

Long term results of surgery and chemotherapy in small cell lung cancer¹

Federico Rea^{a,*}, Donatella Callegaro^a, Adolfo Favaretto^b,
Monica Loy^a, Adriano Paccagnella^b, Umberto Fantoni^c,
Giuliana Festi^c, Francesco Sartori^a

^a*Division of Thoracic Surgery, University of Padua, Via Giustiniani 2, 35128 Padua, Italy*

^b*Division of Medical Oncology, University of Padua, Padua, Italy*

^c*Division of Respiratory Medicine, University of Padua, Padua, Italy*

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Abstract

Objective: The aim of the study is to analyse long-term results of patients with small cell lung cancer (SCLC) treated at the same institution according to a prospective study including surgery, chemotherapy, and radiotherapy. **Methods:** From 1981 to 1995, 104 patients with a proven histology of SCLC underwent surgery, chemotherapy, and radiotherapy. Fifty-one patients with operable stage I or II lesion received surgical resection followed by adjuvant chemotherapy and radiotherapy. Fifty-three patients with proved SCLC and clinical stage III received induction chemotherapy followed by surgery and radiotherapy. All patients received from four to six courses of chemotherapy and 36 had prophylactic cranial irradiation (PCI). All patients had follow-up for at least 1 year, and survival time was calculated from the date of the diagnosis until death or most recent follow-up. **Results:** Ninety-six patients were male and eight female. We performed 29 pneumonectomies, eight bilobectomies, 66 lobectomies and one no resection. Regarding the clinical stage, 35 patients (33.6%) had stage I, 16 patients (15.4%) had stage II and 53 (51%) had stage III. Post-operative pathologic staging revealed stage I in 37 patients (35.6%), stage II in nine patients (8.6%), stage III in 45 patients (43.3%), and in 13 patients (12.5%) there was no more tumor. The 30-day mortality was 2% (two patients). Fourteen patients (13.4%) had post-operative complications. Fifty-one patients (49%) had a relapse. The median follow-up was 55 months. Twenty-six patients remain alive and 78 patients have died. The overall 5-year survival rate was 32%, with an estimate median survival time of 28 months; according to the pathologic stage, the survival data were 52.2%, 30% and 15.3% for stage I, II and III, respectively ($P < 0.001$). The 5-year survival was 41% in patients without SCLC after chemotherapy. **Conclusion:** As with non-small cell lung cancer, survival following surgery and chemotherapy clearly correlates with the stage. At present, it is not clear whether surgery is truly effective for patients with SCLC. In our experience, the complete elimination of small cell lung cancer is associated with an improvement in survival (41% at 5 years). © 1998 Elsevier Science B.V. All rights reserved

Keywords: Small cell lung cancer; Surgery; Chemotherapy; Combined modality treatment

1. Introduction

Small cell lung cancer (SCLC) represents 20–25% of all lung cancer in man and is characterized by a rapid growth

and early dissemination [1,2]. Patients with SCLC have the poorest prognosis; less than 8% of patients with this type of lung cancer currently survive 5 years beyond the initial diagnosis [3]. Surgical resection alone is inadequate therapy for limited SCLC because it results in less than a 5% long-term survival rate [4]. The poor survival rate of patients in the surgical arm of the British Medical Research Council Study [5] led most investigators to abandon surgery as the initial treatment for bronchogenic neoplasm of this cell type.

Since the 1980s the role of surgery in the therapy of

* Corresponding author. Divisione di Chirurgia Toracica, Ospedale Civile di Padova, Via Giustiniani 2, 35128 Padova, Italy. Tel.: +39 49 8212203; fax: +39 49 8212249.

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SCLC has again become the subject of growing interest, apparently prompted by the often-cited publication of Shields et al. [6]. Shields reported that the survival of patients was significantly influenced by TNM staging and that survival could be prolonged by chemotherapy after complete surgical resection.

Although there are indeed a number of positive reports on the combined management of SCLC, including radical surgery, no conclusive data exists from randomized studies that can assign surgery its place in the treatment of this tumor.

The only other randomized trial addressing the question of the place of surgery in this disease was carried out by the Lung Cancer Study Group (LCSG) in conjunction with the Eastern Co-operative Oncology Group and the European Organization for Research and Treatment of Cancer [7,8]. Though the authors concluded that surgery did not improve the survival of SCLC patients, they admitted that the chemotherapy did not include the newly effective etoposide and platinum, and the statistical power was not great, particularly for individual TNM subgroups.

In the present study, we analyse the long-term results of patients with SCLC treated at the same institution (Division of Thoracic Surgery, University of Padua) according to a prospective study including surgery, chemotherapy, and radiotherapy.

2. Material and methods

All patients with limited SCLC seen at the Division of Thoracic Surgery of the University of Padua between 1981 and 1995 were enrolled in a prospective trial of surgery combined with chemotherapy.

The planned treatment consisted of a surgical treatment with post-operative chemotherapy for patients with clinical stages I and II. Patients with a clinical stage III had neoadjuvant chemotherapy followed by surgery (Table 1).

The staging procedures included a complete blood count with white blood cell differential and platelet counts, serum electrolytes, calcium, liver function tests (including serum glutamic oxalacetic transaminase, alkaline phosphatase and bilirubin), and renal function tests (including urea nitrogen and creatinine), chest X-ray, bronchoscopy and computed tomography (CT) of the mediastinum and lung, radionu-

clide scanning of the bone, radionuclide, ultrasound, or computed tomography (CT) scanning of the abdomen, radionuclide or magnetic resonance (MR) scanning of the brain, and a bone marrow aspiration. We did not use mediastinoscopy routinely but only in selected cases, when the CT scan showed enlarged mediastinal lymph-nodes.

In all patients, both clinical and surgical pathologic stages have been reported according to the new International Staging System for Lung Cancer.

From 1981 to 1988 the chemotherapy treatment consisted of Doxorubicin 50 mg/m² on day 1, Cyclophosphamide 1200 mg/m² on day 1 and Vincristine 1 mg/m² on day 1 by bolus intravenous injection (CAV) alternating with courses of cisplatin 60 mg/m² on day 1 and Etoposide 120 mg/m² on days 1, 3 and 5 (DDP/VP16). Cisplatin was administered over a 2 h period together with appropriate hydration and forced diuresis.

In 1988, we partially modified the chemotherapy treatment by passing from the alternating regimes to a single three-drug regimen combining Cisplatin 60 mg/m² on day 1, Etoposide 120 mg/m² on days 1, 2 and 3 and Epirubicin 50 mg/m² on day 1. The regimen was repeated every 3 weeks for a total of four pre-operative cycles or six post-operative cycles.

Post-operative radiotherapy was administered to the mediastinum after completion of both surgical therapy and chemotherapy for all patients with post-operative pathologic stage III disease. The total dose consisted of 40 Gy in 20 fractions.

Prophylactic cranial irradiation was given to the whole brain as 17 Gy in two fractions at the completion of treatment.

All patients had a follow-up for at least 1 year, and survival time has been calculated from the date of the diagnosis until the date of death or most recent follow-up. Survival rate has been calculated with the Kaplan–Meier methods. Survival curves were compared by performing univariate Log-rank test.

3. Results

One hundred and four patients with limited SCLC underwent surgical resection and chemotherapy. Fifty-one patients received surgical resection as their first-line therapy, with adjuvant chemotherapy and radiotherapy being administered post-operatively. Fifty-three patients with proved SCLC and clinical stage III received induction chemotherapy followed by adjuvant surgical treatment and radiotherapy.

Among the 104 patients there were 96 males and eight females; the median age was 57 years (range 30–75 years).

Pre-treatment clinical staging revealed 35 patients with stage I disease, 16 patients with stage II disease and 53 patients with stage III disease.

Table 1

SCLC: Protocol of treatment

Clinical stage		
I–II	Surgery	CAV/DDP-VP16 PEE ^a
III	CAV/DDP-VP16 PEE ^a	Surgery

^aChemotherapy adopted from 1988 to 1995.

CAV, Cyclophosphamide, Doxorubicin, Vincristine; DDP-VP16, Cisplatin, Etoposide; PEE, Cisplatin, Etoposide, Epirubicin.

Pre-operative histologic or cytologic examination revealed SCLC in 62 patients. Initially, 10 patients were thought to have non-SCLC tumors. For 32 patients, malignancy could not be confirmed pre-operatively.

We performed 29 pneumonectomies, eight bilobectomies, 66 lobectomies and one no resection.

The overall 30-day mortality was 2% (two patients). The cause of death was cardio-respiratory failure for both patients. Fourteen patients (13.4%) had post-operative complications (Table 2).

Post-operative histologic examination revealed 83 pure SCLC, eight mixed SCLC and non-SCLC and 13 no residual tumor.

Of 53 patients with clinical stage III disease, 21 patients (45.6%) had a clinical complete response (CR), 25 patients (54.4%) had a clinical partial response (PR); in seven patients we were not able to evaluate the response.

The median follow-up was 76 months (range 15–166 months).

Twenty-six patients remain alive and 78 patients have died.

Regarding the pathologic stage, 37 patients had stage I, nine patients had stage II, 45 patients had stage III and in 13 patients there was no more tumor at specimen (Table 3).

Fifty-one patients (49%) had a relapse; sixteen patients (15.4%) had a relapse at the primary site alone, nine patients (8.7%) had a relapse concurrently at the primary and distant sites. The remaining twenty-six (25%) patients had a relapse at the distant site alone.

For the 104 patients, the overall 5-year survival rate was 32%, with an estimate median survival time of 28 months.

The 5-year survival rate according to the pre-operative clinical stage was 39.5% for patients with stage I, 46.6% for patients with stage II and 24.3% for patients with stage III ($P = 0.0748$).

The 5-year survival rate according to the pathologic stage was 52.2% for patients with stage I, 30% for patients with stage II and 15.3% for patients with stage III; the group of patients without residual tumor at the specimen after chemotherapy and surgery had a 41% 5-year survival rate ($P < 0.001$) (Fig. 1).

The survival rate results according to the 'changing of stage' are shown in Table 4.

Table 2

SCLC: Post-operative complications

Type of complication	No. of patients		
	Surgery first	Adjuvant surgery	Total
Bronchopleural fistula	2	7	9
Cardio-respiratory failure	–	2	2
Empyema	1	–	1
Haemothorax	1	–	1
Chylothorax	1	–	1
Total	5 (9.8%)	9 (16.9%)	14 (13.4%)

Table 3

SCLC: Changing of stage

Clinical stage	No. of patients				
	Pathologic stage				
	I	II	III	No RT	Total
I	23	–	12	–	35
II	4	5	7	–	16
III	10	4	26	13	53
Total	37	9	45	13	104

RT, Residual tumor.

4. Discussion

The role of surgery in the treatment of SCLC is currently unsettled. Decades of experience have shown the inadequacy of local treatment, either by surgery or radiotherapy, as the sole treatment of SCLC [4,5].

The central treatment role of chemotherapy in SCLC is well established by clinical trials [10,11]. Despite the introduction of new chemotherapeutic agents, there has been no significant improvement in either overall survival or cure rate over the past 10 years and less than 20% of patients with limited disease survive more than two years [9].

Failure to achieve control at the primary site remains the single most important obstacle to cure in patients with limited SCLC [10].

An analysis of the site of first relapse demonstrated that, even for patients who have achieved clinical complete response, the primary tumor bed and hilar or mediastinal lymph node areas are the most frequent single sites of failure [11].

Although the likelihood of relapse in the chest may be reduced by up to 50% when thoracic irradiation is administered after chemotherapy, 20–36% of patients will have local recurrence even after combined modality treatment [12,13].

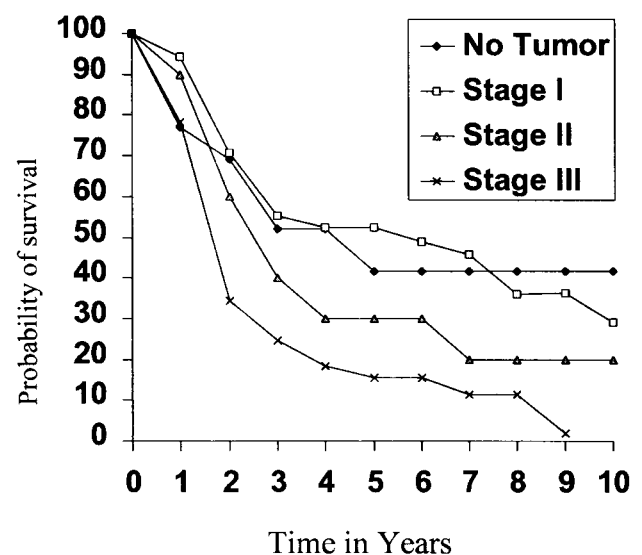
Fig. 1. Overall survival pathologic stage, $P \leq 0.001$.

Table 4

SCLC: 5-year survival in selected patients

Clinical stage	Pathologic stage	No. of patients	5-year survival
I + II	I	27	62.6%
I + II	III	19	16.7%
III	III	26	14.5%

Surgery is a modality that could reduce the incidence of local relapse [14]. Meyer et al. [15] was one of the early advocates of inclusion of surgery in multimodality therapy for SCLC; later a number of additional reports presented results of surgery and adjuvant chemotherapy for SCLC patients by TNM stage [16–23].

The results of our study show an overall 49% of relapse with only a 15.4% of relapse at the primary site alone. The results are similar to those of other studies which included surgery in multimodality therapy for SCLC [9,24].

Even the overall 5-year survival of 32% in our experience is in accordance with other authors using similar multimodality therapy [2,5,25].

Regarding the impact of TNM staging on predicting on outcome in the SCLC, we did not find any correlation between clinical stage and long-term survival, we have to remark that 37% of patients clinically classified stage I and II were understaged. On the other hand, when we consider the pathologic stage, better results are obtained in stage I (52.2% 5-year survival) compared with stage II (30% survival) and stage III (15.3% 5-year survival); this value is significant ($P < 0.001$).

If we consider only the 27 patients clinically classified as stage I and II and then confirmed pathologically stage I, the results are even better (62% 5-year survival). No difference in survival was found in pathologic stage III disease when we consider the group that first received surgery compared to the group that received chemotherapy and then surgery.

We also observed that the complete elimination of SCLC at specimen by pre-operative chemotherapy is associated with an improvement in survival (41% 5-year survival). In this group of patients there was a high percentage of clinical complete response (76%) compared to the overall group of clinical stage III disease (45.6%). Even though chemotherapy was well tolerated we made a change in the regimen adopted until 1988 in order to make the therapy simpler. In our opinion this modification does not affect long-term survival rates.

If we consider the surgical aspect we can see that the 30-day mortality rate of 2% is similar to that of standard surgery. In contrast, for the post-operative complications, we obtained a value of 13.4% that is higher than that of standard surgery; this value is even much higher (16.9%) in patients with clinical stage III – chemotherapy with adjuvant surgery – compared to the patients with clinical stage I-II – surgery with adjuvant chemotherapy – (9.8%).

In conclusion, from an analysis of our experience the following observations were made. (1) In spite of precise

clinical staging the patient with SCLC is understaged and consequently the clinical stage is not correlated with long-term survival. This clinical understaging implies that many more cases will receive surgery first and then chemotherapy. We advise a more aggressive clinical staging and the use of mediastinoscopy in all patients with SCLC who are candidates for a multimodality therapy. (2) The pathologic stage is correlated with long-term survival with a statistically significant difference between stages I, II and III. (3) The value of the post-operative complication rate is higher when surgery follows chemotherapy. (4) In the pathologic stage III, the survival does not change when the surgery is used before or after chemotherapy. (5) When no tumor is found at specimen after chemotherapy, there is an improvement in survival. (6) Until the role of surgery in patients with SCLC is clarified, we believe that chemotherapy remains the first therapy and surgery could be used, in controlled trials, for a local control of the disease after chemotherapy.

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