
The variables used included age, sex, and Karnofsky Performance Scale (KPS) score as potential confounders to the variable of interest: time delay in initiation of chemoradiotherapy after surgery (in days).

They then added other variables, however, including chemotherapy after recurrence, along with use of Gliadel, bevacizumab, lomustine, carmustine, and other adjuvants. In my opinion, adjusting for these factors adds very little to the study but confuses its purpose and clinical relevance. What is the question being asked and what is the outcome being measured?

The paper does not really clarify the distinction between time to tumor recurrence, time to progression, and progression-free survival. While there is some controversy with the precise definition of these terms,¹ I believe many physicians with experience treating glioblastoma (GBM) would agree with the idea of time to tumor recurrence as the time starting from the date of initial diagnosis or surgery, inclusive of the primary chemoradiotherapy framed on the Stupp protocol,² and ending when there is clinical or radiological evidence of new tumor. I would define time to tumor progression similarly, under the assumption that complete resection of the enhancing portion of GBM on MRI does not completely remove the tumor. Progression-free survival is the time from the date of initiation of therapy until the last available date when there is documented evidence that progression has not occurred or the patient has died.¹² The difference is subtle but, I believe, relevant here. The question the study should be asking is: Does delay in initiation of chemoradiotherapy after surgery alter the time to tumor recurrence? Instead, the study lumps in therapies that are initiated after recurrence (and then only in some instances) and then tries to use the Cox method to take them out to see if delay in initiation affects progression-free survival. Why make this so complicated?

When looked at from this perspective, other issues arise. Why did only 74 of the 218 patients get chemotherapy at recurrence? Was surgery performed at recurrence? Was the Gliadel delivered during the first surgery or at the surgery performed at recurrence?

The most important confounding variable in this study, the one that is clinically relevant, is not second-line chemotherapy but the surgery the patient received. A simple biopsy may allow for a shorter delay before initiating chemoradiotherapy compared to a large craniotomy, and a small, subtotal resection may be in between. Large incisions may require more healing. The point is that these two variables—type of surgery and time to heal—must be considered “confounded.” Another closely related confounder is the size and location of tumor, as that determines whether surgery is even feasible. The authors did note these deficiencies. Nevertheless, I believe that they are too central to the question being asked to be ignored. I would point out that TCGA does now have MR images for about half of these patients (https://wiki.cancerimagingarchive.net/display/Public/TCGA-GBM), but the authors did not mention whether they even attempted to analyze those images for size, location, and extent of resection. In addition, the Clinical Data Elements (CDEs) defined in the TCGA Library (https://tcga-data.nci.nih.gov/docs/dictionary) do attempt to make the distinction between the CDEs Progression and Recurrence. It was not noted in the study which TCGA CDEs the authors used.

These points, however, miss the bigger picture. The Cancer Genome Atlas was designed to be a repository to allow for public access to genetic data. The clinical data are a small “sideshow” that was added with the intent to see whether there are any links to the reams of genomic and sequence analysis data, the interpretation of which, in my opinion, requires experience in bioinformatics. It is tempting for clinicians to independently analyze the part that they can understand. I think, however, that the anonymity of the clinical data that allows this information to be made public, the very strength of TCGA, is the biggest problem for clinicians, because we do not know why the data are missing and there is nothing we can do about it.

As of May 2015, TCGA reports clinical data on 521 GBM patients (https://tcga-data.nci.nih.gov/tcga/). The authors found that 218 patients met their criteria.³ Table 1 of their article lists the patients’ characteristics. The only category for which the values add up to a total of 218 is...
sex. Only 79% of patients (n = 173) even had a KPS score. The trouble with the anonymous database is that there is nothing that can be done to rectify this.

At his own institution, a clinician doing a retrospective analysis on a data set has to construct it himself; when something is missing, he can either try to get the data some other way, try to decide if the information is really relevant, or realize that trying to put the data together in a relevant way might introduce too much bias to make a study useful. No matter what, he must use prudence each step of the way. In TCGA, the data have been set up for us: we can go straight to analysis! But there are lots of black holes in that data that no amount of prudence can solve.

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**DISCLOSURE**  
The author reports no conflict of interest.

**References**


**Response**

No response was received from the authors of the original article.

**Stereotactic radiosurgery for AVMs with and without Onyx embolization**

TO THE EDITOR: We recently came upon the article by Lee et al.1 (Lee CC, Chen CJ, Ball B, et al: Stereotactic radiosurgery for arteriovenous malformations after Onyx embolization: a case-control study. J Neurosurg 123:126–135, July 2015). The authors followed 25 patients with an arteriovenous malformation who had Onyx embolization prior to Gamma Knife surgery and compared them to a group of 50 propensity-matched patients without prior embolization. It is a well-written and important study on a question many of us have when treating patients with inoperable or high-risk arteriovenous malformations: does embolization enhance the kill rate of Gamma Knife surgery (i.e., complete nidus obliteration)? They did not find a difference between the 2 groups. Unfortunately, there was one major problem with the article: it is not a case-control study, as proclaimed in the title.

The term “case-control” is often used incorrectly in the neurosurgical literature. We recently reviewed all so-called case-control studies in the 2 main neurosurgical journals (Journal of Neurosurgery and Neurosurgery) and found that just less than half were true case-control studies.2 A case-control study is by definition a retrospective analysis in which a group of patients with a disease or those who have experienced some event are compared with a control group without the disease or event with the purpose of identifying disease causation or association. Tips that may indicate a paper is not a case-control study include the use of the words “outcome” and “cohort,” the evaluation of a specific procedure or surgery, or the use of Kaplan-Meier curves, all of which were used in the paper by Lee et al. Their study is best described as a retrospective matched cohort study because they followed 2 groups of patients in time for specific outcomes (nidus obliteration and adverse radiation effects).

It is important to use the appropriate terminology for study design for a number of reasons. First, it prevents the casual reader, as well as those who may use this article as part of a systematic review or meta-analysis, from being misled. The use of phrases such as “case-control study” or “cohort study” implies a specific type of clinical research design with certain strengths and weaknesses. Second, depending on the scale used, the level of evidence assigned to a case-control study may be different from that assigned to a cohort study (retrospective or prospective). Third, checklists are available for the specific type of study design (e.g., Strengthening the Reporting of Observational Studies in Epidemiology [STROBE])3 that can assist authors when formulating their study design and writing up their results. Reviewers can also use such checklists to identify these key components.

The authors’ incorrect use of terminology should not detract from their article. Instead, it is an opportunity to reiterate the recommendations we made in our article: reviewers need to understand what constitutes a case-control study, authors should consider soliciting the assistance of an epidemiologist or biostatistician who is perhaps more familiar with the mechanics of a case-control study design, and that not only should authors be required to use the STROBE checklist when submitting their article, but reviewers need to understand the 22 items within STROBE.

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