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LOCAL FAILURE IN PATIENTS TREATED WITH RADIOTHERAPY AND MULTIDRUG CHEMOTHERAPY FOR SMALL CELL LUNG CANCER

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Abstract

Fifty-three patients with small cell carcinoma of the lung were treated with chemotherapy and radiotherapy, 40 Gy in the chest tumour. Intrathoracic failure occurred in 89% of the cases with extensive disease and in 60% of those with limited disease. Since 86% of all failures were localized within the target volume, one can conclude that in most cases the radiation dose was too low for eradication of the tumour. The treatment technique resulted in dose inhomogeneities of more than ±5% in 45% of the cases. The high local failure rate might indicate the need of improved radiotherapy, in the first place higher radiation dose. However, 82% of the patients with limited disease and local failure and 50% of those without local failure also developed distant metastases. This might indicate that the curative potential of improved thoracic radiotherapy probably is limited. Besides, lethal treatment toxicity affected particularly patients in whom local cure had been achieved, indicating the difficulty of increasing the treatment intensity without increasing the lethal toxicity in potentially curable cases.

Key words: Small cell lung cancer, radiotherapy, local failure.

Small cell lung cancer (SCLC) is a radioresponsive tumour, but radiotherapy as the only treatment is not sufficient to prolong survival of patients with this disease (1). Modern multidrug chemotherapy regimens prolong survival of the majority of these patients, but most of them still die from their tumour, often with local failure (2–5). The value of irradiation of the primary tumour added to chemotherapy has been much debated and conflicting results have been presented (6–14). A randomized study was initiated in our hospital in 1980 to study this problem. The study had two arms, one with 24 courses with 5 cytostatic drugs, combined in 2 four-drug regimens and the other with radiotherapy, 40 Gy, added to an identical chemotherapy schedule. The results of this trial has been presented in detail (15). Among patients with limited disease, the number of long-term survivors was greater in the irradiated group than in the non-irradidated one, with 4/25 and 0/28 patients respectively surviving 5 years ($p < 0.05$). However, no difference in median survival was registered neither for patients with limited disease nor for those with extensive disease. Nor did radiation treatment affect the number of long-term survivors in patients with extensive disease.

Before the trial began, a high risk for treatment toxicity was anticipated with respect to the combination of irradiation and the protracted chemotherapy. This prompted a limitation of the target volume for radiotherapy, which therefore comprised only the tumour and the nearest part of the mediastinum.

The local failure rate was as high as 88% in the group receiving only chemotherapy, but it was high even in the radiotherapy group, reaching 75%. In the present study we have further analysed the 53 cases in the radiotherapy group with respect to the site of the local failures, particularly asking whether they might have been due to insufficient irradiation dose or portal size. We also analysed the dose inhomogeneity within the target volume as this might have some impact on the treatment result.

Material and Methods

Patients. During the Uppsala study of SCLC between 1980 and 1983, 133 patients were referred to our hospital. All received 3 courses of chemotherapy before randomization. During this first treatment period 17 patients died, and 6 more cases could not be randomized for other reasons. The remaining 110 patients were randomized and

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53 of them were allocated to the radiotherapy arm (15). These 53 cases were included in the present study. There were 37 men and 16 women and the median age was 65 years (range 38–78). Case records and pre- and posttreatment x-ray films were available for all patients. Portal radiograms (made for planning purposes) were available for 51 patients and dosimetry information necessary for analysis for 31 patients. The diagnosis was verified by histo-pathological examination of specimens obtained from broncho- and mediastinoscopy. The staging procedure included chest radiography, routine blood samples, bone marrow biopsies from sternum and iliac crest, liver examination via ultrasound and scintigraphy of the skeleton.

Chemotherapy. Chemotherapy was started immediately after the diagnosis was obtained and consisted of cycles with cyclophosphamide 250 mg/ m^2 on days 1, 2, 3; vincristine 2.0 mg on day 1, doxorubicin 50 mg/ m^2 on day 1 and methotrexate 100 mg/ m^2 on day 1, with leucovorin rescue. The courses were repeated every third week. On day 64, when it was time for the fourth course, chemotherapy was postponed and irradiation of the primary tumour was started. Three weeks after completion of the radiotherapy, chemotherapy was started again, but now lomustine 40 mg/m^2 was given instead of doxorubicin during the following 4 courses. During these courses the dose of cyclophosphamide was 750 mg/ m^2 on day 1. A total of 24 courses during a total treatment time of 18 months were given with alternations of doxorubicin or lomustine every fourth course. Doxorubicin was omitted after a total dose of 550 mg/m^2. Chemotherapy was delayed when leukocytes fell below 2×10^9/l or thrombocytes below 80×10^9/l.

Radiotherapy. The target volume included the primary tumour with a 1.5 cm margin of normal lung tissue and the adjacent part of the mediastinum. Parts above or below the tumour level and the supraclavicular fossae were not included in the field (unless tumour growth had been verified in these regions). A simple anterior-posterior treatment technique was applied. The feasible field indicated by simulator fluoroscopy was directly drawn on the patients. When suitable, especially for large fields, individual shielding with blocks was applied. Compensation filters were not used. During 4 weeks a total, average, midplane target dose of 40 Gy was delivered with 2 Gy fractions; 1 fraction per day, 5 times a week, without split-course pause. The treatments were delivered with 8 MV roentgen radiation from a linear accelerator (Philips SL 75/10).

The dosimetry was based on entrance and exit dose measurements. Three to five semiconductor detectors (16) were positioned on the patient. They were connected to a DPD 5 patient dosimetry system (Therados), and on line linked to a computerized verification system (17). One detector was placed in the centre of the field and the positions of the other detectors were determined during the simulation procedure and estimated to represent the highest and lowest doses that could be expected. During treatment of the anterior field the detectors indicated the entrance dose and untouched they served as exit dose detectors during the treatment of the posterior field. A special computerized program (17) was designed to calculate the average, maximum and minimum midline dose from the measured values.

During the first 2 treatments a reference dose of 1.35 Gy was delivered from each field. From treatment day 3 and on the exposure was adjusted to give an average daily midline dose of 2 Gy based on the obtained measured and calculated results.

Treatment effect analysis. All patients were followed for at least 5 years or until death. Pretreatment, posttreatment and portal x-ray films were examined side by side by 2 of the authors (Figs 1–4). Portal x-ray films were compared with prechemotherapy, preirradiation, and follow-up films. The patients were categorized with respect to the extent of the portal size; 1) comprising the tumour with 1.5 cm margin to all visible tumour before chemotherapy, 2) comprising the reduced tumour after chemotherapy but not the total prechemotherapy tumour and 3) not comprising the whole tumour after chemotherapy. With respect to the magnification of the x-ray image, a margin of 1.5 cm in the patient corresponded to a margin between the visible tumour and the portal border of 2.5–3 cm on the portal x-ray film. Treatment according to category 3 was regarded as violation of the treatment protocol. The local failures were categorized as situated inside the target volume, on the border of or outside the target volume. Patients without a complete local response, with local recurrence indicated by x-ray films or with remaining

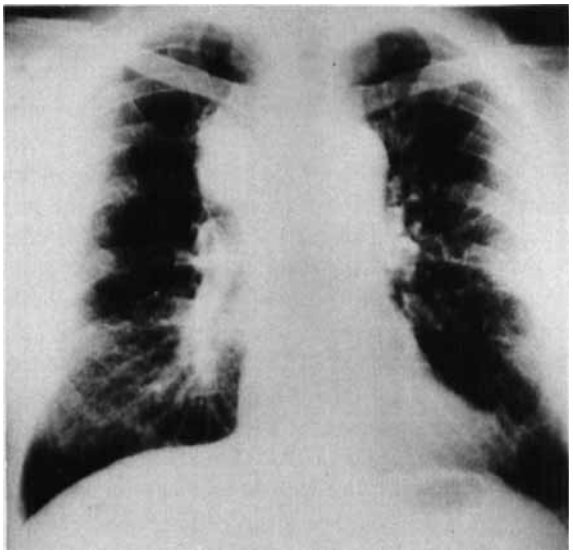

Fig. 1. The intrathoracal tumour of one of the patients in the material, before all treatment.

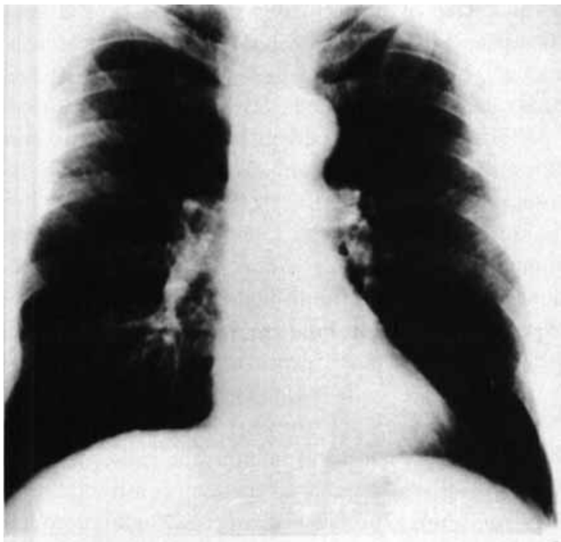

Fig. 2. Same patient as in Fig. 1. Tumour remnant after 3 courses of chemotherapy.

tumour at autopsy were classified as local failures. The follow-up schedule did not include bronchoscopy.

The intrathoracic response was evaluated according to the following criteria; complete response (CR) = disappearance of all evidence of remaining tumour; partial response (PR) = shrinkage of the product of the longest and the perpendicular diameters of the tumour with at least 50%; and no response (NR) = minimal response or lack of response. Autopsy was performed in 37/49 (76%) of the cases.

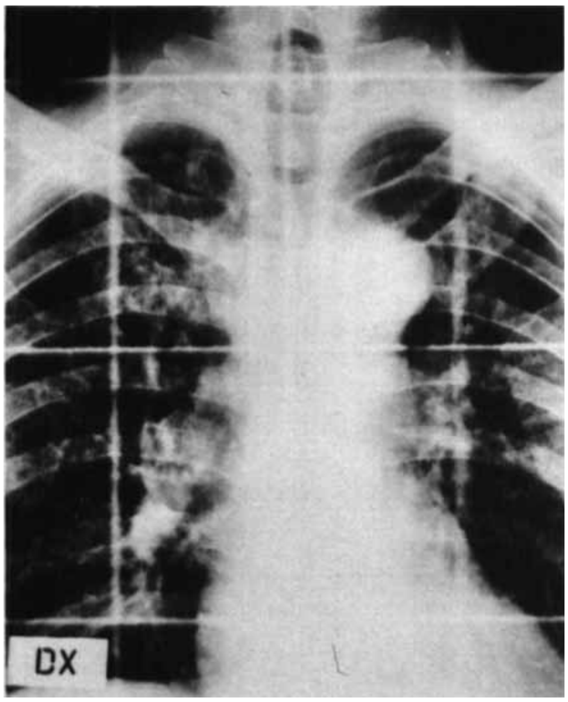

Fig. 3. Same patient as in Fig. 1. The portals of the radiation treatment.

Fig. 4. Same patient as in Fig. 1. Recurrence (marked with an arrow) localized inside the portals.

Results

None of the 53 patients was lost in the follow-up. In 2 cases portal films were missing. Both these patients had only partial remission and thus had local failure, but the adequacy of the treatment volume could not be checked. In 2 further cases the position of the recurrence with respect to the portals could not be settled. Of the remaining 49 evaluable patients, 36 had local failure and thus the frequency of local failures in these cases was 73% (36/49) and in the whole material 75% (40/53). Thirteen cases were judged as locally cured. This was verified by autopsy in 9 cases. The other 4 cases are still alive more than 5 years after treatment with no evidence of local failure. In the 36 cases with local failure this was verified by autopsy in 28. In 5 of the remaining 8 cases only partial remission was achieved. The last 3 cases were primarily evaluated as complete responders but development of local failure was considered to exist according to follow-up x-ray films.

In 24 cases the portals covered the prechemotherapy tumour size (group 1) and 17 of these cases (71%) had local failures inside the portals. There was no intrathoracic failure outside the portals in these cases.

In the second group (13 cases), the portals covered the postchemotherapy tumour (after 3 cycles) but not the whole prechemotherapy tumour. Eleven of these cases (85%) had local failures; 9 (69%) inside the portals, 1 (8%) on the portal border and 1 outside the portals.

In the third group (12 cases), the portals covered neither the prechemotherapy tumour nor the postchemotherapy tumour completely. There were 8/12 (67%) local failures; only 5 (42%) inside the portals, 1 (8%) on the portal border and 2 (17%) outside the portals.

The median survival was similar in all groups; 9.5, 15.5 and 8.4 months for extensive disease patients and 16.0. 11.9 and 15.6 months for limited disease patients in groups 1, 2 and 3 respectively. No patient with extensive disease survived more than 19.3 months. Four cases survived for more than 5 years. Three of these belonged to group 1 and are still alive with no evidence of disease after 60, 80 and 81 months respectively. The 4th long-term survivor was categorized as belonging to the treatment violation group and is still alive after 88 months but was struck with a cerebral metastasis after 60 months. This could be resected and she was afterwards treated with radiotherapy to the brain and is now, 8 years after the primary treatment and 3 years after the treatment of her brain metastasis, living without evidence of disease.

Local failure inside the target volume was found in 20/26 (77%) cases with extensive disease but only in 11/23 (48%) cases with limited disease (Table 1). Intrathoracic failure on or outside the portal border was found in 3/26 (12%) of patients with extensive disease and in 2/23 (9%) of patients with limited disease. The median survival of all cases with local failure inside the portals was 11 months and of cases without local failure 16 months, not a statistically significant difference.

Of the patients with extensive disease 11/28 (39%) had complete remission according to x-ray films but 8 of these 11 failed. Sixteen out of 25 patients (64%) with limited disease had complete remission but 6 of these 16 cases later developed local recurrence.

Thus, 13 patients did not have local failure. Three of these had extensive disease and all 3 died from metastases. Of the 10 locally cured cases with limited disease, 3 are living without evidence of disease, 2 died from treatment-related toxicity without evidence of cancer and 5 developed metastases. One of these 5 cases was cured from a brain metastasis and is still alive without evidence of disease as mentioned above. Another patient with a brain metastasis was also successfully treated with radiotherapy; autopsy was performed when the patient later on died from pericarditis and a lung-embolus and showed no remnant of the metastasis.

The treatment result in the patients with limited disease is summarized in Table 2. Four patients of 25 (16%) are long-term survivors. Four died from treatment-related toxicity; 2 of them without evidence of tumour, one further patient without evidence of tumour after having been cured from a brain metastasis as mentioned above and one patient with metastases to the adrenals. None of these 4 patients had local failure. The causes of death in these 4 patients were; heart failure; constrictive pericarditis and lung embolus; myocardial infarction and respiratory failure and septicemia respectively. Non-lethal heart-toxicity was encountered in 5 more patients. Signs of cardial toxicity were thus found in 9 cases (17%) and fibrosis of the lungs according to chest radiograms in all patients. The portals always included some part of the heart, usually 1/3–1/2 according to frontal x-ray films.

The combined irradiation and chemotherapy probably caused more damage to the heart than the chemotherapy alone, since in the group of 57 patients receiving only cytostatic treatment in the randomized study, no lethal case of heart toxicity was encountered. However, non-lethal heart toxicity was found also in this group, including 2 cases of myocardial infarction and 3 cases of myocardiopathy probably caused by doxorubicin.

One of the 53 patients in the radiotherapy group received further radiation therapy due to a vena cava superior syndrome. In comparison, 10 of the 57 patients in the arm with chemotherapy only developed vena cava superior syndrome requiring palliative chest irradiation.

Table 1

Position of local failure in 26/28 patients with extensive disease (ED) and 23/25 with limited disease (LD) with respect to the extent of the target volume

	Target volume including					
	prechemotherapy tumour volume		postchemotherapy tumour volume		Treatment violation	
	ED	LD	ED	LD	ED	LD
Local failure inside the portals	11	6	5	4	4	1
Local failure on the border	–	–	1	–	1	–
Local failure outside the portals	–	–	–	1	1	1
Local cure	–	7	1	1	2	2

Table 2

Treatment results in 25 patients with limited disease treated with cytostatic drugs and irradiation to the chest

Local treatment effect	n	Complete remission	Distant metastasis	Living >5 years	Intercurrent deaths	Median survival (months)
Failure						
Inside portals	11	5	9	0	0	15.8
Outside portals	2	0	1	0	0	15.8
Unsettled	2	1	1	0	0	10.6
Local cure	10	10	5*	4	4	12.6

*2 cases with brain-metastases cured with radiotherapy and surgery plus radiotherapy respectively. One without brain-metastases at autopsy, the other living with no evidence of disease 3 years after the combined treatment.

Dosimetry according to the method described above demonstrated a dose inhomogeneity of more than ±10% in 10% of the patients, ±5–10% in 35% and less than ±5% in 55%. A detailed description is presented in Table 3 of the lowest and highest doses registered and the local treatment effect and heart toxicity respectively. The frequency of local failure, however, was not greater in the cases with the coolest cold spots, nor was any association found between hot spots and severe local toxicity.

The frequency of metastases in patients with limited

Table 3

Dose inhomogeniety, local treatment effect and local toxicity of irradiation of SCLC

Patient No.	Minimum dose (%)	Maximum dose (%)	Local treatment effects		Heart toxicity
			Immediate	Follow-up	
1	−1.4	+1.4	PR	LF	–
2	−1.0	+1.0	CR	LF	–
3	−12.0	+6.4	CR	LC	–
4	−7.3	+5.2	PR	LF	–
5	−10.1	+10.8	PR	LF	–
6	−8.7	+7.1	CR	LF	–
7	−5.6	+2.8	CR	LC	–
8	−8.6	+5.7	PR	LF	pericarditis
9	−9.0	+5.2	PR	LF	pericarditis
10	−4.2	+4.9	PR	LF	–
11	−8.7	+5.8	NoR	LF	–
12	−4.3	+4.3	PR	LF	–
13	−11.0	+10.3	CR	LF	–
14	−1.0	+1.0	PR	LF	–
15	−8.0	+8.0	CR	LF	–
16	−2.2	+5.1	PR	LF	–
17	−9.9	+7.8	CR	LC	pericarditis
18	−1.0	+1.0	PR	LF	–
19	−2.5	+2.5	CR	LC	–
20	−4.7	+3.6	PR	LF	–
21	0.0	0.0	CR	LC	–
22	−4.0	+8.5	CR	LF	–
23	−3.4	+2.7	CR	LC	–
24	−5.8	+2.8	CR	LF	–
25	−7.0	+9.8	CR	LC	–
26	−3.6	+4.2	CR	LF	–
27	−5.5	+6.2	CR	LF	myocarditis
28	−1.4	+2.0	CR	LF	–
29	−1.0	+1.0	PR	LF	–
30	−3.5	+2.7	CR	LC	–
31	−2.1	+1.4	CR	LC	–

CR: complete remission; PR: partial remission; NoR: no response; LF: local failure; LC: local cure disease and local failure inside the target was studied, to analyse the question whether more patients might have been cured with higher doses of radiotherapy. There were 11 patients in this group (Table 2), 5 had CR but all of these had distant metastases at autopsy. Six had partial remission or no response and of these 3 were autopsied and had distant metastases, and a fourth had verified metastases. Two cases had no symtoms indicating metastases but were not autopsied. Thus at least 9/11 (82%) of the patients in this group had distant metastases. As mentioned above, only 50% of the cases without local failure had distant metastases, 3 of them in the brain only.

Discussion

The interpretation of abnormal findings in postirradiation x-ray pictures of the lung, whether benign changes such as fibrosis, pneumonitis and pneumonia or manifestations of tumour growth, was generally difficult and sometimes impossible, an experience in accordance with other authors' (18, 19). However, the high frequency of autopsies in the present study, (76%), and the long follow-up time, 5 years, gave our data on treatment failure a high degree of reliability.

In our study 15/25 (60%) of the patients with limited disease had local failure. Of the 23 evaluable cases 13 (57%) had local failure and 11 (48%) were localized inside the portals. Similar results have been presented by Livingstone et al. (20). However, this is in conflict with findings of Mira & Livingstone (19), who reported few local failures inside the portals. Results somewhere in between have been presented by Levitt et al. (21). A comprehension of data from 9 studies demonstrated 24 in-field relapses in 82 cases (29%) (19) but the difference was great between different studies with a range from 6 to 50%. The high frequency of local failures found in the present material might have been due to the high autopsy frequency. Another study with a high frequency of autopsies also demonstrated a similar high rate of chest failures (9).

In our study complete remission was achieved in 16 patients with LD and 11 with ED but 6 and 8 cases respectively later developed chest relapse. This indicates that the complete reponse parameter is an unsufficient indicator of local cure, as pointed out by others (22).

The importance of dosimetry control in SCLC has been emphasized (23). A dose accuracy of maximally $\pm 5\%$ has been recommended by Bleehan & Cox (24). In the present study 45% of the cases had greater dose inhomogeneity but this group of patients did not have a higher rate of chest relapse. This suggests that cold spots are of less importance than some other factors determining the effect of radiotherapy.

Three of 24 cases in our study, with portals comprising the prechemotherapy tumour volume, survived 4 years compared with none of 14 patients in whom the postchemotherapy but not the whole prechemotherapy tumour volume was included. This may indicate that the prechemotherapy tumour volume should be the target, in concordance with findings of Mäntylä & Niiranen (25). However, it may be suspected that one reason for insufficient covering of the prechemotherapy tumours was that these tumours were larger and therefore not adequately covered with respect to anticipated lung toxicity.

One conclusion of our study could be that the radiation dose should be increased above 40 Gy in order to cure more patients. However, the possibility of curing more patients with higher doses may be limited since 9 of our 11 patients with limited disease and local failure inside the treatment volume developed distant metastases. Since it is not known if the shedding of metastatic cells from the primary tumour occurred before or after radiotherapy, it is impossible to state whether any of these 9 cases might have been cured with improved radiotherapy. However, 5 of the 10 patients without local failure also developed metastases, and it is hardly probable that a larger fraction of the 11 patients with more therapy-resistant tumours might have escaped distant metastases if they had been cured locally. Moreover, an increased radiation dose may increase the lethal treatment toxicity which might neutralize the positive effect of a possible higher local cure rate.

Since 40 Gy added to chemotherapy cured only 40% of the cases with limited disease locally one may ask which dose is needed to locally cure the majority of these patients. Data from different studies have demonstrated a wide range of local failure rates, from 20% up to 90% (8–10, 15, 26–28) but for several reasons different studies are difficult to compare. A dose–response relationship has been found by some authors (22, 29). In accordance with the present study, other authors have reported that 40–45 Gy is not enough and it has been suggested that 50–60 Gy is a more adequate dose-level (10, 29). Choi & Carey (22) recently reported a local cure rate of 16% after 30 Gy, 51% after 40 Gy and 63% after 50 Gy in studies combining radiotherapy and chemotherapy. In two studies 55 Gy and 60 Gy was applied and a local cure rate of 82% and 96% respectively reported (26, 28). In one of these studies, however, the follow-up time was only 2 years (26) and in the other one survival of cases with limited disease was still low, only 12% after approximately 2.5 years (28).

In vitro studies of SCLC have demonstrated a relatively high radiosensitivity of most cell lines of the classic subtype, with a median surviving fraction after 2 Gy of 0.29 for 23 cell lines from our and other laboratories and with 15/22 (68%) of the cell lines having a surviving fraction of 0.4 or less (30, 31). According to a diagram by Fertile & Malaise (32) there is a correlation between the surviving fraction after 2 Gy (SF2) in vitro and the clinical radiocurability of the corresponding tumour. Extrapolations from this diagram indicate that 40 Gy may cure tumours with a SF2 of 0.19 and 50 Gy tumours with SF2 0.24. According to the distribution of SF2 in the in vitro panel mentioned above 27% had a SF2 below 0.19 and might thus be cured by 40 Gy. Corresponding calculations applying other doses indicate that 50 Gy should cure 32%, 60 Gy 55% and 70 Gy 68% of a population with SCLC if the correlation is valid. A higher cure rate may perhaps be anticipated if the radiotherapy is combined with chemotherapy. The calculated local cure rate of 27% for only radiotherapy compared with the 40% in the combined treatment of the present study might reflect how much chemotherapy adds to the local cure.

Four patients in the present study died from treatment toxicity. In all these cases local cure was achieved and 2 of these cases did not have distant metastases. These results are in accordance with earlier results indicating that the improved local effect of radiotherapy is obtained at the cost of an increased treatment mortality (9). In the present study, however, the benefit of radiotherapy was greater than the disadvantage.

In some studies large-dose fractions have been applied (9, 10, 28). Large-dose fractions might induce a higher degree of late toxicity (33). Besides, some SCLC cell lines have in vitro demonstrated only a small or a moderate shoulder, indicating a lack in their capacity to repair sublethal damage. A decreased toxicity and at the same time preserved tumour damage might thus perhaps be achieved with smaller irradiation fractions. Unpublished in vitro studies from our laboratory indicated that if 10 Gy was delivered in 5 days with 1 Gy, 2 Gy or 5 Gy fractions, the 1 Gy schedule was as effective as the higher dose fractions in killing a human SCLC cell line with almost no shoulder. Since most SCLC cell lines have small or moderate shoulders this may indicate that 2 Gy or perhaps even lower dose fractions might be advantageous with respect to the therapeutic index.

Conclusively, the present study has demonstrated that 40 Gy is an insufficient dose to obtain local cure in the majority of patients with SCLC, limited disease. However, only a few more patients might probably have been cured with a higher irradiation dose because of the high frequency of metastatic disease. Besides, an increase of the dose might have caused an increase in the treatment toxicity. However, with a more advanced treatment planning, avoiding the heart and delivering a more homogenous dose to the target, a total dose to 50–60 Gy and dose fractions of 2 Gy or less, decreasing the toxicity and increasing the efficiency of the radiotherapy might perhaps increase the local cure rate and by that also the rate of long-term survivors.

In patients with extensive disease, irradiation of the primary tumour does not seem to be of any advantage with respect to survival, a conclusion in accordance with other authors' (8).

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