CT Screening for Lung Cancer*

The Value of Short-term CT Follow-up

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**Background:** Although CT screening for lung cancer results in a diagnosis of stage I > 80% of the time, benign noncalcified nodules are also found. We recognized that some nodules appeared to represent infectious bronchopneumonia or other inflammatory processes, as they resolved on follow-up CT, sometimes after antibiotic therapy. To determine the extent to which short-term CT radiographic follow-up might shorten the workup of nodules, we reviewed our experience with baseline and annual repeat CT screenings performed subsequent to the original Early Lung Cancer Action Project series.

**Methods:** The initial CT of 1,968 consecutive baseline and 2,343 annual repeat screenings performed from 1999 to 2002 was reviewed. We identified all those recommended for antibiotics on the initial CT who had a follow-up CT within 2 months and determined whether the nodule(s) resolved, decreased in size, remained unchanged, or grew. We then determined whether further follow-up resulted in a diagnosis of cancer.

**Results:** At baseline, among the 41 individuals who had follow-up CT within 2 months of the initial CT, 12 patients (29%) had complete or partial resolution; none of them subsequently received a diagnosis of lung cancer. On annual repeat screening, among the 39 individuals who had follow-up CT within 2 months of the initial CT, 29 patients (74%) had complete or partial resolution; none of them subsequently received a diagnosis of lung cancer. Among the 29 patients with nodules at baseline that were unchanged or grew, a total of 15 cancers were subsequently diagnosed; among the 10 patients on annual repeat scanning, there were 2 cancers.

**Conclusions:** In asymptomatic individuals undergoing CT screening for lung cancer, short-term follow-up CT within 2 months with or without antibiotics may circumvent the need for further evaluation in some individuals, particularly on annual repeat screening.

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**Key words:** CT; diagnosis; lung cancer; nodules; screening

**Abbreviation:** ELCAP = Early Lung Cancer Action Project

In the course of CT screening in the original Early Lung Cancer Action Project (ELCAP), we came to appreciate that some noncalcified nodules might represent focal infectious bronchopneumonia or other inflammatory processes.1,2 We therefore introduced the use of antibiotics and short-term CT follow-up into our diagnostic regimen of screening,3,4 with the aim of limiting further diagnostic testing of some of the positive results of the initial CT.

In the current baseline regimen of screening,5 for instances in which one or more noncalcified nodules 5 to 14 mm in diameter are identified on the initial CT...

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CT, one option is for a follow-up CT 3 months after the initial CT to determine whether growth can be identified. Noncalcified nodules < 5 mm in diameter are referred to the first annual repeat screening without any additional CTs being performed in the interim, since nodules of this size have an extremely low likelihood of malignancy. An additional option for nodules ≥ 15 mm in diameter is an immediate percutaneous fine-needle aspiration biopsy.

In the current regimen for annual repeat screening, identification of growing noncalcified nodules < 3 mm in diameter are recommended for assessment of further growth by means of follow-up CT 6 months later. For nodules ≥ 3 mm in diameter, follow-up CT 3 months later is the recommendation, with positron emission tomography being an alternative to this. An additional option for nodules ≥ 10 mm in diameter is an immediate biopsy.

In contrast to the above options, an immediate course of antibiotics with follow-up CT 1 to 2 months after the initial one would obviate further testing if the nodule(s) are resolved. We recommended this for multiple nonsolid nodules identified on baseline and for newly seen larger nodules on annual repeat screening based on our experience in the original ELCAP. We wanted to determine to what extent this option allowed for the evaluation to be stopped and whether the workup could also be stopped for those who had partial resolution. To address these questions, we reviewed our experience of baseline and repeat CT screenings performed subsequent to the original ELCAP as it was for these new screenings that the option of recommending antibiotics with follow-up CT in 1 to 2 months was added.

## Materials and Methods

We reviewed 1,968 consecutive baseline and 2,343 annual repeat screenings conducted from 1999 to 2002 after the completion of our initial experience. Minimum age for enrollment was 40 years (median age, 59 years) with a smoking history of at least 1 pack-year (median, 32 pack-years). The initial CT in all of these screenings and subsequent workup was also performed at Weill Medical College of Cornell University. All patients undergoing screening gave informed consent under institutional review board-approved protocols. Details of the imaging and reading protocol have already been described in prior reports.

The definition of positive result of the initial CT test at baseline has been updated from the original ELCAP: for purposes of this report, the latest definition was used: identification of at least one solid or part-solid noncalcified nodule ≥ 5 mm in diameter, and/or at least one nonsolid noncalcified nodule ≥ 8 mm in diameter (Table 1). For repeat screening, the definition of positive result on the initial CT test remained the same as the original definition in ELCAP: any newly identified noncalcified nodule that had grown since the prior screening regardless of size or anything else, except that definition of growth was updated to account for nodule consistency; alternatives to any enlargement, identified visually by the radiologist, of the entire nodule included growth of the solid component of a part-solid nodule; and development of a solid component in a previously nonsolid nodule (Table 1). Given a positive result, further workup proceeded according to the protocol already detailed in the introduction. Partial resolution was defined as any decrease in the nodule size, while evidence of no change or increase required further follow-up or biopsy.

Based on the findings of the initial CT at baseline or annual repeat screening, we identified all those who were recommended for antibiotics who also had follow-up CT within 2 months of the initial CT. As we also recommended antibiotics when solitary or multiple patchy consolidation was identified, we also included these cases. We used the fact that patients undergoing screening returned for CT within 2 months after the initial CT as the surrogate for whether the person actually took antibiotics, as those who were not prescribed antibiotics were recommended for a follow-up CT no sooner than 3 months.

For each of the cases so identified, two radiologists (N.W., C.I.H.) reviewed the initial CT and all subsequent CTs. We classified each case as to the size of the largest noncalcified nodule and whether there was only a single nodule or multiple nodules on the initial CT at baseline or annual repeat screening. We then determined whether the nodule(s) or patchy opacity had grown, decreased, or resolved on the subsequent CT. Clinical follow-up was obtained from each person and referring physician as well as from hospital charts.

## Results

### Baseline Screening

Of the 41 patients who returned for follow-up CT within 2 months of the initial CT in baseline screening, 31 had nodules and 10 had patchy consolidation. Five patients (12%) had complete resolution, and seven patients (17%) had partial resolution (Table 2).

### Table 1—Findings of Baseline and Annual Repeat Screenings

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Annual Repeat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screenings, No.</td>
<td>1,968</td>
<td>2,343</td>
</tr>
<tr>
<td>Positive results, No.</td>
<td>368</td>
<td>254</td>
</tr>
<tr>
<td>Positive results, %</td>
<td>12%</td>
<td>6%</td>
</tr>
</tbody>
</table>

### Table 2—Change in Nodules on Follow-up CT Within 2 Months of the Initial CT at Baseline Screening, According to the Presence of Nodules or Patchy Consolidation

<table>
<thead>
<tr>
<th>Change on Follow-up CT</th>
<th>Nodules</th>
<th>Consolidation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete resolution</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Partial resolution</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>No change/growth</td>
<td>27</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>10</td>
<td>41</td>
</tr>
</tbody>
</table>

*Data are presented as No.
Among the 10 patients with patchy consolidation, 8 patients (80%) completely or partially resolved after antibiotic therapy as compared to 4 patients (13%) of the 31 patients with nodules. Using either complete or partial resolution as the criteria for no further follow-up, 12 patients (29%) would have had their workup stopped and simply been asked to return for the first annual repeat screening. None of the nodules with partial resolution grew subsequently, and none were found to be malignant; they either completely resolved or remained unchanged. None of those patients with patchy opacities had a malignancy diagnosed, but among those 27 patients with noncalcified nodule(s) that did not decrease or grew, 15 cancers were subsequently diagnosed.

### Annual Repeat Screening

Of the 39 patients who returned for follow-up CT within 2 months of the initial CT on repeat screening, 20 patients had nodules and 19 patients had patchy consolidation. Sixteen patients (41%) had complete resolution, and 13 patients (33%) had partial resolution (Table 3). Among the 19 patients with patchy consolidation, 95% (n = 18) completely or partially resolved after antibiotic therapy, as compared to 55% (n = 11 of 20 patients) with nodules (Fig 1). Using either complete or partial resolution as the criteria for no further follow-up, 29 patients (74%) would have had their workup stopped and simply been asked to return for the first annual repeat screening. None of those who showed partial resolution had subsequent growth or were found to have malignancy; the disease was either completely resolved or remained unchanged. None of those with patchy opacities had a malignancy diagnosed, but among those nine patients with noncalcified nodule(s) that did not decrease or grew, two cancers were diagnosed. Among those 10 patients whose nodule(s) remained unchanged or grew, two cancers were subsequently identified.

## Discussion

An important topic of research in CT screening for lung cancer is the development of strategies to either speed up or limit the evaluation of benign nodules. Early on, it was recognized that adult asymptomatic smokers without prior malignancy who had multiple nodules on the initial CT in the baseline cycle of screening probably had inflammatory parenchymal disease. Nodule consistency was also found to help distinguish benign from malignant nodules, since nonsolid and solid nodules were found to be malignant less commonly than part-solid nodules. Finally, once it was recognized that evaluation of nodules < 5 mm in diameter on the baseline screening CT was not productive, such patients were recommended for repeat screening CT in 1 year.

Although patients referred for CT screening for lung cancer are, by definition, asymptomatic, we recognized in our original ELCAP study that very short doubling times of nodules might indicate infectious or inflammatory lesions. Although we initially posited that a new nodule discovered on annual repeat screening CT would have a high likelihood of malignancy, we found that approximately 40% of these nodules had resolved on follow-up CT 1 to 2 months after the initial CT, both with and without having received antibiotics (Fig 1). We thus began to utilize empiric broad-spectrum antibiotic therapy both on baseline and repeat screening when an infectious etiology was deemed a reasonable possibility based on the radiographic characteristics. In the present series, 74% of the nodules and patchy opacities discovered on annual repeat screening had complete or partial resolution after antibiotic therapy, whereas only 29% of them discovered on baseline screening resolved on CT within 2 months of the initial CT. Patchy consolidation or nonsolid opacities had a much higher likelihood of resolution after antibiotic therapy than solid nodules, both on baseline and repeat screening.

It is important to recognize that both the likelihood of malignancy and the likelihood of a bacterial infection are considerably greater for a nodule first discovered on annual repeat CT than on baseline screening. This is logical since the initial baseline CT is likely to contain fibrotic scars from prior bacterial infection that might have a nodular configuration as well as scars from pulmonary infarcts and nodules caused by granulomas due to mycobacterial and fungal infection. On annual repeat screening, however, only a new nodule since the prior year would be considered a positive finding, and thus this is more likely to represent an acute infection or malignancy.

Limitations of this study include a lack of control over which antibiotics were administered and whether or not they were actually taken. General written advice was offered to referring physicians (general internal medicine and internal medicine subspecialists at a university tertiary care medical institution) to follow clinical guidelines in the management of these cases.

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**Table 3—Change in Nodules on Follow-up CT Within 2 Months of the Initial CT at Repeat Screening, According to the Presence of Nodules or Patchy Consolidation**

<table>
<thead>
<tr>
<th>Changes on Follow-up CT</th>
<th>Patchy Nodules</th>
<th>Patchy Consolidation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete resolution</td>
<td>6</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Partial resolution</td>
<td>5</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Nonchange/growth</td>
<td>9</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>19</td>
<td>39</td>
</tr>
</tbody>
</table>

*Data are presented as No.
center) to treat for adult community acquired pneumonia, but the specific choice of the antibiotic regimen was left to the referring physician. Based on our initial findings, we believed it was acceptable to offer all appropriate patients the option of broad-spectrum antibiotic therapy, particularly on repeat screening. It would be reasonable, however, in the future to conduct a study in which people are randomized to antibiotics and no antibiotics with a follow-up CT at 2 months.

The judicious use of antibiotics is important in order to avoid toxicity from antibiotics as well as the emergence of resistant bacterial strains in the general population. Caution against the overuse of antibiotics must be balanced against their potential value in obviating the costly and potentially invasive diagnostic evaluation of positive findings that are not due to lung cancer. In the current series of 1,968 baseline and 2,343 repeat screenings, we estimate that 80 patients took antibiotics. No serious toxicity has been observed in this generally healthy population, and in 41 of the 80 patients (51%), the diagnostic workup could be stopped.

On the basis of this study and the prior ELCAP,1,2 we recommend a course of antibiotics followed by another CT within 2 months to people with patchy consolidation or nonsolid opacities detected on the baseline screening and all those with new nodules on repeat screening. It must be emphasized that the use of antibiotics and short-term CT follow-up is only one of the option in the regimen of CT screening for lung cancer, and further research in this area promises to continue improve the efficiency of CT screening for lung cancer.

REFERENCES