Why Did the Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampus Avoidance in SCLC Not Reveal a Difference?

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3. HA results in higher rates of oncologic failure, counteracting cognitive benefit. There is no evidence of increased rates of new brain metastases after HA-PCI.

Plausible explanations:

1. Memantine and HA have a synergistic effect in preserving cognition. Unlike NRG CC001, memantine was not used in this study. Preclinical data indicate that memantine is synergistic with HA by preventing radiation-induced synaptic remodeling.[4]
2. Patients with SCLC have impaired baseline cognitive function, blunting the potential benefit of cognitive preservation.
3. Underpowered sample.
4. Lack of real-time pretreatment review. Up to a quarter of HA radiation plans can have unacceptable deviations.[5]
5. Weekly image guidance was allowed. NRG CC001 and other studies involving intensity-modulated radiation therapy require daily image guidance to ensure accurate dose delivery.

We commend Belderbos et al.[1] on completing this important study. To better assess the potential benefit of HA-PCI for SCLC, we await the results of NRG CC003 and other studies.

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Why Did the Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampus Avoidance in SCLC Not Reveal a Difference?

To the Editor:

We thank Breen et al.[1] for their well-structured comments on our phase 3 randomized trial of prophylactic cranial irradiation (PCI) with or without hippocampus avoidance (HA) in SCLC (NCT01780675).[2] In this trial, avoidance of the hippocampus with the aim to reduce the incidence of neurocognitive side effects of PCI did not lead to a beneficial effect for patients with SCLC. It is certainly confusing to interpret our results, whereas the phase 3 trial of Brown et al.[3] in patients with brain metastases of solid tumors receiving whole-brain radiotherapy with or without HA did clearly reveal a benefit. In the subsequent texts, we address the "plausible explanations" raised by the authors on why we could not detect less neurocognitive decline in the hippocampus-sparing arm.

Plausible explanations:

1. Memantine and HA have a synergistic effect in preserving cognition. Unlike NRG CC001, memantine was not used in this study. Preclinical data indicate that memantine is synergistic with HA by preventing radiation-induced synaptic remodeling.[4]

The authors stated that the use of memantine could explain the different findings of our trial and the NRG CC001 trial. We do agree that this could be a possible explanation.

Nevertheless, the large placebo-controlled, double-blind, randomized trial of 508 subjects to evaluate the potential beneficial effects of memantine on cognition in patients receiving whole-brain radiotherapy was actually

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Table 1. Standardized Neurocognitive Test Scores at Baseline

Clinical Trial	NCT01780675		NRG CC001	
Treatment arms	PCI	HA-PCI	WBRT + memantine	HA-WBRT + memantine
Cognitive tests mean z-score (SD)				
HVLT-R total recall	−0.60 (1.24)	−0.91 (1.02)	−1.29 (1.28)	−1.31 (1.26)
HVLT-R delayed recall	−0.70 (1.36)	−1.02 (1.19)	−1.29 (1.60)	−1.17 (1.35)
HVLT-R recognition	−0.91 (2.48)	−0.71 (1.45)	−0.72 (1.55)	−0.64 (1.39)
TMT-A, s	−0.67 (1.89)	−0.30 (1.25)	−1.21 (2.49)	−1.29 (2.47)
TMT-B, s	−0.49 (2.03)	−0.76 (2.85)	−3.49 (8.82)	−3.18 (5.69)
COWA	−0.35 (0.76)	−0.42 (0.81)	−0.82 (1.20)	−0.82 (1.16)
CBT composite	−0.63 (1.18)	−0.69 (0.90)	−1.46 (2.08)	−1.40 (1.62)

COWA, Controlled Oral Word Association; CBT, clinical trial battery; HA, hippocampal avoidance; HVLT-R, Hopkins Verbal Learning Test—revised; PCI, prophylactic cranial irradiation; TMT-A, trail making test part A; TMT-B, trail making test part B; WBRT, whole-brain radiotherapy.

a negative trial.[5] The primary end point of the study, delayed recall Hopkins Verbal Learning Test—Revised at 24 weeks, revealed less decline but lacked statistical significance ($p = 0.059$). Lack of significance is likely to be the result of the limited statistical power of 35% because of a high dropout rate owing to tumor progression or death. Nevertheless, the reduced neurocognitive decline after memantine administration could be beneficial especially in the context of HA brain irradiation. The preclinical data on hippocampal avoidance and memantine revealing a synergistic effect is certainly supportive.

2. Patients with SCLC have impaired baseline cognitive function, blunting the potential benefit of cognitive preservation.

It has been reported that even before treatment, neurocognitive deficits exist in SCLC[6] and systemic treatment (chemotherapy) contributes to further brain function impairment. In our trial, neurocognitive impairment was defined as a decline in functioning from baseline (after treatment of the primary tumor). The authors raise the hypothesis that baseline impairment could reduce the probability of additional decline hampering the detection of a potential benefit.

To address this plausible explanation, we produced a similar table as was provided in the NRG CC001 article[3] on the baseline scores of the patients. Patients with SCLC had indeed a lower-than-expected cognitive performance at baseline when compared with sociodemographically corrected norms, as depicted in Table 1. This table also reveals that cognitive performance of patients with brain metastasis from the CC001 trial deviates even more strongly from the (same) normative data, indicating more severe cognitive impairment at baseline in this patient group. On the basis of these data, we do not view the proposed explanation of "impaired baseline cognitive function, blunting the potential benefit of cognitive preservation" very compelling.

3. Underpowered sample.

Our goal was to detect 30% difference in cognitive failure at 4 months, and we indeed had low power to detect a smaller difference. Nevertheless, the Spanish PREMER phase 3 randomized study[7] revealed less cognitive deterioration with HA-PCI in SCLC but had only 118 patients randomized. In our trial, 168 patients were randomized. So, using the Spanish trial as an argument to claim that HA-PCI is beneficial although they randomized only 70% of the patients randomized in our trial seems inconsistent.

4. Lack of real-time pretreatment review. Up to a quarter of HA radiation plans can have unacceptable deviations.

Review of all the treatment plans of the HA-PCI arm concluded that only minor deviations in achieving the treatment constraints were detected. All except one center passed the dummy run before starting to include patients in the trial. Detailed data on quality assurance of the radiotherapy preparation and execution were presented at the 20th World Conference on Lung Cancer 2020.[8]

5. Weekly image guidance was allowed. NRG CC001 and other studies involving Intensity-Modulated Radiation Therapy require daily image guidance to ensure accurate dose delivery.

The trial protocol requested daily or weekly image guidance, and eight of the 10 participating institutions performed daily online image guidance in all patients treated with HA-PCI. Two centers performed image guidance for the first three to four fractions and weekly thereafter. These centers included only six patients treated with HA-PCI. Therefore, it is unlikely that inaccurate image guidance or dose delivery is a plausible explanation for the negative trial results.

In conclusion, on the basis of the "Unlikely explanations and plausible explanations" elegantly composed by the authors, we cannot substantiate most of their suggestions. It is certain that the patients treated in the NRG CC001 trial are not comparable to our patient cohort. We definitely agree that awaiting the results of the NRG CC003 trial evaluating HA-PCI in a similar patient cohort is of crucial importance.

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Using Propensity Score Matching to Balance the Baseline Characteristics

To the Editor:

We read with great interest the article by Arauz et al.[1] focusing on mutation status in the African American population with NSCLC. The authors conducted a whole-exome sequencing on a minority population and identified increased mutation frequency of several tumor suppressor genes in NSCLC. Because of the lack of genomic studies on African Americans, their work contributed to a better understanding of the molecular basis of lung cancer and provided clinicians worldwide with potential optimal interventions for patients with NSCLC. However, it is of some concern that during the study period, there seemed to be a heavy selection bias on mutation landscapes compared between different populations.

We found that there were marked differences in sex, age distribution, smoking status, and other clinicopathologic characteristics between Whites and African Americans included in this study. For example, the proportion of female patients in The Cancer Genome Atlas data set with different histologic types was 55.2% with lung adenocarcinoma and 27.1% with lung squamous cell carcinoma. In comparison, there were only 22.0% women in the African American cohort. Therefore, direct comparisons between these two races may lead to a biased estimation of mutation status in that mutation frequencies were reported to be considerably influenced by the clinicopathologic characteristics of patients. For example, *EGFR* mutations were reported to be more frequent in women and never-smokers.[2]

To make the clinicopathologic characteristics compatible, here we recommend a propensity score matching method,[3] which can minimize the discrepancies between the different groups of patients. The propensity score is designed to remove the effects of confounding in multiple clinical and genetic analyses. It can summarize all of the relevant characteristics in a single composite score, which can be used to ascertain whether there is sufficient overlap in characteristics between groups or not. This method could finally enable balanced and unbiased comparison.[4] Hence, in this study, patients in The Cancer Genome Atlas data set can be selected to compare whether their demographic, socioeconomic status, or other clinical characteristics mimic some of the features of the 82 involved patients in the authors' cohort. Thereupon, ethnicity-related mutations, such as *TP53*, *RB1*, and *CDKN2A*, could be backed up with rational and cogent arguments in this study. In addition, some other oncogenes, which were underestimated previously, can probably be explored as well. Finally, we truly thank the authors for their efforts in this excellent work. It is extremely important to include patients of different races in genomics research, which can help us better understand tumor biology and guide clinical practice.

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