Systematic Postoperative Radiologic Follow-up in Patients With Non–Small Cell Lung Cancer for Detecting Second Primary Lung Cancer in Stage IA

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Hypothesis: Systematic postoperative evaluation of patients with non–small cell lung cancer will identify treatable second primary lung cancer and local recurrences.

Design: Retrospective review from January 1, 1996, to December 31, 2000. The follow-up protocol included an annual computed tomographic examination of the chest with interval chest radiography every 4 months for 2 years and every 6 months for 3 additional years.

Setting: A National Cancer Institute–designated comprehensive cancer center.

Patients: One hundred twenty-four patients with resected non–small cell lung cancer.

Main Outcome Measures: Number and size of second primary and locally recurrent tumors, secondary surgical procedures, and survival of patients who underwent resection.

Results: The median diameter of resected second primary tumors detected by computed tomography was 14 mm (range, 8-28 mm) and by chest radiography was 26.5 mm (range, 23.0-35.0 mm) \( (P<.001) \). Of 14 patients with second primary lung cancer treated surgically, 9 were without evidence of disease at a median of 20 months (range, 4-56 months), 2 were alive with disease at 13 and 37 months, 2 died of unrelated causes but without evidence of disease at 7 and 35 months, and 1 died intraoperatively of a cardiac arrhythmia.

Conclusions: Systematic follow-up of non–small cell lung cancer, including annual computed tomography, detects second primary lung cancer in stage IA. Limited pulmonary resections are often feasible in these patients. Locally recurrent lung cancer is infrequently resectable.

Arch Surg. 2002;137:935-939

It is estimated that 169,400 people will be diagnosed as having lung cancer in the United States in 2002. The 5-year cure rate has risen from 6% to 14% during the past 50 years. Of patients who survive a first non–small cell lung cancer (NSCLC), many develop a second cancer, either a second primary lung cancer (SPLC) or locally recurrent lung cancer (LRLC). Survival after recurrent lung cancer has been dismal owing to the inability to diagnose these lesions at an early stage. Indeed, 38% of SPLCs are not resected because of locally advanced tumors at diagnosis. Survival after SPLC ranges from 4% to 32% in various series, and LRLCs have 2-year survival of approximately 23%. Because of these poor results, some experts believe that comprehensive postsurgical follow-up by thoracic surgeons is not indicated.

The purpose of this study is to evaluate a cohort of patients treated for lung cancers and followed by a single thoracic surgeon (F.W.G.). Intensive follow-up of these patients includes regular radiologic evaluation by computed tomography (CT) and chest radiography (CXR). The hypothesis is that this follow-up regimen will identify SPLC and LRLC at an early, treatable stage.

Patient demographics and treatment for primary NSCLC are given in Table 1. Nine patients had a previous head and neck cancer and 10 had synchronous primary NSCLC. At least 1 CT scan was obtained in 102 of 124 patients; CT identified 79 nodules (range, 1-30) in 45 patients. The median size of noncalcified nodules on CT was 6 mm (range, 2-45 mm).
PATIENTS AND METHODS

An institutional review board–approved retrospective medical chart review was performed on all patients followed in the Thoracic Surgery Clinic at City of Hope National Medical Center between January 1, 1996, and December 31, 2000. Patients were eligible for inclusion in this study if they had a history of NSCLC treated by surgical resection with curative intent. Patients who had been diagnosed as having metastatic lung cancer before 1995 were excluded. Patients who developed distant lung cancer metastases during the study were subsequently excluded from the surveillance methods described in the following paragraphs. Standard resection for primary lung cancer includes lobectomy or pneumonectomy with mediastinal lymph node dissection. Limited pulmonary resections were performed for patients with limited pulmonary reserve.

The following methods represent the approach of a single thoracic surgeon (F.W.G.) to follow this group of patients. At 4- to 6-month intervals, patients underwent a history and physical examination to identify recurrent lung cancer. General imaging follow-up in this group included CXR every 4 months for 2 years, then every 6 months. Diagnostic CT of the chest at 5- to 7-mm slice intervals was performed annually.

Suspicious nodules identified by CT were defined as noncalcified, either singular or multiple. Noncalcified nodules measuring 6 or greater are seldom compatible with a diagnosis of lung cancer. Recommended follow-up for noncalcified nodules 5 mm or less in diameter was CT scanning 3 months later. Biopsy was recommended for nodules demonstrating growth. Evaluation of nodules larger than 3 mm was individualized to each patient and included repeated CT in 3 months, short-term antibiotic treatment followed by another CT scan, 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography, bronchoscopy, fine-needle aspiration, or surgical biopsy.

Second primary lung cancer was defined as a lesion of differing histologic characteristics from the primary lesion or of similar appearance as long as any of the following criteria were met: the disease-free interval was at least 2 years, origin was from carcinoma in situ, or the second tumor was in a different lobe or lung (without common lymphatic or extrapulmonary metastases). Local recurrence was defined as tumor identified in the hilus of the ipsilateral lung, immediately adjacent to the previous tumor, or in the pleura. Mediastinal lymph node disease only was classified as regional recurrence.

Treatment of patients with recurrent lung cancer was individualized. Each case was presented at a multidisciplinary chest tumor conference attended by representatives from thoracic surgery, general and oncologic surgery, radiology, medical oncology, radiation oncology, and pulmonology. A consensus opinion was formed and was used to guide further intervention. Lesions were defined as potentially resectable or unresectable based on their CT appearance and location. Patients considered for surgical resection of recurrent lung cancer were evaluated by standard methods. Limited pulmonary resections were performed for patients with limited pulmonary reserve.

Time-to-event end points were analyzed using the Kaplan-Meier method. Overall survival was calculated from the date of surgery for SPLC until death or last follow-up. The log-rank test was used for testing for survival differences between patient subgroups. All statistical calculations and graphs were performed using S-Plus 2000 (MathSoft Inc, Cambridge, Mass).

Second primary lung cancer was diagnosed in 19 (15.3%) of 124 patients (Table 2). The probability of developing an SPLC was 2.1% per patient per year. All patients were asymptomatic. Computed tomography first identified SPLC in 11 patients. Some recurrent cancers were initially detected by a modality other than CT in this study. In 8 cases not first identified by CT, 6 patients did not follow the annual CT protocol and 1 had negative CT findings 7 months before a suggestive CXR. One SPLC was suggested first on a positron emission tomographic scan after negative CT and CXR findings in a patient with a persistently elevated carcinoembryonic antigen level.

Criteria used for diagnosis of SPLC were a different histologic appearance between the 2 tumors (n=6) and a 2-year disease-free interval with tumor in a different lobe or lung (n=13). Second primary lung cancer was potentially resectable in 18 patients (94.7%). Fourteen patients (73.7%) ultimately underwent resection of SPLC by limited resection (n=13) or completion pneumonectomy (n=1). Of 14 patients with SPLC treated surgically, 9 are without evidence of disease at a median of 20 months (range, 4-56 months), 2 died of unrelated causes but without evidence of disease at 7 and 35 months, and 1 died intraoperatively of a cardiac arrhythmia. Two surgically treated patients have recurrent disease at 13 and 37 months: 1 had a pleural recurrence, and the other developed metastatic disease. No patients treated with limited resection have experienced a subsequent recurrence in that lobe. Second primary lung cancers were staged clinically (n=5) or pathologically (n=14) and were found to be stage IA (n=16, 84.2%), IIB (n=1, 5.3%), IIB (n=1, 5.3%), or IV (probable T4 “satellite” lesion) (n=1, 5.3%). The median diameter of resected SPLC tumors detected by CT was 14 mm (range, 8-28 mm) and by CXR was 26.5 mm (range, 23.0-35.0 mm) (P<.001).

Five patients with SPLC were not treated surgically owing to pulmonary insufficiency (n=3), patient choice (n=1), or a locally advanced bronchial lesion (n=1). These patients were observed (n=3) or treated with external beam radiation (n=2). Nonsurgically treated patients were alive with disease (n=3) or without evidence of disease (n=1) or dead of disease (n=1) at a median of 4 months (range, 1-11 months).

Nine patients had isolated LRLC during the study (Table 2). Eight patients were asymptomatic and 1 had hoarseness. One patient had negative CT and CXR findings but had a local recurrence on bronchoscopy. Only 1 patient was treated surgically, by lobectomy, for a locally recurrent cystic mucinous adenocarcinoma. This patient is without evidence of disease at 33 months. Eight patients were treated nonsurgically owing to locally ad-
advanced lesions (n=4), metastatic disease (n=2), or patient refusal (n=2). Nonsurgical patients were observed (n=3) or were treated with systemic chemotherapy (n=3) or external beam radiation (n=2). Four patients are alive with disease at a median of 6 months (range, 1-19 months) and 4 are dead of disease at a median of 6 months (range, 2-28 months).

Median overall survival for patients with SPLC has not been reached, whereas patients with LRLC survived a median of 28 months ($P=0.08$) ($Figure 1$). Median disease-free survival differed significantly between SPLC (35 months) and LRLC (2 months) ($P=0.02$) ($Figure 2$).

### Table 1. Demographic Characteristics of 124 Study Patients and Initial Tumor Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SPLC</th>
<th>LRLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td>65 (52)</td>
<td>59 (48)</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>66 (39-85)</td>
<td>59 (48)</td>
</tr>
<tr>
<td>Synchronous NSCLC, No. (%)</td>
<td>10 (8)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Stage of most advanced primary tumor, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>64 (52)</td>
<td>48 (39)</td>
</tr>
<tr>
<td>II</td>
<td>20 (16)</td>
<td>21 (17)</td>
</tr>
<tr>
<td>III</td>
<td>40 (32)</td>
<td>30 (24)</td>
</tr>
</tbody>
</table>

*NSCLC indicates non-small cell lung cancer.

### Table 2. Characteristics of 19 Second Primary and 9 Locally Recurrent Tumors*

<table>
<thead>
<tr>
<th>SPLC</th>
<th>LRLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free interval, median (range), mo</td>
<td>29 (9-88)</td>
</tr>
<tr>
<td>Method of identification, No. (%)</td>
<td>CT 11 (57.9)</td>
</tr>
<tr>
<td></td>
<td>CXR 7 (36.8)</td>
</tr>
<tr>
<td></td>
<td>Bronchoscopy 0</td>
</tr>
<tr>
<td></td>
<td>PET 1 (5.3)</td>
</tr>
<tr>
<td>Treatment, No. (%)</td>
<td>Surgical</td>
</tr>
<tr>
<td>Limited resection</td>
<td>13 (68.4)</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>0</td>
</tr>
<tr>
<td>Completion pneumonectomy</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Nonsurgical</td>
<td>5 (26.3)</td>
</tr>
</tbody>
</table>

*SPLC indicates second primary lung cancer; LRLC, locally recurrent lung cancer; CT, computed tomography; CXR, chest radiography; and PET, positron emission tomography.

The rate of developing SPLC is 1% to 4% per patient per year in most series and was 2.1% in this study. Staging of SPLC is incomplete throughout the literature. In studies that completely staged surgically and nonsurgically treated SPLCs, 55% of tumors were identified in stage I, 7% in stage II, 35% in stage III, and 3% in stage IV. This distinction is important in that patients with SPLC found in stage IA have improved survival rates compared with those with a more advanced stage receiving similar treatment. The present study found 16 (84.2%) of 19 tumors in stage IA, with 18 of 19 SPLCs identified in asymptomatic patients.

Local recurrence of lung cancer has an ominous prognosis. It is often unresectable, as is evident in the current group, and survival in these patients is limited. Although there is not a statistical difference in overall survival between SPLC and LRLC in this study, this may be because of the limited follow-up data available at this time. Improved disease-free survival in the SPLC group is reflective of the treatment options available to these patients.

Computed tomography holds the best promise for early detection of lung cancer at this time. In Japan, Moriya et al demonstrated that helical CT was capable of detecting lung tumors as small as 3 mm in diameter and suggested that it could be used in mass screening. In the Early Lung Cancer Action Project, Henschke et al evaluated the use of lung cancer screening with low-dose, non-contrast, spiral CT. Twenty-seven lung tumors were diagnosed using CT, 23 of which were in stage I.

By applying CT to postoperative patients with lung cancer, SPLC is likely to be detected at an early, treatable stage, as shown in this study. Eighteen (94.7%) of 19 patients with SPLC had lesions that were deemed tech-
nically resectable. The actual number of patients undergoing resection is tempered by the significant comorbidities present in this group of patients. However, 73.7% (14/19) of the patients with SPLC in this study underwent some form of surgical treatment, whereas approximately 54% of patients with SPLC throughout the literature are treated surgically.2

The procedure of choice for lung cancer should be lobectomy, as local recurrence is 3 times more likely after a limited resection.14 When treating patients for SPLC after a previous resection for lung cancer, many will not tolerate a second lobectomy or pneumonectomy owing to lack of pulmonary reserve. A reasonable treatment option for very small SPLC in patients with limited pulmonary reserve is a negative-margin limited resection. Van Rens et al15 performed a limited resection in 31% of their patients with SPLC. Type of resection (limited vs more extensive) for SPLC did not predict survival. Because 84% of patients in the present study had stage IA SPLC, limited resections were performed in 13 of 14 patients. At this time, no patient has had a local recurrence at the site of limited resection of SPLC, but further follow-up of this group is needed.

Recently, there has been considerable debate in the literature regarding the postoperative evaluation of patients with lung cancer. Walsh et al7 noted that screening for asymptomatic recurrent lung cancer is unlikely to be cost-effective and is probably not necessary. Gilbert et al7 found that outcomes after lung cancer recurrences detected by a family physician are similar to those detected by a surgeon. However, these studies used CXR as the predominant method of lung cancer surveillance as opposed to annual CT. We believe that early recognition of SPLC and subsequent intervention will salvage a significant portion of these patients. Surveillance with CT, however, must be performed in a controlled setting by experienced personnel because many small benign pulmonary lesions are identified. Careful adherence to a defined protocol is needed to avoid unnecessary interventions.

In summary, aggressive radiologic follow-up of patients with lung cancer, including annual CT, seems warranted, as SPLC can be identified early and treated. The prognosis for patients with LRLC is poor, and surgical treatment options in these cases are less likely to be affected by early detection. A prospective study evaluating CT to detect SPLC is necessary and is currently being designed at City of Hope National Medical Center.

This paper was presented at the 73rd Annual Meeting of the Pacific Coast Surgical Association, Las Vegas, Nev, February 18, 2002, and is published after peer review and revision. The discussion is based on the originally submitted manuscript and not the revised manuscript.

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REFERENCES


E. Carmack Holmes, MD, Los Angeles, Calif: The authors have presented a retrospective review of 124 resected lung cancer patients over a 5-year period. They detected 19 second primary tumors in these patients and 9 local recurrences. I completely agree with their definition of second primary tumors and local recurrences, as originally outlined by Martini. These were the same criteria used by the Lung Cancer Study Group in similar studies.

The risk of second primary tumors in this presentation today was 2.1% per annum. This figure would no doubt have been higher if they had followed their patients longer. I will see when I present some of the Lung Cancer Study Group data. This high incidence of second primary tumors clearly has important implications for follow-up, as the authors have pointed out. There was a 73% resectability rate in these second primary tumors, and 84% of them were stage IA, resulting in an excellent disease-free survival. This indicates that patients under careful surveillance for second primary tumors have a high incidence of cure following resection. I also completely agree with the authors that limited resection in patients with second primary tumors is quite appropriate, and good results will be obtained, even when lobectomy is not performed.

The Lung Cancer Study Group reviewed 900 patients with well-staged resected stage I lung cancer. Actually, the longest time interval to the development of a second primary tumor was 1.24 months. This slide shows 900 patients with T1 N0 disease. The yellow bars represent all 900 patients and the red bars represent those patients who were disease free for at least 5 years. The incidence of second primary malignancies is striking in the entire group, but it is especially impressive in those who survived 5 years or longer. The high incidence of second primary tumors has important implications for the follow-up of these patients since they clearly remain at risk for either new primary pulmonary malignancies for the duration of their lives. In the Lung Cancer Study Group with this extensive follow-
up, we found that patients actually have a 5% per annum risk of developing a second primary lung tumor.

At UCLA, we have an NIH-funded chemoprevention trial in these patients using COX-2 inhibitors. The implications for early detection and chemoprevention are important because lung cancer is the number one cancer killer in the United States, and their recommendations for careful follow-up and surveillance for second primary tumors should be adhered to.

I have just a few questions for the authors. The first question is the role of spiral CT scans in following these patients. We know that spiral CT scans will detect approximately 2 lung cancers for each 1000 spiral CT scans performed, and we also know that many of these lesions that are seen in these spiral CT scans are benign. As a matter of fact, the Lung Cancer Study Group found that 30% to 40% of patients with chest x-ray lesions less than 3 cm in diameter were benign. Do the authors have any information regarding the number of CT scan lesions detected in their patients that were actually benign? Second, do the authors have any information regarding the number of nonpulmonary malignancies that developed in these patients? Clearly, the Lung Cancer Study Group indicates that they are at a very high risk for developing nonpulmonary as well as pulmonary recurrences, and this sort of information is useful in selecting the appropriate test to follow these patients. The final question is do the authors have any data on the survival of patients with synchronous primary malignancies as they mentioned in their manuscript that they did see in some of these patients?

Dr Grannis: I would like to thank you all for staying for this last day of the meeting. I would like to thank the Pacific Coast Surgical Association for allowing me to join this terrific group. I thank the Committee for accepting our paper and for encouraging the presentation, and particularly Dr Holmes for his very kind comments. We will certainly use the information he presented to us in the planning of our subsequent work in this area. Finally, of course, I would like to thank Dr Lamont for the tremendous work he has done on this project.

To address specifically the questions that Dr Holmes asked, the first was the role of CT scan. City of Hope is now one of 20 institutions that are participating in the International Early Lung Cancer Action Project (I-ELCAP), a prospective trial of CT screening to detect lung cancer in smokers. The ELCAP group discovered 27 cancers per 1000 (2.7%) on the initial CT scan in a high-risk group. Patients with a prior lung cancer probably represent a higher-risk group. John Benfield, my predecessor at the City of Hope, found an incidence of approximately 10% in 5 years, and the Mayo Clinic group had a 20% incidence of second lung cancers over a 10-year period. This dovetails very nicely with the 2.1% per year that we have seen here. This is a higher risk group than smokers, where the risk is probably about 2% per decade.

As far as the number of benign nodules is concerned, that is a very important factor. We had about 80 patients in this group of 124 who had some form of small nodule, so that it's very important not to overreact in those patients and do unnecessary diagnostic studies, biopsies, and surgeries. We didn't know what to do starting in 1996, and we flew by the seat of our pants. But in our prospective trial, we will use the same protocols that have been developed as part of the ELCAP experience, using growth as a predictor of malignancy. Using growth in small lesions, the ELCAP group in New York has been very successful in avoiding unnecessary needle biopsies and surgeries. We will certainly follow those protocols. Also, since CT lung cancer screening is so new, these protocols are evolving.

In terms of the nonpulmonary cancers, we have discovered a number of head and neck cancers because, as part of our history and physical, we specifically ask about change in voice, sores in the mouth, dysphagia, etc, and we have picked up a number of head and neck cancers, tongue and laryngeal cancers. We also detected one renal cancer and 2 pancreatic neoplasms on CT scans. We have also noted that patients with head and neck cancer have a very high incidence of developing lung cancer, and so we are collaborating with our colleagues in surgical oncology in a prospective trial that we have submitted as a grant request to the Tobacco Related Disease Projects in California.

We would certainly be very interested in collaborating with Jenny Mau and the group at UCLA who are studying the same thing in a different way using LIFE bronchoscopy.

The next question was in regard to information on survival in patients with synchronous cancers. That is a very important question that we did not specifically address in this study. The 1997 revision of the lung cancer staging indicates that tumors in a different lobe or on the other side are stage IV; we don't believe that that is true. We believe that they are really 2 separate lung primaries in almost all cases. We certainly have a number of long-term survivors in that group, but I don't have the data to give you more exact information on this group of patients.

With regard to the question of whether these lesions could be metastases, whether they are second primaries, or whether they are satellite lesions, I think the only way to answer that question is with molecular biology. We will be collaborating with a group in Rotterdam, Holland, and in our prospective trial they will look at both the primary and the second cancer with a panel of biomarkers to help answer the question.

If you have patients who wish to be screened for lung cancer, we are participating in the International Early Lung Cancer Action Project. There are 3 groups on the West Coast at the present time. One is at Sharp Memorial Hospital in San Diego, one is at City of Hope National Medical Center in Duarte, and one is at Swedish Medical Center in Seattle, Wash. Also, if patients with a prior lung cancer or head and neck cancer wish to participate in a prospective trial for the early detection of lung cancer, we would certainly also be glad to speak with you.