

Long term survival after pulmonary resection for small cell carcinoma of the lung

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ABSTRACT A retrospective review was undertaken of the long term survival of 97 patients with histologically proved small cell carcinoma of the lung resected during the 10 years January 1977–December 1986. Twenty seven patients (28%) had stage I disease, 29 (30%) stage II, and 41 (42%) stage III. Patients with stage I and II tumours were managed by resection alone. Patients with stage III disease received adjuvant chemotherapy (cyclophosphamide, doxorubicin, and vincristine). Pneumonectomy was undertaken in 75 patients, lobectomy in 21, and wedge resection in one patient. Three patients died within 30 days of operation. The cumulative five year survival of all patients, irrespective of tumour stage, was 17%. The cumulative five year survival was 35% for patients with stage I disease, 23% for stage II, and zero for stage III. The median survival for patients with stage III tumours was 17 months. There was no significant difference in cumulative survival between patients with stage I and II disease. Cumulative survival, however, was significantly better for patients with stage I and II disease than for those with stage III disease. The data suggest that for patients with stage I and stage II disease surgery offers the prospect of long term survival.

Introduction

"It has become standard dogma that surgical intervention is unwarranted once a diagnosis of small cell carcinoma of the lung is made. This view may not be entirely substantiated and there is a growing recognition that limited disease and extensive disease behave differently with respect to therapeutic outcome and this observation may make the reintroduction of surgical approaches to this disease a reality."

Anderson and Arentzen, 1980¹

Surgical management of patients with small cell carcinoma of the lung fell into disrepute after the report of a Medical Research Council trial was published in 1968²; the conclusion that surgical resection does not improve long term survival persists to this day. There is evidence, however, that the time has come for a revision of management regimen for patients with small cell carcinoma of the lung,³⁻⁵ particularly for those with limited or stage I and stage II disease.

The policy of our unit has been to practise resection in patients referred with stage I and II disease, though

just as many patients with stage III disease have undergone primary resection with adjuvant post-operative chemotherapy during the same period. This study was undertaken in the light of recently reported but smaller studies on the role of surgery, to see if our results justified this approach.

Methods

A retrospective review was undertaken of 97 consecutive patients who underwent pulmonary resection for small cell carcinoma of the lung from January 1977 to December 1986. There were 62 men and 35 women (age range 34–80, mean 55 years). Hospital and follow up data were retrieved from records held in the department of thoracic surgery and the Edinburgh University department of pathology, where a histological review was undertaken to ensure that the diagnosis of small cell carcinoma was correct in every case. Pathological and TNM staging was performed by correlation of the operative and subsequent histological findings.

Surgical selection from the 127 patients who were actually referred for operation during the 10 years was based on assessment of fitness and the absence of widespread metastatic disease in patients with stage III disease. Although the policy of the surgical unit has been to advocate pulmonary resection for all patients

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with stage I and II disease, this is not the policy of all the referring physicians. The true number of stage I and II patients treated in Edinburgh during the 10 years would therefore have been greater than the 127 referred for surgical advice. Patients were routinely investigated by posteroanterior and lateral chest radiography, bronchoscopy, barium swallow, and diaphragmatic screening. Mediastinoscopy and mediastinotomy were not performed routinely even in patients with a preoperative diagnosis of small cell carcinoma. Radioisotope, ultrasound, and computed tomography investigations for extrathoracic metastases were carried out when indicated by abnormal clinical or biochemical findings. Thirty of the 127 patients referred for surgery did not proceed to thoracotomy because of widespread metastases or poor general fitness.

Management was by pulmonary resection and clearance of ipsilateral metastatic lymph nodes in all patients with stage I or II disease. No patient with stage I or II disease received adjuvant chemotherapy or radiotherapy. Patients with stage III disease received adjuvant chemotherapy two weeks after surgery—initially only those with extrathoracic metastases, but 14 in addition had chemotherapy when no intrathoracic metastases were evident after resection. They received cyclophosphamide (1 g/m²), doxorubicin (40 mg/m²), and vincristine (1 mg/m²) at three weekly intervals for three cycles. Responders received further cycles at monthly intervals for up to one year or until they relapsed.

Survival was defined as the time from operation to death or, in the case of survivors, the last clinical review. Actuarial five year survival was estimated by Kaplan-Meier's product limit method.⁶ Deaths within 30 days of operation were included in the estimation of survival data.

Results

The results of pathological staging are shown in table

Table 1 Tumour stage in the 97 patients

UICC classification	TNM classification	No of patients
Stage I	T1 N0 M0	3
	T1 N0 M0	22
	T2 N0 M0	2
Stage II	T2 N1 M0	29
	T2 N2 M1	6
Stage III	T3 N1 M0	2
	T3 N2 M0	20
	T3 N2 M1	11
	T3 N2 M2	2

UICC—Union Internationale Contre le Cancer; TNM—tumour, nodes, metastases.

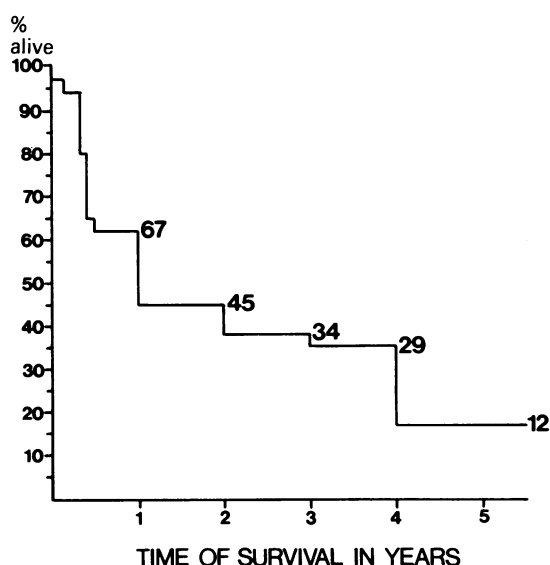


Fig 1 Cumulative survival for the 97 patients undergoing pulmonary resection for small cell carcinoma of the lung. The figures indicate the number of patients entering each time interval during follow up.

1. Twenty seven patients had stage I disease according to the Union Internationale Contre le Cancer (UICC) classification, 29 had stage II disease, and 41 stage III. Nineteen patients of the 41 with stage III disease had preoperative evidence of extrathoracic metastases. In this group of patients pulmonary resection was undertaken as a debulking procedure before adjuvant chemotherapy.

A positive preoperative diagnosis had been made at bronchoscopy in 71 (73%) patients; the remainder had a definitive diagnosis made after resection. Most tumours were in the left lung (67 of the 97) and the upper lobes (65). Sixty three tumours were central and 34 peripheral. Surgical management was by pneumonectomy in 75 patients (eight intrapericardial) and lobectomy in 21; one patient underwent segmental resection. In the 41 patients with metastatic nodal disease there were 70 hilar deposits, three interlobar, 14 subcarinal, 12 subaortic, and 12 paratracheal, and four in a pulmonary ligament.

Three of the 97 patients died within 30 days of operation as a consequence of myocardial infarction, pulmonary embolism, and bronchopneumonia consequent on a bronchopleural fistula respectively. A further 25 patients (26%) suffered substantial non-fatal complications (19 bronchopneumonia, five bronchopleural fistula, and one pulmonary embolus).

The cumulative five year survival for the study group as a whole was 16.8% (fig 1). When the data were analysed according to UICC staging (fig 2), 35.4% with stage I disease, 22.6% with stage II, but

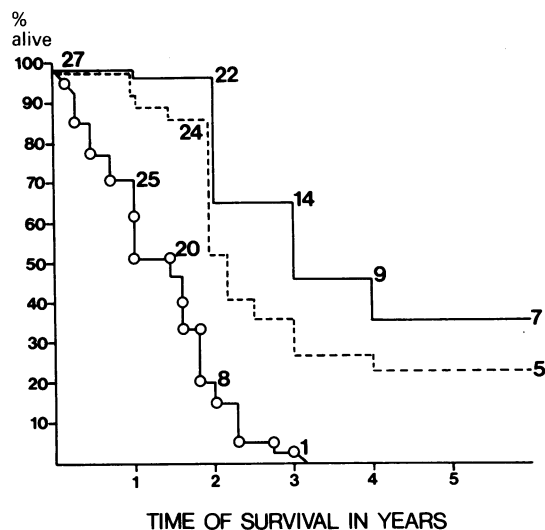


Fig 2 Cumulative survival for patients undergoing pulmonary resection for small cell carcinoma of the lung divided on the basis of UICC staging. The figures indicate the number of patients entering each time interval during follow up. — Stage I (27 patients); ---- stage II (29 patients); stage III (41 patients).

none with stage III survived five years. The median survival for patients with stage III disease undergoing resection and receiving adjuvant chemotherapy was 17 months. There was no significant difference in cumulative survival between patients with stage I and with stage II disease treated by surgical resection alone. Patients with limited disease (stage I and II) had a significantly better cumulative five year survival than stage III patients ($p < 0.01$). Metastatic disease accounted for all deaths during follow up, cerebral metastases being the most frequently identified. No patient with N2 disease survived beyond three years from operation.

Discussion

The management of patients with small cell carcinoma of the lung is controversial and the long term results poor (table 2). Many of the current attitudes to management date back to the Medical Research Council trial, which concluded that long term survival was better in patients receiving radiotherapy than those having surgical resection,² and in consequence the role of surgery has declined.⁷ Radical radiotherapy has now been replaced by chemotherapy as the primary mode of management,⁸ the former now being used in the prophylaxis and management of metastatic disease, particularly in the brain.¹ With a combined modality approach, a survival rate of 42% has been reported at one year and of 15% at two years.⁹

In this study resection alone was undertaken in all

Prasad, Naylor, Walker, Lamb, Cameron, Walbaum

Table 2 Long term survival in patients with limited small cell carcinoma of the lung in published series and this study

Survival	Mode of management (% of patients surviving)				
	RT alone	RT + CT	CT alone	Surgery	Surgery + CT
1 y	30 ⁹	42 ⁹	38 ⁹	24 ² 62 ¹⁴	
2 y	11 ⁹	15 ⁹	7 ⁹	96* 52†	76 ^{10†} 56 ^{10§}
5 y	11 ²			6 ² 23† 25‡ 35* 36 ¹⁴	24 ¹⁵ 59 ³

*This study stage I.

†This study, stage II.

‡Stage I.

§Stage II.

RT—radiotherapy; CT—chemotherapy.

patients with stage I and II disease. Our five year survival rate compares favourably with the results of other management regimens (table 2) and, in particular, with the recent data of Karrer *et al.*¹⁰ On the basis of the long term survival in 112 patients, these authors concluded that initial surgical resection followed by intensive chemotherapy was the appropriate therapeutic approach in patients with limited disease. Their survival figures for patients undergoing resection and postoperative randomisation to one of two chemotherapeutic regimens were 76% at 24 months and 62% at 36 months for patients with stage I disease and 56% and 50% for patients with stage II disease.¹⁰ This compares with 96% and 65% for stage I patients and 52% and 36% for stage II patients at the same time points in our own patients treated by surgery alone. We found no significant difference in the cumulative five year survival between the stage I and stage II patients treated by resection alone, and there was also no difference in survival in these categories between patients treated by pneumonectomy and by lobectomy.

Direct comparison of published data (table 2), however, is often misleading. Most studies contain a small number of unselected patients and the stage of disease in the patients undergoing treatment is often not clear. Most patients included in table 2 were classified as having "limited" disease, though the survival in UICC staged patients is indicated where known. Our conclusions from the data obtained in this study suggest that resection offers the best chance of long term survival in patients with stage I and II disease. Whether or not this is further improved with adjuvant postoperative chemotherapy remains to be seen.

These results must, however, be taken in the context of the overall problem of small cell carcinoma of the

lung. During the 10 years of the study the Edinburgh Lung Cancer Group would have expected to see 1800 small cell cancers from a population of 900 000.¹¹ The relatively small number (127) actually referred for surgical resection reflects the current view of most physicians that small cell carcinoma of the lung is not a surgical condition. Our impression, however, is that many more patients would have been eligible for resection given a different view of the possible benefits of surgical intervention.

The main problem concerns the management of patients with stage III disease. Though advocating primary surgical resection and adjuvant chemotherapy in patients with T1, T1N1, and T2 lesions, Shield *et al*³ advise against surgical resection for patients with other TNM classifications (five year survival 4–9%). Our experience is similar to theirs for stage III patients (median survival 17 months) and reflects the aggressive nature of this disease (median survival for untreated patients with extensive disease five weeks).^{12,13} In a comprehensive review of the role of radiotherapy and chemotherapy in patients with extensive disease, Salazar and Creech recognise that, although some patients may derive benefit from aggressive combined regimens, this may be at the expense of severe toxicity in some patients.⁹

We have used resection as a debulking procedure in our patients with stage III disease before adjuvant chemotherapy. The median survival of 17 months exceeds the median survival for both limited stage disease (12 months)¹⁶ and diffuse disease (5–9 months)^{17–19} reported for chemotherapy alone and indeed for chemotherapy and radiotherapy, 9–16 months.^{18,20,21} Debulking may therefore confer some survival value in these patients and merits further investigation.

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