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Original Paper

Feasibility of Escalating Daily Doses of Cisplatin in Combination With Accelerated Radiotherapy in Non-small Cell Lung Cancer*

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The aim of this study was to determine whether it is feasible to reduce the overall treatment time from 7 to 4 weeks in patients with non-small cell lung cancer (NSCLC) receiving radiotherapy with cisplatin. This follows an EORTC phase III randomised trial (08844) in which cisplatin given before each radiation dose resulted in improved local control and survival, but which had a relatively long treatment period of 7 weeks [Schaake-Koning *et al.*, *N Engl J Med* 1992, 326, 524–530]. 38 patients with confirmed NSCLC (2 stage I, 1 stage II, 18 stage IIIA, 17 stage IIIB) received a total tumour dose of 55 Gy/20 fractions/26 days, from January 1992 to March 1994. Daily fractions of 2 Gy (5 times/week) were given to the macroscopic tumour and the non-involved adjacent lymph node areas. During the same session, a dose of 0.75 Gy was given to the macroscopic tumour (simultaneous boost). Cisplatin 6 mg/m^2 was administered 1–2 h before each fraction, in an escalating total dose, during week 1 in 3 patients, during weeks 1 and 2 in 6 patients, during weeks 1, 2 and 3 in 5 patients and during the whole treatment in 24 patients. 38 patients were evaluable for acute side-effects (WHO). Maximal therapy-related toxicity (WHO) was grade 3 (nausea/vomiting in 2 patients, oesophagitis in 3 patients, dyspnoea in 3 patients, cough in 1 patient). Late side-effects were evaluated in 34 patients. There was grade 2 oesophagitis in 2 patients; grade 3 toxicity in 8 patients (tiredness in 3 patients, dyspnoea in 3 patients, oesophagitis in 2 patients); grade 4 toxicity in 4 patients (dyspnoea in 3 patients, cough in 1 patient). Pulmonary fibrosis grade 3 occurred in 4 and grade 4 in 6 patients. One patient developed a severe (grade 3) radiation pneumonitis. The low incidence of acute and late side-effects with this treatment, combining daily administration of 6 mg cisplatin with radical radiotherapy using a simultaneous boost technique, indicates that escalation of the radiation dose seems feasible.

Key words: non-small cell lung cancer (NSCLC), simultaneous boost technique, combined treatment, cisplatin

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INTRODUCTION

Non-small Cell Lung Cancer (NSCLC) is a common tumour type with a poor prognosis. A large proportion of the patients is inoperable at the time of diagnosis [1, 2]. In locally advanced disease TNM stage II, IIIA and IIIB, the 5-year survival rate is less than 10% after radical radiotherapy and the local control rate varies from 30–60% [1, 3, 4, 6].

Local cure is a prerequisite for long-term survival. Improvement of the local cure rate is correlated with a longer survival [4, 5]. The probability of local cure increases with increasing doses of radiation [4, 6]. Several new ways have recently been tried to enhance selectively the biological effect of radiation on tumour cells [7]. One of these possibilities is the combination of low doses of cisplatin (cDDP) used as a radiosensitiser [8, 9]. This combination has been investigated in

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several phase III studies in NSCLC [10–12]. In 1993, Schaake-Koning and colleagues published the results of the EORTC trial 08844, a randomised phase III study, in which a sensitizing effect was observed of cDDP at a dose of 6 mg/m^2 given 1–2 h before each radiation dose resulting in significantly improved local control and survival [5]. A recent update, after a minimal follow-up period of 4 years, confirmed the superiority of local disease-free survival and overall survival for the daily combined treatment arm [13].

One of the main criticisms of this trial is the relatively long overall treatment time (7 weeks) due to a split period of 3–4 weeks during the radiotherapy [14]. Prolongation of overall treatment time is known to result in a loss of local control in head and neck and cervical cancer [15, 16]. Recently, Cox and coworkers have demonstrated an adverse effect of treatment interruption in patients with unresectable NSCLC presenting with favourable prognostic factors [17]. The results of current phase III studies using treatment schemes with short overall times such as CHART (continuous, hyperfractionated, accelerated radiotherapy) or other hyperfractionated regimens used by the RTOG (Radiation Therapy Oncology Group) are to be awaited [7, 18]. Two phase II studies using a simultaneous boost technique indicate that it is possible to administer a radical dose of radiation in a relatively short overall treatment time with acceptable toxicity [19, 20].

We were interested to know if the same dose of radiotherapy as used in the aforementioned EORTC trial, combined with cDDP, administered as in the best arm of this trial, could be given safely without intercalating a split-period, thus reducing the overall treatment time from 7 to 4 weeks.

PATIENTS AND METHODS

Selection criteria

Between January 1992 and December 1993, 39 patients were entered in the study. All patients were staged by physical examination, haematological and biochemical liver function tests as well as creatinine clearance, bronchoscopy, lung function tests with vital capacity (VC) and forced expiratory volume in 1 second (FeV1) as minimal requirement, ECG, chest X-ray standard films and computed tomography (CT) scan of the thorax. Liver ultrasound, bone scan and CT scan of the brain were performed if metastases were suspected. 1 patient was not eligible because of distant metastases, leaving 38 patients evaluable.

Eligibility criteria for entering the study were: inoperable NSCLC T 1–4, N 0-2 (UICC, 1987), histologically or cytologically confirmed, age < 70 years, performance status 0 or 1 (ECOG/ZUBROD-WHO), weight loss < 5% during the previous 3 months, creatinine clearance > 70 ml/min, FeV1 > 1 l, maximal length of the oesophagus receiving 55 Gy 11 cm, maximal length of the oesophagus receiving 40 Gy 16 cm. Excluded were patients who received previous chemo- or radiotherapy, patients with recent myocardial infarction (< 6 months) or evidence of heart failure, and patients with any form of bone marrow hypoplasia (haemoglobin (Hb) < 6.8 mmol/l, white blood cell (WBC) count < 4 × 10 9/l, platelets < 100 × 10 9/l). Patients in whom it was technically impossible to exclude > 1/2–1/3 of the heart from the large fields or in whom it was impossible to limit the spinal cord dose to 44 Gy were also excluded.

Acute and late side-effects

Patients were followed once a week during and up to 4 weeks after the end of treatment, and every 8 weeks thereafter. For reasons of comparison, the same parameters for acute and late toxicity were used as in EORTC study 08844.

Acute and late side-effects were scored for weight loss, nausea/vomiting, oesophagitis, dyspnoea, cough and haematological toxicity and registered according to WHO criteria. Acute side-effects included all reactions occurring from day 1, the start of radiotherapy until day 70. Late side-effects was expressed as tiredness not attributed to tumour progression, dyspnoea, cough, changes on the chest X-rays, oesophagitis and radiation pneumonitis. For the evaluation of lung damage, chest X-rays were repeated every 8 weeks after radiotherapy. Late lung damage was listed as grade 1 if faint shadowing was seen on the chest X-ray, as grade 2 for moderate shadowing, both without distortion of anatomy; as grade 3 for faint and as grade 4 for moderate or dense shadowing with distortion of anatomy. If possible, lung function tests were conducted 6 and 12 months after end of treatment.

Evaluation of response

Local control was defined as a condition in which no clinical signs of a local recurrence was present and in which at least a decrease of ≥ 50% in the product of the two largest perpendicular diameters of a radiologically measurable disease was documented. Due to the occurrence of fibrotic changes in the irradiated area, a final complete disappearance of all tumours on the chest X-ray was often impossible to evaluate. Persistent radiographic abnormalities consisting of patchy and dense radiographic appearances and lung retraction which were still stable after 12 months were attributed to changes of the lung tissue due to irradiation.

Radiotherapy

All patients were treated with megavoltage photon beams ≥ 5 MV energy. The Elective Planning Target Volume (EPTV) encompassed the known tumour and the first lymph node drainage group not considered pathological with a margin of 1.5 cm at the 90% isodose in the central plane or with a margin of 2 cm to the light beams. Two opposite AP-PA fields or a multiple beam arrangement was used. The dose was defined according to the ICRU 50 report. The Boost Planning Target Volume (BPTV) included in the 90% isodose the known tumour volume with a 1 cm margin of normal tissue. Suspicious lymph nodes with a size of ≥ 1 cm were included. The BPTV was defined and calculated by CT assisted dosimetry, using a multiple field arrangement and the lung correction factor. The EPTV received a dose of 40 Gy administered in 20 daily fractions of 2 Gy, 5 times per week, overall treatment time being 26 days. The daily dose to the BPTV was 0.75 Gy given immediately after the treatment of the EPTV during the same session. Thus, the total daily dose to the BPTV was 2.75 Gy, the total overall dose 55 Gy, administered in 20 fractions, overall treatment time 26 days.

Chemotherapy

cDDP 6 mg/m^2 in an escalating number of doses was administered intravenously (i.v.) 1–2 hours before each fraction of radiotherapy. A daily fluid intake of 2 l was obligatory. 3 patients received cDDP the first treatment week (5 times or 30 mg/m^2), 6 patients had cDDP during fraction 1–10 (10 times or 60 mg/m^2), in 5 patients cDDP was administered for fraction 1–15 (90 mg/m^2) and the remaining 24 patients received cDDP before each treatment fraction (120 mg/m^2). The treatment could be given on an outpatient basis, but

generally the patients were hospitalised for the first week of treatment. Due to hospital facilities, a minority of the patients was hospitalised for the whole treatment. If the patient had oesophagitis grade 1 or higher, the cDDP administration was combined with infusion of an extra 1 litre of fluid.

2 patients received one day less cDDP than planned, in 1 patient because of fever and in the other because of an incorrect serum creatinine test. In one patient, the cDDP administration was stopped after 12 days because of an allergic reaction.

RESULTS

Patient characteristics

1 patient was not eligible because distant metastases were present, leaving 38 patients for evaluation. The mean age of the patients was 57 years, range 32–71 years. 6 patients presented with weight loss of $\geq 5\%$ (Table 1). This could be attributed to a thoracotomy in 1 and a candida oesophagitis in 2 patients.

The vital capacity varied between 6.0 and 2.2 litres with a mean of 4.0 litres. FeV1 values had a range of 4.1 and 1.0 litres with a mean of 2.4 litres. In 4 patients, an additional ventilation-perfusion scintigraphy was performed to ascertain that adequate tolerance for high dose irradiation was present. 36 patients had upper lobe lesions, in 2 patients the tumour was located in the middle lobe.

Treatment characteristics

Details about the radiation portals are shown in Table 2. The overall time was 26 days in 19 patients, and 28–31 days in 18 patients (due to holidays and start of treatment on Tuesday–Thursday). In 1 patient, the overall time was 38 days due to holidays and intercurrent disease. The maximum dose to the spinal cord varied between 41 and 44 Gy in 14 patients, and was 40 Gy or less in 22 patients. In 2 patients, the spinal cord dose exceeded 44 Gy (45 and 47 Gy). The absorbed dose in the oesophagus was 40 Gy or less in 2 patients, 41–45 in 7, 46–50 Gy in 11 and 51–55 Gy in 18 patients.

Table 1. Patient characteristics

		Number of patients
Sex (male/female)		33/5
Histology		
Squamous		15
Adenocarcinoma		11
Large cell		9
NSCLC		3
Performance status	0	24
ECOG	1	14
Weight loss %		
0		25
1–4		7
5–9		6
Stage		
I		2
II		1
IIIA		18
IIIB		17

NSCLC, non-small cell lung cancer.

Table 2. Treatment characteristics

	No. of patients EPTV	No. of patients BPTV
Primary tumour only	0	9
Primary tumour and ipsilateral hilum	0	7
Primary tumour and part mediastinum	10	22
Primary tumour and entire mediastinum	28	0
Length (cm)		
7–10	0	13
11–14	2	22
16	21	2
17–20	15	1

EPTV, Elective Planning Target Volume; BPTV, Boost Planning Target Volume.

Acute side-effects

38 patients were evaluable for acute side-effects. Weight loss during treatment was observed in 35 patients, with a mean of 5% (1–12%). 3 patients exhibited severe nausea/vomiting grade 3/4 (Table 3). In 1 patient, this was not treatment related but attributed to an atrial flutter. In the other 2 patients the toxicity returned to grade 1 after $5HT_3$-antagonist medication.

3 patients experienced severe oesophagitis grade 3 (1 in week 3, 1 in weeks 4 and 5 and 1 in week 5). 2 of these patients received cDDP treatment only during week 1, the other patient had 2 weeks of combined treatment. The oesophageal dose was 43 Gy in one and 55 Gy in other other cases. The irradiated length of the oesophagus in the BPTV was 9 cm in 1 patient and 10 cm in 2 patients. In 1 patient, an accompanying candida infection was suspected at oesophagoscopy, and 8 weeks after end of treatment the complaints disappeared. In the other patients, the complaints resolved completely within 4 weeks after end of treatment.

Severe grade 3 dyspnoea was observed in 3 patients, but

Table 3. Acute side-effects

Grade (WHO)	Nausea/ vomiting	Oesophagitis	Tiredness	Dyspnoea	Cough
0	12	3	12	6	14
1	17	23	13	17	21
2	6	9	12	12	2
3	2*	3‡	1	3§	1
4	1†	0	0	0	0
	38	38	38	38	38

* After $5\text{-}HT_3$ antagonist: grade 1; † Non-treatment-related (atrial flutter); ‡ 1 patient: week 3 only (1 week cisplatin, dose oesophagus 55 Gy, 10 cm length), 1 patient: week 5 only (1 week cisplatin, dose oesophagus 43 Gy, 9 cm), 1 patient: weeks 4 and 5 (2 weeks cisplatin, dose oesophagus 55 Gy, 10 cm, candida). Oesophagoscopy week 4: slight mucosal reaction, healed after week 12; §1 patient: weeks 1 and 2: returned to grade 1 in week 7, 1 patient: weeks 1, 2 and 5: grade 2 week 7, 1 patient: weeks 3, 4 and 10: grade 1 in week 13.

they improved 3, 3 and 7 weeks after the end of treatment. 1 patient exhibited a severe urticaria in the second week of treatment. The cDDP was stopped after the 12th fraction and the symptoms disappeared, suggesting an allergic reaction. 35 patients completed the treatment according to the protocol. 2 patients received one day less of cDDP than scheduled, 1 because of an incorrect creatinine blood test, 1 because of fever. 1 aforementioned patient received 12 days of cDDP instead of 20 because of an allergic reaction to the cisplatin.

Late side-effects

In 4 patients, the follow-up was less than 3 months; therefore 34 patients were evaluated for late side-effects. 3 patients exhibited severe tiredness, but all had progressive disease at that time (Table 4). Dyspnoea in rest was observed in 3 patients, these patients appeared to have progressive local disease. Intake of soft food only was mentioned for 2 patients, but a stenosis of the oesophagus was not demonstrated, and both died soon afterwards of progressive distant metastases. 2 other patients exhibited late oesophageal toxicity which could be attributed to the treatment. 1 patient with acute oesophageal toxicity grade 2, with increasing complaints in week 17, had, at oesophagoscopy, a superficial ulceration; with sucralfate the complaints disappeared in week 24.

1 patient developed chest pain, cough and dyspnoea in week 17, which was interpreted as a radiation pneumonitis. Despite treatment with corticosteriods and antibiotics, complaints were maintained and the chest X-rays remained abnormal. In week 58, local tumour recurrence finally was histologically confirmed.

The actuarial analysis of the risk of developing late side-effects grade 3/4 for cough, dyspnoea, oesophagitis and radiation pneumonitis is shown in Figure 1. Data concerning the lung function 6 months after radiotherapy are known in 4 patients. Both VC and the FeV1 decreased with a mean of 15 and 7%, respectively. The CO diffusion capacity was unchanged in 1 patient and decreased by 14% in another. One year after treatment, a decrease in VC and the FeV1 was seen in 3 patients (mean 21% and 17%, respectively); an increase was observed for the vital capacity in 2 patients (3 and 48%) and in 1 patient the FeV1 increased by 22%. The CO diffusion remained unchanged in 2 patients, increased in 1 (15%) and decreased in 2 patients (5 and 16%). Actuarial crude overall survival is shown in Figure 2. The median survival is 16 months (95% confidence interval: 12.2–21.6).

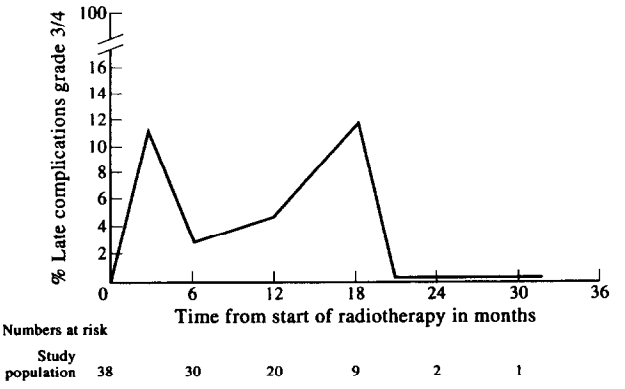

Figure 1. Actuarial incidence of late complications grade 3/4 for cough, dyspnoea, oesophagitis and radiation pneumonitis.

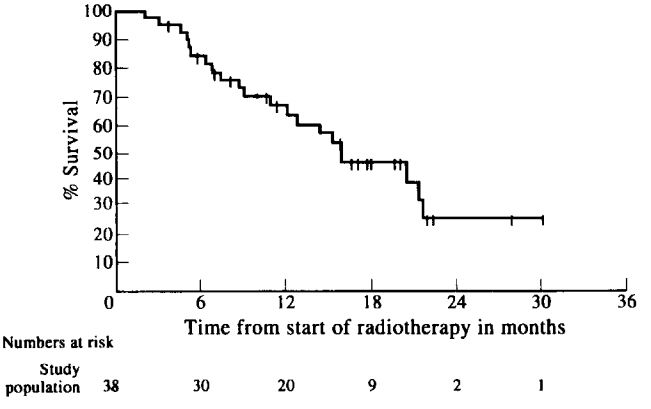

Figure 2. Crude actuarial survival of 38 patients with non-small cell lung cancer treated with escalating daily doses of cisplatin up to 6 mg/m² in combination with radiotherapy 55 Gy/20 fractions.

At the moment of analysis 17 patients are alive and 21 have died. Local recurrence-free interval is shown in Figure 3. At the moment of analysis, 15 patients had developed a local recurrence.

DISCUSSION

In the majority of the patients treated with 55 Gy/20 fractions combined with daily administration of cDDP 6 mg/m², the acute oesophageal side-effects were mild. Severe oeso-

Table 4. Late side-effects

Grade (WHO)	Tiredness	Dyspnoea	Cough	Chest X-ray	Oesophagitis	Radiation pneumonitis
0	14	16	13	1	30	33
1	10	11	9	4	–	–
2	7	1	11	11	2‡	–
3	3*	3	–	6	2§	1‖
4	–	3†	1	12	–	–
	34	34	34	34	34	34

* 2 patients: recurrent tumour, 1 patient: pneumonitis and recurrent tumour; † 2 patients: recurrent tumour, 1 patient radiation pneumonitis and recurrent tumour; ‡ 1 patient: subacute oesophagitis, week 17, oesophagoscopy: superficial ulceration in RT area, treated with sucralfate. No complaints after week 24, 1 patient: subacute oesophagitis, resolved week 12 with sucralfate; § 1 patient: week 11, soft food only. Died week 22 with bone metastases, 1 patient: week 14, soft food only. Died week 20 of progressive tumour; ‖ 1 patient: radiation pneumonitis, week 17 (cough, pain, haemoptysis) treated with prednisone and antibiotics (until week 48), week 58 local recurrence.

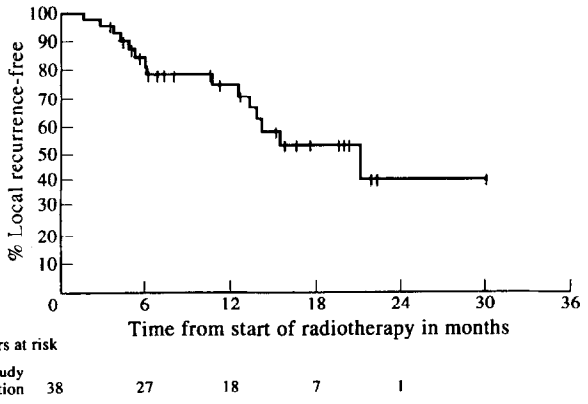

Figure 3. Local recurrence-free interval of 38 patients with non-small cell lung cancer treated with escalating daily doses of cisplatin up to 6 mg/m² in combination with radiotherapy 55 Gy/20 fractions.

phagitis was observed in 3 cases (8%), and none of these had received cDDP for the complete treatment time. In 1 patient, a candida infection partly explained the complaint, in the other 2 cases the duration of severe oesophagitis was restricted to only 1 week. Assuming an α/β of 8 Gy for acute oesophagitis, this treatment scheme equals 59 Gy/2 Gy [21]. This dose is generally well tolerated for the oesophagus. In the EORTC 08844 trial the addition of cDDP did not increase acute oesophageal toxicity. Two other studies, combining high-dose radiotherapy with low-dose daily cDDP, have reported an incidence of severe oesophagitis of 5 and 16, respectively [12, 23]. Hazuka and associates observed 16% incidence of grade 3 oesophagitis in a phase II study combining daily administration of cDDP 5 mg/m² with radiotherapy 61 Gy/33 4 fractions/61/2 wks. In their study the total dose of cDDP and the radiation dose were higher, and the treatment portals might have been larger than in our study.

Treatment-related late oesophageal side-effects were mild and only seen in 2/38 patients (5%) in our study. In 2 other patients, the indicated late oesophageal toxicity was probably not treatment- but disease-related, and thus it is doubtful if it should be reported as an oesophageal side-effect. Due to the eligibility criteria, the length of the oesophagus receiving 40 or 55 Gy was limited to 16 and 11 cm, respectively, and this might explain the low incidence of late oesophageal toxicity.

Severe nausea/vomiting, not responding to 5-HT_3 antagonist treatment was not observed. This means a considerable improvement compared to the observed incidence of nausea/vomiting in the EORTC 08844 trial in which 24/87 (28%) of the patients who received daily cDDP had grade 3/4 nausea/vomiting. In our opinion, this can be attributed to the systemic treatment of patients presenting nausea/vomiting not responding to conventional anti-emetics.

No severe haematological side-effects were observed; the field size of the EPTV and the BPTV was limited in the majority of the patients. This is in agreement with the data of the EORTC 08844 trial in which only 3/87 patients in the daily cDDP arm showed severe haematological toxicity. Hazuka and associates observed haematological toxicity in 17% of the patients, but the total dose of cDDP was higher, the radiation dose was higher and the fields might have been larger in his study [23].

The observed late side-effects for tiredness and dyspnoea did not appear to be treatment-related, as the majority of the patients had progressive disease at the time the toxicity was assessed. This holds true for the only patient in whom a radiation pneumonitis was suspected.

Thus far, clinical studies have not demonstrated an enhancement of pulmonary toxicity with the combined treatment of radiotherapy and cDDP [5, 12, 22–24]. Assuming an α/β of 3.3 to 5 Gy for acute lung damage (up to 6 months), this treatment is isoeffective with 63–61 Gy/2 Gy. At this dose level, the incidence of acute lung damage would be expected to be $\geq$ 90% within the irradiated volume [21]. The volume receiving 55 Gy was limited, however, as, due to the eligibility criteria, all tumours but one were situated in the upper lobe. As the irradiated lung volume might play a role in the occurrence of pulmonary damage, this might explain the observed low incidence of radiation pneumonitis [25].

The observed local recurrence rate in this small series and with a restricted follow-up is in agreement with other studies using radiotherapy only and the data of Trovó and colleagues, but higher than in the EORTC 08844 study [5, 6, 12]. The survival data of this study are limited. The median survival of 16 months, based on a small number of patients, is comparable to several large studies using curative radiotherapy in advanced stages and comparable with the data of other series using radiotherapy and cDDP [5, 12]. As only some of the patients with a follow-up > 1 year had received cDDP for the whole treatment period, the data concerning local recurrence and survival are preliminary and must be interpreted with caution.

Our main conclusion from this study is that a radiotherapy schedule of 55 Gy/20 fractions/26 days using a simultaneous boost technique combined with daily administration of cDDP 6 mg/m² is tolerated and thus a reduction of the overall treatment time from 7 weeks in EORTC trial 08844 to 4 weeks is feasible in this patient category. The incidence of serious side-effects is minimal and mainly oesophageal.

The low toxicity observed in this study indicates that an escalation of the radiotherapy dose might be feasible. Because a dose–effect relationship for local control is observed in non-small cell lung cancer up to a dose of 70 Gy, we feel that a dose escalation should be tested before going into a phase III study. Thus, our next step will be an evaluation of the side-effects of a higher radiation dose up to 66 Gy given in combination with daily administration of cDDP in the same patient group using three-dimensional treatment planning and conformal radiotherapy.

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