

Research Letter

Practice Patterns Related to Mitigation of Neurocognitive Decline in Patients Receiving Whole Brain Radiation Therapy



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Abstract

Purpose: Whole brain radiation therapy (WBRT) is often used as an effective treatment for patients with brain metastasis, although it is also known to have deleterious cognitive effects. Multiple trials have identified strategies to help mitigate neurocognitive decline after WBRT, although there may be barriers to integrating these techniques into routine clinical practice. The aim of this study was to characterize national practice patterns related to neurocognitive preservation strategies used during WBRT.

Methods and Materials: We conducted an online survey of all American Society for Radiation Oncology-registered radiation oncologists (ROs), excluding trainees, regarding their practice patterns and attitudes toward employing memantine and hippocampal avoidance whole brain radiation therapy (HA-WBRT). Pearson χ^2 tests for categorical variables or Student *t* tests for continuous variables were used to assess associations between provider characteristics and prescribing of either memantine or HA. All statistical tests were 2-sided and a *P* value < .05 was considered statistically significant.

Results: Among 4408 ROs invited to participate, 417 (9.5%) completed the survey. Among respondents, 79.6% reported having offered memantine, 72.7% HA-WBRT, and 63.1% both for any of their patients undergoing WBRT. Common reasons for not offering memantine included limitations of current evidence (35.3%) and concerns about adverse effects (22.4%). Common reasons for not offering HA-WBRT included resource-intensive treatment planning and treatment delay (43.9%) and concern about obtaining prior authorization (38.6%). ROs with fewer years in practice (mean 15.7 vs 23.4 years) were more likely to prescribe memantine (*P* < .001), whereas HA was more likely prescribed by central nervous system specialists (*P* < .001) and ROs in academic settings (*P* = .04).

Conclusions: Our survey suggests that the majority of respondents offer approaches for neurocognitive preservation during WBRT for their patients. Further efforts are needed to broaden education and reduce barriers among ROs to improve implementation of neurocognitive-sparing techniques in patients undergoing WBRT.

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Introduction

Whole brain radiation therapy (WBRT) is often employed as an effective treatment to palliate symptoms, improve intracranial control, and decrease the risk of neurologic death in patients with brain metastasis. However, WBRT is also known to have deleterious cognitive effects.¹ Radiation-induced cognitive decline affects over 30% of patients who are alive at 4 months after cranial radiation therapy and has been characterized by a decline in memory, attention, language, executive function, and processing speed.² Considering the improved long-term survivorship for patients with brain metastases, there have been concerted efforts to reduce late radiation-related toxicity and prolong quality of life for patients.

To this end, Radiation Therapy Oncology Group (RTOG) 0614 demonstrated that memantine (vs placebo), an *N*-methyl-D-aspartate receptor antagonist, improved time to cognitive decline and reduced rate of decline in executive function, processing speed, and delayed recognition in patients receiving WBRT.³ NRG-CC001 demonstrated that WBRT with hippocampal avoidance (HA-WBRT) (vs conventional WBRT) successfully reduced the risk of neurocognitive failure.⁴ Findings from these studies have been incorporated into the National Comprehensive Cancer Network⁵ and recent ASCO-SNO-ASTRO (American Society of Clinical Oncology, Society for Neuro-Oncology, American Society for Radiation Oncology) guidelines,⁶ which recommend that for patients undergoing WBRT with a prognosis of at least 4 months, memantine should be offered, whereas HA-WBRT should be considered if no lesions are present near the hippocampus.

Despite these positive outcomes, it is unknown how widely these strategies have been adopted nationally. Prior surveys of radiation oncologists (ROs) performed in the last 4 years indicated modest adoption of memantine and HA-WBRT.^{7,8} Given the importance of neurocognitive function for patient quality of life and the recent publication of NRG-CC001, we sought to explore the current adoption of neuroprotective strategies during WBRT through a nationwide survey of ROs in the United States.

Methods and Materials

We created and distributed an online web-based survey of American Society for Radiation Oncology-registered practicing ROs. The survey was administered using the REDCap platform. Informed consent was obtained at

the beginning of the survey and all responses were anonymous. The survey evaluated respondent practice patterns in treating brain metastases, employment of memantine or HA-WBRT, reasons for not offering these techniques, familiarity with evidence supporting these strategies, and survey influence on knowledge and future practice patterns. Invitations to complete the survey were sent by e-mail on September 2, 2020, and 2 reminder emails were sent, each 3 weeks apart.

Statistical analysis

Descriptive statistics were used to characterize trends in employment of neurocognitive mitigation techniques among respondents. The Pearson χ^2 tests for categorical variables or Student *t* test for continuous variables were used to assess associations between provider characteristics and prescribing of either memantine or HA-WBRT. All statistical tests were 2-sided with a *P* < .05 and analyses were conducted using Stata/MP version 16.0 (Stata-Corp). The study was deemed exempt from our institutional board review.

Results

Among 4408 ROs invited to participate, 417 (9.5%) completed the survey. Among respondents, 79.6% reported offering memantine, 72.7% HA-WBRT, and 63.3% both for any of their patients undergoing WBRT. Among ROs offering memantine, more than half (63.0%) prescribed it to most (51%-100%) of their WBRT patients. Common reasons for not offering memantine included limitations of current evidence (35.3%) as well as concerns about medication cost (23.5%) and adverse effects (22.4%) (Fig. 1A). Among respondents who did offer HA-WBRT, most (66.7%) prescribed this to fewer than half (1%-50%) of their WBRT patients. Common reasons for not offering HA-WBRT included resource-intensive treatment planning and treatment delay (43.9%), concern with obtaining insurance approval (38.6%), and having no patients who met their criteria for HA-WBRT (22.8%) (Fig. 1B).

The majority of respondents were male (69.1%), and the median time in practice was 15 years (interquartile range, 9-25) (Table 1). Most respondents reported practicing in an academic setting (44.0%), followed by community-based hospital practice (32.7%) and private practice (21.6%). In addition to WBRT, most ROs (86.8%) also prescribed stereotactic radiosurgery (SRS)

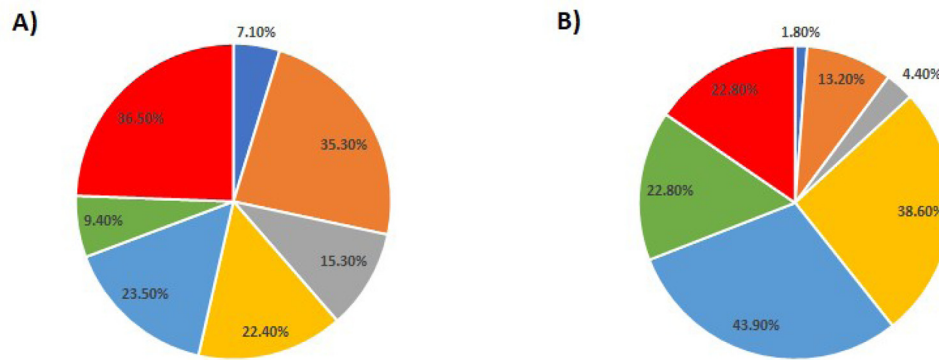


Figure 1 Reasons given by radiation oncologists for not offering (A) memantine or (B) hippocampal avoidance whole brain radiation therapy (HA-WBRT) to patients undergoing WBRT.

Table 1 Breakdown of survey responses among participants*

Demographic characteristics	
Sex	
Male	283 (69.2)
Female	126 (30.8)
Time in clinical practice (y), mean (IQR)	
	15 (9-25)
Practice setting	
Academic	183 (44.0)
Community-based hospital practice	136 (32.7)
Private practice	90 (21.6)
Government (Veterans Administration)	7 (1.7)
Central nervous system specialist	
Yes	121 (29.2)
No	293 (70.8)
Number of ROs in practice	
1-5	175 (42.0)
6-10	80 (19.2)
11-20	84 (20.1)
>20	78 (18.7)
Census region (United States)	
Northeast	86 (20.9)
Midwest	107 (26.0)
South	134 (32.6)
West	84 (20.4)
Clinical characteristics	
Annual number of patients treated with WBRT	
1-5	97 (23.5)
6-10	144 (35.0)

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Table 1 (Continued)

Clinical characteristics	
11-20	116 (28.2)
>20	55 (13.4)
Offer SRS for brain metastases	
Yes	362 (86.8)
No	55 (13.2)
Annual number of patients treated with SRS	
1-5	53 (14.6)
6-10	76 (21.0)
11-20	107 (29.6)
>20	126 (34.8)
Offer memantine with WBRT	
Yes	332 (79.6)
No	85 (20.4)
What proportion of WBRT patients received memantine in the last year?	
1%-25%	60 (18.1)
26%-50%	63 (19.0)
51%-75%	51 (15.4)
76%-100%	158 (47.6)
Offer hippocampal-sparing WBRT	
Yes	303 (72.7)
No	114 (27.3)
What proportion of WBRT patients received hippocampal-sparing in the last year?	
1%-25%	123 (40.6)
26%-50%	79 (26.1)
51%-75%	62 (20.5)

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Table 1 (Continued)

Clinical characteristics	
76%-100%	39 (12.9)
Do you use any other approach to mitigate neurocognitive decline in WBRT patients?	
Yes	28 (6.7)
No	389 (93.3)
What proportion of WBRT patients received another approach in the last year?	
1%-25%	11 (39.3)
26%-50%	6 (21.4)
51%-75%	4 (14.3)
76%-100%	7 (25.0)
Do other ROs in your practice offer approaches to mitigate neurocognitive decline?	
Yes	294 (70.5)
No	123 (29.5)
Self-rated knowledge	
How familiar are you with the RTOG 0614 trial by Brown et al ³ published in 2013?	
Not familiar	17 (4.1)
Familiar	361 (86.6)
Participated or enrolled patients	39 (9.4)
How familiar are you with the RTOG 0933 trial by Gondi et al ⁹ published in 2014?	
Not familiar	23 (5.5)
Familiar	355 (85.1)
Participated or enrolled patients	39 (9.4)
How familiar are you with the trial by Brown et al ⁴ published in 2020?	
Not familiar	76 (18.2)
Familiar	303 (72.7)
Participated or enrolled patients	38 (9.1)
Awareness and future practice patterns	
Has this survey increased your awareness of potential neurocognitive-sparing options with WBRT?	
Yes	146 (35.0)
No	271 (65.0)
Will this survey influence your practice regarding approaches to mitigate neurocognitive decline with WBRT?	
Yes	96 (23.0)
No	321 (77.0)
Abbreviations: IQR = interquartile range; ROs = radiation oncologists; RTOG = Radiation Therapy Oncology Group; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.	
* Data are expressed as n (%) unless otherwise indicated.	

within the past year. Most respondents reported high familiarity with or participation in clinical trials supporting memantine or HA-WBRT approaches, ranging from 81.8% with NRG-CC001 to 95.9% for RTOG 0614. ROs familiar with RTOG 0614 were more likely to offer memantine (82.3% vs 17.7%; $P < .001$) whereas those familiar with RTOG 0933⁹ or NRG-CC001 (75.7% vs 5.6%; $P < .001$) were more likely to offer HA-WBRT. Among ROs unfamiliar with at least 1 of these trials, 74.1% reported increased awareness and 55.6% reported future practice patterns would be influenced by this survey.

ROs who prescribed memantine had fewer years in clinical practice compared with ROs who did not (mean 15.7 vs 23.4 years; $P < .001$). Meanwhile, HA-WBRT was more likely prescribed by self-reported central nervous system specialists (vs non-central nervous system specialists) (32.1% vs 15.7%; $P < .001$) and those in academic settings (vs community practice) (77.1% vs 64.0%; $P = .04$).

Discussion

Our survey on practice patterns in neurocognitive-sparing techniques for patients receiving WBRT found that a large majority of RO respondents now offer memantine (80%) or HA-WBRT (73%) or both (63%) for their patients. However, among those not offering these treatments, there were multiple commonly reported reasons.

Among the more common reasons for ROs to not prescribe memantine were limited evidence, adverse effects, or cost. Prospective data supporting the use of memantine primarily stems from RTOG 0614, which failed to meet its primary endpoint of delayed recall at 24 weeks, despite showing improvement in multiple secondary endpoints. However, memantine is now being used as standard of care in modern trials, like NRG-CC009, comparing SRS to HA-WBRT in patients with small cell lung cancer and fewer than 10 brain metastases. Adverse effects from memantine are uncommon, although they may include fatigue, dizziness, and headache,¹⁰ which in rare cases lead to drug discontinuation. Memantine is also prescribed daily for a period of 6 months after WBRT, which may exacerbate the financial burden for patients with metastatic disease.¹¹ Cost mitigation strategies like the telemedicine platform GoodRx may offer coupons and discounts to substantially reduce this financial stress.¹² Although not mentioned in this survey, another reason for not using memantine may be the poor prognosis of patients receiving WBRT and the provider's perception that such patients may not live long enough to benefit from cognitive sparing. This may be especially true as SRS is being increasingly used to treat a higher number of brain metastases,^{13,14} reserving WBRT for patients with a greater burden of intracranial disease.

The most common reason for not offering HA-WBRT included the increased resource intensity and longer delay

to starting treatment compared with conventional WBRT. Another reason reported by ROs included insurance denials. However, after the publication of NRG-CC001 in April 2020, insurance companies that may have previously denied coverage for HA-WBRT subsequently updated their coverage policies to include this treatment.¹⁵ Nevertheless, peer-to-peer review or prior authorization challenges still persist, which can lead to treatment delays.

The high proportion of RO respondents who now offer memantine or HA-WBRT is substantially greater than that reported in prior surveys that predated NRG-CC001.^{7,8} One study surveyed 196 ROs in 2016 and found 64% reported almost none of their patients received memantine and only 35% considered HA-WBRT for appropriately selected patients. ROs also reported similar reasons for not employing memantine, including limited evidence and memantine cost, and HA-WBRT, including resource intensity and limited insurance coverage. Another survey by Barry et al⁸ in 2017 of 87 ROs found that one-third prescribed memantine. Although these studies reported around one-third of ROs offering memantine or HA-WBRT, our survey reported around 70% to 80%. The delayed adoption of memantine into clinical practice is likely multifactorial, including skepticism surrounding the lack of statistically significant results of RTOG 0614, the poor prognosis of patients receiving WBRT, and increasing utilization of SRS to treat brain metastases.¹⁶ Despite these barriers, our findings show that in the 4 years since these 2 surveys and since the publication of NRG-CC001, the majority of respondents now offer memantine and/or HA-WBRT. Moreover, in our survey, awareness of clinical trial data was associated with a high likelihood of offering neuroprotective techniques. Therefore, educating providers on the merits of these approaches may lead to increased adoption into clinical practice.

Our study is subject to multiple limitations. Notably, given this is a survey study, respondents may not be representative of all practicing ROs, with respondents potentially being more likely to prescribe memantine or HA-WBRT than nonrespondents. This could potentially overestimate the proportion of ROs offering neurocognitive-sparing techniques. Second, our survey may be subject to recall bias, because respondents were asked to provide estimates on practice patterns. Nevertheless, our study is the largest, most recent, and first since publication of NRG-CC001 to investigate neurocognitive-mitigation practice patterns among ROs, and the results can serve to further increase awareness of these techniques.

Conclusion

Our survey suggests that a large majority of respondents now offer approaches for neurocognitive preservation during WBRT for their patients. However, universal and consistent adoption of these approaches may be limited by current

evidence and logistical hurdles to administration. Further efforts are needed to broaden education and reduce barriers among ROs to improve implementation of neurocognitive-sparing techniques in patients undergoing WBRT.

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