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Comparison of neoadjuvant cisplatin-based chemotherapy versus radiochemotherapy followed by resection for stage III (N2) NSCLC☆

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Abstract

Objective: Comparison of prospectively treated patients with neoadjuvant cisplatin-based chemotherapy vs radiochemotherapy followed by resection for mediastinoscopically proven stage III N2 non-small cell lung cancer with respect to postoperative morbidity, pathological nodal downstaging, overall and disease-free survival, and site of recurrence. **Methods**: Eighty-two patients were enrolled between January 1994 to June 2003, 36 had cisplatin and doxetacel-based chemotherapy (group I) and 46 cisplatin-based radiochemotherapy up to 44 Gy (group II), either as sequential (25 patients) or concomitant (21 patients) treatment. All patients had evaluation of absence of distant metastases by bone scintigraphy, thoracoabdominal CT scan or PET scan, and brain MRI, and all underwent pre-induction mediastinoscopy, resection and mediastinal lymph node dissection by the same surgeon. **Results**: Group I and II comprised T1/2 tumors in 47 and 28%, T3 tumors in 45 and 41%, and T4 tumors in 8 and 31% of the patients, respectively ($P=0.03$). There was a similar distribution of the extent of resection (lobectomy, sleeve lobectomy, left and right pneumonectomy) in both groups ($P=0.9$). Group I and II revealed a postoperative 90-d mortality of 3 and 4% ($P=0.6$), a R0-resection rate of 92 and 94% ($P=0.9$), and a pathological mediastinal downstaging in 61 and 78% of the patients ($P<0.01$), respectively. 5y-overall survival and disease-free survival of all patients were 40 and 36%, respectively, without significant difference between T1–3 and T4 tumors. There was no significant difference in overall survival rate in either induction regimens, however, radiochemotherapy was associated with a longer disease-free survival than chemotherapy ($P=0.04$). There was no significant difference between concurrent vs sequential radiochemotherapy with respect to postoperative morbidity, resectability, pathological nodal downstaging, survival and disease-free survival. **Conclusions**: Neoadjuvant cisplatin-based radiochemotherapy was associated with a similar postoperative mortality, an increased pathological nodal downstaging and a better disease-free survival as compared to cisplatin doxetacel-based chemotherapy in patients with stage III (N2) NSCLC although a higher number of T4 tumors were admitted to radiochemotherapy.

Keywords: NSCLC; Induction therapy; Sequential and concomitant radiochemotherapy; Resectability rate; Pathological nodal downstaging; Postoperative complications; Survival; Disease free survival; Recurrence

1. Introduction

Induction chemotherapy followed by resection has been shown to improve the survival in patients with stage IIIA (N2) non-small cell lung cancer (NSCLC) as compared to resection alone in three out of four phase III trials [1–4]. The expected outcome of induction chemotherapy followed by resection in locally advanced but still resectable NSCLC shows a shrinkage of the primary tumor and involved lymph nodes, downstaging and an improved chance for complete resection, as well as early eradication of micrometastases [5]. However, the ideal induction regimen with optimal control of disease and minimal associated morbidity has not yet been defined since the complete pathological response rate after induction therapy is actually around 5–10%.

The results emerging from neoadjuvant chemotherapy followed by resection suggest that post-resectional survival is strongly related to the degree of pathological downstaging achieved by the induction regimen and that mediastinal downstaging seems to be a particularly important prognostic predictor in this respect [6–9]. However, neoadjuvant chemotherapy alone, even with cisplatin-doxetacel-based regimens affords a pathologic complete response of approximately 15% indicating that local control with currently

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available regimens is not optimal in this context [6]. This impression is reinforced by the findings of another prospective study which has assessed the pattern of recurrence after neoadjuvant MVP-based chemotherapy followed by resection [10]. Both studies have found a similar pattern of recurrence with a high rate of local recurrence. These findings suggest that the consideration of radiotherapy in combination with chemotherapy in the context of neoadjuvant treatment of locally advanced, resectable NSCLC may be worthwhile. Several studies have demonstrated the feasibility of neoadjuvant radiochemotherapy followed by resection in this setting and have shown better survival rates as compared with historical results [8,11–15]. This holds especially true for superior sulcus tumors [14,15]. However, there is lack of reports comparing neoadjuvant cisplatin-based radiochemotherapy with cisplatin-based chemotherapy for locally advanced, resectable NSCLC in a standardized setting. Furthermore, the impact of concurrent or sequential administration of irradiation and chemotherapy has not been assessed in this respect.

In this observational study, we compared two non-randomized groups of patients with stage III (N2) NSCLC receiving either neoadjuvant cisplatin-based chemotherapy or cisplatin-based radiochemotherapy followed by resection with respect to resectability, postoperative morbidity, pathological nodal downstaging, survival, disease-free survival (DFS) and pattern of recurrence.

2. Patients and methods

2.1. Patient selection

The studied population consisted of all patients with stage III N2 NSCLC who underwent neoadjuvant cisplatin-based chemotherapy or radiochemotherapy and subsequent resection by the same thoracic surgeon (HBR) between January 1994 and June 2003. Patients were evaluated in an interdisciplinary setting and investigated, treated and followed in a prospective manner. The treatment protocols were approved by the local Ethical Committee and informed consent was obtained.

Inclusion criteria were age <75 years, Karnofsky performance status of $>80\%$, a creatinine clearance of >60 ml/min, cardiopulmonary functions allowing complete resection and mediastinoscopically proven stage III N2 NSCLC without progression after induction therapy as assessed by CT-scan. Selected and potentially resectable T4 tumors with partial involvement of the carina, the vena cava superior or the left recurrent nerve were included. Exclusion of distant metastases was performed by CT scan of the chest and abdomen, bone scan or PET scan, and brain MRI or CT in all patients. Mediastinoscopy was always performed by the same surgeon (HBR) and included biopsy of lymph nodes ATS 7, and 4 and 2 on both sides. Patients with NSCLC of the left upper lobe with enlarged or positive ATS 5 or 6 nodes on CT or PET scan, respectively, plus negative mediastinoscopy underwent thoracoscopic exploration and biopsy of these nodes. Patients with tumor involvement of ATS 5 and 6 nodes were included. Patients with mediastinoscopically proven N3 disease, a malignant pleural or pericardial effusion, T4 tumors with invasion of the esophagus and the aorta or intrapericardial tumor extension were excluded, as well as patients with progressing disease after induction therapy.

Induction therapy consisted of a cisplatin-based chemotherapy in all patients. Preoperative induction treatment allocation was not random, but based on availability of multicenter protocols on neoadjuvant chemotherapy and choice of the referring oncologist. Patients with IIIA disease were considered for neoadjuvant chemotherapy alone or neoadjuvant chemoradiotherapy depending on the year of treatment. Patients with superior sulcus tumors and IIIB disease were to receive neoadjuvant chemoradiotherapy.

In group I (chemotherapy), patients received three cycles of cisplatin (100 mg/m^2) and doxetacel (85 mg/m^2) on day 1, 22 and 43. In group II (radiochemotherapy), patients were treated either with three cycles of cisplatin-based chemotherapy (cisplatin 100 mg/m^2, doxetacel 85 mg/m^2 on day 1, 22 and 43) followed by accelerated radiotherapy up to 44 Gy, or with three cycles of cisplatin-based chemotherapy (cisplatin 60 mg/m^2, vinblastine 6 mg/m^2 on day 1, 22 and 43) and concomitant hyperfractionated accelerated radiotherapy with 2×1.6 Gy/d for 5 days during each cycle of chemotherapy. All patients were treated with megavoltage photon beams >10 MV after three-dimensional treatment planning. The planning target volume included the primary tumor, the ipsilateral hilum and the mediastinum. The resection was performed within 3 weeks after the end of induction therapy.

Resection consisted of complete en bloc removal of the involved lobe(s) or lung together with involved adjacent structures (chest wall, pericardium, subclavian vessels, SVC, part of the carina) according to the extent of the disease found at surgery. Frozen section examination of the bronchial resection margin was routinely performed. Reconstruction of the SVC or subclavian vessels was performed with PTFE grafts, the pulmonary artery with pericardial patch angioplasty and chest wall defects by use of mersilene-methylmethacrylate substitutes if required. Bronchoplastic procedures (sleeve lobectomy) were used in order to avoid pneumonectomy if appropriate. Tension-free end-to-end anastomoses were performed by use of interrupted sutures and wrapped by an intercostal muscle flap. An intrapericardial hilar release was performed if required. Centrally located tumors involving the proximal main stem bronchus and the carina were treated preferentially by a carinal wedge resection with re-implantation of remnant lobe(s) within the carinal defect, or closure of the carinal defect by a latissimus dorsi muscle flap in case of pneumonectomy, in order to avoid carinal pneumonectomy. Bronchial stump coverage was always performed, either by use of an intercostal muscle flap after lobectomy or pneumonectomy without thoracic irradiation, or a latissimus dorsi or diaphragmatic flap after intrapericardial pneumonectomy or pneumonectomy following thoracic irradiation [16,17]. Formal mediastinal lymph node dissection was performed in every patient according to Martini et al. [18]. Division of the azygous vein on the right side and if required of the Botalli ligament on the left side, respectively, were performed in order to achieve appropriate para-and pretracheal lymph node dissection.

Histological examination of the surgical specimen was performed on the primary tumor and all lymph nodes in order to determine the pathological downstaging after induction therapy. All tissue samples were fixed in 4% buffered formalin, embedded in paraffin and 4μ-thick sections were stained with H&E. Histological slides of all tumors were reviewed by trained pulmonary pathologists who had no knowledge of the given induction regimen. Intrapulmonary, peribronchial, hilar and mediastinal lymph nodes were carefully evaluated for metastatic deposits. The tumors were classified using the stage grouping system of the 2002 TNM classification of malignant tumors meaning that pN0 corresponds to tumor-free nodes, pN1 to metastases in ipsilateral intrapulmonary, peribronchial or hilar nodes, and pN2 to metastases in ipsilateral mediastinal or subcarinal nodes. Immunohistochemistry was used for tumor recognition, if required.

Postoperative morbidity and mortality and life-threatening complications were recorded and analyzed up to 90 days after the operation in all patients.

2.2. Follow-up

Patients underwent physical examination, blood chemistry and a chest X-ray every 3 months up to 2 years, every 6 months from 2 to 5 years, and then annually after the resection. A CT-scan of the chest and upper abdomen was performed every 6 months within 2 years after resection and then annually thereafter. Survival and disease-free survival were calculated from the day of surgery until death of the patient or manifestation of tumor recurrence, respectively.

2.3. Statistical analysis

The Chi^2 and Fisher's exact test were used to determine differences in proportions where appropriate. The log rank test was used to compare Kaplan-Meier curves (overall and DFS). Multivariate Cox regression analysis was performed to compare overall survival and DFS according to the treatment performed and adjusted for age, gender and T-stage (T1–3 vs T4). Likewise, the prognostic value of pathological nodal downstaging was also evaluated. Proportionality assumption was tested and the appropriate functional form for continuous co-variables was assessed using fractional polynomials. P values <0.05 were considered significant. Interactions were not assessed because of the small number of events and risk of overfitting. All analyses were carried out using STATA, version 8 (Stat Corp, College Station, TX, USA).

3. Results

Eighty-two patients underwent induction therapy followed by resection for stage III N2 NSCLC, 36 with cisplatin-doxetacel based chemotherapy (group I), and 46 with cisplatin-based radiochemotherapy (group II). Twenty-five patients underwent sequential and 21 concomitant radiochemotherapy. The patient characteristics of the studied population are shown in Table 1. There were 62 men and 20 women with a mean age of 58.5 years (range 35–74 years) without significant differences between the groups. Squamous cell carcinoma was found in group I and II in 47 and 43%, adenocarcinoma in 22 and 22%, large cell carcinoma in 20 and 35%, and poorly differentiated carcinoma in 11% and 0 of the patients, respectively ($P=0.08$). Single station N2 disease was found in group I and II in 58 and 43%, and bulky/multilevel N2 disease in 42 and 57% of the patients, respectively ($P=0.26$). Group I and II comprised T1/2 tumors in 47 and 28%, T3 tumors in 45 and 41%, and T4 tumors in 8 and 31% of the patients, respectively. T4 tumors were more frequently pretreated with radiochemotherapy than chemotherapy ($P=0.03$). There was no significant difference in the extent of resection (lobectomy, sleeve lobectomy, left and right pneumonectomy) in either groups (Table 1). After neoadjuvant chemotherapy and radiochemotherapy, carinal wedge resections were performed in 8 and 9%, reconstructions of the pulmonary artery, subclavian artery and superior vena cava in 3 and 7%, and chest wall resections in 3 and 24% of the patients, respectively.

Table 1
Characteristics of 82 patients undergoing neoadjuvant cisplatin-based chemotherapy or radiochemotherapy and subsequent resection for stage III N2 NSCLC

	Chemotherapy ($n=36$)	Radio-chemotherapy ($n=46$)	P-value
Age (mean±SD)	60 (±9)	57 (±10)	0.17
Gender			
Male	25 (69%)	37 (80%)	0.25
Female	11 (31%)	9 (20%)	
Tumor stage			
T1/T2	17 (47%)	13 (28%)	0.03
T3	16 (45%)	19 (41%)	
T4	3 (8%)	14 (31%)	
Histology			
Squamous cell	17 (47%)	20 (43%)	0.08
Adeno	8 (22%)	10 (22%)	
Large cell	7 (20%)	16 (35%)	
Poorly differentiated	4 (11%)	0	
N2 status			
Single station	21 (58%)	20 (43%)	0.26
Bulky/multilevel	15 (42%)	26 (57%)	
Resection			
Right pneumonectomy	9 (25%)	10 (22%)	0.93
Left pneumonectomy	6 (17%)	9 (19%)	
Lobectomy, bilobectomy	19 (53%)	23 (50%)	
Sleeve lobectomy	2 (5%)	4 (9%)	

Complete resection after chemotherapy and radiochemotherapy was achieved in 92 and 94%, a R1-resection in 6 and 4%, and a R2-resection in 3 and 3% of the patients, respectively ($P=0.9$), (Table 2). Tumor-free bronchial resection margins were found in 81/82 patients, and in all patients with sleeve lobectomy and carinal wedge resection. One of 12 patients with chest wall resection had incomplete resection at the level of the chest wall. All patients undergoing vessel resection and reconstruction (SVC, subclavian vessels, pulmonary artery) had complete resections.

3.1. Postoperative mortality and life-threatening complications

The 90d-mortality rate was 3 and 4% after chemotherapy and radiochemotherapy, respectively ($P=0.6$). After

Table 2
Secondary outcomes of 82 patients undergoing neoadjuvant cisplatin-based chemotherapy or radiochemotherapy and subsequent resection for stage III N2 NSCLC

	Chemotherapy ($n=36$)	Radio-chemo-therapy ($n=46$)	P-value
Completeness of resection			
R0	33 (92%)	43 (94%)	0.95
R1	2 (6%)	2 (4%)	
R2	1 (3%)	1 (2%)	
Pathological nodal downstaging			
pN0	12 (33%)	31 (67%)	<0.01
pN1	10 (28%)	5 (11%)	
pN2	14 (39%)	10 (22%)	
90d-postoperative mortality and morbidity			
Mortality	1 (3%)	2 (4%)	0.64
Pneumonia	1 (3%)	3 (6%)	0.63
ARDS	1 (3%)	7 (13%)	0.09
Pulmonary embolism	1 (3%)	1 (2%)	0.86
Bronchopleural fistula	2 (5%)	2 (4%)	0.81

chemotherapy, one patient died from pulmonary embolism 40 days after pneumonectomy. After radiochemotherapy, two patients died from ARDS 30 days after lobectomy and chest wall resection, and 70 days after sleeve bilobectomy, respectively. The incidence of postoperative complications was not significantly different after chemotherapy or radiochemotherapy for pneumonia (3 vs 6%), pulmonary embolism (3 vs 2%) and bronchopleural fistula (5 vs 4%). However, the incidence of postoperative ARDS was higher after radiochemotherapy (13%) than after chemotherapy (3%), ($P=0.09$). Anastomotic dehiscence or bronchopleural fistulas were not observed after sleeve resections, however, one patient developed stenosis at the level of the anastomosis after sleeve bilobectomy with poststenotic abscess formation and died from ARDS 70 days after operation (Table 2).

3.2. Pathological nodal downstaging

After chemotherapy, histological examination of the surgical specimen revealed pN0 in 33% and mediastinal downstaging (pN0/pN1) in 61% of the patients. After radiochemotherapy, pN0 was observed in 67% and mediastinal downstaging (pN0/pN1) in 78% of the patients. The difference in pathological nodal downstaging between chemotherapy and radiotherapy was significant ($P<0.01$). There was no significant difference between concomitant and sequential radiochemotherapy with respect to pN0 (76 vs 60%) and pN0/pN1 (76 vs 80%) downstaging (Table 2).

The median follow up time was 53 months with an interquartile range of 15.6–111.3 months.

Overall 5y survival of all patients was 40% without significant difference between T1–3 and T4 tumors. The overall survival was not significantly different between chemotherapy and radiochemotherapy (Fig. 1a), nor between concomitant and sequential radiochemotherapy. Pathological nodal downstaging had a significant impact on overall survival ($P<0.01$). Multivariate analysis adjusted for age, gender and T-stage revealed pathological nodal downstaging as the only significant predictor for overall survival (Table 3).

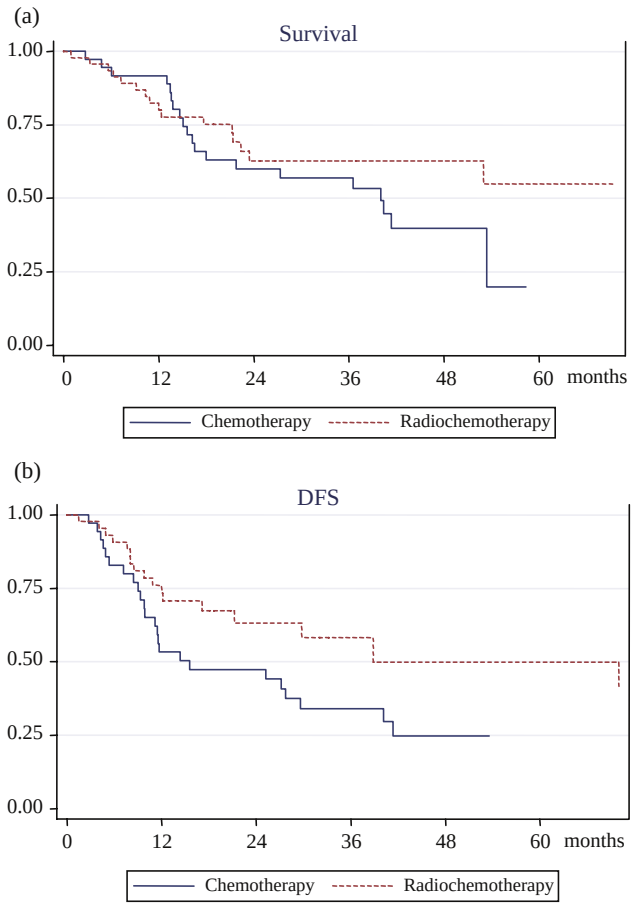

Fig. 1. (a) Overall survival and (b) disease free survival in 82 patients undergoing neoadjuvant cisplatin-based chemotherapy or radiochemotherapy and subsequent resection for stage III N2 NSCLC.

Disease-free 5y-survival was 36% for all patients without significant difference between T1–3 and T4 tumors. The DFS was significantly better after radiochemotherapy as compared to chemotherapy ($P=0.04$), (Fig. 1b). There was no significant difference between concurrent and sequential radiochemotherapy in DFS. Pathological nodal downstaging had a significant impact on DFS ($P=0.04$). Multivariate analysis adjusted for age, gender and T-stage revealed that radiochemotherapy and the absence of persistent mediastinal N2 disease after induction therapy were both associated with a significantly better DFS (Table 3).

3.3. Site of recurrence

After neoadjuvant chemotherapy and resection, 33% of the patients were tumor-free during follow-up, 23% developed local recurrence and 44% distant metastasis. After neoadjuvant radiochemotherapy and resection, 65% of the patients were tumor-free during follow-up, 9% developed local recurrence and 26% distant metastases.

Table 3
Multivariate analysis of the association between selected factors (induction regimen and pathological nodal downstaging), and survival and DFS in 82 patients undergoing neoadjuvant cisplatin-based chemotherapy or radiochemotherapy and subsequent resection for stage III N2 NSCLC

	Hazard ratio	95% CI	*P*-value
Survival			
Treatment			0.38
Chemotherapy	1	-	-
Radiochemotherapy	0.73	[0.36–1.48]	0.38
Pathological nodal downstaging			<0.01
pN0	1	-	-
pN1	2.75	[1.08–6.97]	0.03
pN2	3.19	[1.47–6.90]	<0.01
Disease free survival (DFS)			
Treatment			0.04
Chemotherapy	1	-	-
Radiochemotherapy	0.52	[0.26–1.01]	0.04
Pathological nodal downstaging			0.04
pN0	1	-	-
pN1	1.59	[0.62–4.08]	0.33
pN2	2.37	[1.18–4.77]	0.02

All analyses are adjusted for age, gender and T-stage (T1–3 vs T4).

There was no significant difference between concurrent and sequential radiochemotherapy in this respect.

4. Comment

Lung cancer remains a widespread malignancy and even modest improvements of treatment are potentially beneficial to large numbers of patients. Locally advanced disease without distant metastases is frequently present at diagnosis but survival remains disappointingly low even after complete resection in potentially operable patients. Induction therapy followed by resection has been investigated for potentially resectable stage III NSCLC in order to improve the outcome in these patients. Four prospective randomized trials compared preoperative chemotherapy and surgery with surgery alone and three of them demonstrated a survival advantage after induction chemotherapy [1–4]. Although these three studies [1–3] were criticized for their small sample size, imbalance between groups and poorer-than-expected outcomes in the control groups, it is actually believed that otherwise healthy patients with locally advanced (N2) disease should receive neoadjuvant chemotherapy and subsequent resection in case of response [5].

A number of studies have identified pathologic downstaging after induction therapy as an important prognostic factor which should be taken into consideration for validation of a particular induction regimen [6–9]. The currently used neoadjuvant chemotherapy regimens have shown a disappointingly low complete pathological response rate. Martini et al. found a sterilization rate of 14% after 3 cycles of MVP, and Betticher et al. 15% after 3 cycles of cisplatin/doxetacel induction therapy [6,10]. After neoadjuvant chemotherapy, overall survival seems to be prolonged but local recurrences remain frequent. The two studies have shown distant metastases in 23 and 19%, local recurrence in 12 and 13.5%, and both, local and distant relapse in 11 and 13.5% of the patients, respectively [6,10]. The total local failure rate was thus almost identical in both studies (23 and 27%, respectively). These findings suggest that the addition of radiotherapy may be worthwhile in order to improve local control. Currently, patients with incomplete resection or tumor bearing mediastinal lymph nodes do undergo postoperative adjuvant radiotherapy in many institutions. Although the published results suggest a modest decrease of local recurrence after adjuvant irradiation, there is no evidence of overall survival benefit in these situations [5].

Several phase II trials have demonstrated the feasibility of induction radiochemotherapy followed by resection in locally advanced NSCLC. Results emerging from combined neoadjuvant radiochemotherapy and resection for Pancoast or IIIB NSCLC have suggested a survival benefit as compared to historical controls without induction therapy [5,11–15].

However, neoadjuvant radiochemotherapy has not been compared to neoadjuvant chemotherapy alone for patients with potentially resectable NSCLC in a standardized manner. Furthermore, the optimal sequence of combined radiochemotherapy (concurrent vs sequential) has yet to be determined. Results emerging from the treatment of non-resectable NSCLC by radiochemotherapy suggest that concurrent therapy appears to be superior to sequential treatment with respect to improvement of survival [5]. However, the concurrent approach appears to increase the rate of adverse effects.

In this observational study, we compared two non-randomized groups of patients with stage III (N2) NSCLC receiving either neoadjuvant cisplatin-based chemotherapy or cisplatin-based radiochemotherapy (sequential or concomitant) followed by resection with respect to resectability, postoperative morbidity, pathological nodal downstaging, survival, disease-free survival (DFS) and pattern of recurrence. Preoperative induction treatment allocation was not random, but based on availability of multicenter protocols on neoadjuvant chemotherapy and choice of the referring oncologist. Patients with superior sulcus tumors and IIIB disease were to receive neoadjuvant radiochemotherapy. Patient selection was stringent and included only patients with resectable tumors without progression on CT scan after induction therapy. All patients had mediastinoscopically proven N2 disease [19]. Patients with N3 nodal involvement or with distant metastases were excluded. Patients with bulky and multilevel disease were considered for induction therapy followed by resection if the tumor appeared resectable at the time of enrollment. The two groups were comparable with respect to age, gender, tumor histology, N2 disease (single station vs bulky/multilevel disease) and extent of resection. However, patients with superior sulcus tumors and IIIB disease preferentially received neoadjuvant chemoradiotherapy. Selected T4 tumors if they appeared resectable, such as tumors infiltrating the lateral tracheo-bronchial angle, the left recurrent nerve, and the SVC were also eligible. The inclusion of selected patients with resectable T4 tumors in neoadjuvant protocols seems justified since several reports have demonstrated that their survival does not substantially differ from that observed for T1–3N2 tumors after induction therapy [11,13,20,21]. In fact, our results endorse these

findings since survival and DFS was not significantly different between T1–3 and T4 tumors in our series.

Complete R0-resection after chemotherapy and radiochemotherapy was achieved in 92 and 94%, respectively, without difference between concomitant and sequential radiochemotherapy. There was no difference between the chemotherapy and radiochemotherapy group with respect to R0-resections although there were more T4 tumors or tumors with chest wall infiltration attributed to the radiochemotherapy group. This confirms previous findings that neoadjuvant radiochemotherapy offers a higher degree of local downstaging in tumors with a propensity to invade surrounding structures and where complete resection is difficult to achieve due to anatomical considerations. Several surgical maneuvers have been described to improve complete resection after neoadjuvant therapy such as the division of the azygous vein on the right and of the Botalli ligament on the left side, and the liberal use of intrapericardial dissection and resection if required. Our results endorse the previously reported finding that resection and reconstruction of vascular and tracheo-bronchial structures can be safely performed after induction therapy in order to achieve a complete resection [20,21]. Centrally localized tumors may be completely resected by a sleeve lobectomy and carinal wedge resection followed by implantation of the remnant lobe(s) into the carinal defect. This technique avoids a hazardous carinal resection or sleeve pneumonectomy in pretreated tissues and has been performed in this series on seven patients (three after chemotherapy and four after radiochemotherapy) with a complete resection and without anastomotic dehiscence in all patients. However, one patient developed an anastomotic stenosis 70 days after surgery with subsequent abscess formation, ARDS and death. This was probably related to anastomotic tension despite a hilar release having been performed. Carinal reconstruction after a wedge pneumonectomy may also be performed by use of an extrathoracic muscle flap transposed into the chest cavity and sutured into the carinal defect in order to avoid carinal pneumonectomy [22].

There was no significant difference in postoperative 90d-mortality after neoadjuvant chemotherapy (3%) and radiochemotherapy (4%). The incidence of life-threatening complications such as pulmonary embolism, pneumonia and bronchopleural fistula was also not significantly different between the two induction regimens. However, the incidence of postoperative ARDS was higher after radiochemotherapy (13%) than after chemotherapy (3%), which is in accordance with other reports. Neoadjuvant radiochemotherapy appears to increase the postoperative mortality rate and morbidity as compared to neoadjuvant chemotherapy alone, with mortality rates ranging between 0 and 18% [8,11–15,23,24]. The incidence of postoperative ARDS in our series was mainly observed after right pneumonectomy but it also occurred after lobectomy following radiochemotherapy. Careful postoperative monitoring of patients receiving neoadjuvant radiochemotherapy for several days is mandatory in this respect and fluid overload should be avoided, especially in patients with an impaired pulmonary function and DLCO. Right-sided pneumonectomy after induction therapy bears a postoperative mortality risk of 25% and should be avoided whenever possible [25]. Bronchial stump coverage should be routinely performed in patients undergoing induction therapy and resection [16,17].

Pathological downstaging has been shown to be an important predictor for survival for patients undergoing neoadjuvant treatment following by resection for NSCLC and nodal downstaging seems to be of particular importance in this respect. Our results endorse these findings since multivariate analysis of our data adjusted for age, gender and T-status revealed pathological nodal downstaging as an independent and significant predictor for overall survival and DFS. Radiochemotherapy resulted in a significantly better pathological nodal downstaging than chemotherapy in our patients.

The 5y-overall and DFS of all patients was 40 and 36%, respectively. There was no significant difference between neoadjuvant radiochemotherapy and chemotherapy regarding overall survival, however, radiochemotherapy resulted in a significantly better DFS than chemotherapy alone. A multivariate analysis of our data adjusted for age, gender and T-status revealed that radiochemotherapy was associated with significantly better DFS. Patients with radiochemotherapy were at a significantly lower risk for recurrent disease as compared to chemotherapy alone despite the fact that more T4 tumors were attributed to the radiochemotherapy group. These findings appear to be related to the better capability of neoadjuvant radiochemotherapy for pathological loco-regional downstaging as compared to chemotherapy alone.

There was no significant difference between concomitant vs sequential radiochemotherapy with respect to postoperative morbidity, resectability, pathological nodal downstaging, survival and DFS. However, caution in the interpretation of these results is indicated due to the small sample size.

In conclusion, our results emerging from an observational non-randomised study suggest that neoadjuvant cisplatin-based radiochemotherapy resulted in a similar postoperative mortality, an increased pathological nodal downstaging, a better DFS and a reduced risk for recurrence as compared to cisplatin doxetacel-based chemotherapy in patients with stage III N2 NSCLC although a higher number of T4 tumors were admitted to radiochemotherapy. However, radiochemotherapy was associated with a higher postoperative ARDS rate than chemotherapy.

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