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ORIGINAL PAPER

# Survival difference between patients with single versus multiple metastatic lymph nodes and the role of histology in pathological stage II-N1 non-small cell lung cancer

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**ABSTRACT**

**Background:** Previous studies investigating whether metastatic lymph node count is a relevant prognostic factor in pathological N1 non-small cell lung cancer (NSCLC), showed conflicting results. Hypothesizing that outcome may also be related to histological features, we determined the prognostic impact of single versus multiple metastatic lymph nodes in different histological subtypes for patients with stage II-N1 NSCLC.
**Methods:** We performed a retrospective cohort study using data from the Netherlands Cancer Registry, including patients treated with a surgical resection for stage II-N1 NSCLC (TNM 7th edition) in 2010–2016. Overall survival (OS) was assessed for patients with single (pN1a) and multiple (pN1b) metastatic nodes. Using multivariable analysis, we compared OS between pN1a and pN1b in different histological subtypes.
**Results:** After complete resection of histologically proven stage II-N1 NSCLC, 1309 patients were analyzed, comprising 871 patients with pN1a and 438 with pN1b. The median number of pathologically examined nodes (N1 + N2) was 9 (interquartile range 6–13). Five-year OS was 53% for pN1a versus 51% for pN1b. In multivariable analysis, OS was significantly different between pN1a and pN1b (HR 1.19, 95% CI 1.01–1.40). When stratifying for histology, the prognostic impact of pN1a/b was only observed in adenocarcinoma patients (HR 1.44, 95% CI 1.15–1.81).
**Conclusion:** Among patients with stage II-N1 adenocarcinoma, the presence of multiple metastatic nodes had a significant impact on survival, which was not observed for other histological subtypes. If further refinement as to lymph node count will be considered for incorporation into a new staging system, evaluation of the role of histology is recommended.

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Histology; lymph nodes; lymphatic metastasis; non-small cell lung cancer; pathologic N1

## Introduction

The anatomical extent of non-small cell lung cancer (NSCLC) is staged according to the TNM system to estimate prognosis and guide treatment [1]. The letter 'N' represents locoregional lymph node metastasis and is categorized into N0, N1, N2 and N3 disease, with N1 disease being defined as metastasis to ipsilateral intrapulmonary (#12–14), interlobar (#11) and/or hilar (#10) lymph nodes; N2 as metastasis to ipsilateral mediastinal (including subcarinal) lymph nodes; and N3 as metastasis to contralateral hilar or mediastinal and supraclavicular lymph nodes [2]. In contrast to nodal staging systems in other organs, the N stage in NSCLC depends solely on the anatomical location. The International Association for the Study of Lung Cancer (IASLC) suggested further classification of the nodal descriptor, but in the latest revisions of the TNM classification this remained unaltered due to practical limitations of the database [3]. Previous studies from Japan have shown that the number of metastatic N1 nodes is associated with survival [4–6]. In contrast, studies from Europe did not detect a survival difference between different numbers of involved N1 nodes [7–9]. These disparities in outcome may arise from variation in clinical and perioperative staging but may also arise from variation in biological characteristics between patients from various continents; e.g. squamous cell carcinoma is common in European surgical series, whereas adenocarcinoma

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is more prevalent in Asian series [10]. Histology is not included in the TNM system but proved to be a prognostic factor in pN1 disease. Multiple studies reported better outcomes for patients with squamous cell carcinoma [7,8,11].

To test whether the variation in histology might explain the disparities in outcome between studies performed on this subject, we compared survival between single and multiple metastatic lymph nodes in a large, nationwide series of patients with pathological stage II-N1 NSCLC with particular attention to the role of histology.

## Materials and methods

### The Netherlands Cancer Registry

The Netherlands Cancer Registry (NCR) collects data on all cancer patients diagnosed in the Netherlands. It is notified of newly diagnosed malignancies by the national automated pathological archive and of hospital discharge diagnoses. Data on demographics, diagnosis, staging and treatment is extracted from medical records by NCR personnel. Survival status is updated annually *via* a computerized link with the national civil registry. This study was approved by the NCR Privacy Review Board. In accordance with the regulations of the Central Committee on Research involving Human Subjects, this study did not require approval from an ethics committee in the Netherlands.

Parameters retrieved from the NCR included age, gender, period of diagnosis (2010–2012 or 2013–2016), histological subtype (adenocarcinoma, squamous cell carcinoma and large cell carcinoma/other), TNM pathological tumor stage (pT; 1a, 1b, 2a, or 2b), number of metastatic N1 nodes, affected lung lobe, surgical extent ((bi)lobectomy, pneumonectomy), surgical approach (VATS or open) and adjuvant therapy (radiotherapy, chemotherapy, or none). The protocol for adjuvant chemotherapy was four cycles of cisplatin-based doublets with at least 75 mg/m$^2$ of cisplatin, irrespective of histology [12].

### Patient population

Data from 1580 patients diagnosed with pathological stage II-N1 (T1a-T2bN1M0) NSCLC from 1 January 2010 to 31 December 2016 were retrospectively retrieved from the NCR. Stage information had been collected according to the 7th edition of the TNM Classification of Malignant Tumors [13]. The study population consisted of patients who had a radical resection (at least a lobectomy) and who had histologically proven pulmonary, interlobar and/or hilar lymph node metastasis (pN1) based on the lymph node map of the IASLC [2]. Pathological lymph node examination was performed according to national guidelines [12]. The following patient categories were excluded: carcinoid tumors ($n = 46$), sublobar resections ($n = 20$), neoadjuvant treatment before surgery ($n = 18$), positive resection margins (R1/2) ($n = 150$) and missing information about the number of pN1 nodes ($n = 37$). After exclusions, data from 1309 patients were available for analysis (Figure 1).

Patients were grouped by metastatic involvement of a single pN1 node (pN1a) versus multiple pN1 nodes (pN1b) and by histological subtype. Moreover, we studied the use and impact of adjuvant chemotherapy for these defined patient groups.

### Statistical analysis

Overall survival (OS) was calculated from day of surgery until day of death or 1 February 2020

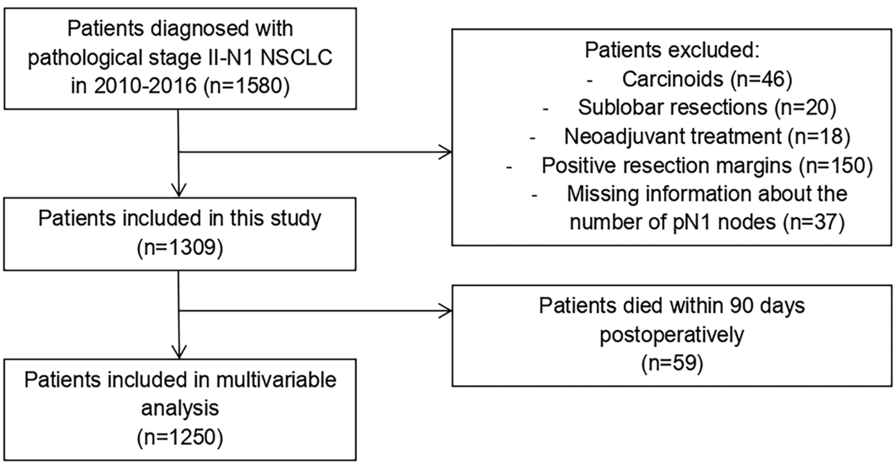


Figure 1. Flowchart of the patient selection process.

using Kaplan–Meier analysis. A multivariable survival analysis was performed using Cox proportional hazards regression analysis to study survival outcome for pN1a versus pN1b, for different histological subtypes and for pN1a versus pN1b stratified by histological subtype and by adjuvant therapy. A 90-day landmark period was applied to avoid impact of postoperative morbidity and mortality and to address immortal time bias, which overestimates the effect of adjuvant therapies [14]. Covariates included in the regression model were age, gender, TNM pathological tumor stage (pT), histology, affected lung lobe, period of diagnosis, surgical extent, surgical approach and adjuvant therapy. Conversion to open surgery after VATS was defined as VATS. Covariates were selected by backward stepwise regression and included in the final model when $p < .05$. Prognostic impact is represented by hazard ratios (HR) and 95% confidence intervals (CI). All analyses were performed in Stata V15 (College Station, TX, USA).

## Results

### *Patient characteristics*

In total, 1309 patients were included (see Figure 1 for the patient selection process). Patient characteristics and five-year OS are shown in Table 1. The median age was 66 years (interquartile range 60–72) with 62% being male. Tumor histology was adenocarcinoma or squamous cell carcinoma in 47.4% and 43.5%, respectively. Lobectomy (including sleeve lobectomy) was the most common resection type (73.6%), followed by pneumonectomy (17.4%) and bilobectomy (9.0%). The median number of pathologically examined lymph nodes (N1 + N2) was 9 (interquartile range 6–13). A single tumor-positive pN1 node was detected in 66.5% of the included patients, two tumor-positive pN1 nodes in 20.9%, three in 6.9% and more than three in 5.7% of patients. Procedures were performed with video-assisted thoracoscopic surgery (VATS) or thoracotomy at an equal rate (50.8% and 49.2%, respectively). Use of VATS increased over time from 34.1% in the period 2010–2012 to 60.9% in the period 2013–2016; 54.1% of patients with pN1a and 54.8% of patients with pN1b received adjuvant chemotherapy. Five-year overall survival of patients treated and not treated with adjuvant chemotherapy was 60% and 43%, respectively.

### *Survival differences between patients with single versus multiple metastatic N1 nodes*

In total, 701 of 1309 (54%) patients had died and median follow-up was 71 months (for censored patients). Thirty-day mortality was 1.9% after VATS and 2.0% after open surgery. Ninety-day mortality was 4.5% (59 patients) in total and was 4.1%, 3.4% and 7.0% after lobectomy, bilobectomy and pneumonectomy, respectively. Ninety-day mortality was not related to histology ($p = .42$) or single versus multiple metastatic N1 nodes ($p = .63$).

**Table 1.** Patient characteristics and five-year overall survival (OS).

| | | n | % | Five-year OS (%) | 95% CI |
|---|---|---|---|---|---|
| Age | 18–59 | 303 | 23.1 | 62.3 | 56.5–67.6 |
| | 60–69 | 557 | 42.6 | 54.6 | 50.2–58.8 |
| | 70+ | 449 | 34.3 | 42.7 | 37.9–47.4 |
| Gender | Men | 811 | 62.0 | 51.0 | 47.4–54.5 |
| | Women | 498 | 38.0 | 54.5 | 49.8–58.9 |
| Period | 2010–2012 | 572 | 43.7 | 55.5 | 51.3–59.5 |
| | 2013–2016 | 737 | 56.3 | 49.4 | 45.4–53.2 |
| Histology | Squamous cell | 621 | 47.4 | 58.4 | 54.1–62.4 |
| | Adenocarcinoma | 570 | 43.5 | 47.8 | 43.6–51.8 |
| | Large cell carcinoma / other | 118 | 9.0 | 46.7 | 37.3–55.6 |
| pT | 1a (≤2 cm) | 190 | 14.5 | 59.5 | 51.9–66.3 |
| | 1b (>2–3 cm) | 228 | 17.4 | 55.9 | 49.0–62.2 |
| | 2a (>3–5 cm) | 644 | 49.2 | 51.7 | 47.7–55.6 |
| | 2b (>5–7 cm) | 247 | 18.9 | 45.2 | 38.6–51.5 |
| pN | 1a (single metastatic lymph node) | 871 | 66.5 | 52.8 | 49.3–56.2 |
| | 1b (multiple metastatic lymph nodes) | 438 | 33.5 | 51.3 | 46.4–56.0 |
| Surgical extent | Lobectomy | 963 | 73.6 | 52.4 | 49.0–55.6 |
| | Bilobectomy | 118 | 9.0 | 52.0 | 42.4–60.8 |
| | Pneumonectomy | 228 | 17.4 | 52.2 | 45.4–58.6 |
| Surgical approach | Open | 644 | 49.2 | 49.1 | 45.0–53.1 |
| | VATS | 665 | 50.8 | 55.3 | 51.3–59.0 |
| Adjuvant chemotherapy | No | 598 | 45.7 | 42.8 | 38.7–46.8 |
| | Yes | 711 | 54.3 | 60.4 | 56.5–64.0 |
| Adjuvant radiotherapy | No | 1292 | 98.7 | 52.2 | 49.4–55.0 |
| | Yes | 17 | 1.3 | 62.7 | 34.8–81.4 |
| Total | | 1309 | 100 | 52.3 | 49.5–55.1 |

Abbreviations: CI: confidence interval; OS: overall survival; pT: pathological tumor stage; pN: pathological nodal stage; VATS: video-assisted thoracoscopic surgery.

**Table 2.** Multivariable survival analysis, excluding deaths within 90 days after surgery.

| | | Multivariable HR | 95% CI |
|---|---|---|---|
| Age | 18–59 | 1 | – |
| | 60–69 | 1.22 | 0.98–1.51 |
| | 70+ | 1.65 | 1.32–2.07 |
| Histology | Squamous cell carcinoma | 1 | – |
| | Adenocarcinoma | 1.55 | 1.31–1.84 |
| | Large cell carcinoma / other | 1.83 | 1.39–2.41 |
| pT | 1a (≤2 cm) | 1 | – |
| | 1b (>2–3 cm) | 1.18 | 0.89–1.58 |
| | 2a (>3–5 cm) | 1.35 | 1.05–1.73 |
| | 2b (>5–7 cm) | 1.84 | 1.39–2.44 |
| pN | 1a (single metastatic lymph node) | 1 | – |
| | 1b (multiple metastatic lymph nodes) | 1.19 | 1.01–1.40 |
| Adjuvant chemotherapy | No | 1 | – |
| | Yes | 0.66 | 0.56–0.77 |

Abbreviations: CI: confidence interval; HR: hazard ratio; pT: pathological tumor stage; pN: pathological nodal stage.

**Table 3.** Prognostic impact of the number of metastatic N1 nodes and adjuvant chemotherapy, stratified by histological subtype.[a]

| | | Squamous cell carcinoma | | Adenocarcinoma | | Large cell carcinoma / other | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| pN | 1a | 1 | – | 1 | – | 1 | – |
| | 1b | 0.86 | 0.66–1.13 | 1.44 | 1.15–1.81 | 1.10 | 0.66–1.85 |
| Adjuvant chemotherapy | No | 1 | – | 1 | – | 1 | – |
| | Yes | 0.55 | 0.42–0.72 | 0.75 | 0.60–0.94 | 0.63 | 0.38–1.04 |

Abbreviations: CI: confidence interval; HR: hazard ratio; pN: pathological nodal stage.
[a]Multivariable analysis controlling for age and pT, excluding deaths within 90 days after surgery.

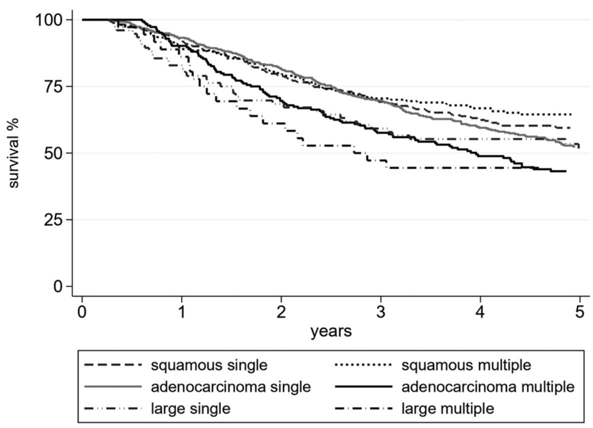


**Figure 2.** Overall survival in patients with pathological stage II-N1 NSCLC, stratified by histology and number of metastatic lymph nodes, excluding deaths within 90 days postoperatively.

Overall, five-year OS was 52%. For patients with pN1a, five-year OS was 53% versus 51% for patients with pN1b. According to multivariable analysis, single versus multiple metastatic N1 nodes, histological subtype, age, pT and adjuvant chemotherapy were defined as independent prognostic factors for OS (Table 2). Survival was significantly worse for patients with pN1b compared to patients with pN1a (HR 1.19, 95% CI 1.01–1.40). Chemotherapy was associated with improved survival and the beneficial effects were not different for pN1a versus pN1b (HR 0.67 versus HR 0.64, respectively).

### *Survival for different histological subtypes*

Survival was considerably worse for adenocarcinoma (HR 1.55, 95% CI 1.31–1.84) and for other histological subtypes (HR 1.84, 95% CI 1.39–2.41) compared to squamous cell carcinoma. A multivariable analysis suggested prognostic interaction between histology and the survival impact of single versus multiple metastatic N1 nodes (Table 3 and Figure 2): a prognostic difference between pN1b and pN1a was only observed for adenocarcinomas (HR 1.44, 95% CI 1.15–1.81), but not for squamous cell carcinomas (HR 0.86, 95% CI 0.66–1.13) or other histological subtypes (HR 1.10, 95% CI 0.66–1.85). Furthermore, the impact of adjuvant chemotherapy seemed more pronounced for squamous cell carcinomas (HR 0.55, 95% CI 0.42–0.72) than for adenocarcinomas (HR 0.75, 95% CI 0.60–0.94), however, the difference in impact was not statistically significant.

## Discussion

### *Main outcomes*

In this study, we explored the role of histology in the prognostic discrimination of single versus multiple metastatic N1 nodes among patients with stage II-N1 NSCLC. Our results show that – overall – distinction of a single versus multiple metastatic pN1 nodes had a small, though significant prognostic impact. When stratifying for histological subtype, the survival impact was observed for adenocarcinoma patients only.

Although without considering the role of histology, several previous studies investigated the prognostic impact of the number of metastatic N1 nodes as well (Table 4) [4–9,11,15–24]. As shown in Table 4, the prognostic impact of the number of N1 nodes appears to be more prominent in Asian studies compared to European studies. Since the presence of multiple metastatic lymph nodes only had a significant impact in adenocarcinoma

**Table 4.** Studies involving patients with N1 NSCLC, published between 2010 and 2022.

| Author Year | Inclusion criteria | Period | N | Multiple nodes % | AC % | Five-year survival | Adjuvant chemo % | Investigated prognostic factor | HR (95% CI or $p$ value) |
|---|---|---|---|---|---|---|---|---|---|
| | Europe / United States | | | | | | | | |
| Casali et al. [15] 2011 | T1-3, major surgery, complete resection; excluding neoadjuvant treatment | 1990–2009 | 384 | 51 (>1 node) | 44 | 46% (OS) | – | Multiple nodes | 0.83 (0.58–1.18) |
| Jonnalagadda et al. [20] 2011 | T1-3; excluding sublobar resections, neoadjuvant radiotherapy and <10 lymph nodes sampled | 1988–2007 | 3399 | 60 (>1 node) | 45 | 36% (OS) | – | Multiple nodes | 1.13 (1.03–1.30) for 2–3 nodes 1.46 (1.30–1.64) for 4–8 nodes |
| Macia et al. [19] 2013 | Complete resection of tumor and lymph nodes; excluding neo-adjuvant treatment | 2005–2009 | 47 | 55 (>1 node) | 36 | 43% (OS) | 70 | Multiple nodes | – ($p = .06$) |
| Haney et al. [8] 2014 | T1-2 | 1997–2011 | 230 | 11 (>1 zone) | 42 | – | 44 | Number of positive N1 nodes | 0.87 (0.75–1.00) |
| Mordant et al. [9] 2015 | Complete resection, complete nodal dissection | 1993–2009 | 450 | 49 (>1 node) | – | 46% (OS) | 43 | Multiple nodes | – ($p = .08$) |
| Borghetti et al. [7] 2016 | Complete resection; excluding in-hospital death | 2001–2011 | 202 | 57 (>1 node) | 41 | 39% (OS) | 25 | Multiple nodes | – (n.s.) |
| Pawełczyk et al. [21] 2016 | T1-4, complete resection; excluding sublobar resections, <6 nodes removed and perioperative deaths | 2007–2009 | 152 | 82 (≥3 nodes) | 47 | 32% (OS) | 72 | Multiple nodes (≥3) | 2.22 vs. 1.74[a] |
| Citak [16] | Complete resection, >2 mediastinal lymph nodes dissected | 2010–2017 | 283 | – | 22 | 54% (OS) | – | Multiple nodes (4–6) | 1.44 |
| Griff et al. [17] 2019 | T1-2, complete lymph node dissection; excluding postoperative deaths <30 days | 2008–2012 | 90 | 51 (>1 node) | 41 | 56% (OS) | 58 | Multiple nodes | 1.50 (0.72–3.16) |
| This study | T1-2, excluding postoperative deaths <90 days | 2010–2016 | 1309 | 33 (>1 node) | 44 | 52% (OS) | 54 | Multiple nodes | 1.19 (1.01–1.40) |
| | Asia | | | | | | | | |
| Wei et al. [5] 2011 | Excluding no nodes examined and postoperative deaths <30 days | 2000–2006 | 213 | 29 (>2 nodes) | (78) | 55% (OS) | – | Multiple nodes (>2) | 1.73 ($p = .03$) |
| Maeshima et al. [11] 2012 | Excluding neoadjuvant treatment and sublobar resections | 2000–2004 | 230 | 50 (>1 node) | 59 | 50% (DFS) | 11 | Multiple nodes | 1.26 ($p = .04$) |
| Liu [18] | Stage II, ≥12 nodes sampled; excluding in-hospital deaths | 1992–2010 | 163 | 46 (>1 node) | 55 | 44% (OS) | – | Multiple nodes | 1.33 ($p = .16$) |
| Saji et al. [6] 2013 | Complete resection with dissection of ≥10 nodes | 2000–2007 | 93 | 14 (≥4 nodes) | (72) | 66% (OS) | – | Multiple nodes (≥4) | 1.60 |
| Katsumata et al. [4] 2019 | Complete resection; excluding sublobar resections and neo-adjuvant treatment | 2003–2012 | 250 | 47 (>1 node) | (69) | 51% (OS) | – | Multiple nodes | 1.41 (1.02–1.95) |
| Maniwa et al. [22] 2020 | Complete resection, ≥6 resected nodes; excluding sublobar resections and neo-adjuvant treatment | 2006–2015 | 177 | 15 (≥4 nodes) | (77) | 66% (OS) | – | Multiple nodes (4–6) | 0.92 (0.37–1.95) |
| Li et al. [23] 2021 | T1-4; excluding sublobar resections and adjuvant chemotherapy | 2004–2016 | 1460 | 53 (>1 node) | 44 | 47% (LCSS) | 0 | Multiple nodes | – ($p < .001$) |
| Samejima et al. [24] 2021 | Complete resection; excluding neo-adjuvant chemotherapy, sublobar resection and postoperative deaths <30 days | 2010–2016 | 173 | 12 (≥4 nodes) | (78) | 73% (OS) 55% (RFS) | – | Multiple nodes (≥4) | 2.06 (0.83–5.16) 2.07 (1.06–4.05) |

Abbreviations: AC: adenocarcinoma; CI: confidence interval; DFS: disease-free survival; HR: hazard ratio; n.s.: not significant; OS: overall survival.
[a]Reference group = pN0; HR 1.74 ($p = .001$) for 1–2 metastatic N1 nodes; HR 2.22 ($p < .001$) for ≥3 metastatic N1 nodes.

patients in this study, the discrepancy in overall survival impact of pN1b between Asian and European patients may be explained by the higher prevalence of adenocarcinomas among Asian patients (Table 4) [10].

An interaction between histology, the extent of lymph node involvement and prognosis was also observed in previous studies [8,17,20]. Other studies suggested that adenocarcinomas have a higher potential to metastasize (regionally and systemically) compared to squamous cell carcinomas [25,26]. Moreover, it was previously shown that adenocarcinomas tend to metastasize to N1 nodes more often *via* lymphatic spread than by direct invasion by the primary tumor, the latter occurring more often in squamous cell carcinomas [27,28]. Since separately involved N1 nodes have a significantly worse prognosis [27,28], the poor prognosis of pN1b adenocarcinoma patients might be explained by this underlying mechanism.

Incorporation of the number of metastatic lymph nodes into future TNM classifications has been considered [3]. However, due to practical limitations such as poor standardization of the counts and variable specimen labeling and handling of fragmented lymph nodes [29], this was deemed to be impractical. Therefore, for the 9th edition, the IASLC has mainly focused on the number of involved lymph node stations and lymph node zones as potential new variables with which to categorize the extent of nodal involvement [30,31]. However, validation of N1 zones was precluded by sample size limitations and distinction between single versus multiple metastatic N1 stations was only associated with a minimal difference (<5%) in five-year survival [31]. Based on our study results, we recommend to evaluate the role of histology if the number of lymph node stations or zones will be considered for incorporation into a future staging system.

### International comparison of results

Similar to most other pN1 studies (Table 4), we included complete resections, with postoperative deaths within 90 days being only excluded from multivariable analysis. Compared to earlier European results reported from the IASLC study [3], the five-year OS for our patient population was considerably better. The higher survival rate might reflect enhanced mediastinal staging over time, causing a shift of previously unrecognized N2 patients with a worse prognosis to the stage III NSCLC group. However, the IASLC study included all pN1 patients (regardless of T stage), thereby hampering direct comparison.

### Adjuvant therapy

Almost half of the patients did not receive adjuvant chemotherapy, probably due to older age, comorbidity, poor performance status, or refusal by the patient. A large population-based series from the USA [32] confirmed the low utilization of adjuvant chemotherapy. In our series, the potential beneficial effect of chemotherapy appeared to be high (HR 0.66, 95% CI 0.56–0.77) compared to the efficacy found in randomized trials, but this effect is overrated due to confounding by comorbidity and performance status. However, a subgroup analysis of the JBR10 trial suggested greater clinical benefit (HR 0.58) of adjuvant chemotherapy in patients with pN1 [33].

### Strengths and limitations

The main strength of this study is that it is a population-based study that included a large number ($n = 1309$) of patients. However, there are several limitations that must be considered when interpretating our data. Firstly, although we were able to report on the total number of resected lymph nodes (i.e. N1 plus N2 nodes), we did not know the separate numbers of resected N1 and N2 nodes. Furthermore, the number of positive lymph nodes depends on the thoroughness of lymph node examination. The median number of pathologically examined lymph nodes was 9. According to the IASLC and NCCN guidelines [34,35], at least 6 lymph nodes must be taken from 3 N1 and 3 N2 stations (including the subcarinal station). Since one lymph node station usually consists of several lymph nodes, our findings suggest that lymph node dissection or sampling might have been performed inadequately in a part of Dutch patient population. Van der Woude et al. [36] recently confirmed this hypothesis by stating that a complete lymph node dissection of both intrapulmonary and mediastinal lymph nodes is performed only in 36% of Dutch patients with clinically staged N1 NSCLC. However, also in other countries lymph node examination is not performed according to formal guidelines, e.g. in a recently published study with data from the American National Cancer Database (NCDB) the median number of sampled lymph nodes in clinical stage I/II NSCLC patients was only 7 [37].

Moreover, it is possible that lymph nodes are sometimes harvested in fragments and each fragment might be counted as a single lymph node by the pathologist [29]. This potential technical limitation might have led to an overestimation of the number of metastatic lymph nodes, thereby biasing the impact of multiple metastatic lymph nodes.

Finally, only tumor classifications according to the 7th edition of the TNM classification were recorded during the study period and information on exact pathological tumor size was not available, precluding conversion to newer editions of the TNM classification. However, the nodal descriptor was not altered between the 7th and 8th TNM edition [3] and also in the proposed 9th edition, the N1 category remains unchanged [31]. Incompatibility between TNM editions also hampers interpretation of trials with novel neoadjuvant regimens [38] and underlines the importance of the efforts of the IASLC Staging and Prognostic Factors Committee [39].

### *Conclusion*

Among patients with stage II-N1 adenocarcinoma, the presence of multiple metastatic lymph nodes had a significant impact on survival, which was not observed in other histological subtypes. However, because of substandard performance of lymph node dissection (in the Netherlands) and technical limitations hampering an accurate estimation of the number of metastatic N1 nodes, incorporation of the number of metastatic lymph nodes in future TNM classifications is considered impractical. If the number of lymph node stations or zones will be considered for incorporation into a new staging system, evaluation of the role of histology is recommended.

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## Data availability statement

Data requests can be directed to the Netherlands Cancer Registry at https://iknl.nl/en.

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