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FROM THE DEPARTMENTS OF PULMONARY MEDICINE, RADIATION THERAPY AND ONCOLOGY, DIAGNOSTIC RADIOLOGY, AND PATHOLOGY, HELSINKI UNIVERSITY CENTRAL HOSPITAL, SF-00280 HELSINKI, FINLAND.

RADIATION PNEUMONITIS AND FIBROSIS FOLLOWING SPLIT-COURSE RADIATION THERAPY FOR LUNG CANCER

A radiologic and physiologic study

K. MATTSON, L. R. HOLSTI, H. POPPIUS, O. KORHOLA, S. STENMAN, L. TAMMILEHTO and M. SALMO

Abstract

Radiographic signs of radiation pneumonitis and fibrosis were assessed and pulmonary function monitored in lung cancer patients after two different split-course radiation therapy schedules, one with a rest interval of 3 weeks and the other with a rest interval of 5 weeks, the total radiation dose being the same in both treatments (55 Gy/20 fractions/7 or 9 weeks). Post-mortem findings were analysed when available. Spirometric measurement of vital capacity, determination of diffusing capacity for carbon monoxide (D_L) and alveolar volume with the single breath technique, and determination of regional distribution of lung perfusion by two different techniques, radiospirometry and gamma camera digital display following intravenous injection of ^{133}Xe, were carried out before and at various times after the completion of irradiation. Of the physiologic parameters, only D_L showed a significant decrease 6 as well as 9 months post-treatment ($p<0.05$). No difference between the two treatment schedules could be shown with regard to grade or time pattern of radiologic changes or decrease in D_L. The findings suggest that measurement of D_L may be of value in monitoring patients included in research protocols for radiation therapy of lung cancer as well as in selection of patients for this treatment.

Key words: Radiation, injurious effects; lung cancer, radiation therapy, split-course, pneumonitis.

Pathologic changes in the lung following irradiation include in the acute phase swelling and desquamation of alveolar cells with formation of hyaline membranes, capillary damage, interestitial and intra-alveolar edema and an increase in the number of reticuline fibers. Later on, fibrosis and shrinkage occur (1). The early and late changes both cause radiologic changes, loss of lung perfusion and lung volume, and disturbance of gas transfer function (D_L) of the lung (6, 9).

Two different modes of split-course therapy were evaluated. The split-course method has been developed empirically. It implies one or two rest periods during the course of radiation therapy. Optimal timing and duration of the rest interval are not determined. Theoretical advantages of rest periods include recovery of normal tissue from radiation injury and shrinkage of the tumor during the rest, leading to improvement in oxygen tension in the remaining tumor cells (4, 7, 8). Thus, split-course therapy could be associated with lower radiation morbidity than standard treatment, without loss of efficacy provided that the dose is escalated about 10 per cent to compensate for the rest interval (3).

Material and Methods

In this study, the patients were randomized (by sealed envelopes) to have either a three or a five weeks rest interval between two treatment courses which consisted of 30 Gy/10 fractions/2-week interval-25 Gy/10 fractions/2 weeks. The total midplane dose was 55 Gy in both fraction schedules. No corrections for lung tissue were made in the dose estimation. Radiation pneumonitis and fibrosis, and pulmonary function, were followed by radiographic and physiologic assessments.

Roentgen irradiation from an 8 MeV linear accelerator was performed from two opposed individually shaped fields including mediastinum, ipsilateral hilus and the primary tumor with a 1 to 2 cm margin. The maximum field size was 150 cm^2 in both treatment groups. In small cell carcinoma, the supraclavicular areas were included in the fields. Two or 3 cycles of chemotherapy were given

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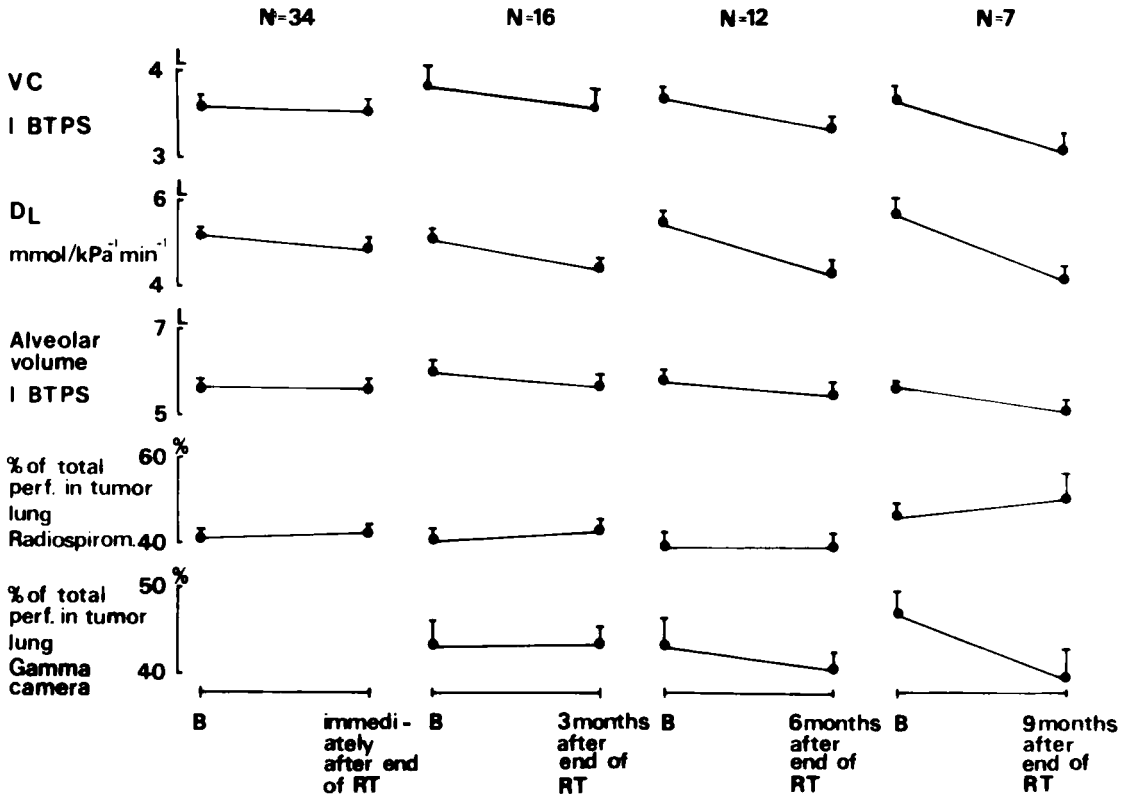

Fig. Changes in pulmonary function variables (mean and SEM) following radiation therapy for lung cancer. Only the changes in D_L 6 and 9 months after completion of irradiation were significant ($p<0.05$).

before radiation therapy, 6 to 9 cycles after the treatment. No chemotherapy was administered during the rest interval. Drug combinations consisted of cyclophosphamide 10 mg/kg on days 1–5 and either vindesine 3 mg/m^2 on days 1 and 4 or vincristine 1.5 mg on days 1 and 4 (CTX-VDS, CTX-VCR), new course every 28th day; cisplatinum (P) 90 mg/m^2 given at 6-week intervals combined either with vindesine 3 mg/m^2 5 × weekly, then every fortnight, or etoposid (VP-16) 50 mg/m^2 on days 1–5 simultaneously, new course every 6th week. Radiologic and pulmonary function assessments were made before, immediately after, and 3, 6, and 9 months after the completion of radiation therapy. The radiologic changes were evaluated from chest films (postero-anterior and lateral views) and from conventional tomograms, and the radiation pneumonitis and/or fibrosis was graded as none, slight, moderate or severe. Physiologic assessment was made by the following methods: spirometric measurement of vital capacity (VC); determination of diffusing capacity for carbon monoxide and alveolar volume with the single breath technique; determination of regional distribution of lung perfusion by two different techniques, radiospirometry and gamma camera digital display following intravenous injection of ^{133}Xe. At autopsy 12 tissue samples from both lungs were studied systematically and graded for the degree of fibrosis as none, mild, moderate or severe.

Table 1

Radiologic assessment of the development of pulmonary radiation injury following split-course therapy with 3 or 5 week rest intervals

Radiologic grade of pneumonitis	Rest interval (weeks)	Duration of follow-up after end of radiation therapy (months)		
		3	6	9
None	3	0	0	0
	5	1	0	0
Slight	3	3	2	0
	5	4	4	0
Moderate	3	4	4	4
	5	3	2	2
Severe	3	0	1	1
	5	0	2	2
Total No. of patients		15	15	9

All patients were previously untreated and had disease limited to one hemithorax. Of 46 patients accepted for the study, 34 were evaluable for the first two assessments of all tests with the exception of the gamma camera examination, 16 were evaluable for at least three assessments: before, immediately after and 3 months after the comple-

Table 2

Mean change from pre-treatment levels (SEM values of change in parentheses) in pulmonary function variables over various observation periods following irradiation for lung cancer. For vital capacity (VC), diffusing capacity (D_L) and alveolar volume, the change is expressed in per cent of pre-treatment value. For lung perfusion measurements, the changes are expressed as the difference between pre- and post-treatment perfusion of tumor lung stated in per cent of total lung perfusion

	Change in pulmonary function (per cent)			
	Immediately after RT (n=34)	3 months after RT (n=16)	6 months after RT (n=12)	9 months after RT (n=7)
VC	−1 (0.22)	−6 (0.75)	−10 (1.20)	−16 (1.90)
D_L	−6 (0.76)	−14 (0.52)	−21* (2.19)	−27* (2.70)
Alveolar volume	−1 (0.09)	−5 (0.68)	−5 (0.68)	−10 (1.83)
Tumor lung perfusion, radiospirometry	+1 (0.29)	+3 (0.45)	0 (0.03)	+5 (0.60)
Tumor lung perfusion, gamma camera	–	0 (0.05)	−3 (0.24)	−8 (1.90)

*$p<0.05$.

Table 3

Post-treatment radiologic changes and post-treatment decrease in D_L in per cent of pre-treatment value (mean ± SEM) at different times following end of irradiation. Number of patients given in parentheses

Radiologic grade of penumonitis and fibrosis	Duration of D_L follow-up after end of radiation therapy (months)		
	3	6	9
None	−25 (1)	–	–
Mild	−12±4 (7)	−17±9 (6)	–
Moderate	−13±3 (7)	−23±6 (6)	−33±6 (6)
Severe	–	−27±4 (3)	−18±8 (3)
Total No. of patients	15	15	9

Table 4

Evaluation of autopsy findings

Rest interval	Age and sex	Duration from end of RT to death (months)	Viable tumor	Grade of fibrosis
3 weeks	71 M	14	No	Moderate
	68 M	20	Yes	Severe
	68 M	11	Yes	Mild
	71 M	27	Yes	Mild
	54 M	15	Yes	Moderate
	57 M	9	No	Moderate
	61 M	8	No	Severe
5 weeks	59 M	7	Yes	Mild
	57 M	8	Yes	Mild
	63 M	10	Yes	Mild
	64 M	21	No	Mild

tion of radiation therapy, 12 could be completely evaluated at 6 months, and 7 at 9 months after the completion of radiation therapy. Eighteen of the 34 evaluable patients had small cell lung cancer (8 received CTX-VDS, 10 CTX-VCR), and 16 had non-small cell lung cancer (9 received P-VDS, 7 P-VP-16). Twelve patients had a rest interval of 3 weeks, and 22 a rest interval of 5 weeks during the split-course irradiation. The treatment groups were well balanced with regard to prognostic factors. A total of 11 patients were subjected to autopsy.

Results

The results of the radiologic assessment of pneumonitis and fibrosis appear in Table 1. No difference between the two groups could be found with regard to grade or time pattern of the radiologic changes.

The various respiratory function variables during the period of follow-up are shown in the Figure and Table 2. D_L showed a marked post-treatment decrease, which was statistically significant ($p<0.05$) 6 and 9 months after radiation therapy. The changes in the other respiratory function variables were small and statistically non-significant.

No correlation was seen between the estimated severity of the post-treatment radiologic changes and the post-treatment decrease in D_L (Table 3).

The degree of radiation fibrosis at autopsy in 11 patients is seen in Table 4. Out of 7 patients with a 3-week rest interval 2 had severe and 3 moderately severe fibrosis. The changes could be demonstrated within as well as outside the actual radiation field. Of the 4 patients examined whose rest period was 5 weeks, none had severe or moderately severe fibrosis.

Discussion

The radiation dose required to sterilize any type of lung cancer is above that tolerated by normal lung tissue and pulmonary toxicity is a major dose-limiting factor in the treatment of lung cancer by irradiation. The rate of development and severity of radiation injury depend on the radiation dose, irradiated volume, dose fractionation,

overall treatment time, coexistent pulmonary disease and simultaneous administration of cytostatic drugs. In this analysis, we evaluated two different split-course regimens in combination with chemotherapy using the same total dose and the same number of fractions (55 Gy/20 F) but an overall treatment time of either 7 or 9 weeks. The D_L showed a marked post-treatment decrease by about one-fourth, 6 and 9 months after radiation therapy with both treatment regimens. No other changes in measured respiratory function variables were significant.

The radiographic appearance of radiation injury mimics infectious processes or tumor recurrence. The evaluation of radiologic changes from chest films or from conventional tomograms, the methods used in this study, gives unreliable information. With the advent of computed tomography (CT) more detailed information concerning tissue density has become available. This piece of information can be used to recognize radiation pneumonitis, thus preventing serious error in patient management and the risk of further lung damage. CT is therefore proposed as an additional tool for the documentation of radiation injury to the lung in research projects where new treatments are being evaluated (5).

Any attempt to rank pulmonary function measurements according to their power of detecting radiation pneumonitis and fibrosis is hampered by the fact that some of the patients die during the follow-up period. The possibility of a bias effect of this selection process cannot be excluded. Furthermore, several factors other than irradiation injury may have contributed to the post-treatment decrease in D_L in our patients, i.e. tumor progression, infection, reduction in total blood volume, and inadequate correction for changes in haemoglobin concentration (1, 6, 9). However, the finding that D_L, contrary to the other physiologic measurements used, decreased significantly and even markedly in the post-treatment period, suggests that D_L may be a useful test for monitoring post-radiation lung pathology. A thorough evaluation of pulmonary function before irradiation is important for selection of the patients and for comparison with repeated test results during the post-treatment period for research purposes. New ideas regarding treatment strategies and fractionation schemes for lung cancer are needed. These may include higher tumor doses to ameliorate local control, hyperfractionation with multiple small daily fractions, and a shortening of overall treatment time which is believed to reduce late effects of irradiation (2). THAMES et coll. (10) have presented radiobiologic data that strongly support the use of hyperfractionation in order to reduce late lung damage. Clinical experience is at present lacking. Furthermore, the combination of irradiation with other modes of treatment potentially prepares the ground for unexpected interactions. For the scientific documentation of such reactions in patients receiving radiation therapy for lung cancer, we propose the use of pulmonary function tests as follows: *For selection:* VC, FEV_1, D_L, PaO_2, $PaCO_2$; *for follow-up*: VC and D_L immediately after and at 1, 2, 3, 4, 6, 9 and 12 months after the irradiation. In the clinical routine, pulmonary function assessment should be performed before treatment. Follow-up tests are of limited value for routine clinical management as radiation fibrosis is not responsive to treatment.

Request for reprints: Dr Karin Mattson, Department of Pulmonary Medicine, Helsinki University Central Hospital, Haartmaninkatu 4, FS-00290 Helsinki, Finland.

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