

Surgery on unfavourable persistent N2/N3 non-small-cell lung cancer after trimodal therapy: do the results justify the risk?

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Abstract

OBJECTIVES: Persistent mediastinal lymph node metastasis after neoadjuvant therapy is a significant negative indicator for survival. Even though there is still no consensus on the matter, some authors advocate a thorough restaging prior to surgery and deny surgery in cases of persistent N2 because of the poor outcome. We analysed our results after trimodal therapy in pN2/N3 stage III non-small-cell lung cancer (NSCLC) and persistent mediastinal lymph node metastasis after neoadjuvant chemoradiotherapy.

METHODS: We conducted a retrospective cohort analysis of 167 patients who received trimodal therapy for stage III NSCLC. Progression-free interval and survival were calculated. T-stage, N-stage, ypT-stage, ypN2/3-stage and surgical procedure were tested as risk factors.

RESULTS: Eighty-three patients with potentially resectable initial pN2/3 underwent 44 pneumonectomies and 76% extended resections. Thirty-five patients showed persistent mediastinal lymph node metastasis after trimodal therapy. Treatment-related comorbidity after an operative therapy was 58%. Hospital mortality was 2.4%. The ypT- and ypN2/N3 stages were significant risk factors and, in the case of persistent mediastinal lymph node metastasis, median progression-free period was 17 months and median survival time was 21 months.

CONCLUSIONS: Persistent but resectable N2/N3 after chemoradiotherapy in stage III NSCLC is the least favourable subgroup of patients in neoadjuvant approaches. If surgery can be carried out with curative intent and low morbidity, completing trimodal therapy is justified, with an acceptable outcome.

Keywords: Lung cancer • Surgery • Neoadjuvant therapy • Outcome

INTRODUCTION

Non-small-cell lung cancer (NSCLC) neoadjuvant protocols have been shown to improve outcome in selected stage III disease. The purpose of neoadjuvant approaches is both to control and eliminate occult distant metastasis and to reduce and downstage the primary tumour and mediastinal metastasis, respectively. Unfortunately, at the present time, the response rate to the neoadjuvant protocol cannot be predicted in advance and the results of neoadjuvant therapy vary considerably—from an unintentional upstaging effect to full pathological response with no vital tumour left: ypUICC stage 0. Most authors dealing with neoadjuvant protocols in NSCLC agree that persistent mediastinal vital tumour after neoadjuvant therapy is a significant negative indicator for survival. Though a consensus view on that issue is still lacking, a thorough restaging is required and surgery is

denied after induction therapy in cases of persistent N2 disease, because of supposedly lower survival benefit and potentially high comorbidity and mortality [1, 2]. However, are the results really so poor when compared to standard therapy? We analysed our results after trimodal therapy in potentially resectable pN2/N3 stage III NSCLC and persistent mediastinal lymph node metastasis after neoadjuvant chemoradiotherapy.

MATERIAL AND METHODS

The Ethics Committee of the University of Tübingen approved the study. Individual consent was not necessary because of its retrospective design. Staging was based on the TNM Classification of Malignant Tumours, 6th edition.

Between 1994 and 2006, 167 patients with stage III/IV NSCLC received a neoadjuvant therapy. Eighty-four patients with T4 and non-confirmed mediastinal N2/N3-metastases were excluded.

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The remaining 83 patients had histologically proven pN2/3 NSCLC and were included in this study.

Patients were accepted for trimodal therapy in cases of confirmed stage III NSCLC and subject to the following criteria:

- i. resectability of primary tumour or expected resectability after neoadjuvant radiochemotherapy,
- ii. resectability of mediastinal metastasis or expected resectability after radiochemotherapy or expected sterilized mediastinum due to radiochemotherapy, and
- iii. adequate general condition of patient, with a Eastern Cooperative Oncology Group (ECOG)-score of 0-2 or Karnofsky Index of more than 50%.

We accepted single- and multilevel and bulky N2 disease as well as formal N3 but not bulky N3 and N2, contralateral hilar N3 or supraclavicular N3 disease for the neoadjuvant approach.

Standard cervical mediastinoscopy was routinely carried out in all patients, with biopsies from stations 2, 4 and 7. In cases of bulky mediastinal disease we did not evaluate all mediastinal lymph node stations but limited mediastinoscopy to confirming malign metastasis.

Two patients with initial stage IV NSCLC had an isolated and resected cerebral metastasis before entering the neoadjuvant protocol.

To rule out distant metastasis, all patients underwent full oncological staging, including CT scanning of the thorax, bone scan, a CT or MRI scan of the head and CT or ultrasound scanning of the abdomen. A bronchoscopy was performed to obtain a specimen from the tumour and to rule out endobronchial tumor involvement. Functional staging consisted of spirometry, body plethysmography and electrocardiogram. Cardiopulmonary exercise testing, as well as a PET/CT and diffusing capacity, was performed as necessary in selected patients. Mediastinoscopy was done to confirm or rule out mediastinal lymph node metastasis.

We employed two different neoadjuvant protocols during the study period. The older protocol was used until 1999 and consisted of two courses of cisplatin (100 mg/m²) and vindesine (3 mg/m²), followed by sequential standard fractionated radiation (2 Gy/day) up to 36 Gy to the tumour and mediastinum and two additional concurrent courses of cisplatin and vindesine. The neoadjuvant therapy was administered by oncologists and radio-oncologists. Surgeons approved trimodal therapy and, although not engaged directly in the processes, were routinely kept informed on progress during chemo- or chemoradiotherapy. After chemoradiotherapy, a full oncological and functional staging was repeated without routine remediastinoscopy. From 1999 we administered four courses of polychemotherapy with carboplatin (AUC2) and paclitaxel (100 mg/m²) once weekly. Subsequently, in week 6, accelerated hyperfractionated radiotherapy was initiated, with two treatments daily (at 1.5 Gy), five times per week, up to a cumulative dose of 45 Gy. Finally, two additional, concurrent cycles of chemotherapy [carboplatin (AUC2) and paclitaxel (50 mg/m²)] were administered.

The planned surgical procedure was carried out if no distant metastasis was detected after restaging; the resectability of primary tumour and mediastinal metastasis via one operative approach were given regardless of N2 or formal N3. In the event that the mediastinal metastases were not accessible with the planned procedure (as in left-sided tumours), either metastasis should be sterilized by radiotherapy, diminish or complete disappear after radiochemotherapy.

In cases where forced expiratory volume after 1 second (FEV₁) was <70% or transfer factor of the lung for carbon monoxide (DLCO) <60%, postoperative FEV₁ or DLCO were calculated by a perfusion scan of the lung or, in more recent years, cardiopulmonary exercise testing. If calculated postoperative FEV₁ or DLCO was <40% or maximum O₂ uptake <15 ml/kg/min, surgical intervention was declined. If maximum O₂ uptake ranged between 15-20 ml/kg/min, a lobectomy was performed. All operations were initiated with curative intent and were performed via a postero-lateral thoracotomy. Sleeve resections were performed whenever possible to preserve organ function, regardless of the neoadjuvant treatment. Lymphadenectomy was routinely performed for positions 5, 6, 7, 8 and 9 in left-sided primary tumours and for positions 2, 4, 7, 8 and 9 for right-sided tumours.

In cases of initial resectable paratracheal N3 disease in primary right-sided tumours, we resected mediastinal metastasis whenever possible. In some cases, individual supraclavicular lymph nodes after neoadjuvant therapy were resected by a separate approach. Non-reachable low-volume N3 disease was assumed to be sterilized by radiotherapy without consequent resection.

Following pneumonectomy or bronchial sleeve resection, bronchoscopy for stump healing was performed before leaving the hospital. Since the year 1999 we have routinely employed stump protection using various materials, including muscle flap of chest wall or diaphragm, pericardial fat tissue, pediculated pericardium and azygos vein. Since 2002 we exclusively use pediculated pericardium.

No patient received an adjuvant procedure such as chemo- or radiochemotherapy immediately after the surgical procedure.

Follow-up was taken from our own outpatient files and from the residents' registration office of Baden-Württemberg, Germany. Cut-off date for follow-up was 31.05.2010.

All statistical calculations were performed using the SPSS Statistics 19 software package (SPSS Inc., Chicago IL, USA).

The Kaplan-Meier method was used to analyse mean and median survival rates and progression-free intervals after operation. Risk factors for survival, including T-stage, N-stage, ypT-stage, ypN-stage and operative procedure were analysed by univariate log-rank test and Cox regression.

Variables were categorized as follows: N-stage in N2 and N3, ypN-stage in N0 & N1 and N2 & N3.

Pearson's chi-squared test was used for comparing qualitative variables. For comparing quantitative variables, unpaired *t*-test was used in case of normal distribution and Mann-Whitney test in others.

RESULTS

Eighty-three patients (68 men and 15 women) received neoadjuvant therapy between 1996 and 2006 for mediastinoscopically proven pN2/N3 NSCLC. Their comorbidities are listed in Table 1. Thirty-two were presented with stage IIIa, 49 with stage IIIb and 2 with stage IV (Table 2).

Twenty patients out of 22 (90%) who were treated with cisplatin/vindesine and standard fractionated radiation completed the neoadjuvant protocol, as did 42 out of 61 (69%) of the group treated by carboplatin/paclitaxel with hyperfractionated radiation. None of our patients showed occult pleural metastases or were intraoperatively considered as non-resectable. Thirty-six lobectomies, three bi-lobectomies and 44 pneumonectomies were necessary for the intended curative surgery. Extended

Table 1: Demographics and comorbidities.

Gender: male/female	68/15
Weight at admission: mean ± SE/range (kg)	79 ± 15/50–140
Height at admission: mean ± SE/range (cm)	173 ± 8/153–195
Body mass index: mean ± SE/range (kg/m ²)	26 ± 4/19–38
Karnofsky index: 60/70/80/90/n.a. (n)	4/23/43/10/3
Coronary artery disease: yes/no/n.a. (n)	6/75/2
Diabetes mellitus: yes/no/n.a. (n)	7/74/2
Renal insufficiency:	
on dialysis/compensated/no/n.a. (n)	0/1/80/2
Haemoptysis: yes/no/n.a. (n)	26/54/3
Weight loss: yes/no/n.a. (n)	37/44/2
Mean ± SE (kg)	1.7 ± 2.7
Smoking prior to surgery: yes/no/n.a. (n)	19/62/2
Mean ± SE (pack years)	36 ± 24
FEV ₁ mean ± SE/range (%)	83 ± 19/36–128
RV mean ± SE/range (%)	110 ± 30/50–202
VCin mean ± SE/range (%)	87 ± 19/38–162
TLC mean ± SE/range (%)	94 ± 16/42–154

Weight loss in kg within 3 months before admission.
n.a.: not available; FEV₁: forced expiratory volume in 1 second; RV: residual volume; VCin: inspiratory vital capacity; TLC: total lung capacity.

Table 2: Tumour stages before entering neoadjuvant therapy

UICC	T	N	M	N
IIla	1	2	0	4
	2	2	0	20
	3	2	0	8
IIlb	1	3	0	1
	2	3	0	7
	3	3	0	3
	4	2	0	32
IV	4	3	0	6
	3	2	1	1
	4	2	1	1

resections were necessary in 64 patients, involving 14 bronchial and 7 vascular sleeve resections, 12 partial resections of left atrium, 5 chest wall resections, 11 partial oesophagectomies and 36 intrapericardial vascular resections.

Mean operating time was 238 min (115–440 min) and mean blood loss was 491 ml (100–1500 ml). Mean chest drain duration was 6 days (0–47 days). Mean postoperative stay was 17 days (10–114 days). Histological analyses showed 43 squamous cell carcinomas, 31 adenocarcinomas and 9 mixed tumours. Thirty-five patients showed persistent mediastinal involvement of the lymph nodes after trimodal therapy with 30 ypN2 and 5 ypN3 respectively (Table 3).

Treatment-related comorbidity after operation was seen in 48 patients (58%), including bleeding, stump insufficiency, new neurological disorders, rhythm disturbances, heart failure, myocardial infarction, renal insufficiency, pneumonia, pleural empyema, respiratory insufficiency, acute respiratory distress syndrome (ARDS) and acute lung injury respectively. Hospital mortality was 2.4% (n = 2). The aggregated follow-up time for all 83 patients were 3347 months with a median overall survival of

Table 3: Pathological tumour stages after trimodal therapy

ypUICC	ypT	ypN	ypM	N
0	0	0	0	21
Ia	1	0	0	12
Ib	2	0	0	1
IIa	0	1	0	2
	1	1	0	4
	2	1	0	4
IIb	3	0	0	4
IIIa	0	2	0	1
	1	2	0	9
IIIb	2	2	0	8
	3	1	0	1
	3	2	0	5
	1	3	0	2
	2	3	0	2
	4	1	0	1
IV	4	2	0	3
	4	3	0	1
	2	0	1	1
	4	2	1	1

29 months and mean overall survival of 40 months. The group with initial formal N3 disease had a median survival of 31 months. Median and mean survival times for persistent ypN2/N3 were 21 and 32 months, respectively (Table 4), and were significantly different in univariate testing ($P < 0.001$), such as for ypN0/1, where median survival is not available but mean survival was 32 months (Table 4).

The ypT-stage ($P = 0.022$) was also a significant indicator for survival in univariate testing, while initial T-stage and N-stage were not. Mean and median progression-free intervals for ypN2/3 were 36 and 17 months, respectively, and significantly different ($P = 0.008$) in univariate testing to ypN0/1, with 95 months for mean progression-free survival. Median progression-free survival data were not available in that group. The performed procedure (pneumonectomy vs lobectomy/bilobectomy) was not a significant negative indicator ($P = 0.538$) for survival.

In multivariate testing using Cox regression, only persistent N2/N3 ($P = 0.004$) reached levels of significance (Table 5).

COMMENT

Stage III NSCLC represents a very heterogeneous group with 12 TNM classification subsets. It is not surprising that a single therapeutic concept cannot satisfy the needs of all subsets. The results achieved using the currently recommended, standard, concurrent radiochemotherapy in stage III NSCLC vary widely, with median survival times in the range 12–27 months and 5-year survival times varying by up to 19% [3, 4]. It is well known that neoadjuvant approaches can considerably improve outcomes in selected patients with stage III NSCLC, depending on regression rate to chemo- or chemoradiotherapy [5, 6]. In stage IIIA, with histological proven N2, a downstaging effect with a cleared mediastinum was one of the first determined factors for survival in neoadjuvant approaches [7]. Most authors dealing with neoadjuvant therapy confirmed this finding [8–12]. Consequently, to optimize outcome after complex and intensive neoadjuvant

Table 4: Survival data in months

	Mean survival/SE (months)	Median survival/SE (months)	95% CI (months)	Mean Progression-free survival/SE (months)	Median progression-free survival/SE (months)	95% CI (months)
ypT						
ypT0	63/9.7	65/38.5	0–140	85/13	n.a.	n.a.
ypT1	57/9.5	31/17.3	0–65	93/12	n.a.	n.a.
ypT2	36/7.0	25/16.7	0–58	54/12	44/18	8–80
ypT3	15/4.6	10/1.3	7–13	17/8	8/4	0–16
ypT4	20/3.4	19/8.5	17–44	9/3	5/2	0–10
pN3	51/11	31/7	17–45	52/14	45/22	1–89
ypN2/3	32/6.0	21/5.4	10.4–31.6	47/10	17/5	7–27
ypN0/1	70/7.5	n.a.	n.a.	96/10	n.a.	n.a.

SE: standard error; CI: confidence interval; n.a.: not available

Table 5: Risk factors for survival

Parameters	Log-rank test	Cox regression		
	P	P	Hazard ratio	95% CI
T-stage	0.744	0.265	0.265	0.613–1.144
N-stage	0.345	0.07	0.071	0.945–3.979
ypT-stage	0.022	0.15	0.117	0.947–1.627
ypN2-stage	<0.001	0.001	0.001	0.142–0.614
Pneumonectomy	0.538	0.42	0.418	0.663–2.692

protocols, several groups, including the American College of Chest Physicians, recommend a thorough, invasive restaging of the mediastinum prior to surgery and denial of surgery in cases of persistent mediastinal involvement of the lymph nodes [1, 8, 13, 14]. However, are the results so bad that surgeons must refuse to deliver surgical therapy to that group?

After neoadjuvant radiochemotherapy we routinely carry out a standard restaging in every patient to rule out progressive disease: this consists of a positron emission tomography-computed tomography (PET-CT) scan, MRI of the brain and bronchoscopy. CT scans alone are not good indicators of the response rate of the mediastinum after radiochemotherapy, because the size of lymph node metastasis can persist in cicatrization after good response and reorganization due to radiochemotherapy and can persist due to a bad response to chemo- or chemoradiotherapy. In the latter situation, surgery alone can make a major contribution to overall therapy where the disease is resectable. Of course, lymph nodes also can disappear at CT in case of excellent regression due to chemo- or chemoradiotherapy. But accepting only these patients for surgery is like cherry-picking and disregards the potential of trimodal therapy in advanced diseases. Even the reliability of a PET-CT is not 100% in identifying persistent tumour after neoadjuvant radiochemotherapy. Hence, in cases of almost full-dose radiochemotherapy and mediastinal metastasis that is considered to be either sterilized or potentially resectable, a routine remediastinoscopy does not reveal additional relevant information. Only in individual cases of assumed progressive disease following radiochemotherapy, or of potentially unresectable disease, do we carry out a repeat mediastinoscopy, endobronchial ultrasound (EBUS) biopsy or further invasive reexaminations of the mediastinum. To identify these candidates it

is necessary to have performed a PET-CT before starting trimodal therapy, repeated at least 3 weeks after the last radiotherapy, to anticipate the full effect of radiochemotherapy on mediastinal metastasis.

We accepted patients with formal N3 disease as defined in the 6th edition of the TNM classification, even though it is well known that curative surgery is by no means part of the standard therapy in this stage of advanced NSCLC. However, all of our patients had limited N3 disease and either the contralateral paratracheal N3 mediastinal metastasis could be resected by an ipsilateral approach—as in right-sided tumours—or the volume of N3 disease was sufficiently small that radiochemotherapy should reliably sterilize these metastases. Alternatively, some individual supraclavicular N3 lymph nodes were considered as singular extensions of the mediastinal metastasis outside the radiation field after radiochemotherapy and were resected as isolated treatments. We had 15 patients with initial, formal N3 status and the median survival time in that group was 31 months, with 5 patients still alive. In our opinion a limited extension of N2 to a formal N3 disease, or a limited formal N3 disease as mentioned above, do not justify refusing surgery or determination of a palliative situation.

Meanwhile, many publications have indicated that neoadjuvant treatment-related comorbidity could be managed and mortality kept low if induction therapy and surgery is carried out in specialized centres [15–18]. We had a hospital mortality rate of 2.4% and this rate does not differ significantly from primary concurrent radiochemotherapy without surgery [3, 4, 19]. So comorbidity and mortality should not be the main reason for not completing surgery in neoadjuvant approaches and persistent N2.

With our data we could clearly demonstrate, with univariate and multivariate testing, that persistent but resectable N2/N3 after induction therapy is a significant risk factor ($P < 0.001/P = 0.004$) for survival with a median survival time of 21 months. Other authors reported outcomes with median survivals from 19–24 months [20, 21]. These findings do not differ greatly from the results of primary resection in resectable stage III NSCLC without induction but with adjuvant chemotherapy and from definitive chemoradiotherapy without a neoadjuvant approach [3, 22–25]. Nonetheless, the latter groups are often not surgically but clinically staged and, what is more important, the results count for non-responders and full responders. Even in the era of PET-CT, it is not possible to apply results isolated for non-responders after chemoradiotherapy because no reliable

reference points exist. In consequence, looking exclusively at non-responders with persistent mediastinal carcinoma, the results of primary radiochemotherapy are probably worse than currently known and also probably worse than our results after trimodal therapy.

The unknown response rate is a major problem because response to chemo- or chemoradiotherapy is a determinative factor in neoadjuvant therapy. Most decisions about neoadjuvant therapy in stage III NSCLC were made before chemo- or chemoradiotherapy had been started and without the knowledge of a possible response rate. In our analysis the pre therapeutic T-stage ($P=0.744$) and N-stage ($P=0.345$) have completely lost their prognostic value and only ypT-stage and ypN2/N3-stage after induction therapy are of prognostic value. However, if a decision is to be made concerning a neoadjuvant approach, it is usually based on an unknown response rate and prognostic non-relevant markers; hence, the decision can sometimes become an equation with three unknowns.

Another point of note is that, despite 35 patients with persistent mediastinal pN2/N3 after trimodal therapy, the median progression-free interval after operation is 17 months and 13 of these 35 patients had no recurrence or progression at all in follow-up. The latter point cannot happen without surgery and is an exclusive advantage of surgery in persistent N2 after neoadjuvant therapy, even though the benefit of this theoretical advantage is very difficult to prove. In contrast to others, we also found no significant difference in survival in respect of the operated procedure. This may also be due to the low number of lobectomies in that group (17%). Nonetheless, our data revealed that pneumonectomies are not a risk factor for survival and are justified, even for persistent but resectable N2/N3.

One limitation of our study is the long study period. Within this period, staging procedures as well as neoadjuvant protocols and available systemic agents had progressed significantly and we did not apply a single strategy. Hence, by using the different strategies (diagnostic and therapeutic) we may have produced a selection bias according to the strategies adopted.

In summary, patients with persistent N2/N3 after chemoradiotherapy in stage III NSCLC are the most unfavourable subgroup in neoadjuvant approaches. At the present time, with a common unknown response rate—and if surgery can be undertaken with curative intent and similar mortality to that of primary radiochemotherapy—surgery to complete the treatment, with acceptable outcome.

Conflict of interest: none declared.

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eComment. Should persistent N2/N3 non-small cell lung cancer be treated by surgery?

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We have read with interest the paper by Steger *et al.* [1] on the efficacy of surgery in persistent N2/N3 non-small cell lung cancer (NSCLC) after induction therapy, and we are very surprised by some questionable authors' choices.

First of all, they treated stage IIIB-N3 patients with trimodal therapy, despite the recent indications to administer only chemoradiotherapy (CRT) and avoided surgery (National Comprehensive Cancer Network guide-lines version 3, 2012). Then, they operated on patients with persistent N2 and even N3-staged cancer, despite the adverse consensus [2]. Many trials demonstrated that surgery should be limited to IIIA-N2 patients with evident nodal down-staging after induction CRT due to poor prognosis in persistent N2 [2] and surgical complications related to induction therapy. Recently Gomez-Caro [3], reporting his surgical experience in patients after induction therapy, suggested to avoid right pneumonectomy due to high postoperative complications. Moreover, he confirmed that down-staging of mediastinal nodes is the strongest predictor of survival and that incomplete resection offers no benefit. That being said, invasive restaging is considered mandatory prior to surgery [4].

Surprisingly Steger *et al.* [1] excluded only patients with disease progression after induction CRT from surgery and treated all patients with resectable tumours, both N2 and N3. They never performed surgical restaging and, in fact, operated on 30 patients with persistent N2, and 5 patients with persistent N3. Lastly, they did not administer adjuvant therapy in any patient. Furthermore, we were also surprised

that 44 pneumonectomies were performed on 83 procedures despite the well-known complications after induction therapy. Anyway, we congratulate the authors for the hospital mortality, which was 2.4% and the acceptable morbidity rate (58%). Focusing on the results, ypN2/N3 had a significantly worse prognosis than ypN0/N1, confirming the common experience. We also note that initial T-stage and N-stage were not significant survival indicators. Again, these evidences should have led the authors to conclude that surgical restaging is essential in prognosis determination and must be always performed. Nevertheless, the authors defended surgery in persistent N2/N3, since median progression-free interval was 17 months, and 13 patients had no recurrences (follow-up not specified). They attributed this last point to surgery. They also reported that overall outcomes in ypN2/N3 are consistent with those of patients treated with definitive CRT, concluding that surgery does not worsen overall prognosis but in singular cases may improve it. Their conclusions could prompt us to reconsider the role of surgery in advanced NSCLC. However, we must underline that their overall outcomes are not encouraging. It would be more interesting to investigate why a small group of ypN2/N3 presented with a better prognosis, in order to identify further prognostic criteria [5].

Finally, we disagree in considering N2/N3 patients a homogeneous population with regard to prognosis and underline that current guidelines recommend adjuvant therapy after induction therapy, especially in cases of residual tumours.

Conflict of interest: none declared

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