Screening for Small-Cell Lung Cancer: A Follow-Up Study of Patients With Lambert-Eaton Myasthenic Syndrome

Maarten J. Titulaer, Paul W. Wirtz, Luuk N.A. Willems, Klaas W. van Kralingen, Peter A.E. Sillevis Smitt, and Jan J.G.M. Verschuuren

ABSTRACT

Purpose
A small-cell lung carcinoma (SCLC) is found in 50% of patients with Lambert-Eaton myasthenic syndrome (LEMS). We evaluated screening to optimize screening strategy for SCLC. It is important to detect these tumors early in newly diagnosed patients with LEMS to offer optimal patient treatment.

Patients and Methods
A large nationwide cohort study of consecutive patients in the Netherlands, seen between 1990 and 2007, were screened for the presence of a tumor using chest x-ray, computed tomography of the thorax (CT-thorax), [18F]fluorodeoxyglucose positron emission tomography (FDG-PET), bronchoscopy, and/or mediastinoscopy.

Results
SCLC was found in 54 patients, and in 46 patients, no tumor was found during a median follow-up of 8 years (range, 3 to 26 years). All patients with SCLC had a positive smoking history and 86% were still smoking at diagnosis. SCLC was found in 92% of these patients within 3 months and in 96% within a year. At first screening, CT-thorax detected an SCLC in 45 patients (83%), whereas chest x-ray found the tumor in only 23 patients (51%). An SCLC was found during secondary screening in another nine patients (median, 3 months; range, 1 to 41 months). In six patients, a lung tumor was found by CT-thorax or FDG-PET, and in three patients, extrapulmonary metastases were found, initially without identifiable tumor mass on CT-thorax.

Conclusion
In almost all patients (96%), the SCLC was found within 1 year of diagnosis. CT-thorax scans detected most of the tumors (93%) and was far more sensitive than chest x-ray (51%). FDG-PET may have additive value in selected cases. We propose a screening protocol based on CT-thorax and FDG-PET.

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INTRODUCTION

Lung cancer is one of the most frequent types of cancer and is the number one cause of cancer-related death in both women and men in the United States and in Europe.1-2 Small-cell lung cancer (SCLC), representing 13% to 20% of all lung cancers, is associated with an aggressive clinical course and poor long-term outcome.3 A small percentage of patients with SCLC have a paraneoplastic neurologic syndrome, of which the most frequent is Lambert-Eaton myasthenic syndrome (LEMS). LEMS is a disease of the neuromuscular junction, characterized by proximal muscle weakness, areflexia, and autonomic dysfunction.4 It is caused by antibodies, directed against P/Q-type voltage-gated calcium channels (VGCC) in the presynaptic nerve terminal.5 The same VGCCs are expressed by SCLC, suggesting that autoimmunization by the tumor is causing LEMS.7

Only 1% to 3% of patients with SCLC have LEMS.5,9 Between 40% to 60% of LEMS patients have SCLC,10-14 which results in an a priori chance of 50% to carry an SCLC at the moment of diagnosis of LEMS.12,13 This is a major clinical concern for the patient as well as for the doctor. Smoking and the absence of HLA-B8 are factors associated with a higher risk of having an underlying tumor.16 Most SCLCs are found within 2 years of diagnosis of LEMS. Discovery of a tumor has been described at more than 5 years after diagnosis of LEMS,17 and one anecdotal case with an interval of even 12 years exists.18

Screening recommendations for SCLC in patients with a paraneoplastic syndrome, like LEMS, consist of repeated radiologic imaging, with,
among other modalities, computed tomography of the thorax (CT-thorax). These screening protocols are based on expert opinion, and no supporting evidence based on clinical data is available. Recent discussions about screening for lung cancer in risk groups\(^2\) have resulted in the start of large randomized controlled trials. The National Lung Screening Trial has been started to determine the use of screening by chest x-ray versus CT-thorax, and the Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) trial will compare CT-thorax versus no screening.\(^2\)

We have determined the outcome of actual screening in a large cohort of patients with LEMS with a high a priori risk of carrying an SCLC. Our results apply to patients with LEMS, but could also be helpful for the design of screening protocols for lung cancer in patients in general.

### PATIENTS AND METHODS

We included all Dutch patients with LEMS with and without SCLC seen in our neurology outpatient clinic between 1990 and 2006. Our clinic is a university neuromuscular center with special interest and expertise in disorders of the neuromuscular junction. Nationwide referral and inclusion started from July 1, 1998, as described before.\(^1\) In 1998, all patients alive were seen. From this moment, all data were collected prospectively.

Diagnostic criteria for LEMS were the presence of VGCC antibodies and characteristic clinical features (proximal muscle weakness, lowered tendon reflexes, autonomic symptoms). Electromyography supported diagnosis if it comprised reduced resting compound muscle action potential amplitude that increased more than 100% after high-frequency repetitive nerve stimulation or maximal voluntary contraction.

After obtaining informed consent, we (P.W., M.T., P.S.S., or J.V.) interviewed and examined the patients. Of 13 patients who could not be seen in our clinic, detailed clinical information was obtained from hospital records. We recorded demographic and clinical features, including date of onset of LEMS, date of diagnosis of LEMS and date of diagnosis of SCLC, and results of diagnostic tests. Because there was no uniform diagnostic screening protocol, our study reflects the results of cancer screening in daily practice in several centers in the Netherlands. A histologic or cytologic diagnosis of SCLC was mandatory. To diagnose a patient as having LEMS without a tumor, a follow-up of at least 3 years after diagnosis of LEMS was necessary. Disease stage was defined as limited if the tumor was confined to one hemithorax and ipsilateral supraclavicular lymph nodes. This is compatible with a TNM/International Association for the Study of Lung Cancer stage I through IIIB.\(^1\)

Patients were considered smokers if they had consumed one or more cigarettes per day for at least half a year or a lifetime consumption of 200 cigarettes or more. Median values for age were compared using the Mann-Whitney U test. Contingency tables were analyzed using a \(\chi^2\) test.

### RESULTS

#### Characteristics

LEMS was diagnosed in 104 patients. Four patients were excluded, because follow-up after diagnosis was less than 3 years. In 54 of 100 patients, an SCLC was found. In 1998, 33 patients were still alive (11 patients with an SCLC). The second, prospective cohort consists of 67 patients, of which 43 had an SCLC. Median follow-up for patients with nontumor LEMS was 8 years (range, 3 to 26 years). Table 1 lists baseline characteristics. Patients with SCLC-LEMS differed significantly from patients with nontumor LEMS: they were older at diagnosis (\(P = .008\)), more often male (\(P = .034\)), and invariably smokers, at diagnosis and in the past (\(P < .0001\)). Two thirds of patients had limited-stage SCLC, a higher percentage than reported in epidemiologic lung cancer reports (40%).\(^3\)

#### Primary Screening

Complete data on screening were available for all patients. A tumor was found before diagnosis of LEMS in only four patients (7%; Fig 1). An SCLC was found at first screening in an additional 41 patients (76%). In these 45 patients, chest x-ray was abnormal in 23 patients (51%), CT-thorax was abnormal in all 45 patients (100%; Fig 2).

### Table 1. Baseline Characteristics of All Patients With LEMS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SCLC-LEMS</th>
<th>NT-LEMS</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>54</td>
<td>46</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>59</td>
<td>54</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>37-77</td>
<td>24-74</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36</td>
<td>21</td>
<td>46</td>
<td>2.3</td>
<td>1.03 to 5.1</td>
<td>.034</td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>25</td>
<td>54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking ever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>54</td>
<td>27</td>
<td>59</td>
<td>39.3</td>
<td>2.3 to 675</td>
<td>(1.5 \times 10^{-7})</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>19</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking only in past</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>44</td>
<td>15</td>
<td>33</td>
<td>11.3</td>
<td>4.2 to 30.1</td>
<td>(6.4 \times 10^{-4})</td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>31</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>35</td>
<td>14</td>
<td>66</td>
<td>11.3</td>
<td>4.2 to 30.1</td>
<td>(6.4 \times 10^{-4})</td>
</tr>
<tr>
<td>Extended</td>
<td>18</td>
<td>31</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: LEMS, Lambert-Eaton myasthenic syndrome; SCLC, small-cell lung cancer; NT, nontumor; OR, odds ratio.

*Smoking only in past was missing for three patients.
*Tumor stage of one patient was missing.
and diagnosis of small-cell lung cancer (SCLC).

In the remaining 55 patients, a tumor was found in nine patients, either between first and second screening or during repeated screening (Fig 2 and Table 2). Median time between diagnosis of LEMS and detection of the SCLC in these nine patients was 3 months (range, 1 to 41 months). Regularly, secondary screening was performed after 6 months.

Fig 1. Time between diagnosis of Lambert-Eaton myasthenic syndrome (LEMS) and diagnosis of small-cell lung cancer (SCLC).

Follow-Up

In five patients, the SCLC was already found between first screening and 6 months. Two tumors were detected because of tumor-related symptoms (patients A and E). In three patients, secondary screening was advanced because of increased suspicion of a tumor. Patient C had an opsoclonus and cerebellar degeneration, patient D was therapy resistant and on respiratory ventilation, and patient B had anti-Hu antibodies. In the first two patients, SCLC was found by CT-thorax, and in the third patient only, [18F]fluorodeoxyglucose positron emission tomography (FDG-PET) body scan was aberrant.

Repeated Screening

By repeated screening, an SCLC was found in three more patients, in two by CT-thorax (patients F and H) and in patient G by FDG-PET body scan. The last patient (patient K) with the longest interval of SCLC diagnosis after diagnosis of LEMS (41 months) was diagnosed with a solitary brain metastasis in 1988. Chest x-ray did not detect a tumor in any of the nine patients during follow-up or secondary screening.

Bronchoscopy and mediastinoscopy were valuable procedures for obtaining a cytologic or histologic diagnosis. However, if imaging techniques did not reveal any abnormalities, bronchoscopy did not reveal a tumor in any patient, as indicated in Table 2.

**DISCUSSION**

In a large cohort of patients with LEMS with SCLC, we demonstrate that the tumors were detected within 3 months after diagnosis of LEMS in 91% and within 1 year after diagnosis in 96%. Overall, an SCLC was found in 54% of patients with LEMS, which is in line with previous publications. SCLC was found more than 1 year after the diagnosis of LEMS in only two patients (Fig 1). In both patients (patients H and K), initial screening had been probably insufficient, as it only consisted of chest x-ray and bronchoscopy (Table 2).

Our study clearly showed that screening by chest x-ray is insufficient. Overall, chest x-ray was abnormal in only 43% of patients. At secondary screening, chest x-ray did not detect any tumor. In 83% of patients, first CT-thorax was abnormal, and in another 9%, follow-up CT-thorax revealed an SCLC. The CT-thorax eventually revealed an SCLC in 92% of SCLC-LEMS patients. Our study reflects the results of cancer screening in daily practice in several centers in the Netherlands without a preexisting diagnostic consensus protocol. All centers routinely performed chest x-ray, CT-thorax, and mostly bronchoscopy, but access to FDG-PET scanning was limited. FDG-PET scanning was introduced for patient care in 1998, but only became fairly accessible in approximately 2002 to 2003. Bronchoscopy and mediastinoscopy, although indispensable for acquiring a cytologic or histologic diagnosis, were available, but were of no value if imaging techniques did not reveal any abnormalities.

There has been discussion about the value of chest x-ray for the screening of SCLC in the general population. Our study comprises data from a group of patients with an a priori risk of more than 50% for an undetected SCLC. It offers valuable information regarding screening efficiency. Although the study group was relatively small compared with the large population-based cohorts from the National Lung Screening Trial and the NELSON trial, our group is well characterized and has a long follow-up period. In our LEMS-SCLC patients...
with a relatively high percentage of limited disease, it was shown that chest x-ray is not a sensitive test for detecting SCLC in contrast with repeated CT-thorax.

It remains possible that a slow-growing tumor can go undetected for years in a small percentage of patients. A time interval of more than 36 months is extremely rare but has been described in a few well-documented cases.\textsuperscript{17,27,31} In all these patients, onset of symptoms was between 1965 and 1987. Two patients had no lung tumor, but breast cancer\textsuperscript{32} and a non-Hodgkin’s lymphoma located in the esophagus.\textsuperscript{30} No causal relationship was shown in these articles, for example, by demonstrating neuroendocrine characteristics or calcium channel expression by the tumor. The four patients having a lung tumor had all been screened only by chest x-ray and bronchoscopy.\textsuperscript{17,27,29,31} In our study, screening was more extensive, minimal duration of follow-up was 3 years, and median follow-up was 8 years, strongly suggesting that all clinically relevant SCLCs were found.

The six SCLCs found because of secondary screening were detected by CT-thorax in three patients and by FDG-PET in the other three patients (Table 2). Unfortunately, FDG-PET scans were not readily accessible for these patients during first screening. It is possible that some patients would have been diagnosed earlier if FDG-PET scan would have been performed at first screening. The added value of FDG-PET scans has been shown before in patients with paraneoplastic anti-Hu syndrome.\textsuperscript{19,20}

In the other three patients with a normal first screening (patients A, E, and K), the SCLCs were found later because of metastases-related symptoms. Patient A had a plexopathy because of growth into the iliosacral plexus. In retrospect, an SCLC metastasis was already visible retroperitoneally on his FDG-PET scan performed at the time of primary screening. Patients E and K presented with neurologic signs and symptoms because of cerebral metastases. Noteworthy is that a simultaneously conducted CT-thorax in patient E showed no abnormalities. These cases stress the fact that primary screening, especially using FDG-PET scanning, should not only focus on the thorax. Because widespread, intracerebral glucose uptake makes FDG-PET scanning less sensitive than magnetic resonance imaging for brain metastases, a magnetic resonance imaging study of the brain could be considered in selected cases. Some primary SCLC tumors remain clinically undetected and are only detected because of associated metastases.

Four of the nine patients in which the SCLC was found at secondary screening had additional features at their diagnosis of LEMS, suggesting a paraneoplastic origin (Table 2, patients A, B, C, and H). These patients should be screened more regularly than other patients with LEMS.

On the basis of the data of this study, we would like to propose a screening protocol (Fig 3). Primarily, the lungs should be screened by CT-thorax. If negative, a total-body FDG-PET scan should be performed. Secondary screening should consist of a CT-thorax every 6 months up to 2 years after diagnosis.

We suggest performing an FDG-PET scan in all patients with LEMS, especially those at primary screening, as well as in patients who never smoked. The incidence of LEMS is 0.8 per million or 240 new LEMS cases each year in the United States, of whom 132 patients (55%) will have an SCLC. Extrapolating our data, 109 SCLCs (45%) will be found by the first CT-thorax. Twenty-two more tumors will be found in the remaining 131 patients during follow-up, almost invariably in smokers. Yearly, 131 FDG-PET scans will be needed for the whole of the United States. One could argue that only patients with LEMS who are current smokers or those with a history of smoking should be screened by CT-thorax. If negative, a total-body FDG-PET scan should be performed. Secondary screening should consist of a CT-thorax every 6 months up to 2 years after diagnosis.

Table 2. Characteristics of Patients With LEMS in Which SCLC Was Found After an Initial Negative First Screening (n = 9)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Chest X-Ray</th>
<th>CT-Thorax</th>
<th>PET-Body</th>
<th>MR/CT-Brain</th>
<th>Bronchoscopy</th>
<th>Time Since First Screening (months)</th>
<th>Reason</th>
<th>Chest X-Ray</th>
<th>CT-Thorax</th>
<th>PET-Body</th>
<th>MR/CT-Brain</th>
<th>Decisive Screening Modality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>62</td>
<td>M</td>
<td>N</td>
<td>N</td>
<td>A</td>
<td>N</td>
<td>NP</td>
<td>1</td>
<td>Plexopathy</td>
<td>CT-thorax</td>
<td>N</td>
<td>A</td>
<td>NP</td>
<td>PET-body</td>
<td>Anti-Hu</td>
</tr>
<tr>
<td>B</td>
<td>60</td>
<td>F</td>
<td>N</td>
<td>N</td>
<td>NP</td>
<td>N</td>
<td>NP</td>
<td>2</td>
<td>Progr LEMS</td>
<td>N</td>
<td>A</td>
<td>NP</td>
<td>PET-body</td>
<td>Anti-Hu; opsoclonus</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>53</td>
<td>M</td>
<td>N</td>
<td>N</td>
<td>NP</td>
<td>N</td>
<td>N</td>
<td>2</td>
<td>Screening</td>
<td>N</td>
<td>A</td>
<td>NP</td>
<td>CT-thorax</td>
<td>Cerebellar degeneration; opsoclonus</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>73</td>
<td>F</td>
<td>N</td>
<td>N</td>
<td>NP</td>
<td>N</td>
<td>N</td>
<td>3</td>
<td>Screening</td>
<td>N</td>
<td>A</td>
<td>NP</td>
<td>CT-thorax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>70</td>
<td>F</td>
<td>N</td>
<td>N</td>
<td>NP</td>
<td>N</td>
<td>NP</td>
<td>4</td>
<td>↑ ICP, ataxia</td>
<td>N</td>
<td>A</td>
<td>A</td>
<td>MRI-brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>56</td>
<td>M</td>
<td>N</td>
<td>N</td>
<td>NP</td>
<td>N</td>
<td>NP</td>
<td>8</td>
<td>Screening</td>
<td>N</td>
<td>A</td>
<td>NP</td>
<td>CT-thorax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>64</td>
<td>M</td>
<td>N</td>
<td>N</td>
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<td>NP</td>
<td>10</td>
<td>Screening</td>
<td>N</td>
<td>N</td>
<td>A</td>
<td>NP</td>
<td>PET-body</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>58</td>
<td>M</td>
<td>N</td>
<td>N</td>
<td>NP</td>
<td>N</td>
<td>N</td>
<td>21</td>
<td>Screening</td>
<td>N</td>
<td>A</td>
<td>A</td>
<td>NP</td>
<td>PET-body</td>
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<td>N</td>
<td>NP</td>
<td>CT-brain</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: LEMS, Lambert-Eaton myasthenic syndrome; SCLC, small-cell lung cancer; CT, computed tomography; PET, positron emission tomography; MRI, magnetic resonance imaging; M, male; F, female; N, normal; A, abnormal; NP, not performed; Progr, progressive; ICP, intracranial pressure.
experience with sensitivity and specificity of CT. It seems reasonable to reduce screening from 4 years to 2 years from diagnosis of LEMS, although our numbers are too low to support stringent recommendations. A recently published expert opinion, not based on patient series, suggested 4 years.\(^{21}\) An SCLC was detected in our series in only one patient more than 2 years after diagnosis. In this patient, screening by CT-thorax and FDG-PET scanning had not been performed, suggesting that the tumor could have been detected earlier if screening had been adequate.

Data are accumulating that suggest an exception can be made for patients under the age of 45 years who have never smoked and carry the HLA 8.1 haplotype.\(^{16,33}\) They represent the idiopathic autoimmune form of the disease, and no patient with this profile in our series developed a tumor. A second CT-thorax after 6 months might be sufficient, and it could be considered to stop routine screening afterwards.

The author(s) indicated no potential conflicts of interest.

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screening LEMS for SCLC

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