Acta Oncologica 28 (1989) Fasc. 5

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THE EFFECT OF THORACIC IRRADIATION FOR CANCER OF THE BREAST ON VENTILATION, PERFUSION AND PULMONARY PERMEABILITY

A one-year follow-up

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Abstract

Regional and overall lung function was studied in 14 women during a one-year follow-up after postmastectomy irradiation for cancer of the breast. The dose was 40 Gy in the chest wall and 20-40 Gy in the apex of the lung. Immediately after irradiation there was a slight increase in pulmonary clearance of $^{99}TC^{m}$-DTPA compared to baseline values. This increase, however, was not restricted to the field of irradiation. Three months after irradiation there were regional defects in the ventilation and perfusion scintigrams in 11 of the patients. At the same time there was a greater decrease in total lung capacity, vital capacity and diffusion capacity for CO than in ventilation and perfusion. One year after irradiation the lung function impairment had only insignificantly regressed. It is concluded that local lung irradiation may cause persistent regional and generalized lung function impairment. The early increase in pulmonary clearance of $^{99}Tc^{m}$-DTPA could not be used as a predictor of subsequent lung function impairment.

Key words: Irradiation pneumonitis, breast cancer pulmonary ventilation and perfusion, pulmonary epithelial permeability.

The earliest reports on adverse effects on the lungs and pleurae appeared in the 1920s when therapy with photons of higher energy began to be used (1–3). In 1961 Emirgil & Heinemann (4) reported the effects of irradiation of the chest on pulmonary function in man, such as decrease in lung volumes, impairment of diffusion capacity and increase in the work of breathing.

Postoperative irradiation for breast cancer is normally restricted to a limited area of the chest and changes in overall lung function should therefore be expected to reflect changes in regional lung function. The changes seen on the chest radiogram after irradiation for cancer of the breast are usually localized infiltrations. They are most often observed from about 3 months after the irradiation and indicate irradiation pneumonitis.

In 1977 pulmonary clearance of inhaled nebulized $^{99}Tc^{m}$-DTPA (PCl, Table 1) was introduced as an index of pulmonary leakiness (5). Shortly afterwards it was established that most patients with diffuse interstitial pulmonary fibrosis have increased pulmonary leakiness (6, 7).

If the roentgenologic pulmonary changes after irradiation are preceded by increased leakiness, measurement of PCl might provide information about lung injury before it becomes evident from chest roentgenography or ventilation and perfusion scintigraphy.

The present study deals with the changes in PCl, ventilation (V) and perfusion (Q), occuring during the first year after postoperative irradiation for breast cancer. The results were compared to changes in chest roentgenogram and a variety of indices of the overall lung function, i.e. spirometry, flow-volume curves, single and multiple breath N_2 wash-out tests and diffusing capacity.

Material and Methods

Irradiation

Fourteen consecutive women consented to participate in the study. They had all been treated by total mastectomy for cancer of the breast, had entered the Danish Breast Cancer Group's study of high-risk patients and were allocated to receive postoperative irradiation due to a tumor size >5cm and/or axillary metastases. In Table 2 the data of the participants are given.

The irradiation was delivered by x-rays from a 6 MeV accelerator with a focus to source distance of 1 m. A 3-field technique was used as advised in the Danish Breast Cancer Group (DBCG 1977), and comprised one field

Accepted for publication 9 September 1988.

Table 1.

Lists of abbreviations

CC%	Closing capacity in percentages of TCL
CV%	Closing volume in percentages of VC
DTPA	Diethylene-triamine-penataacetic acid
FEV_1	Forced expiratory volume in 1 s.
MEF_{50}	Maximum expiratory flowrate at 50% of VC
PCl	Pulmonary clearance of $^{99}Tc^m$-DTPA
PEF	Peak expiratory flow rate
Q	Perfusion
SI	Slope of phase III
TCL	Total lung capacity
TCO	Transfer factor for CO
V	Ventilation
VC	Vital capacity
WOV	Wash-out volume

against the regional lymph nodes in the supra-infraclavicular and axillary region and two tangential fields against the chest wall (Fig. 1). The patient was lying in a standard prepared fixation on her back with the arm on the operated side in at least 90° abduction and the antebrachium maximally rotated. The minimum central axis dose per fraction was 1.85 Gy. Five fractions per week were given up to a total midaxillary and minimum chest wall dose of 40 Gy. Although there was a certain interindividual difference between the lung volume involved in the tangential fields due to differences in thoracic shape, the irradiation of the apex of the lung through the lymph node fields contributed by far the major part of the lung irradiation. The apex of the lung received a dose of between 20 and 40 Gy, whereas the remaining lung only received irradiation in its most superficial parts.

Lung function examinations

The lung function examinations were performed before the irradiation (I), immediately after the end of therapy (II), three months (III), and one year after irradiation (IV). The examinations were:

Examinations of overall lung function. Spirometry was performed with computerized Jaeger equipment. Inspiratory vital capacity (VC) was measured 3 times and the highest estimate was used. Total lung capacity (TLC) and residual volume (RV) were measured by a single breath He-dilution method (8). Forced expiratory volume in one second (FEV_1), peak expiratory flow rate (PEF), and forced expiratory flow rate at 50% of the vital capacity (MEF_{50}) were calculated from 3 flow volume curves. The highest values were used. Closing volume in percentages of VC (CV%) and closing capacity in percentages of TLC (CC%) and the slope of phase III (SI) were measured by a single breath N_2-method. Wash out volume (WOV) was defined as the exhaled volume required to reach 2% N_2 in the expiratory gas when breathing pure oxygen according to Kjellman's (9) slightly modified method of Georg (10). The diffusing capacity was measured as the transfer factor for CO (TCO) by a single breath method. The different

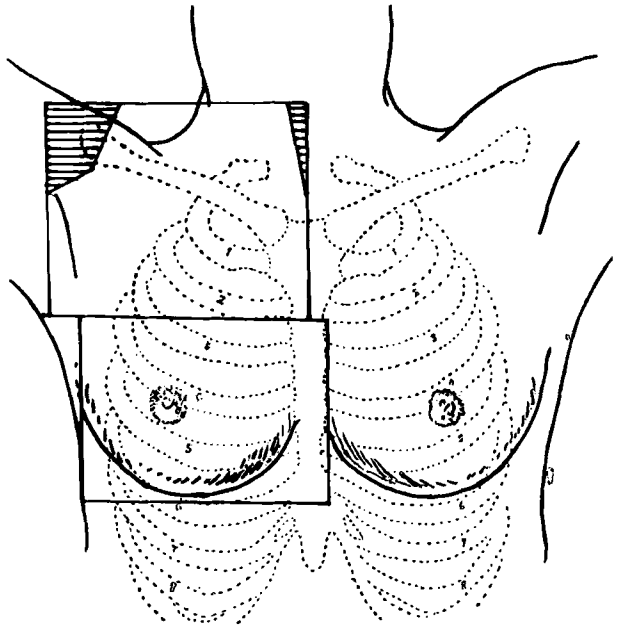

Fig. 1. A schematic drawing of the irradiation field. Upper quadrangle indicates the borders of the lymph node fields. The lower quadrangle indicates the borders of the tangential fields.

lung function variables were expressed as percentages of predicted values (8, 11–13).

Examination of the regional lung function. Sodium pertechnetate ($^{99}Tc^mO_4$) was eluted in isotonic saline from a $^{99}Mb/^{99}Tc^m$ generator (IRE). The $^{99}Tc^mO_4^-$ was chelated to diethylene-triamine-pentaacetate (DTPA, Du Pont), introducing 700 MBq of $^{99}Tc^mO_4^-$ into a kit containing 10 mg of DTPA in a maximal volume of 5 ml isotonic saline. The binding of $^{99}Tc^mO_4^-$ to DTPA was >97% complete by chromatography where the separation of $^{99}Tc^m$-DTPA and $^{99}Tc^mO_4^-$ was achieved with acetone on alufoil cellulose. The subsequent ultrasound nebulizations did not influence the binding of $^{99}Tc^mO_4^-$ to DTPA (14).

Human albumin microspheres were made by introducing 5 ml $^{99}Tc^mO_4^-$ into a kit containing the microspheres (TCK-5; CIS). The latter had a diameter between 23 and 45 μm. Less than 5% $^{99}Tc^mO_4^-$ was free after the labelling procedure. The suspended microspheres were shaken vigorously immediately before withdrawing the dose for injection.

The aerosol was generated in an ultrasound nebulizer (DeVilbiss nebulizer, 35 B) containing the 700 MBq $^{99}Tc^m$-DTPA. The aerosol was inhaled from the nebulizer and on its way to the mouth, it passed a 10-l container and a 1 m long hose to permit settling of larger droplets (7). The median mass diameter of the inhaled particles was measured by light diffraction to be 0.5–2.3 μm (>98% <1.5 μm). A T-valve at the mouth ensured that the expirated particles could be trapped. A nose-clip was used.

The patients inhaled the aerosol using slightly deeper inspirations than tidal volume. The inspirations were slow

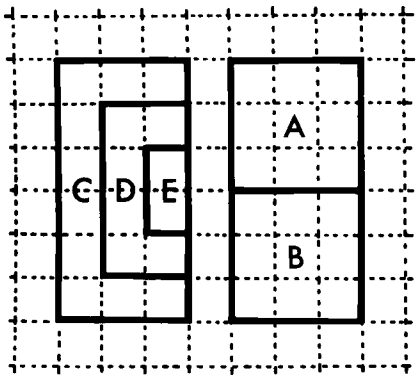

Fig. 2. Regions of interest for determination of regional ventilation, perfusion and $^{99}Tc^{m}$-DTPA clearance. The overall size of the regions were adjusted by the computer to fit the lung field radioactivity as clearly as possible. A: upper half; B: lower half; C: lateral part; D: intermediate part; E: central part.

and were followed by a 3 s pause (breath hold) before each expiration. When inhaled by this maneuvre the site of deposition of small particles (<2 μm) is mainly the alveoli (15). The aerosol was administered for 3 min yielding a maximum count rate of 120000 CPM over the entire lung field.

Immediately after inhalation of the aerosol, the patient was seated with her back against an Anger type scintillation gammacamera (LFOV, Searle Radiographic, Inc.) with a standard field of view size crystal and a parallel 140 KeV collimator. Dynamic aquisition of the detected lung field radioactivity was made for 10 min only since the possible influence of recirculation would then be minimized (5) on a computer (MED II Nuclear Data). The acquisition was framed at 20 s intervals. 70 MBq TCK-5 was injected intravenously and 5 min of acquisition was made in list mode. During the aquisitions, ventilation and perfusion scintigrams were made on polaroid films.

The acquired data were processed to display initial distribution of the activity of $^{99}Tc^{m}$-DTPA. Regions of interest were created (Fig. 2A and B), and the percentual ventilation (V) of the upper and the lower quadrant of each lung was calculated (16). The distribution of the activity following the TCK-5 injection was used to calculate the percentual distribution of the perfusion (Q) of the lungs for the same regions of interest. A V/Q ratio was determined for each region.

PCl was calculated by applying a monoexponential fit to the time activity curve. PCl was characterized by the slope of the time activity curve (7). PCl was calculated for upper and lower quadrant of each lung (Fig. 2A and B) and for peripheral, intermediate and central parts of the lungs as defined in Fig. 2C–E. Physical decay of the $^{99}Tc^{m}$ was corrected for.

Plain chest roentgenography was performed in two projections.

At each examination the patients filled in a standardized questionnaire concerning respiratory symptoms.

An analysis of variance was performed of the changes in lung function during the first year of observation.

Results

Symptoms and overall lung function

Eleven of the 14 patients were heavy smokers, and 4 of these had chronic bronchitis (Table 2). Smoking habits did not change during the follow-up. During the year of observation 5 of the patients experienced pulmonary symptoms not previously present and not ascribable to metastases. In 7 of the 14 patients the roentgenograms eventually showed signs of localized radiation changes, not visible until 3 months after the irradiation.

The irradiation caused an overall lung function impairment, that was consistent with restrictive lung disease (Table 3). At examination II, there was a significant ($p<0.05$) decrease in TCO. At examination III there was also a significant reduction in TLC ($p<0.01$) and VC ($p<0.01$), and TCO had further decreased ($p<0.01$). By the end of the first year the estimates insignificantly tended to return to baseline values. During the year of observation the maximum decrease in TLC, VC and TCO was 14%, 27%, and 24% respectively. There was a 6% increase in FEV_1 between examination I and II. This was probably related to the surgical trauma, and between examination II and III the FEV_1 showed a similar reduction as TLC, VC and TCO. PEF did not change during the observation period. Concerning MEF_{50}, which may yield more information about the small airways than FEV_1 and PEF, there was a significant reduction ($p<0.01$) at examinations III and IV. There were no significant changes in SI, CV% and the CC%. A slight change ($p<0.05$) in WOV was seen at examination IV.

Regional lung function

Ventilation (V). At examination I (Table 4), the ventilation of the mastectomy side was 8% lower than that of the contralateral side ($p<0.05$). At examination II the difference was no longer significant. It is therefore tempting to relate it to the surgical trauma.

At examinations III and IV, the difference in ventilation between the two lungs had reappeared. The impairment was almost completely confined to the upper halves of the lungs of the irradiated side, and was parallelled by defects in the ventilation scintigrams in 11 of the 14 patients. An example is shown in Fig. 3.

At examination III, when the changes were most pronounced, the entire lung field radioactivity reflecting ventilation had on average decreased 3% compared to baseline values.

Perfusion (Q). The greatest effect on perfusion (Table 4) was seen 3 months after the irradiation similar to overall lung function and ventilation. At examination I, the perfusion of the upper halves of the irradiated sites was

Table 2

Physical characteristics, smoking habits, respiratory symptoms, and changes on reoentgenogram (RGT)

No.	Age years	Height cm	Weight kg	Smoking habits			Side of irradiation	Roentgenologic changes		Respiratory symptoms at examination No.			
				Smoker	Smoked Nos of year	Cig. per day		Observed at exam. No.	Type of change	I	II	III	IV
1	48	160	71	Never	–	–	Right	III	Infiltration right, sup.	–	–	–	–
2	49	158	55	Yes	35	20	Right	–	–	–	Coughing	–	–
3	70	165	70	Yes	47	20	Left	III	Infiltration left, sup.	–	–	Coughing dyspnoe	Less pronounced
4	43	156	57	Yes	27	20	Left	–	–	–	–	–	–
5	38	174	63	Yes	20	20	Left	III	Infiltration left, sup.	–	–	–	–
6	50	162	69	Yes	18	20	Left	III	Infiltration left, sup.	–	–	–	–
7	61	163	60	Never	–	–	Right	–	–	–	–	–	Expectoration
8	56	165	59	Yes	17	25	Right	–	–	Signs of chr. bronch.	No change	No change	No change
9	50	172	55	Never	–	–	Left	III	Infiltration left, sup. pleuritis obs.	–	–	–	–
10	48	176	66	Yes	20	25	Right	–	–	Signs of chr. bronch.	No change	Increased expect.	No change
11	40	160	63	Yes	15	30	Left	–	–	Signs of chr. bronch.	No change	No change	No change
12	59	156	65	Yes	20	7	Right	–	–	–	–	–	–
13	68	160	65	Yes	34	20	Right	III IV	Infiltration right, sup. obs. metast.	–	Dyspn.	–	–
14	43	164	69	Yes	32	25	Right	III	Infiltration right, sup.	Chr. bronch.	No change	No change	No change
x̄	51.6	163.6	63.4		25.9[x]	21.1[x]							
SD	9.9	6.4	5.5		10.0[x]	5.8[x]							

Abbreviations. I: The baseline examination before the irradiation. II: The examination at the termination of the irradiation therapy. III: The examination 3 months after the termination of the irradiation. IV: The examination 1 year after the termination of the irradiation.
[x]: x̄ and SD of smokers only.

94% of the contralateral. At examination III it was 68% and it remained low at examination IV (66%). The 11 patients who had defects in the ventilation scintigrams had also defects in the perfusion scintigrams.

At examination III the entire lung field radioactivity reflecting Q had on average decreased 7% compared to the baseline values.

Ventilation/perfusion (V/Q) ratio. The regional V/Q remained fairly constant throughout the 4 examinations (Table 4). Yet there was a slight ($p<0.05$) increase in V/Q of the irradiated lungs compared to the contralateral at examination III and IV. However, this difference was not significant when the upper halves of the lungs were considered separately.

PCl. The effect on the PCl was small (Table 5). It was most pronounced at examination II, and was seen on the

Table 3

Overall lung function (mean values, % of predicted values) during the first year after irradiation

Lung function tests	I	II	III	IV	SEM	p
TLC	111	104	96	97	1.33	<0.01
VC	97	93	85	89	0.94	<0.01
RV/TLC	126	124	125	116	0.63	NS
FEV_1	89	94	83	85	0.37	<0.05
PEF	95	94	87	89	1.36	NS
MEF_{50}	91	83	68	66	1.68	<0.01
SI	213	205	231	207	6.22	NS
CV%	64[x]	71[x]	72[x]	71[x]	3.44	NS
CC%	109[x]	110[x]	106[x]	104[x]	1.55	NS
WOV	174	183	170	153	3.18	<0.05
TCO	67	59	51	58	1.07	<0.01

Abbreviations: I: The baseline examination before the irradiation. II: The examination at the termination of the irradiation therapy. III: The examination 3 months after the termination of the irradiation. IV: The examination 1 year after the termination of the irradiation. [x]: CV% and CC% could only be defined in 11 patiants. Remaining abbreviations are explained in Table 1.

Table 4

Ventilation ($\dot{V}$), perfusion ($\dot{Q}$) and $\dot{V}/\dot{Q}$ at the four examinations during the one year follow-up (mean values in % of total $\dot{V}$ and $\dot{Q}$)

	The irradiated lung						The contralateral lung					
	I	II	III	IV	SEM	p	I	II	III	IV	SEM	p
Ventilation ($\dot{V}$)												
The upper half	19	20	16	18	0.29	<0.01	21	21	22	23	0.30	NS
The lower half	27	28	27	27	0.44	NS	33	32	35	33	0.44	NS
The whole lung	46	48	43	45	0.47	<0.05	54	53	57	56	0.47	<0.05
Perfusion ($\dot{Q}$)												
The upper half	17	16	13	14	0.36	<0.01	18	17	19	21	0.63	NS
The lower half	31	32	29	28	0.53	NS	32	33	37	35	0.48	NS
The whole lung	48	48	42	42	0.50	<0.01	52	54	56	56	0.57	<0.01
$\dot{V}/\dot{Q}$												
The upper half	1.1	1.3	1.2	1.3	0.026	NS	1.2	1.2	1.2	1.1	0.036	NS
The lower half	0.87	0.88	0.93	0.96	0.0071	NS	1.0	0.97	0.95	0.94	0.017	NS
The whole lung	0.96	1.0	1.0	1.1	0.0092	<0.05	1.0	0.98	1.0	1.0	0.0095	NS

Abbreviations: I: The baseline examination before the irradiation. II: The examination at the termination of the irradiation therapy. III: The examination 3 months after the termination of the irradiation. IV: The examination 1 year after the termination of the irradiation.

irradiated side as an insignificant increase in permeability of 20.6% ($p>0.05$) while on the contralateral side it was 38.1% ($p<0.05$). The increase was not restricted to any particular region. At examination I the PCl of the central part of the irradiated lung was surprisingly low, but at examination III it was comparable to the PCl of the other regions. The less pronounced postmastectomy reduction in central PCl may reflect the surgical trauma in the same

Table 5

Pulmonary clearance (%/min) of inhaled $^{99}Tc^{m}$-DTPA (mean values) at the 4 examinations performed during the one year follow-up. The different regions of the lungs are defined in Fig. 1.

	The irradiated lung						The contralateral lung					
	I	II	III	IV	SEM	p	I	II	III	IV	SEM	p
The upper half	3.07	4.72	4.04	3.56	0.30	NS	2.65	4.19	4.42	3.55	0.35	NS
The lower half	2.96	3.23	2.98	2.95	0.17	NS	2.65	3.42	2.76	2.24	0.20	NS
The whole lung	3.00	3.62	3.25	3.15	0.25	NS	2.65	3.66	3.13	2.60	0.20	<0.05
The peripheral part	3.32	4.90	3.98	3.20	0.42	NS	3.42	4.04	3.49	3.66	0.36	NS
The intermediate part	2.72	3.38	3.04	2.84	0.25	NS	3.12	3.33	3.14	3.74	0.39	NS
The central part	1.54	1.65	3.25	3.30	0.35	<0.05	2.28	2.79	2.55	2.81	0.35	NS

Abbreviations: I: The baseline examination before the irradiation. II: The examination at the termination of the irradiation therapy. III: The examination 3 months after the termination of the irradiation. IV: The examination 1 year after the termination of the irradiation.

way as was likely concerning the changes in regional ventilation and FEV_1.

Discussion

The results of this study show that irradiation against the chest for breast cancer may cause both regional and overall impairment of lung function. Pathoanatomical changes in the lung following irradiation for cancer of the breast are most pronounced after about 3 months (17). The changes in regional function were also most pronounced at that time and expressed as an almost parallel reduction in ventilation and perfusion. Defects in the scintigrams were observed in 11/14 patients and seemed to be more consistent than the roentgenologic changes, which were found in only 7/14 patients. This is in agreement with a report by Goldman et al. (18). They, however, reported that the perfusion was restored in a significant number of patients within 6 weeks after the irradiation while our results indicated that some perfusion defects were persistent.

Our results concerning the overall lung function are in accordance with the results of Emirgil & Heinemann (4) who in 1966 reported lung volumes and lung mechanics in 19 patients irradiated for breast cancer; 15 of these patients were included in a cross sectional study 3 months after the end of irradiation and the results were compared to predicted values. Only 4 of their patients were followed over an extended time (12 months). In the present longitudinal study we included flow variables to be able to investigate if the lung function impairment also included an obstructive component. The changes in FEV_1 and PEF were not more pronounced than could be explained as secondary to the changes in TLC, VC, and TCO. The decrease in MEF_{50}, however, was probably too pronounced to be explained as secondary only. If the decrease in TLC is partly due to changes in lung elasticity with increased static recoil pressures, this would tend to

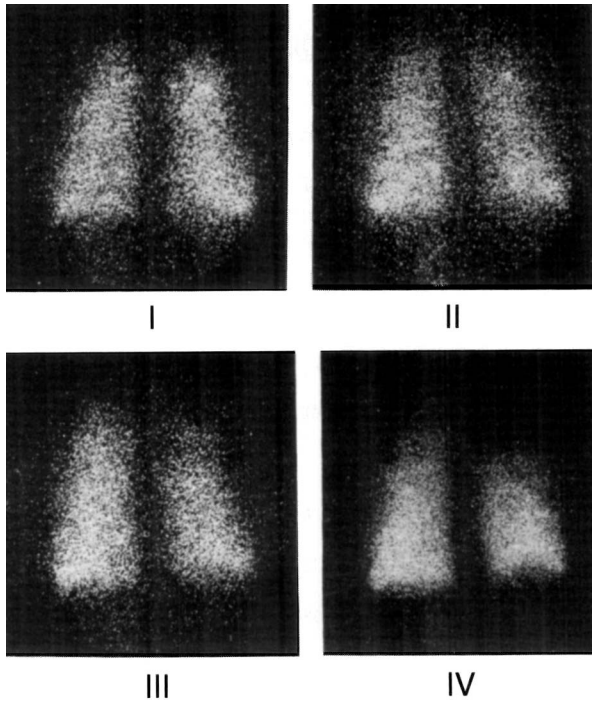

Fig. 3. Example of ventilation scintigrams (posterior acquisition) obtained at examination I–IV. Three months after the irradiation there was a ventilation defect at the right apex. This persisted one year after the irradiation. I: Before irradiation. II: At termination of irradiation therapy. III: Three months after irradiation. IV: One year after irradiation.

increase the airway diameter at the same volume. It might therefore be conjectured that the decreased MEF_{50} reflects some degree of intrinsic obstruction.

The changes in TCO, TLC and VC were greater than the changes in regional ventilation and perfusion. Hence, the effect of localized irradiation need not be entirely localized. In fact several case reports indicate that irradiation pneumonitis is not necessarily restricted to the irradiated volume (19–23). Our results are in line with these observations. The increase in PCl was almost the same in all regions of the lungs but is was small and in most regions not statistically significant. The small generalized increase may indicate that the general effect of irradiation on PCl is only modest. But why did irradiation not cause a more pronounced localized increase in PCl?

The main hindrance for the transport of the $^{99}Tc^{m}$-DTPA from the alveoli to the blood is the integrity of the tight junctions between alveolar cells. The anticipated postirradiation decrease in perfusion (1) does not explain the lack of expected increase in PCl, since PCl is a diffusion rather than a perfusion limited process (24). Pulmonary irradiation is known to cause localized edema, which $^{99}Tc^{m}$-DTPA molecules must pass before they can be cleared from the lungs. This may mask an otherwise increased permeability. Yet at the transition between the edema and airfilled alveoli, i.e. at the terminal bronchi, the epithelium membrane may still be extremely leaky. To demonstrate an increased permeability at the terminal bronchi by means of PCl, however, the $^{99}Tc^{m}$-DTPA aerosol must penetrate all the way through the airways down to the affected alveoli. The ventilation defects that were seen in 11 of the 14 patients indicate that this is not always possible. Anatomical changes of the airways may severely affect the penetration ability of an aerosol (25) thus invalidating the ability of PCl measurements to demonstrate early changes.

We did observe an increased permeability of the central parts of the irradiated lungs compared to the baseline but it did not attain significance until 3 months after the irradiation. The results probably reflected a catch-up in postoperatively reduced permeability rather than a radiation-induced increase.

Smoking severely increases pulmonary permeability (26, 27). Eleven of the 14 patients were smokers and did indeed have increased PCl values even before irradiation. The smokers did not change smoking habits during the follow-up period. Another explanation of the small increase in PCl observed in our patients may therefore be that the lungs were already so leaky that the irradiation only caused small relative increment in leakiness.

In conclusion, postoperative irradiation of the chest after mastectomy in high-risk breast cancer patients caused a significant and partly irreversible regional and generalized impairment of the lung function. The roentgenologic examination alone is likely to underestimate the loss of lung function induced by the irradiation. Although there was an early increase in PCl, this was small and unfit for prediction of later changes in lung function.

ACKNOWLEDGEMENT

This work was supported by the National Cooperation for Prevention of Tuberculosis and Pulmonary Diseases in Denmark.

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