Timing of radiotherapy in newly diagnosed glioblastoma: no need to rush?

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Radiotherapy is a cornerstone of treatment of newly diagnosed glioblastoma. It has convincingly proven its value as part of the optimal management of glioblastoma in randomized trials, and is usually started within 6 weeks after surgery. It was initially tested as monotherapy after surgery but, since the publication of the phase III trial by the European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada in 2005, is universally given in combination with temozolomide chemotherapy. With the current approach, the overall prognosis of newly diagnosed glioblastoma remains, however, poor, with a 2-year survival rate of less than 30%.

Glioblastomas are aggressive, fast-growing brain tumors. Their rapid growth makes many patients and their families as well as their physicians aspire to immediate adjuvant treatment after surgery. Longer waiting times are a source of anxiety among patients because of the presumed deleterious effect of delay on tumor control. With the rise of molecular testing of tissue prior to the initiation of therapy, diagnostic waiting times will increasingly become a part of daily practice. That concern raises an important question, which Blumenthal et al address in this issue of Neuro-Oncology: Is there an optimal window for starting the postsurgical part of glioblastoma treatment? Is delaying the start of radiotherapy beyond 4 weeks from surgery detrimental?

Previous retrospective studies from the pre-temozolomide era have examined the consequences of a short delay up to 6 weeks between surgery and initiation of radiotherapy. Two small single-institution studies found this delay indeed to be detrimental. Remarkably, Blumenthal et al reported in a previous meta-analysis of almost 3000 patients included in 16 Radiation Therapy Oncology Group (RTOG) studies a significantly improved survival in patients with newly diagnosed glioblastoma when radiotherapy was initiated with a short delay (<4 wk) after surgery as opposed to treatment ≤2 weeks from surgery. The overall survival was 12.5 months in patients with a delay of ≤2 weeks (hazard ratio [HR], 0.84; 95% CI, 0.75–0.95). A plausible biological mechanism to explain the unexpected finding of benefit of delayed treatment has not yet been identified. A delay of radiotherapy after surgery could allow time for wound healing, thereby decreasing the risk of postsurgery infections. In rat models, increased tissue damage was observed when radiation therapy was delivered closer to the time of a surgery. Patient selection could, however, also play an important role in the explanation of the observed benefit in overall survival after delayed initiation of radiotherapy. In the above-mentioned study, patients who received radiation earlier were more likely to have a poor performance status and had undergone smaller resections. This suggests that physicians may have referred patients with a poor prognosis earlier to receive radiotherapy and that the improved outcome in patients treated after a short delay reflects an overall better prognosis in these patients.

In this issue of Neuro-Oncology, Blumenthal et al re-address this important question with the results of a meta-analysis of 1395 patients included in 2 more recent RTOG studies (RTOG 0525 and 0825) on timing of radiotherapy in the era of concurrent temozolomide chemotherapy. In this analysis, they did not find a prognostic influence of somewhat delayed radiotherapy (4–6 wk after surgery) compared with early radiotherapy (2–4 wk after surgery). This is in line with 2 other, smaller studies conducted in the chemoradiation era. Blumenthal and colleagues hypothesize that the addition of temozolomide to radiotherapy would lessen the impact of the timing of radiation, so that the presumed benefit of delayed initiation would wane. The important message coming out of this analysis, if true, is that taking a time window up to 6 weeks after surgery before starting adjuvant treatment will not adversely affect outcome. This finding also suggests that the increasing molecular testing of tissue specimens prior to enrollment in prospective studies will not be detrimental for outcome, a very important
observation now that precision medicine is gradually being introduced into the field of neuro-oncology.

Can we take these results for granted? The retrospective design of the study inherently affects the generalizability of the results. Patients treated <3 weeks after surgery were older, more often in a less than perfect condition, and less frequently had a complete resection compared with patients treated >4 weeks after surgery, although these individual prognostic factors did not differ significantly between groups. So, again, treating physicians may have ensured that their patients with a less favorable prognosis were referred quicker for adjuvant therapies after surgery, with less of a hurry in patients with a presumed better prognosis. But, importantly, a multivariate analysis that took known prognostic factors (recursive partitioning analysis class, O6-methylguanine-DNA methyltransferase status) into account confirmed the absence of a difference between patients treated within 4 weeks and after more than 4 weeks from surgery (HR, 0.95; 95% CI, 0.84–1.09). It should be noted though that the study focuses on the time span of 2 to 6 weeks after surgery, but less than 3% of patients were treated either ≤2 or >5 weeks postoperatively, respectively. With a dichotomy of treatment initiated ≤4 or >4 weeks after treatment, actual time differences in the initiation of radiation therapy are matters of days, which may be too small to make much of a difference in the outcome of overall survival.

Blumenthal et al reinforce that patients with newly diagnosed glioblastoma require prompt adjuvant treatment after surgery, but importantly confirm that starting chemoradiation within 6 weeks after surgery is adequate. This window allows the thorough planning of further treatment, including molecular testing inside or outside the context of a clinical trial.

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**References**