This review by Dr. Gore emphasizes the significance of the problem of brain metastases in patients with locally advanced non-small-cell lung cancer (NSCLC). The article should prompt medical and radiation oncologists to consider enrolling patients in the ambitious study of prophylactic cranial irradiation (PCI) led by the Radiation Therapy Oncology Group (RTOG L-0214). Statistics from the ongoing RTOG study are complicated, but essentially, the researchers are looking for a 20% increase in median survival for patients receiving PCI. This would make the impact of PCI in NSCLC comparable to that observed in limited small-cell lung cancer (SCLC).
ized studies in some detail.[2-4] These randomized studies are also summarized in a table in Dr. Gore's article, but their message loses some impact as the table also includes phase II studies. Table 1 above is

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>PCI</th>
<th>Timing of PCI</th>
<th>CNS Failures</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>145</td>
<td>None</td>
<td></td>
<td>6%</td>
<td>NA</td>
</tr>
<tr>
<td>RTOG, 1991[3]</td>
<td>93</td>
<td>30 Gy/10 fx</td>
<td>Started concurrent with sixth fraction of chest irradiation</td>
<td>9%</td>
<td>8.4 mo</td>
</tr>
<tr>
<td></td>
<td>94</td>
<td>None</td>
<td></td>
<td>19%</td>
<td>8.1 mo</td>
</tr>
<tr>
<td>Umsawasdi, 1984[4]</td>
<td>46</td>
<td>30 Gy/10 fx</td>
<td>Following 2 or 4 cycles of chemotherapy (some patients had concurrent</td>
<td>4%</td>
<td>8.4 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>chest irradiation with cycles 3 and 4); PCI sandwiched between chemotherapy cycles</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>51</td>
<td>None</td>
<td></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>RTOG L-0214</td>
<td>524</td>
<td>30 Gy/15 fx</td>
<td>Within 16 wk of completing definitive treatment</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>524</td>
<td>None</td>
<td></td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

CNS = central nervous system; fx = fractions; NA = not available; PCI = prophylactic cranial irradiation; RTOG = Radiation Therapy Oncology Group; VALG = Veterans Administration Lung Group.

* Median survival not stated but survival curves indicate median survival in range of 52+ weeks.

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results of Survey of Beliefs and Recommendations on PCI</td>
</tr>
<tr>
<td>Medical Oncology</td>
</tr>
<tr>
<td>Recommend PCI</td>
</tr>
<tr>
<td>Believe PCI improves survival</td>
</tr>
<tr>
<td>Believe improves QOL</td>
</tr>
<tr>
<td>Believe PCI is associated with toxicity</td>
</tr>
</tbody>
</table>

PCI = prophylactic cranial irradiation; QOL = quality of life.

Adapted from Cmelak et al.[7]
another attempt to show differences between the ongoing RTOG study and these older phase III studies. First, it is clear that the earlier studies contained a relatively small number of patients. The statistical background in the manuscripts does not indicate how the numbers of patients to be accrued was determined. But clearly the studies were not powered to detect an achievable survival difference. Another important difference is that, in the early series, patients were randomized much earlier in the course of their disease (usually after diagnosis, prior to any treatment). It is quite probable that RTOG L-0214 will accrue a much different population of patients than the previous randomized studies.[2-4] The RTOG study mandates a normal brain magnetic resonance imaging scan prior to study entry, whereas the earlier studies had only computed tomography scans or nuclear brain scans. The current study accrues patients only after definitive treatment, randomizing them to PCI or observation within 16 weeks of completing all therapy. Therefore, there is a significant selection factor favoring good performance patients with a response to definitive treatment and no evidence of distant metastases documented following definitive treatment. The drawback of the late accrual and PCI delivery is that many patients will already have relapsed in the brain. A recent retrospective review of patients with stage III NSCLC determined that 46.5% of brain metastases presented within 16 weeks of completion of therapy.[5] Physicians may not be convinced that PCI is safe.

Dr. Gore states that it "took several decades for PCI to be accepted as a safe and effective method of managing central nervous system (CNS) micrometastases in patients with small-cell lung cancer." But PCI is not given to all limited SCLC patients following a complete response to chemotherapy.[6] A national survey of randomly selected institutions in the United States found that during the years 1998-1999, PCI was given to only 23% of patients treated for limited-stage SCLC. What cannot be determined from such a survey is whether PCI was recommended. Cmelak et al surveyed 9,176 oncologists in 1997 to determine if they recommended PCI to their patients with SCLC.[7] The survey also asked the oncologists if they believed that PCI improved survival or quality of life. Only 13% of oncologists returned the survey, but the results (summarized in Table 2) are nonetheless provocative. Cmelak et al concluded that most oncologists recommend PCI in limited-stage SCLC despite the fact that many do not believe that it leads to an increase in survival or quality of life. Perhaps patients pick up on this ambivalence. Are physicians concerned about neurotoxicity following PCI? Probably, but they might also be minimizing the impact of the subsequent development of brain metastases on neurocognitive function. Our ability to control brain metastases once they are diagnosed is not impressive. The RTOG reported the results of the Mini-Mental Status Exam (MMSE) before and after two different regimens of external-beam irradiation for patients with brain metastases.[8] Prior to any therapy, it was noted that fewer than 20% of patients had no neurologic symptoms and were fully active at home or work without assistance. Despite treatment, only 35% to 45% of patients had documented improvement 2 to 3 months later, with a similar percentage of patients showing a decline in the MMSE. Needless to say, progression of brain metastases was associated with a subsequent decline in MMSE scores. Neurocognitive function was also carefully evaluated in a prospective randomized study testing the benefit of motexafin gadolinium in addition to standard cranial irradiation in patients with brain metastases.[9] Approximately half of the patients enrolled in this study had NSCLC. Neurocognitive function was found to be impaired to some extent prior to any therapy in over 90% of patients. Although neurocognitive function and CNS recurrence rates are important clinical objectives, the National Cancer Institute mandated that survival be the primary end point for RTOG L-0214. However, the investigators are making a concerted effort to assess the neuropsychological impact of brain metastases and the use of PCI. MMSE, Hopkins Verbal Learning Test, and Activities of Daily Living Scale data will be collected at study entry and at specified follow-up intervals. Patients may be refusing to participate.

Of the possible reasons for low accrual to RTOG L-0214, patient refusal to participate will be the most difficult to determine. Patients may be concerned about the impact of PCI on their subsequent neurocognitive function and quality of life. In my practice, an increasing number of patients with diagnosed brain metastases are refusing whole-brain irradiation. Many patients specifically request stereotactic radiosurgery only. This might reflect their own research into the efficacy and toxicity of wholebrain irradiation, or it might reflect priming by referring physicians. If we can’t convince patients to have wholebrain irradiation in the setting of established brain metastases, can we convince them to have it in the preventive setting? In summary, the concept of PCI for NSCLC is not new. Older, outdated studies did not demonstrate any survival benefit. But RTOG L-0214, the ongoing phase III study of PCI, has a solid rationale and is sufficiently different from the older studies to warrant strong support. Whether a sufficient number of patients can be accrued remains to be
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