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Bronchoscopic Findings in Patients with a Complete Radiographic Regression of Small Cell Bronchogenic Carcinoma

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Abstract—*Fibre-optic bronchoscopy was performed in 21 patients with small cell bronchogenic carcinoma who demonstrated a complete radiographic regression of their chest lesions after 3–4 months of combination chemotherapy. Fifteen patients showed abnormalities at the site of the original tumour consisting of nodular elevations, narrowing of bronchi and/or fibrous strands or membranes. Microscopic evidence of residual cancer was obtained in 3 cases. In 3 out of 8 patients who underwent a further bronchoscopy after 18 months of treatment, disappearance of nodules was noted at the later examination. Persistent bronchial narrowing was observed in patients who became disease-free 2-yr survivors. It is concluded that tumour regression may be accompanied by scar formation, which complicates the interpretation of post-treatment abnormalities, and that further regression of intrabronchial lesions may occur beyond 3–4 months.*

INTRODUCTION

SMALL CELL bronchogenic carcinoma (SCBC) is highly responsive to combination chemotherapy. With suitable treatment regimens, partial or complete responses are achieved in more than 80% of previously untreated patients. The majority of responders will, however, suffer a relapse of the disease, usually within 2 yr from onset of therapy, and the number of 2-yr disease-free survivors remains in the order of 5–10% [1].

Relapse of intrathoracic tumour is a common ocurrence, even in patients who respond to chemotherapy with a complete radiographic regression of chest lesions. Ihde and co-workers found bronchoscopy to be of value for obtaining prognostic information in patients with a complete roentgenological response [2]. Their study does not, however, provide a detailed presentation of the macroscopic features after therapy. Bye and associates described scar formation in the bronchial tree after chemotherapy for SCBC [3]. Preliminary observations at this department suggested that the interpretation of bronchoscopic findings might be more difficult after chemotherapy than in untreated patients. The present study was designed to describe and classify bronchoscopic abnormalities in patients with a complete radiographic response to chemotherapy and to examine their possible prognostic significance.

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MATERIALS AND METHODS

Between February 1979 and August 1981 57 patients at Renströmska Hospital with SCBC were included in two cooperative prospective randomized therapeutic trials [4]. Eligibility criteria consisted of a histologic diagnosis of SCBC, age below 70 yr, no other malignancy and no previous treatment with irradiation or anticancer drugs.

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

After stratification according to performance status patients were randomized to receive one of three four-drug regimens for extensive disease, as

detailed elsewhere [4], and one of two six-drug regimens for limited disease (cyclophosphamide, CCNU, vincristine, methotrexate, doxorubicin, VP16-213). Neither chest nor brain irradiation were given.

Bronchoscopy and studies of lung function 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. Lung function data will be presented in a separate forthcoming publication.

In patients who were without obvious signs of disease progression after 18 months of therapy bronchoscopy, 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.

A flexible fibre-optic bronchoscope was used (Olympus BF B2 or BF 1T). After premedication of the patient with morphine-scopolamine and local anaesthesia with 1% tetracaine the instrument was introduced through the mouth or the nasal cavity. Visual inspection of the larynx, vocal cords, trachea, carina and the bronchial tree, if possible until the subsegmental level, was performed. Biopsies for histopathologic examination were take from suspicious lesions or from areas of previous tumour involvement. Brushings were not routinely obtained. Abnormal findings were documented photographically. All but two bronchoscopic procedures in this study were performed by the author.

For the purpose of this analysis all bronchoscopic reports and all photographs were reviewed. The presence or absence of the following macroscopic abnormalities at the site of the original tumour were recorded: (1) nodules, i.e. well circumscribed, white, yellow or pinkish elevations with an estimated diameter of 1–5 mm; (2) intrabronchial tumour of larger size; (3) narrowing of bronchial lumen; and (4) fibrous strands or membranes, giving rise to complete or partial bronchial occlusion.

The findings at bronchoscopy after 3–4 months had no influence on the subsequent treatment. Survival was calculated from the first day of therapy.

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 border-line 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 reamining 21 patients form the basis for the following presentation.

Pretreatment findings

Nineteen of the 21 patients had undergone at least one bronchoscopy prior to treatment. Several of these examinations were carried out at other institutions. In one patient (No. 10) no abnormalities were observed. In the remaining 18 patients the report indicated tumour growth in segmental (2 cases) or more central bronchi. Biopsies were positive for tumour in 12 cases.

In two patients pretreatment bronchoscopy was not performed. One of them had an atelectasis of the right upper lobe. The other patient (No. 13) had a peripheral tumour in the right upper lobe and mediastinal lymph node enlargement.

Evaluation after complete radiographic regression

The median duration of treatment before bronchoscopic re-evaluation was 107 days (range, 89–133 days). The findings of this examination are summarized in Table 1. Eleven patients had nodules at the site of the original tumour. Larger intrabronchial tumours were not observed. Narrowing of bronchi (Fig. 1) was recorded in 12 cases and 2 patients showed fibrous strands or membranes (Fig. 2). In 6 patients the bronchial tree appeared completely normal. Three of them had extensive pretreatment tumour growth in central bronchi.

Biopsies demonstrated persistent cancer in 3 patients. One of them had no macroscopic signs of residual tumour. Malignant cells were found in bronchial washings in 2 cases. Both had positive biopsies.

Examination at 18 months

Eight patients were re-examined after 18 months of treatment (Table 2). Progression of intrabronchial tumour was observed in one patient. Biopsies were positive for cancer and washings contained atypical cells with prominent regressive changes, raising the suspicion of malignancy. In the remaining 7 patients no evidence of persistent cancer was found at bronchoscopy. One of them had residual tumour, which was demonstrated by conventional tomo-

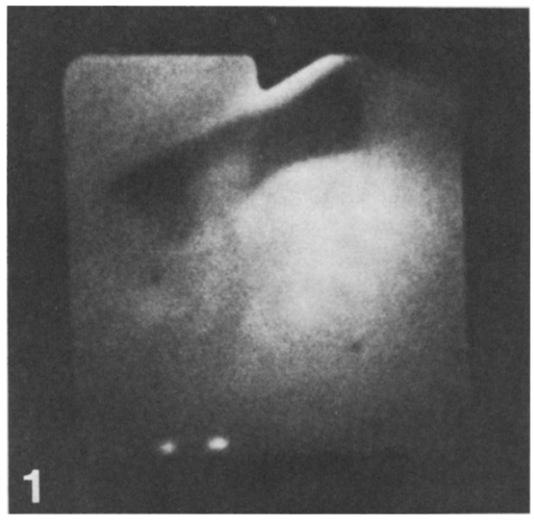

Fig. 1. *Irregular narrowing of right upper lobe bronchus, unchanged at* 18 months (*Pat. No.* 16).

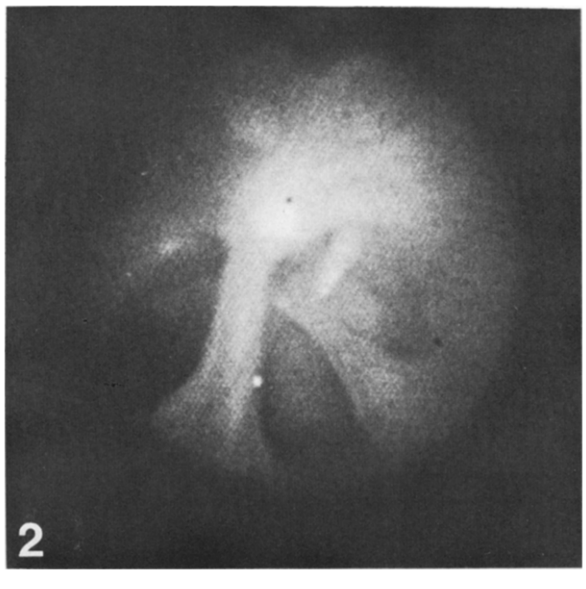

Fig. 2. *Fibrous strands across the orifice of the left lower lobe bronchus* (*Pat. No.* 19).

Table 1. *Findings at bronchoscopy after* 3–4 months *of treatment*

Pat. No.	Nodules	Narrowing	Fibrous strands or membranes	Microscopy Washings	Microscopy Biopsies	Survival (days)
1	–	–	–	–	–	443
2	+	+	–	–	–	352
3	–	–	–	–	–	742
4	+	+	–	–	–	675
5	–	+	–	–	–	994+
6	+	+	–	–	–	666
7	+	+	–	+	+	433
8	+	+	–	–	–	932+
9	–	+	–	–	–	251
10	–	–	–	–	0	992+
11	+	–	–	–	–	367
12	+	+	+	–	–	588
13	–	–	–	–	0	650
14	+	–	–	–	–	265
15	+	–	–	–	–	159
16	–	+	–	–	–	688+
17	+	+	–	–	–	540
18	+	+	–	+	+	342
19	–	+	+	–	–	402
20	–	–	–	–	+	428
21	–	–	–	–	–	201

0 = Biopsies not performed.

graphy. The other 6 patients were judged as clinically disease-free and treatment was discontinued.

Three of the six patients showed regression since the three-month examination. All had nodules after 3–4 months which had disappeared at 18 months. Regression of carinal widening was noted in one patient. In one case the disappearance of nodules was accompanied by the development of a fibrous membrane occluding a segmental orifice. Narrowing of bronchi was essentially unchanged.

Survival and relapse pattern

The prognostic impact of nodular change was examined by comparing survival for patients with and without nodules. Survival was similar in both groups. Median survival for patients with nodules was 433 days (range, 159–901+ days) and for patients without nodules 547 days (range, 201–994+ days).

When compared with respect to prognostic factors (Table 3) the groups appeared to be similar. The groups were also compared with respect to relapse pattern. There was no evidence that the presence of nodules predicted an increased risk of intrathoracic tumour recurrence (Table 4). Among 11 patients who experienced relapse of intrathoracic disease the median time from bronchoscopy to chest relapse for patients with nodules was 210 days (range, 111–447 days) and for patients without nodules 174 days (range, 39–467 days).

The group of patients with microscopically proven residual tumour was too small to permit meaningful conclusions. Survival for these patients was 342, 433 and 428 days respectively.

Four patients are currently alive and clinically disease-free after 994, 932, 992 and 688 days respectively. Three of them had irregular narrowing of lobar bronchi after 3 months. One also had nodules at the 3-month examination which had disappeared at 18 months.

DISCUSSION

In untreated patients with SCBC white tumour nodules, sometimes in a 'cobblestone' pattern, are a common bronchoscopic finding [5]. The presence of nodules after 3–4 months of therapy therefore seemed to be a reasonable indicator of persistent tumour. It should be noted, however, that no proof was obtained that all such nodules actually contained viable tumour cells. Some nodules may well represent remnants of previous tumour undergoing slow resolution while other nodules may be due to persistent cancer. This may, at least in part, explain why the presence of nodules at 3–4 months did not predict a shorter survival or an increased risk of chest relapse in this series of patients. Other explanations may be related both to the presence of small amounts of residual intrathoracic tumour in areas not accessible to bronchoscopic examination in some of the patients without nodules and to the small size of the patient sample.

Table 2. Findings at bronchoscopy after 18 months of treatment

Pat. No.	Nodules	Narrowing	Fibrous strands or membranes	Microscopy Washings	Biopsies
3	-	+	-	-	-
4	+	+	-	(+)	+
5	-	+	-	-	-
6	-	+	+	-	-
8	-	+	-	-	-
10	-	-	-	-	0
12	-	+	+	-	-
16	-	+	-	-	-

(+) = Suspicion about malignancy.

Table 3. Prognostic factors for patients with and without nodules

Prognostic feature	Nodules ($n = 11$)	No nodules ($n = 10$)
Mean performance status (WHO scale)	2.0	1.6
No. of patients with limited disease	5	6
No. of females	4	4
No. of patients without pretreatment weight loss	6	6
No. of patients below 60 yr of age	7	4

Table 4. First site of relapse

	Nodules ($n = 11$)	No nodules ($n = 10$)
Chest	4	7
Outside chest	6	0
Alive without progression	1	3

Other macroscopic abnormalities are obviously even less reliable as signs of residual intrathoracic tumour. The presence of persistent irregular bronchial narrowing in disease-free 2-yr survivors suggests that such narrowing is a non-specific finding which may be caused by scar formation as well as by incomplete tumour regression. Such scarring and the occurrence of fibrous strands and membranes are in accordance with observations by Bye and associates, who found that regression of SCBC under chemotherapy may be accompanied by cicatrization [4].

A disconcerting feature in the study was the low rate of positive biopsies and washings. While the first site of relapse was intrathoracic in 11 patients, thus indicating the presence of persisting chest tumour, microscopic proof of such tumour presence was obtained in only 3 patients. The number of positive biopsies and washings (3/21, 14%) is, however, in good agreement with data from Ihde and co-workers, who found microscopic evidence of tumour in 13 out of 81 (16%) bronchoscopic procedures performed on 38 patients with a complete radiographic response [2].

The difficulty in obtaining microscopic confirmation of residual tumour may be related to extrabronchial tumour location in some patients and to technical problems in other cases. It was often difficult or impossible to grasp minor nodules on the bronchial wall with the biopsy forceps. Bronchial brushings may offer some advantage in this context. If persistent tumour is confined to deeper layers of the bronchial wall superficial biopsies undertaken with small forceps may be inadequate. Transbronchial needle aspiration biopsy, not employed in this study, may be of value in overcoming this difficulty.

The time for the bronchoscopic evaluation was based on the observation that maximum tumour response is achieved within 3 months from the start of combination chemotherapy in the majority of SCBC patients. In one study maximum tumour regression in 26 patients responding to treatment with cyclophosphamide, CCNU and methotrexate was always obtained by 6 weeks [6]. The corresponding figure in an investigation of cyclic alternating combination chemotherapy by the same authors was 12 weeks [7]. Bronchoscopic confirmation of complete response was required in these studies but it is not stated if bronchoscopy was used for evaluation of time to maximum response. Later reports indicate that longer periods of treatment may be needed in occasional patients for the achievement of maximum tumour response [8, 9].

In the present study it was apparent from observations in patients who were re-examined at 18 months that maximum bronchoscopic tumour response had not always been obtained after 3–4 months of therapy. Three patients demonstrated nodular elevations which had disappeared at the 18-month examination. In one patient regression

of carinal widening was noted. Serial bronchoscopic examinations with photographic documentation at predetermined intervals are needed to provide more detailed information about the course of intrabronchial disease. Such information may be of importance for decisions on when to perform restaging procedures for assessment of complete response. It may also affect considerations about the optimal duration of chemotherapy for small cell bronchogenic carcinoma.

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