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Regional Lung Function in Patients with a Complete Radiographic Regression of Small Cell Bronchogenic Carcinoma

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Abstract—*Regional lung function was studied in 21 patients with small cell bronchogenic carcinoma who demonstrated a complete radiographic regression of intrathoracic tumour after 3 months of combination chemotherapy. Spirometry was performed in 20 patients. VC and FEV_1 were, on average, 89 and 88% of predicted normal values. Impairment of ventilation and/or perfusion at the site of previous tumour was documented in 13 patients, while no such abnormalities were observed in 8 cases. Reduction of blood flow was generally more severe than impairment of ventilation. Neither median survival nor disease-free 2-yr survival was improved in patients with normal regional lung function compared to patients with functional impairment. This lack of survival advantage suggests that factors other than persistent tumour, such as scar formation, may contribute to reduction of regional lung function after chemotherapy for small cell bronchogenic carcinoma.*

INTRODUCTION

IN THE past decade considerable progress has been made in the treatment of small bronchogenic carcinoma (SCBC). With combination chemotherapy, partial or complete responses can be obtained in 80–90% of previously untreated patients, resulting in 3- to 5-fold prolongation of median survival and a disease-free 2-yr survival of the order of 5–10% [1].

Most small cell carcinomas originate from the major bronchi and could be expected to cause some disturbances of pulmonary function. In a previous study [2] it was found that pretreatment lung function was usually grossly abnormal in patients with centrally located SCBC and that radiographic tumour regression was paralleled by improvement of spirometric values and regional ventilation. Improvement of regional blood flow was less consistent. It was also apparent that a complete roentgenological response was not always accompanied by normalization of regional lung function.

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A complete radiographic response to treatment offers some prospects for prolonged disease-free survival, and pulmonary function in such patients merits interest since it may have considerable bearing on the quality of life. Many complete responders, however, harbour residual tumours which are not visible on chest films but may give rise to relapse later in the course of the disease. It may be asked if persistent abnormalities of regional lung function in complete radiographic responders could be attributed to residual tumour and thus herald an increased risk of relapse. The purpose of this study was to describe the functional status of a series of complete radiographic responders and to investigate the possible prognostic significance of persistent impairment of regional lung function.

MATERIALS AND METHODS

Patients

Between February 1979, and August 1981, 57 consecutive patients at Renströmska Hospital with SCBC were included in two cooperative prospective randomized therapeutic trials. Inclusion criteria consisted of a histologic diagnosis of SCBC, age below 70 yr, no other malignancy

and no previous treatment with irradiation or anticancer drugs.

Minimum staging procedures included a bilateral aspiration and biopsy from the posterior iliac crest. A bone scan was performed in all patients without other evidence of distant metastatic spread. A liver scan and/or percutaneous liver biopsy was made in patients with clinically suspected liver metastases. The disease was classified as limited if clinically detected tumour was confined to one lung, the mediastinum and supraclavicular lymph nodes. Patients with tumour involvement beyond this area were classified as having extensive disease.

After stratification according to performance status, patients were randomized to receive one of three 4-drug regimens for extensive disease [3] and one of two 6-drug regimens for limited disease, as detailed in Table 1. Neither chest nor brain irradiation were given.

Studies of lung function and bronchoscopy were performed in patients who had no radiographic signs of tumour or borderline roentgenograms after 3–4 months of treatment. The latter category contained cases with non-specific changes of possible post-inflammatory origin as well as cases in which differentiation between tumour and vascular structures was difficult. The results of bronchoscopic evaluation have been presented in a separate report [4].

In patients who were without obvious signs of disease progression after 1½ yr of therapy, bronchoscopy, lung function studies, bone scan and bone marrow examination were performed. Other initially positive examinations were repeated if possible. If no evidence of residual tumour was found, treatment was discontinued and the patients were re-examined at the outpatient clinic every 3 months.

Vital capacity (VC) and forced expired volume in 1 sec (FEV_1) were measured with a water-sealed spirometer [5].

Regional lung function was assessed using a ^{133}Xe technique [6]. The equipment, including the breathing circuit, has been described previously [2]. Briefly, the patients, in a supine position, were examined with four detectors in collimators placed underneath, facing the dorsal

Table 1. Drug dosage and schedule

	Extensive disease	
Regimen A		
Cyclophosphamide	1 g/m²	day 1, i.v.
CCNU	70 mg/m²	day 1, orally
Vincristine	1.3 mg/m²	day 1, i.v.
Methotrexate	20 mg/m²	days 15 and 18, orally
	day 29 = day 1	
Regimen B		
Cyclophosphamide	1 g/m²	day 1, i.v.
CCNU	70 mg/m²	day 1, orally
Vincristine	1.3 mg/m²	day 1, i.v.
Etoposide	70 mg/m²	days 15–18, orally
	day 29 = day 1	
Regimen C		
Cyclophosphamide	1 g/m²	day 1, i.v.
CCNU	70 mg/m²	day 1, orally
Vincristine	1.3 mg/m²	day 1, i.v.
Etoposide	70 mg/m²	days 3–6, orally
	day 29 = day 1	
	Limited disease	
Regimen A		
Cyclophosphamide	1 g/m²	day 1, i.v.
CCNU	70 mg/m²	day 1, orally
Vincristine	1.3 mg/m²	day 1, i.v.
Methotrexate	20 mg/m²	days 15 and 18, orally
Adriamycin	35 mg/m²	day 29, i.v.
Vincristine	1.3 mg/m²	day 29, i.v.
Etoposide	100 mg/m²	days 29–32, orally
	day 50 = day 1	

Table 1—*cont.*

Regimen B		
Cyclophosphamide	1 g/m²	day 1, i.v.
CCNU	70 mg/m²	day 1, orally
Vincristine	1.3 mg/m²	day 1, i.v.
Methotrexate	20 mg/m²	days 15 and 18, orally
Adriamycin	35 mg/m²	day 29, i.v.
Cyclophosphamide	700 mg/m²	day 29, i.v.
Vincristine	1.3 mg/m²	day 29, i.v.
Etoposide	100 mg/m²	days 43–46, orally
CCNU	70 mg/m²	day 57, orally
Adriamycin	35 mg/m²	day 57, i.v.
Vincristine	1.3 mg/m²	day 57, i.v.
Methotrexate	20 mg/m²	days 71 and 74, orally
Cyclophosphamide	1 g/m²	day 85, i.v.
CCNU	70 mg/m²	day 85, orally
Vincristine	1.3 mg/m²	day 85, i.v.
Etoposide	100 mg/m²	days 99–102, orally
Adriamycin	35 mg/m²	day 113, i.v.
Cyclophosphamide	700 mg/m²	day 113, i.v.
Vincristine	1.3 mg/m²	day 113, i.v.
Methotrexate	20 mg/m²	days 127 and 130, orally
CCNU	70 mg/m²	day 141, orally
Adriamycin	35 mg/m²	day 141, i.v.
Vincristine	1.3 mg/m²	day 141, i.v.
Etoposide	100 mg/m²	days 155–158, orally
	day 169 = day 1	

Maximum vincristine dose, 2.0 mg. In all regimens additional doses of vincristine (1.3 mg/m²) were given on days 8, 15 and 22 of the first 4-week cycle.

thorax, and four detectors placed above, facing the frontal thorax. Count rates from corresponding frontal and dorsal detectors were added by a pulse addition unit whereby four signals were formed. Only 81-keV pulses were accepted and fed via rate meters to a multichannel ink recorder (Rika Denki, Kogyo Ltd, Tokyo). The four fields covered almost all the lung parenchyma, each lung being represented by an apical and a basal region.

For determination of regional perfusion about 0.5 mCi of ^{133}Xe was injected intravenously at functional residual capacity (FRC) and flushed centrally by 20 ml saline solution during a short apnoea. The patient then inspired to total lung capacity (TLC) and held his breath for about 10 sec.

For determination of regional ventilation about 0.5 mCi of ^{133}Xe in 0.5 l of oxygen was slowly inhaled from FRC, followed by inspiration of air to TLC and apnoea for about 10 sec. Perfusion and ventilation determinations were repeated twice.

The regional count rates recorded at TLC after an injection or inhalation of ^{133}Xe were added with allowance for background activity and differences in calibration count rates. Regional results were expressed as a percentage of the sum. In addition, ventilation and perfusion of the side which harboured the tumour was calculated as a percentage of predicted normal values, assuming that the right lung contributed 52% and the left lung 48% of the total lung function [7].

RESULTS

Four of the 57 patients had undergone resectional surgery and had no evaluable chest lesions at the onset of chemotherapy. Among the remaining 53 patients, 47 were alive after 90 days of treatment (27/28 with limited disease, 20/25 with extensive disease). Twenty-two of the 47 patients had no radiographic evidence of tumour

or borderline roentgenograms, as judged from posteroanterior and lateral films. One of the 22 patients was exempted from study because of poor general condition and persistent abdominal pain, which proved to be due to metastatic cancer. The remaining 21 patients form the basis for the following presentation.

Pretreatment tumour localization

Bronchoscopy was carried out prior to treatment in 19 of the 21 patients. In 18 cases tumour was visible. Two patients had tumour growth in segmental bronchi, while the remaining 16 patients had partial or complete occlusion of lobar or more central bronchi. One patient (No. 10) with a rounded opacity near the left hilar area and a positive mediastinoscopy had normal bronchoscopic findings.

In two patients pretreatment bronchoscopy was not performed. One of them had an upper lobe atelectasis on the right side, indicating involvement of central bronchi. The other patient was a female with a peripheral tumour in the right upper lobe and mediastinal lymph node enlargement.

The tumour was classified as peripheral (no documented involvement of central bronchi) in 2 patients (Nos 10 and 13) and central in the remaining 19 patients.

Examination after complete radiographic regression

The median duration of treatment before radiospirometry was 104 days (range, 82–129 days). Spirometry was performed in 20 of the 21 patients. The median interval between spirometry and radiospirometry was 1 day (range, 0–9 days).

VC and FEV_1 were, on average, 89 and 88% of predicted normal values. In 15 patients VC and FEV_1 were within normal limits. Two patients had signs of general airways obstruction. A reduction of VC, possibly due to adhesions after a pleural effusion, was observed in one patient. In addition, borderline values of VC or FEV_1 were recorded in two patients.

Regional lung function data are shown in Table 2. In 8 patients, ventilation and perfusion on the affected side were $\geqslant$90% of the predicted normal ('normal regional function', NRF). In the remaining 13 patients these criteria were not satisfied ('impaired regional function', IRF).

One of the two patients with a peripheral tumour, as well as the two patients with pretreatment tumour growth in segmental bronchi, had normal regional function. Normal ventilation and blood flow were also observed in five patients with previous partial or complete occlusion of lobar or main bronchi. All NRF patients had their primary tumours located on the right side.

Table 2. Ventilation and perfusion of the affected lung and survival from start of treatment

Patient No.	Ventilation		Perfusion		Survival (days)
	3 months	18 months	3 months	18 months	
7	92	—	90	—	433
11	100	—	100	—	367
13	106	—	104	—	650
14	98	—	98	—	265
15	96	—	98	—	159
16	115	106	114	108	688+
17	96	—	104	—	540
20	112	—	98	—	428
1	110	—	85	—	443
2	83	—	71	—	352
3	89	90	77	69	742
4	94	88	75	77	675
5	90	81	88	75	994+
6	92	92	87	90	666
8	88	85	85	81	932+
9	90	—	79	—	251
10	100	98	85	100	992+
12	79	83	88	90	588
18	75	—	52	—	342
19	79	—	69	—	402
21	88	—	88	—	201

Regional lung function is expressed as a percentage of predicted normal values. Grouping is according to regional lung function.

In the IRF group all patients showed reduction of regional perfusion at the site of previous lung tumour. Seven patients also had impairment of ventilation in the same area. In all IRF patients except one, impairment of blood flow was at least as severe as reduction of ventilation.

Irregular patterns were observed in two patients with right-sided tumours who had some disturbance of regional lung function on the left side, possibly due to chronic obstructive pulmonary disease.

The relationship between regional lung function and bronchoscopic abnormalities at the site of previous tumour is displayed in Table 3.

Examination at 18 months

Eight patients were re-examined after 18 months of treatment. Relapse of the primary tumour was demonstrated by bronchoscopy in one patient and by tomography in another patient who had normal bronchoscopic findings. No evidence of residual tumour was found in the remaining six patients.

Deterioration of spirometric values was observed in two patients and could be explained by relapse detected at bronchoscopy in one patient and by increased airways obstruction in the other. In six patients the results were essentially unchanged.

Regional lung function (Table 2) showed a slight deterioration in one patient. Normalization of blood flow occurred in another patient. Both became disease-free 2-yr survivors. In the remaining six patients regional lung function was unchanged.

Survival

Of the six patients who were clinically disease-free at 18 months, one died 4 months later because of liver relapse. Autopsy showed persistent tumour in the right lung. Another patient died 20 months after onset of treatment because of brain metastases. There was no evidence of residual lung tumour at autopsy. The remaining four patients are currently alive and clinically disease-free after 994, 932, 992 and 688 days respectively.

There was no survival advantage for patients with normal regional lung function after 3–4 months of therapy. Median survival was 431 days (range, 159–597+ days) for NRF patients and 588 days (range, 201–994+ days) for IRF patients. The three disease-free 2-yr survivors and the patient who died at 20 months without signs of residual lung tumour all belonged to the latter group.

It may be argued that the definition of normal regional lung function is arbitrary and that other criteria may have permitted other conclusions. Attempts to establish a positive relationship between normal regional lung function and survival by other groupings or by calculation of correlations were, however, entirely negative.

When analysed with respect to prognostic factors, the groups appeared to be similar (Table 4). Hence there was no evidence that a preponderance of unfavourable prognostic factors in the NRF group could explain the lack of survival advantage.

The groups were also compared with respect to first site of relapse (Table 5), and the relapse patterns appeared to be similar.

Table 3. Regional lung function and bronchoscopic findings

Bronchoscopic abnormality	Regional lung function: Normal (n = 8)	Impaired (n = 13)
Nodules	5	6
Narrowing	3	9
Fibrous strands or membranes	0	2
Microscopic proof of cancer	2	1

Table 4. Prognostic factors

Prognostic feature	Regional lung function: Normal (n = 8)	Impaired (n = 13)
Mean performance status (WHO scale)	1.6	1.9
No. of patients with limited disease	6	5
No. of females	5	3
No. of patients without pretreatment weight loss	6	6
No. of patients below 60 yr of age	3	8

Table 5. First site of progression

	Regional lung function: Normal (n = 8)	Impaired (n = 13)
Chest	4	7
Outside chest	3	3
Alive without progression	1	3

DISCUSSION

As measured by spirometry, lung function was well preserved in this series of patients. In contrast to surgical lung cancer treatment, which

inevitably leads to permanent loss of lung function, or radiation therapy, which may be accompanied by the development of interstitial fibrosis, chemotherapy seems to permit a remarkably good preservation of lung function in SCBC patients who respond to treatment with a complete roentgenological regression. It follows that loss of lung function should usually not be a limiting factor for the resumption of normal activities in such patients.

The radiospirometric findings demonstrate that although normalization of regional lung function is often achieved, even in patients with extensive pretreatment tumour growth in central bronchi, many patients had some residual impairment of ventilation and blood flow at the site of the primary tumour. A consistent observation in this and a previous study [2] was that blood flow was more severely compromised than ventilation. The simplest explanation for this finding is that pulmonary vessels are more easily compressible than major bronchi.

One of the purposes of this study was to ascertain whether persistent abnormalities of regional lung function could be ascribed to residual tumour. If so, shorter survival and an increased risk of chest relapse could be expected in the IRF group. It was also thought that bronchoscopy could serve as a valuable aid in the interpretation of functional abnormalities.

It turned out, however, that while bronchoscopic abnormalities could easily be described and classified under the main headings of nodules, bronchial narrowing and fibrous strands or membranes [4], the explanation for such findings was less obvious. It became apparent that bronchial narrowing, a reasonable cause of impaired regional ventilation, could be due to both scar formation and persistent tumour. Survival figures and relapse patterns were, therefore, felt to be more useful guides to the interpretation of functional disturbances than bronchoscopy.

No improved survival figures were found for patients with normal regional lung function, and the rate of chest relapse was similar in the NRF and IRF groups. All patients among the original 53 cases who are to date disease-free 2-yr survivors had residual reduction of ventilation and/or blood flow at the site of previous lung tumour. Similar findings were obtained in the patient who died because of isolated CNS relapse 20 months after onset of therapy.

These data strongly suggest that factors other than persistent tumour may be responsible for impairment of regional lung function in SCBC patients with a complete radiographic tumour regression. With reference to bronchoscopic observations of cicatrization in such patients [4, 8], it is reasonable to propose a contributory role of scar formation around bronchi and vessels.

It is interesting to hypothesize whether such a tissue reaction actually increases the likelihood of long-term survival. It may be speculated that 'areactive' tumour regressions are associated with a less favourable prognosis. Because of the small number of 2-yr survivors in this series of patients, our study does not provide any answer to this question. Further studies would be of interest to elucidate the possible role of tissue response for long-term survival in small cell bronchogenic carcinoma.

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