Transient increase of glioma enhancement after irradiation

T1-weighted images after gadolinium administration. (A) Immediately following radiotherapy, showing the post-resection cavity. (C) Two months after therapy, when there were new clinical signs: an area of gadolinium uptake and edema with slight midline shift. (E) One year following radiotherapy, resolution of edema and enhancement.

De Wit et al. determined that increased enhancement of tumors immediately after irradiation does not always imply tumor progression; in some cases it is a transient phenomenon. Such enhancement could be misinterpreted as tumor growth, an important consideration in phase II treatment trials for glioma.

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Pseudo progression of gliomas after radiotherapy

Commentary by Ulrich Herrlinger, MD; and Johannes Dichgans, MD

Contrast-enhancing lesions on MRI are hallmarks of malignant glioma and are used to monitor their response to therapy. According to the established criteria, a 25% increase of contrast-enhancing lesions is regarded as progressive disease.¹ This is based on the presumption that there are essentially no other possible causes for increasing contrast-enhancing lesions.

The report by de Wit et al. in this issue of *Neurology*, however, shows that the situation is more complicated, because changes induced by radiotherapy may mimic tumor progression. It is already well known that radionecrosis, which typically appears 1 to 2 years after radiotherapy, can be difficult to distinguish from progressive tumor. As a feature which has so far only been occasionally described, de Wit et al. report three patients from a prospective trial who showed transient, presumably

non-tumoral progression of contrast-enhancing lesions much earlier, i.e., within 3 months after completion of radiotherapy. So far, there appears to be no radiologic means to distinguish such pseudo-progression from tumor progression. It remains an open question whether PET imaging can provide means to make this distinction.

The present article has major implications for the treatment of patients with glioma in clinical trials: 1) Patients undergoing first-line therapy with chemotherapy and radiotherapy may be misdiagnosed with progressive tumor shortly after radiotherapy. Unless new techniques provide reliable means to distinguish early progression from post-radiotherapy changes, there is no obvious way to avoid this. 2) More importantly, patients with early progression after radiotherapy cannot be eligible for trials on second-line therapy in malignant glioma. The inclusion of these

patients would lead to an overestimation of the therapeutic efficacy of experimental drugs and in some cases to unnecessary further investigations of an ineffective drug.

On a broader scope, the report by de Wit et al. shows that the current response criteria in malignant glioma do not fit all clinical situations and may need some amendment. This applies particularly to the response criteria in trials on local, intratumoral application of drugs or on immunotherapy of glioma where an early transient increase of contrast-enhancing lesions may be frequently observed.

Reference

1. Macdonald DR, Cascino TL, Schold SC Jr., Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990;8:1277-1280.

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