Live fast, die early? The deleterious effects of waiting time in patients with glioblastoma

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In their interesting study, Fazeny-Dörner *et al.* [1] assess survival and prognostic factors of 98 consecutive patients with unresectable glioblastomas. From 1993 to 1995, patients received no antitumoral treatment at all ($n = 36$). In 1996, primary radiotherapy was given starting within 6 weeks after biopsy ($n = 24$). From 1997 to 1998, patients underwent combined radiochemotherapy starting within 2 weeks after biopsy ($n = 38$). Median survival was 9, 13 and 31 weeks in the above-mentioned groups, respectively.

Regarding our experience with more than 400 patients with histologically confirmed glioblastomas including 72 patients who underwent primary radiotherapy [2], I would like to comment on some aspects of the different treatment strategies adopted by our colleagues.

In classic Greek medicine, it was common practice not to treat patients with a dismal prognosis. Obviously, this nihilistic philosophy survived for more than some thousand years in Eastern Austria. But why? In contrast to our Hippocratic ancestors, a wide range of therapeutic options is available to neurooncologists today, including resection, irradiation and chemotherapy. In their landmark trial published in 1978, Walker *et al.* [3] showed that resection followed by radiotherapy yielded significantly better results than resection alone in patients with malignant glioma: median survival was 35 and 14 weeks, respectively. These results, which were confirmed by other randomized trials [4], clearly reveal the key role of radiotherapy *per se* in the treatment of this disease. In view of these findings I do not understand why more than a decade later patients who were judged to have an unresectable glioblastoma were automatically withheld radiotherapy.

A stereotactic biopsy is a minimally invasive procedure which is completed in less than an hour. In experienced hands, it is associated with minimal morbidity. Problems with wound healing are extremely rare. The neuropathological examination takes only a few days. Thus, calculated from the patient's admission to hospital, the definite diagnosis of a glioblastoma can be established in approximately 1 week.

Workload is generally high in radiotherapy departments. Intervals of several weeks from the first contact of the referring institution to the first day of treatment are the rule, not the exception. In the study of Fazeny-Dörner *et al.* [1], patients undergoing radiotherapy alone had a waiting time of 6 weeks and an overall treatment time of 6.5 weeks (total dose 66 Gy, dose per fraction 2 Gy). Median survival in this group was 13 weeks. In other words, the average patient expired 3 days after the last fraction was given. Time only for what sportsmen would call a 'sudden death'?

In patients with high-grade gliomas, Do *et al.* [5] found longer waiting times for radiotherapy to be a significant predictor of overall survival—the risk of death increased by 2% for each day of waiting. In my opinion, the diagnosis of a glioblastoma represents a neurooncological emergency. In this situation, the radiooncologist should ignore two things: (i) the long waiting list of his department and (ii) everything he has heard about high-sophisticated treatment planning. The only thing that really matters is the immediate initiation of radiotherapy. Why not start with some old-fashioned techniques like parallel-opposing fields or even whole-brain radiotherapy and use shrinking-field techniques later on? This concept was consequently realized at our institution, resulting in a maximum waiting time of less than 1 week from the first contact of the referring institution to the first treatment. Overall survival in our patients was 25 weeks.

In patients with high-grade gliomas, the meta-analysis of Stewart *et al.* [6] showed an improvement in median overall survival by adding chemotherapy of approximately 8 weeks. In contrast to this, Fazeny-Dörner *et al.* [1] reported a more than 2-fold increase in median survival time in patients receiving radiotherapy and lomustine (13 versus 31 weeks). The authors speculate that this effect

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might be due to the reduced waiting time in the years 1997–1998 (see above). They seem to be right—median survival in our patients was 25 weeks. Adding Stewart's 8 weeks benefit of a 'hypothetical' chemotherapy (hypothetical as it was not given at our hospital), this might yield a median survival of 33 weeks, which is in the range of the data presented by Fazeny-Dörner *et al.* [1].

To me, it is obvious that the disappointing outcome of the Austrian study [1] with regard to radiotherapy can largely be attributed to problems with interinstitutional patient flow and time-consuming treatment-planning procedures. The lessons to learn from this analysis of patients with glioblastomas are that (i) radiotherapy is effective irrespective of whether the tumor can be resected or not, (ii) an early onset of radiotherapy is of paramount importance and (iii) the role of chemotherapy should not be overestimated.

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