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ORIGINAL RESEARCH

# Neoadjuvant chemoradiotherapy is superior to chemotherapy alone in surgically treated stage III/N2 non-small-cell lung cancer: a retrospective single-center cohort study

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Available online 6 April 2022

**Background:** There is lack of consensus whether neoadjuvant chemoradiotherapy (CHT/RT) is superior to neoadjuvant chemotherapy (CHT) alone in patients with potentially resectable stage III/N2 non-small-cell lung cancer (NSCLC).

**Patients and methods:** We retrospectively evaluated clinical parameters and outcomes in patients with clinical stage III/N2 NSCLC treated with neoadjuvant CHT/RT versus CHT followed by surgery. Nearest-neighbor propensity score (PS) matching was used to correct for pretreatment differences.

**Results:** A total of 84 patients were enrolled. Thirty-four (40%) and 50 (60%) patients received CHT/RT or CHT followed by curative-intent surgery, respectively. Overall 90-day mortality and morbidity were 0% versus 0.04% and 21% versus 18%, respectively, with no significant difference between the CHT/RT and the CHT-alone cohorts ($P = 0.51$ and $P = 0.70$). In the PS-matched cohort, complete pathological response was recorded in 25% after CHT/RT versus 0% after CHT at the time of surgery. Patients receiving neoadjuvant CHT/RT exhibited significantly better 5-year disease-free survival (DFS) [45% versus 16% CHT group; hazard ratio (HR) 0.43, $P = 0.04$]; 5-year overall survival (OS) was 75% after CHT/RT and 21% after CHT (HR 0.37, $P = 0.001$). CHT/RT more often induced pathological mediastinal downstaging ($P = 0.007$), but CHT/RT remained the only independent factor for DFS and OS and did not depend on mediastinal downstaging.

**Conclusions:** In this retrospective PS-matched long-term analysis, neoadjuvant CHT/RT conferred improved DFS and OS compared with CHT alone in stage III/N2 NSCLC. These highly challenging results require confirmation in well-designed randomized controlled trials conducted at highly specialized thoracic oncology centers.

**Key words:** non-small-cell lung cancer, N2 disease, stage III, induction therapy, radical resection

## INTRODUCTION

Despite all novel treatment options, stage III non-small-cell lung cancer (NSCLC) patients still have a poor prognosis with a median overall survival (OS) of 42, 22 and 11 months in pathological stages IIIA, IIIB and IIIC, respectively.[1] Notably, regardless of stage, the presence of pathologically positive N2 lymph nodes (LNs) at surgery is a negative prognostic factor with a 5-year survival rate of 38% with R0 resection.[2] Due to the heterogeneity of locally advanced tumors, treatment options differ and patients should be discussed in a multidisciplinary team including pulmonologists, medical oncologists, radiation oncologists and thoracic surgeons.[3] The currently available treatment options in patients with stage III N2 disease include neoadjuvant chemotherapy (CHT) or neoadjuvant chemoradiotherapy (CHT/RT) followed by surgery, or definitive CHT/RT including ±immunotherapy.[4-8]

Previous studies demonstrated that neoadjuvant CHT/RT leads to increased pathological response and mediastinal downstaging, without consistent better disease-free survival (DFS) or OS compared to neoadjuvant CHT alone.[5,7,9] However, higher mortality rates in the CHT/RT cohort or in patients receiving pneumonectomy were reported as well.[5,9-11] Therefore, it remains unclear if neoadjuvant CHT/RT is superior to neoadjuvant CHT alone followed by radical

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resection.[12] In this study, we retrospectively analyzed our single-center data to investigate if curative-intent surgery after CHT/RT carried out at a high-volume center is feasible and safe and, moreover, if it results in improved long-term outcome in NSCLC patients with stage III/N2 disease.

## PATIENTS AND METHODS

### *Study design*

In this single-center, retrospective cohort study, consecutive patients with clinical stage III/N2 NSCLC undergoing curative-intent surgery after neoadjuvant therapy at the Division of Thoracic Surgery at the Medical University of Vienna between 2002 and 2014 were included (Figure 1). Date of diagnosis was taken as the time of the first radiological examination that raised a suspicion of malignancy. All cases were (re)staged by using the eighth edition of the tumor—node—metastasis (TNM) lung cancer classification.[13] Patients treated with neoadjuvant CHT/RT were compared to those treated with neoadjuvant CHT alone. Peri- and post-operative parameters were analyzed. The study was approved by the ethics committee of the Medical University of Vienna according to the Declaration of Helsinki (EK No. 1448/2017). Additionally, the study was registered at ClinicalTrials.gov (NCT04455984). Outcomes have been reported according to the 'Strengthening the reporting of cohort studies in surgery (STROCSS)' 2019 guidelines.[14]

### *Evaluation, treatment and follow-up*

In all patients in this study, the tumor was histologically verified and patients had clinically or biopsy-proven N2 disease and were, therefore, treated with neoadjuvant therapy. The decision as to which patients with clinical stage III/N2 NSCLC are able to undergo multimodality treatment including induction CHT/RT or CHT followed by surgery after response to neoadjuvant therapy was taken by an experienced multidisciplinary tumor board with the participation of a thoracic surgeon, radiation oncologist, oncologist and radiologist. N2 disease was partially verified by endobronchial ultrasound biopsy or mediastinoscopy. However, in patients who did not undergo invasive mediastinal staging, cN2 LN involvement was indicated if N2 LNs were significantly enlarged [>15 mm in diameter at computed tomography (CT) scan] and/or [$^{18}$F]2-fluoro-2-deoxy-D-glucose—positron emission tomography (FDG—PET) positive and documented after consultation in a tumor board. Accordingly, the type of neoadjuvant treatment was indicated within referral centers with different institutional protocols depending on factors such as age, performance status, comorbidities and anatomical extent of disease. Histology, tumor grade and LN involvement were assessed at the Department of Pathology, Medical University of Vienna. Depending on the final histology report and pathological stage, patients received further adjuvant therapy, also after discussion in the multidisciplinary tumor board. Follow-up visits included regular CT scans to detect disease recurrence or secondary primary tumors. The time point of recurrence was defined as the date of imaging. Biopsy-proven disease recurrence and DFS were calculated from the time of surgery to the time of recurrence. OS was calculated as the time from surgery to the date of death from any cause. Living patients were censored at the time of last contact.

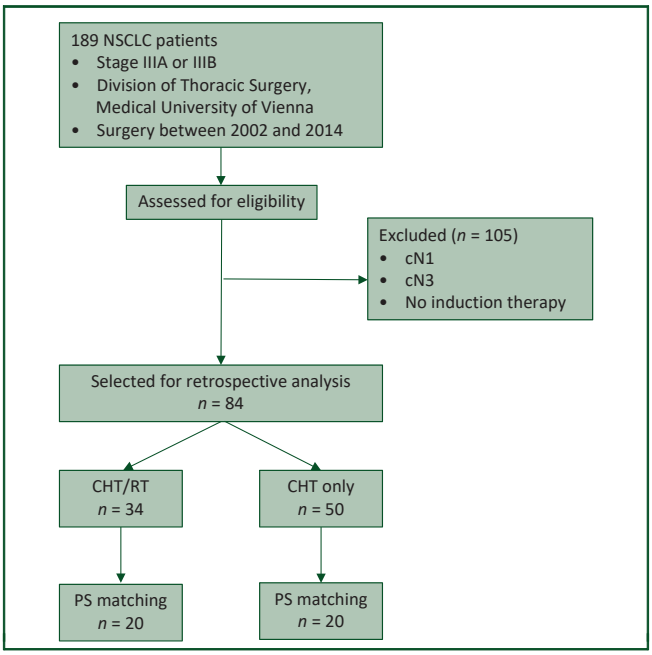


**Figure 1. CONSORT diagram to demonstrate the selection of stage IIIA/IIIB NSCLC cases for surgery after neoadjuvant therapy in this study.**
Where patients were excluded, the reasons for exclusion are indicated.
CHT, chemotherapy; CHT/RT, chemoradiotherapy; cN1, clinical N1 disease; cN3, clinical N3 disease; NSCLC, non-small-cell lung cancer.

### *Data collection and statistical analysis*

Data were retrieved from the institutional thoracic surgery database as well as from the patient's documentation system of the Medical University of Vienna. Additionally, dates of death were reconciled with the death records of 'Statistik Austria'.

Statistical analyses were carried out using the SPSS software (IBM SPSS, IBM Corp., Armonk, NY) and R-software (R Core Team 2017, R Foundation for Statistical Computing, Vienna, Austria). Normally distributed data were presented as mean ± standard deviation and non-normal distributions as median (range). Two independent groups with normal distribution were compared by the unpaired Student's *t*-test. The chi-square test was used for testing differences between two categorical variables. Cox regression analysis was used for univariate and multivariate analysis. Additionally, CHT/RT and CHT groups were matched using nearest-neighbor propensity score (PS) matching with caliper 0.1 (R-package MatchIt). PS matching was carried out according to the following parameters: type of induction therapy, sex, body mass index, year of surgery, age at the time of surgery, diagnosis of chronic obstructive pulmonary disease, diabetes mellitus, arterial hypertension, cardiovascular disease, forced expiratory volume in the first

second % (FEV1) and clinical T stage. OS and DFS were analyzed using the Kaplan—Meier method. Cox regression was used to calculate hazard ratios (HRs) for DFS and OS and to explore prognostic clinical factors. Statistical significance was defined as a two-tailed $P$ value of $<0.05$. All graphical illustrations were created using GraphPad Prism (GraphPad Software, La Jolla, CA).

## RESULTS

### *Patient characteristics and short-term outcome*

The patient cohort consisted of 27 female (32%) and 57 male (68%) NSCLC patients ($n = 84$, median age: 61.5 ± 8.98 years, range: 44.3-82.8 years, Table 1). Median follow-up time for all patients was 33 months; for surviving patients, it was 58 months. Forty percent ($n = 34$) and 60% ($n = 50$) of the patients received neoadjuvant CHT/RT or CHT, respectively. Neoadjuvant CHT consisted of 2-6 cycles of a platinum-based regimen. Neoadjuvant RT had a mean V20 of 21.9% (range: 8%-38%), a mean total cumulative dose of 57 Gy (range: 45-75 Gy) and a total volume of 4013.84 $cm^3$ (range: 2381-6123 $cm^3$). Most patients received concurrent RT (89%, 25/28). In nine patients, data of RT were partly incomplete. Data are shown in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100466. There was no significant difference in neoadjuvant treatment protocols depending on times. Patients in the CHT/RT group were younger (median age: 58 versus 63 years, $P = 0.024$, Table 1); however, there was no significant difference regarding comorbidities or lung function parameters between both groups (Table 2). Patients with stage IIIB disease received significantly more often CHT/RT compared to stage IIIA patients ($P = 0.046$). The most frequent histology was adenocarcinoma in 41 patients (49%), followed by 37 patients (44%) with squamous cell carcinoma (Table 1). The majority of patients (81%, $n = 68$) were diagnosed at stage IIIA (versus 16 patients with stage IIIB disease, 19%; Table 1). Lobectomy was the most frequently carried out resection type ($n = 50$, 60%), followed by pneumonectomy ($n = 27$, 32%), bilobectomy ($n = 6$, 7%) and sublobar resection ($n = 1$, 1%). Extended surgery including bronchial sleeve, vascular sleeve or resections of the chest wall, diaphragm or pericardium was necessary in 38% ($n = 32$) of all cases (Table 1). All surgeries were carried out via thoracotomy. Pneumonectomy was significantly more often carried out in the CHT/RT group (versus those in the CHT-alone group, $P = 0.004$, Table 1). There was neighter a significant difference between stage IIIA and IIIB and the necessity for pneumonectomy (IIIA $n = 21$, IIIB $n = 6$, $P = 0.408$), nor for the survival in patients who underwent pneumonectomy in regard to stage IIIA versus IIIB (OS $P = 0.971$, DFS $P = 0.994$). Complete resection was achieved in all patients ($n = 84$, 100%). All patients underwent mediastinal lymphadenectomy, with no significant difference between the CHT/RT and the CHT-alone groups in the numbers of resected LNs ($P = 0.378$, data not shown).

Overall 90-day mortality and morbidity were 0% versus 0.04% and 21% versus 18%, respectively, with no significant difference between the CHT/RT and the CHT-alone cohorts ($P = 0.51$ and $P = 0.70$, data not shown).

There was no difference in the post-operative complication rates between patients undergoing neoadjuvant CHT/RT and those receiving neoadjuvant CHT only ($P = 0.703$, Table 1). The mean post-operative hospital stay was 11.6 days in the CHT/RT group compared to 7.9 days in the CHT cohort ($P = 0.16$). Notably, we did not observe increased complication rates in patients undergoing pneumonectomy or extended resection (Table 1). Furthermore, the DFS and OS did not differ between the group of pneumonectomy patients and those treated with less invasive surgery [HR 1.066, 95% confidence interval (CI) 0.616-1.845, $P = 0.819$ and HR 1.414, 95% CI 0.817-2.49, $P = 0.216$, respectively, Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100466].

Nodal downstaging (from N2 disease at diagnosis to pN0/1 after surgery) was achieved in 85% ($n = 29$) and 74% ($n = 37$) of patients receiving CHT/RT or CHT alone, respectively ($P = 0.216$) (Table 1). Eighteen of our 84 patients had persistent positive mediastinal LNs (CHT/RT $n = 5$, CHT $n = 13$), whereas 72% ($n = 13$, CHT/RT $n = 5$, CHT $n = 8$) of these patients had single-station N2 disease. Pathological complete responses were, however, observed exclusively in the CHT/RT cohort: 26%; $n = 9$ versus none in the CHT-alone group, $P < 0.001$. Eighteen percent ($n = 6$) and 40% ($n = 20$) of patients in the CHT/RT and CHT groups received adjuvant therapy, respectively ($P = 0.021$, Table 1).

### *Long-term survival*

Seven patients died intercurrently due to myocardial infarction ($n = 2$), suicide ($n = 1$), sepsis ($n = 1$) and tonsillar carcinoma ($n = 1$). The cause of death remained unknown for two patients. In the entire cohort, patients receiving neoadjuvant CHT/RT exhibited significantly longer DFS (54.8 versus 13.4 months in the CHT-alone group; HR 0.425, $P = 0.003$). Neoadjuvant CHT/RT was also associated with improved median OS (82 versus 28 months in the neoadjuvant CHT-alone group; HR 0.373, $P = 0.001$). Neoadjuvant CHT/RT was confirmed as the only independent prognostic factor for both DFS and OS (HR 0.427, $P = 0.011$ and HR 0.422, $P = 0.013$, respectively) in multivariate analysis.

Due to the significant findings, we decided to go one step further and analyzed survival after PS matching, which yielded two groups of $n = 20$ patients each. Median follow-up time in the PS-matched cohort was 48 months for all, and 63 months for surviving patients. In this PS-matched cohort, the clinical T factor was as follows: T1 $n = 3$, T2 $n = 17$, T3 $n = 8$, T4 $N = 12$. Patient characteristics are displayed in Table 1. Patients receiving neoadjuvant CHT/RT showed significantly longer 5-year DFS and OS than those treated with neoadjuvant CHT: 5-year DFS was 45% (95% CI 26% to 78%) versus 16% (95% CI 5% to 53%), $P = 0.04$;

**Table 1. Correlation of clinicopathological features and type of neoadjuvant therapy before surgery in patients with clinical stage III/N2 NSCLC**

| | All patients ($n = 84$) | | | Propensity score match (caliper 0.1) | | |
|---|---|---|---|---|---|---|
| | CHT/RT | CHT | *P* value | PS CHT/RT | PS CHT | *P* value |
| **Patients, *n* (%)** | 34 (40) | 50 (60) | | 20 (50) | 20 (50) | |
| **Age (median ± SD)** | 58.5 ± 8.62 | 62.6 ± 8.85 | 0.024 | 60.93 ± 8.44 | 60.23 ± 10.64 | 0.426 |
| **Gender (male/female)** | 21/13 | 36/14 | 0.33 | 12/8 | 11/9 | 0.749 |
| **Comorbidities, *n* (%)** | 21 (62) | 38 (76) | 0.224 | 13 (65) | 11 (55) | 0.519 |
| **FEV1 <60% ($n = 79$[a])** | 3 | 6 | 0.731 | 1 | 4 | 0.132 |
| **Initial staging, *n* (%)** | | | | | | |
| IIIA | 24 (71) | 44 (88) | 0.054 | 14 (70) | 16 (80) | 0.465 |
| IIIB | 10 (29) | 6 (12) | | 6 (30) | 4 (20) | |
| cT1 | 0 (0) | 12 (24) | | 0 (0) | 3 (15) | |
| cT2 | 15 (44.1) | 14 (28) | | 11 (55) | 6 (30) | |
| cT3 | 9 (26.5) | 15 (30) | | 3 (15) | 5 (25) | |
| cT4 | 10 (29.4) | 9 (18) | | 6 (30) | 6 (30) | |
| **Type of resection, *n* (%)** | | | | | | |
| Pneumonectomy | 17 (50) | 10 (20) | **0.004** | 10 (50) | 3 (15) | **0.018** |
| Bilobectomy | 1 (3) | 5 (10) | | 0 (0) | 2 (10) | |
| Lobectomy | 15 (44) | 35 (70) | | 9 (45) | 15 (75) | |
| Segment resection | 1 (3) | 0 (0) | | 1 (5) | 0 (0) | |
| Extended resection[b] | 22 (64.7) | 15 (30) | | 8 (40) | 6 (30) | |
| **Histological subtype, *n* (%)** | | | | | | |
| **Adenocarcinoma** | 16 (47) | 25 (50) | 0.365 | 9 (45) | 7 (35) | 1.00 |
| **Squamous cell carcinoma** | 16 (47) | 21 (42) | | 9 (45) | 11 (55) | |
| **Large cell carcinoma** | 2 (0.6) | 4 (8) | | 2 (10) | 2 (10) | |
| **Pathological staging, *n* (%)** | | | | | | |
| No tumor | 9 (26) | 0 (0) | **<0.001** | 5 (25) | 0 (0) | **0.017** |
| I | 10 (29) | 16 (32) | | 8 (40) | 6 (30) | |
| II | 8 (24) | 16 (32) | | 6 (30) | 5 (25) | |
| III | 7 (21) | 18 (36) | | 1 (2) | 9 (45) | |
| IV | 0 (0) | 0 (0) | | 0 (0) | 0 (0) | |
| **N2 downstaging (pN0-1), *n* (%)** | 29 (85) | 37 (74) | 0.216 | 20 (100) | 14 (70) | **0.008** |
| **Post-operative complications, *n* (%)** | 7 (21) | 9 (18) | 0.703 | 5 (25) | 6 (30) | |
| Recurrent nerve palsy | 4 (11) | 2 (4) | | 3 (15) | 1 (2) | 0.723 |
| Chylothorax | 2 (6) | 4 (8) | | 1 (2) | 3 (15) | |
| Wound infection | 1 (3) | 1 (2) | | 0 (0) | 1 (2) | |
| Bleeding | 1 (3) | 0 (0) | | 1 (2) | 0 (0) | |
| Bronchopleural fistula | 0 (0) | 0 (0) | | 0 (0) | 0 (0) | |
| Other | 1 (3) | 2 (4) | | 1 (2) | 2 (10) | |
| **Adjuvant treatment, *n* (%)** | 6 (17.6) | 20 (40) | **0.021** | 3 (15) | 9 (45) | **0.014** |
| aCHT | 5 (14.7) | 12 (24) | | 2 (10) | 5 (25) | |
| aRT | 1 (2.9) | 3 (6) | | 1 (2) | 2 (10) | |
| aCHT/RT | 0 (0) | 5 (10) | | 0 (0) | 2 (10) | |

Data shown in parentheses are column percentages. Statistical significant findings are highlighted in bold letters.
aCHT/RT, adjuvant chemoradiotherapy; aCHT; adjuvant chemotherapy; aRT, adjuvant radiotherapy; CHT, chemotherapy; CHT/RT, chemoradiotherapy.
[a]In five cases, FEV1 (forced expiratory volume in the first second) data were not available.
[b]Extended resections include bronchial sleeve, vascular sleeve or resections of the chest wall, diaphragm or pericardium and were stated additionally to type of resection.

5-year OS was 75% (95% CI 58% to 97%) versus 21% (95% CI 8% to 53%), $P = 0.004$, Figure 2.

Nodal downstaging was achieved in 100% ($n = 20$) and 70% ($n = 14$) of patients receiving CHT/RT or CHT alone, respectively ($P = 0.008$) (Table 1). Pathological complete responses were, however, observed exclusively in the CHT/RT cohort: 25%, $n = 5$, versus none in the CHT-alone group, $P = 0.017$. Adjusted for induction treatment, nodal downstaging was no prognostic factor for DFS or OS ($P = 0.85$ and $P = 0.98$, respectively).

## DISCUSSION

Stage III NSCLC is a heterogeneous disease that can be further classified into three subgroups (IIIA, IIIB, IIIC), depending on the extent of the primary tumor and on the number of involved LN stations.[1] According to the current guidelines, treatment options in patients with stage III/N2 NSCLC include neoadjuvant CHT or CHT/RT followed by radical surgery or definitive CHT/RT.[4-7,9,15,16] Scientific knowledge, however, is still insufficient in providing a consensus recommendation regarding the best treatment modality in these patients. Previously published randomized studies were stopped at an early stage due to slow accrual or end of funding.[6,16] These clinical trials, hence, were underpowered, or had a very long recruitment period (>10 years)[7] during which therapeutic modalities might have changed. To make the picture more confusing, some investigators included patients with stage III N0-N3 disease,[5,15] while others excluded patients with T3 or T4 tumors,[4,7,9-11,16] whereby the outcomes are difficult to compare. More importantly, in most previous published studies, the complete resection rate was only between 32% and 91%,[5-7,15,17,18] whereas in our study an R0 resection was achieved in all patients.

**Table 2. Correlation of comorbidities, lung function parameters and type of neoadjuvant therapy before surgery in patients with clinical stage III/N2 NSCLC**

| | All patients ($n$ = 84) | | |
|---|---|---|---|
| | CHT/RT | CHT | $P$ value |
| **No. of patients** | 34 | 50 | |
| **Comorbidities (yes), $n$ (%)** | 21 (62) | 38 (76) | 0.224 |
| **COPD,[a] $n$ (%)** | 13 (38.2) | 21 (42.0) | 0.935 |
| **Diabetes mellitus, $n$ (%)** | 4 (11.7) | 8 (16) | 0.676 |
| **Arterial hypertension, $n$ (%)** | 9 (26.5) | 26 (52.0) | 0.035 |
| **Cardiovascular disease, $n$ (%)** | 5 (14.7) | 12 (24.0) | 0.373 |
| **Previous malignancies, $n$ (%)** | 3 (8.8) | 10 (20.0) | 0.205 |
| **FEV1%[a] (mean ± SD)** | 80.76% ± 19.86% | 78.76% ± 21.63% | 0.677 |
| **FVC%[a] (mean ± SD)** | 87.86% ± 17.91% | 85.31% ± 14.15% | 0.504 |
| **$pO_2$[a] (mmHg, mean ± SD)** | 68.8 ± 16.06 | 75.1 ± 16.35 | 0.126 |
| **$pCO_2$[a] (mmHg, mean ± SD)** | 43.3 ± 14.50 | 38.01 ± 8.99 | 0.075 |

Data shown in parentheses are column percentages.
CHT, chemotherapy; CHT/RT, chemoradiotherapy; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; pO2, partial pressure of oxygen; pCO2, partial pressure of carbon dioxide.
[a]In five cases data were not available.

In the current retrospective single-center study, we analyzed a total of 84 NSCLC patients with clinical stage III (T1-4) N2 disease treated with curative-intent surgery after neoadjuvant CHT or CHT/RT. Importantly, we found that patients receiving CHT/RT treatment exhibit superior DFS and OS compared to those treated with CHT alone.

In line with former and recent guidelines, induction treatment within this retrospective patient cohort was composed of platinum-based CHT with or without radiation treatment. Recent phase I/II studies have investigated the value of newly developed agents such as immunotherapy or targeted therapy in the neoadjuvant setting of locally advanced NSCLC.[19-22] Here, administration of immunotherapy resulted in high clinical and pathological response rates without higher morbidity.[19] Larger trials are currently ongoing to clarify if such encouraging short-term results will translate into improved oncological long-term outcome and thus if immunotherapy will be recommended in the neoadjuvant treatment of stage III/N2 NSCLC in the near future.

For patients with unresectable stage III NSCLC recently, the treatment of choice has become durvalumab following CHT/RT since the PACIFIC trial, which showed improved progression-free survival (PFS) and OS to 5-year OS of 42.9% and 5-year PFS of 33.1%.[23,24] To date, the question if definitive concurrent CHT/RT followed by durvalumab should be compared to neoadjuvant CHT/RT is difficult to answer, due to the fact that stage III disease is very heterogeneous and in the PACIFIC trial only patients with unresectable disease were included. Therefore, it is difficult to compare those results to patients with stage III disease who are surgical candidates. However, studies to investigate the role of neoadjuvant durvalumab and CHT for patients with resectable stage III NSCLC are currently ongoing and results are soon awaited.[25]

Although earlier studies reported increased complication rates and/or perioperative mortality in patients undergoing surgery (and especially pneumonectomy) after neoadjuvant CHT/RT,[6,9,11] in a very recent retrospective study of 5143 patients registered in the ESTS (European Society of Thoracic Surgeons) database, neoadjuvant CHT or CHT/RT followed by lobectomy or pneumonectomy was not associated with increased perioperative morbidity or mortality.[26] In line with this, in the current cohort, we found comparable complication rates, peri- and post-operative

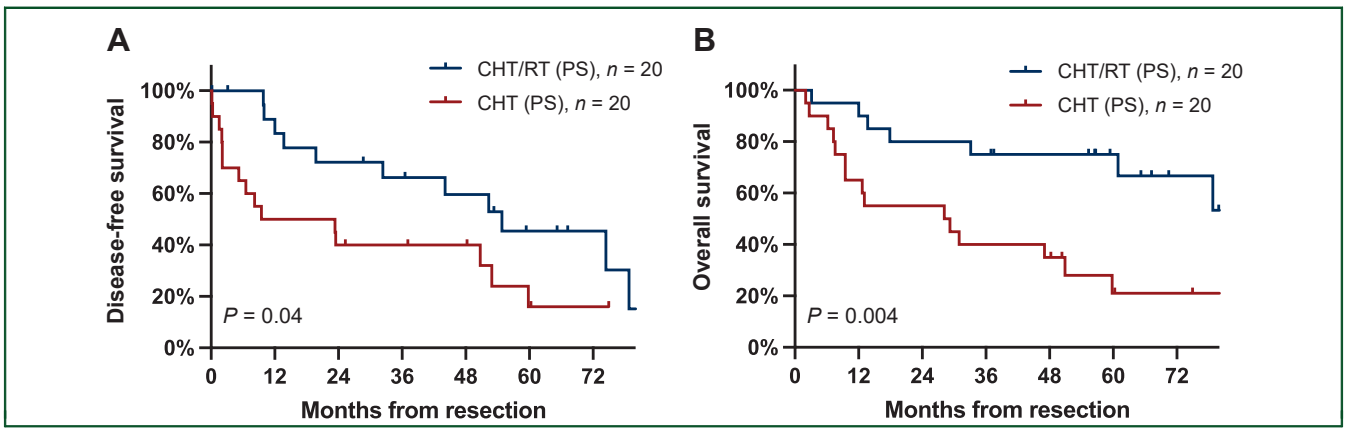


**Figure 2. Comparison of survival outcomes in surgically treated stage III/N2 NSCLC patients after propensity score matching according to neoadjuvant treatment regimen. (A) Patients treated with neoadjuvant CHT/RT showed significantly higher 5-year DFS compared to those receiving neoadjuvant CHT alone [5-year DFS was 45% (95% CI 26% to 78%) versus 16% (95% CI 5% to 53%), $P$ = 0.04, log-rank test]. (B) Combined neoadjuvant CHT/RT was also associated with significantly longer 5-year OS in NSCLC patients [versus CHT alone; 5-year OS was 75% (95% CI 58% to 97%) versus 21% (95% CI 8% to 53%), $P$ = 0.004, log-rank test]. CHT, chemotherapy; CHT/RT, chemoradiotherapy; CI, confidence interval; DFS, disease-free survival; NSCLC, non-small-cell lung cancer; OS, overall survival; PS, propensity score.**

morbidity and mortality and post-operative hospital stay in the CHT/RT versus in the CHT-alone cohort even though extended resections were more common in the neoadjuvant CHT/RT group. Additionally, there was no higher mortality or morbidity rate observed after pneumonectomy. In our patient series, no complication such as a bronchopleural fistula occurred, not even in patients after pneumonectomy, carried out after induction CHT/RT. Our center is a high-volume center with an excellent and experienced interdisciplinary team for intraoperative management as well as post-operative care. As a standard procedure of our internal protocol, the bronchial stamp after pneumonectomy will be always covered with vital tissue, e.g. with a pericardial fat pad, to prevent bronchial stamp insufficiency. Post-operatively, all eligible patients (including those after pneumonectomy) are routinely admitted to the normal ward after surgery. Therefore, all patients after lung resection will be quickly mobilized in the very early post-operative period (beginning at the day of surgery), which helps to prevent complications such as mucus retention, infections and circulatory problems. Additionally, chest drainages will be removed as early as possible in the first post-operative days to further support patient's mobilization. In case of mucus retention, we carry out bronchoscopy for removal of secretion very liberally. Further, an adequate fluid management is essential to avoid lung edema in patients after pneumonectomy. Consequently, in our opinion, high mortality rates after pneumonectomy up to 25% do not reflect the observed morbidity rates when patients are treated in highly experienced centers. Our data thus suggest that surgery carried out in a high-volume center is a valid and safe treatment option in patients with stage III/N2 NSCLC following neoadjuvant CHT/RT.

Several previous studies have shown that N2 patients with mediastinal downstaging (ypN0-1) after induction therapy have significant improvement in OS and DFS compared to those with persisting mediastinal disease (N2 to N2).[27-30] However, these studies did not distinguish between persistent single- and multiple-station N2 diseases. A former study of Misthos et al. showed that having only one metastatic mediastinal LN station confers a significant survival advantage compared to multi-level N2 disease.[31] Also, a very recent validation study of Park et al showed that OS and DFS of patients with N2a1 cannot be sufficiently distinguished from N1a and N1b disease and, therefore, a change in the N descriptor was recommended.[32] In our study, mediastinal downstaging proved to be a significant positive factor in OS and DFS in univariate analysis, but did not persist as an independent factor in multivariate analysis. Eighteen of our 84 patients had persistent positive mediastinal LNs, whereas 72% ($n = 13$) of these patients had single-station N2 disease. Since the majority of patients with persistent mediastinal LNs had pN2a1 disease, our results on long-term survival are consistent with the findings of Park et al.[32]

This retrospective study has several limitations. The results are in harsh contrast to those of large randomized multicenter clinical trials[5,7] and population-based data[9] despite our attempt to equalize inevitable selection bias by using nearest-neighbor PS matching with a rather strict caliper (0.1). As a consequence of the strict caliper of the PS matching, there are only 20 patients per cohort; however, it results in a very accurate statistical matching technique. Inevitably, patients starting with the intention to undergo resection after induction CHT with or without radiotherapy, but who did not proceed to surgery, were not included in this analysis retrospectively investigating outcome achieved in consecutive patients from daily practice. As this retrospective study was mainly carried out at the Department of Thoracic Surgery and selected patients were referred to surgery after discussion in a multidisciplinary tumor board, we cannot say how many patients with clinical stage III/N2 disease started induction therapy but were not able to proceed with surgery. However, all patients who actually underwent surgery were included. Also, in some patients, the diagnosis of N2-positive LNs had not been confirmed by biopsy. Accordingly, enlarged LNs (>15 mm short axis) found in the chest CT scan with contrast medium or increased FDG uptake at PET—CT were classified as cN2 disease and treatment was indicated within a multidisciplinary tumor board. Patients in the CHT/RT group were younger ($P = 0.024$), but inequalities were corrected by PS matching. Moreover, radiotherapy was not administered following a standardized protocol, but the decision for sequential or concomitant administration and dose prescription was made by the referring hospital (range: 45-66 Gy for all but four patients). Our results neither prove nor exclude the possibility that highly specialized thoracic oncology centers with a high-volume thoracic surgery service might yield improved outcome with an intensified multimodality treatment approach for locally advanced NSCLC. Of note, patients included in this study were operated between the years 2002 and 2014; hence, standards in staging and treatments have particularly changed within this period. However, as systemic treatment and especially surgical approaches widely remained unchanged, we feel that these data might be applicable to recently diagnosed stage III (N2) NSCLC patients as well. Furthermore, we tried to partially overcome this issue by using the most recent eighth edition of the TNM lung cancer classification.

## Conclusions

To conclude, in the current single-center retrospective PS-matched analysis, neoadjuvant CHT/RT yielded survival advantage over neoadjuvant CHT alone in stage III/N2 NSCLC patients undergoing curative-intent pulmonary resection. Importantly, suggesting that neoadjuvant CHT/RT can be safely carried out in a high-volume center, we did not observe increased peri- or post-operative morbidity or mortality even after a relatively high proportion of patients undergoing pneumonectomy in our cohort. Well-designed randomized controlled trials at highly specialized thoracic oncology centers with a high-volume thoracic surgery service are needed.

## ACKNOWLEDGEMENTS

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. The authors wish to acknowledge and thank all who contributed to this study.

## FUNDING

None declared.

## DISCLOSURE

The authors have declared no conflicts of interest.

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