Commentary

Commentary on Effects of Radiotherapy With Concomitant and Adjuvant Temozolomide Versus Radiotherapy Alone on Survival in Glioblastoma in a Randomised Phase III Study: 5-Year Analysis of the EORTC-NCIC Trial (*Lancet Oncol*. 2009;10:459-466)

Ute Linz, MD

Recently, un update of the important European Organization for Research and Treatment of Cancer study 26981 was published without correcting deficiencies that already were known and publicized in 2008. In the current commentary, the author specifies those issues to help prevent incorrect conclusions and discusses reasons why the journal that published the update dismissed a letter clarifying those shortcomings. ***Cancer*** **2010;116:1844–6.** © *2010 American Cancer Society.*

KEYWORDS: glioblastoma, chemotherapy, temozolomide, nimustine, Neuro-Oncology Working Group of the German Cancer Society, European Organization for Research and Treatment of Cancer.

Within the peer-review system of scientific publishing, it sometimes happens: Authors forget to refer to a publication or study that is relevant to the topic covered in their article. It also happens that reviewers are not fully aware of all articles published in a certain field and let articles slip through without insisting on corrections. Letters to the editor or commentaries are helpful correctives to air opposing views and to correct misleading impressions. Usually, such corrections are published in the same journal as the article in question to make sure the same audience can be reached. Editors often foster such debate, which is essential in scientific publishing and is an important reason for the existence of journals.

In the article by Stupp et al,[1] an important earlier publication was neglected: that by Weller et al.[2] Moreover, the article contained some deficiencies. Both remained undetected during peer review and thereafter, leading to objectionable conclusions. Unfortunately, the journal rejected a clarifying comment because of "its focus, content, and interest." The article was not even sent out for review. Luckily, *Cancer* published that article,[3] and reactions from the scientific community indicated that the scientific issues raised were as relevant as the economic issues. This may happen, as mentioned above, but it should not happen twice.

Recently, Stupp et al published a follow-up report of their results.[4] Although those authors had been made aware of the deficiencies in their first article and had received a copy of the article by Linz,[3] they again neglected all input as well as any reference to the article by Weller et al.[2] The reviewers of the journal that published the update obviously were unaware of the previously discussed study deficiencies and the correction article. All the more surprising, a letter indicating the shortcomings was rejected, again, without review.

Corresponding author: Ute Linz, MD, Forschungszentrum Jülich GmbH, D-52425 Jülich, Germany; u.linz@fz-juelich.de

Juelich Research Center, Institute of Neurosciences and Biophysics, Juelich, Germany

DOI: 10.1002/cncr.24950, **Received:** June 17, 2009; **Revised:** July 28, 2009; **Accepted:** August 5, 2009, **Published online** February 11, 2010 in Wiley InterScience (www.interscience.wiley.com)

Perhaps it is ill-advised to submit criticism to a journal for which the principal author of a criticized article serves on the Advisory Board. Perhaps it is even less wise to criticize deficiencies of a study that helped to establish a drug as a "gold standard." However, if misleading data are repeated in a well reputed journal and if relevant medical as well as economic considerations that are available are grossly ignored, then it seems urgent to air these views and reservations in the interest of patients and ailing healthcare systems alike. Fortunately, *Cancer* provides the necessary platform for this information.

The first point of criticism concerns the title of the updated article by Stupp et al.[4] Like the original publication,[1] it refers only to "glioblastoma," although at least 7% of patients in the study had other histologies. It is well known that glioblastomas must not be mixed with lower grade gliomas when analyzing survival. In particular, long-term survival might be biased. In keeping with this, 5 of 24 patients who survived for >4 years reportedly did not have glioblastoma but had "another high-grade glioma." The survival curves and tables should have been corrected accordingly.

The results and conclusions reportedly would have remained "unchanged" if the analysis had been restricted to eligible patients with confirmed histology. If a more truthful analysis exists, then why has it not been made the new basis of the update? Room for speculation would be withdrawn. Interpretation of the study results and comparison with others would be more authentic.

The authors rightly note that postoperative radiotherapy has been standard treatment for patients with newly diagnosed glioblastoma for more than 3 decades. Therefore, recent trials often have compared different radiochemotherapy arms rather than comparing a radiochemotherapy arm with a radiotherapy-only arm like the study in question. The randomized study by the Neuro-Oncology Working Group (NOA) of the German Cancer Society (NOA-1) published by Weller et al in 2003 appeared to be particularly successful.[2] However, like data from previous publications, the data reported by Weller et al were ignored in the current update. However, it appears that a comparison would be worthwhile. The update corroborates the impression that the nimustine-based NOA-1 regimen is at least equivalent to the combined treatment regimen of the European Organization for Research and Treatment of Cancer (EORTC) trial.

The rational choice of drugs recommended by the authors requires the existence of compelling predictive assays. A restriction to O-6 methylguanine-DNA methyltransferase (MGMT) appears to be premature. New data from the EORTC trial support the perception that the methylation status of MGMT is mainly a positive prognostic factor rather than a predictive factor that is relevant to treatment.

Patients who had tumors with methylated MGMT status had longer median and 2-year survival independent of treatment (see Table 2 in the article by Stupp et al[1]). Even patients who received radiotherapy only lived longer than patients who had unmethylated MGMT status after combined treatment (median survival, 15.3 months vs 12.6 months, respectively; 2-year survival rate, 23.9% vs 14.8%, respectively). If MGMT methylation status were a strong predictive factor with which to identify patients who may benefit from temozolomide, then patients who have tumors with unmethylated MGMT would not experience an advantage from combined therapy. However, the 2-year survival rate in this group of patients was 14.8% compared with 1.8% for patients who received radiotherapy only.

The Brain Tumor Group of the EORTC, with its many participating centers, should follow the example of its sister association, the Gynecological Cancer Group (CGC). In the recent EORTC-CGC trial 55971, a cell-based chemoresponse assay was used to complement the repertoire of potential predictive molecular markers. In only a few years, that group was able to recruit a large number of patients, and <2 years of follow-up were enough to prove the value of the cell assay in predicting chemoresistance.[5] Considering the short life span of patients with glioblastoma and the low response rate of the available drugs, it seems pertinent to determine whether such assays, which appear to provide a rational basis and a chemotherapeutic strategy in other oncologic fields, also may help to tailor chemotherapy individually for patients with brain tumors.

CONFLICT OF INTEREST DISCLOSURE

The author made no disclosures.

REFERENCES

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987-996.
2. Weller M, Muller B, Koch R, Bamberg M, Krauseneck P; Neuro-Oncology Working Group of the German Cancer Society. Neuro-Oncology Working Group 01 trial of nimustine plus teniposide versus nimustine plus cytarabine

chemotherapy in addition to involved-field radiotherapy in the first-line treatment of malignant glioma. *J Clin Oncol*. 2003;21:3276-3284.

3. Linz U. Chemotherapy for glioblastoma: is costly better? *Cancer*. 2008;113:2617-2622.
4. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. 2009;10:459-466.
5. Verleye L, Coens C, Amant F, et al. Extreme drug resistance for carboplatin predicts resistance to first-line therapy in advanced-stage ovarian cancer: results from the EORTC-CGC/NCIC-CTG neoadjuvant trial. Paper presented at: International Gynecologic Cancer Society 12th Biennial Meeting, Bangkok, Thailand, October 25-28, 2008.