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Multimodality approach towards individualized non-small cell lung cancer treatment

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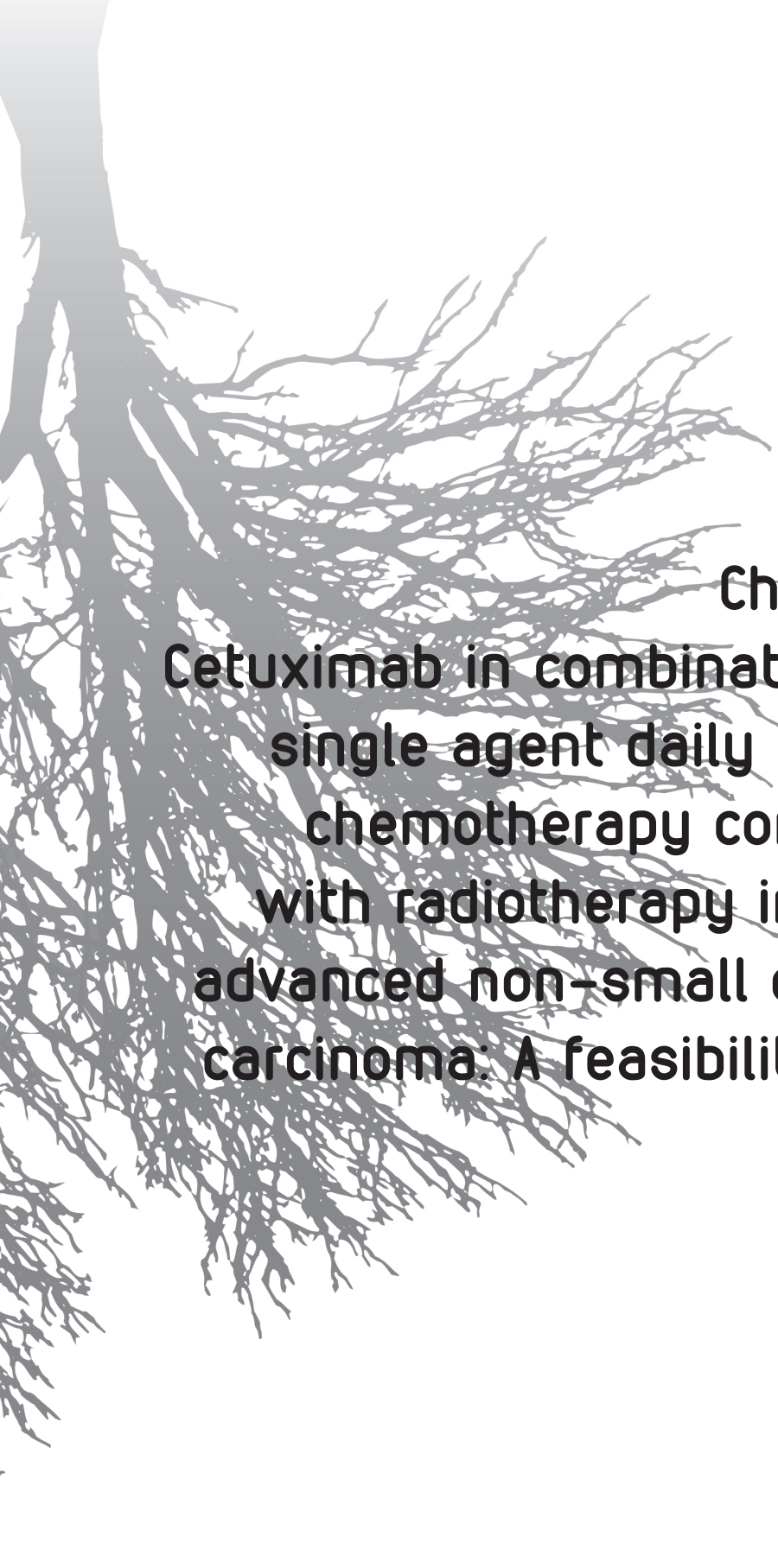
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Chapter VII
**Cetuximab in combination with
single agent daily cisplatin
chemotherapy concurrent
with radiotherapy in locally
advanced non-small cell lung
carcinoma: A feasibility study**

ABSTRACT

Introduction | Despite the benefits from concurrent chemoradiotherapy (CCRT) regimens in patients with locally advanced non-small cell lung cancer (NSCLC), more efficacious treatment options are needed. Cetuximab, a monoclonal antibody that selectively binds to the epidermal growth factor receptor, has demonstrated activity in patients with metastatic NSCLC. This study assesses whether combining cetuximab with CCRT is feasible.

Methods | Patients with inoperable locally advanced NSCLC, received cetuximab (400 mg/m² on day 1, 250 mg/m² q1w in weeks 2–6) in addition to radiotherapy (66 Gy in 24 fractions weeks 2–6) and cisplatin (6 mg/m² q1d during weeks 2–6) daily. Early response was monitored using FDG PET/CT-scans performed 4 weeks after treatment and response was evaluated by CT-scan 6 weeks after the last fraction of radiotherapy.

Results | Between March and July 2008, 12 consecutive patients were enrolled. Ten patients completed protocol treatment. Although generally well tolerated, two patients were unable to complete protocol treatment. Acneiform rash and dysphagia were the most common side effects (grade ≤ 3 according to CTCAE v 3.0). No unexpected toxicities were observed.

Early response monitoring revealed a metabolic response in 8 (out of 10) patients. CT-scan evaluation showed a partial response in 8 patients. Four (out of 12) patients showed progressive disease after 12 months of follow up.

Conclusions | The addition of cetuximab to CCRT in patients with NSCLC was generally well tolerated and early clinical responses were observed with this new therapy combination. A randomized phase II study comparing CCRT with CCRT and cetuximab is ongoing.

INTRODUCTION

Lung cancer is the leading cause of cancer related death in the western world. Non-small cell lung cancer (NSCLC) accounts for 80-85% of all cases of lung cancer and 30% of these patients present with locally advanced disease. Until 1990 patients with locally advanced NSCLC were treated with radiotherapy alone. The addition of chemotherapy to radiotherapy has resulted in a modest increase in survival (1). Our institute has investigated the role of concurrent chemoradiotherapy and was the first to pilot daily single agent cisplatin (6mg/m²) administered concurrently in a close temporal relationship with radiotherapy. A clear survival benefit was the result of adding cisplatin in a concurrent fashion (2;3). This increased survival was found to be related to increased loco-regional progression free survival. A meta-analysis supported the favorable outcome of concurrent chemoradiation (CCRT) (4). Further improvement of the chemoradiation schedule concerned escalation of the radiation dose from 55 Gy to 66 Gy using concomitant boost technique and this was effectuated with an acceptable level of toxicities (2;3;5). A recent meta- analysis of concurrent versus sequential chemoradiotherapy (CRT) showed an absolute 3-year overall survival benefit of 6.6% for concurrent over sequential CRT due to improved local control while the incidence of distant metastasis was not significantly affected by the addition of chemotherapy (6)

Cetuximab is a chimeric IgG1 monoclonal antibody that specifically binds to the epidermal growth factor receptor (EGFR) with high affinity, internalising the receptor and preventing the ligands EGF and TGF- α from interacting with the receptors, thereby effectively blocking ligand-induced EGFR phosphorylation (7;8). The EGFR is over-expressed in many solid tumors including NSCLC and is associated with an unfavorable outcome of disease. In an experimental setting EGFR expression becomes elevated after radiation and affects radiosensitivity (9;10). Conversely, inhibition of the EGF receptor can induce long lasting responses in a subset of NSCLC patients (11;12).

Improvement of treatment results in patients with NSCLC may be effectuated by combining chemotherapy with targeted therapy or by an individualized approach of biomarker adapted chemotherapy (13;14). A successful example of the implementation of targeted therapy is the treatment of locoregional advanced squamous cell carcinoma of the head and neck with RT plus cetuximab improving locoregional control and survival without increase of toxicity related to the radiotherapy (15). The feasibility of induction chemotherapy followed by radiotherapy and cetuximab in stage III NSCLC has been shown recently(16-18) and cetuximab has been found to potentiate the effects of chemotherapy and radiotherapy in experimental settings (7;19;20). Cetuximab (initial dose 400 mg/m² and subsequent weekly doses of 250 mg/m² on day 1) was well tolerated and regarded safe in several studies regarding colorectal -, head & neck- and lung cancer. The main side effects of cetuximab monotherapy consist of hypersensitivity related infusion reactions and acneiform skin reactions.

In this study we have assessed the feasibility of the addition of weekly cetuximab to high dose radiotherapy and concurrent daily cisplatin.

PATIENTS AND METHODS

Study design

Twelve consecutive patients with locally advanced NSCLC were enrolled to receive weekly cetuximab in combination with concurrent chemoradiation consisting of daily cisplatin, and fractionated radiotherapy. All patients were deemed irresectable prior to the start of chemoradiotherapy. Primary endpoint was the incidence and grade of toxicities. Secondary endpoints were early treatment response, overall response; progression free survival and survival at 12 months follow up.

Patient Population

Patients with a histological or cytological confirmed diagnosis of NSCLC, stage II/III irresectable disease and/or inoperability, without malignant pleural effusion were eligible for this study. The treatment options were discussed in a multidisciplinary fashion after completion of all diagnostic and staging procedures. Staging occurred according to the IASLC version 6(21;22). All patients were treated with intentional chemoradiation.

Further inclusion criteria included WHO (ECOG) performance status 0-1, age 18 years or older and the presence of at least one measurable target lesion (according to RECIST 1.0) with adequate haematological, renal and hepatic functions. Exclusion criteria were: known active other malignancies, unless definitive treatment was completed 5 years or more before study entry; ipsilateral radiotherapy to the chest, serious cardio-vascular diseases within the last 6 months, uncontrolled hypertension, pregnancy, previous treatment with EGFR-targeted drugs or monoclonal antibodies and symptomatic peripheral neuropathy (National Cancer Institute's common toxicity criteria, version 2, grade ≥ 2). Written informed consent was obtained from each patient before the start of study treatment. The study was approved by the local independent ethics committee and was designed in accordance with the International Conference on Harmonisation and Good Clinical Practice and the Declaration of Helsinki.

TREATMENT AND ASSESSMENT

Concurrent chemoradiotherapy

The treatment scheme is shown in Table 1. The initial dose of cetuximab was 400 mg/m² intravenously (i.v.), followed by a weekly dose of 250 mg/m² i.v. given on day 1, administered for a total of 6 infusions. Radiotherapy and cisplatin started one week after the initial dose cetuximab. Daily cisplatin was given from the first radiotherapy fraction onwards. The daily cisplatin dose was 6mg/m² given 1-1.5 hour before RT as an intravenous infusion (50 ml NaCl 0.9% solution) given as a bolus (+/- 10ml).

Radiotherapy

For all patients treatment planning was performed using intensity-modulated radiotherapy, with 4 dimensional treatment planning CT-scan, prepared with intravenous contrast (0.3 cm slice thickness). Patients were positioned supine; all fields were treated with the patient in the supine position. The involved irradiation fields encompassed the primary tumor and pathological lymph nodes on the 18-Fluorodeoxyglucose Positron Emission Tomography (FDG PET) scan. The Gross Tumor Volume (GTV) and normal structures were delineated according to the institutional protocol; Margins for the Clinical Target Volume (CTV) and Planning Target Volume (PTV) were added. The delineations were approved during a multidisciplinary meeting and the treatment was given using cone beam CT guidance. All patients were treated with mega voltage photon beams of 10 MV. The PTV was irradiated with 2.75 Gy per fraction with a multiple beam arrangement, for 5 days a week to a total number of 24 fractions over a period of 32 days (Table 1). The dose was specified according to the ICRU 50 guidelines, using advanced tissue inhomogeneity corrections. In the optimal plan the mean lung dose and other organs at risk were kept within specified constraints (spinal cord dose ≤ 50 Gy, esophagus: V35 $<65\%$; whole heart ≤ 40 Gy and ≤ 50 Gy to 2/3 and ≤ 66 Gy to 1/3). The Mean Lung Dose was kept below 20 Gy.

Patient Evaluation

Physical examination and laboratory tests were performed twice a week during treatment. The tumor was measured at onset of therapy and response was evaluated according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 (23). Six weeks after the end of treatment response to therapy (complete, partial response, stable disease, and progressive disease) was assessed using CT-scan. All patients were discussed in a weekly multidisciplinary meeting to assess resectability after treatment. A FDG PET/CT (Gemini TF, Philips, Eindhoven, the Netherlands) was assessed as an

Table 1. Concurrent chemoradiation with weekly cetuximab.

	D1	D8	D15	D22	D29	D36-D39
Cet:	•	•	•	•	•	•
CDDP:		X X X X X	X X X X X	X X X X X	X X X X X	X X X X X
Rt:		↑↑↑↑↑	↑↑↑↑↑	↑↑↑↑↑	↑↑↑↑↑	↑↑↑↑↑

- = Cetuximab 400mg/m² on D1, 250 mg/m² on D8, D15, D22, D29, D36
- X = Cisplatin/ cDDP 6mg/m² before each RT fraction
- ↑ = Radiotherapy (RT) 2.75 Gy x 24 fractions

early response monitoring tool and was performed within 4 weeks prior to the start of treatment and 4 weeks after CCRT was finished. This early time-point was chosen to support selecting patients for resectability after CCRT. The interval between FDG administration and scanning was 60 minutes +/- 10 minutes. Low-dose CT images (40 mAs, 5 mm slices) were acquired without oral or intravenous contrast. FDG tumor uptake was quantified using SUVmax, (SUVmax = Standard Uptake Value, maximum activity concentration/ (injected dose/body weight)) which was defined as the maximum tumor concentration of FDG divided by the injected dose and corrected for the body weight of the patient. Metabolic tumor response was assessed using the European Organization for Research and Treatment of Cancer (EORTC) criteria for SUV measurement (24). According to other studies on (chemo-) radiotherapy in lung cancer patients the definition of complete metabolic response was slightly altered to: no tumor FDG uptake or SUVmax in the tumor similar to that in the mediastinum, instead of the SUVmax in the surrounding normal tissue (25).

RESULTS

Between March and July 2008, 12 consecutive, eligible patients were enrolled. Patient characteristics are shown in Table 2. A total of 15 patients were screened for CCRT with cetuximab. During the screening phase distant metastases became evident in three patients. In two patients bone metastasis were diagnosed on repeat PET/CT (made because of a 4-6 week interval between PET/CT and the start of treatment). In the third patient a MRI confirmed metastatic disease in the brain.

Of the 12 treated patients eight patients had irresectable disease due to N2 or N3 disease, while four patients had irresectable tumors due to tumor location or invasion into surrounding structures.

Treatment exposure

Ten out of 12 patients completed the full treatment schedule of cetuximab, radiotherapy and cisplatin. One of the patients stopped cetuximab in week 6 due to acneiform skin rash grade 3 CTC (Common Terminology Criteria for adverse events, version 3.0). Another patient did not receive the last dose of cisplatin in week 6 due to an overall 30% increase of creatinine during the treatment course. All patients completed radiotherapy treatment within 32 days.

Toxicity data/ adverse events

All 12 patients were evaluable for toxicity. The combined regimen was generally well tolerated. The most common side effects were cetuximab related acneiform dermatitis and dysphagia (see Table 3). The maximal toxicity score for both side effects was grade 3 and both side effects did resolve completely. One patient developed grade 4 anorexia. No unexpected side-effects were encountered.

Table 2. Patient and tumor characteristics

Characteristics	N= 12
Gender	
Male	6
Female	6
Age	
Median	60
(range)	(44-77)
Performance score	
WHO 0	9
WHO 1	3
Smoking status	
Never	1
Former	4
Current	7
Ethnical background	
Caucasian	11
Azian	0
Latin	1
Histology/Cytology	
Adenocarcinoma	4
Large cell carcinoma	1
Squamous cell carcinoma	7
T-stage	
T0	1
T1	2
T2	2
T3	3
T4	4
N- Stage	
N0	4
N1	-
N2	7
N3	1
Extent of disease	
Stage IIb	2
Stage IIIa	6
Stage IIIb	4
EGFR Mutation	
Yes	0
No	3
NA/ not enough tissue	9
Kras mutation	
Yes	1
No	2
NA/ not enough tissue	9

Haematological toxicities are shown in Table 3 for all 12 patients. During treatment haematological toxicity did not exceed grade 2. In one patient neutropenia (grade 4) and leucopenia (grade 3) were observed two weeks after completion of treatment. This leucopenia was not accompanied by fever or infection.

A total of three serious adverse events (SAE) were documented in two patients. One concerned a 64-year old male, who was admitted as a consequence of generalized weakness during the 2nd week of treatment and vomiting. Tube feeding was initiated and the patient recovered fully within five days. The second patient, a 44 year old female was admitted to the hospital twice: the first time after an episode of mild haemoptysis in the 2nd week of treatment. No firmly established cause of haemoptysis could be determined but presumably both the tumor and the vulnerable mucosa may have contributed to this. She fully recovered and treatment was continued. In the 4th week she was readmitted because of dehydration and weight loss due to an episode of diarrhoea, fatigue and oesophagitis. After tube feeding she regained weight and she completed treatment.

Late toxicity

Six out of the 12 patients suffered from mild radiation pneumonitis (grade 1-2) between week 30 and 40 of the follow-up. In one patient the pneumonitis was associated with clinical bronchiectasis. Another patient developed an oesophageal stenosis (dysphagia in week 31), for which a single dilation procedure was performed.

Table 3. Toxicity during treatment by maximum grade (CTCAE v 3.0)

Toxicity N = 12	Maximum grade		
	2	3	4
Acneiform rash	7	4	0
Anorexia	0	1	1
Cough	1	0	0
Dysphagia	2	3	0
Fatigue	2	2	0
Nausea	1	1	0
Pain	0	1	0
Pneumonia	1	0	0
Vomiting	0	1	0
Anaemia	0	0	0
Leucopenia	2	1	0
Neutropenia	1	0	1
Platelets	0	0	0

Response

For early metabolic response monitoring, FDG PET/CT-scans were performed at baseline and 4 weeks after the last fraction of RT in 10 out of 12 patients. One patient did not receive a second FDG PET/CT-scan due to logistic reasons; another patient refused a second FDG PET/CT-scan. The median SUVmax of the primary tumor at baseline FDG PET/CT was 11.4 (SD 7.7). After CCRT treatment the median SUVmax was 4.5 (SD 2.6). The individual metabolic responses are shown in Figure 1. Baseline CT-scans were compared with scans obtained 6 weeks after the end of treatment (week 13). Eight patients exhibited partial response and three patients stable disease, in one patient locally progressive disease was observed on CT-scan.

In two patients CCRT was followed by surgery as advised in our multidisciplinary team meeting: one patient underwent lobectomy of the right upper lobe. Interestingly the CT response evaluation (RECIST criteria) had shown stable disease, but the resected tumor pathological analysis showed a complete response. In the second patient, mediastinoscopy revealed persistent N2-disease, so the surgical approach was abandoned.

One year follow up

Four patients have shown progressive disease after a total follow up of 12 months (Figure 2a). Local recurrence was observed in one patient, after 6 months. Three other patients developed distant metastases within one year: one patient showed brain metastasis within 3 months following the completion of CCRT; one patient developed metastasis in the contra lateral lung after 4 months, the other patient showed liver and bone metastasis after one year exactly. After 12 months 10 patients are still alive (Figure 2). The patient with local progression died 12 months after registration. Of the eight patients with no disease progression, one patient died 6 months after treatment due to pulmonary embolism; this SAE was analyzed and scored unrelated to treatment.

CONCLUSIONS & DISCUSSION

In this feasibility study cetuximab could be safely combined with concurrent high-dose radiotherapy and daily cisplatin in patients with NSCLC in an outpatient setting. Skin toxicity and other toxicities were manageable and comparable with previous reports of CCRT in NSCLC and cetuximab in various cancer types(3;5;6;15). The rate of grade 3 and higher oesophagitis, a fairly common toxicity in CCRT, was comparable with 5% and 17% in EORTC studies with concurrent cisplatin and radiation with 66Gy and compared to other CCRT regimen (3;5;26-28). In the last years the introduction of Intensity-Modulated Radiation Therapy (IMRT) allowed dose escalation by conforming the dose more precisely to a 3-Dimensional treatment volume, reducing toxicity (29).

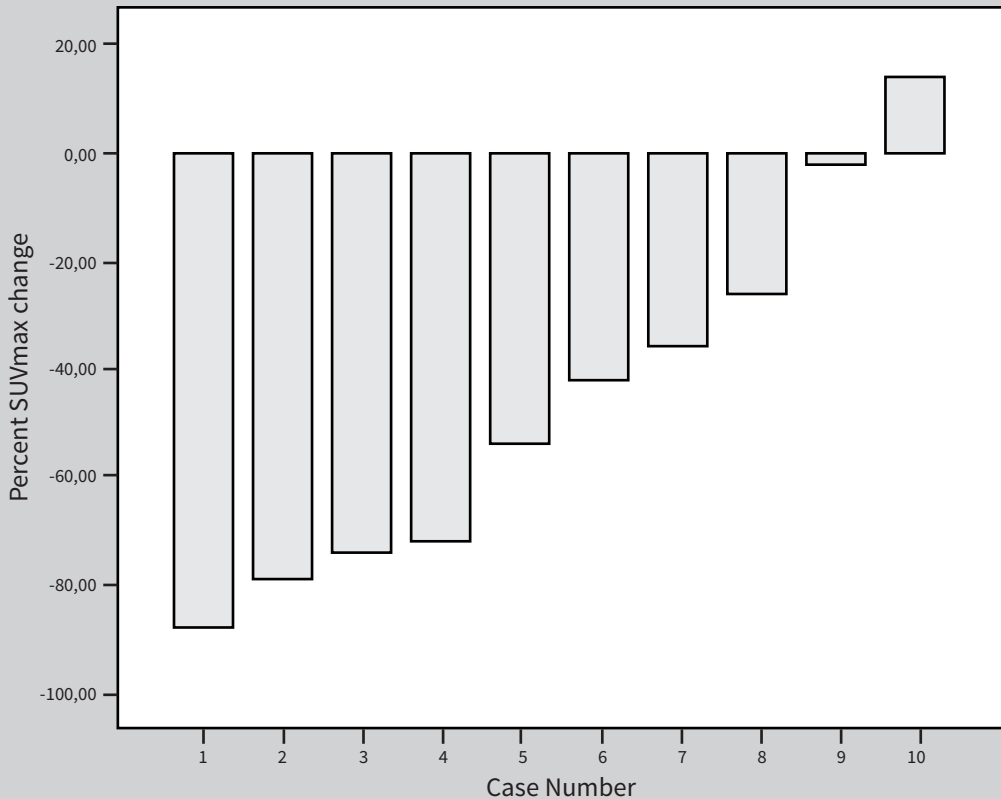


Figure 1. The percent change in SUVmax between baseline FDG PET/CT scanning and the FDG PET/CT after completion of CCRT treatment in 10 patients.

The anti tumor effects of cetuximab in combination with daily cisplatin and high-dose radiotherapy result in a promising response rate of 66% and a PFS of 12 months in 8 patients. Ten patients were alive at 12 months. Cetuximab has shown its efficacy in combination with chemotherapy in patients with metastatic colorectal cancer (30), and in combination with radiotherapy or chemotherapy in patients with squamous cell cancer of the head and neck(15). A recent phase III study has demonstrated that adding cetuximab to 1st-line standard chemotherapy significantly prolonged overall survival in the broad category of patients with metastatic NSCLC(17;31). In contrast to EGFR tyrosine kinase inhibitors (TKIs), the benefit of cetuximab in NSCLC is independent of the EGFR mutation status or histological subtype (31). EGFR and KRAS mutation status were not standardly determined in this feasibility study due to lack of tissue samples and these small samples sizes no more than 2 mutations should be expected.

It is known that cetuximab can act as a radiosensitizer (32) but also may exert antibody-dependent cell-mediated cytotoxicity (33-36). It will be important to further define these mechanisms that will help to optimize treatment with this new antibody.

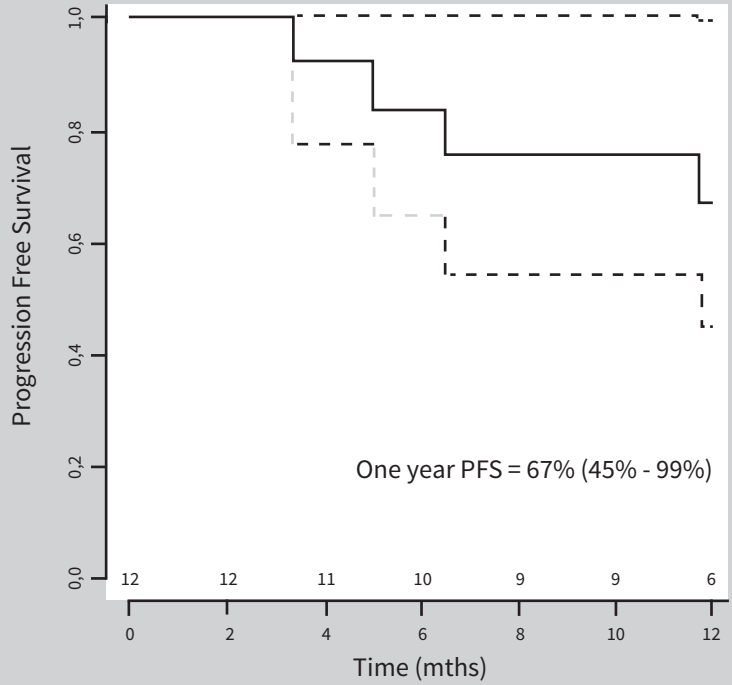


Figure 2A. Progression Free Survival

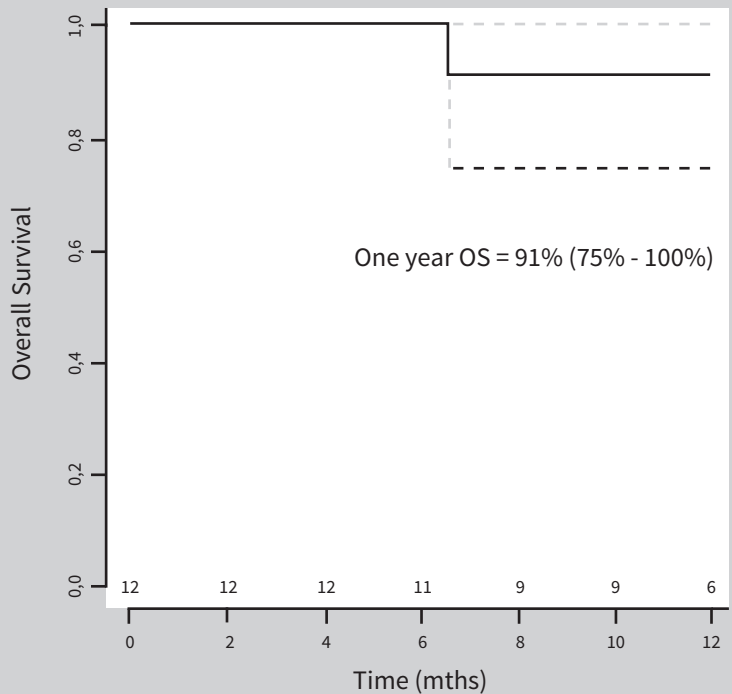


Figure 2B. Overall Survival

Response evaluation according to RECIST in patients treated with CCRT has proven not to be an optimal evaluation method in NSCLC. Tumor can often not be distinguished from radiation-induced pulmonary fibrosis or tumor necrosis. FDG PET/CT has been proposed for early prediction of response, showing promising results in colorectal, breast and oesophageal cancer (37-39). In NSCLC patients, reduction of metabolic activity during chemotherapy is also closely correlated with final treatment outcome (40). FDG PET response monitoring of chemotherapy has been shown to be more accurate than CT for response monitoring (41). Despite the promising results of FDG PET/CT for early accurate response monitoring, there have been concerns regarding the role of FDG PET/CT early after (chemo-) RT, because of the probability of false-positive results secondary to treatment-induced inflammatory changes (42).

In this study, according to RECIST, 8 patients showed a partial response. However, one of the patients with stable disease according to the RECIST criteria had a dramatic response on PET/CT (85%) and underwent a successful lobectomy with no vital tumor present. Another patient with maximal partial response revealed a response of 80% (see Figure 3) and has thus far not shown disease activity. In both cases metabolic response showed a better correlation with the clinical outcome than the response evaluation according to RECIST. Large cohorts will be necessary to determine the optimal metabolic response cut-offs.

In conclusion, high-dose intensity modulated radiotherapy combined with daily cisplatin in combination with cetuximab is feasible and well tolerated. A randomized phase II study comparing CCRT with CCRT and cetuximab within the Netherlands is ongoing. In the phase II study correlative analysis with molecular pathology, serum markers, and other patient characteristics will take place.

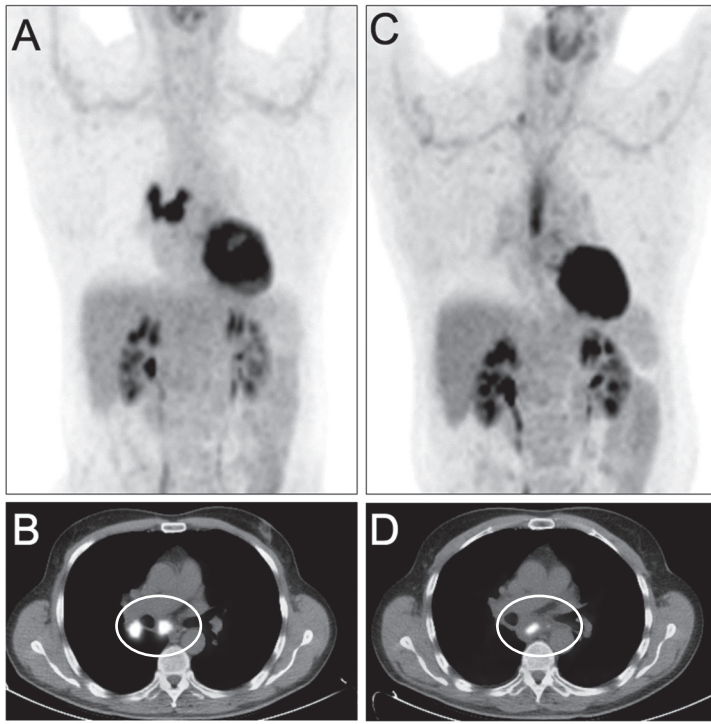


Figure 3. An example of a treated patient: A baseline FDG-PET/CT was performed, showing FDG uptake in the primary tumor and subcarinal metabolite activity (A, B). Four weeks after treatment FDG-PET/CT showed complete metabolic response and an FDG uptake in the esophagus due to radiation esophagitis (C,D).

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