REVIEW ARTICLE

Surgery in small cell lung cancer: when and why

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Summary

Small cell lung cancer (SCLC) is considered a systemic disease at diagnosis, because the potential for hematogenous and lymphogenic metastases is very high.

For many years, the diagnosis of SCLC was considered a contraindication for surgery because radiotherapy was at least equivalent in terms of local control, and the rate of resectability in SCLC patients was poor. When chemotherapy became the mainstay of treatment for SCLC, radiotherapy was its logical complement, and surgery was progressively abandoned.

However, some centers continued to support surgery because experience suggested that in selected patients it was possible to achieve a long-term survival. In the search for predictors of long-term survival it became evident that the TNM staging system was effective for SCLC.

The rationale for surgery in the context of SCLC is based on 3 factors:

a) Several historical series of patients operated for limited-stage SCLC reported some long-term survivors, showing that cure could be achieved.

b) After chemotherapy and radiotherapy, the rate of local relapse is 20-30%. The assumption that surgical resection might be superior for local disease control has been suggested but not yet proved.

c) The surgical intervention can precisely assess pathological (p) response to chemotherapy, identify carcinoids erroneously diagnosed as SCLC, and treat the non-small cell lung cancer (NSCLC) component of tumors with a mixed histology.

Even if some controversies exist, it is accepted that surgery can be proposed as the first treatment in patients with T1 or T2 lesions with no evidence of lymph node involvement, followed by adjuvant chemotherapy.

In more advanced stages of disease, chemotherapy should be the first step of treatment and surgery can be proposed to responding patients, before radical radiotherapy, depending on the p-stage of disease. Such an intensive multidisciplinary approach should be always employed in the context of controlled clinical trials.

Key words: multimodality protocols, small cell lung cancer, surgery

Introduction

The role of surgical intervention in the multimodality management of SCLC continues to be controversial. At most, only 5-8% of patients with this disease can be considered initially as potential surgical candidates. These are patients who can be clinically classified as having stage I, II or resectable stage IIIa disease, as defined by the International TNM system proposed in 1986 [1]. This small group of patients comprises 15-25% of patients with limited disease. Actually, this number is even smaller, if one excludes those patients with N2 disease.

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Historical background

Twenty to twenty-five percent of all primary bronchogenic carcinomas are of the small cell subtype. Dissemination to regional lymph nodes and/or distant sites

can be identified in more than 90% of patients at the time of initial presentation [2].

Furthermore, in patients with apparently limited-stage or operable tumors, widespread micrometastatic disease is highly likely to be present, and these subclinical deposits proliferate if only local therapeutic modalities, such as surgery or radiotherapy, are employed.

This explains why almost all surgical series from the prechemotherapy era reported 5-year survival rates approaching zero for patients with SCLC [3,4].

To assess the role of surgery in the treatment of SCLC, a prospective randomized trial was conducted by the Medical Research Council of Great Britain [5,6]. Seventy-one patients were prospectively randomized to undergo surgery, and 73 to receive thoracic irradiation (30 Gy or more over 20-40 days). The median survival for patients in the surgical and radiotherapy arms were 199 and 300 days, respectively. At 5 years, one surgical and 3 radiotherapy patients were alive (p=0.04), and at 10 years, only the 3 patients in the radiotherapy arm remained alive. It was concluded from this study that radical radiotherapy was preferable to surgery, but that neither of the treatment policies was really effective.

The investigators stated that it would be improbable that any advance in therapy could exert a significant effect on the death rate from this disease in the absence of successful smoking prevention programs.

How true these words are, even today!

The results of this study led to trials of preoperative radiotherapy followed by surgery for patients with SCLC.

Several prospective phase II trials showed that it was possible to combine these two local treatment modalities safely, but few patients achieved long-term survival [7-9].

The observation in the 1970s that patients with SCLC were dying from systemic metastases led to the hypothesis that chemotherapy might add to the effectiveness of local radiotherapy.

Bergsagel et al. from the Princess Margaret Hospital were the first to show a modest survival advantage with the addition of single-agent, low-dose cyclophosphamide [10].

The British Medical Research Council Lung Cancer Working Party also showed that adding low-dose cyclophosphamide and 1-(2-chloroethyl)-3 cyclohexyl-1-nitrosourea (CCNU) to radiotherapy resulted in a significant prolongation of progression-free but not overall survival [11].

At the same time, other investigators were applying the same adjuvant chemotherapy principles to surgical patients.

In 1977, Shields et al. reviewed the results of 4 Veterans Administration Surgical Adjuvant Group (VASOG) adjuvant chemotherapy studies, and undertook a separate analysis of the 148 patients (47%) in those trials who had SCLC [12]. No survival advantage was seen for the patients in the chemotherapy arms of either of the trials that evaluated single-agent nitrogen mustard or single-agent cyclophosphamide. A small survival advantage was seen for patients in the chemotherapy arm of a 3-arm trial in which patients were randomized to receive prolonged intermittent courses of CCNU and hydroxyurea or no further therapy.

In 1982, Shields and his colleagues also made other important observations from their analysis of the SCLC patients in the VASOG trials [13]. They demonstrated the importance of tumor, node, metastasis (TNM) staging, which has long been recognized to have prognostic significance for NSCLC. Sixty percent of patients with T1N0M0 tumors were alive at 5 years, whereas there were almost no 5-year survivors among the patients who presented with either T2-3 tumors or with mediastinal lymph node involvement. Patients with low stage II tumors had an intermediate 5-year survival of approximately 30%.

These observations suggested that there could be a small subpopulation of patients with SCLC for whom it might be appropriate to consider a surgical approach.

In a retrospective review of 40 patients with SCLC who underwent potentially curative resection between 1959 and 1972, Shore and Paneth reported an overall 5-year survival rate of 25%. Four of 10 patients (40%) without nodal involvement achieved long-term survival compared to 9 of 26 patients (25%) who had hilar or mediastinal nodal involvement [14].

SCLC usually presents with a central mass associated with hilar and mediastinal lymphadenopathy. Lennox et al. observed that patients who had large proximal tumors and who required a pneumonectomy were less likely to achieve long-term survival. The 2- and 5-year survival rates for patients who required only lobectomy were 32% and 18%, respectively, compared to 14.4% and 7.2% for pneumonectomy patients [15].

It is unusual for SCLC to present as a solitary pulmonary nodule. In the VASOG review of solitary pulmonary nodules, only 15 (4%) patients were found to have small cell pathology, and 11 were able to undergo surgery [16]. One-, 5-, and 10-year survival rates for those 11 patients were 63.6, 36.4, and 18.2%, respectively. Since most of these patients had undergone surgery before the chemotherapy era, it may be assumed that approximately one-third were cured by their surgery alone as measured by survival at the 5-year mark.

From this historical review it is clear that local treatment, whether surgery or radiation, or both, is inadequate therapy for SCLC.

Rationale for surgery

Improved control at the primary site

Response rates of 80% or more are achieved with current combination chemotherapy for SCLC, and complete clinical response is seen in approximately 50% of patients with limited-stage disease [17].

However, most patients relapse shortly after discontinuing treatment, and the 2-year survival rate is 20% or less in most series.

For patients with limited disease, the most frequent site of failure is the primary tumor and the hilar or mediastinal lymph nodes.

In total, up to 50% of patients fail at the primary site, and for half of those patients, the primary site may be the only area of failure.

Similar results have been found at autopsy. In a review by Elliot et al., residual tumor was identified at autopsy in the primary site in 64%, and in the hilar and mediastinal lymph nodes in 53% of patients with limited disease who had at some time achieved a complete clinical response [18].

Two meta-analyses of thoracic radiotherapy for SCLC have been published [19,20]. The survival data for almost 2000 patients in 16 trials were available, and data on local control rates were available for 9 studies. Both meta-analyses showed that thoracic irradiation resulted in a reduction in local relapse rate from 47.9 to 23.3% (p <0.0001) [19]. They also demonstrated a small but significant survival benefit for patients who received radiotherapy [19,20].

Based on the results of these meta-analyses, the standard therapy for patients with limited stage SCLC now consists of combination chemotherapy and thoracic irradiation with or without prophylactic cranial irradiation.

Median survival longer than 20 months and 5-year survival rates of approximately 20% have been reported [17,21].

However, even the most successful combined-modality treatment programs report isolated initial relapse at the primary site in 20-25% of patients, and a cumulative risk of local recurrence of 50% [21].

This high local failure rate led several authors to question whether surgical resection would result in improved local control. They postulated that control of bulky disease in the chest by surgery and eradication of low-volume micrometastatic disease by systemic chemotherapy would result in an increased cure rate.

Small studies from several centers suggested that this might, indeed, be the case.

The University of Toronto Lung Oncology Group reported only 2 local recurrences in 35 patients treated with combined-modality therapy that included surgical resection [22].

Similar results were reported by Comis et al., who observed no local recurrences in 16 patients who underwent adjuvant surgical resection after induction chemotherapy [23].

Histological heterogeneity of small cell lung cancer

It has been suggested that more favorable results of surgical resection have occurred in those patients with intermediate small-cell type histology (neuroendocrine carcinoma, intermediate cell type) than in those with the lymphocytic (oat) –cell type (neuroendocrine carcinoma, small-cell type), although the difference has not been reported to be statistically significant [24-27].

Others have not accepted that the cell type makes any difference in survival rate [28-30].

The incidence of foci of NSCLC cells (SCLC found in combination with others histologies such as adenocarcinoma or squamous cell carcinoma) has been reported to be between 5 and 15% initially and to be increased to as high as 25-35% after neoadjuvant chemotherapy [22,31,32].

Surgical series of SCLC report higher percentages of mixed histological tumors. The University of Toronto Lung Oncology Group reported mixed histology in 14 of 79 patients (17.7%) who underwent initial surgery followed by adjuvant chemotherapy and in 3 of 40 patients (7.5%) who had surgical resections after induction chemotherapy [33].

Investigators for the Eastern Cooperative Oncology Group reported that mixed-histology tumors were more likely to present as peripheral lesions on chest x-ray, although they found that all other clinical characteristics were similar to those of the pure SCLC patients [34].

However, with resection, the adverse effect of this tumor heterogeneity becomes nonoperative, and the clinical course of the disease is primarily correlated with the pathological/postsurgical TNM (pTNM) stage of the disease [26,35,36].

Additionally, many have maintained that typical and atypical carcinoids frequently have been mistakenly identified as SCLC and that this accounts for some of the long-term survivors included in the surgically resected series of limited SCLC.

This approach has generally been criticized by

having the histopathology reviewed by several pathologists, but, unfortunately, at times the differentiation of the various pulmonary neuroendocrine neoplasms cannot be absolute. The use of immunohistochemistry with specific monoclonal antibodies to more completely differentiate the various neuroendocrine tumors may put this particular issue to rest [37].

Salvage resection

The most selective approach to the use of surgical therapy in SCLC patients is that of salvage resection in a few patients who have failed to respond or have relapsed after chemotherapy for limited disease or the tumor has obstructed the pulmonary artery and the perfusion of the lung (Figures 1, 2 and 3).

The University of Toronto Lung Oncology Group has reported 28 such operations. The indications were no response in 5 patients, partial response (residual ≥ 3cm) in 12, initial response followed by progression during chemotherapy in 3 and relapse after complete response in 8. The projected postsurgical resection 5-year survival rate was 23%. All patients with stage I disease were alive at the time of the report, compared with only 1 with stage II and 2 with stage III disease. Relapse or failure to respond to chemotherapy was thought to be due to the presence of some NSCLC cells or a mixed tumor in 10 of the 28 patients [38].

Yamada et al. reported on 9 patients who underwent surgery, 2 of whom had failed to respond to chemotherapy, 6 who had achieved partial response and 1 who had achieved complete response. Four patients achieved long-term disease-free survival ranging from 3 to 11 years [39].
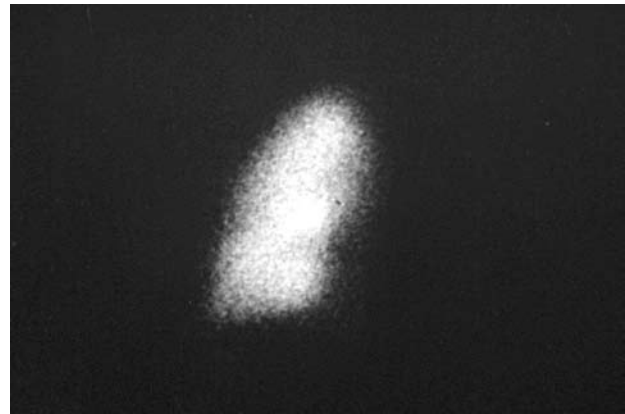

Figure 2. The same patient. Pulmonary perfusion scanning: the left lung has no perfusion.

Therefore, because a small number of patients who have tumors of mixed histological type may be cured by surgical treatment, consideration should be given to a second biopsy for patients who have localized chemotherapy-resistant SCLC.

In summary, a few studies have attempted to evaluate whether surgery might be useful as salvage therapy for selected patients who have limited SCLC.

Surgical treatment alone

One of the major reviews of surgical resection in SCLC was from the Veterans Administration Surgical Oncology Group (VASOG) [40]. In this report, the
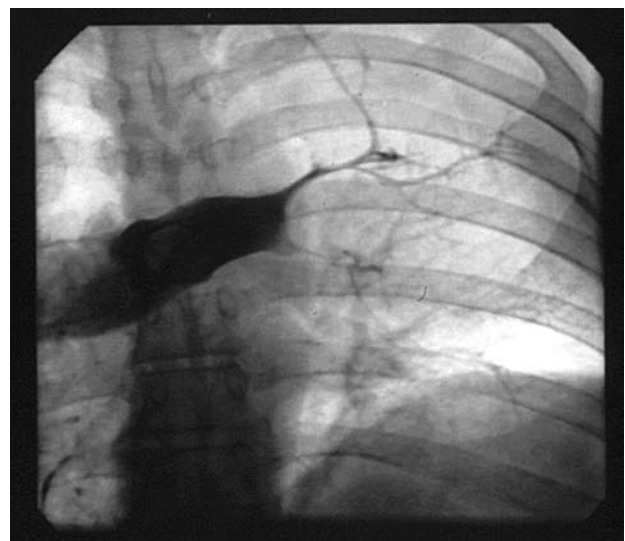

Figure 1. Chest radiography: atelectasis involving the entire left lung.

Figure 3. The same patient. Pulmonary angiography: obstruction of the left pulmonary artery by the tumor.

results of resection of patients with SCLC entered into the Group's randomized prospective adjuvant chemotherapy trials were retrospectively analysed. Of 148 patients, 132 survived after 30 days postoperatively and were available for follow-up study. In these 132 patients, an overall 5-year actuarial survival rate of 23% was recorded. A 5-year survival rate of 59.5% was observed in 26 patients who were staged as having postoperative T1N0M0 disease. Five-year survival rates in the other surgical stages were lower: for T2N0M0 28.2%, for T2N1M0 8.4% and for T3N1M0 and T2N2M0 less than 1.4%. Only one patient with N2 disease had have long-term survival. Most patients were salvaged by surgical resection of their SCLC, either without or with only the use of ineffective postoperative chemotherapy in their management.

Earlier, Hayata et al. had reported similar results following the resection of peripheral lesions of the intermediate SCLC type [41]. They attained an overall 5-year survival rate of 28.1% in those patients who had undergone complete resection of their local disease.

Shore and Paneth reported an overall 5-year survival rate of 25% after resection in 40 patients with SCLC [42]. Hilar lymph node involvement was present in the majority of the resected patients, as well as in the long-term survivors.

In Europe, resection can only be considered in patients with stage I and II disease.

Prasad et al. reported 5-year survival rates of 35% and 23% in stage I and II disease, respectively [43].

In contrast, in the report by Sorensen et al. only 8.45% long-term survival rate was noted in 71 patients managed in a similar manner [44].

However, in 1992 Shah et al. reported an overall 5-year survival of 43.3% in 28 patients with SCLC [45]. There were 14 stage I, 5 stage II and 11 stage III (10 were pT3N0M0 and 1 pT3N1M0) patients. The survival rates in each stage were 57.1%, 0% and 55.5%, respectively.

Smit et al. reported similar results [46]: 50% 5-year survival in stage I and II patients, and 20% 5-year survival in stage III patients. These results are from a total of 20 patients (21 patients, excluding a patient with final diagnosis of atypical carcinoid), 16 of whom had complete resection (Table 1). The explanation for these salutary results in these series remains elusive.

Initial surgical resection followed by chemotherapy

In one from 4 of the VASOG trials, in which postoperative intermittent lomustine (CCNU) and hydroxyurea were used, the small number of patients who received this combination chemotherapy postoperatively had a significantly improved long-term survival rate over those who did not (80.8 vs. 38.1%, respectively). The favorable results of these trials led several investigators to use combination chemotherapy to all patients following complete resection of SCLC.

Meyer reported 80% and 50% 5-year survival rates in a small number of highly selected SCLC patients with stage I and II disease, respectively, following resection and adequate standard postoperative chemotherapy (Table 2) [47].

In Japan, Ohta et al. reported 50.8% 5-year survival rate in patients with stage I disease who were managed by initial surgical resection followed by intensive postoperative chemotherapy. Very few long-term survivors with stage II disease were recorded (5-year survival was 11.9%), but there was a 14.8% 5-year survival rate for those with stage III disease. No patient with N2 disease survived for 5 years [48].

Other similar studies in the late 1980s, usually with small numbers of patients, have been reported with varying results, but all have shown the probable efficacy of postoperative chemotherapy after resection of stage I or II SCLC over surgical resection alone [49-51].

Table 1. Survival rate by pathological stage for SCLC patients with surgical treatment alone

| First author (year) | Reference | Patients, n | Pathological stage | | | |
			I %	II %	III %	Total %
Hayata (1978)	41	42	–	–	–	28.1
Shields (1982)	40	132	59.5	28.2	1.4	23
Shore & Paneth (1980)	14	40	–	–	–	25
Sorensen (1986)	44	77	–	–	–	8.45
Prasad (1989)	43	97	35	23	0	17
Shah (1992)	45	28	57.1	0	55.5	43.3
Smit (1994)	46	20	50	50	20	–

Table 2. Survival rate by pathological stage for SCLC patients with adjuvant chemotherapy after surgery

First author (year)	Reference	Patients, n	Survival per pathological stage			
			I %	II %	III %	Total survival % (years)
Hayata (1978)	41	72	26	17	0	11 (5y)
Shields (1982)	40	132	51	20	3	28 (5y)
Meyer (1986)	47	30	50	50	0	? (5y)
Wada (1995)	66	17	37	–	33	32 (5y)
Osterlind (1986)	67	36	22	–	–	22 (3.5y)
Maassen (1986)	55	124	34	21	11	20 (3y)
Shepherd (1988)	52	63	48	24	24	31 (5y)
Karrer (1995)	54	157	56	29	33	? (4y)
Macchiarini (1991)	58	42	52	–	13	36 (5y)
Hara (1991)	59	37	64	42	11	? (5y)
Davis (1991)	29	32	50	42	21	36 (3y)
Lucchi (1997)	61	92	47.2	14.8	14.4	32 (5y)
Cataldo (2000)	62	60	40	36	15	? (5y)
Kobayashi (2000)	63	59	55	33	23	? (5y)
Suzuki (2000)	64	62	76	38	40	57 (5y)
Badzio (2001)	65	67	–	–	–	27 (5y)
Rostad (2004)	93	38	44.9	–	–	? (5y)

Two of the early major studies relative to initial resection followed by chemotherapy are those of the University of Toronto Lung Oncology Group (TLOG) and the International Society of Chemotherapy Lung Cancer Study Group (ISC) [35,52-54].

In the TLOG study, the most frequent drug combination postoperatively was cyclophosphamide, doxorubicin and vincristine. Postoperative regional thoracic irradiation and prophylactic cranial irradiation were used in many patients.

In the ISC I (preoperative diagnosis of SCLC known) and II studies (diagnosis of SCLC unknown until surgical resection), patients were randomized to receive either 8 courses of cyclophosphamide, doxorubicin and vincristine, or 2 courses of 3 sequential drug combinations: cyclophosphamide, lomustine and methotrexate; CAV; and ifosfamide plus etoposide. Local thoracic irradiation was given infrequently and prophylactic cranial irradiation was given to all patients free of disease at the completion of postoperative chemotherapy.

In the TLOG study, 63 patients underwent initial resection, and in 22 of them the diagnosis was not established until the examination of the surgical specimen. The tumors were pure SCLC in 54 and mixed SCLC and NSCLC in 9 patients. Six of the 63 patients had microscopic residual disease. The preoperative and postoperative stages coincided in only 35% of the patients, and unsuspected mediastinal node involve-ment was identified in 17 (27%) patients. The projected 5-year survival rate for the entire group was 31%, the 5-year survival rate for stage I was 48%, for stage II 24.5% and for stage IIIA 24%.

In the ISC studies, 182 patients were studied. The postoperative pathological TNM staging showed more advanced disease than the preoperative clinical TNM staging in more than 25% of the patients and less advanced disease in 10%. The cell types of the tumors were oat-cell type in 34%, intermediate type in 57%, and SCLC combined with adenocarcinoma or squamous cell carcinoma in the remaining 9%. The resection was determined to be complete in 150 patients and incomplete in 32. The actuarial 4-year survival rate was 43% for the entire group, but it was 47% and 23%, respectively, for the complete and incomplete resection groups. In stage IIIA non-N2 disease, the projected 4-year survival rate was 71%, and in stage IIIA N2 disease it was 33%. The actuarial survival for patients with N0 disease up to 80 months showed 61% survival rate. Interestingly, the projected 5-year survival of patients with N1 and N2 disease (24.5% and 24%, respectively) was the same with the survival obtained by chemoradiation alone. In the entire group of patients, 75% of treatment failures occurred within the first 30 months due to disease progression; in 21%, the cause of death was not directly tumor-related, and in 4% the cause was unknown.

In both the ISC and TLOG studies, the results of

resection of N1 disease were not dissimilar to those of N2 disease. The futility of an incomplete resection in stages II and IIIA N2 is evident from the ISC study, since the projected 36-month survival rates (52% and 24%, respectively) are similar to those obtained when treating all limited-disease patients with chemoradiation therapy alone.

In addition to the two aforementioned series, a number of other studies reporting satisfactory long-term survival in small numbers of SCLC patients undergoing surgical resection followed by chemotherapy have appeared in the literature.

Maassen and Greschuchma reported 3-year overall survival of 20%, but only 18 of 24 patients had a correct preoperative histological diagnosis of SCLC [55].

Karrer et al. reported long-term survival rates 61% and 35% for patients with stage I and stage II disease, respectively [56,57].

In the series by Macchiarini et al. the long-term survival rates for patients with pT1N0, pT2N0, and pT3N0 disease were 65%, 43% and 13%, respectively, and the total 5-year survival was 36% [58].

Hara et al. reported long-term survival rates 64%, 42% and 10.7% for patients with stage I, II and III disease, respectively [59].

In the series by Davis et al. [60] the overall 5-year survival was 36%, as was in the series by Macchiarini et al. [58].

Lucchi et al. reported 5-year survival rates 47.2% for p-I stage, 14.8% for p-II stage and 14.4 % for p-III stage and overall 5-year survival rate 32%. The 5-year actuarial survival rate was 22.6%, and N0 patients had a significantly better survival than N1 and N2 patients [61].

In the series by Cataldo, long-term survival rates were 40%, 36% and 15% for p-stage I, II, III, respectively [62].

In 2000, Kobayiashi et al. reported 55%, 33% and 23% 5-year survival rates in patients with p-stage I, II, III, respectively [63].

In the series by Suzuki et al. and by Badzio et al. the overall 5-year survival rate was 57% and 27%, respectively [64,65].

Because so few patients with SCLC are surgical candidates, the TNM staging system is not generally applied to this subtype of lung cancer, and instead, patients are classified simply as having limited or extensive disease. The patients in the reviews summarized in Table 2 differ from limited-stage SCLC patients overall in that they all underwent pretreatment surgical resection, and therefore detailed pathological stage was available. The results clearly show that the TNM staging system is highly prognostic for patients with limited-stage SCLC.

Inoue et al. reported their results after surgical treatment of 91 patients who had undergone pulmonary resection for SCLC according to the new international TNM staging system. The 5-year overall probability of survival was 37.1%. The 5-year survival rate was 56.1% for stage p-IA, 30% for stage p-IB, 57.1% for stage p-IIA and 42.9% for stage p-IIB. In the stages p-IA-IIB patients who underwent a completion resection, the 5-year survival rate of the patients treated by operation with chemotherapy was better than that of patients treated by operation alone. In addition, the 5-year survival rate of the patients who had 4 or more courses of chemotherapy was 80%.

These results suggest that operation should be considered for stages p-IA-IIB patients and more than 4 courses of combination chemotherapy might be desirable in these resectable cases.

In every study, the best survival rate was achieved in patients with p-stage I tumors, and the poorest survival rate was seen in patients with p-stage III tumors. On average, it would appear that approximately 50% of patients with p-stage I SCLC may be cured with a combined-modality approach that includes surgical resection and adjuvant combination chemotherapy.

In the early trials, virtually no patient with stage III tumors achieved long-term survival. In the later reviews in which more aggressive combination chemotherapy regimens were employed, long-term survival ranged from 11% to 35% [55-57].

In all series, the survival of stage II patients was intermediate between that of patients with stages I and III. In fact, stage for stage, the survival rates are very similar to those seen after surgical resection of NSCLC.

All of the studies that employed intensive combination chemotherapy reported survival rates that appear to be superior to the survival rates seen in patients following surgery without adjuvant chemotherapy. Since it is likely that the improved survival is attributable to postoperative chemotherapy and not to improvements in surgical techniques or supportive care, it seems appropriate to recommend that chemotherapy be given in all patients who have undergone resection for limited-stage SCLC.

The short-term toxicity of such treatment is usually quite manageable and reversible, and the long-term toxicity is minimal.

The Toronto Group recommend no more than 6 treatment cycles, since survival does not seem to be superior for patients in the retrospective studies who received 12-18 months of postoperative treatment [52,66,67]. Whether fewer than 6 cycles may also be adequate is unknown.

In the study reported by Hara et al. 11 patients

treated before 1981 received only 1 postoperative course of combination chemotherapy, and 26 patients treated from 1982 to 1989 received 2 courses followed by consolidation radiotherapy [59]. Although the 5-year survival rates for patients with stage I and II tumors were excellent, only 10.7% of patients with stage III tumors were alive at 5 years. These results appear to be somewhat poorer than those achieved by other groups who administered a more prolonged course of adjuvant chemotherapy, although firm conclusions cannot be drawn from these retrospective analyses.

Littlewood et al. treated two young patients by pneumonectomy followed by a single course of very-high dose chemotherapy and autologous bone marrow transplantation [68]. Both patients relapsed 118 and 80 weeks after treatment. It would appear, therefore, that a brief course (maximum 6 treatment cycles) of standard-dose combination chemotherapy should be the treatment of choice for patients.

Neoadjuvant chemotherapy or chemoradiotherapy followed by adjuvant surgical resection

Following the encouraging results with initial surgery followed by adjuvant chemotherapy discussed previously, several groups began prospective studies of chemotherapy followed by surgery.

The initial reports of preoperative (neoadjuvant) chemotherapy followed by resection in the responders suggested favorable results in small numbers of patients [69-72].

However, the prospective studies reported by Prager et al. and Meyer et al. were disappointing [73, 74]. Only one-third to one-half of the patients entered into these studies were ultimately considered to be surgical candidates, and fewer underwent surgical resection. The survival rates were poor, and no patient with documented N2 disease had long-term survival. Improved selection of patients resulted in more favorable results, especially in patients with postsurgical stage I disease, although no differences could be identified in the 3 clinical stage groups [22,32,33].

In the TLOG neoadjuvant reports, 72 patients were identified prospectively as potential candidates for resection (excluding patients with peripheral lesions). All underwent intensive neoadjuvant chemotherapy. The overall response rate to chemotherapy was 80% (complete response 38%, partial response 42%). After completion of the neoadjuvant chemotherapy, 57 patients were believed to be candidates for resection, but various reasons (protocol randomization, patient's refusal) only 38 patients underwent operation. The overall projected 5-year surgical rate was 36%. In an attempt to assess the contribution of resection, the survival of the resected patients was compared to that of patients who were eligible for operation but did not undergo it. A significantly better survival rate (p=0.049) of the surgical group was noted. Another observation in the Toronto study was the confirmation of the poor survival rate after resection of persistent N2 disease. A reduction in local recurrence was, however, noted in this subset of patients.

The Innsbruck Group reported the results of resection in 24 patients with stage IIIa N2 SCLC [75]. An overall 24% projected 5-year survival rate was recorded, but, more importantly, in 13 patients who completed the comprehensive therapy protocol, there was a projected survival rate of 52%.

This comprehensive multimodality approach consists of an initial cycle of chemotherapy (cyclophosphamide, doxorubicin, vincristine plus cisplatin and etoposide), followed by radical resection when there is at least a 50% partial remission. The surgical resection is followed by a second cycle of chemotherapy, a split course of local thoracic and supraclavicular irradiation, a third cycle of chemotherapy and a second split course of local irradiation and simultaneous prophylactic cranial irradiation. Although some have questioned the efficacy of this approach, these encouraging results suggest that additional studies should be carried out in selected patients with limited N2 disease [76,77].

The prospective randomized neoadjuvant trial conducted by the North American Lung Cancer Study Group (LCSG) has not confirmed the value of neoadjuvant chemotherapy followed by resection plus thoracic irradiation, compared to chemotherapy followed only by irradiation in the management of limited-stage SCLC [78,79]. In the LCSG study, 144 of 217 patients who had achieved an objective response following 5 courses of cyclophosphamide, doxorubicin and vincristine chemotherapy were randomized to undergo either surgical resection of their disease followed by thoracic irradiation and prophylactic cranial irradiation, or thoracic irradiation and prophylactic cranial irradiation only. The remaining 73 patients were not believed to be candidates for resection because of the disease extent, their general medical status, or because they refused the surgical option. Sixty-eight patients were randomized to the surgical option and 76 to radiation therapy alone. Including the patients who underwent surgery off-study, 83% of the patients randomized to the resection group had their tumor resected (6.8% were incomplete resections). Analysis of the surgical specimens revealed persistent SCLC in 73% of the patients, no SCLC in 27%, and NSCLC in 11%. In 6 patients only NSCLC was present, and in 2 the NSCLC was associated with persistent SCLC.

Survival was essentially the same at 24 months for both randomized groups, approximately 20%. Clinical and postsurgical stage did not identify any favorable group or groups of patients. Of interest was the observation that survival was least favorable in those patients with residual NSCLC in the resected specimen. It was concluded that the addition of surgical resection was of no benefit in the management of localized SCLC over conventional treatment alone. It should be noted that only 4 patients (about 5.7%) in the surgical group were initially classified as having clinical stage I disease.

The number of patients with stage I disease in the radiation therapy alone group was not stated but it may be assumed to be of approximately the same order. Thus, almost all patients in this study may be considered to have had more advanced initial disease, with either N1 or N2 involvement.

In addition to this large randomized study, numerous reports of the use of neoadjuvant chemotherapy prior to surgical resection in smaller series of usually more highly selected patients have been reported. Some of these, such as the reports by Yamada et al. and Zatopek et al. revealed no benefit relative to long-term salvage by this approach [80,81].

However, the report of Namikawa et al. showed 75% 2-year survival in 9 patients with stage I disease [82]. Wada et al. reported 80% 5-year survival in stage I and II patients who received chemotherapy first, in contrast to a 37.7% survival in those undergoing initial surgical resection. Unfortunately these data were not statistically significant [66]. In stage III (IIIA or IIIB) patients, the survival rates in the neoadjuvant therapy group and adjuvant therapy group were 10% and 0%, respectively. These authors also noted that, again, the preoperative presence of N2 or N3 disease presaged a poor result.

In 1997, Fujimori et al. reported that patients with clinical stages I and II disease had significantly longer survival than did those with stage IIIA disease (3-year survival rates 73.3% and 42.9%, respectively) with neoadjuvant chemotherapy prior to surgical intervention [83].

The report of Nakamura et al. included 32 patients who were administered induction chemotherapy and 37 patients who underwent initial surgery. The overall 5-year survival rate was 49.5% in stage p-I, 40% in stage p-II, 12.5% in stage p-IIIA, 10% in stage p-IIIB, and 0% in stage p-IV [84] (Table 3, [85-91]).

Multidisciplinary therapy series

In 1998 Rea et al. reported the results of their study from the treatment with surgery, chemotherapy and radiotherapy in 104 patients with SCLC. The overall 5-year survival rate was 32%, with an estimated median survival of 28 months. According to the pathologic

Table 3. Prospective trials of induction chemotherapy followed by surgical resection for SCLC

First author (year)	Reference	Patients, n	Clinical stage I	II	III	Chemo	CR/PR (ORR%)	CSR (%)	CPR (%)
Prager (1984)	73	39	2	12	25	CAVE X2-4	13/21 (88)	11/8(21)	2(5)
Williams (1987)	85	38	–	–	–	CAE X3	5/26(82)	25/21(55)	4(11)
Johnson (1987)	86	24	3	7	14	CAVX 6+EP	(100)	23/15(62)	9(37)
Baker (1987)	87	37	–	–	–	CAE x2	1/19(54)	20/50(54)	2(5)
Shepherd (1989	88	72	21	16	35	CAV X6+EP	27/30(80)	38/33(36)	3(4)
Benfield (1989)	89	8	–	5	3	CAEV x2	5/2(88)	8/8(100)	0
Zatopek (1991)	81	25	10	1	24	COPE x3	10/14(96)	14/10(40)	5(20)
Hara (1991)	90	17	4	6	7	Various	4/10(82)	17/17(100)	?
Fujimori (1997)	83	22	–	–	–	CAV	5/16(95.5)	21/22(95.5)	?
Ederhardt (1997)	91	46	6	2	38	EP	15/28(94)	32/23(50)	11(24)
Nakamura (2004)	84	32	5	7	20	CDDP+ VP-16 CBDCA+VP-16 CAV Chemo+RT	4/32(71.9)	–	3(9.4)

chemo=chemotherapy, CR=complete response, PR=partial response, OPR=overall response rate, CSR=complete surgical resection, CPR=complete pathological response, A=doxorubicin, C=cyclophosphamide, E=etoposide, O=vincristine, V=vincristine, P=cisplatin, CDDP=cisplatin, CBDCA=carboplatin, VP-16=etoposide, CAV=CPA+ADR, CPA=cyclophosphamide, ADR=adriamycin, RT=radiotherapy

stage, the survival data were 52.2%, 30% and 15.3% for stage I, II and III, respectively [92].

Rea et al. concluded that "…In our experience, the complete elimination of SCLC is associated with an improvement in survival (41% at 5 years)" [92].

Kobayashi et al. reported a 23% 5-year survival in 30 patients with bulky N2 SCLC who underwent surgery and concluded that surgical excision of the primary tumor with adjuvant therapy might be necessary to achieve long-term survival and maintain good performance status, and to improve quality of life in these patients [93].

In Lewinski's et al. report with 75 stage I-IIIA patients, many of them with bulky cN2, SCLC received induction chemotherapy with 3 courses of VP16-based treatment. Forty-six patients underwent thoracotomy and 35 of them had resection; the median survival in all 35 patients was 18 months, the 5-year tumor-free survival rate was 29% and the 10-year tumor-free survival rate was 23% [94].

The report of Su et al. from China with 51 cases of limited-stage SCLC showed that 1-, 3-, and 5-year survival rates for patients treated by surgery combined with chemotherapy were 77.5%, 38.5%, and 23.8%, respectively, and those with surgery alone were 41.7%, 16.7% and 8.3%, respectively [95].

Daddi et al. reported on 125 patients with neuroendocrine lung tumors; 20 of them with stage I and II SCLC had undergone surgical excision, with 30% 5-year survival. Twenty-one percent of the patients treated by induction chemotherapy and surgery, and in few cases by surgery and adjuvant chemotherapy, are alive without evidence of the disease for 5 years [96].

The report of Brock et al. included 82 patients with SCLC. Treatment consisted of surgery alone in 11% of the cases, surgery with neoadjuvant chemotherapy in 22%, and surgery with adjuvant chemotherapy in 55%. Prophylactic cranial irradiation was given to 23% of the patients. The 5-year survival of the entire cohort was 42% [97].

Evaluation of indications for surgical treatment

Although the role of surgery in SCLC patients remains a matter of controversy, it is accepted that surgery can be proposed as the first treatment in patients with T1 lesions with no signs of lymph node involvement. This approach is justified from the results of studies that reported acceptable survival rates in stage I SCLC when this was treated by surgery alone [42,45].

Many of the patients in those studies had a small peripheral nodule diagnosed as SCLC at thoracotomy.

In patients with preoperative diagnosis and stage I disease, who are considered for primary resection, adjuvant chemotherapy is strongly recommended and may improve survival compared to surgery alone [44,60,98].

The use of surgery after chemotherapy has been investigated by several authors [32,73].

A study of stage I patients who underwent surgical resection following chemotherapy showed a favorable 5-year survival.

A comparison of patients who had chemotherapy before and after surgery showed no significance differences [72].

The results from surgical series of patients with stage II SCLC are confusing. Some studies reported 5-year survival of 28-50%, similar to that of stage I patients [45,60].

Other investigators reported disappointing results for long-term survival [61].

For this reason, and because of the higher probability of mediastinal involvement in clinical N1 disease, it seems logical to perform surgery only after chemotherapy, and in the context of clinical trials.

No sufficient data are available to assess the role of surgery in N2 SCLC. Salzer et al. reported an overall 5-year survival of 25% in 25 N2 patients after radical resection of the disease [99]. Although no definitive conclusion can be drawn on this basis, given the small population examined in that study, its retrospective nature, and the heterogeneity of the combined treatments, other studies have confirmed the feasibility of surgery after induction chemotherapy in locally advanced, stage II and III SCLC.

Prospective phase II trials showed that in potentially resectable, locally advanced SCLC with limited mediastinal involvement, surgery after chemotherapy was feasible, morbidity was acceptable, and long-term survival was similar to that for NSCLC of the same stage [54,74].

The concept of salvage surgery in SCLC was investigated by Shepherd et al. [22]. The indications for surgery included:

a) little or no response to chemotherapy
b) residual mass >3 cm
c) progression during treatment after initial response
d) relapse after response and
e) elimination of the perfusion and deficiency of the chemotherapeutic agents to reach the tumor (Figures 1,2,3).

Of 18 patients with pure SCLC, only 2 were alive 5 years after surgery. It is of interest that 8 patients in the series presented a mixed SCLC and NSCLC histology.

The results from that study do not support the use

of salvage surgery for non-responding SCLC patients, except for patients with a doubtful diagnosis.

Recommended role of surgical treatment of small cell lung cancer

Intraperative diagnosis of small cell lung cancer

When SCLC is diagnosed at thoracotomy, the choice of the procedure depends on the disease extent, i.e. whether it involves a small peripheral nodule with no lymph node metastases or a central mass with multiple mediastinal involvement. It is logical to perform lung resection and mediastinal dissection if the surgeon judges that local control can be achieved without risking postoperative complications compared to exploratory thoracotomy [100].

In case of T1 or T2 lesions, even if a single mediastinal station harbors microscopic metastases, lobectomy and radical lymphadenectomy can be the procedure of choice.

In case of multiple mediastinal metastases, resection is not worthwhile, and theoretically the mediastinal devascularization can impair the efficacy of chemotherapy. With single or multiple hilar metastases, resection is justified absolutely if the lymph node status does not require pneumonectomy. If so, exploratory thoracotomy may be the best choice.

There are not studies about the value of sleeve resections in these situations.

For centrally located lesions without nodal involvement, pneumonectomy can be performed. However, after pneumonectomy, especially after right pneumonectomy, radiotherapy may not be tolerated at the proper therapeutic doses, and extended surgical intervention can be detrimental in terms of radicality, pulmonary function, morbidity and mortality [101,102].

Preoperative diagnosis of small cell lung cancer

When a diagnosis of SCLC is made preoperatively, an accurate mediastinal dissection is essential, particularly after clinical complete response to chemotherapy.

The best procedure is lobectomy. Pneumonectomy following induction treatment carries a higher risk of respiratory complications and thus it should be performed only in selected cases [101,102].

Since all of these patients are potentially candidates for postoperative radiotherapy, it is recommended that the bronchial stump be protected with flap (Figures 4,5,6).

Figure 4. Intercostal muscle flap coverage of the bronchial stump postoperatively.

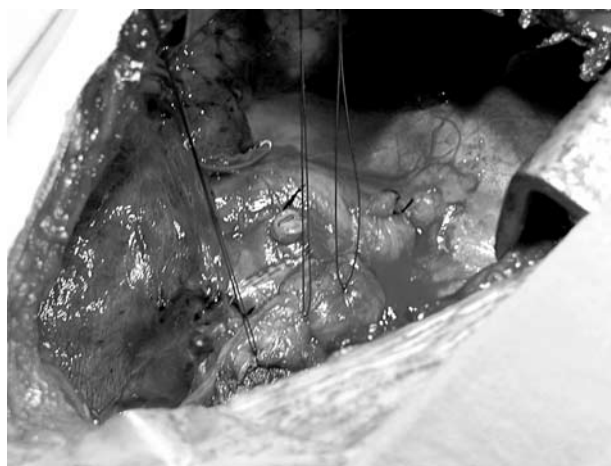**Figure 5.** Reinforcement of the bronchial stump after surgery with flap.

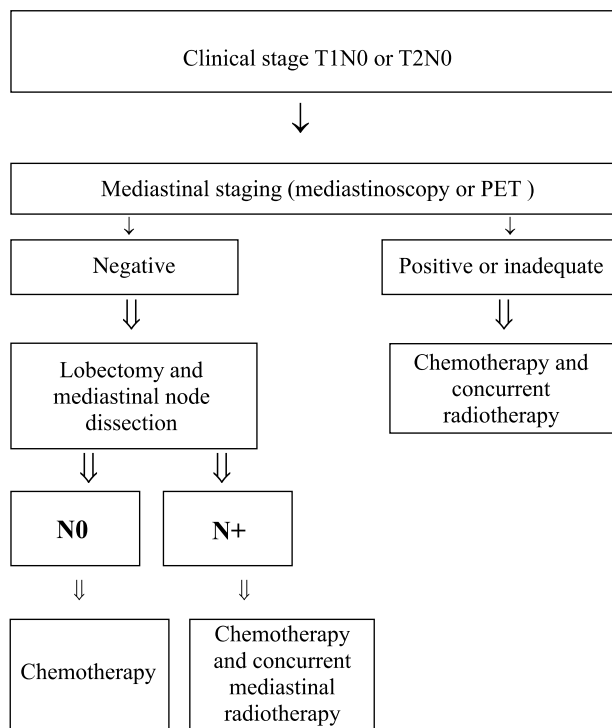**Figure 6.** The bronchial stump coverage and suture line reinforcement after pneumonectomy.

Figure 7. Work-up and initial treatment strategies for clinical stage T1N0,T2N0 small cell lung cancer.

Conclusions

The up to date available data indicate that surgery can be effective in the treatment of SCLC with T1 or T2 lesions without lymph node involvement.

The surgical excision can be considered as the first step of treatment in small T1 or T2 peripheral lesions, followed by chemotherapy.

In more advanced stages of SCLC, chemotherapy should be the first treatment of choice and surgical intervention can be proposed to responding patients, before radical radiotherapy, depending on the pathological stage of disease [103] (Figure 7).

Such an intensive multidisciplinary approach should be always employed in the context of controlled clinical trials [104].

References

1. Mountain CF. A new international staging system for lung cancer. Chest 1986; 89 (Suppl): 225S-233S.
2. Hansen HH, Dombernowsky P, Hirsch FR. Staging procedures and prognostic features in small cell anaplastic bronchogenic carcinoma. Semin Oncol 1978; 5: 280-287.
3. Martini N, Wittes RE, Hilaris BS et al. Oat cell carcinoma of the lung. Clin Bull 1975; 5: 144-148.
4. Mountain C. Clinical biology of small cell carcinoma: relationship to surgical therapy. Semin Oncol 1978; 5: 272-279.
5. Working-party on the evaluation of different methods of therapy in carcinoma of the bronchus: comparative trial of surgery and radiotherapy for the primary treatment of small cell or oat-cell carcinoma of bronchus. Lancet 1966; 2: 979-986.
6. Fox W, Scadding JG. Medical Research Council comparative trial of surgery and radiotherapy for primary treatment of small cell or oat-cell carcinoma of the bronchus. Ten –year follow –up. Lancet 1973; 2: 63-65.
7. Bates M, Levison V, Hurt R, Sutton M. Treatment of oat-cell carcinoma of the bronchus by preoperative radiotherapy and surgery. Lancet 1975; 1: 1134-1135.
8. Levison V. Preoperative radiotherapy and surgery in the treatment of oat-cell carcinoma of the bronchus. Clin Radiol 1980; 31: 345-348.
9. Sherman DM, Neptune W, Weichselbaum R, Order SE, Piro AJ. An aggressive approach to marginally resectable lung cancer. Cancer 1978; 41: 2040-2045.
10. Bergsagel DE, Jenkin RDT, Pringle JF. Lung cancer: Clinical trial of radiotherapy alone vs. radiotherapy plus cyclophosphamide. Cancer 1972; 30: 321.
11. Medical Research Council Lung Working Party. Radiotherapy alone or with chemotherapy in the treatment of small cell carcinoma of the lung.Br J Cancer 1979; 40: 1-11.
12. Shields TW, Humphrey EW, Eastridge CE, Keehn RJ. Adjuvant cancer chemotherapy after resection of carcinoma of the lung. Cancer 1977; 40: 2057-2062.
13. Shields TW, Higgins GA, Matthews MG, Keehn RJ. Surgical resection in the management of small cell carcinoma of the lung. J Thorac Cardiovasc Surg 1982; 84: 481-488.
14. Shore DF, Paneth M. Survival after resection of small cell carcinoma of the bronchus. Thorax 1987; 35: 819-822.
15. Lennox SC, Flavell G, Pollock DJ, Thompson VC, Wilkins JL. Results of resection for oat-cell carcinoma of the lung. Lancet 1968; 2: 925-927.
16. Higgins GS, Shields TW, Keehn RJ. The solitary pulmonary nodule. Ten-year follow-up of Veteran's Administration-Armed Forces Co-operative study. Arch Surg 1975; 110:570-575.
17. Shepherd FA. The role of chemotherapy in the treatment of small cell lung cancer. Chest Surg Clin North Am 1997; 7:113-133.
18. Elliot JA, Osterlind K, Hirsch FR, Hansen HH. Metastatic patterns in small cell lung cancer: correlation of autopsy findings with clinical parameters in 537 patients. J Clin Oncol 1987; 5: 246-245.
19. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small cell carcinoma of the lung? A meta-analysis. J Clin Oncol 1992; 10:890-895.
20. Pingnon JP, Arriagada R, Ihde D et al. A meta-analysis of thoracic radiotherapy for small cell lung cancer. N Engl J Med 1992; 327:1618-1624.
21. Murray N, Coy P, Pater J et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small cell lung cancer. J Clin Oncol 1993; 11: 336-344.
22. Shepherd FA, Ginsberg RJ, Evans WK et al. Reduction in local recurrence and improved survival in surgically treated patients with small cell lung cancer. J Thorac Cardiovasc Surg 1983; 86: 498-504.
23. Comis R, Meyer J, Ginsberg S et al. The impact of TNM stage on results with chemotherapy and adjuvant surgery in small cell lung cancer. Proc Am Soc Clin Oncol 1984; 3:226 (abstr # C-884).
24. Gould VE, Linnoila RI, Memoli VA, Warren WH. Neuroendocrine cells and neuroendocrine neoplasms of the lung. Pathol Annu 1983; 18: 287-330.

25. Ohta M, Hara N, Nakada T et al. **Survival of patients with** resected small cell carcinoma of the lung. Lung Cancer 1982; 22: 459-466.

26. Inglehart JD, Wolf WG, Vernon WB, Shelburne JD, Sabiston DC Jr. Electron microscopy in the selection of patients with small cell carcinoma of the lung for medical versus surgical therapy. J Thorac Cardiovasc Surg 1985; 90: 351-360.

27. Ishida T, Nishino T, Oka T. Surgical treatment of patients with small cell carcinoma of the lung: a histochemical and immunochemical study. Jpn J Surg Oncol 1989; 40:188-193.

28. Matthews MJ, Rozencwerg M, Staquet MJ, Minna JD, Muggia FM. Long-term survivors with small cell carcinoma of the lung. Eur J Cancer 1986; 16: 527-531.

29. Davis S, Stanley KE, Yesner R, Kuang DT, Morris JF. Small-cell carcinoma of the lung. Survival according to histologic subtype: a Veterans Administration Lung Group study. Cancer 1981; 47:1863-1866.

30. Ichinose Y, Hara N, Ohta M et al. **Comparison between** resected and irradiation small cell lung cancer in patients in stages I through IIIa. Ann Thorac Surg 1992; 53: 95-100.

31. Adelstein DJ, Tomashefski JF, Snow NJ, Horrigan TP, Hines JD. Mixed small cell and non-small cell lung cancer. Chest 1986; 89:699-704.

32. Shepherd FA, Ginsberg RJ, Patterson GA, Evans WK, Feld R, for the University of Toronto Lung Oncology Group. 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: 177-186.

33. Shepherd FA, Ginsberg RJ, Feld R, Evans WK, Johansen E. Surgical treatment for limited small cell lung cancer. J Thorac Cardiovasc Surg 1991; 101: 385-393.

34. Magnum MD, Greco FA, Hainsworth JD, Hande KR, Johnson DH. Combined small cell and non-small cell lung cancer. J Clin Oncol 1989; 7:607-612.

35. Karrer K, Shields TW, Denck H et al. The importance of surgical and multimodality treatment for small cell bronchial carcinoma. J Thorac Cardiovasc Surg 1989; 97: 168-176.

36. Fraire AE, Roggli VL, Vollmer RT et al. **Lung cancer heterogeneity:** prognostic implications. Cancer 1981; 47: 1863-1866.

37. Rusch VW, Klimsta DS, Venkatraman ES. **Molecular markers** help characterize neuroendocrine lung tumors. Ann Thorac Surg 1996; 62: 798-810.

38. Shepherd FA, Ginsberg R, Patterson GA et al. Is there ever a role for salvage operation in limited small-cell lung cancer? J Thorac Cardiovasc Surg 1991; 101: 196-200.

39. Yamada K, Sajio N, Kojima A et al. A retrospective analysis of patients receiving surgery after chemotherapy for small-cell lung cancer. Jpn J Clin Oncol 1991; 21: 39-46.

40. Shields TW, Higgins GA Jr, Matthews MJ, Keehn RJ. Surgical resection in the management of small cell carcinoma of the lung. J Thorac Cardiovasc Surg 1982; 84: 481-488.

41. Hayata Y, Funatsu H, Suenasu K et al. **Surgical indications** in small-cell carcinoma of the lung. Jpn J Clin Oncol 1978; 8: 93-100.

42. Shore DF, Paneth M. Survival after resection of small-cell carcinoma of the bronchus. Thorax 1980; 35: 819-822.

43. Prasad US, Naylor AR, Walker WS et al. Long –term survival after pulmonary resection for small-cell carcinoma of the lung. Thorax 1989; 44:787.

44. Sorensen HR, Lund C, Alstrup P. Survival in small –cell lung carcinoma after surgery. Thorax 1986; 41:479-482.

45. Shah SS, Thompson J, Goldstraw P. Results of operation without adjuvant chemotherapy in the treatment of small-cell lung cancer. Ann Thorac Surg 1992; 54:498-501.

46. Smit EF, Groen HJM, Timens W et al. Surgical resection for small-cell carcinoma of the lung: a retrospective study. Thorax 1994; 49:20-22.

47. Meyer J. Five-year survival in treated stage I and II small-cell carcinoma of the lung. Ann Thorac Surg 1986; 42: 668-669.

48. Ohta M, Hara N, Ichinose Y et al. **The role of surgical resection** in the management of small-cell carcinoma of the lung. Jpn J Clin Oncol 1986; 16: 289-296.

49. Cataldo I, Bedini AV, Bidoli P, Ravasi G. Surgical resection plus chemotherapy for stage I-II small cell lung carcinoma (SCLC).Lung Cancer 1988; 4 (Suppl): A85.

50. Soresi E, Borghini U, Grill R et al. **Effectiveness of adjuvant** chemotherapy in resected SCLC-limited disease. Lung Cancer 1988; 4 (Suppl): A156.

51. Watkin SW, Donnely RJ, Green JA. Surgical resection and adjuvant chemotherapy for limited stage small cell carcinoma. Lung Cancer 1988; 4 (Suppl): A85.

52. Shepherd FA, Evans WK, Feld R et al. Adjuvant chemotherapy following resection for small-cell carcinoma of the lung. J Clin Oncol 1988; 6: 832-838.

53. Karrer K. Is the progress in cancer treatment results adequate or are we confronted with a more or less worldwide stagnation? (Guest Editorial). J Cancer Res Clin Oncol 1990; 116: 425-430.

54. Karrer K, Ulsperger E. Surgery for cure followed by chemotherapy in small cell carcinoma of the lung. Acta Oncol 1995; 34: 899-906.

55. Maassen W, Greschuchna D. Small-cell carcinoma of the lung –to operate or not? Surgical experience and results. Thorac Cardiovasc Surg 1986; 34: 71-76.

56. Karrer K, Denck H, Karnicka-Mlodkowska D et al. **The** importance of surgery as the first step in multimodality treatment of small cell bronchial carcinoma. Int J Clin Pharm Res 1990; 10: 257-263.

57. Ulsperger E, Karrer K, Denck H, for ISC Lung Cancer Group. Multimodality treatment for small cell bronchial carcinoma. Eur J Cardiothorac Surg 1991; 5: 306-310.

58. Macchiarini P, Hardin M, Basolo F et al. **Surgery plus adjuvant** chemotherapy for T1-3 N0 small cell lung cancer. Am J Clin Oncol 1991; 14: 218-224.

59. Hara N, Ichinose Y, Kuda T, Asoh H, Yano T, Kawasaki Mohta M. Long term survivors in resected and non-resected SCLC. Oncology 1991; 48: 441-447.

60. Davis S, Crino L, Tonato M, Darwish S, Pelicci PG, Grignani F. A prospective analysis of chemotherapy following surgical resection of clinical stage I-II small cell lung cancer. Am J Clin Oncol 1993; 16: 93-95.

61. Lucchi M, Mussi A, Chella A et al. **Surgery in the management** of small cell lung cancer. **Eur J Cardiothorac Surg 1997;** 12: 689-693.

62. Cataldo I. Long term survival for resectable SCLC. Lung Cancer 2000; 29: 130-132.

63. Kobayashi S, Okada S, Hasumi T, Sato N, Fujimura S.The significance of surgery for bulky N2 small-cell lung cancer: a clinical and in vitro analysis of long-term survivors. Surg Today 2000; 30: 978-986.

64. Suzuki R, Tsuchiya R, Ichinose Y et al. **Phase III trial of** postoperative adjuvant cisplatin/etoposide (PE) in patients with completely resected SCLC. PROC Am Soc Clin Oncol 2000; 19: 142a (abstr).

65. Badzio A, Jassem J, Kurowski K et al. **The role of surgery in**

limited disease SCLC: retrospective comparative study. Eur J Cancer 2001; 37(S6): 61.

66. Wada H, Yokomise H, Tanaka F et al. Surgical treatment of small cell carcinoma of the lung: advantage of preoperative chemotherapy. Lung Cancer 1995; 13: 45-46.

67. Osterlind K, Hansen M, Hansen HH, Dombernowsky P. Influence of surgical resection prior to chemotherapy on the long-term results in SCLC. A study of 150 operable patients. Eur J Cancer Clin Oncol 1986; 22: 589-593.

68. Littlewood TH, Smith AP, Bentley DP. Treatment of SCLC by pneumonectomy and single course high dose chemotherapy. Thorax 1987; 42: 315-316.

69. Hara N, Ohta M, Ichinose Y. Surgical adjuvant chemotherapy for lung cancer. Proc 14th Intern Congr Chemother, Kyoto 1985; 155-157.

70. Pazdur R, Rossof AH, Jensik R. Pulmonary resection following chemotherapy in small cell bronchogenic carcinoma. Proc Am Soc Clin Oncol 1982;I:C-561 (abstr).

71. Valdivieso M, McMurtery M, Farha P et al. Increasing importance of adjuvant surgery in the therapy of patients with small-cell lung cancer. Proc Am Soc Clin Oncol 1982; I: C-576(abstr).

72. Shepherd FA, Ginsberg RJ, Feld R, Evans WR, Johansen E. Surgical treatment for limited small-cell lung cancer. The University of Toronto Lung Oncology Group experience. J Thorac Cardiovasc Surg 1991; 101: 385-393.

73. Prager RL, Foster JM, Hainsworth JD et al. The feasibility of adjuvant surgery in LS-SCLC : a prospective evaluation. Ann Thorac Surg 1984; 38: 622-626.

74. Meyer JA, Gullo JJ, Ikins PM et al. Adverse prognostic effect of N2 disease in treated small cell carcinoma of the lung. J Thorac Cardiovasc Surg 1984; 88: 495-501.

75. Salzer GM, Muller LC, Huber H et al. Operation for N2 small cell lung carcinoma. Ann Thorac Surg 1990; 49: 759-762.

76. Bunn PA Jr. Operation for stage IIIa small cell lung cancer? Ann Thorac Surg 1990; 49: 691.

77. Ginsberg RJ. Operation for small –cell lung cancer-where are we? Ann Thorac Surg 1990; 49: 692-693.

78. Lad T, Thomas P, Piantadosi S. Surgical resection of small cell lung –a prospective randomized evaluation. PROC Am Soc Clin Oncol 1991; 10: 224 (abstr #835).

79. Lad T, Piantadosi S, Thomas P et al. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. Chest 1994; 106 (Suppl 6): S3025-S3028.

80. Yamada K, Saijo N, Kojima A et al. A retrospective analysis of patients receiving surgery after chemotherapy for small cell lung cancer. Jpn J Clin Oncol 1991; 21: 39-45.

81. Zatopek NK, Holoye PY, Ellerbrock NA et al. Resectability of small-cell lung cancer following induction chemotherapy in patients with limited disease (stages II-IIIb). Am J Clin Oncol 1991; 14: 427-432.

82. Namikawa S, Den T, Kimura M, Kusagawa M. The role of surgical resection and the effects of neoadjuvant therapy in the management of small cell lung cancer. Surg Today 1994; 24: 342-346.

83. Fujimori K, Yokohama A, Kurita Y, Terashima M. A pilot phase 2 study of surgical treatment after induction chemotherapy for resectable stage I to IIIA SCLC: Chest 1997; 111: 1089-1093.

84. Nakamura H, Kato Y, Kato H. Outcome of surgery for small cell lung cancer: response to induction chemotherapy predicts survival. Thorac Cardiovasc Surg 2004; 52: 206-210.

85. Williams CJ, McMillan I, Lea R et al. Surgery after initial chemotherapy for localized small-cell carcinoma of the lung. J Clin Oncol 1987; 5: 1579-1588.

86. Johnson DH, Einhorn LH, Mandelbaum I, Williams SD, Greco FA. Postchemotherapy resection of residual tumor in limited stage small cell lung cancer. Chest 1987; 92: 241-246.

87. Baker RR, Ettinger DS, Ruckdeschel JD 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.

88. 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: 177-186.

89. Benfield GF, Matthews HR, Watson DC, Collins FJ, Cullen MH. Chemotherapy plus adjuvant surgery for local small cell lung cancer. Eur J Surg Oncol 1989; 15: 341-344.

90. Hara N, Ohta M, Ichinose Y et al. Influence of surgical resection before and after chemotherapy on survival in small cell lung cancer. J Surg Oncol 1991; 47: 53-61.

91. Eberhardt W, Wilke H, Stamatis G et al. Preliminary results of a stage-oriented multimodality treatment including surgery for selected subgroups of limited disease small cell lung cancer. Lung Cancer 1997;18 (Suppl 1):61 (abstr #235).

92. Rea F, Callegaro D, Favaretto A et al. Long term results of surgery and chemotherapy in small cell lung cancer. Eur J Cardiothorac Surg 1998; 14: 398-402.

93. Kobayashi S, Okada S, Hasumi T, Sato N, Fujimura S. The significance of surgery for bulky N2 small-cell lung cancer: a clinical and in vitro analysis of long-term survivors. Surg Today 2000; 30: 978-986.

94. Lewinski T, Zulawski M, Turski C, Pietraszek A. Small cell lung cancer I-IIIA: cytoreductive chemotherapy followed by resection with continuation of chemotherapy. Eur J Cardiothorac Surg 2001; 20: 391-398.

95. Su XD, Huang ZF, Rong TH, Yang MT. Combined surgical treatment for limited small cell lung cancer: clinical analysis of 51 cases. Ai Zheng 2003; 22: 1099-1101.

96. Daddi N, Ferolla P, Urbani M et al. Surgical treatment of neuroendocrine tumors of the lung. Eur J Cardiothorac Surg 2004; 26: 813-817.

97. Brock MV, Hooker CM, Syphard JE et al. Surgical resection of limited disease small cell lung cancer in the new era of platinum chemotherapy: its time has come. J Thorac Cardiovasc Surg 2005; 129: 64-72.

98. Simon GR, Wagner H. Small cell lung cancer. Chest 2003; 123: 259S-271S.

99. Salzer GM, Muller LC, Huber H et al. Operation for N2 SCLC. Ann Thorac Surg 1990; 49: 759-762.

100. Rostad H, Naalsund A, Jacobsen R et al. Small cell lung cancer in Norway. Should more patients have been offered surgical therapy? Eur J Cardiothorac Surg 2004; 26: 782-786.

101. Waddell TK, Shepherd FA. Should aggressive surgery ever be part of the management of small cell lung cancer? Thorac Surg Clin 2004; 14: 271-281.

102. Chua YJ, Steer C, Yip D. Recent advances in the management of small-cell lung cancer. Cancer Treat Rev 2004; 30: 521-543.

103. Riedel RF, Crawford J. Small-cell lung cancer: A review of clinical trials. Semin Thorac Cardiovasc Surg 2003; 15: 448-456.

104. Szczensy TJ, Szczensa A, Shepherd FA, Ginsberg RJ. Surgical treatment of small cell lung cancer. Semin Oncol 2003; 30: 47-56.