Europ. J. Cancer, Vol. 16, pp. 527–531

0014-2964-80/0401-0527 $02/00/0

Long-Term Survivors with Small Cell Carcinoma of the Lung

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INTRODUCTION

PHYSICIANS concerned with the treatment of lung cancer have had little basis for encouragement. The relatively recent identification of greater responsiveness to chemotherapy and radiation therapy of small cell carcinoma as compared to other histologic types of lung cancer has generated many clinical trials. Hopes have been stimulated that the dismal outlook of patients with these tumors will be altered. Noticeable gains in median survival are being reported in non-resectable disease [1–4]. Documentation of clinical and pathologic features in patients with small cell carcinoma of the lung who survive more than 2.5 yr was initiated in an effort to identify factors, including modes of therapeutic intervention, associated with favorable outcome.

MATERIALS AND METHODS

Following a meeting sponsored by the Cancer Therapy Evaluation Program, National Cancer Institute in May 1977, members of the International Association for the Study of Lung Cancer were invited to submit histologic slides and basic clinical information on patients with small cell carcinoma of the lung who had survived more than 2.5 yr [2, 5]. The cut-off was selected arbitrarily as an intermediate figure designed to eliminate the relatively few patients that might be alive with persistent disease at 2 yr, while still permitting contributions from trials which had been initiated in the past several years. Slides and clinical information were forwarded to one of us (M.J.M.). Upon verification of the pathology, the clinical information was analyzed and various features such as geographic source of material, sex and age of patient, histologic subtypes, location of biopsy material, known location of disease at onset, therapeutic modalities and eventual outcome were catalogued.

Almost all slides have been reviewed by Dr. R. Yesner (Yale University Medical School, New Haven, CT). In addition, a panel of pathologists including Drs. D. Carter (Yale University Medical School, New Haven, CT), J. Eggleston (Johns Hopkins University Hospital, Baltimore, MD), M. Janis (Albert Einstein College of Medicine, Bronx, NY) and A. Gazdar and L. Ortega (V.A. Medical Center and George Washington University School of Medicine, Washington, DC) has reviewed slides presenting diagnostic difficulties.

Pathologic diagnoses used in this study were made according to the classification proposed by the pathology panel of the Working Party for Therapy of Lung Cancer [6]. Subtypes include the classic lymphocyte-like or oat-cell type (21) and intermediate forms, i.e., polygonal, tubular or fusiform variants (22). Tumors containing both components were classified as No. 21/22. Some tumors showed components of intermediate small cell and anaplastic large cell carcinoma and have been classified as subtype 22/40. One tumor showed both a small cell carcinoma and an epidermoid carcinoma and has been classified as a combined tumor, subtype 23.

Accepted 26 July 1979.
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RESULTS

Data have been received on 121 patients. Of these, 24 are not evaluable at present because representative slides were not available for review (thirteen), lack of verification of original diagnosis by the pathology panel (seven) and/or ineligibility because of lack of confirmation of 2.5-year survival (four).

The majority of patients (70%) were from the U.S.A. or Canada (Table 1). There was no evidence of variation in diagnosis by cell type according to geographical distribution. There were pronounced differences in the dates of diagnosis according to country of origin. Thus, diagnosis was made prior to 1970 in 21% of the U.S.A. patients and in 69% of the Japanese patients.

Table 1. *Source of material*

Country	No. of patients
U.S.A.	47
Canada	20
Japan	15
Poland	8
Miscellaneous	7
Total	97

The mean age of the patients at diagnosis was 56 years, with a range from 30 to 80 years; 78% of the patients were male. There was no apparent relationship between age or sex and cell subtype. Among the evaluable patients, the most frequent diagnosis was subtype 22 (45%), followed by subtype 21 (28%), subtype 21/22 (16%), subtyoe 22/40 (10%) and subtype 23 (1%). A carcinoid pattern was encountered in six cases, associated in five with subtype 22 and in one with subtype 22/40.

Table 2 summarizes the treatment modalities and the patients' status at the time of report. Surgery either alone (24%) or with adjuvant therapy (21%) was the primary treatment modality in 44 patients. Six of the 23 patients treated by surgical intervention alone subsequently received radiotherapy and/or chemotherapy for recurrences. Radiotherapy was given either alone (20%) or with chemotherapy (25%). Of note, 8 patients received chemotherapy alone, including one patient who received cranial irradiation at 6 months because of a positive brain scan. One patient whose initial diagnosis was 'possible lymphoma' received no antitumour treatment during life and had widespread small cell tumor at autopsy.

Of the 96 treated patients, 53 were alive at the time of report (Table 2). Recurrent disease was noted in 21/96 patients. Eight of these patients died with disease within 30–33 months of diagnosis and one was alive with disease at 34 months. Recurrent disease was noted in 10 other patients within 36–51 months. Two patients treated by surgery alone succumbed to recurrent disease at 8 and 9 years respectively.

Incomplete information is available on the extent of disease at presentation. The overwhelming majority of patients presented with regional disease confined to the lung and/or ipsilateral chest, with or without cervical lymph node involvement (Table 3). Staging of disease at time of diagnosis is impossible to document. However, of the 44 surgically resected patients, at least 12 (27%) had positive broncho-hilar lymph nodes and 3 (7%) had mediastinal lymph nodes identified at surgery. One patient in this surgical group was considered to have extensive disease on the basis of central nervous system involvement. Of the

Table 2. *Treatment modalities and patient status*

Treatment	Number of patients		
	Total	Alive (ED)*	Deceased (ED)*
Surgery	44 (45%)	24 (1)	20 (11)
alone	23	13 (1)	10 (6)
+radiotherapy	8		8 (4)
+chemotherapy	11	9	2 (1)
+radio- and chemotherapy	2	2	
Radiotherapy	44 (45%)	22 (2)	22 (7)
alone	19	10 (1)	9 (1)
+chemotherapy	25	12 (1)	13 (6)
Chemotherapy alone	8 (9%)	7	1
No therapy	1 (1%)		1 (1)
Total	97 (100%)	53 (3)	49 (19)

*(ED)=No. of patients with evidence of disease.

Table 3. Treatment modalities and extent of disease at diagnosis

		No surgery	
	Surgery*	Radiotherapy†	Chemotherapy
No. of patients	44	44	8
Extent of disease			
Regional	43	41	4
Extensive	1	3	4
Lymph nodes			
Broncho-hilar	12	6	
Mediastinal	3	8	2
Cervical		6	2
Other sites			
CNS	1		1
Liver, bone marrow		1	
Bone (scan+)		1	2
Subcutaneous		1	
Transcarina			1

*Surgery with or without other treatment modalities.
†Radiotherapy alone or with chemotherapy.

Table 4. Treatment modalities and survival beyond 5 and 10 years

	No. of patients surviving at		
Treatment	Total evaluable	5 yr	10 yr
Surgery	44	18 (16)	14 (10)
alone	23	8 (6)	6 (6)
+radiotherapy	8	3 (3)	4
+chemotherapy	11	6 (6)	4 (4)
+radio- and chemotherapy	2	1 (1)	
Radiotherapy	44	10 (6)	1 (1)
alone	19	7 (5)	1 (1)
+chemotherapy	25	3 (1)	
Chemotherapy alone	8	1 (1)	
Total	96	29 (23)	15 (11)

( )=No. of patients at risk.

44 patients who received radiation therapy alone or with chemotherapy, 20 (45%) presented with thoracic or cervical lymph node metastases. Three patients in this group were considered to have extensive disease on the basis of positive bone scan (one), subcutaneous nodule (one) and positive bone marrow and liver biopsies (one). Four of the 8 patients receiving chemotherapy alone were considered to have extensive disease on the basis of bone scans (two), transcarinal disease (one) and central nervous disease, diagnosed by craniotomy (one).

Of the 96 treated patients, 29 (30%) survived over 5 years and 15 (15%) over 10 years among these 15, 11 (73%) were still alive at the time of report (Table 4). The longest survivor was treated by surgery alone and was alive 15.7 years from the date of diagnosis. There was no difference in survival according to cell subtype.

The length of survival varied with different types of treatment, probably reflecting the role of earlier stage of disease at diagnosis and the modalities of therapy used over the past two decades. Of the 44 patients who underwent surgery, 18 (41%) survived over 5 years; 14 survived 10 years and 10/14 were alive at report. Of the 44 patients receiving radiotherapy with or without chemotherapy, 10 (23%) survived over 5 years, 6/10 are still at risk and one of these has survived over 11 years. Only one patient receiving chemotherapy alone has passed the 5-year interval; however, all but one of the 8 patients receiving chemotherapy were alive at last report.

The patient diagnosed by craniotomy was alive 3.7 years later. It is not known whether this patient received cranial irradiation.

DISCUSSION

A registry of long-term survivors provides a very indirect measure of effectiveness of therapy in a given disease process. Nevertheless, it does establish a data base for analyzing factors associated with favorable outcome, including documentation of favorable effects of therapy. A similar registry in leukemia not only established the independence of cure from the morphology of the leukemia but identified the ability to stay in complete remission following therapy as the single most important prognosticator of long-term survival [7].

In patients with small cell carcinoma of the lung with a favorable outlook, certain interesting points have been observed in this preliminary analysis: (1) Special histologic subtypes do not appear to account for long term survival, their distribution being roughly similar to Dombernowsky's staging series [8]. (2) Stage at presentation is obviously important; however, some patients with metastatic disease achieve long-term disease free survivals. (3) Survival over 5 years offers some hope of freedom from disease. Only rare relapses were recorded beyond this interval. This tends to substantiate the report by Brigham *et al.* [9] who estimated that the doubling time of small cell carcinoma of the lung ranges from 26 to 160 days, with a median of 77 days, suggesting that these tumors have an intermediate to slow growth pattern. Doubling times of these lengths predict that highly effective therapy which reduces tumor burden to a level approaching one cell, but which does not eradicate the last cell, might be followed by disease free intervals of 4–5 years before clinical recurrence (i.e., >20 doublings). Thus, they suggested that the likelihood of a so-called "cure" should not be entertained in patients with disease free intervals under this time level. (4) Chemotherapy trials in recent years have yielded prolonged survivals. Longer follow-up is needed to fully assess the ultimate impact of this treatment modality. (5) Surgery in appropriately staged candidates may provide meaningful survival to a subset of patients with small cell carcinoma.

We hope that additional contributions to the Registry and their subsequent analyses will indicate important parameters associated with long-term survival and will document the potential for increasing the salvage of patients with disseminated disease.*

*This survey concerns only patients with small cell carcinoma of the lung who have survived at least 2.5 years from time of histologic diagnosis. All investigators interested in contributing to this Registry are invited to send a representative slide of diagnostic pathology obtained prior to treatment (or at surgery) to Dr. Mary Matthews, NCI-VA Medical Oncology Branch, Veterans Administration Medical Center, 50 Irving Street, N.W., Washington, DC 20422, U.S.A.

The following information should accompany this material:

1. Patient's name, social security number or hospital registration number, sex and age at diagnosis.
2. Initial pathologic diagnosis: date specimen taken and source: a. Lung (specify lobe): b. Bronchus (specify); c. Pleura; d. Liver; e. Bone; f. Brain; g. Lymph node (specify); h. Other (specify).
3. Other known site of disease at time of initial diagnosis.
4. Mode of therapy: Surgery alone; radiotherapy alone; chemotherapy alone; combinations (specify). Anticancer agents used.
5. Date last known alive. Date of death if no longer alive. Was the patient free of disease when last seen? Results of autopsy if available.
6. Name of Principal Investigators; department; hospital; address.

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