

Whole brain radiotherapy for brain metastases from non-small cell lung cancer: the end of an era?

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Up to 30–50% of patients with non-small cell lung cancer (NSCLC) will at some point in their course of disease develop brain metastases (1,2). In selected patients, local aggressive treatment in the form of surgery or radiosurgery may be indicated; however, particularly patients with large volume metastatic brain disease have traditionally been treated with whole brain radiotherapy (WBRT). Although the general belief is that WBRT results in symptom palliation, decrease of steroid needs and even survival prolongation, up till now the evidence for such benefit of WBRT over best supportive care has been largely lacking, with the exception of a small Radiation Therapy Oncology Group (RTOG) study in the early 1980's (3).

In a recent *Lancet* paper, Mulvenna and colleagues report on the outcome of the Quartz trial, a multicenter prospective randomized non-inferiority trial in patients with brain metastases from NSCLC (4). Compared were treatment with WBRT (20 Gy/5 fractions) and best supportive care, including dexamethasone in both arms, in a total of 538 patients who were considered ineligible for surgery or radiosurgery after discussion in a multidisciplinary team. The primary outcome measure of the trial was quality-adjusted life-years (QALYs), derived from the combination of survival and weekly reported EQ-5D questionnaires.

The authors of this study are to be complimented for their comprehensive data collection and analysis in a poor prognosis group of patients. Data collected include a median of five and six assessments of quality of life in both arms, data on dexamethasone usage and changes in performance status over time. For the whole group, the difference in the primary endpoint measure was only

4.7 QALY days in favor of WBRT and no overall survival benefit could be demonstrated from WBRT. Notably, no difference in the rates of steroid dose reduction or cessation up to 12 weeks after randomization could be demonstrated, an argument often used in support of palliative WBRT.

However, do these results imply that WBRT can be regarded obsolete for patients with brain metastases from NSCLC? In order to answer this question, a deeper look into the patient population of the Quartz trial is essential. In a multicenter setting with 72 participating centers, accrual completion took almost 7.5 years, indicating on average inclusion of a single patient per center per year. The overall survival reported was only 9.2 and 8.5 weeks, for the WBRT and BSC arms, respectively. Although this survival was measured from the date of randomization, this characterizes a poor prognosis group of patients with an estimated 6-month survival from the survival curves in the order of a mere 10%.

A three-class recursive partitioning (RPA) system has been developed and validated by the RTOG to describe different prognostic groups of patients with brain metastases. Patients within RPA Class I, the most favorable prognostic group, have a Karnofsky performance score (KPS) of ≥ 70 , an age ≤ 65 years and controlled primary tumor without extracranial metastases. In contrast, the poorest prognosis patients in RPA Class III are characterized by a KPS score of < 70 . The remainders of patients are classified as RPA Class II (5).

While at a first glance, better prognosis patients were included with RPA class I patients in 8% and 3% of the WBRT and BSC arm, respectively, there must have been reasons for these patients to be considered non-eligible for

aggressive local treatment, and eligible for the trial. Reasons for this can't be extracted from the data but could include a large number or volume of the brain metastases.

As in most series of brain metastases patients, the vast majority of patients are included within the intermediate RPA Class II group, however, it has to be realized that prognostic classification systems account for the status but not the extent, nor the site of extracranial disease, making the RPA Class II a heterogeneous group of patients. Additionally, if patients are considered eligible for a trial including a BSC arm, one could question how much effort will have been undertaken to characterize the presence or absence of extracranial disease. A few other limitations regarding patient selection have to be mentioned here for completeness. Firstly, the analysis was performed on an intention-to-treat basis, which is certainly the best approach. However, almost 20% of patients in the WBRT group did not receive radiation or received radiation to lesser doses. Also there is mention of some cross-over in the BSC arm, where some patients eventually did undergo WBRT. Finally, it is a pity that not only newly diagnosed patients were included, but also up to 18% of patients with progressive brain metastases, albeit in both arms.

Having highlighted some restrictions of this trial, particularly regarding patient selection, it has to be accredited that this does not compromise the importance of the outcomes of the Quartz trial. It remains apparent that poor prognosis patients, i.e., patients with RPA Class III, do not benefit from WBRT, and as such the trial provides evidence-based support for the general practice of withholding treatment other than BSC for this group. In contrast, even although not powered for sub-analyses, the trial outcomes show that patients with well-known favorable characteristics, i.e., younger age, absence of extracranial disease progression, i.e. RPA Class I patients and a more favorable subset of patients within RPA Class II, do appear to benefit from WBRT. This more favorable subset of patients with brain metastases from NSCLC are increasingly considered for treatment with radiosurgery as a single modality, both from the perspective of increasing local control as well as for reasons of avoiding (hippocampus-related) neurotoxicity. In the last few years there has been a growing trend towards the use of radiosurgery alone for brain metastases, initially for up to four lesions, but a recent publication also reported on this approach with acceptable toxicity and favorable survival outcome in patients with up to ten brain metastases. This development by itself will decrease the use of WBRT in

patients with brain metastases from NSCLC (6-8). And finally, of course, advances in systemic treatment and more specific genomic characterization of lung tumors and matched targeted therapies have resulted in profound clinical benefit for patients. Increasing central nervous system bioavailability of compounds targeting for instance EGFR or BRAF may potentially impact survival and even be used as an alternative for WBRT (9).

In conclusion, the recently concluded Quartz trial is groundbreaking in that it is the first prospective randomized study providing evidence that poor prognosis patients with brain metastases from NSCLC do not benefit from WBRT, and BSC should be regarded standard of care in these patients. As explained, this does not hold true for younger patients, with limited or absent extracranial disease, in whom in addition to the possibility of WBRT other treatment approaches including radiosurgery alone or systemic treatment may be indicated as an alternative to WBRT.

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Footnote

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