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Reaction on the Interpretation of the Hippocampus Avoidance Prophylactic Cranial Irradiation Trial in SCLC (NCT01780675)

To the Editor:

We thank Mladkova et al.[1] for their important comments on our phase 3 randomized trial of prophylactic cranial irradiation (PCI) with or without hippocampus avoidance (HA) in SCLC (NCT01780675).[2] This trial, using avoidance of the hippocampus with the aim to reduce the incidence of neurocognitive side effects of PCI, could not detect a benefit. Remarks on the interpretation of the evidence and suggestions raised by the authors are addressed in the subsequent texts.

1. The power calculation

In the randomized trial NCT01780675, we aimed to detect a 30% difference in cognitive decline on a single prespecified hippocampal dependent test (power range: 82%–95%). We may have been too ambitious to aim for a 30% difference on this test, and we cannot rule out possible smaller differences.

Our trial was not powered to detect the 10% difference in cognitive failure recently identified in the CC001 phase 3 trial of Brown et al.[3] in patients with brain metastases of a variety of solid tumors receiving whole-brain radiation therapy with or without HA. This trial used a different end point, in which cognitive failure was defined as a failure on any of the six cognitive test outcomes. Using the end point and analytical approach of the CC001 to our data, we observed in an exploratory analysis a significant difference ($p = 0.0088$) between our study arms, only favoring the standard treatment without HA.

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Considering the small difference of 10% favoring HA in the CC001 trial, the cost-effectiveness of HA-PCI should be investigated.

2. The authors are correct in the calculation of absolute number of failures. There have been 13 failures (28%) in the PCI arm and 16 failures (29%) in the HA-PCI arm. Those percentages have unfortunately been swapped in the manuscript. The small difference in the 95% confidence interval can be explained by the fact that we applied a Yates' continuity correction.

The missing values for the primary end point were expected at the design stage. They were not imputed and were assumed to be not related to the study arm. Comparison of baseline characteristics for the assessable subset of 102 patients did not reveal any differences between the arms. Reasons for not being assessable for the primary end points displayed in the consort diagram also do not reveal any worrying patterns.

The reported number of deaths in the text (53 died in the PCI arm) relates to their total number, also beyond 24 months. In addition, the number of patients at risk displayed in Figure 3*A* (32 patients alive in the PCI arm) takes into account censoring.

The consort diagram (Fig. 1) reveals indeed that of the 80 patients who received HA-PCI, 56 underwent neurocognitive testing at 4 months. For the breakdown, 10 died, four declined, six had disease progression, and four had other reasons. The amount that the authors state (23 died, 14 declined, 12 had disease progression, and seven had other reasons) is the breakdown for all patients included in the trial.

The authors state that more details on the patients who were excluded from the analysis would help to evaluate potential biases. We do not think that this would be helpful. In the initial trial design, we anticipated on the percentage of patients who would not be available for the 4-month neurocognitive testing (estimated at 40%). This would be determined by the percentage of patients included with stage IV disease because of death or progressive disease. The assumption that we made was rather accurate; 101 assessable patients of 168 randomized equaling 60%.

3. Use of the cause-specific Cox model

We agree that the competing risk approach may be debatable. The purpose of this analysis was only to

mimic the approach of the CC001 trial. Nevertheless, we think that the cause-specific approach could produce very pessimistic incidence of the neurocognitive failure because many patients died without neurocognitive failure reported.

The authors wondered whether the cognitive failure rates per group would change if standardized rather than raw scores were used. The primary end point was total recall on the Hopkins Verbal Learning Test—Revised at 4 months; a decline of at least five points from baseline was considered a failure. This definition of decline is based on the reliable change index criteria and can only be calculated using raw scores. The same holds true for the primary end point of the CC001 trial, which is based on changes in raw scores greater than the reliable change index as well. In our original approach, we also used linear mixed models to evaluate the longitudinal profiles of the cognitive tests using raw scores. We now checked for the total recall score of the Hopkins Verbal Learning Test—Revised if using standardized scores would change the conclusion. This was not the case.

4. The NRG oncology trials using hippocampal avoidance require central pretreatment and post-treatment reviews to define acceptable and unacceptable deviations for treatment volumes and planning.

We agree that this is a very critical point. Contrary to the NRG trials, we did not include a pretreatment review of the hippocampus delineation. Nevertheless, we organized a dummy run to train the physicians in the trial.[4] The results revealed observer variation to be acceptable, with some observers delineating too big. The RTOG-atlas hippocampus outlining protocol describes to exclude the fimbria, which was included in some cases of the interobserver variation study of hippocampus delineation among the trial participants.[4] Another variation was that part of the amygdala was included in the hippocampus delineation. Therefore, these interobserver variations (localized in the posterior and medial anterior border of the hippocampus) were mainly enlarging the hippocampus area to spare. This would have affected the incidence of brain metastases, but rather would have a beneficial effect on neurocognitive functioning in the HA-PCI arm.

Moreover, we have performed extensive quality assurance on the dose constraints for patients receiving HA-PCI[5]; treatment plans complied with the dose constraints in the trial protocol in the vast majority of cases. For 93% of the patients, the dose constraint on the mean dose to the hippocampi was achieved ($\leq$8.5 Gy). In all treatment plans, the volume of the PTV receiving 115% of the prescribed dose did not exceed 1%.

We thank Mladkova et al.[1] for their important remarks on the interpretation of the evidence and agree with their conclusion that the results of ongoing trials evaluating HA-PCI are to be awaited.

CRediT Authorship Contribution Statement

Jose Belderbos: Conceptualization, Investigation, Writing—original draft, Writing—reviewing and editing.

Dirk De Ruysscher, **Sanne B. Schagen:** Conceptualization, Investigation, Writing—reviewing and editing.

Katrien De Jaeger, Friederike Koppe, Maarten Lambrecht, Yolande Lievens, Edith Dieleman, Jaap Jaspers, Jan Van Meerbeeck, Fred Ubbels, Magriet Kwint, Sabine Deprez, Michiel De Ruiter: Investigation, Reviewing.

Marianne Kuenen: Project administration, Reviewing.

Willem Boogerd: Conceptualization, Reviewing.

Karolina Sikorska: Data curation; Formal analysis Writing—reviewing and editing.

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