Current Patterns of Care for Patients with Extensive-Stage SCLC: Survey of U.S. Radiation Oncologists on Their Recommendations Regarding Prophylactic Cranial Irradiation

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ABSTRACT

Introduction: Conflicting data from randomized clinical trials incite the debate over the appropriate use of prophylactic cranial irradiation (PCI) for patients with extensive-stage SCLC (ES-SCLC) who achieve clinical response to systemic chemotherapy. The current pattern of practice among U.S. radiation oncologists is unknown.

Methods: We surveyed practicing U.S. radiation oncologists through a short online questionnaire. Respondents’ characteristics and their self-rated knowledge base were analyzed for association with their treatment recommendations.

Results: We received 473 responses from practicing U.S. radiation oncologists. More than half of the respondents had been practicing for more than 10 years after completing residency training, and 70% had treated more than 10 patients with lung cancer per year. Of the respondents, 90% recommended brain magnetic resonance imaging (MRI) before initiation of PCI and 98% recommended PCI for patients with ES-SCLC after systemic chemotherapy. Half of the respondents followed their patients with brain MRI after completion of PCI. One-third of the respondents prescribed memantine to patients undergoing PCI. Among the respondents, recent graduates ($p = 0.004$) and physicians practicing in academic centers ($p = 0.005$) were more likely to prescribe memantine. Self-rated knowledge base was not associated with any treatment recommendations.

Conclusions: Our analysis revealed that among the respondents, there was a very high adherence to current National Comprehensive Cancer Network guidelines, which recommend providing universal PCI and obtaining brain MRI before initiation of PCI for patients with ES-SCLC with clinical response to systemic chemotherapy. These guidelines and practice patterns are not supported by clinical evidence because patients in the European Organization for Research and Treatment of Cancer trial did not undergo brain MRI before PCI and the Japanese randomized trial has shown a possible detrimental effect of PCI on overall survival when brain MRI was incorporated. A critical reevaluation of current guidelines is essential to determine the appropriate management of these patients.

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Keywords: Survey; Prophylactic cranial irradiation; Small cell lung cancer; Radiation oncology; Pattern of practice

Introduction

SCLC is found in 10% of patients with lung cancer and is one of the least curable histological subtypes, with a 5-year survival of approximately 3.5%. It is characterized by rapid growth and early metastases development. Brain metastases are common, with a 10% prevalence at presentation and a 50% incidence within 2 years of diagnosis. At the time of diagnosis 70% of patients have extensive-stage SCLC (ES-SCLC), which is initially treated with systemic chemotherapy and has a
higher rate of brain metastases than limited-stage SCLC. For patients with ES-SCLC who respond to chemotherapy, clinical evidence indicates benefit from addition of prophylactic cranial irradiation (PCI) and thoracic consolidation radiotherapy (RT).

Current National Comprehensive Cancer Network (NCCN) guidelines recommend PCI for patients with ES-SCLC on the basis of the overall survival (OS) benefit seen in a European Organization for Research and Treatment of Cancer (EORTC) randomized trial published in the New England Journal of Medicine in 2007. Importantly, this trial did not incorporate brain imaging before PCI and during the follow-up of patients in both the PCI and observation arms. A similar randomized trial conducted in Japan and presented at the 2014 annual meeting of the American Society of Clinical Oncology revealed a trend (hazard ratio for death = 1.38, 95% confidence interval: 0.95–2.01, p = 0.09) toward a detrimental effect of PCI in patients with ES-SCLC. The critical difference in the Japanese trial was incorporation of brain magnetic resonance imaging (MRI) before PCI and during the follow-up. Presentation of this trial fueled the debate over the appropriateness of a policy of universal PCI for patients with ES-SCLC.

We designed an online survey to learn how U.S. radiation oncologists counsel patients with ES-SCLC regarding both PCI and consolidation thoracic RT and what factors influence physicians’ clinical recommendations. In this manuscript we present the analysis of responses related to PCI recommendations.

Methods

Survey Instrument Development

The study was approved by the Oregon Health and Science University institutional review board. The online survey was developed with the Research Electronic Data Capture (REDCap) software licensed by the Oregon Clinical and Translational Research Institute for use by the Oregon Health and Science University. The survey contained 22 potential questions regarding respondent demographics, thoracic consolidation RT practices, PCI therapy, and use of memantine with PCI. Branching logic was used to tailor the questions on the basis of previous responses, so most respondents did not see all 22 questions. Respondents self-rated their knowledge of three landmark trials for patients with ES-SCLC: a Yugoslavian single-institutional randomized trial by Jeremic et al. which revealed improvement in OS for patients with complete response at distant sites and either complete or partial response in thorax with the addition of accelerated hyperfractionated RT to concurrent chemotherapy, a northern European randomized trial NTR1527 by Slotman et al. which showed improved OS at 2 years with the addition of consolidation thoracic RT to patients with clinical response to chemotherapy, and the Radiation Therapy Oncology Group (RTOG) 0937 trial (which closed to accrual owing to excessive toxicity in the consolidation RT arm). On the basis of the response selection for the first two published trials, we have assigned a score of 0 (“I do not know this study”), 1 (“I know the main conclusion but do not know the details of the trial and would not be able to quote the numbers”), or 2 (“I have read the article and feel comfortable discussing the results”). On the basis of the response selection for the closed RTOG 0937 trial, we assigned a score of 0 (“I am not familiar with this study”), 1 (“I am familiar with this study but did not know it was closed to accrual owing to toxicity early this year”), 2 (“I am familiar with this study and know that it was closed to accrual owing to toxicity”), and 3 (“I am familiar with this study, and my institution enrolled patients on this study when it was open”). These individual scores were summed to obtain a knowledge score (KS) between 0 and 7, with 0 representing the least familiarity and 7 representing an expert level of knowledge. KS approached a normal distribution with a mean value of 3.81 (SD = 1.86). On the basis of distribution, two knowledge models were developed: binary (less knowledgeable [KS 0–3] versus more knowledgeable [KS 4–7]) and three-group (low knowledge [KS 0–2], intermediate knowledge [KS 3–4], and high knowledge [KS 5–7]).

Data Collection

The data sample was collected through two Internet-based, anonymized surveys of radiation oncologists in the United States. The survey was initially sent to 6967 potential participants from a developed database of radiation oncologists compiled through the American Society for Radiation Oncology (ASTRO) directory. These participants were then contacted through e-mail using the REDCap tool and invited to take the survey. The invitation contained instructions on participation, contact information for questions, and use of results. E-mail invitations were originally sent on September 7, 2015. Participants who had requested to be removed on account of nonapplicability were not sent a reminder e-mail, whereas potential respondents who did not complete the survey were contacted with a reminder e-mail on September 15, 2015, to maximize response rate.

Statistical Analysis

Respondents were characterized by years since residency completed, number of patients with lung cancer treated in the past year, practice setting, region of practice, and the knowledge base, as already discussed. These five variables were analyzed for correlation with
respondents’ treatment recommendations. Chi-square analysis was used to examine the correlations between characteristics and knowledge base with treatment questions. The Cochran-Armitage test for trend was used to evaluate the trend in change for ordinal categorical variables. A p value less than 0.05 was considered statistically significant. SAS 9.4 software (SAS Institute, Inc., Cary, NC) was used for statistical analysis.

Results

Survey Respondents

The survey was sent to 6967 e-mail addresses, some of which could likely belong to the same individuals, as both personal as well as institutional e-mail addresses were used. We received 499 failed/undeliverable automatic responses, 55 nonapplicable/ineligible responses, and 497 completed responses, among which 24 were from non-radiation oncologists and thus excluded from analysis. The characteristics of the 473 radiation oncologists who completed the survey are summarized in Table 1. More than half of the respondents had been practicing for more than 10 years after completing residency training, and 70% had treated more than 10 patients with lung cancer per year. Respondents self-rated their knowledge of three landmark trials for patients with ES-SCLC, as described in Methods. With the binary model, the distribution of the respondents was split, with 46.06% in the less knowledgeable category and 53.94% in the more knowledgeable category. With the three-group model, the distribution was as follows: 24.95% in the low-knowledge category, 36.67% in the intermediate-knowledge category, and 38.38% in the high-knowledge category.

Recommendation of New Postchemotherapy Brain MRI

Respondents’ treatment recommendations are summarized in Table 2. More than 90% of the respondents obtained new brain MRI studies after patients with ES-SCLC complete systemic chemotherapy. There was no statistically significant correlation between respondent

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<th>Table 1. Characteristics of Radiation Oncologists Who Completed the Survey</th>
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*Respondents allowed to select as many as applied.*

ES SCLC, early-stage small cell lung cancer; PCI, prophylactic cranial irradiation therapy; CR, complete response; PR, partial response.
characteristics (years since completion of residency training \( p = 0.8720 \), number of patients with lung cancer who have been treated \( p = 0.8954 \)), or knowledge base \( p = 0.3848 \) for the binary model and \( p = 0.1788 \) for three-group model) and recommendation of new baseline brain MRI. There was a trend among radiation oncologists in private practice toward avoiding new baseline brain MRI \( p = 0.055 \).

### Recommendation of PCI

Almost all the respondents (98%) recommended PCI to their patients. Respondents were most enthusiastic about recommending PCI in patients who achieve complete clinical response after systemic chemotherapy but thought that PCI is appropriate in patients with partial responses in either the thorax or metastatic sites (Tables 2 and 3). Only half of the respondents indicated that a recommendation of PCI leads to patients actually receiving PCI most of the time in their practice. Because of the low number of physicians who did not recommend PCI, no statistical analysis could be performed to characterize these 11 physicians in terms of their experience and knowledge. Ten of these physicians treated more than 10 patients with lung cancer per year, and six were in the high-knowledge group. Among these 11 physicians, eight were concerned about the neurotoxicity of PCI and six believed that serial brain imaging was a better alternative.

### Memantine Administration during PCI

Of the respondents, 36.4% recommend memantine for patients undergoing PCI. Among the respondents, radiation oncologists with recent residency training were more likely than more senior physicians to prescribe memantine \( p = 0.0004 \), as were physicians practicing in academic setting \( p = 0.0005 \) in comparison with their colleagues in private practice.

### MRI Follow-up

Among the respondents, 50% followed their patients with serial brain MRI. There was no statistically significant association between the imaging follow-up recommendation and respondent characteristics and knowledge base. There was a trend \( p = 0.0796 \) toward a higher chance of following patients with brain MRI among physicians in the academic centers. Among respondents who do follow their patients with serial brain MRI, 59% recommend brain MRI every 3 months, 40% recommend it every 6 months, and almost no one recommends it on a monthly basis.

### Discussion

There is an ongoing debate in the literature on the appropriateness of universal prophylactic irradiation for patients with ES-SCLC. We refer the reader to an expert discussion of both sides of this debate. A randomized study carried out by the EORTC showed a reduction in the risk of development of symptomatic brain metastases at 1 year from 40% to 15% and improvement in OS from 13% to 27% with addition of PCI. This publication established PCI as a standard of care for patients with ES-SCLC with clinical response to systemic chemotherapy. Importantly, the EORTC study did not incorporate brain imaging before PCI or during the follow-up of patients randomized to observation. A similar randomized trial carried out in Japan, but incorporating brain imaging with MRI before PCI and at regular intervals during patient follow-up, revealed a trend toward a worse OS among patients in the PCI arm. This study was presented at the American Society of Clinical Oncology in 2014, and the publication is awaited with great impatience. One potential explanation for the divergence of treatment outcomes between these two randomized trials is the use of brain MRI. Between 25% and 35% of patients in complete remission after initial chemotherapy are found to have asymptomatic brain metastases on brain MRI studies. Inclusion of patients with asymptomatic brain metastases in the PCI arm, coupled with the lack of early detection of brain metastases in the control group in the absence of brain imaging during the follow-up, could have stacked the results of the EORTC trial in favor of PCI. At the same time, only patients with no visible brain metastases by MRI were enrolled in the Japanese randomized study, and symptomatic or asymptomatic brain metastases (that were salvaged early in the course of disease with whole-brain RT [WBRT]) developed in only two-thirds of patients randomized to observation. This important difference in trial design could explain the opposite outcomes of the two randomized trials.

Our survey analysis, which was based on responses from 473 practicing radiation oncologists in the United States, shows that 90% of physicians recommend brain MRI after completion of systemic chemotherapy and 98% recommend PCI. This approach—universal PCI for
patients with ES-SCLC with incorporation of pretreatment brain MRI—is endorsed by the current NCCN guidelines.6

Only 11 physicians in our survey do not recommend PCI, relying more on serial brain imaging with salvage WBRT when needed, citing concerns about neurotoxicity related to PCI. Indeed, 60% of patients receiving PCI experience neurocognitive decline at 1 year.16 Pooled analysis of RTOG trials 0212 and 0214 revealed an association between PCI and decline in verbal memory and overall quality of life.17 RTOG 0614, a randomized trial of memantine versus placebo in patients undergoing WBRT for treatment of brain metastases, was technically a negative trial; however, it showed a positive effect of memantine on a number of secondary end points: memantine delayed the time to cognitive decline and reduced the rate of decline in memory, executive function, and processing speed. Although PCI dose is slightly lower than the WBRT dose (25 versus 30 Gy in 10 fractions), memantine is likely to protect the brain from the neurotoxic effect of PCI as it does in the WBRT setting. Our survey revealed that only a third of respondents prescribe memantine to patients undergoing PCI. Recent training status and practice at an academic center were associated with a higher chance of physicians prescribing memantine with PCI to their patients. We believe that in the absence of randomized evidence, extrapolation of data from RTOG 0614 should make more physicians consider neuroprotection with memantine during brain irradiation.

Despite an almost universal acceptance of PCI benefit among our respondents, it was surprising to note that only 50% of respondents indicated a good compliance with this recommendation among patients. Perhaps other providers, such as medical oncologists, have a different view on the role of PCI and give their patients a divergent recommendation. We are currently in the process of surveying medical oncologists with the same online questionnaire. Our data show that half of the respondents routinely follow their patients after PCI with regular brain imaging. We had not anticipated this response and did not include a question on whether radiation oncologists offer their patients stereotactic radiosurgery (SRS) after completion of PCI in case brain metastases develop. New data are emerging on SRS use in select patients with brain metastases from SCLC,18,19 and this high percentage of patients being followed with brain imaging may suggest that more physicians are offering SRS treatment for patients after PCI failure. Future surveys and patterns of care analyses will shed light on this interesting clinical topic.

The knowledge base self-assessment was a unique aspect of this study. The selection ES-SCLC trials was guided by the initial intent to determine physicians’ use of consolidation thoracic RT in patients with ES-SCLC after systemic chemotherapy. This analysis is forthcoming in a separate manuscript. We did not find a correlation between the KS and the treatment recommendations, which could be related either to the selection of studies for the purpose of knowledge base assessment in this survey or to the fact that most physicians practice on the basis of published NCCN guidelines regardless of the depth and breadth of their knowledge on a clinical subject. The greatest limitation of our study is the low response rate, with a sample size of 473 evaluable responses. Our findings have to be interpreted with great caution, as they may not be representative of other radiation oncologists who chose not to participate in the survey. To simplify the survey design and analysis, no free text response was allowed.

Conclusion

The goal of this study was to broadly sample U.S. radiation oncologists in their approach to patients with ES-SCLC after clinical response to systemic chemotherapy. We saw an almost universal adherence to the current NCCN guidelines. A critical reassessment of current guidelines is essential, possibly requiring a new randomized clinical trial with incorporation of new imaging and treatment modalities, such as brain MRI with novel contrast agents, SRS, targeted and immunomodulatory agents, and tumor treating fields. The incorporation of memantine into routine practice with PCI is not as widespread as could be supported by extrapolation from WBRT data from the randomized RTOG 0614 trial.

Acknowledgments

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