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EC NEUROLOGY
Review Article

Challenges Facing Level I Evidence in Treatment of Low Grade-Gliomas and Subsequent Uncertainties

Peter Fawzy[1,2]* and Tiffany Karpin[3]

[1]*Department of Neurosurgery, Gold Coast University Hospital, Southport QLD, Australia*

[2]*Griffith University, School of Medicine, Southport QLD, Australia*

[3]*Bond University, School of Medicine, Robina QLD, Australia*

***Corresponding Author:** Peter Fawzy, Neurosurgery Principal House Officer, Gold Coast University Hospital, Senior Lecturer, Griffith University School of Medicine, Benowa, Queensland, Australia.

Received: December 18, 2023; **Published:** January 04, 2023

Abstract

Background: The current era of molecular characterisation has contributed greatly to our understanding and management of low-grade gliomas; however, this has also contributed to a paucity in level 1 evidence.

Review: Diagnostic breakthroughs in LGGs are moving quicker than our experimental capacity can react. The design, analysis, and clinical application of first level evidence is struggling to compete with the considerable variability in the natural course of LGGs and the rapidly evolving utility of molecular characterisation of tumours. This poses several uncertainties to researchers, clinicians and more importantly, patients.

Conclusion: Individualised case-by-case decisions based on best available evidence, albeit lacking level 1 evidence, must be made by considering the tumour behaviour, clinical course and specific patient needs and goals.

Keywords: *Biomarkers; Glioma; Low-Grade; Astrocytoma; Oligodendroglioma*

Abbreviations

LGG: Low Grade Glioma; RCT: Randomised-Controlled Trial; WHO: World Health Organisation; IDH: Isocitrate Dehydrogenase; EORTC: European Organisation for Research and Treatment of Cancer

Introduction

Low-grade gliomas (LGGs) are a unique group of primary brain tumours encompassing astrocytomas and oligodendrogliomas, they are histologically defined as grade 2 on the traditional World Health Organisation (WHO) classification system. However, this definition is lacking with the advent and rapid expansion of the molecular characterisation of this group of morphological tumours. LGGs have been shown to demonstrate a high risk of malignant transformation, and a considerable variability in their natural course [1]. In the era of evidence-based medicine, these factors pose significant challenges to the design, analysis, and application of randomised-controlled trials (RCTs). This paper aims to explore the reasons for this conundrum and the subsequent uncertainties faced by researchers, clinicians and more importantly, patients.

LGGs: A complex definition and a heterogenous course

The natural history of LGGs is highly variable between patients. There is a latency period of apparent stability, with some gliomas progressing very slowly while others undergo rapid malignant transformation from the time of diagnosis, even when uniformly treated [2]. Several systems have been used to define a LGG as high risk. The most common definition is that employed in the Radiation Therapy Oncology Group 9802 trial [3]. In this trial, a high-risk patient was defined as being ≥ 40 years of age, or, if younger than 40, as having an incomplete resection. This definition however encompasses a wide range of the grade 2 infiltrating gliomas, does not distinguish astrocytomas from oligodendrogliomas, or consider the molecular characteristics, such as isocitrate dehydrogenase (IDH) mutations, 1p/19q co-deletion or CDKN2A/B status. These characteristics have been shown to play an important prognostic impact on survival outcomes and contribute to the heterogenous course of patients with LGGs, see diagram 1 for a summary of these risk factors [4,5].

The absence of this molecular information has been a major limitation of most landmark studies on LGGs over the past decade. Patients have been mostly recruited based on histopathology only, at a time when the utility of molecular biomarkers was not yet established in clinical practice as knowledge of these biomarkers has been rapidly evolving. Consequently, these studies provided limited evidence for molecularly stratified treatments, and were found to have flawed recruitment when adjusting for biomarkers. A key example was demonstrated by the European Organisation for Research and Treatment of Cancer (EORTC) 22033-26033 trial [6]. The EORTC investigators aimed to compare radiotherapy versus temozolomide in LGG patients. Post-hoc molecular analysis, inspired by the publication of the revised WHO classification in 2016 at the time, revealed not only a variable mix of IDH-mutant astrocytomas and oligodendrogliomas, but also 15% of patients thought to be LGGs were found to be primary glioblastomas (IDH Wild type). Similarly, Jakola., *et al*. (2017) [7] discovered a 26.8% glioblastoma (IDH wild type) inclusion rate upon retrospective molecular analysis of their LGG cohort. A much more recent example is the CODEL trial [8]. The investigators in this trial found a marked disparity in progression free survival rates between their experimental arms and had to redesign their aim and methodology half-way through the project after adjustment for IDH status.

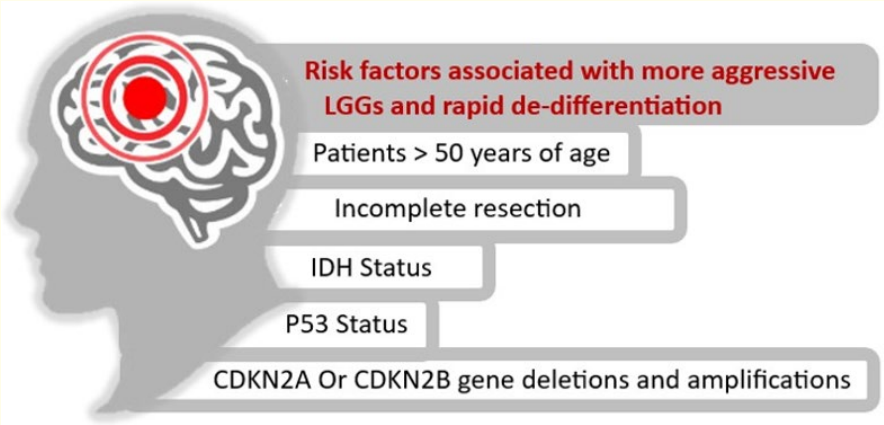

Figure 1

RCTs: A slow train

The question is whether RCTs will ever align with the rapidly expanding knowledge of prognostic biomarkers. RCTs take several years to develop, making it incredibly challenging to adjust recruitment and assess new therapies in a timely manner. For example, the trial by Buckner., *et al*. (2016) [9] looking at radiation alone versus chemo/radiotherapy combination, took 12 years to follow-up 251

patients, and a total of 18 years was spent from recruitment to publication. Another very recent trial was the CATNON, published in June 2021 in *The Lancet Oncology*, looking at concurrent versus adjuvant temozolomide to radiotherapy in adults with newly diagnosed 1p/19q non-co-deleted anaplastic gliomas. It took the investigators eight years to recruit patients and another six years for the results to be published, concluding that adjuvant temozolomide was associated with a survival benefit, while limited benefit was found with concurrent temozolomide [10].

RCTs for surgery in LGGs

No RCT comparing surgical resection with biopsy has been conducted to date in LGG patients. The closest approach to patient randomisation between biopsy and surgery originates from a retrospective population-based study comparing two Norwegian hospitals with two different surgical philosophies - watchful waiting versus early gross total resection (GTR) [7]. A significant overall survival (OS) benefit was found in the surgical group - 14.4 years versus 5.8 years in the surveillance group ($P < 0.01$). While the optimal timing of surgery remains controversial [12], the benefits of surgery on OS and seizure-control is clear [13,14], and have been shown to stand even when adjusted for molecular markers [11,15].

While British guidelines have acknowledged this evidence, the role of surgery is still not clearly recognised in most international guidelines under the argument that there are no RCTs [2]. This raises the ethical dilemma of whether it is acceptable to enrol a patient in an RCT comparing initial biopsy versus surgery when OS is about 14 - 15 years with GTR vs 6 - 7 years with biopsy, only to claim that the benefit of surgery has finally been demonstrated with Level I evidence. Additionally, there are several confounding factors that would limit the design of an RCT for surgery, as outcomes in LGGs tend to be highly dependent on tumour location and surgical expertise as these tumours are notoriously known for affecting eloquent brain regions. Another limitation would be keeping the pace with rapid advances in surgical techniques and intraoperative imaging/mapping, as such a randomised trial would last for at least five to ten years [16].

The struggle of LGG patients

The diagnosis of LGGs is often made in young or middle-aged patients who are at a productive time of their lives. This is a time where patients are ascending in their careers, child-bearing and unrestricted in their everyday activities, such as driving. The challenge with the absence of level I evidence, lies in balancing surveillance versus intervention (surgery, chemotherapy and radiotherapy), and recognising the distinction between treating the tumour and treating the patient. The belief in the 1990s was in favour of surveillance [17]. This was based on the rationale that deferring treatment, such as radiation therapy, might minimise long-term complications such as radiation necrosis, and cognitive impairment. This hinges on the hope that intervention will occur before malignant transformation ensues. However, this cannot be guaranteed even with close follow-up, which places patients under substantial psychological distress, and the constant feeling of a "ticking time bomb". This is particularly challenging in cases where seizures are well-controlled and the lesion is static, as there may be no compelling argument for surgery. Hence, it is essential for clinicians to discuss uncertainties in management decision making and explain why it is incredibly challenging to extrapolate evidence from current studies or recruit patients in a trial with such a variable disease course (See figure 2 for a summary of key challenges). Several patients may be understanding whilst others may wander around seeking several expert opinions in an attempt to answer a dilemma which cannot be solved [1].

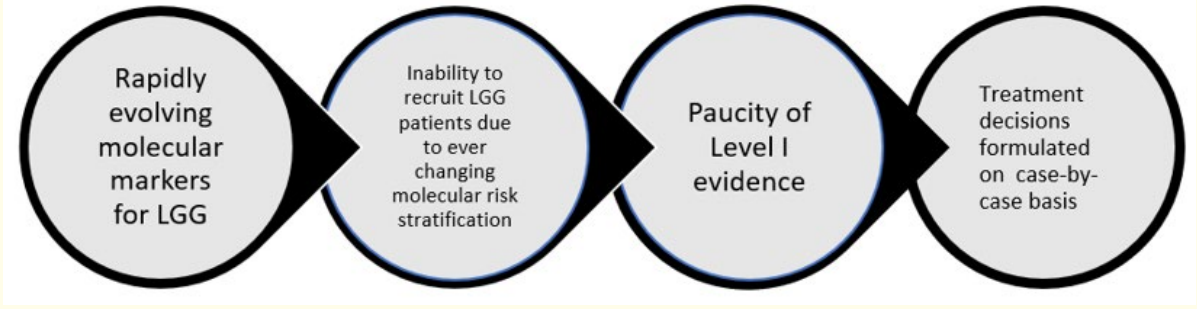

Figure 2: *A summary of key challenges limiting level 1 evidence in management of LGGs.*

Conclusion

Genetic findings and biomarker revolutions in LGGs are moving quicker than our experimental capacity can react. The design, analysis, and clinical application of RCTs must compete with the considerable variability in the natural course of LGGs and the rapidly evolving utility of molecular characterisation of tumours. Well-designed, molecularly enriched RCTs are necessary to inform future treatment. Until then, individualised case-by-case decisions must be made by considering the tumour behaviour, and patient needs. Ultimately, there is a dire need for an intervention to keep LGGs low-grade.

Declarations

The authors have no potential conflict of interest to disclose.

Authors' Contributions

Dr Peter Fawzy: Concept and design, acquisition, drafting of the manuscript, critical review of the manuscript for important intellectual content. Review final version of manuscript according to journal edits and review process.

Dr Tiffany Karpin: Acquisition, drafting of the manuscript and critical review of content. Review final version of manuscript according to journal edits and review process.

Acknowledgements

Dr Ashish Jonathan (Consultant Neurosurgeon at Gold Coast University Hospital) for providing guidance on direction of article.

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Volume 16 Issue 1 January 2024