

Surgical resection for small cell carcinoma of the lung: a retrospective study

E F Smit, H J M Groen, W Timens, W J de Boer, P E Postmus

Abstract

Background – A retrospective review was undertaken of the survival of 21 patients with histologically proven small cell carcinoma of the lung resected between 1977 and 1991.

Methods – Twenty one patients (20 men) of median age 60 (range 44–73) years underwent surgical resection. Patients were subjected to standard clinical staging procedures. Preoperative diagnosis was small cell carcinoma of the lung in 13, non-small cell lung cancer in one, and uncertain in seven patients. Clinical staging was stage I disease in 11 and stage II in 10 patients.

Results – Resection included pneumonectomy in 12 cases, lobectomy in eight, and one wedge resection. Resection was complete in 16 patients. Postoperative histopathological examination confirmed small cell carcinoma of the lung in 19 specimens and mixed small cell and non-small cell carcinoma of the lung in two. Pathological staging was stage I in 11, stage II in three, and stage III in seven patients. The final pathological diagnosis of the resected specimens (n=18) was atypical carcinoid in one, pure small cell carcinoma of the lung in 15, and mixed small cell and non-small cell carcinoma of the lung in two patients. Fourteen patients also received chemotherapy and 10 received prophylactic cranial irradiation postoperatively. Excluding the patient with a final diagnosis of atypical carcinoid, the median survival (n=20) was 29 months (range two to 133+). Median survival for patients with pathological stage I and II disease (n=13) was 40 months (range nine to 133+) and for patients with pathological stage III disease (n=7) 20 months (range two to 116+). The median disease free survival was 23 months. Eleven patients relapsed between two and 101 months. There was no advantage for those patients who received postoperative chemotherapy.

Conclusion – Curative resection offers the best chance for long term survival in patients with small cell carcinoma of the lung with very limited stage disease.

(Thorax 1994;49:20–22)

Small cell lung cancer accounts for up to 25% of all lung cancers. The hallmarks of this cell type are its propensity for early and widespread haematogenous dissemination

and its sensitivity to cytotoxic chemotherapy. Although combination chemotherapy has improved the prognosis during the last two decades, median survival has reached a plateau at approximately one year, with a small fraction – about 5% – surviving beyond five years.¹ Ever since the randomised British Medical Research Council trial² which demonstrated no survival advantage for surgery over radiotherapy, a diagnosis of small cell carcinoma of the lung has been considered by many to be a specific contraindication for surgery, regardless of the stage of disease. However, studies performed during the 1980s^{3–7} have reassessed the place of surgery. We retrospectively analysed our experience in 21 patients with small cell carcinoma of the lung treated initially by resection followed, in most cases, by combination cytotoxic chemotherapy.

Methods

Between 1977 and 1990 21 patients of more than 500 with small cell carcinoma of the lung referred to our hospital were considered suitable for surgical resection. Their characteristics are summarised in table 1. Preoperative diagnostic and staging procedures included physical examination, routine full blood count, blood chemistry including liver and renal function tests, chest radiography, computed tomographic scanning of thorax and upper abdomen, isotopic bone scans, isotopic or ultrasonographic liver scans, and fibreoptic bronchoscopy. A brain scan and bilateral bone marrow biopsies were also performed in patients known preoperatively to have small cell carcinoma of the lung. Mediastinoscopy was only performed in patients with computed tomographic evidence of possible mediastinal involvement by tumour – that is, a lymph node greater than 1 cm in diameter. Preoperative staging was by the TNM classification.⁸ No patient had received chemotherapy or radiotherapy before surgery or had any previous malignancy. The extent of disease was deter-

Table 1 Patient characteristics

Median (range) age (years)	60 (44–73)
Male/female	20/1
Preoperative	
Histological diagnosis	8
Cytological diagnosis	6*
No pathological diagnosis	7
Histological/cytological preoperative diagnosis	
Small cell lung cancer	13*
Non-small cell lung cancer	1
Histological postoperative diagnosis	
Small cell lung cancer	19*
Mixed non-small cell/small cell	2

* One patient had atypical carcinoid on pathological re-evaluation.

Department of
Pulmonary Diseases
E F Smit
H J M Groen
P E Postmus

Department of
Pathological Anatomy
W Timens

Department of
Thoracic Surgery
W J de Boer

University Hospital
Groningen,
The Netherlands

Reprint requests to:
Dr P E Postmus,
Department of Pulmonary
Diseases, Free University,
De Boelelaan 1117, 1007
MB Amsterdam,
The Netherlands.

Received 19 June 1992
Returned to authors
14 April 1993
Revised version received
16 August 1993
Accepted for publication
11 October 1993

mined at thoracotomy and by pathological staging after surgery also by the TNM system. All available surgical specimens (n = 18) were re-examined by a pathologist (WT).

Fourteen patients received postoperative chemotherapy. As the study spanned 13 years, chemotherapy protocols varied. One patient also received thoracic irradiation to the mediastinum. Ten patients received prophylactic cranial irradiation after completion of chemotherapy. At relapse patients were treated with chemotherapy, radiotherapy or both, if appropriate.

Survival was calculated from the date of surgery. Survival curves were constructed according to the product limit Kaplan-Meier method. Deaths within 30 days of operation were included in the estimation of survival data. Comparison of survival curves was made by the Mantel-Haenszel (log rank) test. For comparison of intergroup differences the χ^2 test was used, a p value of <0.05 being considered significant.

Results

The study population included 20 men and one woman of median age 60 (range 44–73) years. A preoperative histological or cytological diagnosis of small cell carcinoma of the lung was made in 13 patients, one patient was subsequently diagnosed as having non-small cell lung cancer, and in seven patients a diagnosis of malignancy could not be established before surgery. Preoperatively 11 patients were considered to be clinical stage I and 10 stage II. Of the patients without a preoperative diagnosis six were stage I and one stage II. Surgery included pneumonectomy in 12 patients (of whom nine had a preoperative diagnosis of small cell carcinoma of the lung), lobectomy in eight, and wedge resection in one. Complete mediastinal lymph node staging at surgery was not performed. In 16 patients the operation was considered curative, but five patients had microscopic residual disease in the resection margins when staged pathologically. Surgical complications included one bronchopleural fistula and one empyema. Immediate postoperative pathological examination of the resected specimens revealed 19 pure small cell tumours and two mixed small and non-small cell tumours. The pathological TNM staging was stage I for 11 patients, stage II for three, and stage IIIA for seven (table 2). A comparison between clinical and pathological staging is given in table 2.

Pathological re-evaluation of the resected

Table 2 Comparison of preoperative (clinical) stage with postoperative (pathological) stage (UICC classification)

Preoperative stage	Postoperative stage			Total
	I	II	IIIA	
I	9	1	1	11
II	2	2*	6	10
Total	11	3*	7	21*

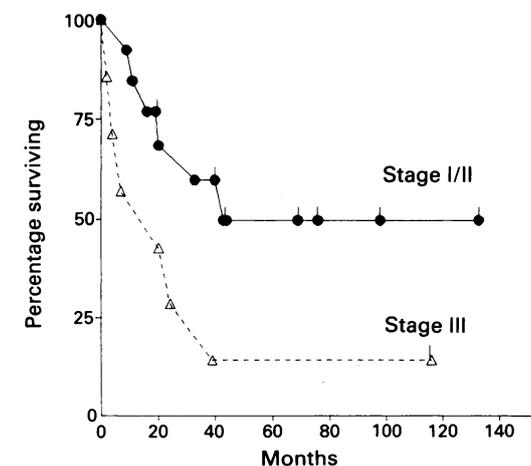
* One patient had atypical carcinoid on pathological re-evaluation.

specimens (n = 18) revealed one carcinoid, 15 pure small cell carcinoma of the lung, and two mixed small cell and non-small cell carcinoma of the lung.

All patients were offered postoperative chemotherapy. Four patients refused because they considered the operation surgically curative; one refused because of deteriorating performance status. Two patients died before chemotherapy was due to commence. Starting within six weeks of surgery 2–5 courses of a 3–4 drug chemotherapy regimen were administered to 14 patients, including 12 with pure small cell carcinoma of the lung, one with mixed small cell and non-small cell cancer, and one with atypical carcinoid.

Survival at the end of 1991 for the 20 patients with a diagnosis of small cell carcinoma of the lung is shown in the figure. The patient with an atypical carcinoid was excluded. The median survival was 29 months (range two to 133+ months). Median survival for patients with pathological stage I and II disease (n = 13) was 40+ months (range nine to 133+ months) and 20 months (range two to 116+ months) for patients with stage III disease (n = 7) (p < 0.05). No significant difference was found when survival was analysed for preoperative clinical stage. Median survival for patients with clinical stage I (n = 11) was 33 months (range four to 133+ months) and 29 months (range two to 166+ months) for those with clinical stage II (n = 9). Median survival in patients following pneumonectomy (n = 11) was 25 months (range two to 116+ months), which was similar to those undergoing lobectomy (n = 9), 33+ months (range nine to 133+ months).

Seven patients are alive and disease free at 19 to 116 months after surgery. Another relapsed (or had a second primary) 101 months after resection but is alive on chemotherapy with disease (133 months). One patient died 50 days after surgery at home from an unknown cause and one died with no evidence of disease nine months postoperatively. Ten patients died as a consequence of recurrent tumour between four and 43 months after resection. The patient with a postoperative empyema died after four months, and a patient with a



Survival curves for patients according to pathological stage (UICC classification). p < 0.05, log rank test.

bronchopleural fistula died after 39 months from metastatic disease following completion of chemotherapy. The median disease free survival was 23 months. Postoperative chemotherapy had no major effect on either median time to relapse – 19 months in untreated patients ($n=7$) *v* 14 months in chemotherapy treated patients ($n=13$) – nor on the relapse pattern.

Discussion

Assessing the role of surgery in small cell carcinoma of the lung from the literature is difficult because of the small numbers of patients in predominantly retrospective studies. It is evident, however, that surgery, either alone or as part of a multimodality treatment for the occasional patient who presents with stage I or II disease, can result in long term survival.³⁻⁷ In a Canadian study the five year survival was 51% for patients with stage I disease, 28% for those with stage II, and 19% for patients with stage III small cell carcinoma of the lung.³ These results compare favourably with survival rates following chemotherapy of about 5% at five years in large series.¹ However, Osterlind *et al*⁹ reported on 150 apparently operable patients with small cell carcinoma of the lung, of whom only 52 were resected but all were treated with chemotherapy. Surgery itself had no effect on long term survival. Another large multicentre study also failed to find a significant difference in survival for patients with limited small cell carcinoma of the lung who underwent surgery after chemotherapy.¹⁰ Shepherd *et al*⁴ reported a significant survival advantage for patients who underwent resection after chemotherapy over those who remained inoperable after chemotherapy. However, fewer than 50% of the patients entered in this prospective study underwent surgery. Indeed, Williams *et al*⁵ in their prospective study of adjuvant surgery after chemotherapy found survival was similar for patients presenting with limited disease and treated with chemotherapy alone.

Several authors have stressed the importance of re-evaluating the histological diagnosis after surgery in small cell carcinoma of the lung. Warren *et al*¹¹ reclassified 12 out of 46 resected small cell carcinoma of the lung specimens as well differentiated small cell neuroendocrine carcinomas. When comparing the survival data of patients with well differentiated neuroendocrine carcinoma with those with equivalent stage I true small cell carcinoma of the lung there was a highly significant advantage for the former. Quiox *et al*¹² found

that in patients with small cell carcinoma of the lung presenting with a solitary pulmonary nodule the final diagnosis was correct in only 60% of cases.

It is tempting to conclude that, for selected patients with small cell carcinoma of the lung, surgery is the best treatment. The five year survival of our 20 patients is 25%. As in other studies there was a significant difference in median survival between patients with pathological stage I and II disease and those with pathological stage III.^{3,6,13} However, there was no survival difference between those with clinical stage I and II disease, reflecting the limitations of clinical staging.^{3,14} We conclude that surgery should be considered in patients with favourable preoperative staging. The relapse rate and survival among patients who did or did not receive adjuvant chemotherapy was similar and five of the untreated patients had stage I disease.

- 1 Johnson BE, Grayson J, Makuch RW, Linnoila RI, Anderson MJ, Cohen MH, *et al*. Ten year survival of patients with small-cell lung cancer treated with combination chemotherapy with or without irradiation. *J Clin Oncol* 1990;8:396-401.
- 2 Fox W, Scadding JG. Medical Research Council comparative trial of surgery and radiotherapy for primary treatment of small celled or oat-celled carcinoma of the bronchus. Ten year follow-up. *Lancet* 1973;ii:63-5.
- 3 Shepherd FA, Ginsberg RJ, Feld R, Evans WK, Johansen E. Surgical treatment for limited small cell lung cancer. The University of Toronto Lung Oncology Group experience. *J Thorac Cardiovasc Surg* 1991;101:385-93.
- 4 Shepherd FA, Ginsberg RJ, Patterson GA, Evans WK, Feld R. A prospective study of adjuvant surgical resection after chemotherapy for limited small cell lung cancer. A University of Toronto Lung Oncology Group study. *J Thorac Cardiovasc Surg* 1989;97:177-86.
- 5 Williams CJ, McMillan I, Lea R, Mead G, Thompson J, Sweetenham J, *et al*. Surgery after initial chemotherapy for localized small-cell carcinoma of the lung. *J Clin Oncol* 1987;5:1579-88.
- 6 Karrer K, Shields TW, Denck H, Hrabar B, Vogt-Moykopf I, Salzer GM. The importance of surgical and multimodality treatment for small cell bronchial carcinoma. *J Thorac Cardiovasc Surg* 1989;97:168-76.
- 7 Baker RR, Ettinger DS, Ruckdeschel JD, Eggleston JC, McKneally MF, Abeloff MD, *et al*. The role of surgery in the management of selected patients with small-cell carcinoma of the lung. *J Clin Oncol* 1987;5:697-702.
- 8 Mountain CF. A new international staging system for lung cancer. *Chest* 1986;89(Suppl):225-33.
- 9 Osterlind K, Hansen M, Hansen HH, Dombernowsky P. Influence of surgical resection prior to chemotherapy on the long term results in small cell lung cancer. A study of 150 operable patients. *Eur J Cancer Clin Oncol* 1986;22:589-93.
- 10 Lad T, Thomas P, Piantidosi S. Surgical resection of small cell lung cancer: a prospective randomized evaluation. *Proc 6th World Conference on Lung Cancer, Melbourne* 1991, Abstract no 604.
- 11 Warren WH, Memoli VA, Jordan AG, Gould VE. Re-evaluation of pulmonary neoplasms resected as small cell carcinomas: significance of distinguishing between well-differentiated and small cell neuroendocrine carcinomas. *Cancer* 1990;65:1003-10.
- 12 Quiox E, Fraser R, Wolkove N, Finkelstein H, Kreisman H. Small cell lung cancer presenting as a solitary pulmonary nodule. *Cancer* 1990;66:577-82.
- 13 Prasad US, Naylor AR, Walker WS, Lamb D, Cameron EWJ, Walbaum PR. Long term survival after pulmonary resection for small cell carcinoma of the lung. *Thorax* 1989;44:784-7.
- 14 Kreisman H, Wolkove N, Quiox E. Small cell lung cancer presenting as a solitary pulmonary nodule. *Chest* 1992;101:225-32.