.6%)
Node radio	
≤40 %	454 (94.6%)
>40 %	5.4 (5.4%)
8 pTNM subclassification	
N1a	298(62.1%)
N1b	77 (16%)
N2a1	105 (21.9%)
Number positive nodes	
<3	419 (87.3%)
>3	61 (12.7%)

last visit. The log-rank test was used to assess differences between subgroups. Significance was defined at the $P \leq .05$ level. The Hazard risk and the confidence limits were estimated for each variable using the Cox univariate model and adopting the most suitable prognostic category as referent group. A multivariate Cox proportional hazard model was also developed using stepwise regression (forward selection) with predictive variables which were significant in the univariable analyses. Enter limit and remove limit were $P = .10$ and $P = .15$ respectively.

Results

The final analysis was led on 480 patients that met the inclusion criteria. Adenocarcinoma was the predominant histology (57.3%), 373 patients resulted pN1 while 107 presented skip metastases. Clinical and pathological characteristics are reported in Table 1. The median number of resected lymph node was 19 (range 1-84) (Table 2).

Five year overall survival (5YOS) resulted 53.9%, with a median follow-up of 39 months (range 1-151)

At univariable analysis young age ($P<.001$), T1-2 tumors ($P=.030$), number of resected nodes≥10 ($P=.040$), lymph node ratio ($P=.026$) resulted significant prognostic factors (Table 3).

No differences in survival were present comparing pN1 patients with pN2a1 patients (Figure 1) ($P=.59$) and comparing stage II vs. stage III (Figure 2) ($P=.13$).

Multivariable analysis confirmed as independent negative prognostic factors T ≥ 3 (HR:1.385, 95%CI:1.037-1.851, $P=.027$), age≥68 years (HR1.637, 95%CI:1.245-2.152) (Table 3), while the NR raises the statistical significance (HR 0.670, 95%CI 0.444-1.010, $P=.056$).

In adenocarcinoma patients, no survival differences were present comparing pN1 and pN2a1 ($P= .614$), number of resected lymphnodes ($P=.161$), pStage ($P=.675$) and adjuvant therapy administration ($P= .294$), while NR resulted a significant prognostic factor, with a worse survival in case of NR≥ 20% ($P=.003$, HR:1.905;95%CI 1.243-2.919).

In SCC patients, no survival differences were present comparing pN1 and pN2a1 ($P= .093$), number of resected lymphnodes ($P=.128$), pStage ($P=.241$), adjuvant therapy administration ($P= .138$), and NR ($P=.986$), while a worse survival was present comparing multiple vs. single metastatic lymphnodes ($P=.047$, HR:1.553;95%CI:1.006-2.396).

Adjuvant therapy was administered in the 51% of pN1 patients and in the 72% of pN2 patients, without survival difference according its administration in pN1 ($P=.893$) and in pN2 ($P=.718$) patients.

Table 3 Univariable Analysis and Multivariable Analysis

Variable	UNIVARIABLE		MULTIVARIABLE	
	P Value	HR (95% C.I.)	*P* Value	HR (95% C.I.)
Sex (Male vs. female)	0.575	1.094(0.799-1.449)	-	-
Age <68 vs. > 68 years	<0.001	1.036(1.019-1.053)	0.001	1.035(1.012-1.053)
Histology (Adenocarcinoma vs. squamous cell)	0.563	1.084(0.825-1.426)	-	-
Side (right vs. left)	0.968	1.006(0.768-1.316		
Pt stage (T1-2 vs. T3-4)	0.03	1.377(1.031-1.840)	0.021	0.709(0.529-0.750)
8 TNM stage (IIB vs. IIIA-B)	0.221	1.192(0.900-1.579)	-	-
Nodal involvement (N1 vs. skip metastases)	0.596	1.090(0.792-1.500)		
Surgery (lobectomy vs. bilo/pneumonectomy)	0.875	1.092(0.697-1.710)	-	-
Number of resected nodes (<10 vs. ≥ 10)	0.04	1.388 (1.015-1.898)	0.421	1.134(0.789-1.630)
Number of metastatic nodes (single vs. multiple)	0.789	1.038(0.792-1.359)	-	-
Node ratio (≤20 % vs. > 20%)	0.026	1.488(1.048-2.115)	0.056	0.670 (0.444-1.010)
Adjuvant therapy (yes vs. no)	0.834	1.031(0.771-1.380)	-	-
8tnm subclassification	0.772		-	-
n1a ref.	-	-		
n1b	0.656	1.085(0.758-1.554)		
n2a1	0.512	1.118(0.801-1.559)		

HR: Hazard Ratio; CI: Confidence Interval.

Figure 1 Overall survival according to the kind of nodal involvement.

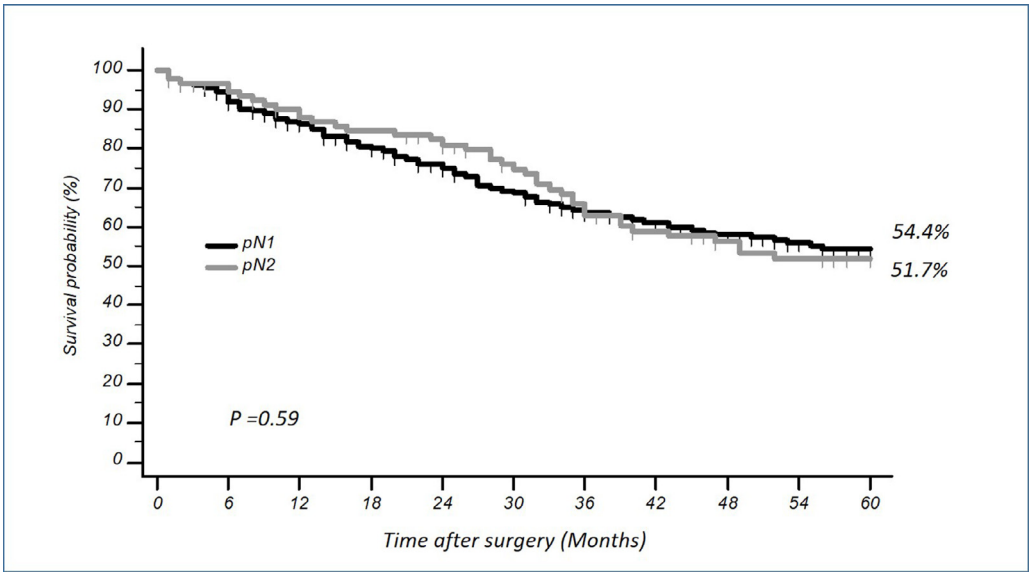
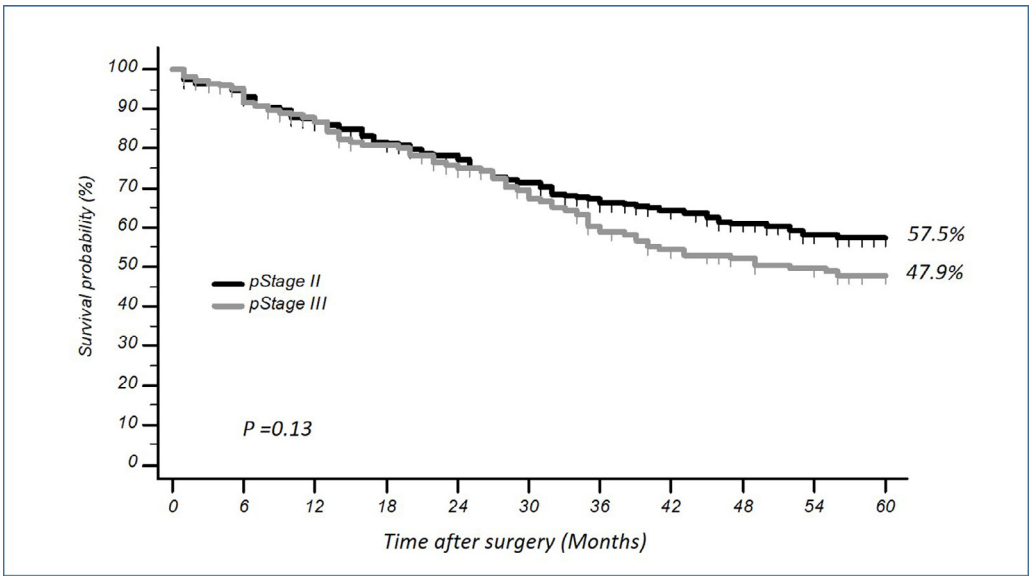


Figure 2 Overall survival according to the pathological stage.



Discussion

In this study, we investigated the possible clinical outcome of patients with pathological N1 involvement or skip metastases presence with the aim to evaluate possible differences. We found that these 2 groups of patients, inserted in 2 different stages in the TNM staging system, did not present significant survival difference. These findings seem to confirm the previous studies results reporting a similar prognosis in pN1 and pN2A1 patients,[8,9] suggesting that patients with N2 involvement with skip metastases are more similar to patients with hilar involvement than patients with mediastinal node metastases. The better prognosis of patients with skip metastases compared to other kind of N2 involvement has been established by different studies with a large number of patients,[7,17,13] such as the worse prognosis when the number of involved mediastinal stations increase.[17] Moreover, it is important to notice that patients with skip metastases seem to present a significantly better prognosis also in case of single N2 station involvement. In particular, considering adenocarcinoma patients only, Chiappetta et al. reported a significant better survival rate in patients with skip metastases compared to patients with concomitant N1 involvement in single station N2 metastases.

In this study, we also investigated the possible role of histology in defining survival difference, but our results are similar considering adenocarcinomas and squamous cell carcinomas. In particular, in both histological groups, no survival differences were present comparing kind of nodal involvement (N1 vs. N2skip) or stage (II vs. III), confirming that this kind of nodal involvements did not influence prognosis in histological subgroups.

Similarly, other studies investigated the prognosis in patients with hilar involvement compared to patients with skip metastases, with interesting but not definitive results considering possible confounding factors such as the limited number of patients or variability in adjuvant treatment administration.

In particular, Park et al.,[13] in their validation study of the TNM nodal subclassification proposal, did not find survival differences comparing N2a1 with N1a or N1b patients, while a significant difference was present comparing N2a1 with any kind of other N2 subgroup. Moreover, the authors performed additional analysis changing subgroups, showing interesting results. In a comparison between N1+N2a1 vs. N2a2 vs. N2b, there were a significant difference comparing all groups in term of recurrence free and overall survival, and identical results were present considering N1a vs. N1b+N2a vs. N2b. However, as the authors said, in this second subgroup proposal the survival advantage of N2a1 was lost.

Wang et al.[18] also confirmed the absence of survival differences comparing N1 vs. N2a1 patients, while the 3 groups presented a significantly better disease free and overall survival compared to other N2 patients. Interestingly, the authors performed a subanalysis of N1a vs. N1b vs. N2a1 patients, without significant differences in terms of disease free survival, but in overall survival terms, N1a and N2a1 presented a similar prognosis (P=.56), while N1b presented a significant worse outcome (P=.007).

Another validation study by Tsitsias et al[19] did not find any significant difference comparing N1a vs. N1b vs. N2a1, a result in line with our findings reporting a similar survival outcome comparing N1a vs. N1b and suggesting the possibility of inclusion in the same subgroup. However, in their study only 19 patients were categorized as N1b, and, despite our and other studies[19] are in agreement with their results, other investigators reported a significant difference among N1 subgroups.[8,13] However, from all these studies seems that N1 and skip metastases represent a limited nodal disease, compared to multistations nodal involvement that presented

a significant worse prognosis compared to these groups, being the spectrum of more extended disease.

These contrasting results are difficult to be interpreted, but it is evident that further studies are needed to define this issue with more information especially about tumour histology and adjuvant therapies administration.

Indeed, despite adjuvant therapy administration is indicated in any kind of N2 involvement, it should be evaluated in case of N1 involvement and should be under oncologist decision.[1,2] Moreover, in these studies, high heterogeneity in adjuvant therapy administration and protocols is evident, especially in multicentric analysis. More in detail, Li et al.[17] reported an adjuvant therapy administration rate of about 42% in both N2 and N1 patients and did not consider it in survival analysis. Similarly Tsitsias[19] reported an adjuvant therapy administration rate of 50% but a with a significant survival improvement in these patients. By the way, a subgroup analysis not reported for N1, N2a1 or other N2 patients.

On the other hand, in other studies the adjuvant therapy administration presented higher rate, with the 80% in the study of Park et al.,[13] and 86% in the study of Wang,[18] including any kind of N2 involvement and with data on its prognostic role only in dr Wang study.

In our study, adjuvant therapy was administered in the 56% of patients, in the 72% of N2 patients compared to the 51% of N1, confirming this heterogeneity and the difficulties to evaluate its impact on survival in these groups of patients.

However, the basis of this similar outcome in patients with skip metastases and N1 involvement may be explained accepting the first intercepted lymph node theory. Indeed, it is quite clear on anatomical studies that lung lymphatic drainage may be variable, and some lung portion may directly drain to mediastinal stations in a variable rate from the 10 to the 20%.[11-13] Moreover, different studies on skip metastases revealed the increase of this phenomenon in association with peculiar characteristics. Gorai et al,[20] investigating the risk factors for skip metastases in cIA NSCLC, founded out that the level of visceral pleural invasion resulted and independent risk factor for skip metastases occurrence. Based on this finding, the authors suggested that in these patients a radical mediastinal node dissection may be opportune. It is interesting to notice that visceral pleural invasion is difficult to assess preoperatively and in many cases also intraoperatively, but lymphadenectomy may be adapted according to intraoperative findings also in small peripheral nodules when pleural retraction is detected.

Another point to underline regarded the anatomical tumour location that may favour the skip metastases development instead the firs drainage to hilar stations. Despite this topic is far to be definitively defined, different studies reported an increase skip rate in right side tumour,[13,21] and Li et al.[17] reported a significant increased rate of skip in right lung tumors while left lower lobe tumors presented a significant lower skip rate.

In consideration of the topic reported, seems quite clear to considered skip metastases as nodal metastases in the first intercepted station, such as happen in N1 patients in those the lymphatic drainage follows a standard anatomical way.

For this reason, patients with skip metastases may be challenging to be treated especially regarding the adjuvant therapy administration. Indeed, only few studies analysed in depth the clinical characteristics of patients undergone adjuvant therapy for skip metastases. In particular, Chiappetta et al.[6] evaluated the effect of adjuvant therapy according to number of involved nodes, reporting a significant survival advantage in case of multiple nodal metastases, while no difference were present in case of single metastatic node. In the present study, considering only N1 and N2a1 involvement, adjuvant therapy did not influence survival in the entire cohort but also considering histological subgroups, strengthening the hypothesis that these two groups of patients presented an extremely similar disease, even if large prospective ad hoc studies are needed to confirm this hypothesis.

Moreover, in recent years different studies are investigating the neo-adjuvant therapy role also in stage II, and will be interesting to test if neoadjuvant therapy, and in particular neo-adjuvant immuno or target therapy will ensure a higher survival rate compared to adjuvant therapy in these peculiar group of patients.[21–23]

This study presents some limitation, due to its retrospective nature and due to the involvement of different institutions. Indeed, despite only high volume centres for lung cancer treatment have been included with similar pre-, intra and postoperative patients management, a intercentre variability could not be excluded. In particular, differences among adjuvant protocols and indication may variate among centres, but the main aim of the study was to evaluate the survival outcome in N1 and N2a1 patients and not to evaluate the adjuvant treatment role. Moreover, especially for N1 patients, a "case by case decision" for adjuvant therapy is present due to the contrast survival results or the low survival advantage when it is administered.[1-3] Another limitation regards the absence of information about histological subtypes or molecular characterization, which is now important to plan tailored therapeutic strategy in terms of follow up and treatments. Unfortunately, for the retrospective and multicentric nature of the study, we did not have and it is not possible to recover this information. However, the aim of our study was mainly focused on the prognosis of 2 different subgroups of patients, with N1 or skip metastases, to verify the possible same prognostic group inclusion. We think that further ad hoc studies will permit a better prognosis definition among these subgroups also based on histological and molecular characterization.

Another limitation regards the intraoperative lymph node dissection, that was under surgeon discretion and may present variability among the different centres. For this study, we involved centres with large experience on lymphadenectomy and that follow the ESTS guidelines and definition. Despite this, we did not have information if a systematic sampling or a lymphadenectomy was performed for each patients, so we did not consider the kind of lymphadenectomy but only objective data such as the number of resected nodes or stations. The effectiveness of the nodal assessment should be proven by the high number of resected nodes, that is one of the strengths of this study: more than 20 harvested nodes with the 80% of patients that had more than 10% of resected nodes. Moreover, it is important to notice that the high median number of resected nodes and the similar survival of N1 and N2a1 patients may reasonably exclude the risk of undetected other nodal metastases. This result should balance also the possible variability in terms of preoperative nodal sampling performed during bronchoscopy. Indeed, no information

were available regarding the number of investigated nodal stations, and also considering the intercentre variability, we included only information regarding the pathological nodal stage. On the other hand, the extent of lymphadenectomy and the number of patients are the major strength of this study.

Conclusion

In this large multicentre cohort, patients with hilar involvement or skip metastases presented the same survival outcome, suggesting that it was the same stage of disease. This result suggests a similar subgroup inclusion and patient management.

Clinical Practice Points

- Patients with N1 or skip metastases were categorized in different stage subgroup in 8th edition of the TNM staging system. This subgroup division presents some limitations, with survival curves that presented a better or same overall survival in skip metastases patients compared to N1 subgroups.
- We conducted an analysis comparing this 2 groups of patients and we did not found significant difference in terms of survival rate. Our results may confirm the hypothesis of the first intercepted nodes, and that skip metastases are due to the direct lymphatic drainage to mediastinal stations, by-passing hilar nodes.
- For this reason, patients with skip metastases may be included in the same stage of patients with hilar involvement. Moreover, these patients may be managed as N1 patients, discussing on not only the surgical indication in case of N2 disease, but also the needed of adjuvant therapy in postoperative. However, further prospective studies may clarify the effective role of adjuvant therapy in patients with N1 or N2 skip disease, assessing the best treatment strategy in this peculiar group of patients.

Disclosure

None declared by all the authors.

References

1. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.*. 2017;28:iv1–iv21.
2. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
3. Ramnath N, Dilling TJ, Harris LJ, et al. Treatment of stage III non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143:e314S–e340S D) Li H, et al. Lung adenocarcinoma: are skip N2 metastases different from nonskip? J Thorac Cardiovasc Surg 2015;150:790e5.
4. Gunluoglu Z, et al. The prognostic significance of skip mediastinal lymphatic metastasis in resected non-small cell lung cancer. *Eur J Cardiothorac Surg Off J Eur. Assoc Cardiothorac Surg*. 2002;21:595.
5. Riquet M, et al. Skip mediastinal lymph node metastasis and lung cancer: a particular N2 subgroup with a better prognosis. *Ann Thorac Surg*. 2005;79:225e33.
6. Chiappetta M, Lococo F, Leuzzi G, et al. Survival analysis in single N2 station lung adenocarcinoma: the prognostic role of involved lymph nodes and adjuvant therapy. Cancers (Basel). 2021;13:1326. doi:10.3390/cancers13061326.
7. Asamura H, Chansky K, Crowley J, et al. The international association for the study of lung cancer lung cancer staging project: proposals for the revision of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncology*. 2015;10:1675–1684.
8. Chiappetta M, Lococo F, Leuzzi G, et al. External validation of the N descriptor in the proposed tumour-node-metastasis subclassification for lung cancer: the crucial role of istological type, number of resected nodes and adjuvant therapy. *Eur J Cardiothorac Surg*. 2020;58:1236–1244. doi:10.1093/ejcts/ezaa215.
9. Katsumata S, Aokage K, Ishii G, et al. Prognostic impact of the number of metastatic lymph nodes on the eighth edition of the TNM classification of NSCLC. *J Thorac Oncol*. 2019;14:1408–1418. doi:10.1016/j.jtho.2019.04.016.
10. Legras A, Mordant P, Arame A, et al. Long-term survival of patients with pN2 lung cancer according to the pattern of lymphatic spread. *Ann Thorac Surg*. 2014;97:1156–1162. doi:10.1016/j.athoracsur.2013.12.047.
11. Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P. Members of IASLC Staging Committee The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2009;4:568–577.
12. Riquet M, Hidden G, Debesse B. Direct lymphatic drainage of lung segments to the medi-astinal nodes. An anatomic study on 260 adults. *J Thorac Cardiovasc Surg*. 1989;97:623–632.
13. Park BJ, Kim TH, Shin S. Recommended change in the N descriptor proposed by the international association for the study of lung cancer: a validation study. *J Thorac Oncol*. 2019;14:1962–1969. doi:10.1016/j.jtho.2019.07.034.
14. Lardinois D, De Leyn P, Van Schil P, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. *Eur J Cardiothorac Surg*. 2006;30:787–792.
15. Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in theforth-coming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11:39–51. doi:10.1016/j.jtho.2015.09.009.
16. Li X, Li X, Fu X, et al. Survival benefit of skip metastases in surgically resected N2 non-small cell lung cancer: a multicenter observational study of a large cohort of the Chinese patients. *Eur J Surg Oncol*. 2020;46(10 Pt A):1874–1881. doi:10.1016/j.ejso.2019.12.015.
17. Li H, Hu H, Wang R, et al. Lung adenocarcinoma: are skip N2 metastases different from non-skip? *J Thorac Cardiovasc Surg*. 2015;150:790–795. doi:10.1016/j.jtcvs.2015.03.067.
18. Wang L, Ye G, Xue L. Skip N2 metastasis in pulmonary adenocarcinoma: good prognosis similar to N1 disease. *Clin Lung Cancer*. 2020;21:e423–e434. doi:10.1016/j.cllc.2020.02.027.
19. Tsitsias T, Okiror L, Veres L, et al. New N1/N2 classification and lobe specific lymphatic drainage: Impact on survival in patients with non-small cell lung cancer treated with surgery. *Lung Cancer*. 2021;151:84–90. doi:10.1016/j.lungcan.2020.11.005.
20. Gorai A, Sakao Y, Kuroda H, et al. The clinicopathological features associated with skip N2 metastases in patients with clinical stage IA non-small-cell lung cancer. *Eur J Cardiothorac Surg*. 2015;47:653–658. doi:10.1093/ejcts/ezu244.
21. Ilic N, Petricevic A, Arar D, et al. Skip mediastinal nodal metastases in the IIIa/N2 non-small cell lung cancer. *J Thorac Oncol*. 2007;2:1018–1021.
22. Heymach JV, Mitsudomi T, Harpole D, et al. Design and rationale for a phase III, double-blind, placebo-controlled study of neoadjuvant durvalumab + chemotherapy followed by adjuvant durvalumab for the treatment of patients with resectable stages II and III non-small-cell lung cancer: the AEGEAN trial. *Clin Lung Cancer*. 2022;23:e247–e251. doi:10.1016/j.cllc.2021.09.010.
23. Yan W, Zhong WZ, Liu YH, et al. Adebrelimab (SHR-1316) in combination with chemotherapy as perioperative treatment in patients with resectable stage II to III NSCLCs: an open-label, multicenter, phase 1b trial. *J Thorac Oncol*. 2023;18:194–203. doi:10.1016/j.jtho.2022.09.222.