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Ventilation/Perfusion Relations in Patients with Small Cell Anaplastic Carcinoma of the Lung, Obtaining Complete Remission during Combination Chemotherapy*

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Abstract—^{81m}Kr *ventilation lung scans,* ^{99m}Tc *perfusion lung scans and lung function tests were performed in 25 patients with small cell lung cancer during combination chemotherapy in order to characterize the physiological changes in responding patients. After* 3 months *of chemotherapy* 12 *patients had obtained complete remission (CR), with total disappearance of all visible tumor tissue at the chest X-ray,* 5 *had obtained partial remission,* 2 *had progressive disease and* 6 *had died. Prior to treatment a mixed pattern of restrictive and obstructive lung function decrease was observed. The patients had a significant decrease in both ventilation and perfusion* ($P < 0.01$) *of the affected lung and a ventilation perfusion mismatch was seen. Three months after initiation of treatment the patients who obtained CR had a statistical improvement* ($P < 0.01$) *of TLC, VC and FEV in* 1 sec, *rendering them statistically inseparable from a healthy control group. The ventilation of the affected lung in patients obtaining CR increased statistically* ($P < 0.01$), *but only a minor increase in perfusion* ($P < 0.1$) *was seen so that the ventilation–perfusion ratio remained distorted. It is concluded that even though an increase of static and dynamic lung function parameters, including the ventilation of the affected lung, are seen in patients with small cell lung cancer obtaining complete remission during combination chemotherapy, a marked functional decrease of the perfusion and a ventilation–perfusion mismatch remain.*

INTRODUCTION

COMBINATION chemotherapy has improved the prognosis of patients with small cell carcinoma of the lung (SALC). More than 80% of the patients respond to treatment, irrespective of the stage of the disease. In patients with localized disease 40% obtain complete remission, and of these approximately half can expect a survival of more than 3 yr [1].

The predominantly perihilar location of most small cell lung cancers is known to cause a pattern of mixed restrictive and obstructive lung function reduction [2] and a reduction of the perfusion and ventilation of the affected lung [3]. Although the elements of restrictive and obstructive lung function reduction disappears in patients who obtain complete remission with normalization of the chest X-ray during combination chemotherapy, [4] neither this nor the chest X-ray are optimal to predict the prognosis of the patients.

The aim of this study was to characterize the ventilation V, the perfusion Q and the V/Q ratio in patients with small cell carcinoma of the lung who had obtained complete roentgenological remission 3 months after initiation of intensive chemotherapy.

MATERIALS AND METHODS

Patients

Twenty-five consecutive patients (median age 54 yr, range 47–68 yr) with histologically proven small cell carcinoma of the lung and a measurable lesion on the chest X-ray were included.

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The patients had a performance status of more than 2 according to the scale of WHO [5].

All the patients had been smoking more than 15–20 cigarettes a day for more than 20 yr. None of the patients had received treatment for chronic obstructive pulmonary disease or had chest surgery performed before the antineoplastic treatment. Pulmonary infections were treated with antibiotics prior to treatment.

Before the initiation of antineoplastic chemotherapy the extent of the disease was evaluated by a staging procedure including chest X-ray, bilateral bone marrow examination from the iliac crest and peritoneoscopy with liver biopsy.

A patient was evaluable if re-examination was possible 3 months after initiation of chemotherapy. That excluded six patients who died early in the course. Twelve of the 19 evaluable patients had CR, and in two patients no change was seen at the chest X-ray. Performance status according to WHO [5], age, sex and history of previous pulmonary diseases together with the smoking habits of the 17 responding patients are summarized in Table 1. In Table 2 the localization of the tumor, the results of the bronchoscopy before and 3 months after initiation of chemotherapy, the response to treatment and the survival of the patients are shown.

Table 1. Pretreatment data of the 17 responding patients

	Performance status	Age	Sex*	Prior pulmonary disease	No. of cigarettes per day
1	0	57	M	0	30
2	0	62	M	0	30
3	1	55	M	0	20
4	1	56	F	cold	20
5	0	67	M	0	30
6	1	64	M	0	15
7	1	69	M	0	30
8	1	50	F	0	20
9	2	60	M	0	20
10	2	49	M	0	15
11	1	48	M	0	40
12	2	61	M	0	20
13	1	51	M	0	20
14	1	41	M	0	20
15	0	53	M	0	20
16	1	64	M	0	20
17	1	57	M	0	20

*M: male; F: female.

Table 2. Results of treatment in 17 responding patients

	Affected lung*	Bronchoscopy I	Bronchoscopy II	Response	Survival	Ventilation; No. of quadrants Pre-treatment reduction	Ventilation; No. of quadrants Post-treatment improvements	Perfusion; No. of quadrants Pre-treatment reduction	Perfusion; No. of quadrants Post-treatment improvements
1	R	+	-	CR	305+	1	0	1	1
2	R	+	+	CR	243+	1	1	1	1
3	R	+	(no)	CR	248+	2	0	1	1
4	R	+	(no)	CR	330+	1	1	1	0
5	R	+	-	CR	545+	1	0	2	1
6	L	+	-	CR	555+	2	2	1	1
7	L	+	(no)	CR	492+	2	1	2	1
8	R	+	-	CR	300+	1	0	1	0
9	R	+	(no)	CR	582+	2	2	2	2
10	L	+	-	CR	308+	2	1	2	2
11	R	-	(no)	CR	245	1	1	1	1
12	L	+	-	CR	395	1	1	1	1
13	R	+	(no)	PR	275+	2	1	2	2
14	R	-	-	PR	245+	1	1	1	1
15	L	+	+	PR	260+	2	1	2	2
16	L	+	+	PR	260+	1	1	1	1
17	L	+	(no)	PR	153	2	2	2	2

*L: left; R: right. Bronchoscopy: I: before treatment; II: 3 months after initiation of treatment. +, tumor; -, no tumor.

Treatment

All the patients were randomized to one of five different combination chemotherapeutic regimens consisting of cyclophosphamide, vincristine, CCNU, methotrexate, adriamycin and VP-16 (Table 3). No chest irradiation was given.

Response evaluation

Based on the changes on the chest roentgenogram, the antineoplastic effect of the regimens were evaluated according to the recommendation given by WHO [5]: complete remission (CR): complete disappearance of all visible tumor tissue; partial remission (PR): decrease in the measurable lesion by more than 50%; no response (NR): less than 50% decrease of the measurable lesion; progressive disease (PD): more than a 25% increase of the measurable lesion.

Ventilation–perfusion scintillation

The scanning was performed by the means of a Searle LFOV gamma camera with 37 photomultiplier tubes and a parallel-hole high resolution collimator (140 Kev). The ventilation and perfusion of the lungs were investigated with a dual isotope technique described by Fazio and Jones [6] in an anterior and posterior projection. The ventilation scans were performed with ^{81m}Kr, which was inhaled through a mouthpiece connected to a one-way valve. Three hundred thousand counts were collected to produce the ventilation scan picture on Polaroid.

While the patient was still sitting in front of the gamma camera an injection of 3–4 mCi ^{99m}Tc microspheres was given intravenously. After a couple of minutes a dual isotope ventilation-perfusion scan was recorded on a Nuclear Data Med II computer in the two projections. Then the ^{81m}Kr supply was disconnected and a lung perfusion image was recorded on Polaroid, collecting 300,000 counts.

Spill-over of ^{81m}Kr gamma energy into the ^{99m}Tc window was less than 3%. The total time required for the examination was approximately 20 min, and the radiation dose absorbed in the lungs was calculated to be 105 mrad [7].

To analyse the regional lung function the analogue pictures of the lungs were divided into upper and lower quadrants.

Pulmonary function

Routine lung function tests were performed on the same day as the ventilation–perfusion study. The forced expiratory volume in one second (FEV_1), the forced vital capacity (FVC), the peak expiratory flow (PEF) and the midexpiratory flow (MEF_{50}) from the best of three flow volume curves were calculated. Vital capacity (VC), residual volume (RV) and total lung capacity (TLC) were measured with an He-dilution technique.

The carbon monoxide diffusion capacity (DL_{CO}) was measured by means of the single breath method. All DL_{CO} measurements were corrected according to haemoglobin concentration [9]. The measurements of VC, RV, TLC and DL_{CO} were performed in duplicate. The determinations of DL_{CO} were required to agree within 2 ml/min/mm Hg. If the first two determinations did not meet this requirement, further measurements were made until two such values were obtained.

Table 3. The chemotherapeutic treatment regimens

Regime 1	L				L			L			L													
	C		M		C		M	C		M	C													
	V	V	V	V	V			V			V													
Regime 2	L							L																
	C		M		A			C		M		A												
	V	V	V	V	E			V				E												
Regime 3	L				L			L			L													
	C		E		C		E	C		E	C													
	V	V	V	V	V			V			V													
Regime 4	L				L			L			L													
	C				C			C			C													
	VE	V	V	V	VE			VE			VE													
Regime 5	L							L			L													L
	C		M		C		E			M	C		E		C		M							
	V	V	V	V	V			V			V				V									V
					A			A							A									A
Weeks:	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!

Agents and doses: L = CCNU, 70 mg/m² p.o.; C = cyclophosphamide, 700–1000 mg/m² i.v.; V = vincristine, 1.3 mg/m² i.v. (max: 2 mg); M = methotrexate, 20 mg/m² p.o. (days 15 and 18); A = adriamycin, 30–35 mg/m² i.v.; E = VP-16-213, 100 mg/m² p.o. (days 1–4).

The observed values were expressed as % of predicted values [10]. The statistical analysis of the data from the trial was performed by using Student's t test for paired samples.

RESULTS

Three months after initiation of chemotherapy 12 out of 19 patients had obtained complete remission. Five patients obtained partial remission and in two patients no change was seen at the chest X-ray.

Ventilation and perfusion of the unaffected lung in patients obtaining CR

Prior to treatment only one patient had a defect of the unaffected lung on the ventilation and perfusion scan. This was situated in the lower quadrant and was sustained during treatment. After 3 months of combination chemotherapy the ventilation scans of all the patients remained unchanged, but four patients developed perfusion defects: two in the upper quadrant and two in the lower quadrant, resulting in a ventilation–perfusion mismatch.

Ventilation of the affected lung in patients obtaining CR

Before treatment the average ventilation of the affected lung was 30% of the entire ventilation and was significantly reduced ($P < 0.001$) compared to the unaffected lung. After treatment the average ventilation of the affected lung had improved by 38%. Though the improvement in ventilation of the affected lung was significant ($P < 0.01$), the ventilation was still decreased compared to the unaffected one, but not significant.

In Fig. 1 the ventilation of the upper (A) and lower (B) quadrants after treatment has been compared to the pretreatment values. Before treatment only three patients had a significantly reduced ventilation (less than 10%) of the upper quadrant (Fig. 1A), and although the average ventilation of the upper quadrant improved by 42% after treatment ($P < 0.001$), most of this improvement could be attributed to two of the patients whose pretreatment values had been significantly reduced.

The ventilation of the lower quadrant (Fig. 1B) was slightly more impaired than that of the upper. But again only four patients had significantly reduced values (less than 15%). After treatment the average ventilation of the lower quadrant improved by 35% ($P < 0.01$), but most of the improvement was seen among the patients whose pretreatment values had been significantly reduced.

Perfusion of the affected lung in patients obtaining CR

In Fig. 2 the perfusion of the upper (A) and lower (B) quadrants after treatment is compared to the pretreatment values.

Before treatment the perfusion of the upper quadrant was significantly reduced (less than 10%) in six patients. After treatment the average perfusion of the upper quadrant (Fig. 2A) improved by 21% (NS). Although the perfusion in three of the six patients whose pretreatment values had been significantly reduced improved by more than 10% 3 months after initiation of chemotherapy, the effect of the average perfusion of all 12 patients was counteracted by a similar decrease in perfusion among two of the patients whose pretreatment values had been normal.

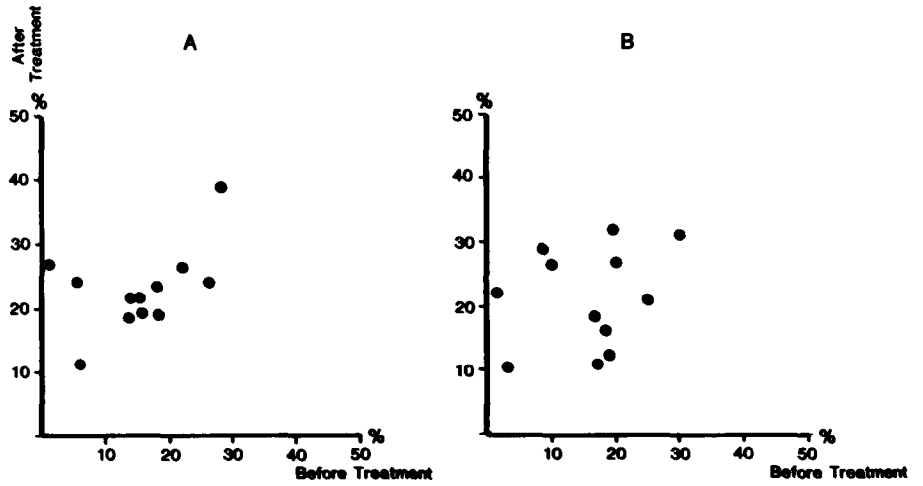

Fig. 1. The ventilation of the affected quadrant before and 3 months after initiation of treatment. A: upper quadrant; B: lower quadrant.

Seven of the 12 patients had a significant reduction of the perfusion (less than 15%) before treatment. After treatment the average perfusion of the lower quadrant improved by 43% ($P < 0.05$). As can be seen from the figure this improvement was limited to four of the 12 patients. The results of the remaining eight patients lie close around the line of identity.

The ventilation–perfusion ratio in the affected lung in patients obtaining CR

Prior to treatment the V/Q ratio of the upper quadrant of the affected lung varied between 0.15 and 2.93 (Fig. 3A). After treatment this variation had decreased (range: 0.7–1.8). Although the V/Q ratio of the lower quadrant (Fig. 3A) increased significantly in one patient and decreased significantly in another, the variation before and after treatment remained unaltered.

Survival rate in relation to ventilation and perfusion patterns

In Table 2 the survival of the 17 patients who obtained a response has been compared to the pattern of ventilation and perfusion before and after treatment. In the three patients who died after the termination of this study, no change was seen either in the ventilation or in the perfusion of the affected lung during treatment. This indicates that a relation between the survival and the improvements in the regional lung function may exist, but at present the data are inadequate to allow any conclusion.

Lung function

Table 4 shows the results of the measurements of the different lung function parameters before and 3 months after initiating of treatment in the 12 patients who obtained complete remission. Before treatment the TLC, VC and DL_{CO} values

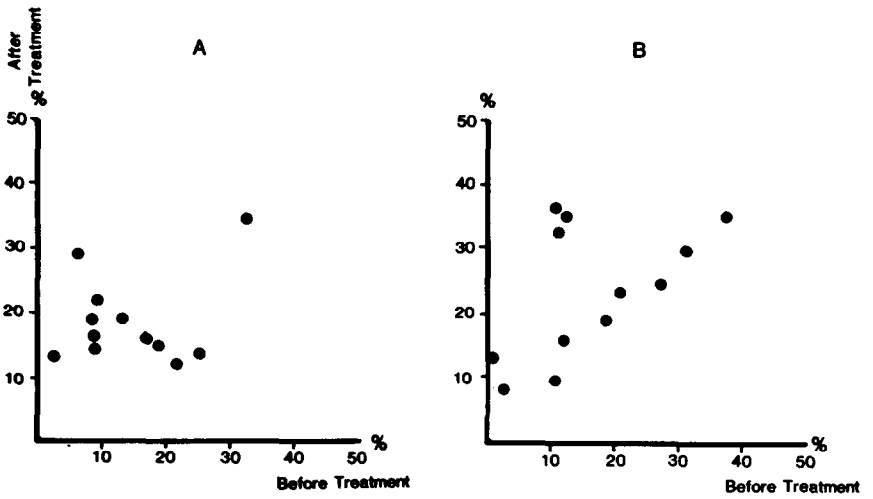

Fig. 2. The perfusion of the affected quadrant before and 3 months *after initiation of treatment. A: upper quadrant; B: lower quadrant.*

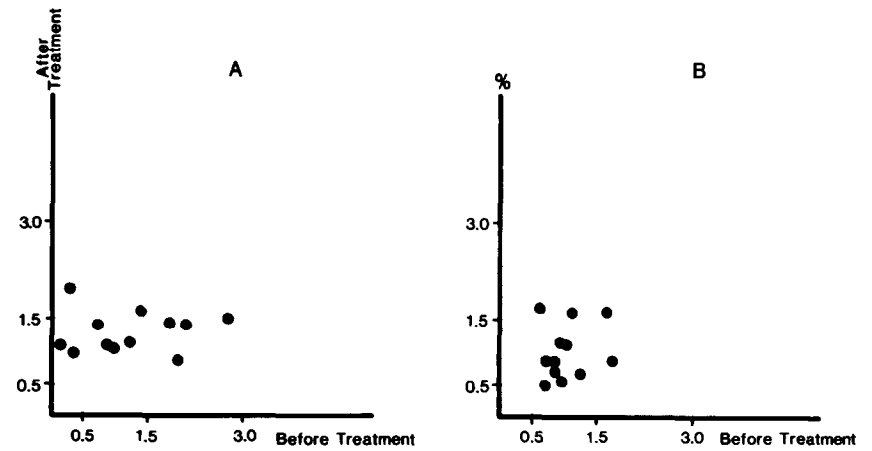

Fig. 3. The ventilation–perfusion ratios before and 3 months *after initiation of treatment. A: upper quadrant; B: lowr quadrant.*

Table 4. Lung function before and 3 months after initiation of treatment

	PEF		FEV_1		MEF_{50}		VC		RV		TLC		DL_{CO}	
	I	II	I	II	I	II	I	II	I	II	I	II	I	II
$\bar{x}$	4.21	5.30	1.76	2.12	2.04	2.33	2.80	3.25	1.73	2.19	4.54	5.43	13.14	13.11
S.D.	2.55	2.24	0.80	0.85	1.41	0.80	1.21	1.04	0.40	0.52	1.20	1.19	4.52	4.97
P	<0.01		<0.05		<0.2		<0.1		<0.005		<0.01		<0.5	

were almost equally reduced, as were the PEF, FEV_1 and the MEF_{50} values, thus indicating a presence of a mixed pattern of restrictive and obstructive lung disease.

Three months after initiation of treatment, TLC and RV had significantly improved ($P<0.01$ and $P<0.05$ respectively), resulting in an unchanged RV/TLC %.

The VC values did not improve significantly ($P<0.1$). A significant increase was seen in both PEF ($P<0.01$) and FEV_1 ($P<0.05$), while no increase was seen in MEF_{50} ($P<0.2$).

DISCUSSION

Improved therapeutic regimens for treatment of SALC have been obtained in recent years in terms of increased survival time and increased number of patients who obtain long-term disease-free survival. These results have intensified the need for a proper evaluation of quality of life. Estimations of lung function after treatment are valuable in this respect [4], and lung function studies might prove useful in combination with the clinical response to predict the individual prognosis. Three previous studies concerning lung function in patients with small cell bronchogenic carcinoma during combination chemotherapy have been published. Østerlind *et al.* [10] have shown that the peak flow of responding patients (complete and partial responders) rises, with a median of 70% compared to pretreatment values, making the group statistically inseparable from a healthy control group. In a previous study [4] the authors have evaluated a variety of lung function variables in patients with SALC and an almost normalization of the static volumes of the lungs and flow rates of the larger airways was found, while no change was seen in the variables reflecting the function of the small airways. In a comparable group of patients Bake *et al.* [11] have performed regional lung function studies with ^{133}Xe and found that patients obtaining complete remission and a long-term disease-free survival had no functional defects 3 months after initiation of chemotherapy. The pretreatment values reported by Bake *et al.* were almost identical to those found in this study, indicating that the deterioration of the pretreatment lung function in patients with small cell lung cancer was more pronounced than could be expected from the chest roentgenogram.

But contrary to the findings by Bake *et al.*, we found that even if a patient obtained complete remission during chemotherapy with disappearance of all signs of disease on the chest roentgenogram, a notable decrease remained in both ventilation and even more in the perfusion of the affected lung during the period of remission. This discrepancy can be explained by the fact that continuous tidal inhalation of the inert ^{81m}Kr gas results in an equilibration of the gas in the lungs which expresses the ventilation rather than the volume, while continuous tidal inhalation of ^{133}Xe expresses volume rather than ventilation [12]. The use of ^{99m}Tc microspheres provides a measure of fractional pulmonary blood flow, whereas intravenously given ^{133}Xe mainly quantifies pulmonary blood flow in the ventilated areas [13].

Prior to treatment one patient had a significant perfusion defect in the lower quadrant of the unaffected lung. After initiation of treatment a further four patients developed perfusion defects in the unaffected lung. The appearance of these perfusion defects during treatment may be explained by the fact that the perfusion pressure decreases in the unaffected lung as a consequence of treatment.

In a previous study using ^{131}I macroaggregated albumin, Garnett *et al.* [14] have shown that approximately 20% of patients with bronchogenic tumors have affected perfusion in the unaffected lung without any signs of tumor at the chest X-ray. By using ^{133}Xe radiospirometry, Lindell *et al.* [15] have shown that both ventilation and perfusion are decreased in patients with roentgenologically occult lung cancer diagnosed by sputum cytology. This indicates that major physiological changes are seen in regional lung function even before the tumor is detectable by chest X-ray.

As perfusion defects are seen in both chronic obstructive lung disease [16] and in patients with bronchogenic carcinoma, it is impossible to determine to what extent the perfusion defects are caused by the tumor, the presumed chronic obstructive lung disease or as a sequela to the antineoplastic treatment.

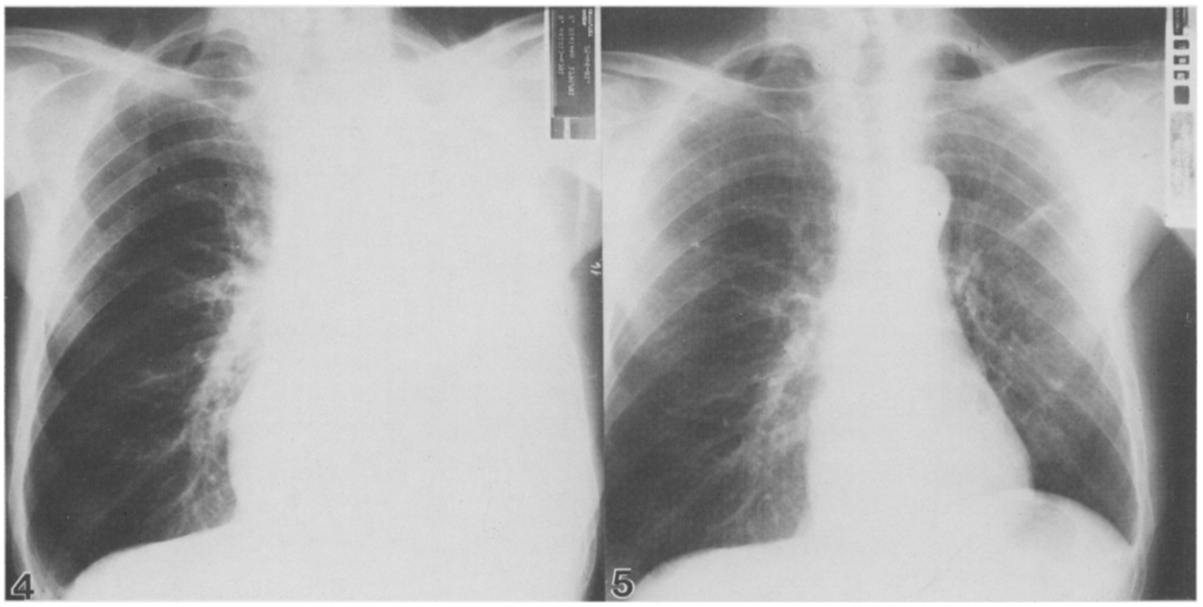

Fig. 4. Chest X-rays before treatment.
Fig. 5. Chest X-ray after obtaining of complete remission.

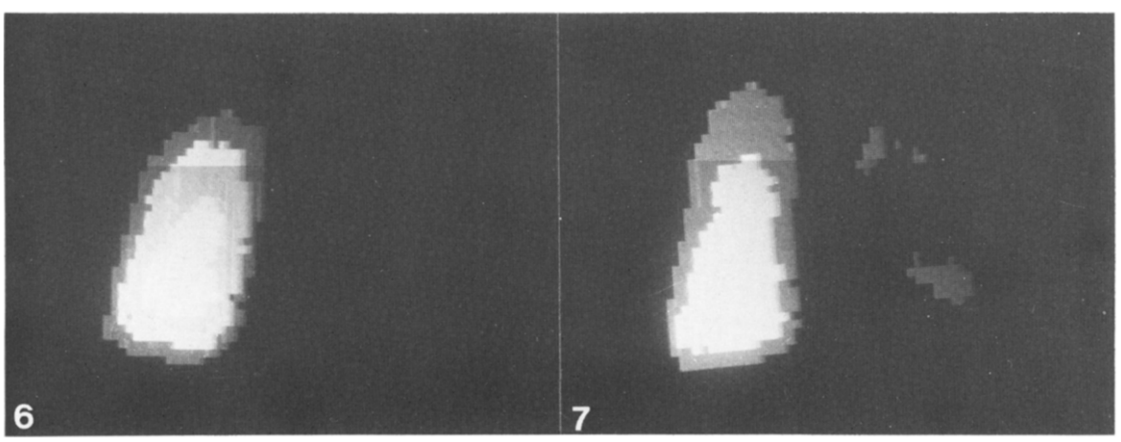

Fig. 6. Ventilation scan before treatment showing suspended ventilation of the affected lung.
Fig. 7. Ventilation scan after obtaining complete remission showing suspended ventilation.

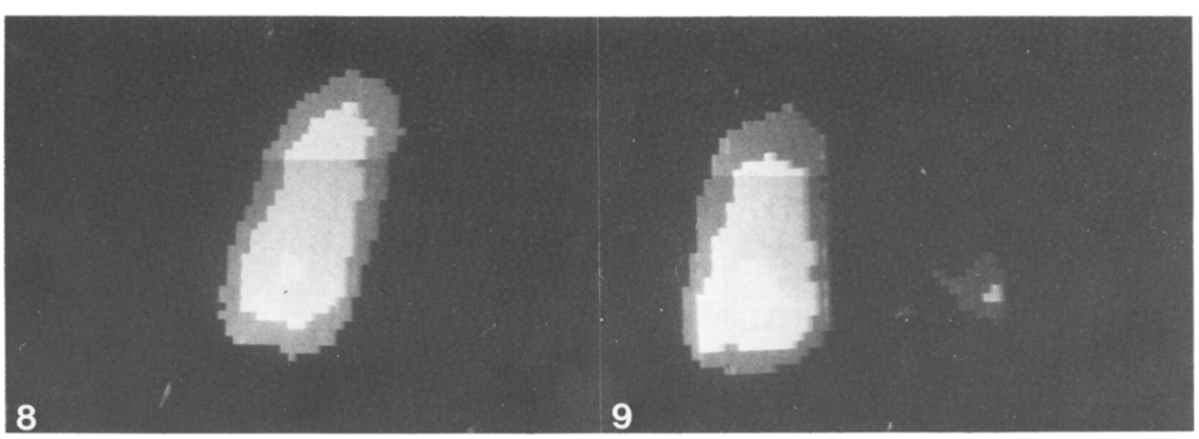

Fig. 8. Perfusion scan before treatment showing suspended perfusion of the affected lung.
Fig. 9. Perfusion scan after obtaining of complete remission showing suspended perfusion.

We found that even though a normalization of the conventional lung function variables and ventilation is seen in patients who obtain complete disappearance of the tumor on a chest X-ray, regional disturbances in perfusion often remain. Our data are inconclusive as to whether this can be used to predict the individual prognosis but are consistent with the fact that most of the patients are likely to relapse, and therefore it may be valuable to monitor the disease not only with a roentgenogram but also with regional lung function measurements.

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