Surgery in the tri-modality treatment of small cell lung cancer. Stage-dependent survival

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Received 21 January 2006; received in revised form 26 April 2006; accepted 1 May 2006

Abstract

Objective: Patients with small cell lung cancer (SCLC) are frequently denied surgical treatment despite growing body of evidence for a longer duration of remission and overall survival, if surgical intervention is integrated in a tri-modality therapy concept including chemotherapy, surgery, and radiotherapy. Methods: A retrospective analysis was performed using data derived from 95 patients with SCLC operated upon over a period of 9 years. A subset of these patients was primarily operated upon and being diagnosed as SCLC only after thoracotomy, received radio-/chemotherapy postoperatively (n = 64, group I). The second cohort had surgery after neoadjuvant chemotherapy which was continued postoperatively in addition to thoracic and cranial radiotherapy (n = 31, group II). The patients in the second group were further divided into two subgroups: complete histological regression of tumor tissue in the mediastinal lymph nodes (group IIA), and those with persistent mediastinal lymph nodal involvement detected after thoracotomy (group IIB).

Results: Group I patients had stage I or II disease, whereas group II patients had clinical stage IIIA or IIIB. The overall 30-day mortality rate was as low as 5%. The median survival was 31.3 months for patients in group I, 31.7 months for adjuvant surgery with complete regression of mediastinal nodes (group IIA), and 12.4 months for adjuvant surgery without regression of mediastinal nodes (group IIB).

Conclusions: Surgical intervention is promising and warrants prospective trials to be evaluated as an important adjunct to multi-modality therapy regimen in SCLC as regards to its impact on relapse free and overall survival.

Keywords: Lung cancer; Surgery; Mediastinal lymph nodes; Neoadjuvant chemotherapy; Radiotherapy

1. Introduction

Small cell lung cancer (SCLC) has considerable propensity for early metastatic dissemination. As a result, systemic chemotherapy remains the cornerstone of treatment. Disregarding the initial tumor stage, it has been reported that more than 80% of the patients show objective response to various chemotherapies [1]. Despite radio-/chemotherapy, local or extra-thoracic recurrences occur in the majority of patients who then will finally succumb to their disease [2]. That is why the most recent treatment strategies are concerned about better local control in addition to the intensive systemic therapy. Unfortunately, subgroups that would benefit from additional surgery have not been identified yet.

It has been observed that neoadjuvant chemotherapy in non-small cell lung cancer (NSCLC) leading to a remission in the mediastinal lymph nodes is a favorable prognostic factor [3]. As the relapse patterns of SCLC and NSCLC do not differ substantially, specially in the metastatic adenocarcinoma in NSCLC, the aim of this work was to study the effect of both primary and ‘adjuvant’ surgery on survival in SCLC as part of a trimodality therapy regimen.

2. Patients and methods

Ninety-five patients with small cell lung cancer who were operated upon during a period of 9 years were included in this retrospective study. Fifteen patients showing no change or tumor progression after chemotherapy were excluded from the analysis because they were not operated upon.
In 64 of these patients (67.4%), histological diagnosis was preoperatively neither bronchoscopically nor mediastinoscopically possible. Thus, the diagnosis of small cell lung cancer could only be established after thoracotomy (group I). For this group we proceeded with surgery, provided there was no mediastinal lymph node invasion and distant metastases being excluded in the preoperative staging. Postoperatively adjuvant chemotherapy and irradiation of the chest (45 Gy) as well as prophylactic cranial irradiation (30 Gy) were scheduled. If the diagnosis was achieved preoperatively (31 patients, stages IIA and IIB), definitive surgery followed neoadjuvant chemotherapy, which was continued postoperatively in addition to thoracic (45 Gy) and cranial (30 Gy) radiotherapy (group II).

The surgically resected mediastinal lymph nodes after systematic lymph node dissection were evaluated histopathologically for the presence of viable tumor cells (group IIA lymph node-negative, group IIB lymph node-positive).

2.1. Staging

We did not stage according to limited or extensive disease because we think the TNM classification system better reflects the stages of disease, resulting in more precise staging, discriminating between choices of very different options of therapy.

The diagnostic work-up for all patients consisted of: X-ray of the chest, as well as thoracic, brain and abdominal computer assisted tomography, bronchoscopy, skeletal scintigraphy, and mediastinoscopy.

2.2. Restaging before 'adjuvant' surgery

All the diagnostic procedures for primary staging were repeated, with the exception of mediastinoscopy which was only repeated if mediastinal masses of unknown significance still persisted after neoadjuvant chemotherapy. In the time period in which the study was performed there was no endobronchial ultrasound (EBUS) available to evaluate the mediastinal lymph nodes.

2.3. Histopathological diagnosis

For a histological diagnosis patients were subjected to bronchoscopical biopsy and bronchoalveolar lavage to harvest tissue or cells for examination. The diagnosis of SCLC has been secured by immunohistochemistry in addition to the routine histopathological examination.

2.4. Pre- and postoperative chemotherapy

As patients were referred to us from different centers, there was no uniform approach to chemotherapy, different modern protocols as platin doublets or anthracycline-containing regimen were used, and typically four, but no more than six cycles have been administered.

Using the Kaplan—Meier curve [4], survival was estimated starting at the time of operation. Comparison of survival, taking different discriminative factors into consideration, was tested for significance by the log rank test [5].

3. Results

In the majority of patients, the diagnosis of small cell lung cancer was only achieved after thoracotomy (n = 64). All of these patients had tumor stage I (n = 20) or II (n = 44) according to the staging system of Mountain 1997 [6]. Patients who underwent neoadjuvant chemotherapy were preoperatively diagnosed as N2-disease or as T4-tumors after bronchoscopy and mediastinoscopy (stage IIA, n = 25, and stage IIB, n = 6).

Mediastinal lymphadenopathy was reevaluated by a mediastinoscopy if a reduction of size was not seen after neoadjuvant chemotherapy (15 patients). In all 15 cases no tumor cells could be histologically demonstrated invading the lymph nodes harvested mediastinoscopically (false negative in two patients). The remaining 16 patients were not subjected to mediastinoscopy before definitive surgery, and the lymph nodes harvested intraoperatively proved to be invaded with malignant cells in 15 cases (N2 disease).

The clinical tumor stages are shown in Table 1.

Histologically, most of the tumors (84%) were pure small cell carcinoma, whilst combined small cell carcinoma comprised 16% each.

3.1. Surgery

Lobectomy was the most commonly performed operation (n = 75). In 9 patients a bilobectomy was performed and in 11 patients a pneumonectomy was necessary due to centrally located tumors or tumors crossing the interlobar fissure affecting more than one lobe.

3.2. Morbidity

The most common postoperative complications were atrial fibrillation (n = 6), atelectasis requiring bronchoscopy (n = 5), pneumonia (n = 3) and wound infection (n = 2).

3.3. Mortality

The overall 30-day mortality was 5%. Two patients died related to combined respiratory and circulatory failure. Three patients died of myocardial infarction, pneumonia,

![Table 1](image)

Pre-treatment clinical tumor stage (cTNM) of 95 patients with trimodality therapy for small cell lung cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Group I, n = 64</th>
<th>Group IIA, n = 16</th>
<th>Group IIB, n = 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA: T1 N0</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB: T2 N0</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIA: T2 N0</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB: T3 N0</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA: T1-3 N2 (n = 25)</td>
<td>14</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>IIIB: T4 N1-2 (n = 6)</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Group I: patients diagnosed as SCLC only after thoracotomy.
Group IIA: surgery after neoadjuvant chemotherapy with complete histological regression of tumor tissue in the mediastinal lymph nodes.
Group IIB: surgery after neoadjuvant chemotherapy with persistent mediastinal lymph nodal involvement.

n = number of patients.
and severe cardiac arrhythmia, respectively (Table 2). If we determine the mortality in relation to the performed procedure, we have a mortality of 3.57% for patients undergoing lobectomy, and a mortality of 18.18% in patients subjected to pneumonectomy (2 mortalities out of 11 pneumonectomies).

3.4. Survival

After primary operation, patients had a median survival of 31.3 months. Patients with multi-modality therapy and clearance of lymph node metastases in the resected specimen had a mean survival of 31.7 months, while patients with vital tumor in mediastinal lymph nodes despite neoadjuvant chemotherapy preoperatively had a very poor median survival of 12.4 months (Fig. 1).

3.5. Follow-up

As regard to the follow-up, it was carried out using written forms sent to the primary care physicians responsible for the medical care of the patients. The patients were followed up for 1–60 months postoperatively, with a mean follow-up period of 28.7 ± 18.4 months (as discussed in Section 3).

4. Comment

Bimodal therapy, consisting of chemotherapy and irradiation, has been considered as a standard approach for the treatment of SCLC for the last three decades, as this combined therapy has a significant advantage over surgery alone. However, the role and relevance of surgical intervention has never been defined in a multidisciplinary approach. The sequence of chemotherapy, radiotherapy, and lung resection are still the subject of ongoing controversial discussions [7].

It is quite evident that the patient population in our study does not reflect the typical distribution of stages in patients with SCLC commonly favoring advanced extensive disease manifestations. It represents, however, the typical stage distribution in patients with SCLC who are referred to surgery. In our patient collective we found an incidence of 21% in stage I and 46% in stage II. This could be attributed to the fact that our clinic is in an industrial and mining region where regular routine medical check-ups are obligatory, leading to early incidental detection of the lesions, in addition to the high selectivity in reference to surgery. Badzio et al. [7] in 2004 presented a similar pattern with 38% of his patients having N0, 32% N1, and 40% N2 affection. A similar incidence of stages I and II with 51.5—59% and stage IIIA of 30.4—48.5% was also presented in other studies [8,9]. Eberhardt and Korfee [10] in 2003, on the other hand, presented a study with 26% of patients in stages I and II, versus 39% in stage IIIA and 35% in stage IIIB.

Another evident finding is the substantial number of patients with T3 N0 affection (44 cases). Through the preoperative mediastinoscopy and the intraoperative sampling, lymph nodes were proven free of tumor invasion. To exclude that these patients had a locally malignant tumor or slow growing carcinoid, special attention was drawn to these cases and the nature of SCLC has been secured by immunohistochemistry in addition to the routine histopathological examination.

5. Primary operation

Few reports exist about promising long-term results after surgical treatment of small cell lung cancer stage I without any type of adjuvant therapy. The Brompton group reported a 5-year survival of 57.1% in a study comprising only 14 patients [11]. None of the five patients with stage II enjoyed a 5-year survival. In addition to the small number of patients in the

<table>
<thead>
<tr>
<th>Group</th>
<th>Primary surgery</th>
<th>Adjuvant surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Lobectomy, bilobectomy (n = 84) 57</td>
<td>14 13</td>
</tr>
<tr>
<td>IIA</td>
<td>Pneumonectomy (n = 11) 7</td>
<td>2 2</td>
</tr>
<tr>
<td>IIB</td>
<td>Surgical margin</td>
<td></td>
</tr>
<tr>
<td>R0 resection (n = 90) 64</td>
<td>14 12</td>
<td></td>
</tr>
<tr>
<td>R1 resection (n = 5) 0</td>
<td>2 3</td>
<td></td>
</tr>
<tr>
<td>Mortality (n = 5) 3</td>
<td>1 1</td>
<td></td>
</tr>
<tr>
<td>Median survival (months) 31.3</td>
<td>31.7 12.4</td>
<td></td>
</tr>
</tbody>
</table>

**Group I**: patients diagnosed as SCLC only after thoracotomy.
**Group IIA**: surgery after neoadjuvant chemotherapy with complete histological regression of tumor tissue in the mediastinal lymph nodes.
**Group IIB**: surgery after neoadjuvant chemotherapy with persistent mediastinal lymph nodal involvement.

Fig. 1. Cumulative survival in 95 patients with trimodality therapy for small cell lung cancer using Kaplan–Meier survival curve. Group I: patients diagnosed as SCLC only after thoracotomy; group IIA: surgery after neoadjuvant chemotherapy with complete histological regression of tumor tissue in the mediastinal lymph nodes; group IIB: surgery after neoadjuvant chemotherapy with persistent mediastinal lymph nodal involvement.
study, further selection was attributed to the fact that all patients with mediastinal lymph node metastases were primarily excluded from the study protocol.

A recently published retrospective study from Norway also supports the potential significance of surgical therapy for the management of stage I small cell lung cancer: The 5-year survival rate was 44.9% in the resected group but only 11.3% in conservatively treated patients [12].

In our study of 64 patients with stages I and II who all had postoperative chemotherapy as well as cranial and thoracic radiation, a 5-year survival of 43% and a median survival of 31.3 months were observed. According to a publication of a group from Danzig (surgery followed by chemotherapy versus non-surgical management), a median survival of 28 and 17 months in stages I and II, respectively, in the surgical arm, and 13 or 12 months in the non-surgical arm was demonstrated [7].

The published 5-year survival after primary surgery, demonstrate variable results ranging from 43.3 to 13% [11,13]. This had to be expected, as heterogeneous tumor stages were included in all these studies, validity of the data was further diluted by missing information on histological subtypes.

Four to six cycles of adjuvant chemotherapy are generally advised postoperatively, and in case hilar or mediastinal lymph nodes are affected, additional thoracic irradiation is indicated [7]. As part of the trimodality approach, therapy of the patients in our study comprised four to six cycles of adjuvant chemotherapy (cisplatin or carboplatin, etoposide), as well as thoracic and cranial irradiation postoperatively. According to a meta-analysis of randomized studies, cranial irradiation reduces the risk of cerebral metastasis in stage I patients to about 50% and has a modest impact on survival [14].

6. Adjuvant surgery

Our data support the importance of restaging the mediastinal lymph nodes after neoadjuvant chemotherapy. Out of 16 patients who had no radiological evidence of nodal enlargement and thus not been subjected to mediastinoscopy, 13 patients proved to have N2 disease in the postoperative histopathological examination of the resected lymph nodes. Alternative to mediastinoscopy, endobronchial ultrasound (EBUS) is now available as a very useful diagnostic tool in that setting.

Our patients with stage III disease had benefit from ‘adjuvant lung resection’, only if mediastinal lymph nodes harvested during surgery proved to be free of metastatic spread (Fig. 1).

In the 15 patients with persistence of viable tumor cells in the mediastinal lymph nodes, none survived more than 3 years. This was reflected by a median survival time of 31.7 months in patients with negative lymph nodes, and 12.4 months in patients with positive lymph nodes, respectively. These results coincide with the results presented by Lewinski et al. in 2001 in a prospective study of 75 patients: After three courses of induction treatment, 46 patients underwent thoracotomy and 35 of them were resected. The median survival in the ypN0 and ypN1 subsets was 25.1 months, whereas in ypN2 disease, the median survival was only 13.8 months. The authors conclude that surgery should not be performed in the patients with persistent N2 disease [8].

In comparison to these data, patients with limited stage disease SCLC treated only with chemotherapy had a median survival of 10—15 months. With addition of chest radiotherapy, survival was further prolonged to 12—20 months [15]. This demonstrates the additional benefit of surgery in the setting of trimodality therapy.

According to Nakamura et al. [9], response to chemotherapy is an important prognostic factor, as patients with pathological down-staging showed a survival benefit in comparison to those without any change of the initial staging (5-year survival 30% and 15%, respectively, p = 0.03).

7. Conclusions

 Patients with small cell lung cancer stages I and II can be treated with promising results using a combination of primary surgery and adjuvant chemotherapy as well as thoracic and cranial irradiation. Also the promising results in patients with small cell lung cancer stage IIIA, which comprises the important second group without mediastinal nodal affection, warrant a prospective clinical trial to evaluate surgery as an important adjunct to multi-modality therapy regimen in SCLC as regards to its impact on relapse free and overall survival. Patients in stage III seem to benefit from lung resection after neoadjuvant chemotherapy if complete clearance of viable tumor cells in mediastinal lymph nodes is achieved preoperatively. Thus, after neoadjuvant chemotherapy, we restage all patients to rule out the presence of N2 disease prior to definitive surgery. This could be accomplished through remediastinoscopy or EBUS.

References


