Weekly Chemoradiation (Docetaxel/Cisplatin) Followed by Surgery in Stage III NSCLC; a Multicentre Phase II Study

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Abstract. *Background: This prospective study analyzed the feasibility and efficacy of weekly concurrent chemoradiation (docetaxel/cisplatin) followed by surgery. The primary endpoint was radiological response. Patients and Methods: Six chemotherapy (docetaxel/cisplatin) cycles were administered on days 1, 8, 15, 22, 29 and 36 with concurrent thoracic radiotherapy in fractions of 1.8 Gy, to a total dose of 45 Gy. Patients underwent surgery depending on results of invasive mediastinal re-staging. Results: Forty-two out of 45 NSCLC stage III patients were evaluable. Nineteen patients showed partial/complete response (46%), 14 stable disease (34%) and eight (20%) progressive disease. Toxicity was mild. The 30-day postoperative mortality was 4.2%. Twenty-four patients (59%) proceeded to surgery and 20 (49%) underwent a complete resection (R0). Conclusion: Weekly concurrent chemoradiation (docetaxel/cisplatin) in stage III NSCLC results in a radiological response rate of 46% and mediastinal downstaging in 56%. Complete resection in downstaged patients was achieved in 49% of all patients.*

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The 2003 ASCO guidelines (1) recommend (platinum-based) chemotherapy in association with thoracic radiotherapy for selected patients with unresectable locally advanced non-small cell lung cancer (NSCLC). However, the optimal sequencing of chemotherapy and radiotherapy has so far not been established and it is therefore unclear whether or not surgery plays a role in combined modality treatment for stage III NSCLC. Albain *et al*. recently published new data concerning this topic and suggested that patients with NSCLC stage III can benefit from surgery after combined modality treatment with a survival benefit, especially when a lobectomy is performed (2).

A variety of multimodality-therapies that include chemotherapy, surgery and/or radiotherapy have recently been assessed in clinical phase III trials (2-4). However none showed a significant survival difference.

Taxanes are known to have radio-sensitizing potential (5, 6). Docetaxel has demonstrated greater radio-sensitizing potential, possibly through different mechanisms such as immunomodulation or antiangiogenesis effects (7-10). Toxicity of docetaxel can be decreased through a weekly administration schedule (11). Several phase I and II studies report that cisplatin and docetaxel both administered at 20 mg/m^2 once a week can be combined with radical thoracic radiotherapy (12-20).

This study analyses the results of a chemoradiotherapy regimen consisting of docetaxel/ cisplatin and involved-field concurrent thoracic radiotherapy for a total dose of 45 Gy. Following invasive mediastinal restaging, patients with pathological mediastinal downstaging underwent a thoracotomy

with the aim of a radical resection. The remaining patients continued radiotherapy for a maximum of 60 Gy in order to maximize local control rates.

The primary objective of this phase II study was radiological response rate. Secondary endpoints included toxicity, efficacy in terms of radical resection rate and pathologic response, postoperative morbidity and mortality and overall survival (OS).

Patients and Methods

Patients. Patients with stage III NSCLC were eligible in this prospective multicentre phase II trial. Patients were staged according to the guidelines of the National Comprehensive Cancer Network and ACCP guidelines (21). All patients were entered after written consent was obtained according to local medical ethical committee regulations.

Eligibility criteria included pathologically proven primary stage IIIA/IIIB NSCLC (every T, N2 and/or N3 and M0, except malignant pleural effusion or scalene/supraclavicular lymph node involvement), age between 18 and 76 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, platelet count 100×10^9/l, absolute neutrophil count $>2\times10^9$/l , normal liver and renal functions with a creatinine clearance >60 ml/min. The calculated postoperative forced expiratory volume in 1 second and CO transfer coefficient were >40% of the predicted and maximum oxygen consumption (VO2max.) were required to be more than 15 ml/min/kg.

Concurrent chemoradiotherapy. Chemotherapy consisted of six cycles of cisplatin and docetaxel. Both drugs were administered weekly on day 1, 8, 15, 22, 29 and 36 at a dose of 20 mg/m^2 as an intravenous infusion along with an appropriate hydration and anti-emetic regimen.

Treatment was stopped in those cases where the disease progressed or unacceptable toxicity occurred. Dose reductions were specified per protocol. Following one cycle of induction cisplatin/docetaxel, concurrent chemoradiotherapy (CCRT) commenced on day 8. Thoracic radiotherapy was delivered in once-daily fractions of 1.8 Gy, five fractions a week, to a total dose of at least 45 Gy. Consequently, the overall treatment time for radiotherapy was five weeks. No interruptions were allowed except in the event of a grade III or IV esophageal or pulmonary toxicity, or a grade IV hematological toxicity (NCIC-CTC grading system v3.0). The use of a planning computed tomography (CT) scan and a 3-D treatment planning program with a beam-eye-view facility was mandatory. The gross tumor volume (GTV) included all tumor identified prior to start of the treatment with initial staging. Mediastinal lymph nodes with a short-axis diameter larger than one centimeter were included in the GTV. The GTV was contoured using both the lung and mediastinal windows settings. The clinical target volume (CTV) included the ipsilateral hilus, even in cases where it was radiologically normal. The CTV included the GTV plus a symmetrical margin of one centimeter. The planning target volume (PTV) was delivered by adding a margin of one centimeter to the CTV but this margin should only be 0.5 centimeter in case of a contralateral N3 node. The full dose of 45 Gy could be delivered to the spinal cord, and preference was given to sparing pulmonary tissue in order to limit the V20, which was defined as volume of both lungs minus the PTV receiving a threshold dose of 20 Gy (22).

In patients who were not eligible for radical resection due to persistent N2/N3 disease or irresectable T4 disease, additional radiation treatment up to 60 Gy was considered when the gap between the end of the pre-operative dose (45 Gy) and recommencing radiotherapy was limited to less than three weeks and when disease progression outside the previous planning target volume was absent.

Response assessment. Tumor response after CCRT was assessed using the response evaluation criteria in solid tumors (RECIST) with CT scan and FDG-positron-emission tomography (PET) scan. FDG-PET was also used to evaluate disease progression outside the chest.

Invasive restaging. A planned re-evaluation took place within a few days after completion of CCRT. Patients initially staged as having T4N0-1 disease, who did not progress during CCRT, proceeded directly to explorative thoracotomy. Patients initially staged as having N2 or N3 disease and without disease progression after CCRT proceeded to a mediastinal evaluation using (repeat)-mediastinoscopy, esophageal ultrasonography (EUS), EBUS, video-assisted thoracoscopic surgery (VATS) or parasternal mediastinoscopy. During mediastinoscopy, biopsies were taken from lymph node stations 2R, 2L, 4R, 4L and 7, according to Naruke *et al*. (23).

Surgery. All patients with potentially resectable disease at re-staging proceeded to thoracotomy with intent to achieve a R0 resection (24). Surgery was to be performed between three to four weeks after the last fraction of radiotherapy.

Statistics. In this phase II study, the primary outcome was the summed percentage of radiological complete and partial responses. For a sample size calculation, a summed proportion of complete and partial response of 0.6-0.65 is expected and proceeding to a comparative randomised phase III is decided upon when the lower end of the one-sided 95% confidence interval exceeds 0.5. According to power analysis, a sample size of 40 patients was required.

Interim analysis was performed after the inclusion of ten patients; if more than three patients died due to treatment toxicity or more than four patients experienced grade IV esophageal toxicity, the study would have been terminated.

Survival was estimated from the date of inclusion, using the Kaplan-Meier survival analysis method (25). Survival comparisons were analyzed by the log rank test (26). The difference was considered statistically significant when the p-value was <0.05.

Results

From March 2005 to September 2006, 45 patients with stage III NSCLC were entered into this study of whom 42 were eligible.Three patients discontinued the study; one patient was diagnosed with a mesothelioma and the other two patients did not meet the criteria of NSCLC stage III. Patient characteristics are provided in Table I (n=42). Thirty-two patients (76%) had pathological proof of mediastinal nodal involvement (29 with N2-disease). Ten patients with cT4 disease underwent no invasive mediastinal staging before chemoradiation because of gross involvement of the mediastinum (Table I).

Table I. *Pretreatment characteristics of patients and type of mediastinal lymph node assessment in patients eligible for treatment (n=42).*

	Numbers of patients (%)
Gender	
Male	27 (64%)
Female	15 (36%)
Median age, years (range)	59 (41-78)
ECOG performance status	
0	26 (62%)
1	16 (38%)
Histological type	
Squamous	16 (38%)
Adenocarcinoma	4 (10%)
Large cell	22 (52%)
Stage	
IIIA	25
cT1-3N2M0	25 (60%)
IIIB	17
cT4N0-1M0	4 (9%)
cT4N2M0	10 (24%)
cT1-3N3M0	3 (7%)
Type of mediastinal staging	
Mediastinoscopy	7 (17%)
EUS**	17 (41%)
Mediastinoscopy anterior	1 (2%)
Thoracotomy	1 (2%)
TBNA ***	6 (14%)
No invasive staging	10 (24%)

ECOG: Eastern Cooperative Oncology Group; EUS: Esophageal ultrasonography; TBNA: transbronchial needle aspiration.

Chemoradiotherapy. Thirty-six patients (86%) received six cycles of docetaxel and cisplatin without dose-reduction or delays. Six patients did not receive all cycles of chemotherapy for different reasons which are summarized in Table II. No grade III or IV haematological toxicity was observed. Results of radiotherapy and side effects of CCRT are also shown in Table II. The mean V20 was 21.4% (range: 6.0-34.0%). In 9 patients with persistent N2/N3 disease, additional radiotherapy up to 60 Gy was considered, except for one patient who had already received 65 Gy and one patient received concomitant radiotherapy up to 75 Gy (Table II). In all patients who underwent radiotherapy up to 60 Gy the median gap was 8 days (mean: 17 days, range 6-52 days).

Response rate. Forty-one patients were evaluable after CCRT. Radiological response rate after neo-adjuvant chemoradiotherapy is presented in Table III. Nineteen patients had complete or partial radiological response (46%). Fourteen patients had stable disease (34%) and in 8 patients progressive diease (20%).

Restaging. Thirty-five (85%) patients underwent invasive restaging. Complete clearance of mediastinal disease was achieved in 56% (23/41). When downstaging was found at restaging, none of the patients showed persistent N2 disease during thoracotomy. Seven patients (49%) with radiologically stable disease (7/14) did have complete clearance of tumor in mediastinal lymph node metastases by invasive restaging and six of them proceeded to thoracotomy (Table III).

Surgery and treatment-related complications. The median time from the end of induction therapy to surgery was 27 days (range 10-43 days) in 24 patients. Results of surgical therapy are shown in Tables II and V. Histopathologically proven downstaging and a complete resection (R0 resection) were obtained in 20 patients (50%). One patient only underwent explorative thoracotomy still suffering from persisting N2 disease. Two patients were diagnosed with persistent N2-disease. One had a complete mediastinal response according to the PET-scan after CCRT and proceeded directly to thoracotomy. Although the second patient had mediastinal micrometastases at restaging, thoracotomy was still performed. The third patient who did not undergo a R0 resection had positive resection margins.

Four patients (10%) showed a pathological complete response after chemoradiation and surgery. Treatment-related complications are shown in Table II. In-hospital (30-day) mortality occurred in one patient (4.2%). This patient underwent a right-sided pneumonectomy and developed acute respiratory distress syndrome three days after the operation and died one day later.

Survival. By April 2010, 27 patients had died after a median follow-up of 28 months. The estimated median survival for the whole group was 60% at 1 year, 50% at 2 years and 30% at five years. Survival in responders treated with CCRT and surgery (n=24) or CCRT alone (n=18) is shown in Figure 1. At the time of this analysis (April 2010), 13 patients were still alive of whom 12 underwent CCRT and surgery. Eleven (11/21) patients in this group had a complete resection and show no signs of disease progression.

Patterns of disease failure. Patterns of disease failure are shown in Table IV. Local and distant failures after definite CCRT were observed in 6 and 1 patient(s) , respectively, and after CCRT/resection in 1 and 8 patient(s) respectively (p=0.003).

Discussion

Complete and partial responses, the primary end points of this study, were observed in 46% of patients. In addition, pathological clearance of malignant mediastinal disease was achieved in 23/41 (56%) patients. No acute (non)-haematological toxicity was encountered and a low incidence

Table II. *Treatment results and complications*.

	Number of patients
Chemotherapy (n=42)	
Patients receiving 6 cycles	36
Patients receiving less than six cycles	6
Progression during chemotherapy	2
Fatal haemoptysis	1†
Hepatic dysfunction	1
Fever of unknown origin	1
Change to other regimen because of cerebrovascular incident	1
Dose of radiotherapy (n=42)	
Patients receiving 45 Gy	30
CRT and operation	23
Unknown	2
Because of metastasis after CRT	5
Patients receiving up to 75 Gy (54-75 Gy)	9
50 Gy*	1
54 Gy	3
58 Gy	1
60 Gy	2
65 Gy	1
75 Gy	1
Patients receiving less than 45 Gy	3
Fatal haemoptoe	1
Brain metastasis	1
Leptomeningeal metastasis	1
Side-effects after chemoradiation	
Radiation pneumonitis grade II	1
Oesophagitis grade III	3
Skin rash grade II	1
Restaging procedures (n=34)	34
Mediastinoscopy	16
Remediastinoscopy	2
EUS	8
Surgical exploration	1
TBNA	6
Transthoracal needle aspiration	1
Patients undergoing surgery (n=24)	24
Pneumonectomy	10
Right-sided/left-sided	1/9
Sleeve lobectomy	1
Bilobectomy	1
Lobectomy	11
Explorative thoracotomy	1
Complicatons after chemoradiation and surgery: (n=19)	19
Major complications <30 days	
ARDS	1†
Rethoracotomy subcutaneous emphysema/haemorrhage	1/1
Empyema	1
Minor complications <30 days	
AF	5
Upper airway infection	1
Pneumonia	4
Wound dehicense	1
Gastric haemorrhage	1
Major complications >30 days	
Hypovolemic shock due to gastric haemorrhage	1
Rethoracotomy	1
Persistant atelectasis pneumonia	1
Complications after chemoradiation (60 Gy) (n=1)	
Minor complications >30 days	
Radiation pneumonitis CTC-grade II	1

CRT: Concurrent chemo-radiotherapy; EUS: esophageal ultrasonography; TBNA: transbronchial needle aspiration; ARDS: acute respiratory distress syndrome; *progression during radiotherapy; †died; CTC: common toxicity criteria.

of treatment-related pneumonitis was observed (2.4%) probably due to the constraints put on the V20 (median 20.4%) (22). Oesophagitis grade III was encountered in 3 patients (7%), the latter low figure is probably due to use of involved-field radiotherapy and gating techniques. These results are comparable to those obtained by Katayama *et al*. (27) using a similar treatment schedule. Although in their study the objective response rate induction therapy was numerically higher (73%), pathological downstaging of mediastinal lymph nodes was achieved in 59% of patients (27).

In this study, 20 patients (49%) underwent a complete resection (R0) resection of whom 6 (15%) had stable disease as their best response to induction treatment. Several studies have shown that pathological response in mediastinal lymph nodes predicts prolonged survival (3, 28-31). Albain *et al*. published data on 126 patients with stage IIIA and IIIB NSCLC, treated with concurrent chemoradiation followed by surgery (31). In the patients that were resected, the strongest predictor for long-term survival was absence of mediastinal lymph node metastasis. Therefore, a careful selection of patients through accurate pathological restaging at completion of (induction) chemoradiation is critical, preferably by using restaging tools such as (re)mediastinoscopy, EUS-FNA, EBUS-FNA, VATS or thoracotomy. When downstaging is not established, adjuvant radical radiotherapy has to be continued at least up to 60 Gy, as this is standard treatment for patients with irresectable stage III NSCLC. Cerfolio *et al*. even proved that pulmonary resection is save after concurrent chemoradiation with 60 Gy (32). Concurrent chemoradiation can induce extensive fibrosis and necrosis of the tumor and mediastinum at surgery (2). It follows that radiological response is not the optimal parameter by which to select patients for post-induction surgery as patients with radiologically stable disease may have complete clearance of mediastinal malignant disease, as was found in the study under discussion.

Table III. *Radiological response after chemoradiation compared to mediastinal restaging and surgery.*

Radiological response		Mediastinal restaging (path)	Surgery
CR	3 (7%)	3 Downstaging	2R0, 1R2 (pN2)
PR	16 (39%)	12 Downstaging	12 RO
		1 Persistent N2*	1 expl Tx (pN2)
		2 Not performed	1 R0, 1 R2 (pN2)
SD	14 (34%)	7 Mediastinal downstaging (1 tracheal carcinoma)	5 R0, 1 R0 (resection margin +)
		7 Persistent N2	
PD	8 (20%)	3 Persistent N2	
		1 Persistent N3	

*Explorative thoracotomy; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

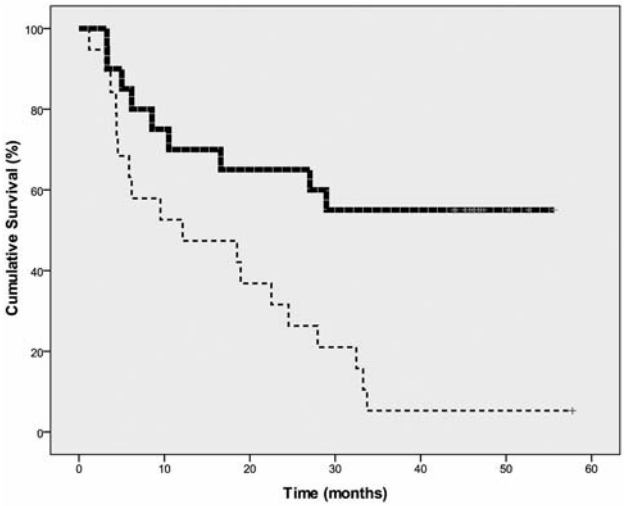

Figure 1. *Survival in responders treated with chemoradiation and surgery (n=24) (bold line) and in non-downstaged patients who only received chemoradiation (n=18); (dotted line) (p=0.002).*

Table IV. *Patterns of disease failure after resection and radiotherapy (n=32 p=0.003).*

	Local failure	Distant failure
Adjuvant radiotherapy (n=9)	6	1
Surgery (n=23)	1	8

The 30-day mortality in this study was 4.2%. The types of surgery and induction treatment used are the major determinants of morbidity and mortality. Pneumonectomy has been reported to have significant negative influence on survival (3, 30). Three recent randomized studies observed a significant higher mortality after induction therapies followed by a pneumonectomy as compared to lesser resections (2-4). Therefore several authors advocate against pneumonectomies after pre-operative chemoradiotherapy (2-4).

In this study, approximately 58% of the patients with a (curative) resection (R0) were alive after 46 months compared to less than 10% of the patients without resection (p=0.001). Katayama *et al*. reported comparable results (27). With a median follow-up of 32 months, the 3-year overall survival rate was 66% and 93% in 14 patients achieving pathological mediastinal downstaging (27).

No adjuvant chemotherapy was administered in this study. The GLCCG trial and the Intergroup trial 0139 both used some form of consolidation chemotherapy (2, 4). Following the report by Hanna *et al*. (33) that showed no difference in survival between patients that received adjuvant chemotherapy as compared to those that did not, in this study it was decided to omit consolidation chemotherapy.

Two phase III trials have been conducted in the last decade that investigated the role of preoperative chemoradiation. In the GLCCG trial, surgery preceded by chemoradiation in addition to preoperative chemotherapy, or chemotherapy alone failed to show significant differences in progression free survival or overall survival between the treatment groups (4). In the Intergroup trial 0139 (2), CCRT followed by surgery *vs*. CCRT, did not show a difference in its primary endpoint (overall survival). There was an absolute 5-year survival benefit of 7% for the surgery arm, although this did not achieve conventional statistical difference (2). After 5 years, more patients were alive without progression in the CCRT with surgery arm, but more patients died without progression in the CCRT with surgery arm (2).

The trial of Albain *et al*. provides clear arguments in favour of surgery in well-selected subsets of patients. Surgery can improve survival in patients in whom a complete resection (R0) is possible after chemoradiation with less extensive resection (lobectomy, sleeve-lobectomy). To improve this strategy it is important to investigate less toxic chemoradiation scedules to reduce complications after surgery.

Table V. *Clinical TNM classification and pathological TNM classification after operation.*

	cTNM	Invasive staging cN/cT4	cTNM after CRT	Radiological response	Restaging ycN	After operation	Died (†) Pneumonectomy (IO)
1	cT4N2	cT4/cN2	cT2N0	PR	ycN0	pT2N1Mx	IO
2	cT2N2	cN2	cTxN0	SD	ycN0	pT3N0mx	†
3	cT2N2	cN2	cT2Nx	PR	ycN0	pTxN0M	IO
4	cT2N2	cN2	cT2N0Mx	PR	ycN0	pTxN0Mx	IO
5	cT2N2	cN2	cT2Nx	SD	ycN0	pT3N1M0	†, IO
6	cTxN2	cN2	cT2N2	SD	ycN2		
7	cT4N2	N.E.	cT4N2	SD	ycN2		†
8	cT2N2	cN2	cT2N2	SD	ycN2		†
9	cT1N3	cN3	cT1N0	PR	ycN0	pT1N0Mx	
10	cT2N2	cN2	cT4N2	PD	N.E.		†
11	cT4N0	N.E.	cT4N0	PR	ycN0	pTxN0Mx	
12	cT4N0	N.E.	cT4N0	SD	ycN0	pTxN0Mx	†
13	cT4N2	cT4	cT2N0	PR	ycN0	pT2N0Mx	†, IO
14	cT4N2	N.V.	cT4Nx	PR	ycN0		†
15	cT4N2	N.V.	cT4N0	SD	ycN0		†
16	cT3N2	†					
17	cT4N2	cT4/cN2	cT4N0	SD	ycN0	pT2N0Mx	
18	cT2N2	cN2	cT1N0	PR	Yc0	PT0N0Mx	
19	cT2N2	cN2	cT0N0	CR	ycN2	pT1N2Mx	
20	cT4N0	N.E.	cT4N0	SD	ycN0	pT1N0Mx	IO
21	cT4N2	N.E.	cT4N2	SD	ycN0	pT3N0Mx	†
22	cT3N2	cN2	cT3N2	PD	ycN2		†
23	cT2N2	cN2	cT1N1	PR	N.E.	pT1N1Mx	†
24	cT2N2	cN2	cT2N2M1	PD	N.E.		†
25	cT2N2	cN2	cT2N2	SD	ycN3		
26	cT2N2	cN2	cT1N0	PR	N.V.	pT1N2Mx	
27	cT3N2	cN2	cT2N2	PR	ycN0	pT2N0Mx	†, IO
28	cT2N2	cN2	cT1N0	PR	ycN0	pT1N1Mx	
29	cT2N2	cN2	cT1N0	PR	ycN0	pT1N0Mx	
30	cT4N0	N.E.	cT3N0	PR	N.E.	pT0N0Mx	
31	cT2N2	cN2	cT2N2M1	PD	N.E.		†
32*	cT2N2	cN2	cT1N2Mx	PR	ycN2	pTxN2Mx	†
33	cT1N3	cN3	cT1N3M1	PD	ycN3		
34	cT2N2	cN2	cT0N0Mx	CR	ycN0	pT0N0Mx	IO
35	cT2N2	cN2	cT2N2MX	PD	ycN2		†
36	cT2N2	cN2	cT0N0Mx	CR	ycN0	pT0N0Mx	IO
37	cT3N2	cN2	cT3N0Mx	PR	ycN0	pT3N0Mx	†, IO
38	cT2N2	cN2	cT2N2Mx	SD	ycN2		
39	cT2N3	cN3	cT1N2/3	SD	ycN2		†
40	cT4N2	N.E.	cT4N2M1	PD	ycN2		†
41	cT4N2	cT4	cT4N2M1	PD	ycN2		†
42	cT4N2	N.E.	cT4N2Mx	SD	ycN2		†

*Explorative thoracotomy.

It can be concluded that although weekly docetaxel/cisplatin with concurrent radiotherapy in stage III NSCLC results in a radiological response rate of 46% and mediastinal downstaging in 56% of patients, complete resection in downstaged patients was achieved in 49%. This induction regimen is feasible with limited toxicity and seems to be effective in stage III NSCLC.

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