Part 10 of 12: Asymptomatic Solitary Pulmonary Nodule in a Healthy 54-Year-Old Man

Dear Colleague:

Clinical decisions regarding the detection, characterization, and treatment of pulmonary lesions must be made in light of the high prevalence of malignancy and the poor survival rate for lung cancer. Solitary pulmonary nodules on chest radiograph are commonly seen in pulmonary medicine, about 1/500 chest X-rays. In the literature, the prevalence of malignancy in these cases ranges from 10% to 68%.

This TREATMENT REPORTER focuses on a 54-year-old executive with a 1.9 cm solitary pulmonary nodule, first detected with spiral CT scan. This type of CT scan detects more small thoracic nodules than standard CT, because the single-breath hold eliminates the patient motion artifact. The treatment choices featured in this case highlight the role of surgical resection, platinum-based and novel chemotherapies, and prophylactic cranial irradiation in the treatment of small-cell lung cancer.

We are pleased to offer you part 10 of the 12-part series, Case Studies in Recurrent Gynecologic and Lung Cancer: Chemotherapeutic Innovations. These case-based newsletters, designated for .25 CME credit each, will comprise gynecologic cancers and lung cancer. Presentations of patient cases and discussion of relevant treatment dilemmas and options by a distinguished faculty of oncologists are designed to update you on the latest clinical trial results and their implications for clinical practice.

We hope you find this series helpful and informative, and that the discussions will assist you in incorporating this information into your clinical practice.

Sincerely,

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Patient Description
Mr. S is a 54-year-old executive with a 60 pack-year smoking history. He presented to his physician after spiral computed tomography (CT) imaging, performed during an “executive physical,” revealed a 1.9-cm nodule in the left upper lobe, with no evidence of hilar or mediastinal adenopathy. Mr. S denied cough, hemoptysis, and shortness of breath. He also denied any pain, anorexia, or weight loss. His past medical history was remarkable for mild exercise-induced asthma. He claimed no prior exposure to asbestos.

His physical exam was unremarkable except for the presence of mild end expiratory wheezes.

Single time point positron emission tomography (PET) imaging demonstrated an increased standardized uptake value (SUV) of 2.5 at 70 minutes in the nodule, consistent with malignancy. No other abnormalities were found. Laboratory examination demonstrated normal liver function tests and hematologic indices, a serum creatinine level of 0.9 mg/dL, and a prostate-specific antigen of 0.9 ng/dL. A fine-needle aspiration (FNA) biopsy of the nodule demonstrated only scant atypical cells.

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Diagnostic Evaluation

Question 1: Which of the following next steps would you recommend?

a. Repeat spiral CT scan in 3 months
b. Evaluation for possible primary tumor with CT scan (nonspiral) of abdomen and pelvis, and colonoscopy
c. Mediastinoscopy and biopsy
d. Surgical resection and biopsy

Discussion

(d) Despite the nondiagnostic FNA, this patient’s PET scan result of 2.5 SUV suggested that the probability of malignancy was about 94%. This high likelihood of malignancy combined with this patient’s good health form the basis of the decision for surgical resection and biopsy. This option would not only provide confirmation of malignancy and pathologic diagnostic information, but also potentially curative treatment.

A repeat spiral CT scan in 3 months would provide little diagnostic information about the nodule. Suspicion of malignancy would be raised if the nodule increased in size, but malignancy could not be ruled out if the size remained stable.

Prior to biopsy of the nodule, abdominal and pelvic CT scan plus colonoscopy to investigate a possible extra-pulmonary primary tumor would add significant cost to the diagnostic evaluation, while providing a low yield of diagnostic information. In contrast, these diagnostic tests performed after the biopsy—and only if the biopsy findings were consistent with metastasis—would have a much greater yield of information and with greater cost-effectiveness.

Perfoming a mediastinoscopy with biopsy is a reasonable consideration, particularly in a patient in which there is a higher likelihood of mediastinal involvement. However, for Mr. S, who has no mediastinal involvement appreciated on the PET and CT of the mediastinum, the yield of mediastinoscopy with biopsy is low (<10%).

Case Continues

Mr. S underwent a left upper lobectomy. Pathology revealed a 2.4-cm, poorly differentiated, small-cell lung cancer (SCLC). Hilar and mediastinal lymph node biopsies did not demonstrate malignant involvement. Further staging, including magnetic resonance imaging (MRI) of the head, bone scan, and CT of the abdomen and pelvis, was negative. The final diagnosis, therefore, was limited-stage SCLC.
Radiotherapy was not needed for Mr. S, however. In this case, the full resection and lymph node sampling eliminated the need for thoracic radiotherapy and gave this patient a good chance for local control.

Case Continues

Mr. S was treated with four cycles of cisplatin and etoposide. The therapy was well tolerated except for grade 1 to 2 nausea and vomiting, as well as grade 3 neutropenia. At completion of treatment, prophylactic cranial irradiation (PCI) was discussed with the patient.

Prophylactic Cranial Irradiation

(a) PCI decreases the risk of brain metastases, and modestly improves both overall survival and disease-free survival.\textsuperscript{1,12} Without PCI, the risk of brain relapse is 50% to 60%\textsuperscript{19} and patients suffer neurologic and neurocognitive deficits that are not always ameliorated by therapeutic irradiation. Therefore, PCI is highly recommended for all patients with complete response.\textsuperscript{1,14} Mr. S, with minimal initial disease and complete response to primary therapy, is a good candidate for PCI. The benefits of PCI, however, must be evaluated in light of its potential adverse effects, particularly its potential effect on cognitive function.\textsuperscript{1} This benefit-to-risk ratio must be thoroughly discussed with and understood by the patient.

Brain metastases are detected in approximately 10% of patients with SCLC at the time of presentation and are diagnosed later in the disease in another 20% to 25%.\textsuperscript{1,12,17} The likelihood of development increases with survival.\textsuperscript{1,13,17} These metastases are sometimes the only site of relapse and are frequently clinically disabling. In the absence of radiation therapy to the central nervous system, actuarial analysis reveals a probability of brain metastases ranging from 50% to 80% in patients who survive 2 years.\textsuperscript{16,18}

To curtail the development of brain metastases, PCI has been recommended by many lung cancer specialists since the mid-1980s.\textsuperscript{19,20} Not all specialists, however, recommend PCI, nor do all patients consent to this treatment. The effectiveness of PCI in decreasing the risk of brain metastases has been demonstrated in clinical trials, but this is not achieved without the potential for significant adverse effects, including cognitive effects.

A meta-analysis\textsuperscript{12} of seven trials comprising almost 1000 patients between 1977 and 1995, evaluated PCI in patients who had initial complete response to induction therapy (chemotherapy or chemoradiotherapy). A significant survival advantage was seen in patients with PCI compared with patients without PCI, with 3-year survival rates increasing from 15% to almost 21%. PCI also significantly decreased the risk of brain metastases and increased the likelihood of disease-free survival. The meta-analysis was not able to assess the effect of PCI on cognitive function because most of the studies did not provide a baseline assessment.

Early trials of PCI demonstrated neurotoxicity, including deterioration of memory and calculation ability.\textsuperscript{11-15} The results of several later prospective neuropsychologic trials,\textsuperscript{11-15} however, indicate that PCI is not associated with significant neurologic toxicity. Furthermore, these studies suggest that patients with SCLC have some measure of cognitive impairment before the initiation of PCI.

The potential for neurotoxicity of PCI may be decreased by administering it after completion of chemotherapy.\textsuperscript{1} The optimal dose and fraction size to maximize efficacy, yet minimize risk of toxicity, requires further study.\textsuperscript{15}

Case Continues

In light of the potential for negative cognitive effects, Mr. S refused PCI. He was well for 22 months, when he presented with right hand weakness. MRI of the head revealed multiple brain metastases, the largest being 2 cm in diameter. Further evaluation, including bone scan and CT scan of the chest and abdomen, revealed two liver metastases. FNA of the liver lesion was consistent with recurrent SCLC. The patient received steroids and phenytoin to suppress potential seizures. Therapeutic radiotherapy was initiated at a dosage of 4500 cGy over 3 weeks.

Selecting Second-Line Chemotherapy

(f) Treatment with any of the above options is reasonable for this patient. Patients like Mr. S, who have relapsed more than 3 months after initial treatment, are considered to have chemosensitive, relapsed disease. Treatment options for these patients include retreatment with the initial therapy (if >6 months), treatment with novel agents, such as topotecan or irinotecan, or oral etoposide.\textsuperscript{7}

Cisplatin/etoposide is appropriate, especially if this combination was not used as first-line therapy. In the event that cisplatin/etoposide was utilized initially, then non-cross-resistant agents, such as topotecan and irinotecan, would possibly have more antitumor activity.

Several novel agents have shown activity in SCLC, including topoisomerase I inhibitors (eg, topotecan, irinotecan), semisynthetic vinca alkaloids (eg, vinorelbine), novel antimetabolites (eg, gemcitabine), and members of the taxane family (eg, docetaxel, paclitaxel). Many of the more active agents employed in second-line treatment (eg, topotecan, irinotecan, docetaxel, vinorelbine) are non–cross-resistant to first-line therapies.\textsuperscript{7} They exhibit novel mechanisms of action, targeting various processes of cell division.\textsuperscript{19} Additionally, many of these agents have shown synergy with other agents (both first- and second-line agents) in \textit{in vitro} tumor model studies, thereby providing the rationale for their use in various combination regimens.\textsuperscript{19}

Topotecan, a topoisomerase I inhibitor, is an established treatment in recurrent SCLC, with tumor response rates of 11% to 31% reported in platinum-sensitive extensive-disease patients with good performance status (Eastern Cooperative Oncology Group [ECOG] ≤2).\textsuperscript{25-29} Median survival ranged from 25 to 36 weeks in these SCLC patients. The primary dose-limiting toxicity associated with topotecan therapy is hematologic (ie, grade 3/4 neutropenia), with approximately 70% and 29% of patients experiencing grade 4 neutropenia and thrombocytopenia, respectively.\textsuperscript{25} It is approved for administration by intravenous infusion daily at a dose of 1.5 mg/m\textsuperscript{2} for 5 days every 21 days.
may choose weekly topotecan, it is not an approved therapy. Clinical trials studying the safety and efficacy of weekly topotecan are under way.

Single-agent activity of irinotecan, another topoisomerase I inhibitor, has shown modest activity in patients with previously treated SCLC.\(^1\) Irinotecan has primarily been evaluated in combination regimens. Noda et al.\(^3\) compared irinotecan/cisplatin with etoposide/cisplatin in treatment-naive patients with extensive-stage SCLC. Study enrollment was terminated early due to findings at interim analysis of a statistically significant difference in median survival between patients randomized to the two groups: 12.8 months in the irinotecan/cisplatin group versus 9.4 months in the etoposide/cisplatin group (\(P = .002\)). The rate of overall survival at 1 and 2 years was also significantly greater in the irinotecan/cisplatin group compared with the etoposide/cisplatin group. Confirmatory trials are under way in the United States.

Patients with relapsed SCLC have shown response to oral etoposide, particularly patients who had an initial response to previous chemotherapy and who have been treatment-free for at least 90 days.\(^14\)

### Conclusion

SCLC is an aggressive tumor associated with high rates of regional or distant metastases at diagnosis. Patients with limited-stage SCLC are treated with combined therapies with the intent to cure. These therapies include surgical resection, platinum-based combination chemotherapy, and prophylactic cranial irradiation. Despite the high response rates to aggressive combined therapies, however, the probability of relapse is high. Patients who relapse are candidates for second-line or salvage chemotherapy.

Several novel agents, as single or combination chemotherapy, can extend survival and improve quality of life. Due to the high rates of relapse, further development and refinement of novel combinations and schedules are needed to improve patient outcomes in SCLC.

### References

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Please select the most appropriate response to each question.

1. PET imaging may be used to estimate the probability of malignancy of a solitary pulmonary nodule.
   - True
   - False

2. Standard first-line therapy for limited-stage SCLC includes either surgical resection alone, radiotherapy alone, or platinum/etoposide alone.
   - True
   - False

3. PCI is highly recommended only for patients with initial complete response and later brain metastasis as the only site of relapse.
   - True
   - False

4. Retreatment with initial therapy is appropriate for patients who relapsed more than 6 months after initiation of initial therapy.
   - True
   - False

5. Topoisomerase I levels have been demonstrated to remained suppressed for up to 7 days after a single dose of a topoisomerase inhibitor.
   - True
   - False
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Thank you for your participation.