The Restaging of Responding Patients With Limited Small Cell Lung Cancer*  
Is It Really Useful?

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A retrospective review of data on patients entered on two limited small cell lung cancer studies of the National Cancer Institute of Canada (BR.3 and BR.6) was undertaken to determine the value of restaging and rebronchoscopy in responding patients. An economic evaluation was also done. Repeat scans (brain, liver) and bronchoscopy were carried out in 190 patients and 5 (2.6 percent) were positive, despite other evidence suggesting response. One hundred thirty-nine of 324 patients who achieved complete response on the two trials underwent rebronchoscopy. Among these, 122 (87.7 percent) were negative and eight (5.8 percent) were inconclusive. Nine (6.5 percent) were positive despite other evidence suggesting the patient had achieved a complete response. A small group of nine patients with positive rebronchoscopy survived for a shorter time than the group with negative or inconclusive rebronchoscopies. The survival difference was only statistically significant when analyzed using the log rank test, but it was not significant when analyzed by the Wilcoxon test. The economic analysis showed that it costs $11,333 per patient reclassified when scans were redone in these patients. The cost could even have been higher had we used present-day scanning techniques (computed tomography and magnetic resonance imaging), although they might be slightly more sensitive. The cost of rebronchoscopy per patient reclassified was $14,960. Therefore, we recommend that restaging (scans or rebronchoscopy) not be done in responding patients with limited small cell lung cancer, thus potentially saving health care dollars as well as reducing patient inconvenience with no detrimental effect on survival.  
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SCLC = small cell lung cancer

In recent years, it has become standard practice to do extensive staging prior to the initiation of treatment in patients with small cell lung cancer (SCLC). The purpose of this staging is to accurately categorize patients as having either limited or extensive disease according to the Veterans Administration staging system. Initial staging procedures prior to treatment usually include at least a physical examination, hematology, chemistry, liver, bone, and brain scans and bone marrow aspirates and biopsies. In a study setting, and not infrequently in patients in the community, extensive restaging is done after completion of treatment to confirm a complete response even in patients who initially had no evidence of disease outside the lungs and ipsilateral supraclavicular nodes.

Such restaging is time-consuming and potentially uncomfortable and inconvenient to the patient, does not usually result in a change in the clinical treatment of patients, and may add to the cost of the medical care of these patients. Therefore, it is important to evaluate its contribution to the treatment of these patients. We have undertaken a retrospective review of patients with limited SCLC entered on two consecutive multicenter cross-Canada clinical trials (BR.3 and BR.6) under the direction of the Clinical Trials Group of the National Cancer Institute of Canada. We attempted to find out if the restaging procedures had significant predictive value for long-term disease-free or overall survival and to identify the economic impact of these procedures.

METHODS AND MATERIALS

Patients eligible for this retrospective review included all patients entered on BR.3 and BR.6. Schemata for these two trials are shown in Figure 1. The results of BR.3 and a preliminary description of BR.6 have been published. BR.3 enrolled patients from December 1981 to October 1984 and BR.6 enrolled patients from February 1985 to December 1986.

We examined two approaches to restaging: (1) repeat scans in patients who had responded to therapy (including those with stable disease, and (2) repeated bronchoscopy in those patients who had obtained a complete response based on physical examination, laboratory tests, and chest radiograph.

In both studies, all patients underwent standard initial staging procedures, including complete history, physical examination, hematology, and chemistry studies, as well as bone scans, brain scans (computed tomographic [CT] or radionuclide) and an evaluation of the liver (CT, ultrasound, or nuclear medicine). In patients who responded to chemotherapy on the basis of chest radiograph and clinical examination and who were still responding at the end of

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their therapy, repeat scans for confirmation of response were required in BR.3, but not in BR.6. Therefore, the analysis of the value of repeated scans in this report includes only patients on BR.3. However, bronchoscopy was recommended for patients who achieved a complete response at the end of all therapy on both studies. At the time of this analysis, the median follow-up from randomization for BR.3 was 6.6 years and for BR.6 it was 4.0 years.

An economic evaluation of a policy of restaging patients with stable disease or evidence of response to treatment was also carried out. The costing was performed using standard techniques to identify health care costs from the perspective of the health care system (treating institution and physicians). Patient-related costs, including out-of-pocket expenses and time lost from work, were not included. The approach taken was similar to that used in two previously published economic evaluations by our group and will not be described in detail herein. All costs are in 1989 Canadian dollars and no discounting of costs was performed.

Costs for scans were obtained from the published 1989 Schedule of Benefits of the Province of Ontario Health Insurance Plan. These costs included technical and professional components for all scans except for the technical component of CTs. The cost of the technical component of the CT scan was derived from actual costs incurred at the Mount Sinai Hospital in Toronto. The cost of bronchoscopy was calculated using the Hotel Approximation method. It was assumed that all bronchoscopies were performed on an outpatient basis (performance of bronchoscopies on an inpatient basis would result in higher costs than those outlined herein). Direct medical care costs included the capital and maintenance costs of the bronchoscope, nursing costs, medication and equipment costs (including biopsy forceps and brushes), and laboratory costs (pathology, cytology, and microbiology). Hotel costs, including overhead costs, were not determined separately for this evaluation but were
included at a conservative rate of 30 percent of medical care costs, slightly lower than that identified in previous evaluations we have conducted in the Canadian health care system. 6,7 The costs of complications of bronchoscopy were not included. The costs shown herein are therefore conservative estimates of the true costs.

To quantify the costs associated with restaging, we performed an economic analysis of three different approaches to restaging. The first of these consists of a series of scans to evaluate liver, bone, and brain; the second includes bronchoscopy only; and the third includes the scans plus bronchoscopy.

RESULTS

Repeated Scans in Patients Who Responded to Therapy on BR.3

Of the 298 eligible patients entered into this study, 254 met protocol response requirements (complete response, partial response, or stable disease) for repeated scanning. Of these, 64 did not have scans carried out for a variety of reasons, leaving 190 patients for the analysis. A total of five patients (2.6 percent) had scans that were positive despite other evidence suggesting response. This included one patient with a complete response, two with a partial response, and two with stable disease. The scans that were positive included three bone, one liver, and one CT of the abdomen (adrenal metastases). The characteristics of the patients in whom scans were abnormal compared with those in whom scans were normal are shown in

Table 1. There were no obvious preexisting clinical parameters to suggest that even the small number of abnormal scans could have been predicted by other means.

Patients Undergoing Bronchoscopy on BR.3 and BR.6

The characteristics of the 324 patients who achieved and maintained a complete response at the end of therapy and were hence eligible for bronchoscopy whether they actually had bronchoscopy are shown in Table 2. Most (88 percent) of the patients had an Eastern Cooperative Oncology Group status of 0 or 1 and the median age was 62 years. Male subjects predominated over female subjects as in most series. More patients came from the BR.3 study than BR.6. There was no significant imbalance of alkaline phosphatase or lactate dehydrogenase in the two patient groups.

Of the 139 patients who had bronchoscopy, 9 (6.5 percent) were positive, 122 (87.7 percent) were negative, and 8 (5.8 percent) were inconclusive. There was no statistically significant difference in clinical features (Table 3) between those with positive and negative bronchoscopies with the exception that all positive cases came from the BR.3 trial.

Survival of Patients Who Were Bronchoscopyed

Survival for the 324 complete responders is shown
in Figure 2. The median survival from allocation was 601 days. There were no differences in survival of patients who were bronchoscopyed versus those who were not (Fig 3). The median survival of those who were bronchoscopyed was 553 days versus 621 days if they were not bronchoscopyed. This suggests that there was no major bias in selecting patients for bronchoscopy, a conclusion supported by the lack of differences in the characteristics of the two populations.

The small group of nine patients with positive bronchoscopyes survived for a shorter time than the group with negative or inconclusive bronchoscopyes (Fig 4); this survival difference was statistically significant with the log rank test ($p = 0.020$) but not with the Wilcoxon test ($p = 0.088$).

**Results of Economic Analysis**

The costs of the restaging procedure are shown in Table 4. It can be seen that the cost of scans varied from $76 for an abdominal ultrasound to $300 for an abdominal CT scan. The scans most commonly performed in the BR.3 study were radionuclide bone and brain scans and an abdominal ultrasound. The total cost of an outpatient bronchoscopy was $1,122 and the major items contributing to that cost are shown in the table.

The costs of restaging for each patient reclassified as a nonresponder for the three different approaches to restaging are shown in Table 5. The first approach, that of performing only the scans most commonly used in BR.3, resulted in an additional cost of $11,333.
per patient reclassified. Using the approach to staging more commonly used today (CT scans of brain and abdomen and a radionuclide bone scan) and assuming the positive yield increases by 50 percent with the use of these more sensitive scans, the cost per patient reclassified increases to $15,911. The cost of bronchoscopy per patient reclassified was $14,960. This cost is lower than might have been anticipated given the relative costs of scans and bronchoscopy because bronchoscopy identified a larger number of patients with residual disease (6.5 percent) than did scans (<3 percent).

**Discussion**

An evaluation of patients on two consecutive limited SCLC studies carried out by the National Cancer Institute of Canada Clinical Trials Group clearly suggests that there is little clinical benefit associated with the performance of repeated scans in patients who are responding by other criteria. The frequency of “mixed responses” in patients who showed progression on scans while showing response in chest radiographs occurred less than 3 percent of the time in the BR.3 study. The fact that this observation was made when patients were only treated for six courses of therapy and then went onto close follow-up with reinduction only if relapse occurred highlights the lack of clinical usefulness of restaging these patients. Even with this relatively short period of therapy, repeating the scans contributed little to the clinical treatment of these patients but clearly added to the cost of health care based on our economic analysis as well as resulting in significant inconvenience to patients. We therefore recommend that, in future clinical trials or as part of standard patient care, repeated scans not be carried out in patients with limited disease who show evidence of response in chest radiographs. We did not address this issue in patients with extensive disease in whom there may be a greater likelihood that “mixed responses” may be observed. However, even in that situation, at present we are repeating only those scans that were abnormal initially, which is probably adequate.

The role of bronchoscopy is more controversial. A number of studies in the past have suggested that up to 30 percent of patients with SCLC may be found

**Table 4—Costs of Restaging Procedures**

<table>
<thead>
<tr>
<th>Item</th>
<th>Unit Cost (1989 Canadian $)</th>
</tr>
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<tbody>
<tr>
<td>Liver imaging</td>
<td></td>
</tr>
<tr>
<td>CT scan</td>
<td>$300</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>76</td>
</tr>
<tr>
<td>Radionuclide scan</td>
<td>109</td>
</tr>
<tr>
<td>Brain imaging</td>
<td></td>
</tr>
<tr>
<td>CT scan</td>
<td>270</td>
</tr>
<tr>
<td>Radionuclide scan</td>
<td>118</td>
</tr>
<tr>
<td>Radionuclide bone scan</td>
<td>146</td>
</tr>
<tr>
<td>Outpatient bronchoscopy</td>
<td>$1,122</td>
</tr>
<tr>
<td>Physician $207</td>
<td></td>
</tr>
<tr>
<td>Nursing* $169</td>
<td></td>
</tr>
<tr>
<td>Bronchoscope† $132</td>
<td></td>
</tr>
<tr>
<td>Equipment/supplies‡ $222</td>
<td></td>
</tr>
<tr>
<td>Laboratories $133</td>
<td></td>
</tr>
<tr>
<td>Hotel $259</td>
<td></td>
</tr>
</tbody>
</table>

*Includes setup, procedure, and clean-up costs, recovery room costs, clerical and support staff costs.
†Includes capital and maintenance costs.
‡Includes biopsy forceps and brushes, disposable equipment, drugs.

**Table 5—Cost of Different Restaging Policies**

<table>
<thead>
<tr>
<th>Policy</th>
<th>Cost per Patient Reclassified (1989 Canadian $)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scans only</td>
<td></td>
</tr>
<tr>
<td>(1) Abdominal ultrasound, radionuclide scans of brain and bone</td>
<td>$11,333</td>
</tr>
<tr>
<td>(2) CT liver and brain, radionuclide bone scan*</td>
<td>15,911</td>
</tr>
<tr>
<td>Bronchoscopy only</td>
<td>14,960</td>
</tr>
<tr>
<td>Bronchoscopy plus scans in (1)</td>
<td>13,924</td>
</tr>
<tr>
<td>Bronchoscopy plus scans in (2)</td>
<td>15,317</td>
</tr>
</tbody>
</table>

*This calculation assumes the use of CT scans improves the rate of positive scans by 50 percent.
to have positive rebronchoscopies despite the fact that radiographs of the chest are considered normal.\textsuperscript{6,8} We looked at our two studies to see if rebronchoscopy data were useful or not in the treatment of these patients. About one half of the patients did not have rebronchoscopy performed, in most cases because the patients refused to comply, despite the fact that it was part of the written protocol. When we looked at those who had a positive rebronchoscopy, it was found that nine (6.5 percent) patients had positive results. The characteristics of these patients were not significantly different from the patients who had a negative rebronchoscopy or those who had an inconclusive result. The survival for those patients who had rebronchoscopy and those who did not was identical. However, if one looks specifically at the subgroup of patients who had positive repeat rebronchoscopies (nine patients), there was a significantly shorter survival in those with positive rebronchoscopies compared with those with negative rebronchoscopies when analyzed by the log-rank test, but not with the Wilcoxon test, which looks primarily at long-term effects.

We have shown that the costs of restaging are high in comparison to their clinical benefits. The benefits of restaging are restricted to the early identification of patients who have residual disease after completion of the planned initial therapy. There are no therapeutic interventions that have been shown to significantly prolong survival in those patients who are reclassified as nonresponders and the costs of this restaging cannot therefore be translated into a cost per additional year of survival. They simply represent the costs of the advance knowledge that the patients have residual disease. This early knowledge of residual disease not only has adverse economic implications but it may have a negative impact on the “quality of life” of a patient who had previously been classified as a responder. It may also lead to further unnecessary (and costly) treatment in this group of patients.

Even though it is recognized that the early identification of minimal residual disease on restaging does not lead to additional treatment, it is possible that it could result in the withholding of treatment, such as prophylactic cranial irradiation, that is often given to complete respondents. If this were the case, there could be a potential economic saving associated with routine restaging. The impact of this potential saving would vary according to local treatment policies for radiation in the presence or absence of minimal residual disease and to the cost of radiation. For example, if detection of minimal residual disease resulted in a decision not to give prophylactic cranial irradiation that otherwise would have been administered, the cost of cranial irradiation would be saved. In Canada, this would amount to approximately $1,000 (ten fractions at $100 per fraction)\textsuperscript{7} per patient reclassified, thereby reducing the costs shown in Table 5 by $1,000 for each patient reclassified. If irradiation costs were higher (eg, $500 per fraction), costs in Table 5 would be reduced correspondingly (eg, by $5,000). The final costs of restaging would still be positive but of smaller magnitude, and a policy of restaging would still be associated with additional costs but no additional benefits.

The situation with respect to chest irradiation is somewhat different. In the studies reported herein, this irradiation was commonly administered as 4,000 cGy in 15 fractions and it was usually administered before restaging scans and rebronchoscopy. When performed in this sequence, the results of the restaging procedures would not alter the costs associated with chest radiation. If restaging was performed before chest radiation, the number of positive scans would not change and the cost of restaging per patient reclassified would be as shown in Table 5. However, the rate of detection of residual disease on bronchoscopy might increase. If one assumes this rate is doubled and that the administration of chest radiation can be avoided in these patients, then the net cost of restaging using preradiation bronchoscopy can then be calculated.

If one uses the rebronchoscopy positivity rates identified in this article and assumes that the costs of chest radiation are avoided in those with positive results, the cost of rebronchoscopy per patient reclassified can be calculated. If radiation is administered as 4,000 cGy in 15 fractions at $100 per fraction, the cost per patient reclassified would fall to $13,460. If these radiation costs were higher (because of a larger number of fractions or a higher cost per fraction), the cost per patient reclassified would decrease further but would not reach zero until radiation costs equaled bronchoscopy costs (ie, $14,960). If the positivity rate of rebronchoscopy doubled over that reported herein (because the procedure was performed before rather than after radiation), and the costs of radiation avoided were $7,480 or higher, then a net economic saving might result. This could occur when chest radiation was administered as a large number of fractions and the cost per fraction was high (eg, 20 fractions at $400 per fraction or 30 fractions at $250 per fraction). This is particularly likely if both chest and cranial irradiation are avoided when responding patients are reclassified as nonresponders. In Canada, given our treatment policies and radiation costs, there are no scenarios in which the net cost of restaging is negative. However, if radiation costs are high and both chest and cranial irradiation are withheld as a result of reclassification of response status, there would be a net economic saving associated with the routine use of restaging procedures and the latter approach would be favored economically. Readers should consider their
existing treatment policies, the effect to which they would be influenced by the detection of residual disease on routine restaging, and local radiation costs to identify the net economic implication of restaging in their center.

Although the economic evaluation was performed in the Canadian health care system, it is likely similar results would be obtained in the United States. The American unit costs might be somewhat higher than those in Canada because of higher costs in general, but it is unlikely the general conclusion of the economic evaluation (ie, that restaging results in increased costs) would be altered, even when the costs saved as a result of withheld radiation are considered.

We, therefore, recommend that patients with limited SCLC who achieve a complete response based on chest radiographs or CT scan of chest not have repeated scans or rebronchoscopies to confirm their complete response. This will save significant health care dollars as well as reducing patient discomfort and inconvenience.

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REFERENCES