Misuse of The Cancer Genome Atlas?


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, 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, 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.1,2 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 affect 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.4 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]) 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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Surgical treatment of VA stenosis in the endovascular era

TO THE EDITOR: We read the recently published article on vertebral artery (VA) transposition by Rangel-Castilla et al. 1 (Rangel-Castilla L, Kalani MYS, Cronk K, et al: Vertebral artery transposition for revascularization of the posterior circulation: a critical assessment of temporary and permanent complications and outcomes. J Neurosurg 122:671–667, March 2015) and would like to make several comments.

Although there is an enormous amount of debate about the pros and cons of carotid endarterectomy (CEA) and carotid artery stenting (CAS), the treatment of VA stenotic lesions has received much less attention. However, about 20% to 25% of ischemic strokes occur in the vertebrobasilar territory. 2 In addition, VA stenosis is the second most common supra-aortic branch lesion after internal carotid artery (ICA) stenosis. 3

Another significant point is the evaluation of the presenting symptoms in patients with VA stenosis. Unless the patient is presenting with transient ischemic attack (TIA) or posterior circulation stroke, other symptoms require detailed neurological examination and exclusion of other possible causes, such as hypotension and otological and cardiac disorders.

Of the possible management options for VA stenosis, surgical treatment is technically demanding because of difficult access to the vessel origin, and it may seem too aggressive for this small, but important, artery. Reported complications after surgical treatment, such as cranial neuropathies, lymphocele, wound infection, pneumothorax, and perioperative posterior circulation stroke or TIA, clearly lead us to question the validity of this procedure.

The improvements that have occurred in surgical techniques since 1991, in combination with digital arteriography, a trained anesthesia team, and established uniform management protocols, have been associated with significant improvement in outcomes of surgery, but the results are still not satisfactory. 4 In their recent article on VA–carotid artery transposition, Rangel-Castilla et al. report a postoperative complication rate of 45.5%. 5 Considering these results, one could reasonably question whether there is any benefit to this procedure.

A review published in 2012 6 included 690 patients (737 lesions) with extracranial VA stenosis treated endovascularly and showed excellent technical success and low complication rates. Our recent study 7 showed similar results: a 5.5% complication rate and good long-term outcomes (primary patency rates at 1, 3, 5, and 7 years of 98.4%, 87.3%, 87.3%, and 87.3%, respectively). Other advantages of the endovascular approach are shorter hospital stays, quicker recovery, and the possibility of simultaneous endovascular treatment of the subclavian artery.

Nevertheless, surgical treatment may be the only viable therapeutic option for patients in whom an attempt at endovascular treatment has failed or those who have lesions or anatomy unfavorable to endovascular treatment.

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References

Response
We appreciate Drs. Babic’s and Radak’s thoughtful comments on our article and would like to respond to their comments.

Endovascular technology is constantly evolving and improving. It now offers excellent therapeutic alternatives to the management of cerebrovascular diseases. The endovascular treatment of vertebral artery origin (VAO) stenosis has not received as much attention as carotid ar-
tery disease. Endovascular stenting and angioplasty of the VAO is becoming more popular because, compared with open neurovascular techniques, it is a simpler procedure technically, resulting in shorter hospital stays and faster recovery for patients. As with any endovascular procedure, the learning curve is steep, yet it is common for vascular and neuroendovascular surgeons to quickly adopt this modality as the first choice for VAO stenosis management.

When selecting the best method for revascularization of the VAO, however, the durability of the treatment should be a crucial deciding factor. Patients who underwent angioplasty and stenting at our institution have shown a restenosis rate of 43.3%. Other series have shown an 11% rate of restenosis with the use of drug-eluting stents. In comparison, results of microsurgical revascularization have shown greater durability. Berguer et al. reported a 97% stroke-free rate at 5 years, and Hanel et al. reported a 93% stroke-free rate at 29 months, with only 1 case of recurrent stenosis. Our results demonstrated a 100% stroke-free outcome and 4.5% rate of asymptomatic restenosis. We believe that it is very important for patients to be aware of the durability of different treatment options.

In our paper, we presented an array of temporary complications, which included recurrent laryngeal nerve palsy, intraoperative thoracic duct injury, temporary Horner’s syndrome, and perioperative transient ischemic attack. However, only 1 patient (4.5%) had a permanent complication. We agree with Drs. Babic and Radak that VA transposition is a technically demanding procedure, and ideally it should be performed by experienced vascular or cerebrovascular neurosurgeons. Anatomical knowledge and gentle tissue manipulation are the bases for avoiding complications in patients undergoing this procedure.

To summarize, we believe that the durable option of VA transposition should be considered when patients are treated initially, when endovascular treatment fails, or when patients have lesions or anatomy unfavorable for endovascular therapy. Perhaps in the near future, the use of better balloons, such as the dual-ostial balloon, and stents may decrease the rate of restenosis. Until then, there will still be a need for microsurgical treatment of VAO stenosis in the endovascular era.

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References

Internal neurolysis for trigeminal neuralgia

TO THE EDITOR: Ko et al.’s article reporting on the results of internal neurolysis (IN) for trigeminal neuralgia (TN) highlights the fact that neurovascular compression is not the cause of TN in all instances and that some form of destructive procedure on the trigeminal nerve anywhere along its length will provide pain relief but will also result in some measure of sensory loss (Ko AL, Ozpinar A, Lee A, et al: Long-term efficacy and safety of internal neurolysis for trigeminal neuralgia without neurovascular compression. J Neurosurg 122:1048–1057, May 2015). The authors present the results for a small group of 27 patients who underwent IN rather than partial sensory rhizotomy (PSR). One of the main limitations of their study is the small size of the patient group as well as its heterogeneity. Some had undergone prior surgery (10), others had sensory changes prior to the IN procedure (4), some had an element of concomitant pain (12), and others had only classic TN. Previous studies have shown that PSR can produce outcomes equal to those obtained with microvascular decompression (MVD). For example, in comparing MVD with PSR (all procedures performed by the same surgeon), Zakrzewska et al. showed that recurrence rates for patients undergoing each procedure for the first time were 16% for MVD and 30% for PSR. Moreover, recurrences tended to be more frequent in those who underwent these procedures as a second intervention: 30% for MVD and 25% for PSR. However, satisfaction was markedly different in the 2 treatment groups because of the resultant complications, in particular, those of sensory change. Four percent of the patients who underwent MVD and 20% of those who underwent PSR were dissatisfied with the outcome, and this was due not just to pain recurrence but also to complications. Numbness was reported in 48% of those who underwent PSR and in only 5% of those who underwent MVD. Young and Wilkins also showed that 33% of all patients undergoing PSR reported no sensory changes, but 18% had dense numbness.

Zakrzewska et al. have published the questionnaire used in their study, and given that numbness was one of the features specifically looked at in Ko et al.’s study, the questionnaire may be useful for comparing data. Ko et al. used the Barrow Neurological Institute (BNI) questionnaire, which measures 2 concepts with 1 question, introducing considerable bias, and has not been psychometrically tested. It is not clear if this questionnaire was completed by the patients or by the clinicians reviewing the records. Moreover, the pain of TN is so severe that pa-
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Patients live in fear of its return, so some will not stop taking medications even though they are pain free. The pain postsurgery must be carefully phenotyped, as we have shown that the reported facial pain is not always TN. A burning sensation, which is more neuropathic pain than TN, was reported in 24% of patients undergoing PSR compared with 5% of patients undergoing MVD.5

The Brief Pain Inventory (BPI)-Facial is a potentially excellent scale to use and has been psychometrically tested, but ideally it should have been used preoperatively and then postoperatively. The authors give a composite score for the facial aspects of this questionnaire, whereas each question should have been reported separately to identify the impact of sensory change. Sensory change is unlikely to affect one’s ability to brush teeth, eat hard foods, or open the mouth widely, whereas touching the face or eating a meal can be significantly affected. Akram et al.1 have suggested that comparing studies would be made easier if authors used a checklist and the same psychometrically tested outcome form.

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DISCLOSURE
The author reports no conflict of interest.

References

Response
We appreciate Dr. Zakrzewska’s careful reading and interpretation of our paper reporting on the long-term outcomes of IN for TN without neurovascular compression. She provides an excellent summary of our findings, as well as the limitations of our study. There are a few points that we would like to address.

The weaknesses of retrospective observational studies are well known. We acknowledge that a small sample size and heterogeneous population can be problematic. The fact remains that this is the first meaningful analysis of the outcomes for this procedure; as Dr. Zakrzewska herself has pointed out, previous studies have fallen well short of modern evidentiary standards.2 In contrast, our study provides outcome measures over time, with Kaplan-Meier statistics and a follow-up of more than 3 years in a majority (62%) of the study population.

We acknowledge that the BNI questionnaire has the shortcomings described, but this scale is a familiar and widely applied outcome measure, and its use does facilitate comparison with other large, published series despite its flaws. The addition of the BPI-Facial scale is intended to address some of the weaknesses of the BNI score. A complete description of the administration of these questionnaires, whether by an independent observer over the

FIG. 1. Average BPI-Facial individual questionnaire responses. The BPI-Facial asks subjects to rank interference with face-specific activities: eating a meal, touching one’s face, brushing or flossing one’s teeth, smiling or laughing, talking, opening one’s mouth widely, eating hard foods. For each activity, average subject response is grouped by BNI score (1–5 from the left, on the x-axis; there were no subjects with a score of 4). The BPI-Facial scores are highly correlated with BNI scores for all activities. The BPI-Facial scores are significantly affected by BNI score, with no interaction between activity type and BNI score (2-way ANOVA: main effect: F = 57.14, p = 0.00; BNI*Activity: F = 0.31, p = 0.99).
phone in the majority of cases or by a review of the charts in a small minority appears in our Methods. No baseline measure for either scale was possible given the study design, which is a weakness. The use of alternate questionnaires for rating postoperative patient satisfaction was considered, but the referenced questionnaire is quite lengthy, and concerns for patient convenience and for maximizing the response rate were given precedence considering the already small sample size. All of these concerns were acknowledged in our report.

We deeply appreciate Dr. Zakrzewska’s reference to the Surgical Trigeminal Neuralgia Score for evaluating the quality of reports. While not explicitly referenced in our paper, this checklist was instrumental in the preparation of what we believe to be a high-quality paper according to its criteria.

Lastly, we did not notice any trend in the individual components of the BPI-Facial scores versus a composite score. In patients with unsatisfactory outcomes (BNI score > 2), the mean and ranked responses for each question were not significantly different (ANOVA, $F = 1.29$, $p = 0.27$; or Kruskal-Wallis, chi-square = 10.3, $p = 0.11$). All individual question responses were significantly correlated to BNI score (all $\rho > 0.55$, all $p = 0.000$). Average scores for each question, grouped by BNI score, are shown in Fig. 1.

The need for further outcome studies for IN is necessary. While direct comparison to other ablative therapies for the treatment of TN via a multicenter, prospective randomized study would be ideal, it is unlikely. At minimum, a larger sample size with follow-up times approaching those obtained for MVD would be needed to more thoroughly characterize outcomes and prognostic factors for success.

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