Small cell lung cancer in Norway. Should more patients have been offered surgical therapy?

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Objective: The final outcome of patients with small cell lung cancer (SCLC) is poor with an overall 5-year survival rate of less than 10%. Therefore, the question of surgery in patients with a technically-operable solitary tumor has been raised. The purpose of this study was to identify the proportion of patients with operable SCLC and to assess the prognosis of different treatment strategies. For patients who were operated, we compared the resection specimens from patients with more than 5-year survival with those with shorter survival to see whether the specimens belonged to different subclasses of SCLC.

Methods: In Norway all clinical and pathologic departments submit reports on cancer patients to the Cancer Registry. The Registry also has a law-regulated authority to collect supplemental information regarding diagnosis, treatment and outcome for all cancer patients from the hospitals in charge. All reports on patients diagnosed as having SCLC in limited disease or unknown stage during the time interval 1993–1999 were reviewed. Patients with a T2-tumor, in whom a pneumonectomy would have to be performed, were classified as potentially operable. Five-year relative survival was calculated for patients diagnosed in 1993–1997.

Results: During the actual period 2442 individuals with SCLC were identified. The majority was treated with conventional chemotherapy or concurrent chemoradiotherapy while 38 underwent surgical therapy. Following reclassification of 697 patients reported to have limited disease or unknown stage 180 were judged to be in stage I. In addition to the 38 resected patients 14 were considered fit for surgery technically and medically while 97 were found to be potentially operable treatment modalities apart from surgery yielded a 5-year survival rate, 7%. For stage I (N = 96) the rate was 11.3% in conventionally treated patients compared to 44.9% for those who underwent surgical resection. By pathological review of surgical specimens a diagnosis of SCLC was confirmed in all patients treated by surgery in the groups with long and short survival.

Conclusion: This investigation demonstrates that patients with SCLC having a peripherally located tumor should be referred to surgery, as long time survival is far better than for conventionally treated patients.

Keywords: SCLC; Surgical resection; Survival

1. Introduction

Small cell lung cancer (SCLC) comprises 15–20% of all malignant lung tumors and in the majority of cases the tumor has disseminated or is locally advanced at the time of diagnosis and thus unresectable. The apparent futility of surgery as treatment for patients with resectable SCLC tumors was demonstrated in several studies from the 1960s and forward [1–3]. Thus, chemoradiotherapy has been the standard treatment since the early 1970s. However, the final outcome is still poor with an overall 5-year survival of less than 10% [4]. Relapses usually occur within 2 years despite treatment even in patients with very limited disease [5–8]. The question of surgery in SCLC, especially when the tumor presents as a technically-operable solitary nodule (T1–T2) without signs of distant metastases or involvement of mediastinal lymph nodes (N0–N1), has again been raised [2,3].

This study was undertaken to identify the proportion of patients with lung cancer who had a technically-operable SCLC at the time of diagnosis in a national, unselected...
patient population (Norway) 1993–1999. We also wished to assess the prognosis of different treatment strategies chosen for patients reported to have SCLC, classified as limited disease at time of diagnosis during the time period 1993–1997. For patients who were operated, we wished to compare the resection specimens from patients with more than 5-year survival with those with shorter survival to see whether the specimens belonged to different subclasses of SCLC.

2. Materials and methods

The investigation included all patients in Norway with a diagnosis of SCLC between 1993 and 1999. In Norway, notification of all forms of cancer is mandatory and regulated by law. All clinical and pathologic departments submit reports on cancer patients to the Cancer Registry. The Registry also has a law-regulated authority to collect supplemental information as needed regarding diagnosis, treatment and outcome for all cancer patients from the hospitals in charge. Furthermore, the Registry receives death certificates from the Central Bureau of Statistics regarding all patients having cancer as the cause of death. All reports on patients diagnosed as having SCLC/limited disease (LD) or unknown stage during the time interval 1993–1999 were reviewed. The tumor was reclassified from the two-stage system originally introduced by the Veterans Affairs Lung Study Group (VALSG) to the more descriptive TNM staging system of Mountain [9] which describes the extent and burden of the disease more accurately. If cancer reports were insufficiently filled in for the investigators (HR, AN) to perform reclassification, supplemental clinical information and in some cases radiological investigations (CT thorax) were reviewed. Patients classified as having stage Ia and Ib disease (T1-2 N0 M0), in whom a lobectomy would have to be performed, were considered technically operable in this setting. These tumors were classified as being peripherally located. Tumors, which were visible on bronchoscopy in whom a pneumonectomy would have to be performed, were classified as centrally located.

Five-year relative survival was calculated for those patients diagnosed in 1993–1997.

The resection specimens from all patients with SCLC treated by surgery in 1993–1997 were examined by two experienced pathologists independently of each other to verify the histological diagnosis. The revised reports were then divided into two groups according to length of survival of the patients; those with short survival (<5 years), and those with long survival (>5 years), to see whether short or long survival could be due to differences in histology. Specimens reclassified as indeterminate were further characterized by immunohistochemistry with antibodies to cytokeratin, CD 56, synaptophysin and chromogranin.

3. Results

During the time period 1993–1999 lung cancer was diagnosed in 13,489 patients in Norway. Two thousand four hundred and forty two individuals had SCLC representing 17 and 20% of all lung cancers in men and women, respectively (Table 1). The incidence of SCLC was stable throughout the period in men whereas an increase was seen in women. The majority of patients were treated with combined chemotherapy or concurrent chemoradiotherapy, doxorubicin, cyclophosphamide, vincristin or a cis-platinum containing regimen. Surgical resection was performed in 38 patients, 1.8 and 1.2% of all patients with SCLC in men and women, respectively. There was no age difference in operated and not operated patients. Lobectomy was the most common procedure while seven underwent pneumonectomy (Table 2). Additional treatment modalities were given to 25 patients: 16 were given combined chemotherapy, two received radiotherapy and seven combined chemoradiotherapy.

Clinical and pathologic staging in 36 operated patients are given in Table 3. Two patients underwent resection abroad, thus their complete data are therefore not available. The preoperative diagnostic accuracy for staging was 61% (22 of 36). Nine patients were transferred from stage I to stage II because hilar node invasion was discovered during surgery. Three of these were alive 5, 4 and 4 years postoperatively. The remaining died from 1 month to 4 years after the resection.

Following reclassification of 697 patients reported to have limited disease or unknown stage, 180 of them were
judged to be in stage Ia or Ib. Patients registered with extensive disease \( (N = 1745) \) were not reclassified.

The aim of the remaining part of the study was to identify the proportion of patients in whom surgery from a technical point of view could have been performed, (stage Ia and Ib) in addition to the 38 patients that had been resected. We reviewed case histories from the remaining 142 conventionally treated patients considered to have stage I disease. In 31 patients definite medical contraindications were identified, the most frequent being advanced cardiovascular disease or poor general health (Table 4). Finally, 14 patients with disease in stage Ia were considered fit for surgery technically and medically while 97 with stage Ib disease were found to be potentially operable. The majority of the latter had centrally-located tumors, which only could have been removed by pneumonectomy. Thus, in these 111 patients no medical risk factors associated with surgery were identified.

### 3.1. Survival

A total of 1727 patients were treated for SCLC during the period 1993–1997. The 5-year relative survival rate was calculated for patients treated with combined chemotherapy, radiotherapy, concurrent chemoradiotherapy, palliation and surgical resection (Table 5), and presented graphically year by year according to different treatment modalities (Fig. 1). All patients who survived 5 years had peripheral tumors, three of them had minor resections. Nine of these 10 patients, received adjuvant treatment; chemotherapy \( (N = 5) \) or chemoradiotherapy \( (N = 4) \). All five patients who underwent pneumonectomy died within 5 years. Treatment modalities apart from surgery yielded a 5-year survival rate <7%. For stage Ia and Ib \( (N = 96) \) the survival rate was 11.3% [95% confidence interval: 4.2%, 18.4%] in conventionally treated patients compared to 44.9% [CI: 23.9%, 65.9%] for those who underwent surgical resection. The term ‘other combinations’ denotes steroids added to one or more of the treatment regimens.

Of 140 patients with IIIb disease only eight were alive after 5 years while 39 of 40 patients with disease in stage IV at the time of diagnosis died within 3 years.

### 3.2. Pathological findings

By pathological review of surgical specimens a diagnosis of SCLC was confirmed in all patients treated by surgery in the groups with long and short survival, respectively. In cases where immunohistochemistry was performed the neuroendocrine nature of the tumor was confirmed. Only one patient had a mixed tumor of SCLC and adenocarcinoma. There was no difference in the specimen subclasses between survivors and non-survivors.

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**Table 3**

Relationship between c-stage and p-stage in 36 resected patients with SCLC

<table>
<thead>
<tr>
<th>c-stage</th>
<th>p-Stage</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ia</td>
<td>Ib</td>
</tr>
<tr>
<td>Ia</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Ib</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>12</td>
</tr>
</tbody>
</table>

**Table 4**

Medical contraindications in patients considered to be technically operable

<table>
<thead>
<tr>
<th>Medical contraindications</th>
<th>Stage Ia</th>
<th>Stage Ib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Other diseases</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Poor general condition/advanced age</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Reduced pulmonary function</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>27</td>
</tr>
</tbody>
</table>

**Table 5**

Five-year relative survival in 1727 patients with SCLC in the period 1993–1997 related to treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Relative survival (%)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined chemotherapy</td>
<td>606</td>
<td>1.4</td>
<td>[0.4–2.4]</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>100</td>
<td>3.5</td>
<td>[0–7.4]</td>
</tr>
<tr>
<td>Concurrent chemoradiotherapy</td>
<td>426</td>
<td>7.4</td>
<td>[4.9–9.9]</td>
</tr>
<tr>
<td>Other combinations</td>
<td>56</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Palliation</td>
<td>510</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Surgical resection</td>
<td>29*</td>
<td>44.9</td>
<td>[23.9–65.9]</td>
</tr>
</tbody>
</table>

\* Eighteen patients received adjuvant treatment.
4. Discussion

The major findings of this study was that the 5-year survival rate after surgical resection was excellent compared to other treatment modalities and that more patients in the series could have been operated upon. By pathological review of the surgical specimens the preoperative diagnosis of SCLC was confirmed. Few studies have performed TNM-staging of patients with SCLC. Sheperd et al. [10] found in their retrospective study that appropriate staging was important for evaluation of surgery in the management of patients with SCLC. Patients with SCLC are usually classified as having limited or widespread disease. Limited disease includes stages I, II, IIIa and IIIb, while disseminated disease applies to stage IV. Nearly 26% of patients reported as having SCLC/LD in the present series were found to be in stage I (a and b). The percentage of patients with SCLC stage Ia and Ib and thus candidates for surgical resection has previously been found to be less than 10%. [11–13]. The relatively high proportion of patients reported to have SCLC/LD and classified to be in stage I disease in this series may result from inadequate preoperative investigations because additional diagnostic procedures were stopped when the histological diagnosis of SCLC was given. They were then considered inoperable and candidates for conventional chemoradiotherapy.

Still, many lung physicians do not consider patients with SCLC as candidates for surgery, even patients with peripherally located tumors only. From our point of view peripheral lesions suspicious of malignancy should be removed surgically without preoperative confirmed histology unless serious contraindications exist. Preoperative needle biopsies of such lesions are unnecessary in the majority of cases. It is likely that patients with SCLC/LD do not undergo adequate preoperative investigation. Thus, some patients in our material considered to have technically resectable tumors may in fact have had more advanced disease. Before surgical resection rigorous staging procedures are necessary in these patients, bone marrow biopsies and CT scanning of the brain should be performed. On the other hand, as long as a diagnosis for SCLC is considered a contraindication for surgery no further diagnostic work will usually be conducted.

Morphologically, SCLC often appears different in small biopsies than in surgical specimens. Compared to small preoperative biopsies the cell size in resected specimens appears larger, there is less crush artifact, greater preservation of cytoplasm and often better-preserved cell boundaries [14]. This may explain why a diagnosis of combined small cell (SC)/large cell (LC) carcinoma or large cell carcinoma may erroneously be made on a surgical specimen [14]. By applying the criteria given by Nicholson [14], we could not find any combined SC/LC or LC carcinoma among our patients treated with surgery.

The favorable survival rate of 44.9% in the small group of resected patients in the present series is better than in some other reports [2,15], but comparable to Sheperd et al [16] who obtained a projected 5-year survival rate of 36% in a group of patients which also included stages II and IIIa, (36 and 48 patients, respectively). Similarly, Hara et al. [17] reported a 5-year survival rate of 64% for stage I and 45% for stage II in resected patients. In the present series of operated patients the influence of adjuvant chemoradiotherapy on survival cannot be evaluated because of small number of patients in each group. The effect of such therapy is not clearly documented [2]. However, in 37 operated patients with SCLC, there was a more favorable 5-year survival in those given adjuvant chemotherapy [18].

Since SCLC often have proved to be a disseminated disease in spite of results of preoperative investigation, the majority of authors claim that the role of surgery in SCLC must be in the context of combined modality treatment given as pre- or postoperative chemotherapy to eradicate micrometastases [10,18,19].

It is worth noticing that seven of the resected patients required pneumonectomy for radical treatment. None were alive after 5 years. It is possible that centrally-located T2 tumors have a different biology than peripherally located T2 tumors. The 5-year survival rate in patients with disease in stage Ia and Ib who did not undergo surgery was rather poor (11.3%). Maranzano et al [20] achieved a 5-year survival rate of 25% in 55 patients with limited SCLC treated with chemotherapy. This is an impressive result since this group of patients probably contained some with more advanced disease than stage Ia and Ib.

5. Conclusion

This investigation demonstrates that patients with SCLC in stage Ia and Ib having a peripherally located tumor should be referred to surgery as long time survival is good. The patients must, however, be subjected to an extensive preoperative investigation as the probability of metastasis is high in patients with this histologic subtype of cancer. Our results also indicate that patients with newly developed indeterminate solitary nodules can be operated on without preoperative percutaneous fine needle cytology as the patients should be treated surgically independent of type of malignant histology.

References


