Perspective

The Road Less Traveled: Should We Omit Prophylactic Cranial Irradiation for Patients With Small Cell Lung Cancer?

Terence T. Sio,[1] Anussara Prayongrat,[2] Yun Zhang,[3,4] Qin Lin,[5] Ting Xu,[6] Zhongxing Liao,[6] Jinbo Yue[4]

Abstract

New randomized data from Japan have raised questions regarding the use of prophylactic cranial irradiation for patients with extensive-stage small-cell lung cancer but without detectable brain metastases on magnetic resonance imaging. In the present focused review, we examine the general role of prophylactic cranial irradiation in the management of small-cell lung cancer and present relevant controversies from both sides of the discussion. Future directions for clinical investigation and research are also highlighted. Strategies for neurocognitive protection, including memantine use and hippocampal sparing using modulated radiotherapy techniques, are also presented.

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Introduction

Since the "2-dimensional era," with the introduction of megavoltage-based external beam radiotherapy (RT) for cancer, several randomized trials[1] have led to the establishment of prophylactic cranial irradiation (PCI) as a component of the standard of care for patients with both limited- and extensive-stage small-cell lung cancer (SCLC) that responds to initial systemic therapy.[2] However, with improvements in imaging methods, systemic therapy, and radiation delivery, the role of PCI for such patients has been challenged (and rightfully so), especially in recent years. For patients with limited-stage SCLC, several randomized trials and 2 large meta-analyses[3,4] have shown that PCI significantly reduces the incidence of new brain metastases (by almost one half, from 59% to 33% at 3 years) and deaths from brain metastases. However, those improvements came at the price of increased neurologic complications and toxicity in exchange for a consistent and statistically significant increase in 3-year overall survival (OS) rates of ~5%. However, those studies were performed before the advent of modern imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and some did not require baseline or pre-RT/postchemotherapy brain imaging at all. The role of PCI for extensive-stage SCLC was recently challenged even further when a Japanese multicenter trial, although underaccrued, showed that PCI had a detrimental effect on OS. The patients in that trial had all undergone MRI at baseline, and those in whom brain metastases were found were excluded from the trial. In the present focused review, we examine the current clinical view and evidence for use of PCI for patients with an initial response to platinum-based doublet therapy who subsequently require additional intracranial disease control.

PCI for Limited SCLC

Whole brain RT (typically to doses of 30 Gy given in 10 daily fractions) has been used effectively to palliate symptoms and disease progression caused by brain metastases from a variety of types of cancer and has sometimes been associated with improved survival compared with that obtained with steroid supportive therapy. Because SCLC has a high propensity for intracranial metastasis (nearly 60%-70% during the course of the disease), clinicians hypothesized many years ago that the use of a lower dose of whole

T.T.S., A.P., and Y.Z. contributed equally to this work.

[1]Department of Radiation Oncology, Mayo Clinic Arizona, Phoenix, AZ
[2]Department of Radiation Oncology, King Chulalongkorn Memorial Hospital, Chulalongkorn University Bangkok, Bangkok, Thailand
[3]School of Medicine and Life Sciences, University of Jinan-Shandong Academy of Medical Sciences, Jinan, Shandong, China
[4]Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong Cancer Hospital affiliated to Shandong University, Jinan, Shandong, China
[5]Department of Radiation Oncology, Xiamen Cancer Hospital, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China
[6]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

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Address for correspondence: Jinbo Yue, MD, PhD, Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong Cancer Hospital affiliated to Shandong University, 440 Jinyan Road, Jinan, Shandong 250117, China
E-mail contact: jinbo.yue@gmail.com

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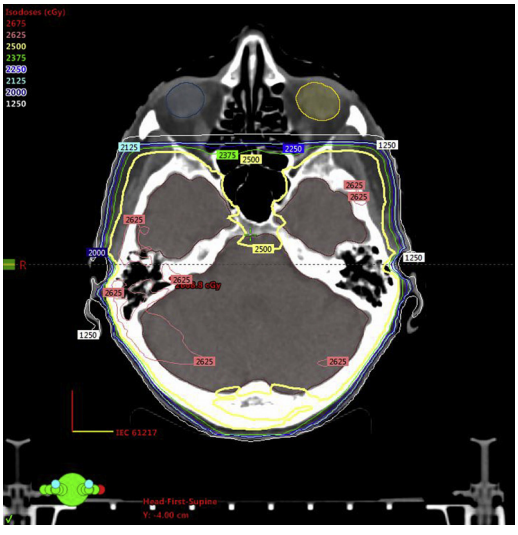
brain RT for prophylaxis could eliminate microscopic deposits and positively affect survival. This hypothesis was proved correct by 2 large meta-analyses,[3,4] comprising tens of randomized trials. Clinically, the most common and best-studied fractionation scheme is 25 Gy, given in 10 once-daily fractions (Figure 1).[5]

Many trials have shown the benefits of PCI in terms of future disease control. Some additional evidence was available in support of using PCI for patients with limited-stage SCLC with a complete response of thoracic disease after chemo-RT, although evidence of tumor response was determined from radiographs rather than modern-day CT scans.[6] Currently, a partial response of lung disease to chemo-RT is required before PCI is given, consistent with the experience with extensive-stage SCLC showing that patients with either complete and partial responses after chemo-RT can benefit from PCI.[7,8] The landmark meta-analysis that established the level 1 evidence for PCI for limited-stage SCLC included 7 trials, all performed before the era of MRI, when brain disease was detected mostly by CT. Individually, none of the 7 studies reported an OS benefit; however, collectively a small difference in OS was noted, as well as unequivocal evidence of improved disease-free survival.[3] The hypothesis was that PCI could be treating microscopic brain metastases that would have otherwise been detected by modern imaging (eg, MRI), which would represent a classic example of stage migration and bias favoring the use of PCI.

Figure 1 Scan of a 78-Year-old Woman With Newly Diagnosed Small-Cell Lung Cancer of the Left Lung. Magnetic Resonance Imaging Also Revealed Extensive Nodal and Bony Metastases But No Brain Involvement. She Completed 4 Cycles of Etoposide and Carboplatin (Carboplatin Was Used instead of Cisplatin Because of Concerns for Renal Insufficiency), With Concurrent Proton-Based Thoracic Radiotherapy to 45 Gy in 30 Fractions (Twice Daily) for Consolidation. After Achieving a Near-Complete Response and Excellent Performance Status, She Subsequently Received Prophylactic Cranial Irradiation (PCI) to 25 Gy in 10 Fractions. She Also Took Memantine for 6 Months (Off-Label Use). At 14 Months After PCI, She Was Alive With No Evidence of Intracranial Relapse. (In This Case, Proton Therapy Was Delivered Using a "Field-In-Field" Technique, With Multileaf Collimators Used to Minimize the Occurrence of "Hot Spots" Across Opposed Lateral Fields)



Given the advent of modern-day imaging techniques such as MRI, it is quite reasonable to re-examine the role of PCI, especially for earlier stage, limited SCLC. A retrospective analysis from the Memorial Sloan Kettering Cancer Center showed that the cumulative incidence of brain metastases for patients with stage I/II SCLC was only 10% at 2 years and 12% at 5 years; 34 of their 89 patients (38%) with stage I/II disease did receive PCI.[9] Enthusiasm for the use of PCI for patients with stage I SCLC has diminished. In a retrospective, multi-institutional study of 74 patients who underwent stereotactic ablative RT for stage I SCLC, only 23% received PCI,[10] and the use of PCI was not associated with improved clinical outcomes in a similar cohort.[11] In another retrospective study of elderly patients from the MD Anderson Cancer Center, patients with large tumors might not have benefitted from PCI in terms of OS, even those with a complete response to chemo-RT.[12] This finding is notable considering that ~60% of all patients with newly diagnosed limited-stage SCLC are aged > 70 years.[13]

Occasionally, very early-stage SCLC (usually T1N0) is treated surgically, and, as a result, the diagnosis of SCLC is often incidental. Such patients are few, and no high-level evidence is available to support the decision to offer PCI to such patients. The risks of brain metastasis after complete resection are believed to be low. A retrospective study from Zhu et al[14] indicated that the risk was < 10% according to the postoperative pathologic examination findings. Notably, however, the National Comprehensive Cancer Network (NCCN) guidelines[15] have recommended PCI for patients with limited-stage SCLC after complete resection if the patients have good performance status and neurocognitive functioning (a category 2A recommendation that was based on lower level of evidence but uniformly agreed on by the panel).

Some institutions have reported their experience with forgoing PCI for patients with limited-stage SCLC. Ozawa et al[16] suggested that PCI might be less beneficial for patients with limited-stage SCLC when close observation with MRI and stereotactic radiosurgery are available, which is possible in most modern RT centers. Similarly, another Japanese study demonstrated that the outcomes of treatment without PCI were improved over those of historical patients because of the use of more rigorous imaging methods, including CT, MRI, and positron emission tomography scanning.[17]

With modern combined-modality treatments and improved disease staging, patients with limited SCLC now have a greater chance of survival that could extend to years. Because PCI does have neurologic sequelae in the long term, future randomized trials addressing the role of PCI for patients with limited-stage SCLC are urgently needed. Such trials are likely to need large numbers of patients to reveal any advantages in disease-specific survival or OS.

PCI for Extensive SCLC

The role of PCI for extensive-stage SCLC is even more controversial, and the debate will likely continue for quite some time into the future. A 2007 report from the European Organization for the Research and Treatment of Cancer clearly showed a survival benefit