Accelerated Hyperfractionated Radiotherapy Combined with Induction and Concomitant Chemotherapy for Inoperable Non-small-cell Lung Cancer

Impact of Total Treatment Time

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Tumour cell proliferation during conventionally fractionated radiotherapy (RT) can negatively influence the treatment outcome in patients with unresectable non-small-cell lung cancer (NSCLC). Accelerated and hyperfractionated RT may therefore have an advantage over conventional RT. Moreover, earlier studies have suggested improved survival with addition of cisplatin-based chemotherapy (CT). We present here the results of combined treatment with induction and concomitant CT and accelerated hyperfractionated RT in a retrospective series of patients with advanced NSCLC. Between August 1990 and August 1995, 90 consecutive patients, aged 42–77 years (median 63 years), with locally advanced unresectable or medically inoperable NSCLC and good performance status were referred for treatment: stage: I 23%, IIIa 37%, IIIb 40%. Patient histologies included: squamous cell carcinoma 52%, adenocarcinoma 34% and large cell carcinoma 13%. The treatment consisted of two courses of CT (cisplatin 100 mg/m^2 day 1 and etoposide 100 mg/m^2 day 1–3 i.v.), the second course given concomitantly with RT. The total RT dose was 61.2–64.6 Gy, with two daily fractions of 1.7 Gy. A one-week interval was introduced after 40.8 Gy to reduce acute toxicity, making the total treatment time 4.5 weeks. Concerning toxicity, 33 patients had febrile neutropenia, 10 patients suffered from grade III oesophagitis and 7 patients had grade III pneumonitis. There were two possible treatment-related deaths, one due to myocardial infarction and the other due to a pneumocystis carinii infection. The 1-, 2- and 3-year overall survival rates were 72%, 46% and 34%, respectively; median survival was 21.3 months. Fifty-nine patients had progressive disease: 21 failed locoregionally, 29 had distant metastases and 9 patients had a combination of these. Pretreatment weight loss was the only prognostic factor found, except for stage. However, the results for stage IIIb were no different from those for stage IIIa. We conclude that the survival results compare favourably with those of most other studies with a manageable toxicity.

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Non-small-cell lung cancer (NSCLC) is an increasing cause of cancer death in several parts of the world (1). Traditionally, the chance of cure has been considered optimal when surgery is included in the therapy. A recently published retrospective analysis of all resected patients in West Sweden during a 10-year period demonstrated a 5-year survival rate of 38% among the resected patients, and a resection rate of only 20% of all newly diagnosed patients with NSCLC (2). About 50% of the patients have distant metastases at diagnosis (3), and palliative treatment would be the only option for this group. In patients with locally advanced unresectable disease (stage IIIb and the majority of stage IIIa) or patients with less extensive tumours who are medically inoperable, conventionally fractionated radiotherapy with about 2 Gy per fraction to a total dose of up to 60 Gy has yielded a 5-year survival rate of about 5% (4). Both local and distant failure is a problem for such patients and both the local and systemic treatments need to be improved.

In an attempt to improve the therapy for this patient group, we designed a treatment schedule which takes several problem areas into account. First, one reason for failure of the local radiation might be tumour progression during a course of conventionally fractionated radiotherapy with treatment times of 6–7 weeks. Cell proliferation studies on tumours of non-small-cell lung cancer have shown comparatively short potential doubling times, with several values of three days or less (5). This was part of the

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rationale for the British CHART trial (6, 7), where an accelerated treatment arm showed significantly better survival compared with conventional fractionation in advanced NSCLC (7). The impact of the overall treatment time on the radiotherapy results has been studied by Koukourakis et al. (8). They estimated the daily dose lost because of treatment protraction beyond 20 days to 0.2–0.45 Gy/day. However, in contrast to the CHART philosophy, we think it is important to maintain a high total dose when accelerated fractionation is used in order not to lose the effect on slowly proliferating tumours. This resulted in a fractionation schedule with 1.7 Gy twice daily for 5 days a week up to a total of 61.2–64.6 Gy. In order to overcome excessive acute normal tissue reactions, a break of one week was introduced in the middle of the treatment. This could be a negative factor for rapidly proliferating tumours, but even with the break the total treatment time was reduced by two weeks to 4.5 weeks instead of 6.5 weeks with conventional fractionation.

Second, a large proportion of patients with presumed localized disease treated with radiotherapy develop distant metastases. Several trials have studied the value of induction chemotherapy, with conflicting results. However, a meta-analysis including 22 trials and over 3000 patients comparing induction chemotherapy plus radiation with radiotherapy alone established a small but significant survival benefit for the combined approach, the absolute survival benefit being 2% at five years (9). The survival gain was more pronounced for the cisplatin-containing regimens. In our treatment schedule, two cycles of chemotherapy were included with cisplatin 100 mg/ m^2 i.v. day 1 and etoposide 100 mg /m^2 i.v. days 1–3.

The third issue concerns concomitant treatment. Theoretically, cisplatin could act as a radiation sensitizer (10). The possible gains with concomitant chemo-radiotherapy are improved local control and a decreased rate of distant metasases. The previous discussion about total treatment time can also apply to protracted induction chemotherapy, but whether and how previous chemotherapy alters tumour cell kinetics and the response to radiotherapy is not clearly elucidated. Some studies show improved results with concomitant treatment (11, 12), but acute normal tissue reactions will increase. It is therefore not possible to give extensive concomitant chemotherapy when the acute radiotherapy reactions approach the upper tolerance level. Our solution was to give one of the chemotherapy cycles concomitantly with the initiation of the radiotherapy.

The present study is a retrospective review of a consecutive series of patients with locally advanced NSCLC treated in a single institution according to the guidelines of the regional management programme for lung cancer.

MATERIAL AND METHODS

Patient selection

All patients with locally advanced or medically inoperable and a histologically or cytologically confirmed diagnosis of non-small-cell lung cancer who were referred to Sahlgrenska University Hospital between August 1990 and August 1995 for radiotherapy with curative intent were considered for this treatment schedule. Guidelines for patient selection also included a good performance status (WHO 0–2) and acceptable pulmonary function (FEV $1 \geq 1$L). Patients with pleural effusion or known distant metastases were not accepted. No specific age limit was set, and treatment for other malignancies was not a contraindication. Before therapy, all patients underwent bronchoscopy, chest x-ray, a thoracic CT scan and CT or ultrasound examination of the upper abdomen. No other metastatic work-up was made unless symptoms were present. Patients who were preliminarily scheduled for surgery were subjected to mediastinoscopy or explorative thoracotomy. A few patients with incomplete resections were included in this treatment schedule, but for reasons of comparison the preoperative staging has been used in all cases for further analyses.

Treatment plan

Chemotherapy. The planned treatment included two courses of cisplatin (100 mg/m^2 i.v. day 1) and etoposide (100 mg/m^2 i.v. days 1–3). The first course was given as induction and the second concurrently with radiotherapy, starting on day 22. Both drugs were administered by intravenous infusion. Pre- and post-hydration with a total of 2 L NaCl and furosemide i.v. were used as well as adequate antiemetic drugs before and after cisplatin. If there was a relative contraindication to cisplatin, such as impaired renal function or hearing loss, it could be replaced by carboplatin at a dose of 350 mg/m^2. G-CSF was used occasionally at the end of the study period, but only in patients with febrile neutropenia after the first chemotherapy course. (See Fig. 1 for treatment schedule.)

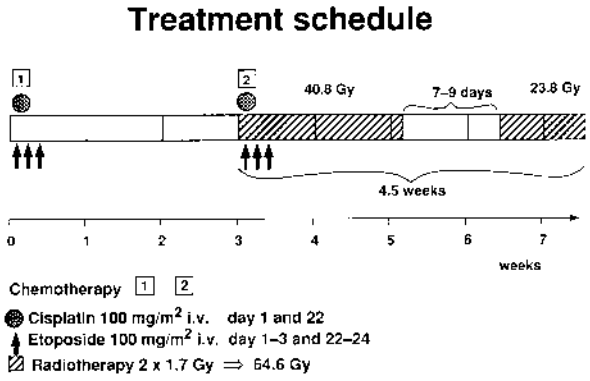

Fig. 1. The treatment schedule with induction and concomitant chemotherapy combined with accelerated hyperfractionated radiotherapy.

Radiotherapy. Radiotherapy was administered with 1.7 Gy twice daily, with a minimum interfraction interval of 6 h, 5 days a week to 61.2 Gy in 36 fractions 1990–1993 or 64.6 Gy in 38 fractions (1994–1995). The dose was increased because of good tolerance in the first period. A planned break of 9 days was introduced after 40.8 Gy to reduce the acute toxicity, resulting in a total treatment time of 4.5 weeks. The target volume consisted of the primary tumour with a 1.5–2 cm margin, the ipsilateral hilum, mediastinum, and, for upper lobe tumours, the medial supraclavicular fossa. This volume was treated to 40.8 Gy. A boost volume was defined as the primary tumour, the ipsilateral hilum, and the involved nodal regions treated with up to 61.2–64.6 Gy. The maximum dose to the spinal cord was limited to 45 Gy, and 20 Gy was the maximum dose to a significant volume of the contralateral lung. Dose planning was CT-assisted, mostly ending up in a 3–4 field arrangement. Specially shaped lead shields and multileaf collimators were used and corrections were made for tissue inhomogeneities. Linear accelerators with 5–15 MV were used for the treatment.

Toxicity and response evaluation

Acute and late radiation toxicity, for example oesophagitis and pneumonitis, was prospectively assessed according to the RTOG/EORTC criteria (13). Toxic side effects of chemotherapy were retrospectively evaluated according to the WHO criteria (14). The response was evaluated 1–3 months after completion of therapy. All patients had a chest x-ray and most patients a CT-scan of the thorax. Bronchoscopy was not routinely used for response evaluation. Complete response was defined as complete resolution of all symptoms and signs of tumour for at least 4 weeks. Partial response was defined as a 50% reduction in the sum of the products of perpendicular diameters of measurable lesions for at least 4 weeks. After completion of therapy, patients were followed every 3 months for 2 years, and every 6 months thereafter.

Statistics

Survival was measured from the date of diagnosis in order to compare the results of this study with clinical series based on cancer registry data, and because there was no specific randomization date. Survival curves were estimated by the Kaplan-Meier method. Differences in survival estimates between groups of patients were evaluated using logrank analysis (15). For comparison of proportions, the χ^2 test or, when appropriate, the Fisher exact test was used.

RESULTS

Patient characteristics

From August 1990 to August 1995, 90 consecutive patients (median age 63 years) were enrolled in this study. Patient characteristics are presented in Table 1. Performance status was 0–1 in 92% of patients and 52% had no pretreatment weight loss; 23% of the patients had stage I disease, 37% had stage IIIa, whereas 40% had stage IIIb disease. Nine patients (10%) had an incomplete resection, while 4 others had an exploratory thoracotomy before chemoradiotherapy.

Table 1

Patient and tumour characteristics

Total number	90
Age median	63
Range	42–77
Male/ female	52/38
Performance status	
0	17
1	66
2	6
3	1
FEV1, median	2.2 l
Range	0.9–3.7 l
Weight loss > 1 kg	41
Stage	
I	21
IIIa	33
IIIb	36
T1	11
T2	37
T3	13
T4	29
N0	39
N1	1
N2	35
N3	12
NX	3
Histological subtype	
Squamous	47
Adenocarcinoma	30
Large cell	12
Adenosquamous	1

Accomplishment of treatment

Chemotherapy was given in a total of 149 cycles. Eighteen patients did not receive any chemotherapy at all, 7 because of heart disease, 3 due to patient refusal, 1 because of active tuberculosis, 1 because of advanced age and poor general condition and 6 for unknown reasons (protocol violation, above all at the beginning of the study, when there were less data supporting combined therapy). Five patients were considered to have contraindications to cisplatin and received carboplatin instead. Sixty-three patients (70%) were treated with concomitant chemotherapy, 5 patients received only one cycle because of toxicity and 6 patients received more than one cycle as induction, for pragmatic reasons.

Radiation therapy was delivered at full dose in 96% of the patients. The treatment was interrupted at 59.5 Gy in one patient due to impaired general condition, at 48.7 and 46.7 Gy respectively in two patients because of myocardial infarction during treatment, and at 40.8 Gy in one patient due to discovery of distant metastases. The mean area of the anterior field of treatment in the large volume was 242 cm^2 (range 77–459) and of the boost area 194 cm^2 (range 56–375). In 41 patients no volume reduction was made.

Toxicity

The most important acute toxicity with this treatment schedule was febrile neutropenia, which occurred in 33 patients (39%), all of whom received concomitant chemotherapy. They needed hospital admission and intravenous antibiotics. Oesophagitis grade 3 according to RTOG/EORTC (13) (need for intravenous nutrition or tube feeding) was seen in 10 patients (11%) and 7 (8%) suffered from pneumonitis grade 3 according to RTOG/EORTC (13). The irradiated volume and pretreatment lung function (FEV1) did not predict the risk of pneumonitis. There were two possible treatment-related deaths; one patient died of Pneumocystis carinii pneumonia one month after completion of the therapy, another patient died of myocardial infarction one week after the radiotherapy had finished. Concerning late toxicity, one patient developed oesophageal stenosis four months after completion of the therapy. No other severe late toxicity was seen.

Response and survival

Responses were assessed retrospectively. Twelve patients had a complete response and another 30 patients had a partial response, resulting in an overall response rate of 47%. The disease had stabilized in 22 patients and disease progression was seen in 5. However, a large group of patients (23%) was considered non-evaluable with regard to response, including the ten incompletely resected patients.

The 1-, 2- and 3-year overall survival rates were 72%, 46% and 34%, respectively (Fig. 2). The median survival was 21.3 months, with a minimum follow-up of 22 months. Survival according to tumour stage is shown in Fig. 3. Patients with stage I disease had a significantly longer survival than those with stage III disease, but there was no difference in survival between stages IIIa and IIIb. The 1-, 2- and 3-year survival rates were 81%, 67% and 56%, respectively for stage I, 70%, 39% and 29% for stage IIIa, and the corresponding rates for stage IIIb were 69%, 41% and 25%, respectively. Patients with no nodal disease (N0) fared better ($p < 0.005$), but there was no survival difference between N2 (ipsilateral) and N3 (contralateral) disease.

Age, sex, pretreatment pulmonary function and tumour histology had no effect on survival but pretreatment weight loss was a significant negative prognostic factor for the outcome (see Fig. 4). Patients who experienced significant treatment toxicity (e.g. sepsis, oesophagitis and pneumonitis) had no altered survival compared to the whole group.

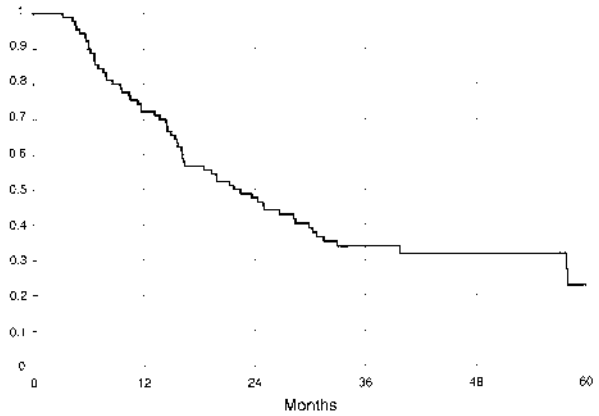

Fig. 2. Overall survival for the 90 patients treated with combined therapy.

Progression of the disease has occurred in 59 patients so far; 33 patients had distant metastases, 4 also combined with local failure. The most common metastatic sites were the skeleton (n = 13) and the brain (n = 12). At the time of analysis (May 1997), 29 patients were still alive and 24 of them free from disease.

DISCUSSION

This treatment schedule for inoperable NSCLC was designed to optimize the non-surgical therapy with the main focus on local tumour control. Before the introduction of the present study schedule, patients with similar characteristics were treated in a randomized study comparing conventionally fractionated radiotherapy (2 Gy once daily) to a total dose of 56 Gy with the same radiotherapy preceded by 2–3 cycles of cisplatin and etoposide (16). When analysing the effect of this treatment, the main problem was considered to be insufficient primary tumour steriliza-

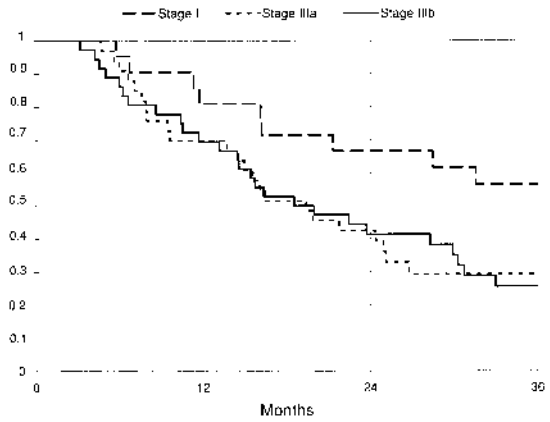

Fig. 3. Overall survival according to tumour stage.

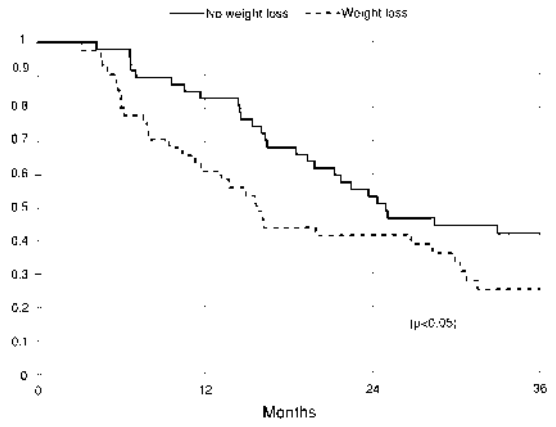

Fig. 4. Overall survival according to pretreatment weight loss.

tion, and local failure in more than 90% of the patients in both treatment arms. Radiotherapy was then changed and was accelerated and slightly hyperfractionated to a somewhat higher total dose level of 64.6 Gy in 4.5 weeks. This shorter treatment time should be of benefit to patients with rapidly proliferating tumours and of no harm to the slower ones when the total dose is so high that it can be considered radical. The overall survival rates for the whole group of patients at 2 and 3 years were 46% and 34%, respectively, with a median survival of 21.3 months and a minimum follow-up that exceeded median survival. For stage III patients, the 2- and 3-year survival rates reached 40% and 27%, with a median survival of 19.4 months. These results compare favourably with our own historical results and those of other studies (4, 16). The response rate reported here, however, is not impressive, with 13% CR and 33% PR, although 23% of patients were considered non-evaluable. We think this reflects the difficulties in evaluating the response after radical radiotherapy, where consolidation of lung parenchyma due to the high dose volume is common. Neither post-therapeutic bronchoscopy nor CT was routinely used, which might have increased the response evaluation accuracy. We therefore ascribe the improved survival data in the present study, as compared to historical ones, to better local treatment resulting in better local tumour control.

Accelerated fractionation has shown a survival advantage in the randomized CHART trial, with a 2-year survival of 30% in the study arm and 20% for the control group (7). In the CHART trial, no chemotherapy was used. However, cisplatin-based induction chemotherapy has shown a survival benefit in several studies when combined with radiotherapy, documented in a meta-analysis (9, 17). This effect has mainly been ascribed to a reduced rate of distant metastases (18–20). In the present treatment regimen, one of the chemotherapy cycles was given concomitantly with radiation. The principal reason for this was to keep the total treatment time as short as possible. However, there was also the possibility of an increased therapeutic ratio based on more pronounced radiation enhancement by cisplatin on tumour tissue as compared to normal tissue encompassed in the radiation treatment volume. There is one recently published randomized study comparing induction with concomitant chemotherapy in combination with radiotherapy, with a significantly better survival for the latter schedule (21).

Acute side effects within the radiation treatment volume are pneumonitis and oesophagitis; 8% of patients reached a grade 3 pneumonitis reaction, which is no more than has been seen in our historical controls. The reported range of pneumonitis for combined treatment in the literature is 4–25% (6, 12, 13, 20, 22–24). Proposed risk factors for development of pneumonitis, such as large irradiated lung volumes and impaired pretreatment pulmonary function, were not of significant importance in this study. On the other hand, oesophagitis was more common, with 11% reaching a grade 3 reaction. One case of late stenosis was seen. The range of grade 3 reactions reported in the literature is 6–53% in comparable treatment series (6, 12, 13, 20, 22–27). The main basis for the increased rate of oesophagitis is the cell kinetics of the oesophageal mucosa and the increased cell kill produced by the accelerated radiation fractionation. However, the impact of the radioenhancing effect of the concurrently administered cisplatin cannot be assessed. The main toxic effect of this treatment schedule was febrile neutropenia, which occurred in 39% of the patients, all of whom had received concomitant chemotherapy. This relatively high incidence is in the upper range of that for published combined treatment series (20, 22–24, 26, 27) and may have caused the death of one patient from Pneumocystis carinii infection. It is possible that prophylactic antibiotics to at-risk patients and more extensive use of cytokines could have reduced this toxicity.

Recently, an Australian group performed a four-armed trial comparing accelerated and conventionally fractionated radiotherapy with and without concomitant carboplatin. There was no significant difference in survival between the groups but there was a trend toward better survival in the chemotherapy arms (28, 29). However, the result did not support an advantage resulting from accelerated radiotherapy. In purely hyperfractionated radiotherapy schedules, where total treatment time is not changed from that of conventional fractionation, the low dose per fraction of about 1.1–1.3 Gy causes more pronounced damage to tumour tissue compared with to normal tissue. This improved therapeutic ratio enables a higher radiation dose to be given for the same rate of normal tissue side effects and therefore potentially a better local tumour control. In one randomized trial comparing hyperfractionated high-dose radiotherapy with and without carboplatin–etoposide chemotherapy, the 3-year survival was 23% for the combined schedule compared with 11% for

Table 2

Author	Published year	n	Total dose	Daily dose	Chemotherapy	Survival			Toxicity oesophagitis (%)
						2 years (%)	3 years (%)	Median	
Studies with accelerated radiotherapy									
Saunders (6)	90	62	54	3 × 1.5		34	18 (extrapolated)	–	32
Brindle (13)	93	21	60	2 × 1.5		29	14	10.8	9.5
Studies with accelerated and/or hyperfractionated radiotherapy combined with chemotherapy									
Shaw (22)	93	23	60	2 × 1.5	Cisplatin Etoposide	51	–	26	13
Alberto (25)	95	65	63	2 × 1.5	Cisplatin Mitomycin c Vindesine	28	18	15.7	9
Byhart (26)	95	42	69.6	2 × 1.2	Cisplatin Vinblastin	28	–	12.2	24
Ball (29)	96	51	60	2 × 2	Carboplatin	24	–	15.8	–
(randomized)		54	60	1 × 2	Carboplatin	44	–	21.6	
		46	60	2 × 2	No chemo.	35	–	14.6	–
		53	60	1 × 2	No chemo.	26	–	14.5	–
Jeremic (12)	96	65	69.6	2 × 1.2	Carboplatin Etoposide	43	23	22	8
(randomized)		66	69.6	2 × 1.2	No chemo.	26	11	14	6
Lee (20)	96	76	69.6	2 × 1.2	Cisplatin Etoposide	35	–	18.9	53
Le Pechoux (27)	96	34	60	2 × 1.25	Cisplatin Vindesine	33	12	14	9
Present study		90	64.6	2 × 1.7	Cisplatin Etoposide	46	34	21.3	11

radiotherapy alone (12). The same radiation schedule of 1.2 Gy twice a day to 69.6 Gy has recently been studied in a three-armed RTOG-ECOG trial and compared with conventional fractionated radiotherapy to 60 Gy with and without induction chemotherapy. The best result was achieved when chemotherapy was used and hyperfractionation was better than conventional fractionation only (30). These studies support the finding that a radiation dose-response relationship exists for local tumour control in NSCLC and that a dose escalation is clinically meaningful, at least if hyperfractionation is used. The phases II and III data with accelerated radiotherapy and combined treatments including chemotherapy and radiotherapy given either accelerated or hyperfractionated are presented in Table 2.

To improve selection of patients for the regimen described in this paper, some potential prognostic factors were studied. With the exception of stage, where stage I showed significantly better results ($p < 0.025$), the only prognostic factor found was pretreatment weight loss ($p < 0.05$). These findings were confirmed in a multivariate analysis and are in agreement with results in earlier studies (31). The 25 patients who survived for less than one year were compared with the 65 patients who survived longer but no specific characteristics were found in this group.

In conclusion, we think the survival results are encouraging and that toxicity is manageable with this treatment schedule for patients with advanced NSCLC. The results compare favourably with those of most other studies with comparable patients and indicate that tumour clonogen repopulation is of importance for the scheduling of radiotherapy in NSCLC. For optimal local tumour control, the total radiation dose is of importance, and based on the results of the hyperfractionated studies, should preferably be increased above the dose level in the present study. The optimal fractionation for such a regimen cannot yet be established. An increased cell kill of chemotherapy should improve both local and distant tumour control. The results of the present study should be confirmed in a phase III trial, which we are now planning.

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