

A Thought-Provoking Retrospective Study on Survival and Toxicity After Reirradiation for Recurrent High-Grade Gliomas

TO THE EDITOR: Fogh et al¹ recently published a large single-institution study on hypofractionated stereotactic reirradiation for recurrent high-grade gliomas in which 147 patients were included, the vast majority (71%) with glioblastoma. The median initial radiotherapy dose was 60 Gy, and the median reirradiation dose was 35 Gy in 3.5-Gy fractions. Median time from diagnosis to reirradiation was 8 months. Given the time from diagnosis to completion of first-line radiotherapy, which cannot be shorter than 6 to 7 weeks, the median interval between the two radiotherapy series must have been approximately 6 months (not reported in the study). As in other studies of different therapeutic approaches (chemotherapy, radiotherapy, targeted agents, and so on) for recurrent high-grade gliomas, patients with poor performance status or other adverse prognostic features were excluded. Thirty-three percent of patients received chemotherapy at recurrence with reirradiation (various regimens), but outcome was not improved by additional chemotherapy. Resection at recurrence before reirradiation (60% of patients) also failed to prolong survival. Reirradiation was well tolerated. These findings are in accordance with other studies discussed by Fogh et al and summarized in Nieder et al.²

However, there is at least one important and unique aspect in the Fogh et al study¹ that is not discussed in greater detail. This aspect might have contributed to the favorable toxicity results and highlights an area of controversy in reirradiation of high-grade gliomas. It might also have considerable impact on the clinical practice of reirradiating patients with such tumors. It appears that the question should no longer be whether or not reirradiation is a valid treatment option for selected patients, but how the target volume should be defined. Post-operative changes might complicate target volume delineation,³ a critical process in the radiotherapy planning and execution chain. If parts of the tumor do not receive the prescribed radiation dose, rapid progression in such underdosed regions might be expected. On the other hand, including unnecessarily large areas (so-called security margins) increases the risk of toxicity and is not desirable in patients undergoing reirradiation. Fogh et al defined the gross tumor volume (GTV) on the basis of gadolinium-enhanced T1 weighted magnetic resonance imaging (MRI), a method which is generally used in clinical practice. However, they chose neither to include edema nor to apply any margin for microscopic tumor growth or set-up uncertainty. In other words, the GTV equalled the planning target volume. This nonstandard approach apparently did not compromise the outcome but might have contributed to the favorable therapeutic ratio. Median survival was 11 months (10 months in patients who did not receive

chemotherapy). These figures are no worse than those reported in previous retrospective series, for example, one from my former institution Saarland University Medical School, Homburg/Saar, Germany, where median survival was 8.5 months (nonstereotactic reirradiation with large planning target volume and without any chemotherapy).⁴ Should we consider gadolinium-enhanced, MRI-based GTV as the appropriate target volume? Importantly, there is data suggesting that positron emission tomography with various (eg, amino-acid) tracers^{5,6} magnetic resonance spectroscopy and other modalities⁷ might improve visualization and delineation of high-grade gliomas. Such modalities might further broaden the therapeutic window of reirradiation by limiting the size of the PTV but require validation in larger series. A prospective multicenter trial, the GLIAA (Amino-acid PET [positron emission tomography] Versus MRI Guided Reirradiation in Patients With Recurrent Glioblastoma - A Randomized Phase II Trial) study is expected to open in 2011 (coordinating investigator: Anca L. Grosu, MD, University of Freiburg, Freiburg, Germany). This and other prospective studies will eventually define the best available imaging techniques to avoid geographical miss and irradiation of unnecessarily large volumes of normal tissue. Given a median survival from first diagnosis of 23 months in patients with glioblastoma, Fogh et al have made an important contribution and should undoubtedly be congratulated for their commitment to improve the outcome in patients with high-grade gliomas.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author indicated no potential conflicts of interest.

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