Eur J Cancer Clin Oncol, Vol. 24, No. 4, pp. 749–752, 1988.
Printed in Great Britain

0277–5379/88$3.00+0.00

Long-term Survival in Small Cell Carcinoma of the Lung

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Abstract—*A series of* 1019 *patients with small cell carcinoma of the lung, treated at the Department of Radiotherapy and Oncology at the Helsinki University Central Hospital during the period* 1963–1982, *included* 19 *patients who survived for* 5 *years or more after the diagnosis. The clinical data of these patients were retrospectively studied in order to elucidate factors which may have contributed to the more favourable outcome.*

All of the 5*-year survivors were previously untreated, and all had a good performance status at the time of diagnosis. In* 95%, *the disease was limited to one hemithorax, and* 74% *had a stage I or II tumour. All treatment modalities, except immunotherapy, were used during the two decades. Surgery alone, or with adjuvant radiotherapy, and/or chemotherapy, was the primary treatment in eight of the long-term survivors* (42%). *Chemotherapy, either alone or in combination with radiotherapy, was the primary treatment in* 10/19 (53%) *patients and radiotherapy alone was given to one of the* 5*-year survivors. The objective response rate to the primary treatment was* 100% *and complete response was achieved in* 95%. *There were seven carcinoma related deaths after* 5*-year disease-free survival. The first site of relapse was the central nervous system in three cases and the liver in three cases. Acute myocardial infarction was the cause of death in five patients. One patient died of the other carcinoma and six are still alive with no evidence of SCCL.*

In conclusion, a good performance status at diagnosis, no pretreatment weight loss, the extent of disease and good response to the primary treatment appeared to be prognostically important in the present study. Some patients with very limited disease may benefit from primary treatment comprising surgery and adjuvant chemotherapy.

INTRODUCTION

In 1959 small cell carcinoma of the lung (SCCL) was definitely established as a special type of lung cancer, histologically separable from other, 'non-small cell' carcinomas of the lung [1]. Since that time, SCCL has been considered the most rapidly progressing form of lung cancer with extremely poor prognosis. When untreated, the median survival time after diagnosis of SCCL is 1–3 months [2]. Because of the high frequency of systemic metastases at the time of diagnosis, prolonged survival is also rare in actively treated patients. During the past 10 years, combination chemotherapy (CT) has produced objective tumour regression in as many as 70–90% of the patients with SCCL, and a median survival time of 8–15 months has been achieved [3, 4]. Only a small proportion of patients survive 2 years or longer [5]. As an analysis of such long-term survivors might provide insight into factors associated with a more favourable outcome, a retrospective study was undertaken of patients treated for SCCL at the Helsinki University Central Hospital between 1963 and 1982.

PATIENTS AND METHODS

The basic patient series was compiled from the files of the Department of Radiotherapy and Oncology and the Department of Pulmonary Diseases of the Helsinki University Central Hospital. The clinical records and chest roentgenograms of these patients, including those obtained from other hospitals participating in the treatment of these patients, were reviewed and relevant information abstracted. The primary diagnosis of SCCL was based on histology or cytology. A pathology review was undertaken to confirm the original diagnosis for those patients who had survived for at least 24 months. In addition, morphological subclassification was made, when possible, according to the current WHO classification [6]. The TNM

Accepted 20 November 1987.
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Table 1. Some characteristics of 19 5-year survivors

Age	Sex	Karnofsky (%)	Weight loss (kg)	Subtype	Extent of disease LD/ED	Stage	Treatment	Survival (months)	Cause of death
61	M	100	0	Oat cell	LD	I	S	116	Alive
62	M	100	0	Oat cell	LD	I	S	174	AMI
68	M	80	0	Intermediate	LD	I	S	73	Ca-related
58	M	100	0	Intermediate	LD	I	S + RT	186	Alive
30	M	100	0	Oat cell	LD	I	S + CT	123	Alive
66	M	100	0	Unclassified	LD	I	S + CT	72	Alive
64	M	100	0	Oat cell	LD	I	S + RT + CT	69	AMI
65	M	100	0	Intermediate	LD	I	S + RT + CT	63	AMI
60	M	100	0	Oat cell	LD	I	RT alone	134	Ca-related
69	F	70	0	Unclassified	LD	I	RT + CT	65	Ca-related
52	F	100	0	Oat cell	ED	III (M1)	RT + CT	136	Ca-related
51	M	80	0	Intermediate	LD	I	RT + CT	81	AMI
41	M	100	0	Oat cell	LD	III (M0)	RT + CT	109	AMI
69	M	100	3	Intermediate	LD	III (MO)	CT + RT	75	Alive
63	M	100	10	Intermediate	LD	II	CT + RT	66	Ca-related
53	M	100	0	Oat cell	LD	III (MO)	CT + RT	94	Ca-related
60	M	100	0	Unclassified	LD	III (MO)	CT + RT	79	Ca-related
64	M	80	0	Oat cell	LD	II	CT + RT	65	Alive
71	M	100	9	Oat cell	LD	II	CT + RT	68	Other Ca

LD = Limited disease, ED = extensive disease, S = surgery, RT = radiotherapy, CT = chemotherapy, AMI = acute myocardial infarction.

classification according to the UICC [7] criteria was applied to every patient. The therapy given and the response towards it were recorded. Complete response (CR) was defined as disappearance of all clinical evidence of active tumour for at least 4 weeks. A 50% reduction in the sum of all measurable or evaluable lesions was required for a partial response (PR). Other patients were recorded as non-responders (NR). Duration of remission and the first site of relapse were noted. Autopsy data, when available, were included. The patients were followed up till death or to 31 December 1985. Calculation of survival time was started from the date of diagnosis.

The survival time and duration of remission were measured by the product-limit method of Kaplan and Meier [8]. Chi-square tests were used to compare group means [9].

RESULTS

The source material consisted of 1019 patients. Nineteen patients (1.9%) survived for 5 years or longer. Table 1 presents some characteristics of these 5-year survivors. The median age was 61 years (range 30–71). There were two females and 17 males. Performance status was good according to the Karnofsky scale [10] and there was only one patient with extensive disease (ED). Pretreatment weight loss occurred only in three cases. Of the 19 5-year survivors, three could only be classified broadly as SCCL (named unclassified) without further subtyping because the diagnostic material was small or traumatized. The other patients were subclassified into oat cell (10 patients, 53%) and pure intermediate (six patients, 32%) subtypes.

Eight of 19 patients (42%) were primarily treated with surgery, either alone or with adjuvant therapy. Adjuvant radiotherapy (RT) was given at 44–55 Gy to the mediastinum by the split-course irradiation technique. Adjuvant CT consisted of: cyclophosphamide + vincristine or cyclophosphamide + CCNU + methotrexate, 3–7 cycles within 1 year. RT alone was administered to one patient; 60 Gy by split-course irradiation to the primary tumour and the mediastinum, and 4/19 (21%) had received CT after relapse. Six of 19 (32%) received combination CT with local RT as their primary treatment. The CT regimens given included either cyclophosphamide + vincristine or cyclophosphamide + vincristine + CCNU + methotrexate. RT consisted of 50–55 Gy by the split-course technique to the primary tumour, the mediastinum and the supraclavicular areas. RT was administered after the second or the third CT cycle. Response to the primary therapy was CR in 18 cases (95%). One patient could not be assessed for response by chest X-ray because of surgery. There were seven carcinoma related deaths (41%) among which the first site of relapse was central nervous system (CNS) in three cases and the liver in three cases. Acute myocardial infarction was the cause of death in five patients (39%) who were without evidence of SCCL

at their time of death; in two cases this was verified at autopsy. One patient died of another carcinoma and six are still alive with no evidence of disease after 65–183 months from diagnosis.

DISCUSSION

The present study was designed to evaluate factors affecting the survival of an unselected group of patients. Some of the patients were treated according to some protocol, but for the most part, the series consisted of patients diagnosed and treated in the community setting using a variety of methods and approaches, this being especially the case with the long-term survivors.

Survival depends on many factors. Initial performance status at the time of diagnosis is one of the most important single factors affecting survival [11, 12]. First observed by Zelen, this relation has later been confirmed by numerous studies in cancer patients [13]. Also in the present study the 5-year survivors exhibited a good performance status (100/90/80%) according to the Karnofsky scale; only one patient had performance status 70% at time of the diagnosis.

Having limited disease at presentation is obviously important in terms of survival, although some patients with metastatic disease achieved long disease-free survival [2, 5]. A great majority (95%) of the 5-year survivors in this study presented with limited disease confined to one hemithorax. Only one patient had ED because of supraclavicular lymph node metastases. Fifty-eight per cent of the 5-year survivors had a stage I tumour compared with 6% for the entire series of 1019 patients.

Pretreatment weight loss appears to be an important negative prognostic factor [14–16]. It was recorded in only three of the 5-year survivors in the present study. Sex and age are not so clearly related to survival [12, 14], but in early stages of lung cancer females tend to have a better prognosis than males [12]. Among the patients of this study there were only two females and the other had the only ED, however. Patients' age was also equal among the 5-year survivors than among the whole study population (1019 patients).

Several effective chemotherapeutic agents have been induced over the last decade, and local therapy alone has lost its status as the exclusive treatment of choice in SCCL [4, 17]. The treatment of this patient series during 20 years has been, of course, variable. This is mostly true also for the 5-year survivors among whom all treatment modalities are presented with the exception of exclusive chemotherapy. The objective response rate for these patients was 100%. The response to primary treatment appears to be prognostically significant, and CR has been observed to be very important [3, 17–19].

It also seems that in extreme limited disease patients might benefit from surgery with adjuvant chemotherapy. In this series three of the 19-year survivors were treated by surgery alone without adjuvant treatments. There are also historical reports of long-term survival in a few cases treated by surgery alone. Higgins *et al.* found four of eleven cases of SCCL surviving 5 years [21]. These results were similar to those reported by others [22]. Clearly there is a need for a prospective randomized study of surgery vs. surgery plus adjuvant CT in apparently localized SCCL. Sörenson *et al.* concluded that certain patients with SCCL should be treated by surgery without adjuvant chemotherapy, as the latter might reduce long-term survival because of late toxicity [20]. Among the 5-year survivors of this study, two patients who received adjuvant CT and RT after surgery died from acute myocardial infarction, whereas another two patients, who only received CT for adjuvant treatment, are still alive.

Because of the nature of the growth rate of SCCL, patients cannot be considered cured until their disease-free survival time exceeds 5 years [23]. There was one man in the present material, however, who survived 11 years and then had a relapse affecting the central nervous system, the primary site and the skin, which indicates the very long doubling time of this special tumour case. The brain was the first site of relapse in 43% of the 5-year survivors in this study. Improved systemic treatment and longer survival time have brought about an increased incidence of brain metastases [24]. Nowadays many institutions administer radiotherapy in the form of prophylactic cranial irradiation (PCI) in an attempt to reduce the development of CNS metastases. Reports so far published do not show significant differences in median survival between patients who have and those who have not received PCI [25–27]. It appears, however, that those patients, who have achieved long disease-free survival and CR to their primary treatment might benefit from PCI [28].

In conclusion, a good performance status at diagnosis and no pretreatment weight loss appeared prognostically favourable in the present study. The extent of disease at diagnosis proved a very important prognostic factor. Good response to primary treatment was also of great importance, for a favourable prognosis. The mode of treatment should be such that even the last tumour cell is eradicated during the primary treatment. Some patients with limited disease may benefit from primary treatment comprising surgery and adjuvant chemotherapy.

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