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Surgery in the management of small cell lung cancer[1]

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Abstract

Objective: We analyzed our experience in the period January 1975–December 1995 aiming to confirm the role of surgery in the multimodality treatment of small cell lung cancer (SCLC). **Methods:** 127 patients (5.28% of the overall lung resections for carcinoma) underwent surgery for SCLC. The median age was 60 years (range 34–73). In 87 patients (68.5%) a pre-operative tissue diagnosis was effected and those patients underwent a complete staging procedure. Fifteen patients received up to six complete courses of neoadjuvant and adjuvant chemotherapy. The surgical procedures included: 50 pneumonectomies, 71 lobectomies and six wedge resections. Two patients experienced a local recurrence and a completion pneumonectomy was performed. **Results:** The median follow-up is 66 months (range 6–214). The 5-year actuarial survival rate is 22.6% (median 18 months). Twenty-three patients are still alive, 21 of them being disease-free. Considering the most conspicuous group of patients ($n = 92$) treated by surgery and adjuvant chemotherapy, the survival data were 47.2, 14.8 and 14.4% for Stage I, II and III, respectively ($P = 0.001$). N0 patients had a significantly better survival than N1 and N2 patients ($P = 0.035$). **Conclusions:** Surgery and adjuvant chemotherapy might represent an effective form of treatment of limited SCLC without lymph-node involvement. The role of surgery is yet to be verified as regards N1 and N2 status, where even neoadjuvant chemotherapy has not achieved the hoped-for results (no patient reaching a 2-year survival). © 1997 Elsevier Science B.V.

Keywords: Small cell lung cancer (SCLC); TNM Stages; Surgery; Chemotherapy; Survival

1. Introduction

Following the report of Shields and associates [20], there was an increasing evidence that surgery might play a role as a local-regional treatment for certain patients with limited SCLC, selected on the basis of the TNM staging [1,14]. As a matter of fact, the treatment of patients with limited disease SCLC by chemotherapy alone is disappointing, as less than 15% of the patients would be alive at 2 years from the diagnosis [2,3].

Despite additional use of thoracic irradiation the local tumor recurrence rate is high, frequently as first manifestation of general recurrence [3,11]. As a consequence, for the last 10 years, surgery has been applied as a part of a combined treatment, in an adjuvant or a neoadjuvant setting, in most of centers [4,6,7,12,15,17].

The results of ongoing randomized multicenter trial will clarify the real role and timing of surgery in the multimodality treatment of limited SCLC [9].

In previous reports we identified a cohort of patients with limited disease who might benefit by surgical treatment [1], and the optimal treatment for T1-3N0M0 SCLC [12]; here we report the overall results of surgery and combined treatments in 127 patients.

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Table 1
Characteristics and staging of 127 patients who underwent surgery for limited SCLC

Characteristics	Surgery	Surgery plus adjuvant therapy	Neoadjuvant therapy plus surgery	Total
No.	20	92	15	127
Sex				
Male	19	83	12	114
Female	1	9	3	13
Age				
Median	59	60	60	60
Range	49–66	34–73	49–73	34–73
Clinical staging				
T1-2N0	10	66	6	82
T3N0	3	11	2	16
T1-2N1	3	7	0	10
T3-N1	1	0	0	1
T1-3N2	3	8	7	18
Pathological staging				
T1-2N0	3	37	12	52
T3N0	2	10	1	13
T1-2N1	6	13	0	19
T3-N1	2	2	0	4
T1-3N2	7	30	1	38
T0N0	0	0	1	1

2. Materials and methods

One hundred and twenty-seven patients with limited SCLC underwent surgical resection at the Service of Thoracic Surgery of the University of Pisa between 1975 and 1995.

There were 114 males and 13 females with a median age of 60 years (range 34–73). Both clinical and pathological staging for all patients have been reported according to the new International Staging System for Lung Cancer [14] (Table 1).

In 87 patients (68.5%) a pre-operative tissue diagnosis was effected, and those patients underwent a complete staging procedure. This included: a detailed history and physical examination, the evaluation of the Performance Status according to Karnofsky, a complete blood count and biochemical profile, cardiac and pulmonary function tests, chest X-ray, bronchoscopy, computed tomography of chest (after 1978), the upper abdomen and brain, abdominal ultrasonography, bone scan, Gallium-67 scan (after 1980), bilateral bone marrow biopsy and aspiration. Pre-operative mediastinoscopy was not routinely performed provided there was an absence of Gallium up-take on the mediastinum and no bulky mediastinal lymph-node involvement (greater than 1.5 cm) evident on CT.

The surgical procedures consisted of: 50 pneumonectomies, 71 lobectomies (five en bloc-resections and one sleeve lobectomy) and six wedge resections (Table 2). All but one were radical resections according to standard rules. All diagnostic and surgical materials were reviewed and the diagnosis was confirmed by our pathologists.

Fifteen patients, all of them in the first period (1975–1982), were treated by surgery alone. In the same period, five patients died peri-operatively. Ninety-two patients received surgery as their first line therapy, followed by adjuvant chemotherapy and, in the case of hilar or mediastinal lymph-node involvement, also by radiotherapy. A group of patients ($n = 15$), as part of a controlled clinical trial, were submitted to neoadjuvant chemotherapy.

As a consequence of the long period considered in this report, the chemotherapeutic regimen was not uniform. At the beginning, patients received cyclophosphamide (C), doxorubicin (A), and vincristine (V), on day 1, every 3 weeks. From 1980, adjuvant treatment consisted of cyclophosphamide (C), epidoxorubicin (E), on day 1, and etoposide (VP-16), on days 1, 3 and 5, every 3 weeks. In a short period (1988–1992), a small group of patients ($n = 7$), as part of a controlled clinical trial, underwent a high-dose single-agent chemotherapy (E) repeated every 3 weeks and for a maximum of six courses. In the neoadjuvant setting, three courses of a CEVP-16 for N0-patients ($n = 8$) and a platinum (P)-based regimen (PEVP-16) for N2-patients ($n = 7$) were used every 3 weeks. Three courses of the pre-operative regimen were administered in the post-operative period.

Post-operative radiotherapy was administered to the mediastinum after chemotherapy to most patients ($n = 34$) with stage II or III disease. The dosage ranged from 45 to 60 Gy in 4–6 weeks with five fractions per week.

Prophylactic cranial irradiation (PCI) for 30 Gy in 10 fractions over a period of 2 weeks was not routinely performed ($n = 13$).

Table 2
Surgical procedures and postoperative complications

	Surgery	Surgery plus adjuvant therapy	Neoadjuvant therapy plus surgery	Total
Procedure				
Lobectomy	8	54	9	71
Pneumonectomy	12	32	6	50
Wedge resection	0	6	0	6
Residual disease				
None	20	91	15	126
Microscopic	0	1	0	1
Gross	0	0	0	0
Complications				
Morbidity[a]	1	7	1	9
Mortality[a]	5	0	0	5

[a] Bronchopleural fistula, emphyema, supraventricular arrhythmia, atelectasis.

2.1. Statistical analysis

All statistical analyses were carried out using the Statistica (Stat-Soft) software system. Overall survival was calculated from the date of operation until death or the date of last follow-up (censored). Patients who died in the perioperative period were not considered in the survival analysis. Patients who died due to cause(s) other than primary SCLC ($n = 5$) without evidence of disease were censored at death.

Survival was estimated by the product-limit method [8] and the differences in their distributions were evaluated by the log-rank test, for univariate analysis. The level of significance was a priori set at $P < 0.05$; all tests were two-sided.

3. Results

Peri-operative mortality was 3.9% ($n = 5$). Major postoperative complications included one bronchopleural fistula, five supraventricular arrhythmias, two prolonged atelectasis and one empyema. The pTNM stages in patients who underwent surgery with or without adjuvant therapy showed more advanced disease than the cTNM in 40 (35.7%) patients, and less advanced in 11 patients (9.8%). Considering the 15 patients treated by primary chemotherapy, we verified 14 partial and one complete response. Fifty-four (42.5%) patients had oat-cell SCLC, 58 (45.6%) an intermediate form and 15 (11.9%) had SCLCs combined with adeno- or squamous cell carcinomas.

With a median follow-up of 66 months (range 6–214) the overall 5-year actuarial survival rate is 22.6% (median 18 months) (Fig. 1). Twenty-three patients are still alive, 21 of these being disease-free. Among the 99 dead patients, five died due to other causes (one accident, three different tumors and one myocardial infarction) than primary tumor.

Five (4.1%) patients had a local relapse without evidence of systemic disease, while 13 patients (10.6%) developed a relapse concurrently at the primary and distant sites. Only 17 (13.9%) patients had brain as first site of relapse (Table 3).

All patients treated by surgery alone ($n = 15$) died within 2 years from the operation. As regards patients treated with primary chemotherapy, all seven N2 patients died within 2 years from diagnosis, while among the eight N0 patients (described in a previous report [13]) two are long-term survivors.

In the main group of patients ($n = 92$) treated by surgery and adjuvant therapy, 21 patients are still alive (2 with disease). The 5-year survival of this group was 32.1% (Fig. 2). Considering survivals according to Stage and N status, patients with Stage I ($P = 0.001$) and N0 status ($P = 0.035$) had a better prognosis (Fig. 3 and Fig. 4). No significant difference in survival was found within T-status categories. Also, there was no significant correlation between histology and survival.

Two patients who developed a local relapse following adjuvant chemotherapy at 20 and 24 months from the first operation, and underwent a completion pneumonectomy, were interesting cases; one of them is still alive and well after 64 months, while the other died 15 months after the second operation.

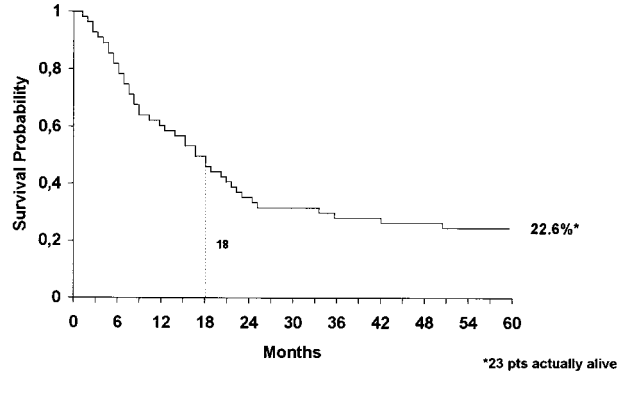

Fig. 1. Overall 5-year actuarial survival.

Table 3
Site of first relapse

	Surgery	Surgery plus adjuvant therapy	Neoadjuvant therapy plus surgery	Total
Patients alive				
Disease-free	0	19	2	21
With disease	0	2	—	2
Patients deceased				
From disease	15	66	13	94
Other causes	5[a]	5	0	10
Site of relapse				
Local	0	5	0	5
Local plus systemic	1	10	2	13
Brain	4	11	2	17
Bone	1	8	1	10
Liver	1	10	2	13
Multiple	6	13	5	24
Other	2	11	1	14

[a] Peri-operative deaths.

4. Discussion

The results presented in this report confirm what we have previously assessed in a smaller series of patients about the role and timing of surgery in the multimodality treatment of limited SCLC [1,12,13].

Surgery has been proved effective in decreasing the local relapse rate, which remains the most frequent single site of failure in patients with limited SCLC, treated by aggressive chemotherapeutic regimens and thoracic irradiation [3,11]. However, surgery alone, as reported by the Medical Research Council [4] and from our initial experience [1], is not sufficient for the cure of even an early-stage SCLC.

Current chemotherapeutic multi-drug regimens, in an adjuvant setting, have resulted in a satisfying long-term survival (32.1%) for a conspicuous group ($n = 92$) of selected patients. Note that pre-operative selection of the patients, chosen to be treated by surgery, is the main issue of this report, as well as others [5,15,17]. If, on the one hand, only N0 patients seem to receive maximal benefit from the surgical approach (45.7% at 5 years), on the other hand, the prediction of lymph-nodal involvement by conventional imaging and invasive procedures (also whenever mediastinoscopy is routinely performed) has, until now, not been satisfactory. In our experience, in line with the largest studies [19], 38 out of 90 cN0-patients (42%) had a more advanced disease at the operation. This is the major obstacle in the correct planning of surgery in the multimodality treatment of limited disease, which may be overcome by new and promising nuclear imaging techniques. At the moment of writing, we have planned to perform a clinical trial on the usefulness of F-18 fluorodeoxyglucose positron emission tomography in the detection of mediastinal lymph-nodal involvement in surgical SCLC.

Until an acceptable diagnostic accuracy can be reached it will be difficult to compare results obtained from surgical treatments with those from chemo-radiotherapy and from adjuvant and neoadjuvant treatments [18,21,22]. Within the limits of this comparison, we have previously reported no gain in terms of survival in

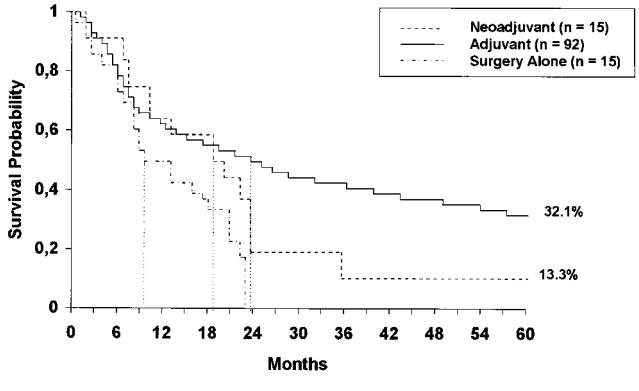

Fig. 2. Five-year survival according to different therapies.

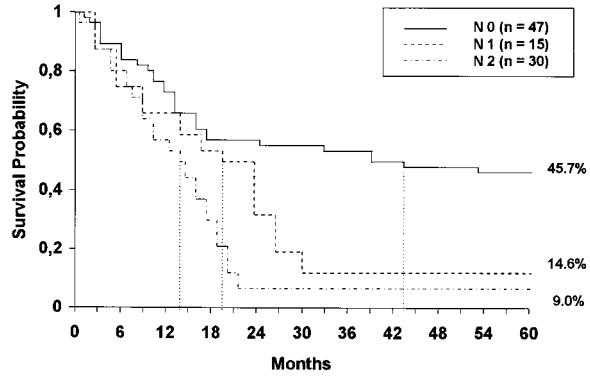

Fig. 3. Five-year survival according to the stage in patients ($n = 92$) who underwent adjuvant therapy.

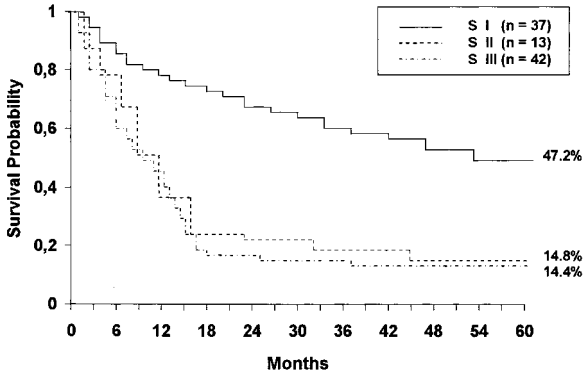

Fig. 4. Five-year survival according to N status in patients ($n = 92$) who underwent adjuvant therapy.

N0 SCLC patients by neoadjuvant treatment [13]. Subsequently, we had experience with a neoadjuvant chemotherapeutic approach in N2 SCLC patients, but, similarly, no patient was alive after 2 years from the operation, and we thought it prudent to stop recruitment. The role of neoadjuvant chemotherapy followed by surgical therapy in limited SCLC will be clarified by the ongoing multicenter randomized trials. Until that moment, we think it reasonable to perform surgery followed by adjuvant treatment for clinical N0 patients with pre-operative diagnosis of limited SCLC.

We did not use prophylactic cranial irradiation (PCI) in most of patients, and our opinion, in agreement with a recent update [10], is that PCI should be considered as an optional treatment which, because of its toxicity, must not be administered outside of a clinical trial [16].

A more careful clinical staging, distinguishing the patients who may really benefit from surgery, and new adjuvant therapeutic strategies, including new active drugs (paclitaxel, docetaxel, CPT-11, topotecan and others), are what we would like to propose, in the future, to a selected, unfortunately small, group of patients with limited SCLC. However, these patients, without a systemic and lymph-nodal spread, have a reasonable hope of being cured by a multimodal approach including surgery as first step.

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