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Effect of hemithorax irradiation alone or combined with doxorubicin and cyclophosphamide in 47 pleural mesotheliomas: a nonrandomized phase II study

C-J. Lindén*, C. Mercke**, U. Albrechtsson+, L. Johansson++, S-B. Ewers**

Effect of hemithorax irradiation alone or combined with doxorubicin and cyclophosphamide in 47 pleural mesotheliomas: a nonrandomized phase II study. C-J. Lindén, C. Mercke, U. Albrechtsson, L. Johansson, S-B. Ewers. ©ERS Journals Ltd 1996.

ABSTRACT: In order to assess the value of radiotherapy in the treatment of pleural mesotheliomas, we studied tumour response and survival after hemithorax irradiation alone (RT), or radiotherapy combined with doxorubicin and cyclophosphamide chemotherapy (RTCT).

Forty seven patients with pleural mesotheliomas received irradiation of the diseased hemithorax at 8 MV (megavolt) photons to a total dose of 40 Gy, administered in 20 daily fractions of 2 Gy for 5 days a week. One month after RT, patients aged ≤70 yrs with a good performance status were offered supplementary chemotherapy (CT) with doxorubicin 30 mg·m^{-2} body surface on Day 1 and Day 8, combined with cyclophosphamide 600 mg·m^{-2} on Day 1, in cycles of 21 days. Tumour response was evaluated by computed axial tomography (CAT) before and 1 month after RT and/or CT.

Only 3 of the 47 (95% confidence interval (95% CI) -0.6–13%) irradiated tumours responded with a partial response (PR). In 31 patients treated with RT alone, one PR was observed; whereas, in the combined treatment group, 2 out of 16 responded with PR to RT. CT with doxorubicin and cyclophosphamide induced only 2 out of 16 PRs (95% CI -3.4–28.4%), and the combined treatment consisting of RT followed by CT induced 2 out of 16 PRs. The median survival following the initiation of RT was 7 months in all patients (n=47), 6 months in the RT group (n=31), and 13 months in the combined RTCT group (n=16). Chest pain, performance status and body weight were not favourably affected by the radiotherapy.

We conclude that hemithorax irradiation of pleural mesotheliomas with a moderately high dose is not useful, since it produces no improvement in chest pain, few objective tumour responses and no prolongation of survival.

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Depts of *Lung Medicine, **Oncology, +Radiology, and ++Pathology, University Hospital, S-221 85 Lund, Sweden.

Correspondence: C.J. Lindén
Dept of Lung Medicine
University Hospital
S-221 85 Lund
Sweden

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Malignant pleural mesotheliomas (MPM) cannot be cured remedially by surgery, chemotherapy or radiotherapy. The relentless progression of the tumour has not been affected by current therapeutic modalities [1]. The rareness of the tumour has made clinical trials difficult to conduct, and randomized phase II [2, 3] and III studies are consequently sparse. In an uncontrolled comparison between treated and untreated patients with pleural mesothelioma, LAW *et al*. [4] found no survival differences. It has been suggested that the search for effective treatment should be conducted by phase II studies [1, 5], to find a treatment potent enough to warrant phase III studies.

Radiotherapy has been reported to produce relief of chest pain [6] and objective tumour responses [7]. In a large overview of the literature and a compilation of various small uncontrolled studies, HILLERDAL [8] found indications that radiotherapy yielded survival which was at least as good as that produced by surgery or chemotherapy.

However, in these older studies, only plain chest radiography was used to assess tumour response. The introduction of computed axial tomography (CAT scan) and, subsequently, magnetic resonance tomography (MRT) has greatly improved the prospects for correctly delineating the extent of the tumour. A CAT scan is now regarded as mandatory for response evaluation in pleural mesothelioma [9]. Consequently, response evaluation in studies performed before the era of computed tomography must be regarded as unreliable.

In 1981, we began a prospective phase II trial in order to assess the tumour response of pleural mesotheliomas to radiotherapy (RT) and chemotherapy (CT) by means of CAT scan, which had recently been introduced at University Hospital, Lund. We intended to use this new technique in a sequential phase II study to thoroughly evaluate the effects of irradiating the diseased hemithorax with a fractionated dose of 40 Gy, followed by systemic chemotherapy using a combination of doxorubicin and cyclophosphamide.

These chemotherapeutic agents were chosen because, at the beginning of the 1980s, they were regarded as the most potent available for the treatment of pleural mesothelioma [10]. Due to the expected low accrual rate of mesothelioma patients in our study, we felt it was not feasible to randomize the supplementary chemotherapy. Instead, patients in good general condition 1 month after radiotherapy were offered chemotherapy, whereas patients with poor performance were left without further therapy, apart from palliation.

Materials and methods

Patients

Between November 1981 and July 1990, all patients referred for treatment to the Department of Pulmonary Medicine at the University Hospital in Lund with a histologically proven pleural mesothelioma were included in an uncontrolled phase II study of the effect of irradiating the diseased hemithorax with a total dose of 40 Gy, fractionated as 2 Gy·day^{-1} for 5 days a week. Patients in good condition 1 month after radiotherapy were offered supplementary chemotherapy consisting of doxorubicin and cyclophosphamide. The study was approved by the Medical Research Ethics Committee at the University of Lund.

During the first half of the 1980s, the diagnosis was usually based on conventional light microscopy together with histochemical staining. Immunohistochemical methods were not fully reliable until about 1985.

Fifty two patients were enrolled in the study and treated according to the protocol. All the tumour biopsies have been re-evaluated by one of the authors (LJ). In addition to conventional light microscopy, immunohistochemical staining was used with a panel of monoclonal antibodies [11]. Five patients initially classified as pleural mesotheliomas were excluded after re-evaluation. Three of these patients received radiotherapy alone, and two patients were treated with combined therapy. Of the five patients not satisfying the histological criteria for a mesothelioma diagnosis, one lacked tumour tissue for re-evaluation. Four tumours initially regarded as mesotheliomas were reclassified as angiosarcoma, rhabdomyosarcoma, hepatocellular carcinoma and carcinoma of the uterine corpus, respectively. Three of the cases with reclassified tumours were autopsied, and two of the reclassifications were based mainly on autopsy findings (uterine and hepatic carcinomas).

Of the 47 mesothelioma patients included in the study, only three were female. The median age of the patients was 65 (range 41–77) yrs at diagnosis. Before radiotherapy, patients with pleural effusion had pleurodesis induced with quinacrine (Atabrine) if possible (n=28). No patient included in the study had received any prior chemotherapy or undergone debulking surgery apart from a diagnostic surgical biopsy of the pleural tumour.

Smoking habits were assessed by a personal interview before the start of treatment. A person was defined as being a nonsmoker if fewer than 1,000 cigarettes had been consumed throughout his/her lifetime, and as an ex-smoker if this figure was exceeded and if the person had quit more than 6 months before the interview. The remainder were regarded as active smokers. Patients were regarded as having been exposed to asbestos if they had either a positive history of exposure to asbestos signs of pleural plaque on CAT scan and/or at autopsy, or an increased number of asbestos bodies in slices of lung parenchyma obtained at autopsy [12]. Performance status was determined prospectively according to the Karnofsky scale [13] before entry to the study. The subjective experience of pain was scored prospectively by means of a pain scale, graded from 0 to 4: Grade 0 = no pain at all; grade 1 = pain without any need for analgesics; grade 2 = pain requiring relief by means of non-morphine analgesics; grade 3 = severe pain requiring the use of oral morphine analgesics; and grade 4 = pain requiring the use of continuous epidural administration of morphine, or some other type of parenteral administration. Survival was calculated from the start of radiotherapy until death. All patients had complete follow-ups from the start of radiotherapy until death.

Histopathological diagnosis

In all cases, the diagnosis of mesothelioma was based on examination of pleural tumour specimens obtained by open surgical pleural biopsy in 21 cases, thoracoscopic biopsy in 22 cases, autopsy in one case and other types of biopsy in three cases. Cytology was regarded as an inadequate basis for a diagnosis of mesothelioma. Slices were stained with haematoxylin and eosin. Immunohistochemical staining was performed as described previously [11]. Staining for carcinoembryonic antigen (CEA) was negative in all cases. In addition, all cases were positive to cytokeratin (CAM 5.2 in combination with AE1/AE3 or MNF116). Determinations of CEA concentrations In pleural fluids and plasma were normal in all cases studied. In doubtful cases, light microscopic examination was supplemented by transmission electron microscopy.

The primary diagnosis was confirmed by an autopsy in 24 cases. The mesotheliomas were classified as epithelial, mixed or sarcomatous types according to World Health Organization classification (WHO) [14].

During the period of the study, a total of 66 patients with a pleural mesothelioma were diagnosed. Six patients were found to have a pleural mesothelioma only at autopsy, and two patients were also falsely classified initially as adenocarcinomas of unknown origin and, therefore, not included in the study. Fifty eight patients with a pleural mesothelioma remained for a choice of treatment.

Inclusion criteria

To be included in the study, a patient had to fulfil the following requirements: 1) a histologically proven diagnosis of pleural mesothelioma based on a biopsy of the pleural tumour; 2) a performance index of 70 or more according to the Karnofsky scale [13]; 3) an age of less than 80 yrs for radiotherapy (RT) and an age of

less than 70 yrs for combined therapy (RTCT); 4) a calculated postirradiation vital capacity exceeding 1.5 L, after an expected total loss of gas exchange function in the irradiated lung (dynamic spirometry combined with a ventilation/perfusion scan of the lungs was used to examine the pulmonary function prior to inclusion in the study); 5) normal arterial blood gas values with the patient examined in the supine position; 6) normal haematological, hepatic, renal, neurological and cardiovascular functions; 7) proper function of the contralateral kidney as examined by intravenous renography (the irradiation port included part of the ipsilateral kidney, resulting in potential damage to the renal function); and 8) informed consent for participation in the study.

Study design

During the study period, 58 pleural mesotheliomas confirmed by immunohistochemical re-evaluation were eligible for inclusion. Three patients refused RT after being informed about the treatment. Pulmonary function in two subjects was too poor for RT, whilst six had a performance of less than 70 on the Karnofsky scale. Forty seven patients were eligible and agreed to receive hemithorax irradiation according to the protocol.

One month after the termination of RT, patients were re-evaluated by CAT scan and made a clinical visit to decide whether the criteria for supplementary CT had been fulfilled. Although they were eligible for inclusion in the study, four patients refused supplementary CT after RT. Seven patients were older than 70 yrs, six had acute irradiation pneumonitis, and 1 had radiation-induced hepatopathy one month after the completion of RT. Moreover, four patients had prematurely discontinued irradiation due to a deterioration in their general condition, and seven scored less than 70 on the Karnofsky scale 1 month after RT.

A complicating empyema after pleurodesis made CT unsuitable in one case. Treatment with doxorubicin was regarded as being contraindicated in one case with poor myocardial function. Consequently, only 16 patients were eligible and consented to receive supplementary chemotherapy with doxorubicin and cyclophosphamide.

Staging and response evaluation

Tumour staging was based on a contrast-enhanced CAT scan of the chest and upper abdomen. Mediastinal nodes with a diameter larger than 15 mm were regarded as pathological. All CAT scans were re-evaluated by one of the authors (UA) after completion of the study. Tumour response was defined according to a modified WHO standard [15], and for staging purposes we used the recently proposed tumour, node, metastasis classification (TNM) system (Union Internationale Contre le Cancer (UICC) 1992) for pleural mesotheliomas [16].

Tumour response to therapy was measured by means of a CAT scan before and 1 month after RT and/or CT. Due to difficulties in exactly delineating tumour invasion in the neighbourhood of the parietal and visceral pleura by CAT scan, T1 and T2 tumours could not be distinguished. Consequently, in this study, stages I and II were not separated from one another.

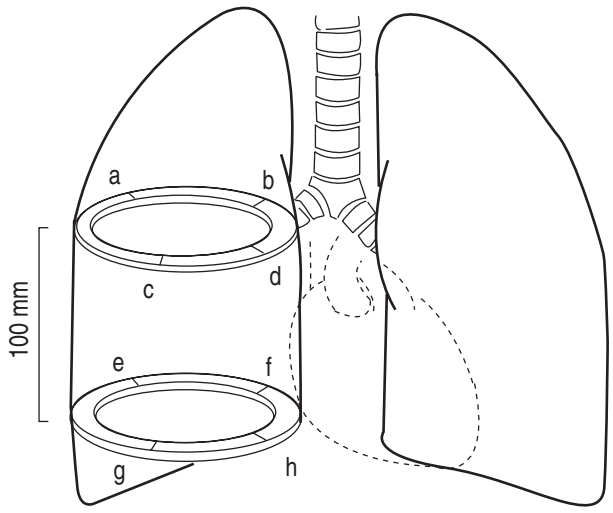

Fig. 1. – The tumour response to treatment was evaluated by measuring the thickness of the tumour peel at the level of the carina and at a level 100 mm caudal to the carina. At each level, a maximum of four diameters, (a–d) for the carina level and (e–h) for the level 10 cm below carina, were measured by computed axial tomography. The sum of the tumour diameters at both levels (a–h) was used as a measurement of the tumour diameters. The same locations for measurement of the tumour diameters (a–h) were used before and after treatment.

In all examinations, the perpendicular diameter of the pleural tumour peel was measured at the level of carina and also at a level around 100 mm below the level of the carina (fig. 1). If possible, 3–4 perpendicular measurements of the thickness of the tumour peel were made at each level. The tumour diameters were measured at positions on the tumour which were easily reproducible and comparable between different examinations during the course of the therapy.

The sum of 2–4 tumour diameters at each of the two levels was used as a measurement of the tumour size (fig. 1). The same tumour diameters were measured before and after treatment intervention. The tumour diameters were calculated directly from data from the CAT scans and, in cases where the primary data from CAT scans were not available, measurements were made from film copies of the examinations. In such cases, partial response (PR) was not reported, due to the inaccurate nature of such measurements. Patients dying during RT or CT or after therapy, but before the scheduled time for re-evaluation (1–2 months), were regarded as having progressive disease (PD).

Radio- and chemotherapy

The diseased hemithorax, including the pleural cavity and the lung, was scheduled to be irradiated to an absorbed dose of 40 Gy. The radiation was fractionated as a daily dose of 2 Gy, 5 days a week for 4 weeks. The photon irradiation therapy was given with two opposing anterior-posterior/posterior-anterior portals from a linear accelerator with an output of 8 MV energy. The prescribed dose was calculated as the mid-plane dose without corrections for lung density. Wedge filters were not used. The medial border of the treatment portals was

Table 1. – Haematological parameters and drug dose used in chemotherapy

Neutrophils $\times 10^9 \cdot L^{-1}$	Platelets $\times 10^9 \cdot L^{-1}$	Dose %
>4.0	>125	100
4.0–3.0	125–100	75
3.0–2.0	100–75	50
2.0–1.0	75–50	25
<1.0	<50	0

the midline of the body, with a margin of 2 cm, and the oesophagus was thus irradiated. Because the pleural sinus was included in the radiation portals, the stomach and part of the kidney were irradiated in left-sided cases. In right-sided mesothelioma, the liver and consequently the pleural sinus were shielded after 20 Gy.

Patients aged ≤70 yrs were offered CT if they met the inclusion criteria and were in good general condition 1 month after the completion of the RT. Sixteen patients agreed to supplementary CT. Chemotherapy was planned to continue until the maximum recommended dose of doxorubicin, *i.e.* 450 $mg \cdot m^{-2}$, was reached, until toxicity, or until overt progression and declining performance status. CT was given in cycles of 21 days. Doxorubicin was given at a dose of 30 $mg \cdot m^{-2}$ on Days 1 and 8, combined with cyclophosphamide 600 $mg \cdot m^{-2}$ on Day 1 in each cycle.

Treatment intervals were usually kept constant. If the haematological parameters were subnormal on the day scheduled for treatment, the doses of both drugs were reduced equally according to the schedule presented in table 1. One month after the final CT course, the tumour response was evaluated by chest radiographs combined with a CAT scan of the chest and upper abdomen.

Statistical methods

The data are median (range) unless otherwise specified. Groups were compared using the sign-test, Mann-Whitney U-test or the Kruskal-Wallis test. Univariate prognostic factors were analysed by multiple linear regression. The calculations were made using the Statistica program package (StatSoft Inc., Tulsa, OK, USA). A p-value of <0.05 was considered significant.

Results

Radiotherapy

Forty seven patients with a pleural mesothelioma were included in the study and received hemithorax irradiation on the diseased pleural cavity. Sixteen patients aged less than 70 yrs and in good general condition 1 month after the termination of RT received combined CT with doxorubicin and cyclophosphamide. Forty two patients received the planned 40 Gy of RT in 20 fractions of 2 Gy. Four patients in the RT group did not complete the irradiation due to rapidly deteriorating performance, and received 26–38 Gy before withdrawal. Furthermore, one patient developed acute radiation-induced pneumonitis after 38 Gy, resulting in the discontinuation of RT and treatment with corticosteroids during the subsequent chemotherapy. This was the only patient who received CT in spite of ongoing treatment for active pneumonitis. After this patient, active pneumonitis requiring corticosteroid treatment was regarded as a contraindication for supplementary CT, since doxorubicin is known to activate radiation-induced pneumonitis [17], a fact which was initially overlooked in this study.

Survival from the initiation of RT until death is shown in table 2. All patients had a complete follow-up until death. The median survival for all treated mesotheliomas (n=47) was 7 months, 6 months for the RT group (n=31) and 13 months in the combined therapy group (n=16). Since no randomization took place between RT and RTCT, these groups are not comparable due to the unequal distribution of prognostic factors and, as a result, they were not analysed further. No patient survived for more than 4 yrs after RT, and two cases surviving for more than 3 yrs had irradiation therapy only (fig. 2).

Table 2. – Tumour response and survival according to hemithorax irradiation, chemotherapy and combined therapy in 47 patients with pleural mesothelioma

	Treatment modality							
	Radiotherapy alone (n=31)		Radio- and chemotherapy (n=16)				All cases (n=47)	
	RT		RT	CT	RT+CT		RT±CT	
Response	Pts n	Survival months	Pts n	Pts n	Pts n	Survival months	Pts n	Survival months
CR	0	-	0	0	0	-	-	-
PR	1	5	2	2	2	21	3	11
SD	17	6	10	7	4	18	27	8
PD	12	2	4	7	9	7	16	4
NE	1	54	0	0	1	8	1	54
Survival#		6				13		7

RT: radiotherapy; RT+CT: radiotherapy combined with chemotherapy; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not possible to evaluate; Pts: patients. #: survival is given in months (median).

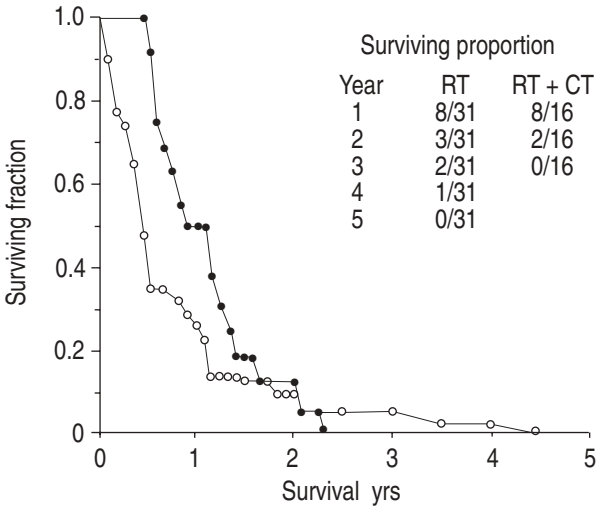

Fig. 2. – Survival after hemithorax irradiation alone (RT) or radiotherapy combined with doxorubicin and cyclophosphamide chemotherapy (RT+CT) in 47 patient with pleural mesothelioma. —●— : RT+CT; —○— : RT only.

In the RT group (n=31), nine cases were not re-evaluated by CAT scan 1 month after RT as scheduled due to the rapid clinical progression of the disease and concomitant declining performance. Seven of these patients died within 2 months, *i.e.* before the scheduled time for re-evaluation by CAT scan. Four of them did not even complete the RT. Case No. 8 survived for 3 months after the start of radiotherapy, but was not evaluated by CAT scan due to deteriorating performance.

Furthermore, Case No. 9 of those not re-evaluated 1 month after the termination of RT had acute radiation pneumonitis before the time of evaluation with poor general condition, and was therefore not re-evaluated by CAT scan. He died 5 months after RT without being autopsied. The response to RT in these nine cases which were not re-examined by CAT scan was regarded as progressive disease (PD). The CAT scan in one case in the RT group could not be evaluated for the response to RT due to difficulty delineating the tumour contours because the tumour peel was surrounded by pleural effusion of high density.

As a result, 21 of the 31 patients in the RT group could be fully evaluated by CAT scan for response as scheduled. In three patients, the tumour responses were evaluated by means of the CAT scan film due to the loss or nonfunctioning of original data disks for evaluation in the computer system. In 18 of the 31 patients, a detailed tumour-response evaluation could be made with optimum measurements of the tumour diameters. All 16 patients in the combined therapy group were examined by CAT scan before and after RT and could be fully evaluated for their response to RT. To summarize, 38 of the 47 mesotheliomas were examined by CAT scan before and 1 month after radiotherapy, and all but one could be evaluated for response.

The tumour response to RT for all patients (n=47), to CT (n=16) and to combined therapy (n=16) is shown in table 2.

Only 3 of the 47 patients had a partial response (PR) to RT: one of the 31 in the RT group and two of the 16 in the RTCT group. The sum of the tumour diameters in the three PRs decreased to 16, 26 and 28% of the pretreatment sum of diameters. Furthermore, three patients had minor responses, with decreases in the pretreatment sum of diameters to 65, 67 and 68%. Body weight, performance and pain were assessed 1 and 6 months after the completion of irradiation. Forty one and 28 patients were still alive and could be evaluated in terms of these parameters 1 and 6 months after RT, respectively.

Performance status according to the Karnofsky scale decreased from 87 (mean) to 78 (n=41; $p<0.005$), body weight decreased from 72 to 68 kg (n=41; $p<0.005$) and pain score increased from 0.8 (mean) to 1.2 (n=41; $p<0.05$) at re-evaluation 1 month after the termination of RT. Therefore, inspite of RT, performance status and body weight decreased, whereas pain increased.

However, in patients surviving 6 months or more after RT (n=28), body weight did not decrease ($p=0.11$) further between 1 month (69 kg (mean); n=28) and 6 months (68 kg; n=28). Pain score did not increase further ($p=0.18$; n=28) between 1 month (0.9 (mean); n=28) and 6 months (1:1; n=28) after RT. Performance status, on the other hand, continued to decrease between one (84) and six (71) months after RT (n=28; $p<0.0005$).

Chemotherapy

Sixteen patients were eligible for and agreed to receive supplementary CT with doxorubicin and cyclophosphamide, starting 1–2 months after the completion of RT. A median of 8 (range 3–16) courses of chemotherapy was administered. Two patients responded to CT with PR, causing a decrease in the sums of the postirradiation diameters to 24 and 29%.

Two patients had PR to the RTCT, resulting in a decrease in the sum of the tumour diameters to 14 and 25% of the preirradiation diameters. One of the PRs to CT occurred in a patient with a PR to RT. In this case, therefore, RT caused a decrease in the tumour size to 26% of the preirradiation measurement and chemotherapy caused a further decrease in the size of the tumour to 29% of the postirradiation sum of diameters. Thus, as a result of RTCT, this tumour decreased to 14% of its pretreatment size. The second PR to CT occurred in a patient who had stable disease (SD) (97% of pretreatment diameters) after RT, but whose tumour size decreased to 25% of the pretreatment size after chemotherapy. However, the second patient with PR to RT who was given supplementary CT died after 11 courses of continuous chemotherapy without being re-evaluated by CAT scan. At autopsy, however, this patient was found to have progressive disease.

Side-effects

Eleven patients had acute radiation pneumonitis with acute onset of fever, shortness of breath, malaise and deteriorating general condition requiring corticosteroid treatment for long periods.

With the exception of one patient treated at the beginning of the study with chemotherapy in spite of ongoing corticosteroids for radiation-induced pneumonitis, the onset of radiation induced pneumonitis was regarded as a contraindication for supplementary CT containing

Table 3. – Univariate analysis of the influence of pretreatment parameters on survival after hemithorax irradiation ± chemotherapy in 47 pleural mesotheliomas

Parameter	Cases n	Survival months	p-value
Pain score			0.03
0	27	13	
1	2	15	
2	13	6	
3	4	1	
3	13	6	
4	1	5	
Clinical stage+			0.011
1+	-	-	
2	30	11	
3	14	6	
4	3	2	
Smoking habits			0.049
Nonsmoker	8	15	
Ex-smoker	24	6	
Smoker	15	8	
Histological type			0.218
Epithelial	20	9	
Mixed	18	7	
Sarcomatous	9	6	
Performance status†			0.353
100–90	29	8	
80–70	18	7	
Side location			0.521
Right	26	9	
Left	21	6	
Gender			0.632
Male	44	7	
Female	3	8	
Asbestos exposure			0.775
Yes	41	7	
No	6	14	
Age yrs			0.832
<60 yrs	23	7	
>60 yrs	24	8	

+: clinical stage according to Union Internationale Contre le Cancer (UICC) 1992 [16] (no tumour was classified as stage I due to diagnostic difficulties; †: performance status according to the Karnofsky scale [13].

doxorubicin or as a reason for withdrawal from ongoing CT if the radiation pneumonitis occurred during CT. All patients had almost complete radiation-induced fibrosis of the irradiated lung six months after the termination of RT according to chest radiographs and CAT scans. Two bronchopleural fistulas occurred as possible complications of RT. The steep decrease in body weight in the month following radiotherapy is probably partly explained by the radiation-induced oesophagitis, due to the oesophagus being encompassed by the radiation portals.

Prognostic factors

The relationship between pretreatment variables and survival is depicted in table 3. A low pain score, an early tumour stage and no smoking were related to a more favourable prognosis in univariate analysis.

Discussion

We found that moderate high-dose hemithorax irradiation and supplementary chemotherapy produced low rates of shortlived tumour response in pleural mesotheliomas. The low rates of tumour response did not affect median survival times. Radiotherapy alone or in combination with doxorubicin and cyclophosphamide was unable in every case to prevent the fatal progression of the disease. Furthermore, we could not detect a palliative pain-reducing effect of the radiotherapy administered to the patients.

Radiotherapy is normally only part of a multimodality treatment programme, and is usually used in an adjuvant setting after preceding surgery [18–20] and/or chemotherapy [20]. Little is therefore known of the effect of radiotherapy alone [21], as its effects are usually masked by surgery or chemotherapy.

In studies evaluating the response to radiotherapy [7, 22, 23], response rates have been low [7] and have usually been evaluated by conventional chest radiography [7, 22, 24], regarded nowadays as suboptimal [25]. None of these studies has used CAT scans for response evaluation.

Consequently, to our knowledge, this study of 47 pleural mesotheliomas is the largest known series of previously untreated pleural mesotheliomas evaluated prospectively for response to radiotherapy by means of CAT scans with complete survival follow-up. The steep decrease in body weight in the month following radiotherapy is probably partly explained by the radiation-induced oesophagitis, due to the oesophagus being encompassed by the radiation portals.

The very low rate of tumour response to radiotherapy in this study is in accordance with the findings of other authors [6, 7, 22–24]. Minor responses noted by CAT scan in the present study might have been interpreted as PR by conventional chest radiography.

We evaluated the tumour response 1 month after the termination of radiotherapy, which might not have been the optimum time for pleural mesotheliomas, as radiotherapy itself affects the evaluation due to the increasing density of the lung parenchyma secondary to radiation-induced fibrosis. On the other hand, we believe that our schedule for evaluation is ideal in terms of the radiological aspects, since it is known that the density of the lung parenchyma begins to increase 1–2 months after radiotherapy [24].

The low response rate that was observed to combined doxorubicin and cyclophosphamide matches the lack of response observed in the randomized, single agent study of doxorubicin and cyclophosphamide by SÖRENSEN *et al.* [2]. Moreover, in recent compilations of the activity of doxorubicin and cyclophosphamide as single agents, the response rates were equal to the present results [21, 26].

The median survival of only 7 months for all the patients in this study is in accordance with other reports of radiotherapy in pleural mesotheliomas [6, 7, 25, 27]. However, even in 100 Finnish pleural mesotheliomas subjected to aggressive multimodal treatment, including debulking surgery, high-dose radiotherapy (20–70 Gy) with varying fractionation schedules and/or chemotherapy, the median survival was only 8 months [20].

In the present study, no patient in the RTCT group survived for more than 2 yrs, and only one patient in the RT group survived for 4 yrs.

There appears to be a general consensus that radiotherapy in mesotheliomas does not increase survival [23, 27]. On the other hand, several authors have observed that radiotherapy produces good alleviation of chest pain [6, 23, 24]. Some authors have observed a dose-response relationship, as total doses above 40 Gy have yielded a better reduction in pain than lower doses [24]. In contrast to these observations, we were unable to detect any beneficial effect by hemithorax irradiation on performance status, body weight or pain score. This could be due to a lower total dose of irradiation in this study. However, a dose of 50 Gy has been reported to result in fatal complications in 2 of 12 treated cases [23].

In this study, we observed 11 cases (11 out of 47) of acute radiation pneumonitis requiring long periods of continuous corticosteroid treatment combined with antibiotics in order to manage the accompanying respiratory infections. The high frequency of radiation-induced pneumonitis in this study could, in part be a "radiation recall" effect [17] due to the administration of doxorubicin after radiotherapy in 16 cases. The steep decline in body weight during the month following irradiation could also be due, in part, to the side-effects of RT, especially the transient, acute, radiation-induced oesophagitis. We therefore advocate that the side-effects of radiation therapy should also be taken seriously when aggressive irradiation is evaluated in future studies.

The prognosis for mesothelioma is heavily dependent on certain prognostic factors. In multivariate analysis, the treatment factor has usually not been a factor of major importance for the prediction of survival [28]. The prognostic factors which are frequently recognized as indicating a survival advantage include a good performance status [1, 28–30], low age [28, 29, 31], epithelial histology [28–30], early tumour stage [1, 29, 32], lack of chest pain [28, 29], lack of asbestos exposure [33, 34], a low S-phase fraction [30] and female gender [30, 31].

In our comparatively small study, with its accompanying low statistical power, we found that pain score, tumour stage and smoking were prognostic factors in univariate analysis. Furthermore, pain score was strongly related to tumour stage and performance status. Although pain has been observed as a prognostic factor in other studies [28–29], no previous study has applied a specially developed pain score prospectively in this disease.

In conclusion, we found that the hemithorax irradiation of pleural mesotheliomas with a moderately high dose of radiation is not useful, since it did not alleviate pain, produced little or no objective tumour response, did not affect survival outcome and was in all of the cases unable to halt the relentless progression of the disease. Furthermore, hemithorax irradiation including whole-lung irradiation induced severe fibrosis of the lung parenchyma and a moderately high frequency of acute pneumonitis requiring chronic corticosteroid therapy.

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References

1. Alberts AS, Falkson G, Goedhals L, Vorobiof DA, Van Der Merwe CA. Malignant pleural mesothelioma: a disease unaffected by current therapeutic maneuvers. *J Clin Oncol* 1988; 6: 527–535.
2. Sörensen PG, Bach F, Bork E, Hansen HH. Randomized trial of doxorubicin *versus* cyclophosphamide in diffuse malignant pleural mesothelioma. *Cancer Treat Rep* 1985; 69: 1431–1432.
3. Chahinian AP, Antman K, Goutsou M, *et al*. Randomized phase II trial of cisplatin with mitomycin or doxorubicin for malignant mesothelioma by the Cancer and Leukemia Group B. *J Clin Oncol* 1993; 11: 1559–1565.
4. Law MR, Gregor A, Hodson ME, Bloom HJG, Turner-Warwick M. Mesothelioma of the pleura: a study of 52 treated and 64 untreated patients. *Thorax* 1984; 39: 255–259.
5. Krarup-Hansen A, Hansen HH. Chemotherapy in malignant mesothelioma: a review. *Cancer Chemother Pharmacol* 1991; 28: 319–330.
6. Voss AC, Wöllgens P, Untucht HJ. Das Pleuramesotheliom aus Strahlentherapeutischer Sicht. *Strahlentherapie* 1974; 148: 329–332.
7. Eschwege F, Schlienger M. La radiothérapie des mésothéliomes pleuraux malins: a propos de 14 cas irradiés à doses élevées. *J Radiol Electrol* 1973; 54: 255–259.
8. Hillerdal G. Malignant mesothelioma 1982: review of 4,710 published cases. *Br J Dis Chest* 1983, 77: 321–343.
9. Maasilta P, Vehmas T, Kivisaari L, Tammilehto L, Mattsson K. Correlations between findings at computed tomography (CT) and at thoracoscopy/thoracotomy/autopsy in pleural mesothelioma. *Eur Respir J* 1991; 4: 952–954.
10. Aisner J, Wiernik PH. Malignant mesothelioma: current status and future prospects. *Chest* 1978; 74: 438–443.
11. Johansson L, Lindén CJ. Review of malignant mesotheliomas in Lund, Sweden, 1980–1990: histopathological and immunohistochemical features - preliminary results. *Eur Respir J* 1993; 3: 61–63.
12. Johansson L, Albin MP, Jakobsson K, Welinder H, Attewell-R, Ranstam J. Ferruginous bodies and pulmonary fibrosis in dead low-to-moderately exposed asbestos cement workers. *Br J Ind Med* 1987; 44: 550–558.
13. Karnovsky DA, Abelman WH, Craver LF, Burchenal JH. The use of nitrogen mustards in the palliative treatment of carcinoma: with particular reference to bronchogenic carcinoma. *Cancer* 1948; 1: 634–656.
14. The World Health Organization. Histological typing of lung tumours. *Am J Clin Pathol* 1982; 77: 123–136.
15. World Health Organization. WHO handbook for reporting results of cancer treatment. Geneva, WHO Offset Publication, 1979; No. 48.
16. Ruffie P. Mesothelioma chemotherapy. *Eur Respir Rev* 1993; 3 (11): 199–203.
17. McInerney DP, Bullimore J. Reactivation of radiation pneumonitis by adriamycin. *Br J Radiol* 1977; 50: 224–227.
18. Hilaris BS, Dattatreyudu N, Kwong E, Kutcher GJ, Martini N. Pleurectomy, intraoperative brachytherapy, and postoperative radiation in the management of malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys* 1984; 10: 325–331.
19. Sugarbaker DJ, Heher EC, Lee TH, *et al.* Extrapleural

pneumonectomy, chemotherapy, and radiotherapy in the treatment of diffuse malignant pleural mesothelioma. *J Thorac Cardiovasc Surg* 1991; 102: 10–15.
20. Mattsson K, Holsti LR, Tammilehto L, *et al.* Multimodality treatment programs for malignant pleural mesothelioma using high-dose hemithorax irradiation. *Int J Radiat Oncol Biol Phys* 1992; 24: 643–650.
21. Antman KH, Pass HI, DeLaney T, Li FP, Corson J. Benign and malignant mesothelioma. *In*: De Vita VT, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology. Philadelphia, J.B. Lippincott Co., 1993; pp. 1489–1508.
22. Musk AW, Woodward SD. Conventional treatment and its effect on survival of malignant pleural mesothelioma in Western Australia. *Aust NZ J Med* 1982; 12: 229–232.
23. Ball DL, Cruickshank DG. The treatment of malignant mesothelioma of the pleura: review of a 5 year experience, with special reference to radiotherapy. *Am J Clin Oncol* 1990; 13: 4–9.
24. Gordon W, Antman K, Greenberger JS, Weichselbaum RR, Chaffey JT. Radiation therapy in the management of patients with mesothelioma. *Int J Radiat Oncol Biol Phys* 1982; 8: 19–25.
25. Maasilta P, Kivisaari L, Holsti LR, Tammilehto L, Mattsson K. Radiographic chest assessment of lung injury following hemithorax irradiation for pleural mesothelioma. *Eur Respir J* 1991; 4: 76–83.
26. Aisner J. Current approach to malignant mesothelioma of the pleura. *Chest* 1995; 107: 333s–344s.
27. Sinoff C, Falkson G, Sandison AG, De Mûelenaere G. Combined doxorubicin and radiation therapy in malignant pleural mesothelioma. *Cancer Treat Rep* 1982; 66: 1605–1607.
28. Calavrezos A, Koschel G, Hüsselmann H, *et al.* Malignant mesothelioma of the pleura: a prospective therapeutic study of 132 patients from 1981–1985. *Klin Wochenschr* 1988; 66: 607–613.
29. Antman K, Shemin R, Ryan L, *et al.* Malignant mesothelioma: prognostic variables in a registry of 180 patients, the Dana-Faber cancer institute and Brigham and women's hospital experience over two decades, 1965–1985. *J Clin Oncol* 1988; 6: 147–153.
30. Tammilehto L. Malignant mesothelioma: prognostic factors in a prospective study of 98 patients. *Lung Cancer* 1992; 8: 175–184.
31. Spirtas R, Connelly RR, Tucker MA. Survival patterns for malignant mesothelioma: the SEER experience. *Int J Cancer* 1988; 41: 525–530.
32. Ruffie P, Feld R, Minkin Q, *et al*. Diffuse malignant mesothelioma of the pleura in Ontario and Quebec: a retrospective study of 332 patients. *J Clin Oncol* 1989; 7: 1157–1168.
33. Law MR, Ward FG, Hodson ME, Heard BE. Evidence for longer survival of patients with pleural mesothelioma without asbestos exposure. *Thorax* 1983; 38: 744–746.
34. Hirsch A, Brochard P, De Cremoux H, *et al.* Features of asbestos-exposed and unexposed mesothelioma. *Am J Ind Med* 1982; 3: 413–422.