

# Prognostic factors of resected node-positive lung cancer: location, extent of nodal metastases, and multimodal treatment

## Prognosefaktoren des resezierten, nodal positiven Lungencarcinoms: Lokalisation und Ausdehnung der Lymphknotenmetastasierung, multimodale Therapie

### Abstract

**Objective:** To investigate the prognostic significance of location and extent of lymph node metastasis in resected non-small cell lung cancer (NSCLC), and to weigh up the influence of treatment modalities on survival.

**Patients and method:** On exploratory analysis, patients were grouped according to location and time of diagnosis of nodal metastasis: group I, pN2-disease in the aortopulmonary region (N=14); group II, pN2-disease at other level (N=30); group III, cN2-disease with response to induction treatment (ypN0; N=21); group IV, cN2-disease without response to induction treatment (ypN1-2; N=27); group V, pN1-disease (N=66).

**Results:** From 1999 to 2005, 158 patients (median age: 64 years) with node-positive NSCLC were treated at our institution either by neoadjuvant chemo-radiotherapy plus surgery or by surgery plus adjuvant therapy (chemotherapy, radiotherapy, or both). Operative mortality and major morbidity rates were 2% and 15%. Five-year survival rates were 19% for group I, 12% for group II, 66% for group III, 15% for group IV, and 29% for group V ( $P < .05$ ). On multivariate analysis, time of N+-diagnosis, extent of nodal involvement and therapy approach were significantly linked to prognosis.

**Conclusion:** The survival of patients with node-positive NSCLC does not depend on anatomical location of nodal disease, but strongly correlates to extent of nodal metastases and treatment modality. Combined therapy approaches including chemotherapy and surgery may improve long-term survival.

**Keywords:** chemotherapy, induction therapy, lung cancer, radiotherapy, surgery

### Zusammenfassung

**Ziel:** Evaluierung der prognostischen Bedeutung der Lokalisation und des Ausmaßes der regionären Lymphknotenmetastasierung beim resezierten, nicht-kleinzelligen Lungencarcinoms (NSCLC), sowie des Einflusses der Therapiemodalitäten auf das Langzeitüberleben.

**Patienten und Methode:** Im Rahmen der explorativen Analyse wurden die Patienten nach Lokalisation und Zeitpunkt der Diagnose der Lymphknotenmetastasierung gruppiert: Gruppe I, pN2-Erkrankung in der aorto-pulmonalen Region (N=14); Gruppe II, pN2-Erkrankung in anderer Lokalisation (N=30); Gruppe III, cN2-Erkrankung mit Ansprechen auf die Induktionstherapie (ypN0; N=21); Gruppe IV, cN2-Erkrankung ohne Ansprechen auf die Induktionstherapie (ypN1-2; N=27); Gruppe V, pN1-Erkrankung (N=66).

**Resultate:** Im Zeitraum 1999–2005, wurden 158 Patienten (Altersmedian: 64 Jahre) mit nodal-positivem NSCLC entweder einer neoadjuvan-

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ten Chemo-Radiotherapie und chirurgischen Resektion oder der chirurgischen Resektion plus adjuvanter Therapie (Chemotherapie, Radiotherapie, oder beides) unterzogen. Die chirurgische Mortalität und höhergradige Morbidität betragen 2% respektive 15%. Die Überlebensanalyse ergab 5-Jahresüberlebensraten von 19% für die Gruppe I, 12% für die Gruppe II, 66% für die Gruppe III, 15% für die Gruppe IV und 29% für die Gruppe V ( $P < 0,05$ ). Bei der multivariaten Analyse korrelierten Zeitpunkt der Diagnose und Ausmaß der Lymphknotenmetastasierung sowie das therapeutische Konzept signifikant mit der Prognose der Erkrankung.

**Schlussfolgerung:** Die Prognose der Patienten mit nodal-positivem NSCLC wird nicht von der anatomischen Lage der befallenen Lymphknotenstationen beeinflusst, sondern von dem Ausmaß der regionären Lymphknotenmetastasierung und den Therapiemodalitäten. Multimodale Konzepte unter Einschluss der Chemotherapie und Chirurgie können das Langzeitüberleben dieser Patientenpopulation verlängern.

**Schlüsselwörter:** Chemotherapie, Chirurgie, Induktionstherapie, Lungencarcinom, Radiotherapie

## Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality in the world. Currently, only few cases are diagnosed at an early stage of tumour: at the time of detection only 15% of patients have a disease localized to their lung, in 22% of cases the cancer has spread to regional lymph nodes, and in 55% distant metastases are already present, while 8% of cancers remain unstaged [1].

Patients with NSCLC and metastases in the ipsilateral nodes of the mediastinum (N2) represent a population with markedly prognostic heterogeneity, ranging from cases with multiple confluent or extranodal invasion, evident at the clinical/radiological staging, to cases with multilevel nodal disease detected only at mediastinoscopy, up to patients with limited nodal spread and normal appearance on CT scan, revealed accidentally in the final pathology report [2], [3], [4]. Similar heterogeneity has been advocated for N1-disease, although recent reports do not confirm this finding [5], [6]. The presence of clinically evident, bulky nodal disease is accompanied in most cases – regardless of the intensity of treatment – by poor survival. On the other hand, metastasis in a single nodal station with closed anatomical relationship to the lobe of origin of the primary tumour has been correlated with a more favourable outcome, comparable with that of N1-disease [7].

In recent years, the results of many studies have led to the evolution of standard management of nodal positive NSCLC, as chemotherapy either in the neoadjuvant or in the adjuvant setting has become a mainstay of treatment [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20]. Nevertheless, there is a still ongoing debate whether selected patients with node-positive NSCLC with “more favourable” prognosis should be primarily treated with surgery alone. Particularly, patients with nodal disease restricted to a single station proximal to the primary tumour are often considered surgical candidates – as for

instance the situation of a tumour in the left upper lobe with lymph node metastasis in the aorto-pulmonary (A-P) region. However, the benefit of surgery alone may be limited, with 5-year survival rates in the order of 20 to 25% [2], [21], [22]. The aim of our exploratory data analysis was to investigate the prognostic significance of anatomical location and extent of lymph node metastasis in resected NSCLC, e.g. by comparing isolated N2-disease in the A-P region with other sites of nodal metastasis, as well as to identify the optimal therapy approach for node-positive NSCLC.

## Materials and methods

### Patient population

In a retrospective analysis, we reviewed a series of 158 patients with non-small cell lung cancer (NSCLC) found to be node-positive either at mediastinoscopy or at the time of surgical resection. All patients were treated at the Department of Thoracic Surgery of the Niels-Stensen-Kliniken, Ostercappeln, Germany between 1999 and 2005. Median age was 63 years (range 33–84), the majority of patients was male (80%) and showed a WHO performance status of 0–1 (91%). About two-thirds of the patients (70%) had an acceptable pulmonary reserve, the forced expiratory volume at 1 second (FEV1) measuring 70% or more of the predicted value.

Patients were staged by chest X-ray examination, computed tomography scan of chest and upper abdomen, magnetic resonance imaging of the brain, abdominal ultrasound, bone scintigraphy, and bronchoscopy. As positron emission tomography (PET) was not available at the time of the study, cervical mediastinoscopy was done in most cases (77%) for nodal staging; reasons for not including mediastinoscopy in the remaining cases were: peripheral T1-tumor, and mediastinal lymph nodes not enlarged (less diameter  $< 1$  cm) on imaging studies. Pa-

tients with negative nodes at mediastinoscopy underwent primary surgical resection, whereas those with N2-disease underwent induction chemotherapy and concurrent chemo-radiotherapy, and were subsequently operated on.

## Induction therapy in patients with N2-nodes at mediastinoscopy

As one of the participating centres of the Münster study, we adopted a modified induction protocol as described by Thomas and coworkers [9].

In patients with N2-nodes at mediastinoscopy, induction therapy consisted of 2 courses of platin-based chemotherapy, followed by concurrent chemo-radiation based on twice-daily hyperfractionated accelerated radiotherapy and single-agent chemotherapy (cisplatin) as radiosensitizer. Eligible patients were scheduled for two courses of chemotherapy with cisplatin 70 mg/m<sup>2</sup> intravenously (IV) on days 1 and 7 (or 8) and etoposide 150 mg/m<sup>2</sup> IV on days 3, 4, and 5. Since 2001, cisplatin was administered at 100 mg/m<sup>2</sup> IV and etoposide was replaced by gemcitabine 1000 mg/m<sup>2</sup> IV on day 1 and 8. The cycles were repeated every 22 days. As scheduled, concurrent chemoradiotherapy was started at week 7 with twice-daily hyperfractionated accelerated radiotherapy (1.5 Gy per fraction >6 hours apart, 5 days a week, up to a total dose of 45 Gy over a period of 3 weeks) and single-agent chemotherapy (cisplatin 8 mg/m<sup>2</sup> IV daily) during the whole course of irradiation.

Two weeks after completion of radiotherapy, complete restaging procedures except of mediastinoscopy were performed and followed by definitive surgery, 4 to 6 weeks after the end of radiation. Mediastinal restaging was based essentially on computed tomography criteria: enlarged mediastinal lymph nodes with the minimum diameter greater than 2 cm have been considered as harbouring persistent metastatic disease, and in that case patients were excluded from surgical resection. In all other cases surgical exploration was planned.

## Surgical procedures

Surgical procedures included lobectomies, sleeve lobectomies or pneumonectomies as indicated. In all cases a systematic lymphadenectomy of the interlobar, hilar, and ipsilateral mediastinal lymph node stations was performed, and labeled according to the *New Regional Lymph Node Classification for Lung Cancer Staging* [23]. These N-stage descriptors have not been substantially changed in the *Seventh Edition of the TNM Classification for Lung Cancer* [6], [24].

## Adjuvant therapy

As most patients were treated in an era before adjuvant chemotherapy became standard of care for stage IIIA-NSCLC, the majority of those treated by primary surgery received adjuvant radiotherapy. After induction chemo-

radiotherapy and surgery, adjuvant treatment with two additional courses of chemotherapy was planned if the tumour was classified as responder. Non-responders did not receive any adjuvant treatment and underwent second-line chemotherapy as disease progression was assessed.

In case of incomplete resection of the primary tumour, a radiotherapy-boost, after-loading therapy, or both were delivered according to the site of residual tumour.

## Grouping according to the lymph node status

For the purpose of this study, patients were grouped according to the location and the timing of diagnosis of nodal disease as follows:

- **group I**, N2-disease in the A-P region at thoracotomy (level 5 and 6);
- **group II**, N2-disease at any other level at thoracotomy (level 2, 3, 4, 7, 8, 9);
- **group III**, N2-disease at mediastinoscopy (level 2, 4, 7) with complete response to induction treatment;
- **group IV**, N2-disease at mediastinoscopy (level 2, 4, 7) with partial or no response to induction treatment;
- **group V**, N1-disease in the hilar or interlobar region at thoracotomy (level 10, 11). We decided to include tumours with hilar N1-metastases in the exploratory analysis, because these have been advocated as having a prognosis comparable to single-level N2-disease [5].

The grouping system is graphically represented in Figure 1. The clinical characteristics of the groups are indicated in Table 1.

## Response evaluation

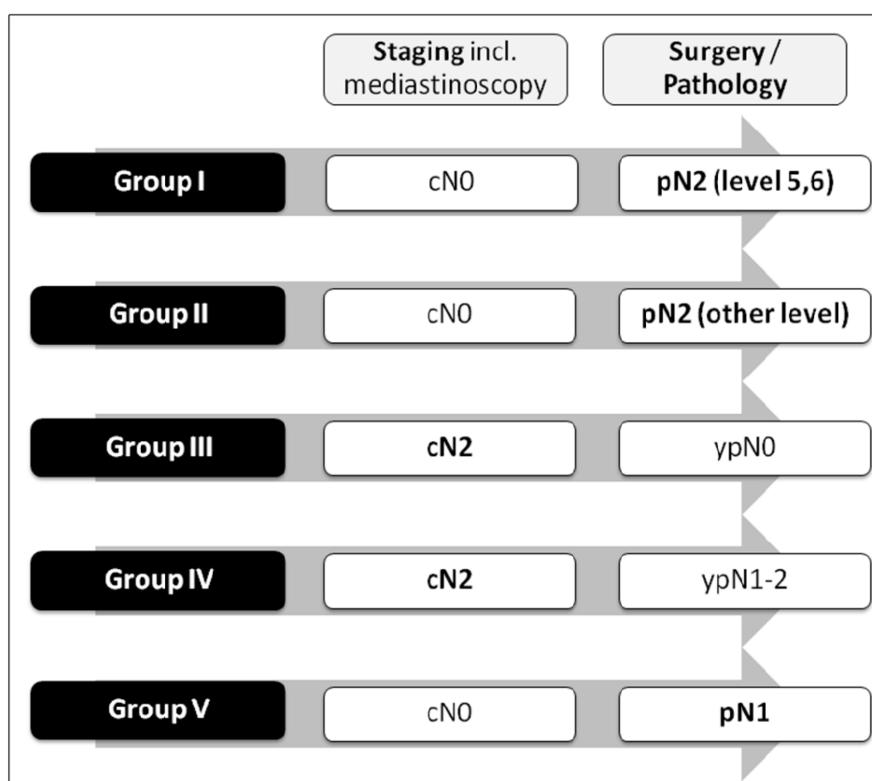
Before and after treatment, patients were staged using the 1997 International Union Against Cancer (UICC) criteria [25], as to the time of analysis the *Seventh Edition of TNM Classification of Malignant Tumours* was not yet definitely approved [26]. Responses to treatment were assessed using standard EORTC/NCIC criteria [27]. Surgical resection was defined as complete if the following criteria were met: free resection margins proved microscopically; systematic nodal dissection or lobe-specific systematic nodal dissection; no extracapsular nodal extension of the tumour; and the highest mediastinal node removed to be negative. Lymph node mapping at mediastinoscopy or surgery was accomplished according the classification of Mountain and Dresler [23].

## Follow-up and statistical methods

All patients were monitored every 3 months for the first 2 years from the end of treatment and from then on every 6 months. Survival was measured from the first day of chemotherapy (mediastinoscopy positive N2-groups) or from the day of surgery (other groups) until death, loss

**Table 1:** Comparison between groups of patients with node-positive NSCLC: clinical data. *Group I*, N2-disease in the AP-region; *group II*, N2-disease at any other level; *group III*, N2-disease at mediastinoscopy with complete response to induction treatment; *group IV*, N2-disease at mediastinoscopy with partial or no response to induction treatment; *group V*, N1-disease in the hilar or interlobar region.

Clinical features	Group					P value
	I n=14	II n=30	III n=21	IV n=27	V n=66	
Age						.002
Median [yr]	68	65	59	60	66	
WHO-performance status						NS
0–1	13	27	19	23	62	
2	1	3	2	4	4	
cT classification						NS
cT1–2	12	27	15	21	57	
cT3–4	2	3	6	6	9	
Cervical mediastinoscopy						<.001
not performed	5	13	–	1	17	
negative	8	17	–	–	49	
positive N2	1	–	21	26	–	
Histology						NS
squamous	6	14	8	11	34	
non-squamous	8	16	13	16	32	



**Figure 1:** Patient grouping according to the site and the timing of diagnosis of nodal disease

to follow-up, or the time of evaluation for this report. Statistical group comparison was accomplished to explore homogeneity bias: differences between categorical and continuous variables were comparatively analyzed using Pearson's  $\chi^2$ -test and Student's t-test, respectively. Survival curves were estimated by the method of Kaplan and Meier; differences in the curves between groups of pa-

tients were evaluated using a log-rank test [28]. Multivariate analysis was based on the Cox proportional hazard model [29]. All indicated *P* values are two-tailed. Analysis was carried out using a software package (Statistical Program for the Social Sciences, release 10.0.7; SPSS Inc., Chicago, IL).

**Table 2: Comparison between groups of patients with node-positive NSCLC: treatment data. Group I, N2-disease in the AP-region; group II, N2-disease at any other level; group III, N2-disease at mediastinoscopy with complete response to induction treatment; group IV, N2-disease at mediastinoscopy with partial or no response to induction treatment; group V, N1-disease in the hilar or interlobar region.**

Treatment data	Group					P value
	I n=14	II n=30	III n=21	IV n=27	V n=66	
Type of surgery						NS
lobectomy	7	25	16	17	47	
sleeve lobectomy	6	2	3	5	14	
pneumonectomy	1	3	2	4	5	
explorative thoracotomy	–	–	–	1	–	
Surgical complications						NS
mortality	–	1	–	1	1	
major morbidity	1	4	3	5	10	
Completeness of resection						NS
R0	11	28	21	25	62	
R1–2	3	2	–	2	4	
pT classification						<.001
T0 (ypT0)*	–	–	5	2	–	
T1–2	13	22	16	22	59	
T3–4	1	8	–	3	7	
Adjuvant chemotherapy						.016
no	11	18	15	23	58	
yes	3	2	6	4	8	
No. of cycles (median)	6	6	2	3	3	
Adjuvant radiotherapy						<.001
no	5	8	18	19	45	
yes	9	22	3	8	21	
radiation boost (20 Gy)	–	1	1	4	1	
radical dose 40–50 Gy	3	5	2	2	11	
radical dose 60–70 Gy	6	12	–	1	6	
unknown	–	4	–	1	3	

\*Complete regression of the primary tumour after induction treatment (groups III and IV)

## Results

### Results of treatment

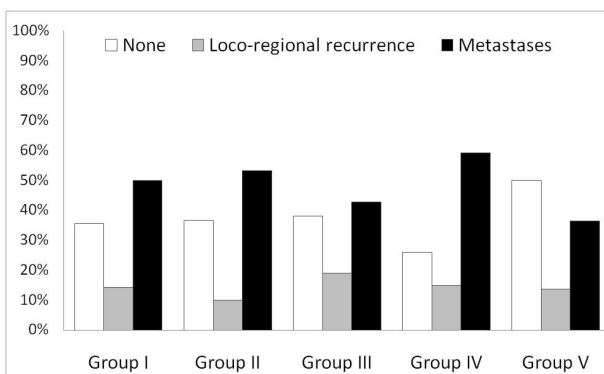
In the groups of patients undergoing multimodality therapy (III and IV), grade 3–4 toxicity was observed in 19% of cases. Due to preoperative patient selection by a multidisciplinary panel of experts, surgical resection of the tumour was possible in 157 (99%) of patients; in only one case the tumour was technically inoperable at thoracotomy. Lobectomy was the most frequent (71%) surgical procedure; sleeve-lobectomy was performed in a higher number of cases as compared with pneumonectomy (19% vs. 9%). Surgical mortality and major morbidity were 2% and 15%, respectively, and there was no significant difference between groups. Resection was incomplete in 11 (7%) patients. As a result of induction therapy, some

cases showed complete pathologic response of the primary tumour in the multimodal groups (24% in group III, and 7% in group IV, respectively). A complete or near complete clearance of lymph node metastases was observed in 86% and 14% of cases of group III, respectively. According to the results of the pathological examination, adjuvant radiotherapy was delivered to 54% of patients in the surgical groups, and chemotherapy with or without radiotherapy to 12%; 44% of patients did not undergo postoperative treatment. In the multimodality therapy groups, 42% of patients received adjuvant therapy (21% radiotherapy and 21% chemotherapy with or without radiotherapy, respectively). A detailed comparison between the groups according to the treatment is presented in Table 2.



## Tumour relapse

Among the 158 patients, 98 (62%) suffered a relapse of their tumour: this was loco-regional in 15 (9%), at distant site in 64 (41%), combined loco-regional and distant in 13 (8%), and as a second lung primary in the remaining 6 (4%). Figure 2 illustrates the percentage distribution of the first site of tumour relapse according to the modality of nodal involvement. Loco-regional recurrence rate among the groups was relatively homogeneous, ranging from 13% to 29%. On the other hand, we observed broader differences in the incidence of systemic relapses: in group V was 38%, in group I, II and III 50%, 53% and 52%, respectively, whereas in group IV rose to 70%. Nevertheless, at statistical analysis the differences concerning first site of failure, frequency and type of local recurrence and metastases were not statistically significant.



**Figure 2: Percentage distribution of the first site of tumour relapse in node-positive NSCLC patients according to the modality of nodal involvement. Group I, N2-disease in the AP-region; group II, N2-disease at other level; group III, N2-disease at mediastinoscopy with complete response to induction treatment; group IV, N2-disease at mediastinoscopy with partial or no response to induction treatment; group V, N1-disease in the hilar or interlobar region.**

## Survival analysis

Overall, patients were followed up for a median period of 41 months (range 4–104 months). Only three (2%) patients were lost to follow-up after 4, 6, and 12 months, respectively.

The median survival time for the whole patient population was 27 months (95%-CI: 22-32), with a 3- and 5-year survival rate of 38% and 27%, respectively. On survival analysis according to our grouping system, responders after induction therapy (group III) had the best prognosis: their median survival time of 84 months (95%-CI: 59-109) was significantly better than that of group II ( $P=.001$ ) and group IV ( $P=.004$ ), whereas the differences to group I and group V did not reach the statistical significance ( $P=.060$  and  $P=.094$ , respectively) (Figure 3).

On univariate analysis, following clinical and pathological features had no significant impact on survival: WHO performance status (0–1 vs. 2), gender, site of the primary

tumour, lobe of origin, cT classification, histology, type of surgery, surgical complications, R-status.

Major prognostic factors were the type of lymph node involvement according to the cited grouping system ( $P=.0029$ ) (Figure 3), pT classification ( $P=.0429$ ), number of involved nodal levels ( $P<.0001$ ) (Figure 4), and type of therapy added to surgery ( $P=.0284$ ) (Figure 5).

We analyzed separately patients undergoing either local therapy modalities only (surgery with or without radiotherapy) or therapy protocols including chemotherapy (in neoadjuvant setting, adjuvant setting, or both): survival was better in the chemotherapy group, although the difference was not statistically significant ( $P=.22$ ). Thus, in order to identify subsets of patients who benefit from multimodal therapy including chemotherapy, the chemotherapy group was split in a subgroup receiving induction chemoradiotherapy with complete response to therapy (CxRtS-R), a subgroup receiving induction chemoradiotherapy without complete response to therapy (CxRtS-NR), and a subgroup receiving adjuvant chemotherapy (Cx adjv), respectively, and these were compared with the local therapy group (local Tx). Survival curves showed the CxRtS-R group to be associated with the best outcome, and the CxRtS-NR group with the worst; thereafter, patients undergoing adjuvant chemotherapy did better as compared with those receiving local therapy only. Survival differences were statistically significant ( $P=.0075$ ; Figure 6).

On multivariate analysis, type and extent of lymph node involvement as well as the type of therapy added to surgery were significantly linked to prognosis of patients with node-positive NSCLC ( $P=.002$ ,  $P=.004$  and  $P=.007$ , respectively).

## Discussion

In the current study, we analyzed whether anatomical location and extent of lymph node metastases influence the prognosis of NSCLC. Also, we compared management strategies of resected node positive NSCLC patients according to type and location of nodal involvement.

Despite of the retrospective, and thus potentially biased nature of the study, and the limited sample size, some interesting findings have emerged from data analysis to address the primary issues.

### Anatomical location of nodal disease

The first finding was that there were no significant differences in survival between N2-disease in the AP-region and N2-disease at other level, even when stratifying groups by extent of nodal involvement, i.e. single vs. multilevel. An additional observation was that in the A-P region subgroup survival was not influenced by multilevel nodal metastases, while such constellation in other mediastinal locations clearly worsened the prognosis.

The relationship between anatomical location of primary tumour and lymph node metastases and prognosis of

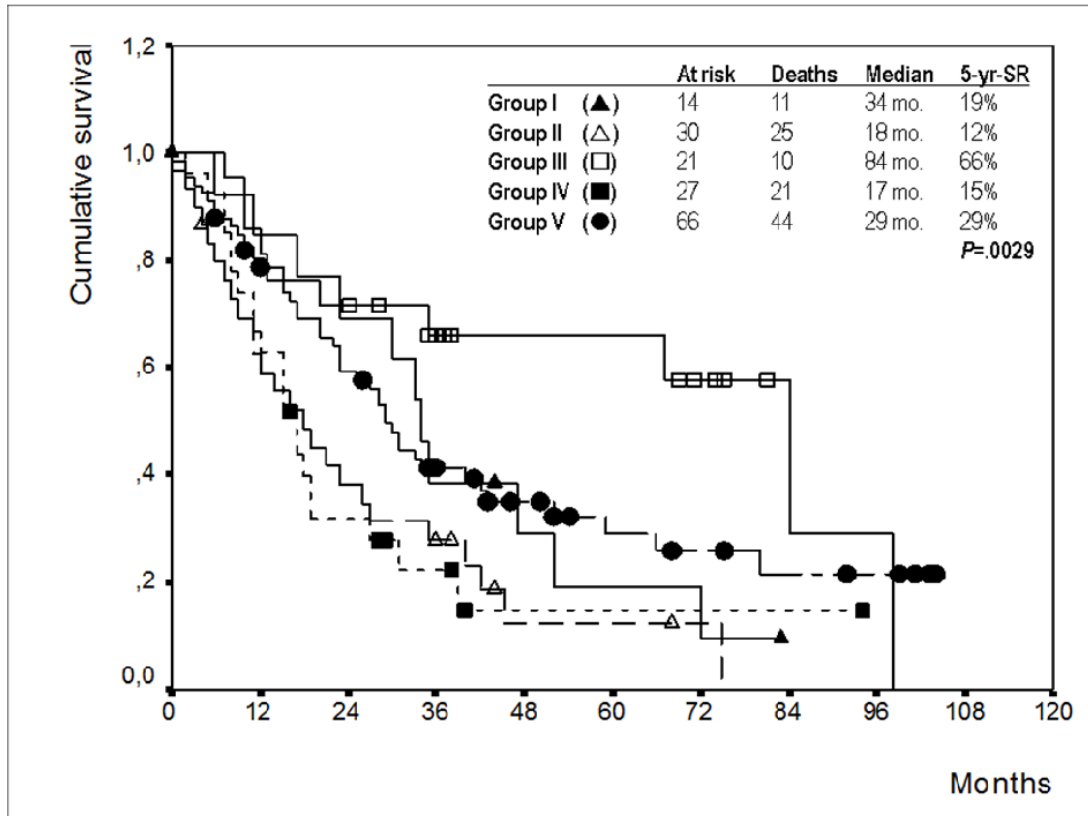


Figure 3: Overall survival of patients according to the modality of nodal involvement. *Group I*, N2-disease in the AP-region; *group II*, N2-disease at other level; *group III*, N2-disease at mediastinoscopy with complete response to induction treatment; *group IV*, N2-disease at mediastinoscopy with partial or no response to induction treatment; *group V*, N1-disease in the hilar or interlobar region. 5-yr-SR, 5-year survival rate.

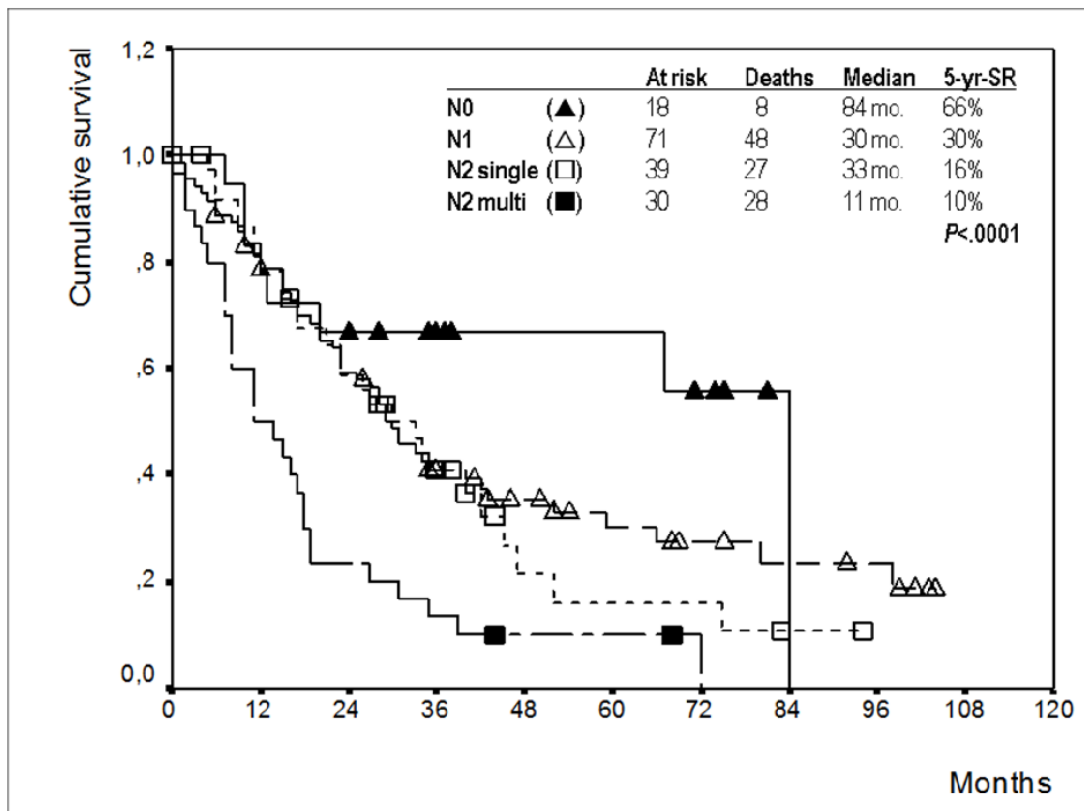


Figure 4: Overall survival of patients according to the amount of lymph node involvement. *N2 single*, single level nodal metastasis; *N2 multi*, multilevel nodal metastasis.

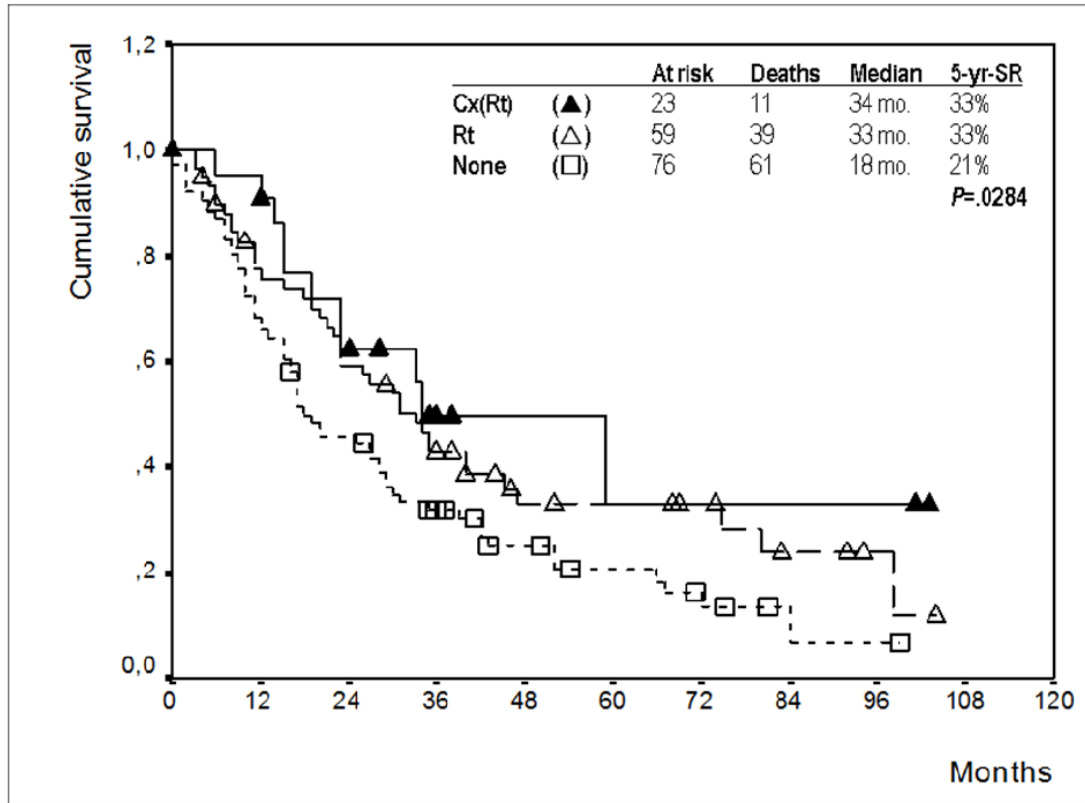


Figure 5: Overall survival of patients according to the type of adjuvant therapy. *Cx(Rt)*, chemotherapy with or without radiotherapy; *Rt*, radiotherapy.

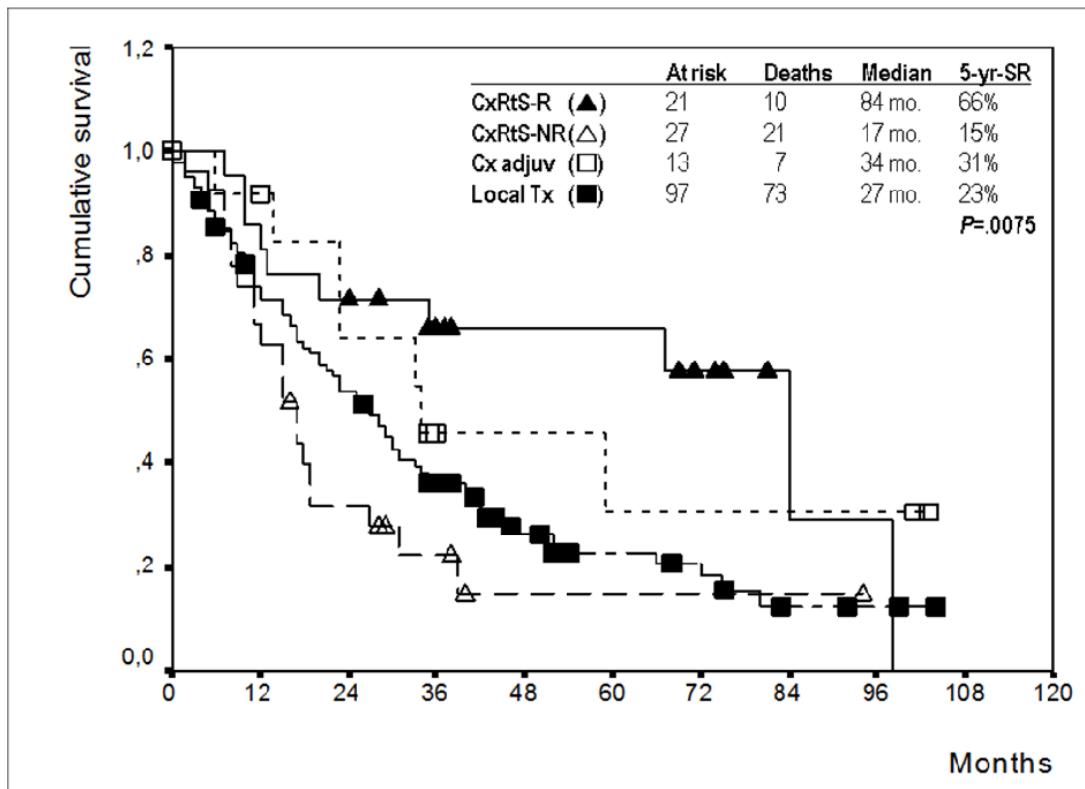


Figure 6: Overall survival of patients according to the treatment modality. *CxRtS-R*, chemo-radiotherapy and surgery with complete nodal response to therapy; *CxRtS-NR*, chemo-radiotherapy and surgery without complete nodal response to therapy; *Cx adjuv*, adjuvant chemotherapy; *Tx*, local treatment modality (surgery with or without radiotherapy)



NSCLC has been investigated in the past. Keller and colleagues analyzed the results of the Eastern Cooperative Oncology Group (ECOG) 3590 trial by site of primary tumour and pattern of lymph node metastases [21]. Particularly, they compared survival of patients with single-level mediastinal involvement with that of patients with N1-disease originating in the same lobe: median survival was 35 months for the former group and 65 months for the latter one, respectively ( $P=.02$ ). This is in contrast to our finding of comparable prognosis for patients with either N1- or single-level N2-disease (median survival: 30 vs. 33 months, respectively;  $P=ns$ ). This can be explained by the different therapeutic approaches for patients with N1-disease between the studies: in fact, all patients in the ECOG 3590 trial received either adjuvant chemoradiotherapy (52%) or adjuvant radiotherapy (48%), while in our series adjuvant therapy was administered to only 41% of N1-patients.

Interestingly, Keller et al. observed that in patients with tumour originating in the left upper lobe survival of the subgroup with single-level N2 metastases was comparable to that of the subgroup with N1 disease (median survival, 51 vs. 49 months;  $P=ns$ ) [21]. This is in accordance with our finding of similar outcomes between the two subgroups (median survival of 32 months for single-level A-P region N2 patients vs. 30 months for N1 patients;  $P=ns$ ).

## Extent of nodal involvement

Another remarkable result of our study was the effect of continuous worsening of prognosis with increasing extent of nodal involvement (Figure 2), although the difference between N1-disease and single-level N2-disease was not statistically significant. The presence of multilevel involvement carried disappointingly low survival rates, with a median survival time of 10 months. This confirms previous reports of the literature: Sagawa et al. [22], in fact, reported that 41% of 94 patients with a single involved mediastinal level were 5-year survivors, and the difference between the ratio for these patients and that in the patients with 2 or more involved levels (13%) was highly significant ( $P=0.001$ ) [22]. In an analysis of patients with resected N2-disease NSCLC, Andre et al. reported that the 5-year survival rates for patients with single-level and multilevel N2 disease detected during surgery were 34% and 11%, respectively ( $P=.0001$ ). In that series, the survival of patients with multilevel disease was close to that of patients with preoperatively detected N2 and stage IIIB disease. On the other hand, the prognosis of patients with single-level disease was similar to that of cases with stage IIB reported in the literature [30]. Similar findings on the prognostic power of extent of nodal involvement have been also outlined by Keller and coll. [21], and Riquet and coll. [31].

## Therapeutic approach to node-positive disease

On the multivariate analysis of our series, the third major determinant of survival, beyond time of diagnosis and extent of nodal involvement, was the addition of systemic therapy to surgery.

Patients receiving postoperative chemotherapy, alone or in combination with radiotherapy, did significantly better as compared with patients treated by surgery alone, but there were no relevant differences with the group undergoing adjuvant radiotherapy. In order to investigate the relative contribution of systemic therapy in improving survival, we compared patients treated by approaches including chemotherapy (pre- or postoperatively) with those treated by local procedures, i.e. surgery with or without radiotherapy, exclusively. Survival analysis showed a moderate advantage for the chemotherapy group, but this was not statistically significant (5-year survival rates, 36% vs. 27%;  $P=ns$ ). By splitting the chemotherapy group into subpopulations according to the timing of systemic therapy, we could identify categories of patients with markedly different prognosis. Patients receiving induction chemotherapy with clearance of nodal metastases (“responders”) had a very favourable long-term outcome, whereas those without mediastinal clearance (“non responders”) did worst; patients receiving chemotherapy in an adjuvant setting had an intermediate prognosis, though superior to the local therapy group, as shown in Figure 5.

We would like to focus on patients groups with a “clinical” N2-disease – thus with preoperatively detected nodal disease: In previous series, surgery alone did not lead to a survival advantage in these patients; even in cases of “complete” resection, long-term survivors were the exception rather than the rule [30]. Thereafter, several randomized trials of the early 90’s showed a clear benefit of multimodality protocols including induction chemotherapy prior to surgery for clinical N2-disease [32], [33]. However, such improvement in the prognosis was not reserved for all patients, as the persistence of nodal disease at surgery was associated with poor outcome despite complete resection [34], [35], [36], [37]. This justified our decision to split the patients group with clinical N2-disease undergoing induction chemo-radiotherapy and surgery into two subgroups according to the nodal response. Responders showed the best long-term outcome (median survival: 84 months; 5-yr survival rate: 66%), comparable with stage I disease; this result reflects an effective control of either locoregional disease and occult metastases. On the other side, non-responders (median survival: 17 months; 5-yr survival rate: 15%) fared worse even than the group of patients treated by surgery alone or in combination with radiotherapy. As most of them (74%) died of recurrent disease, it is recognisable that chemotherapy failed to eradicate either nodal metastases in mediastinum and distant micrometastases, which later appeared as a recurrence. Thus, the presence of persistent lymph node

metastases after induction therapy should be considered as a reliable marker of non-controlled disease. The contribution of surgical resection to improve survival in such cases is questionable.

The group of patients receiving adjuvant chemotherapy showed an intermediate outcome between the two former groups. It is likely that this group includes potential “responders” and cases with chemo-resistant occult disease. Unfortunately, the adjuvant setting lacks a response marker such as the nodal status to discriminate responders from non-responders.

For patients with clinical N2-disease undergoing induction therapy, the crucial point is to detect persistent disease before surgery, in order to discriminate “true” resectable cases from those at high risk of occult metastases. However, the issue of accurate restaging of mediastinal nodes is still a matter of debate. Computed tomography (CT) scan has shown limited value in restaging of lung cancer, particularly in the detection of mediastinal lymph node metastases [38]. Positron emission tomography with 18F-2-fluoro-2-deoxy-D-glucose (FDG-PET) has gained an accepted value for the response evaluation after induction treatment, particularly when integrated with CT scan [39], [40]. Recently, the minimally invasive techniques of transoesophageal endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and endoscopic transbronchial ultrasonography with fine needle aspiration biopsy (EBUS-FNAB) have become clinically available and may reach high accuracy in the primary staging of lung cancer, under the condition that the suspicious lymph nodes on CT or PET scan are targeted. A systematic exploration of the mediastinum is usually not included. Thereafter, its value in the restaging setting is not adequately defined and requires further investigation [41], [42], [43]. Finally, remediastinoscopy is generally considered by many thoracic surgeons as a hazardous and inaccurate procedure, especially after induction protocols including radiotherapy. However, some reports on repeat surgical exploration of mediastinum as part of multimodality protocols suggested remediastinoscopy to be a safe and accurate tool [38], [44], [45].

Whereas the overall survival benefit of platinum-based chemotherapy, either in the adjuvant or in the neoadjuvant setting, over surgery alone has been accepted on the basis of randomized trials and meta-analyses [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [46], [47], [48], the optimal timing of chemotherapy in multimodality protocols remains still under investigation. Induction therapy has claimed some potential advantages: treatment of occult metastases at the earliest possible time, downstaging of primary tumours that could result in a higher rate of complete resection, higher compliance to treatment, and an in-vivo assessment of tumour chemosensitivity with a solid end-point represented by pathologic response. Theoretical disadvantages include a delay in potentially curative surgery (e.g. in the non-responders population), and increased surgical morbidity and mortality, especially when pneumonectomy needs to be performed. Nevertheless, current evidence

on neoadjuvant chemotherapy shows an effect that is comparable to the one described in meta-analyses on adjuvant chemotherapy [49], [50]. For this reason, several comparative trials randomizing between adjuvant and neoadjuvant chemotherapy are addressing this question. In conclusion, survival of patients with N2-NSCLC does not depend on the anatomical location of nodal disease, but is strongly correlated to the extent of nodal metastases or rather the number of involved node levels. The outcome of patients with node-positive NSCLC seems to be significantly influenced by the treatment modality, as the addition of chemotherapy to surgical resection, with or without radiotherapy, may improve long-term survival rates. Our series confirms previous findings, that the clearance of mediastinal lymph node metastases after induction treatment in association with complete surgical resection offers the best prognosis among these patients; therefore, all staging efforts should be applied to identify those patients, for whom resection is associated with prolonged survival. If this is possible at the present time, one of the major goals for the next future will be to enhance the rate of mediastinal downstaging, e.g. by means of targeted induction treatment. As a targeted drug therapy is currently feasible in about 20% of adenocarcinomas, further investigations should address this issue in at least a subset of patients with node-positive lung cancer.

## Notes

### Competing interests

The authors declare that they have no competing interests.

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