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Prognostic relevance of regional lymph-node distribution in patients with N1-positive non-small cell lung cancer: A retrospective single-center analysis

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ABSTRACT

Objective: Lymph node (LN) metastases predict survival in patients with non-small cell lung cancer (NSCLC) treated with curative surgery. Nevertheless, prognostic differences within the same nodal (N) status have been reported. Consequently, the International Association for the Study of Lung Cancer (IASLC) proposed to stratify patients with limited nodal disease (pN1) from low (pN1a) to high (pN1b) nodal tumor burden. This study aimed to validate the IASLC proposal in a large single-center surgical cohort of patients with pN1 NSCLC.

Material and Methods: Data from 317 patients with pN1 NSCLC treated between January 2012 and December 2016, were retrospectively analyzed. Associations between distribution of LN metastases and survival were analyzed for different classification models—toward nodal extension (pN1a: one station involved; pN1b: multiple stations involved) and toward location (pN1 in the hilar [LN#10/11] or peripheral zone [LN#12-14]).

Results: Tumor-specific survival (TSS) in the entire pN1 cohort was 67.1% at five years. Five-year TSS rates for pN1a and pN1b patients were comparable (67.6% vs. 66.5%, $p = 0.623$). Significant survival differences from pN1a to pN1b were observed only in patients with adenocarcinoma histology and completed adjuvant chemotherapy (5-year TSS: pN1a, 80.4% vs. pN1b, 49.6%; $p = 0.005$). TSS for LN metastases in the hilar zone/peripheral zone or in both zones was 68.2% and 59.9%, respectively ($p = 0.068$). In multivariate analysis, adjuvant chemotherapy, squamous cell histology, and nodal disease limited to one zone nodal disease were identified as independent beneficial prognostic factors ($p < 0.05$).

Conclusion: pN1 in only one region (hilar or lobar) was associated with better outcome than metastatic affection of both regions after surgery and adjuvant therapy. A stratification towards single (pN1a) and multiple (pN1b) N1-metastases was found of prognostic relevance only in adenocarcinoma. Prospective multicenter analysis of prognostic subgroups in N1 NSCLC is required to evaluate its clinical impact for consideration in future TNM classification.

1. Introduction

Lung cancer is one of the leading causes of death worldwide [1]. Approximately 80% of lung cancer patients are consistent with non-small cell histology (NSCLC) [2]. The Tumor-Node-Metastasis (TNM) system is used to classify and stratify patients by prognosis according to tumor size (T), lymph node (LN) involvement (N) and presence of distant metastases (M). Its actual valid 8th edition was implemented in 2016 using clinical information from 70,976 consecutive NSCLC patients treated between 1999 and 2010 in 16 countries [3]. In patients with limited thoracic disease (non-stage IV), nodal metastases have been repeatedly identified as a strong prognostic predictor [4,5]. The N descriptor describes the extent of LN metastases and comprises three categories: N1 (ipsilateral hilar or ipsilateral lobar LN metastases); N2 (ipsilateral mediastinal LN metastases; subcarinal LN metastases); and N3 (contralateral hilar or mediastinal LN metastases; supraclavicular LN metastases).

For N1-positive NSCLC, radical surgical treatment followed by adjuvant chemotherapy is recommended [6–9]. Tumor resection (at least lobectomy) is accompanied by radical LN compartment dissection to enable precise nodal staging and to plan stage-dependent adjuvant treatment, thus improving survival [10–12]. Resected intra-thoracic LNs are consecutively numbered following a commonly used LN mapping system that was introduced by Mountain and Dresler (M-D map) in 1997 and modified in 2009 [13].

To analyze possible prognostic differences within the same N1

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category, the IASLC nodal map distinguishes N1 nodes more precisely into a hilar/interlobar zone (M-D map: levels 10/11), and a peripheral zone (M-D map levels 12–14) [14]. The clinical relevance of further sub-classification has been noted by several authors who found a worsening prognosis from peripheral N1 (levels 12–14) to more centrally affected N1 LN metastases (levels 10/11) [15,16].

The prognostic value of a more detailed subclassification of the N1 descriptor has been recently discussed by the IASLC in a proposal addressing the implementation of the revised 8th TNM-edition for NSCLC. The adjusted pN1 cohort from the IASLC database comprises data from 3554 patients with completely resected NSCLC. A better outcome was demonstrated for patients with N1 metastases in only a single level (pN1a) compared with multiple-level N1 (pN1b) [17]. No precise information is available regarding histology, extent of tumor resection (lobar/sublobar), and adjuvant (chemo) therapy. Moreover, European data (applicable data only from Norway and Serbia) accounts for only 15% of all analyzed N1 patients (n = 544).

The aim of our study, therefore, was to validate the different N1 subclassification systems proposed by the IASLC in a large European cohort of pN1 patients. All patients underwent curative intent lung cancer surgery in a single high-volume thoracic center in Germany (Thoraxklinik Heidelberg, Heidelberg University, Heidelberg, Germany). Associations between the distribution of pN1 LN-metastases and survival were analyzed and compared with existing data.

2. Material and methods

Data from 484 consecutive surgical patients with pN1 NSCLC, who were treated at the authors' institution between January 2010 and December 2016, were retrospectively reviewed. Patients treated with neoadjuvant therapy and those who underwent only sublobar or incomplete tumor resections were excluded. Furthermore, patients with a histology other than adenocarcinoma or squamous-cell carcinoma, and those who died independent of tumor progression within 90 days after surgery were also excluded. Ultimately, 317 patients were eligible for further analysis.

Preoperative standard workup in all patients included cardiopulmonary function tests according to individual risk profiles. All patients underwent rigid tracheobronchoscopy for endoscopic evaluation. Distant metastases were ruled out using abdominal, bone, and brain sectional imaging, and, in more recent cases by PET-CT. Endobronchial ultrasound and transbronchial needle aspiration were routinely used for invasive mediastinal nodal staging. Inconclusive results (especially in N2 compartment) were reevaluated by surgical standard mediastinoscopy upfront surgery. Tumor staging of all patients was performed following the 7th edition of the TNM-classification system, which was valid during the complete treatment period. All patients were discussed in the authors' multidisciplinary tumor board. Surgical procedures included anatomical resections depending on tumor extent (such as lobectomy, bilobectomy, and pneumonectomy). Systematic radical compartment dissection of mediastinal (N2) and hilar/interlobar LNs (N1) was an integral part of each procedure.

2.1. LN assessment

All dissected intrathoracic LNs were primary allocated to hilar (#10), interlobar (#11), and lobar (#12-14) compartments according to the M—D map (for non-Asian patients) [13]. Retrospectively, metastatic nodes were classified into potential prognostic subgroups:

- Classification by nodal tumor burden: subdivision to pN1a (only one compartment involved) and pN1b (more than one compartment involved) according to the most recent IASLC proposal [17].
- Classification by location of metastatic node: Assignment to hilar zone (nodes #10, #11) and peripheral zone (nodes #12-14) as defined in the IASLC map [14].

2.2. Staging, adjuvant therapy and follow-up

All tumors were classified according to the 7th TNM-edition that was valid at time of diagnosis. Restaging of all tumors towards the recent 8th edition was internally performed in order to evaluate associated changes of prognostic factors. Nevertheless, survival data was calculated following the 7th edition in order to avoid a mismatch between the date of treatment decision and validity of the connected TNM-edition. All patients were discussed in the multidisciplinary tumor board for adjuvant therapy before discharge. According to postoperative recovery, constitution, and risk profile, all patients were recommended to undergo 4 cycles of adjuvant platinum-based doublet chemotherapy. Follow-up visits were scheduled at the outpatient service every 3 months. Recurrence of disease resulted in whole-body restaging and interdisciplinary discussion. Suspicious recurrent lesions were further classified according to their localization (intrathoracic only, distant only, or multiple).

2.3. Survival analysis

Tumor specific survival (TSS) was defined as the time from the date of surgery to the date of tumor-related death or last follow-up in censored, alive patients. Disease-free survival (DFS) was defined as the date of surgery to the date of first detection of recurrence. To analyze prognostic differences within pN1 patients undergoing standard postoperative therapy, univariate survival calculation focused on patients who underwent complete adjuvant chemotherapy.

Data were collected and analyzed using SPSS version 25 (IBM Corporation, Armonk, NY, USA). Cumulative survival was calculated using the Kaplan-Meier product method, while the log rank-test was used to calculate univariate differences, and the Cox-regression model for multivariate analysis. Differences with $p < 0.05$ were considered to be statistically significant.

3. Results

3.1. Patient characteristics

Data from 317 patients (102 females [32.2%]), with a mean (± SD) age of 64.9 ± 9.7 years were retrospectively analyzed. The majority of tumors were upper lobe tumors (n = 191 [60.3%]), solely located on the right (n = 171 [53.9%]). Lobectomies were performed in 207 (65.3%) patients, pneumonectomies in 89 (28.1%), and bilobectomies in 21 (6.6%). Extensions to bronchial sleeve resections were performed in 52 (16.4%) patients. T-stage was pT1 in 32 (10.1%) patients, pT2 in 150 (47.3%), pT3 in 90 (28.4%), and pT4 in 45 (14.2%). Moreover, 182 (57.4%) patients were classified as stages IIA/B and 135 (42.6%) patients were classified as stage IIIA. There were 170 (53.6%) squamous cell carcinomas and 147 (46.4%) adenocarcinomas. The major predominant adenocarcinoma subtypes were as follows: solid (n = 51 [34.7%]), acinar (n = 42 [28.6%]), and papillary (n = 31 [21.1%]) (Table 1).

3.2. LN assessment

At initial clinical staging, 105 patients were classified cN0 and 43 patients were classified cN2. cN1 was stated in 169 patients (53.3%). Thus, nodal upstaging (cN0 but pN1) was observed in 33.1%, downstaging (cN2 but pN1) in 13.6%.

Pathological N1a status (one compartment involved) was found in 207 (65.3%) patients and pN1b (more than one compartment involved) in 110 (34.7%). Of all 207 pN1a patients, 41 (12.9%) exhibited metastases in LN #10, 52 (16.4%) in LN #11, and 114 (36.0%) in LNs #12/13/14. Following IASLC zonal classification, nodal metastases were located exclusively in the hilar (# 10/11) or peripheral zone (#12,13,14) in 93 (29.3%) and 149 (47.0%) patients, respectively. N1

Table 1
Patient characteristics.

	n (%)
No. of patients	**317 (100)**
Gender	
Male	215 (67.8)
Female	102 (32.2)
Age, years: mean (range)	**64.9 (40-89)**
Surgical procedure	
Lobectomy	207 (65.3)
Bilobectomy	21 (6.6)
Pneumonectomy	89 (28.1)
T-Status	
pT1a/b	32 (10.1)
pT2a/b	150 (47.3)
pT3	90 (28.4)
pT4	45 (14.2)
Tumor Stage (UICC 7)	
Stages IIA/IIB	182 (57.4)
Stage IIIA	135 (42.6)
Tumor Stage (UICC 8)	
Stage IIB	138 (43.5)
Stage IIIA	179 (56.6)
Nodal subdivision (stations involved)	
pN1a (one station involved)	207 (65.3)
pN1b (multiple stations involved)	110 (34.7)
Nodal subdivision (distribution to zones)	
Hilar zone only (nodes #10/11)	93 (29.3)
Peripheral zone only (nodes #12-14)	149 (47.0)
Both zones involved	75 (23.7)
Histology	
Squamous cell carcinoma	170 (53.6)
Adenocarcinoma	147 (46.4)
Adjuvant chemotherapy	
Yes	198 (62.4)
No	119 (37.5)
Recurrence at Follow up	
No recurrence	197 (62.1)
Local intrathoracic	31 of 120
Single distant	70 of 120
Multiple	19 of 120
Tumor-specific survival (1-/ 3-/ 5-year)	**90.5%/73.4%/67.1%**
Squamous cell carcinoma	**90.8/75.0%/69.8%**
Adenocarcinoma	**89.4/71.6%/63.9%**
Disease free survival (5-year)	**56.4%**

metastases in both hilar and peripheral zones were found in 75 (23.7%) patients.

3.3. Adjuvant treatment and tumor recurrence

A total of 198 (62.4%) patients underwent adjuvant platinum-based chemotherapy. In 119 (37.5%) patients, adjuvant chemotherapy was not administered. Reasons included comorbidity or questionable evidence with regard to patient age (n = 87 [73.1%]), patient refusal (n = 27 [22.6%]), or progressive disease in the meantime (n = 5 [4.2%]). At the time of last analysis (January 2019), 197 patients (62.1%) were free of recurrence. The calculated DFS at five years was 56.4%. Tumor recurrence was detected in 120 (37.9%) patients, 70 of whom developed distant metastases.

3.4. Long-term survival and prognostic factors

Of the 317 patients, 217 (68.5%) were alive in January 2019 after a median follow up of 35 months. The TSS rate at 5 years was 67.1% (Fig. 1). According to T-category, five-year TSS was 91% for T1, 74% for T2, 53% for T3, and 57% for T4 tumors. These differences were statistically significant (i.e., $p < 0.05$), except for the comparison of T1 and T2 ($p = 0.075$). Comparison of clinical and pathological nodal status revealed no prognostic benefit for incidental finding of N1 (cN0 but pN1 vs. cN1 and pN1, 62.3% vs. 72.1% at five years, $p = 0.277$).

Conclusively, stages IIA/IIB (T1N1/T2N1) were associated with significantly better survival than stage IIIA (T3N1/T4N1) (76.6% vs. 53.8%, respectively; $p = 0.001$) (Fig. 2). Squamous cell carcinoma was associated with a slightly higher survival rate at five years (70%) than adenocarcinoma (64%); however, the difference was not statistically significant ($p = 0.35$). Survival significantly improved in N1 patients who underwent adjuvant chemotherapy (TSS 72% vs. 57% at 5 years; $p = 0.003$).

Comparable survival was observed when all 317 N1 patients were separated into N1a and N1b groups (5-year TSS 67.6% vs. 66.5%; $p = 0.623$).

In univariate subgroup analysis of patients treated with adjuvant chemotherapy, survival differences (comparing pN1a with pN1b) were found only in patients with adenocarcinoma histology (5-year TSS 80.4% [pN1a] vs. 49.6% [pN1b]; $p = 0.005$) (Fig. 3), not in those with squamous cell carcinoma (5-year TSS 69.6% [pN1a] vs. 79.7% [pN1b]; $p = 0.58$). For patients who did not undergo adjuvant therapy, stratification according to the pN1a/pN1b model appeared to have no prognostic impact (adenocarcinoma: 5-year TSS, 47.9% [pN1a] vs. 56.4% [pN1b], $p = 0.82$; squamous cell carcinoma: 5-year TSS, 62.2% [pN1a] vs. 69.1 [pN1b], $p = 0.96$).

Following a location based nodal subgrouping (only hilar zone or peripheral zone), no prognostic difference in between these two groups was observed (74.2% vs. 69.5% at five years $p = 0.849$). Patients with metastases in both the hilar and peripheral zone demonstrated a trend toward poorer survival than those with only one zone affected (hilar or peripheral zone only: 68.2%; both zones: 59.9%, $p = 0.068$) (Fig. 4A). Univariate analysis according to histological subtype revealed that this classification model (toward zones) had a significant influence on survival in patients with adenocarcinoma ($p = 0.001$) but not in those with squamous cell carcinoma ($p = 0.806$) (Fig. 4B and C).

Multivariate analysis of pN1-patients showed that adenocarcinoma histology, high tumor stage, high nodal burden (affection of hilar and peripheral zone) and absence of adjuvant chemotherapy were associated with worse survival compared to the comparators (Table 2). Classification following the pN1a/pN1b model had no significant prognostic impact in multivariate analysis, nevertheless a trend towards better survival for patients with single metastases (pN1a) was observed.

4. Discussion

A total of 317 patients with N1-positive NSCLC, who underwent curative intent surgical therapy, were retrospectively analyzed. Involvement of multiple nodal locations (pN1b) and advanced regional nodal extension (i.e., LN metastases in the central hilar and peripheral zone) were associated with poor prognosis in patients with adenocarcinoma histology.

The individual course of disease in patients with non-metastatic cancer is strongly determined by the presence of LN metastases, reflected in different N descriptors in the TNM-staging system [14]. Nevertheless, prognostic differences have been described within patients stratified according to the same N category [18]. Saji et al. analyzed 689 surgical patients and identified a low number of nodal metastases (1–3 LN metastases) as a beneficial prognostic factor. Moreover, > 4 LN metastases in the N1 compartment was associated with even poorer survival than limited (1–3 LN metastases) pN2-stage. However, only 91 pN1 patients were analyzed [19]. Analysis of the IASLC pN1 cohort also revealed a decrease in survival the more metastatic N1-nodes exist. The authors, therefore, proposed to subdivide pN1 positive NSCLC patients into pN1a (a single station involved, 58% alive at 5 years) and pN1b (multiple stations involved, 50% alive at 5 years) in future TNM-classifications [17]. Analysis of our patients confirmed differences in survival between patients with pN1a and pN1b LN involvement; nevertheless, these were statistically significant only in those with adenocarcinoma histology.

Comparing global data in terms of prognostic relevance of nodal

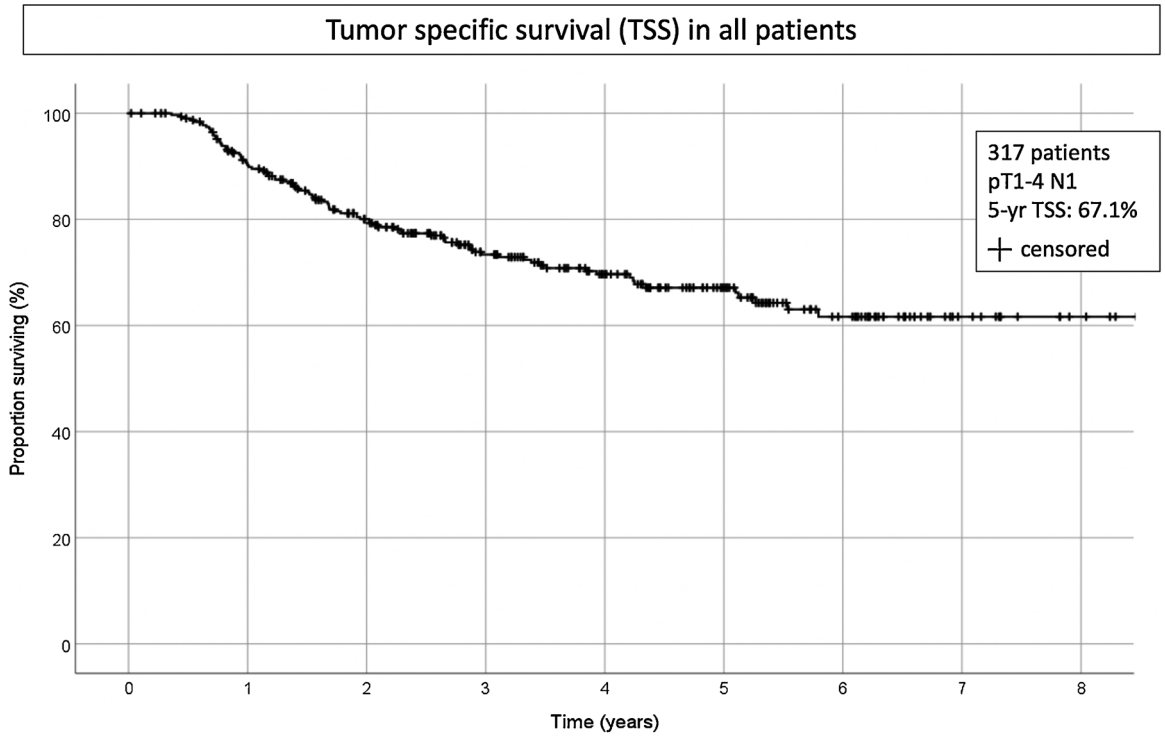

Fig. 1. Tumor specific survival at 5 years was 67.1% for the entire cohort (317 patients, incomplete and sublobar resections excluded; histology other than squamous-cell carcinoma or adenocarcinoma excluded). TSS: Tumor specific survival.

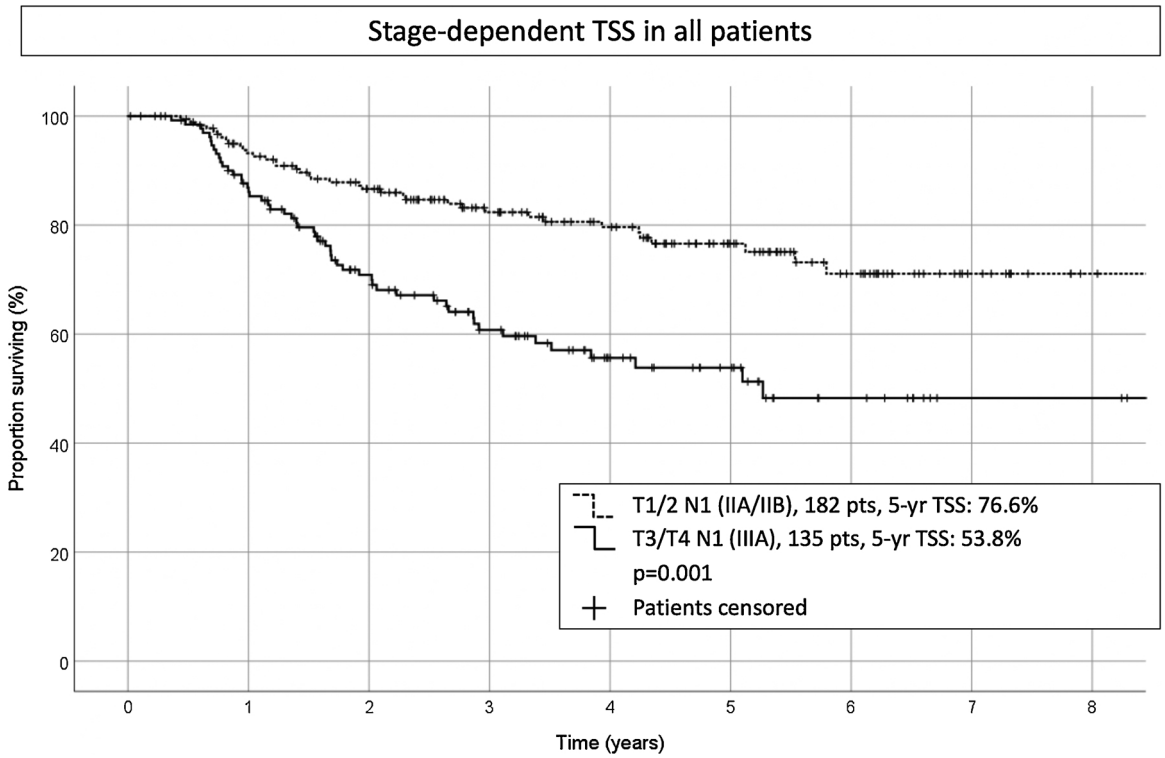

Fig. 2. Tumor stage was clearly identified as an independent factor with influence on survival irrespective of tumor histology and adjuvant therapy. Survival was significantly worse in more advanced disease (stage IIIA vs. IIA/B, p = 0.001). TSS: Tumor specific survival.

metastatic patterns, it is important to note that LN staging varies between Asia and western/European countries. Discrepancies among the "Naruke" map (Asia) [20] and the "Mountain-Dresler" modification (rest of the world) [13] harden consistent allocation to N1- and N2-level compartments (e.g., inferior border of the main stem bronchus: Naruke: N1, Mountain-Dresler: N2). These variations may explain the striking deviation of 5-year survival rates in European (36%) and Asian patients (61%) found in the IASLC database. Moreover, European information is under-represented, with only 544 pN1 patients from Norway and Serbia analyzed. In contrast, pN1 data from 2496 Asian patients, representing

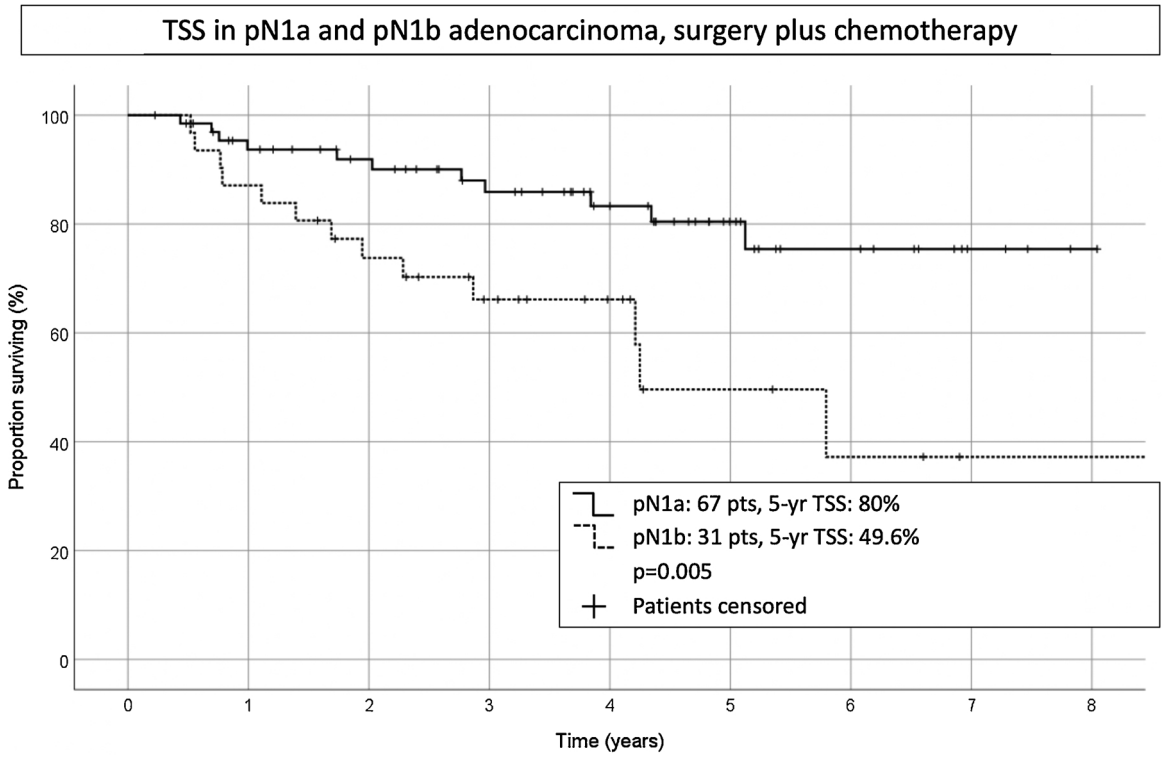

Fig. 3. Dividing pN1-patients into pN1a and pN1b was found to have prognostic impact in one subgroup of our patients: significant difference in survival could be demonstrated in patients with adenocarcinoma histology and complete adjuvant chemotherapy. TSS: Tumor specific survival.

65% of all worldwide pN1-patients, were found to be eligible for evaluation [17].

We believe that our analysis can serve as an important addition to the existing data. All pN1-patients in our series were classified according to the M—D system, in which the observed TSS of the entire group was 67.1% at 5 years. Interestingly, five-year survival in patients without adjuvant therapy was still calculated to be 57%, which is > 20% higher than the reported survival rate of the European IASLC cohort, reaching 36%. The observed discrepancy in the survival rates is difficult to explain. The large data set and its retrospective characteristics may result in incomprehensible information regarding the adjuvant therapy regimen. Furthermore, frequency and thoroughness of follow-up-intervals affect the latency to detection of recurrent disease and, therefore, influence survival. Third, individual differences regarding the invasiveness of intraoperative mediastinal nodal staging (from nodal sampling to complete compartment dissection) are prognostically relevant. A more restrictive nodal examination during surgery may underestimate true nodal extent, thus influencing subsequent therapy and course of the disease [11,21–23].

To overcome prognostic variations caused by different classification systems or discrepancies in intraoperative nodal allocations, Rusch et al. proposed to group LNs into “zones,” as described in a validated international IASLC map [14]. Following this model, we also found that N1 metastases in more than one zone (i.e., hilar and peripheral) were associated with poorer prognosis compared with single-zone involvement. However, in our series, these findings were identified as a significant prognostic factor only in adenocarcinoma, not in squamous cell carcinoma. A correlation between distribution patterns of N1 LNs and survival has been repeatedly demonstrated [24,25]; nevertheless, differences between distinct histological subtypes were not observed. In large surgical NSCLC populations, controversial results with regard to prognostic differences favoring either adenocarcinoma or squamous cell carcinoma have been reported [26–29]. Notably, these series and, as mentioned above, the IASLC database, consist of a large Asian study population. These harbor a significantly higher incidence of lung adenocarcinoma than the western or European countries, which must be taken into account during data interpretation [27,30,31]. Our series supports recent results in Caucasian pN1 NSCLC [32–34] and may serve as a valuable contribution to the existing European source data in the IASLC database. Nevertheless, the clinical impact of these findings remains debatable as long as prospective multicenter analysis of individual patient data has not been implemented. Currently, except a partial influence of the T-descriptor, adjuvant treatment decision merely follows the pathological N-status irrespective of the individual nodal burden. Consequently, upcoming revisions of the TNM-system should strongly take into account nodal subgroups in order to prospectively evaluate possibly relevant changes in treatment or follow-up strategies. In the light of recent developments in targeted and immunotherapy in advanced lung cancer, the relevance of novel therapeutic approaches should be underlined in future prospective clinical workup of nodal subgroups with prognostic relevance.

We analyzed a large surgical single-center cohort of patients with N1-positive NSCLC, and identified adenocarcinoma histology and advanced nodal extent (pN1b, multiple N1 zones affected) as poor prognostic factors. Our results support the recent survival data from pN1 patients housed in the IASLC database. For future analysis, our carefully selected data could serve as an important addition to the sparse previous European contribution to the IASLC database. We suggest that upcoming proposals for future TNM-classifications should assess the value of a more detailed stratification of N1 patients toward histology, nodal extent, and anatomical compartment distribution.

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Declaration of Competing Interest

None.

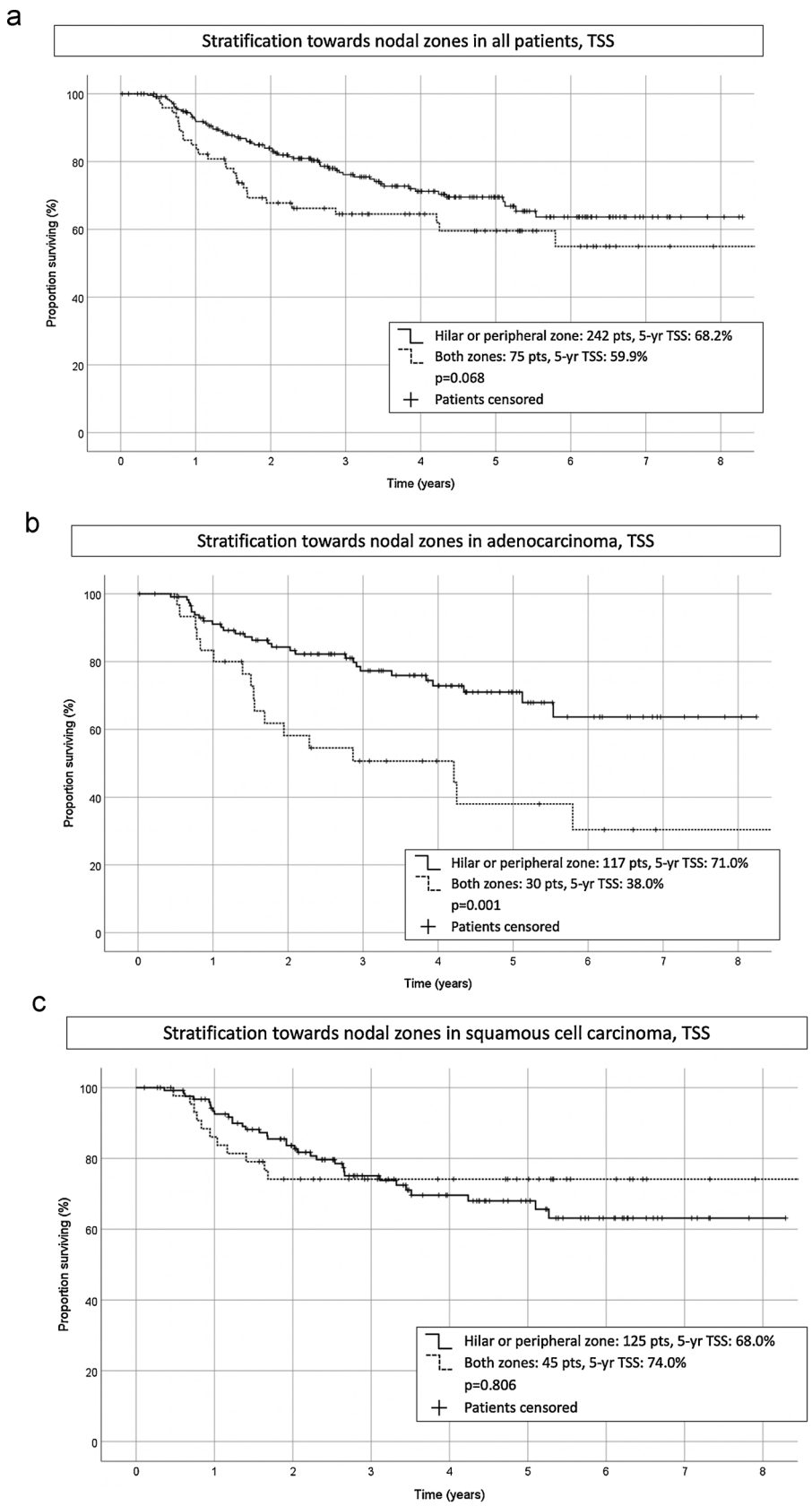

Fig. 4. Survival analysis with respect to the location based model (hilar vs. peripheral zone, according to IASLC [14]). A tendency towards poorer prognosis was found in patients with multiple nodal zones involved (A). Univariate analysis after stratification towards histological subtype showed significant poorer survival in patients with adenocarcinoma (B, p = 0.001). No difference was found in patients with squamous cell carcinoma (C, p = 0.806).

Table 2
Multivariate analysis identified ECOG-stage, tumor stage, histology, chemotherapy treatment and nodal tumor burden as individual factors with prognostic impact.

Comparative factor	Tumor specific survival (TSS)		
	HR	[95%-CI]	p-value
Age	0.996	[0.97-1.02]	0.74
ECOG			
0	1	Reference	–
1	1.904	[1.16-3.11]	0.01
Histology			
Squamous cell carcinoma	1	Reference	–
Adenocarcinoma	1.896	[1.19-3.00]	0.006
Adjuvant Chemotherapy			
No	1	Reference	–
Yes	0.516	[0.31-0.84]	0.008
Tumor Stage			
IIA/B	1	Reference	–
IIIA	2.301	[1.46-3.62]	< 0.0001
Metastatic nodal station			
pN1a (single)	0.383	[0.13-1.06]	0.066
pN1b (multiple)	1	Reference	–
Metastatic nodal region			
Single zone (hilar or peripheral)	1	Reference	–
Multiple zone (hilar and peripheral)	3.43	[1.17-9.62]	0.024
Extent of resection			
Lobectomy	1		
Bilobectomy/Pneumonectomy	1.334	[0.81-2.18]	0.25

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