

# Prophylactic Cranial Irradiation for Limited-Stage Small-Cell Lung Cancer: Survey of US Radiation Oncologists on Current Practice Patterns

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## Abstract

**In this survey of 309 practicing US radiation oncologists, almost all respondents recommended prophylactic cranial irradiation (PCI) and pre-PCI brain magnetic resonance imaging (MRI)—practices endorsed by national guidelines. Only a third followed their patients with serial brain MRI after PCI, and about one third recommended memantine for patients undergoing PCI. This survey establishes a practice-pattern baseline for future clinical trials.**

**Purpose:** Prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer (LS-SCLC) is considered the standard of care. Meta-analysis of 7 clinical trials indicates a survival benefit to PCI, but all of these trials were conducted in the pre-magnetic resonance imaging (MRI) era. Therefore, routine brain imaging with MRI before PCI—as recommended by National Comprehensive Cancer Network guidelines—is not directly supported by the evidence. Current US practice patterns for patients with LS-SCLC are unknown. **Materials and Methods:** We surveyed practicing US radiation oncologists via an institutional review board-approved online questionnaire. Questions covered demographic information and treatment recommendations for LS-SCLC. **Results:** We received 309 responses from US radiation oncologists. Ninety-eight percent recommended PCI for patients with LS-SCLC, 96% obtained brain MRI before PCI, 33% obtained serial brain imaging with MRI after PCI to detect new metastases, and 35% recommended memantine for patients undergoing PCI. Recommending memantine was associated with fewer years of postresidency training ( $P < .001$ ), fewer lung cancer patients treated per year ( $P = .045$ ), and fewer LS-SCLC patients treated per year ( $P = .024$ ). **Conclusion:** Almost all responding radiation oncologists recommended PCI and pre-PCI brain MRI for LS-SCLC patients with disease responsive to initial therapy. Only a third of respondents followed these patients with serial brain MRI. Approximately one third provided memantine therapy to try to limit neurocognitive effects of PCI. Further research is warranted to determine the best treatment for patients with LS-SCLC. This survey can inform the development of future trials that depend on participation from radiation oncologists.

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## Introduction

Small-cell lung cancer (SCLC) represents 10% to 15% of lung cancer cases and carries a poor prognosis, with a 7% five-year survival rate compared to 24% for non-SCLC.<sup>1</sup> If cancer is confined to the ipsilateral hemithorax and can be safely encompassed within a

single radiation portal, it is considered limited-stage SCLC (LS-SCLC), according to the Veterans Administration's 2-stage classification system.<sup>2</sup> LS-SCLC carries more favorable outcomes, with 5-year survival rates over 25% and median survival around 25 to 30 months when treated aggressively.<sup>3,4</sup> However, even when

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limited to the ipsilateral hemithorax at the time of diagnosis, SCLC has a high propensity to metastasize.<sup>5</sup> A common site of metastasis is the brain; over 50% of patients with SCLC develop brain metastases within 2 years of diagnosis.<sup>6</sup>

Standard treatment for LS-SCLC involves chemotherapy plus concurrent thoracic radiotherapy (RT), followed by prophylactic cranial irradiation (PCI) for patients with disease completely or partially responsive to initial therapy.<sup>7</sup> The recommendation for PCI is based on several meta-analyses, clinical trials, and a retrospective review—all with patient data from the 1970s to 1990s—that demonstrate decreased incidence of intracranial metastases and a small but significant benefit in overall survival.<sup>8-10</sup> Brain imaging before PCI played a highly variable role in these studies, with some using computed tomography (CT) scans, others not requiring brain imaging unless patients were symptomatic, and still others making no mention of imaging.<sup>11</sup> These studies precede the era of magnetic resonance imaging (MRI), which detects brain metastases with greater sensitivity, and thus leads to a more than doubled detection rate of asymptomatic lesions.<sup>12</sup> Many of these brain metastases—between 11% and 33%—are asymptomatic at the time of diagnosis, whereas all brain metastases in the CT era were symptomatic.<sup>12-14</sup> Therefore, it is plausible that many patients in the control arm of these older trials had small, asymptomatic brain metastases that would have been detected by brain MRI had it been available. This could have stacked the deck in favor of PCI intervention, making it appear better than it would have in the current age of standard brain MRI before PCI. The same reasoning likely explains the difference in outcomes between 2 randomized controlled trials of PCI in extensive-stage SCLC: a 2007 trial<sup>15</sup> showing a survival benefit to PCI, and a recently published Japanese trial<sup>16</sup> finding no such benefit. Indeed, National Comprehensive Cancer Network (NCCN) guidelines<sup>7</sup> have been amended to allow observation of patients with extensive-stage SCLC with frequent brain imaging instead of PCI.

The debate over PCI must also take into account its risks, particularly of neurotoxicity and cognitive decline. This risk is established for whole-brain RT (WBRT) in the presence of known brain metastases, but it is debated for PCI, which uses lower doses of radiation.<sup>10</sup> Memantine, an *N*-methyl-D-aspartate (NMDA)-receptor antagonist classically used in the treatment of Alzheimer disease, was shown in a randomized trial to delay cognitive decline in patients treated with WBRT for brain metastases.<sup>17</sup> Whether the neuroprotective effect of memantine can be extrapolated to patients with LS-SCLC undergoing PCI has not been studied directly.

We designed an online survey to learn how US radiation oncologists treat patients with LS-SCLC. We analyzed the responses related to PCI, brain imaging, and memantine administration. We hypothesized that most respondents would adhere to national guidelines and recommend PCI as well as pre-PCI brain MRI for patients with LS-SCLC. In contrast, because NCCN guidelines do not recommend routine brain imaging during follow-up after PCI and only recently added a suggestion to consider memantine therapy for PCI patients,<sup>7</sup> we hypothesized that most respondents would not endorse these practices. Current NCCN guidelines at the time the survey was completed by respondents made no mention of memantine at all.<sup>18</sup>

## Materials and Methods

### Survey Instrument Development

This study was approved by the Oregon Health & Science University (OHSU) institutional review board (IRB 000149). The online survey was designed using the REDCap web application, managed by the Oregon Clinical & Translational Research Institute for use in OHSU projects.

The survey contained 39 questions, with respondents answering only pertinent questions that were based on prior responses via branching logic. Once respondents identified themselves as radiation oncologists, questions covered demographic information and treatment recommendations for patients with LS-SCLC, including dose, fractionation schedule, timing of RT with chemotherapy, target volume, elective nodal irradiation, PCI, and the administration of memantine with PCI. Questions also covered self-rated knowledge of 4 important trials involving the treatment of LS-SCLC, though none dealt directly with PCI and thus will not be discussed here.

### Data Collection

The data sample was collected through an anonymous online questionnaire of radiation oncologists in the United States. Using the REDCap software, e-mail invitations for the questionnaire were sent to 6954 potential participants, using e-mails from a publically available database of US radiation oncologists. The invitations contained information about the study, a link to the survey, instructions for completion, and contact information. An initial invitation was sent on October 18, 2016, followed by one reminder e-mail on October 22, 2016. Participants who asked not to be contacted again were removed from the database.

### Statistical Analysis

Respondents were characterized by practice setting, practice region, years since completing residency training, number of lung cancer patients treated with definitive intent in the past year, number of LS-SCLC patients treated in the past year, and self-rated knowledge of 4 trials. These characteristics were analyzed for correlations with responses on treatment practices. The chi-square test, or Fisher's exact test in cases of small sample sizes, was used to determine differences between groups for categorical variables. The Cochran-Armitage test was used to analyze trends in categorical variables.  $P < .05$  was deemed statistically significant. R 3.3.3 software (2017-03-96; R Foundation for Statistical Computing, Vienna, Austria; <http://www.r-project.org/>) was used for statistical analysis.

## Results

### Survey Respondents

Survey invitations were sent to 6954 e-mail addresses, including many that were inactive or duplicates, as the database contained both personal and institutional e-mail addresses, so the true number of potential participants is unknown. For context, recent estimates suggest there are around 4500 to 5000 radiation oncologists in the US.<sup>19</sup> We received 732 undeliverable/failed automatic replies, 11 ineligible responses, and 315 completed responses, 309 of which were from radiation oncologists. Only the responses from the 309

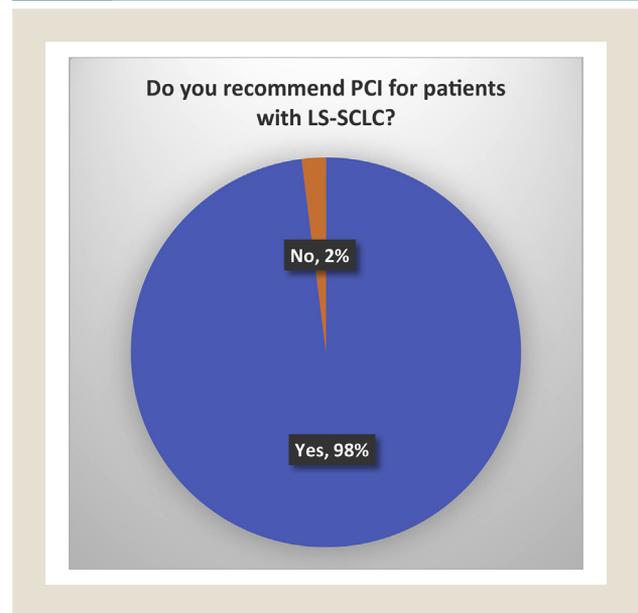
**Table 1** Background Characteristics of 309 Radiation Oncologists Who Completed the Survey

Characteristic	N (%)
<b>Practice Setting</b>	
Private	182 (58.9)
Academic	127 (41.1)
<b>Practice Region</b>	
Central	79 (25.6)
Northern	72 (23.3)
Pacific	58 (18.8)
Southern	66 (21.4)
Western	31 (10.0)
Other	3 (1.0)
<b>No. of Years Since Completing Residency Training</b>	
Currently in residency training	11 (3.6)
0-2	20 (6.5)
3-5	49 (15.9)
6-10	61 (19.7)
>10	168 (54.4)
<b>No. of lung Cancer Patients Treated With Definitive Intent in Past Year</b>	
0	6 (1.9)
1-2	7 (2.3)
3-4	13 (4.2)
5-10	41 (13.3)
>10	242 (78.3)
<b>No. of Limited-Stage Small-Cell Lung Cancer Patients Treated in Past Year</b>	
<5	137 (44.3)
5 or more	172 (55.7)

radiation oncologists were analyzed, and their characteristics are summarized in Table 1. The majority worked in private practice (59%) as opposed to an academic setting (41%), and just over half (54%) had more than 10 years of experience since completing residency training. In the past year, over three quarters of respondents (78%) had treated more than 10 lung cancer patients with definitive intent, and over half (56%) had treated 5 or more patients with LS-SCLC.

### Almost All Respondents Recommended Brain MRI and PCI for LS-SCLC Patients

For patients with LS-SCLC with good performance status, 98% of respondents recommended PCI as a general rule (Figure 1). Of the respondents who recommended PCI, 96% obtained brain imaging with MRI before PCI (Figure 2A), and 1 (33%) in 3 routinely obtained serial brain imaging with MRI when following patients after PCI to detect development of new brain metastases (Figure 2B). Recommending serial brain MRI was not significantly associated with any background characteristics, including practice setting ( $\chi^2 P = .49$ ) and number of LS-SCLC treated in the past year ( $\chi^2 P = .39$ ). There were 7 respondents who did not recommend PCI, and all 7 said they routinely obtained serial brain MRI when following patients after thoracic RT.

**Figure 1** Pie Chart Showing Recommendation of PCI for Patients With LS-SCLC. For Patients With LS-SCLC and Good Performance Status, 302 (98%) of 309 Respondents Recommended PCI as a General Rule

Abbreviations: LS-SCLC = limited-stage small-cell lung cancer; PCI = prophylactic cranial irradiation.

### Memantine Was Recommended by a Third of Respondents for Patients Undergoing PCI

Thirty-five percent of respondents recommended memantine therapy for patients undergoing PCI (Figure 3). The closer a respondent was to residency training, the more likely he or she was to recommend memantine (Cochran-Armitage test for trend  $P < .001$ ). Respondents who treated more lung cancer patients per year were less likely to recommend memantine ( $\chi^2 P = .045$ ), as were those who treated more LS-SCLC patients per year ( $\chi^2 P = .024$ ). There was no significant association between practice setting and recommending memantine ( $\chi^2 P = .79$ ).

## Discussion

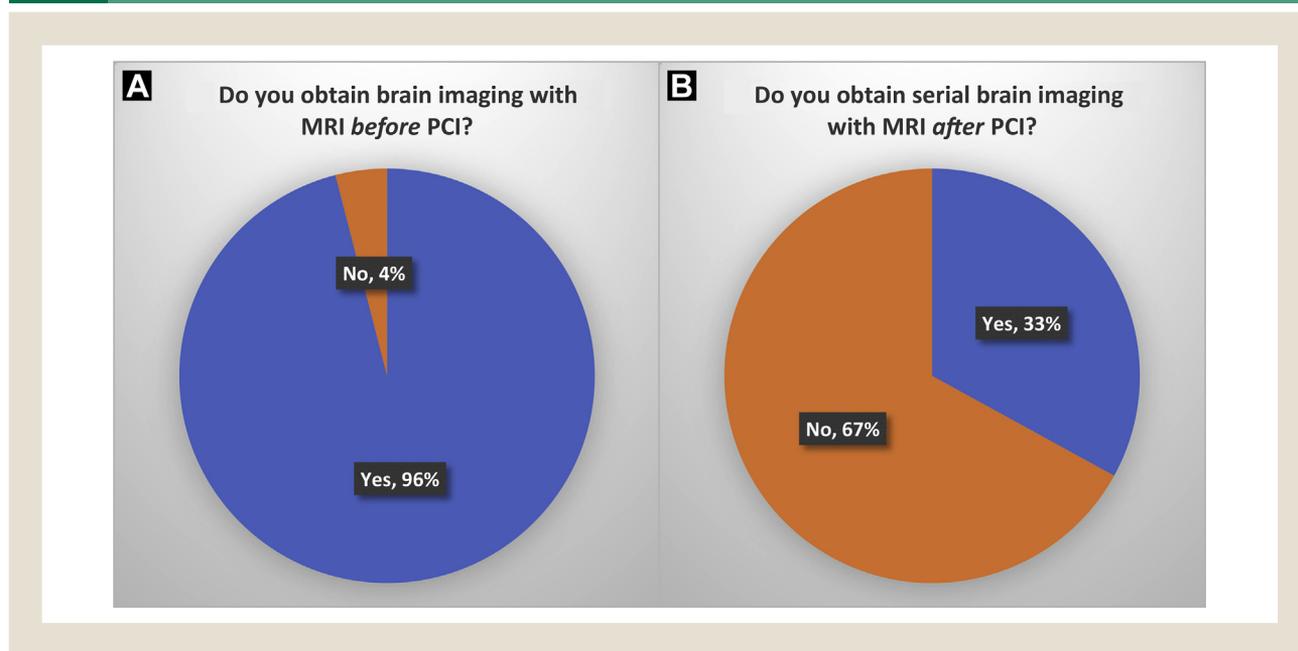
### PCI With Brain MRI: Does the Evidence Support It?

NCCN guidelines recommend PCI for LS-SCLC patients whose disease completely or partially responds to initial therapy, as well as brain MRI (preferred) or CT with contrast before PCI.<sup>7</sup> Our survey found almost universal adherence to these recommendations, with 98% of respondents endorsing PCI and 96% obtaining pre-PCI brain MRI. By comparison, in a 2016 survey of radiation oncologists in Canada, 100% recommended PCI for patients with a good radiographic response, but only 46% routinely offered pre-PCI brain imaging.<sup>20</sup>

There is evidence in the form of multiple clinical trials and meta-analyses that PCI improves overall survival when patients receive brain imaging with CT or no brain imaging at all,<sup>12-14</sup> but there is no direct evidence that the survival benefit persists when brain MRI is used for screening patients before PCI or for surveillance instead of PCI. Recent studies in extensive-stage SCLC have fueled the debate about the benefits of PCI in the MRI era.<sup>21</sup> A 2007

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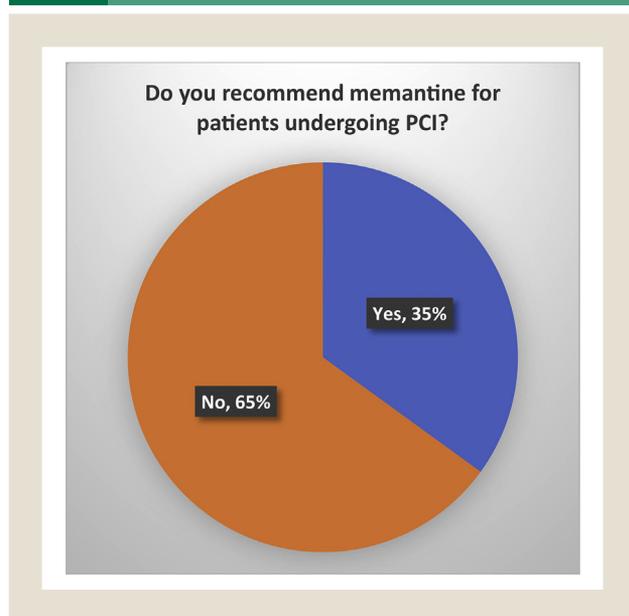
**Figure 2** Pie Charts Showing MRI Before and After PCI. Of 302 Respondents Who Recommended PCI, 290 (96%) Obtained Brain MRI Before Administering PCI (A), and 101 (33%) Routinely Obtained Serial Brain Imaging With MRI When Following Patients After Thoracic Radiotherapy and PCI to Detect New Brain Metastases (B)



Abbreviations: MRI = magnetic resonance imaging; PCI = prophylactic cranial irradiation.

randomized trial by the European Organization for Research and Treatment of Cancer (EORTC) in patients with extensive-stage SCLC showed that PCI decreased the rate of symptomatic brain metastases by 25.8% at 1 year and increased 1-year overall survival by 13.8%.<sup>15</sup> However, only 29% of patients had brain imaging at

**Figure 3** Pie Chart Showing Recommendation of Memantine for PCI. Of 302 Respondents Who Recommended PCI, 106 (35%) Recommended Using Memantine for Patients Undergoing PCI



Abbreviation: PCI = prophylactic cranial irradiation.

diagnosis, and it was not stated how many patients had brain imaging just before randomization and PCI. In a 2017 Japanese randomized trial of extensive-stage SCLC mandating brain MRI before randomization and at regular intervals afterward, the survival benefit of PCI disappeared.<sup>16</sup> A 2016 survey, conducted when this recent Japanese data was still in abstract form, showed that the vast majority of US radiation oncologists recommended both brain MRI and PCI for patients with extensive-stage SCLC: 98% recommended PCI, and over 90% obtained new brain MRI after patients completed systemic chemotherapy.<sup>22</sup>

One Japanese retrospective analysis of patients with LS-SCLC saw no significant survival advantage to PCI when MRI was used regularly before randomization, though the sample size was small and it was not a randomized controlled trial.<sup>23</sup> Although MRI alone may not account for the differences between the EORTC and Japanese studies,<sup>24</sup> it is clear that the recommendation of both brain MRI and PCI rests on shaky ground. One ongoing trial for SCLC patients, NRG CC003, mandates brain MRI for all patients but is comparing standard PCI to hippocampal avoidance PCI rather than investigating the benefit of PCI over no brain radiation. Further research is needed to bolster current practice patterns in the MRI age, in hopes of promoting early detection and treatment of clinically relevant brain metastases while avoiding unnecessary imaging and radiation of the brain.

#### ***Routine Brain MRI During Follow-up***

Of the respondents recommending PCI, a third routinely used serial brain MRI in follow-up after thoracic RT and PCI to detect new brain metastases. Of the 7 respondents who did not recommend PCI, all of them routinely used serial brain MRI after thoracic RT. NCCN guidelines do not recommend routine brain MRI or

CT during surveillance, but in patients not receiving PCI, they say “surveillance for metastases by brain imaging should be performed.”<sup>27</sup> The value of routine screening rests on the efficacy of salvage techniques for brain metastases. There are promising data surrounding stereotactic radiosurgery, especially in terms of local tumor control,<sup>25,26</sup> and alternative dose and fractionation schedules for WBRT could provide benefits in select patients.<sup>27</sup> Unfortunately, we did not ask our respondents whether they use stereotactic radiosurgery for recurrent, progressive SCLC brain metastases, or whether this practice correlates with obtaining post-PCI serial brain imaging. In the current landscape of better imaging, new contrast agents, and evolving salvage techniques, the optimal combination of brain MRI and PCI remains unclear. For now, the benefits of screening and surveillance with MRI should be weighed in each patient against the costs, such as the timetabled fear of finding new disease that frequent imaging might trigger in patients.

### Memantine for PCI and WBRT

About a third of respondents recommended therapy with memantine, an NMDA-receptor antagonist, for patients undergoing PCI. Radiation oncologists earlier in their careers were more likely to initiate memantine therapy, perhaps indicating a greater willingness to embrace the novel use of this medication. In contrast, physicians who treated more lung cancer and LS-SCLC patients per year were less likely to recommend the use of memantine. It is unclear why this association exists, though perhaps those better versed in lung cancer are more familiar with the evidence for memantine in this setting, which is less than substantial.

The use of memantine for PCI patients may stem from a 2013 phase 3 clinical trial of patients undergoing WBRT for brain metastases, which showed that memantine delayed onset of cognitive decline and provided benefits in some aspects of cognitive functioning at several time points.<sup>17</sup> However, the primary end point—delayed recall at 24 weeks—did not reach statistical significance. To our knowledge, no studies have examined the use of memantine in patients undergoing PCI. Interestingly, a 2016 survey of 196 US radiation oncologists showed that 64% almost never used memantine for patients undergoing WBRT for brain metastases,<sup>28</sup> about the same proportion as in our survey, in which 65% did not recommend memantine for PCI patients. There is limited direct evidence for memantine in WBRT but none in PCI, yet the adoption rate is the same in both scenarios.

Given the neurotoxic risks of radiation to the brain—either palliative or prophylactic—along with the possible benefits of memantine and similar agents, more research should be done to shed light on ways to improve cognitive functioning and quality of life in patients undergoing these treatments. One area of active research is hippocampal-avoidance WBRT, an alternative method for limiting neurocognitive decline. A phase 3 randomized trial (NRG-CC001) is comparing traditional WBRT with hippocampal-avoidance WBRT in patients with brain metastases—with both arms receiving memantine—although patients with SCLC are excluded.

### Limitations

The greatest limitation of our study is a low response rate, possibly the result of survey fatigue, with a sample size of 309

eligible responses from radiation oncologists. Our findings should be interpreted with caution, as they may not be representative of US radiation oncologists as a whole. Response or participant bias could have affected the results, as there might have been differences between those who chose to complete this online survey and those who did not. In comparing our sample of radiation oncologists to samples from other recent surveys and an online directory of radiation oncologists, it does not appear there are substantial differences in demographics, in terms of practice setting,<sup>29,30</sup> practice region,<sup>31</sup> or number of years in practice.<sup>30</sup>

Unintended bias from the authors in how questions were worded or ordered in the survey may have affected the answers provided. Recall bias could also have influenced the accuracy of responses, given that some responses relied on memory of recent practice patterns. Finally, acquiescence bias cannot be totally accounted for.

## Conclusion

The goal of this survey was to broadly sample radiation oncologists in the United States on their approaches to patients with LS-SCLC. Our survey reveals near-universal endorsement of PCI and pre-PCI brain MRI—practices recommended by NCCN guidelines. A third of clinicians also routinely screen patients with serial brain MRI during follow-up, and a third recommend using memantine for patients undergoing PCI. The lack of clinical trials directly supporting PCI for LS-SCLC patients in the MRI era is concerning. The Southwest Oncology Group is planning an international randomized trial of PCI versus observation with MRI in patients with both limited-stage and extensive-stage SCLC. Further research is critical to determining the best care for patients with LS-SCLC, perhaps investigating topics such as brain MRI with novel contrast agents, PCI with hippocampal avoidance and other advanced techniques, stereotactic radiosurgery, tumor-treating fields, memantine, and quality of life. Until then, our survey of US radiation oncologists shows remarkable adherence to NCCN guidelines regarding PCI, and it establishes a practice-pattern baseline for future clinical trials for patients with LS-SCLC.

### Clinical Practice Points

- For patients with LS-SCLC whose disease exhibits at least a partial response to initial chemoradiotherapy, current NCCN guidelines recommend PCI and pre-PCI brain MRI. However, these practices are not directly supported by the clinical trials that shaped them, as the trials were conducted in the pre-MRI era.
- A Japanese phase 3 trial in extensive-stage SCLC showed that there was no survival benefit to PCI versus observation when brain MRI was mandated before randomization and at regular intervals afterward. NCCN guidelines have just been amended to allow observation with frequent brain imaging instead of PCI in patients with extensive-stage SCLC. To our knowledge, no similar randomized trial incorporating brain MRI has been conducted for LS-SCLC.
- Our survey reveals that almost all responding US radiation oncologists recommend PCI and pre-PCI brain MRI, in line with national guidelines. After PCI, only a third of respondents routinely follow patients with serial brain MRI.
- A phase 3 trial found that memantine delayed cognitive decline in patients treated with WBRT for brain metastases, but the

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primary end point was not met. No trials have studied memantine in the context of PCI for LS-SCLC patients.

- In our survey, about a third of respondents recommend memantine for patients undergoing PCI.
- Further clinical trials may be necessary to prove that the survival benefit of PCI still exists in the modern era. Our survey establishes a practice-pattern baseline for such clinical trials.

### Acknowledgment

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### Disclosure

The authors have stated that they have no conflict of interest.

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