Editorial

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Biomarkers in Medicine

Utilizing systematic reviews and meta-analyses effectively to evaluate brain tumor biomarkers

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Within the last 30 years, the number of evidence-based systematic reviews and meta-analyses in the field of brain tumor biomarkers has grown exponentially, with no indication of slowing down. Yet, intrinsic to this growth is the risk of compromise in quality due to such a rapid rise in quantity. Such studies concerning brain tumor biomarkers have already been shown to demonstrate methodologic vulnerabilities and drifts in conclusions over time [1]. Being aware of these possible deficiencies will assist a reader in inferring the most practical and valid conclusions about brain tumor biomarkers [2]. Correspondingly, there are a number of steps we believe a reader can take to ensure their interpretation of systematic reviews and meta-analyses are appropriate and we detail them herein.

Selecting appropriate studies

The quality of conclusions from a systematic review and meta-analysis on a particular biomarker in neuro-oncology reflects the quality of the included studies [2]. For example, if only studies of poor quality are pooled, then the quality of the pooled conclusions will also be low. The issue facing the field of brain tumor in particular is that approaches to diagnosis and treatment evolve very quickly, particularly in this era of genetic sequencing [3]. This means the relevance and pertinence of older versus newer biomarker studies may not always be equal. In the case where they are not, systematic reviews and meta-analyses that pool them nevertheless will produce findings that trend toward the null, and ultimately underestimate true biomarker significance. These concerns are further amplified when one considers the potential for publication bias of positive studies only, as well as small-study biases that can over-represent the pertinence of a particular biomarker [4]. Thus, careful and justifiable selection criteria that respect the contemporary management strategies and detection criteria of the time are very crucial in producing the most accurate findings in these types of studies [5].

Study selection from different time periods, and by proxy different treatment eras, can greatly impact the prognostic significance of brain tumor biomarker systematic reviews and meta-analyses. For example, the significance of *IDH1* mutations and CD133 biomarkers in glioblastoma have been shown to be underestimated by older studies, and so pooling newer studies with older studies diminishes their contemporary prognostic significance [1]. One reason for this pattern is the treatment of glioblastoma changes over time, which can confound certain biomarkers via biological interactions. For example, methylated *MGMT* is known to increase the efficacy of temozolomide [6]. Therefore, pooling studies from both the pre-temozolomide era and the temozolomide era itself would theoretically decrease the prognostic significance of that biomarker, versus pooling studies from the temozolomide era only. Taken further, multiple methods to determine *MGMT* methylation status exist, such as pyrosequencing and methylome profiling, with differing inter-method reliabilities [7]. Biomarker studies from different periods may reflect different

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methodologies, introducing another degree of variability when pooling studies from large time periods. Therefore, it is up to the reader to be wary of how studies have been selected by systematic reviews and meta-analyses [8]. Focus should be given to what time periods included studies encompass, in terms of common treatments and detection methods. This will allow readers to be clear about whether there is a risk that the statistical significance of the pooled findings have been diluted.

Reporting practical summary statistics

Meta-analyses produce a quantitative value by which to summarize their findings. With respect to biomarkers, these can include hazard ratios, mean differences and incidence rates [9]. The question arises then when given the option, which summary statistic is most appropriate for a biomarker. Hazard ratios may be the best statistic to rely on when evaluating how important a biomarker is to the overall survival of a brain tumor diagnosis. Mean differences in survival may better quantify prognosis and alter management strategies based on a biomarker. Incidence rates of biomarkers may better stratify a diagnosis or risks of a diagnostic procedure. Because brain tumors are highly variable in prognosis and clinical courses, the summary statistics used to study a biomarker by any meta-analysis should be practical to the reader, which may differ depending on the clinical scenario [2]. What remains constant, however is the need for error estimations for any of the statistics, including 95% CI, standard errors and total cohort sizes, to facilitate heterogeneity and certainty analysis of the pooled outcomes [10]. It is these additional quantitative steps that separate meta-analyses from a simple arithmetic averaging and make them more applicable to clinical practice.

Consider the evaluation of the mutation methionine substitution for lysine at site 27 of histone 3 (H3 K27M) in malignant diffuse intrinsic pontine glioma, a sub-diagnosis within the brainstem of the broader diagnosis of diffuse midline gliomas [11]. A meta-analysis can demonstrate that the presence alone of this mutation in the setting of brainstem glioma confers three-times greater risk of mortality than without the mutation [12]. This demonstrates then the importance of searching for this biomarker in this setting. A meta-analysis can demonstrate that the mean difference in survival of these patients with and without that mutation is 2.3 years [12]. This value is extremely useful in determining future management given that the average life expectancy with the mutation is 12 months, as well as being particularly useful in having the conversation of aggressive versus palliative care. Finally, a meta-analysis can demonstrate the overall risk of surgical biopsy to the brainstem in order to ascertain mutation status is a very dangerous procedure and has an overall diagnostic success incidence of 96%, as well as incidences of permanent morbidity and mortality being 0.6% each [13]. These values are important when discussing with patients the advantages and disadvantages of pursuing molecular diagnosis of the mutation by means of surgery.

Making valid interpretations

A common misconception is that systematic reviews and meta-analyses are designed to provide an absolute answer to a question, akin to the primary studies that are pooled. This is technically not the case, as rather, these evidence-based studies are designed to summarize the current state of the literature highlighting both the most common trends and the statistical heterogeneity between studies [14]. In the context of biomarkers for brain tumors, one can therefore approach these studies as tools to evaluate the consistency of the published studies, as well as identify areas for future studies to address. Measures of intra-study heterogeneity (summarized by I^2 and p-heterogeneity values) can provide such an insight, with it being accepted that the studies which pool into a summary statistic with a significant p-heterogeneity are significantly heterogeneous, and those without are statistically comparable and consistent [10]. In short, the findings of systematic reviews and meta-analyses in this setting are elegant demonstrations of how consistent associations and trends are in the current literature, as well as appraise the quality of the studies currently published. Readers should not try to infer biological and physiologic mechanisms of the biomarker based on findings of these studies alone, as that is beyond their scope and purpose [15].

For example, a meta-analysis reported a significant association of *IDH1/2* mutations with incidence of preoperative seizures in low-grade gliomas and not in high-grade gliomas [16]. Importantly, in the results the authors reported the I^2-value and p-heterogeneity associated with the summary statistic, indicating the inter-study heterogeneity and its statistical significance, respectively [10]. Furthermore, the authors assessed the quality of evidence and risk of bias of each study contributing to the pooled findings using a qualitative scoring system, with the most common systems being the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) assessment [17] and the Newcastle–Ottawa Scale (NOS) [18]. Doing so gives the reader an even better idea of how valid and pertinent the individual studies contributing to the overall findings were. Knowing this will allow the reader to judge how

reliable the reported pooled results are, given the intrinsic bias risks of all meta-analyses, as mentioned earlier. This, then could influence how much the reported biomarker associations impact the reader, as pooled results that are highly variable from low-quality studies are not as convincing as those that are highly consistent from high-quality studies [19]. It is important to also note what the authors did not do was to try to establish the biological mechanism of how *IDH1/2* mutations induce preoperative seizures, but rather simply imply that this area needs future studies to investigate.

Conclusion

Biomarkers are important in the diagnosis and management of brain tumors. Correspondingly, efforts to augment statistical power and mitigate outlying studies via systematic reviews and meta-analyses benefit our understanding of where the contemporary literature stands on particular associations and trends. Yet, there are a number of steps readers can take to ensure that their interpretations of the findings of any systematic review and meta-analysis are as appropriate, practical and valid as possible. We have highlighted three such steps and encouraged continual appraisal of these studies to maximize both quality and quantity in the future.

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