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The Extent of Resection and Prolonged Survival in Glioblastoma Multiforme. Cause and Effect, Correlation, or Neither?

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Editorial

Brain tumors constitute barely 2% of human cancer; Glioblastoma Multiforme (GBM) is the most common malignant primary brain tumor in adults and it is known for its invasive and aggressive behavior [1-4]. Despite its low prevalence, it constitutes an enormous problem in several ambits. AGBM diagnosis constitutes a tragic event for the patients and families and a challenging situation for the health care team that projects and delivers treatment. Regardless of the best multidisciplinary treatment, the mean length of survival is 14 months, with an expected 5-year survival rate 5 % [5]. Financial impact is also very high; Jiang et al., [6] have found the mean total cumulative costs per patient from 3 months pre-diagnosis to 12 months and to 5 years post-diagnosis to be $201,749 and $268,031.

During the last two decades, a significant improvement in the ominous prognosis of GBM has not been seen [4-7]. Current standard treatment for a patient with a magnetic resonance image suggestive of high-grade glioma consists of multidisciplinary input and maximal safe resection, followed by radiotherapy and concomitant adjuvant chemotherapy [8].

In the context of multidisciplinary input for treatment planning, surgical intervention constitutes the initial mainstay of treatment; it obtains and procures tissue for histopathologic and molecular analysis, it can improve the initial neurological status and patient's performance through an appropriate and safe decompression, and it can aid the adjuvant treatment through cytoreductive surgery, but no consensus exists regarding the optimal extent of resection necessary to improve survival [2,9].

The concept of maximal safe resection, is more a philosophical one, that a clear and defined surgical goal; no standard exists for the evaluation of neurosurgical decision. Regarding the extent of resection, a wide practice variation has been described in cohort studies evaluating patterns of care in patients with glioblastoma [10]. Surgical intervention, the mainstay of treatment in GBM, can go from minimally invasive biopsy to craniotomy with a goal of gross total resection [2,9].

To the best of our knowledge, it has not been published to this date a singular treatment protocol that based on the extent of resection consistently improves the length of survival in GBM patients. There is an ongoing strong debate on this concept [4-6]. Even when it is widely accepted that surgery is a crucial step in the multidisciplinary approach, no consensus exists related to the amount of tumor needed to extend survival time [4-7].

The ongoing debate concerning surgical intervention goes beyond the proportion of resection. It includes other relevant topics, such as the most appropriate way to measure it or the recommendation of some authors to surgically avoid certain anatomical areas: the caudate nucleus, thalamus and ventricles [10].

Contemporary literature statements related to the extent of resection in GBM can be found as:

"More extensive resections are associated with longer survival in glioblastoma, often recognized as a causal relation" [10].

"The Extent of Surgical Resection (EOR) has been documented as conditioning survival in GBM patients in retrospective studies" [9].

"This study also found that older patients undergoing surgery have increased survival times compared with those undergoing needle biopsy" [11].

Aware of the dilemma, arguably using the hierarchical classification of evidence based medicine, it would be possible to clarify the meaning of a causal relationship [10], and what we mean and assume when analyzing correlation [2,7].

The terms "cause and effect" and "correlation" are not synonymous: its comprehension and analysis require an understanding of biostatistics [12].

Man Hung describes four ways in which correlation between variables may be incorrectly interpreted; the first one is precisely causal inference [12]. No statistical method designed to determine correlation (Pearson's correlation coefficient, Spearman's rho, Kendall's tau), or correlation and prognosis (regression) is able to produce results that implies causality [13]. Under no circumstance the statement that an independent variable causes a change in the dependent variable is appropriate if the research design is either comparative or associational. An active independent variable is a necessary but not sufficient condition to make cause and effect conclusions; in order to take the next step of inference that one variable causes the other, or testing a causal hypothesis, the suitable statistical methods include randomized controlled trials or path analysis and structural equation modeling applied in a proper research design [12].

Establishing cause and effect is one of the most challenging aspects of designing research studies.

The three criteria needed to establish cause and effect are: association, time ordering (or temporal precedence), and non-spuriousness [14].

Regarding glioblastoma multiforme, extent of resection and survival, in a cause (extent of surgical resection) and effect (improve of survival) approach, the mental process to appropriately design a randomized clinical trial does not appear as a simple matter, but there is an excellent, very elegant paper already published by Stummer et al., [15], an impeccable designed research which concludes that in patients "with suspected malignant glioma amenable to complete resection of contrast-enhancing tumor, fluorescence derived from 5-aminolevulinic acid enables more complete resections of contrast-enhancing tumor, leading to improved progression-free survival in patients with malignant glioma"; its conclusion is related to "progression-free survival", however they are not able to conclude that more complete resection causes "extension of survival".

Regarding glioblastoma multiforme, extent of resection and survival, in an association approach (extent of surgical resection and improve of survival), several examples of research studies can be found. The current ultimate paper may be the one from Brown et al., [7]. They have reviewed and analyzed 37 studies and concluded that "compared with subtotal resection, gross total resection substantially improves overall and progression-free survival, but the quality of the supporting evidence is moderate to low". They, again, do not find correlation with extended survival but with progression-free survival, and arguably might imply in their conclusion a cause and effect phenomena, which cannot be concluded based on the statistic method utilized. Furthermore, as correlation coefficients give no indication of the direction of causality, perhaps the conclusion might also be: "compared with death, progression-free survival substantially improves gross total resection, but the quality of the supporting evidence is moderate to low" [13].

Other authors have not found statistically significant correlation between extent of resection and improved survival [5].

One of the reasons that correlation can not imply causality between two variables is because there may be other measured or unmeasured variables affecting the results [13].

When non-experimental methods are used, as in observational correlational studies, the relationship seen between the two variables is vulnerable to bias from anything that was not measured (unobserved variables), it is required, if possible, to rule out alternative explanations for the observed relationship between two variables. A spurious or false relationship may exist when what appears to be an association between the two variables is actually caused by a third extraneous variable [12].

Regarding GBM survival and extent of resection, which other alternative variables could explain the correlation described?

Several, for example, numerous authors have found correlation between overall survival and preoperative Karnofsky Performance Scale; Chambless et al., have found better correlation using the postoperative Karnofsky Performance Scale. These findings debatably mean that less morbidity and delayed mortality may occur in patients with better neurological performing obtained by means of mass decompression.

Another explanation may be that tumors in non-eloquent areas are more prone to have greater extent of resection than tumors located in eloquent areas, so it is possible that the main variable would be the brain area in question, and not the extent of resection.

Probably the most accurate concept to this date, regarding GBM and extent of resection is the one by Brown et al: Although cytoreductive surgery is the cornerstone of therapy in GBM, no consensus exists regarding the optimal extent of resection necessary to improve survival [4-7].

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