Oncology is changing: the challenge of effectively assessing response within clinical trials in low-grade gliomas

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The current WHO classification of primary central nervous system (CNS) tumors recognizes four separate tumor grades (I–IV), which can be grouped into low-grade (I and II) or high-grade (III and IV), depending on the absence or presence of high-grade histopathological features, such as microvascular proliferation and necrosis.

Low-grade gliomas are tumors that have glial differentiation and lack—by definition—the above high-grade features [1].

Infiltrating low-grade gliomas of adults include diffuse astrocytoma, oligoastrocytoma, and oligodendroglioma; the estimated prevalence of these tumors is around 34 per 100,000 individuals, while their incidence, according to the above different entities, is 0.14, 0.10, and 0.30 new cases per 100,000 individuals, respectively [1, 2].

Low-grade gliomas tend to occur in the third and fourth decade of life, despite a slow tumor growth, their outcome is often fatal, with a relapse rate after radical surgery that is similar to that observed in high-grade gliomas; as a consequence, median survival is still unsatisfactory (even though longer than in high-grade gliomas), with the prognosis which is related to age, performance status, lesion size, midline involvement, and histology [3]. Furthermore, seizures (which can be the only clinical manifestation of these tumors) and cognitive deficit are extremely common

among patients with low-grade gliomas, highlighting the relevance of maintaining quality of life in these patients.

One of the most compelling challenges in these tumor is response assessment within clinical trials.

Indeed, overall survival (OS)—the Sacred Grail of Medical Oncology—is often confounded, like in many other neoplastic diseases, by the use of salvage treatments at recurrence; moreover, the relatively long life expectancy of these patients and the small clinical benefit expected require many years of follow-up and huge sample size, respectively.

As far as progression-free survival (PFS), the slow growth rate of these tumors, as well as the rare occurrence of true objective responses, makes it a relatively useless end-point for clinical trials. Furthermore, progression, which is usually assessed using a combination of clinical and radiological findings, is also challenging *di per se*; in the absence of the emergence of new contrast enhancement, progression is diagnosed when a small, incremental—and often asymptomatic—increase in size on T2-weighted and FLAIR MRI are recorded. In clinical trials, where MRI are performed serially, the risk is to overdiagnose progression in patients who are clinically stable, not to count radiation-therapy induced changes in white matter which may further complicate the diagnosis of progression.

On the other hand, there are patients who may experience a worsening of seizures—often associated with a concomitant deterioration of cognitive functions—without any significant radiological changes.

For all these reasons, the Response Assessment in Neuro-Oncology (RANO) group has recently published a cornerstone review paper in *Lancet Oncology* [4] assessing the value of both imaging and clinical endpoints in trials for low-grade gliomas, thus providing a novel response assessment criteria for non-enhancing tumors.

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Besides proposing a well-defined MRI and PET imaging protocol for these tumors, together with clear-cut response criteria (which notably included also clinical events), the authors reviewed available tools to assess neurocognitive functioning, symptom burden and quality of life, and stressed the relevance of seizure activity and steroid use in these patients [4]. Finally, they called for the inclusion and validation of these measures in clinical trials [4].

Once again, from this paper, it is clear not only that the art of Oncology is rapidly evolving, but also that our approach to patients with specific tumors is radically changing; integration of radiological techniques with clinical judgement and tumor-specific end-points will substitute usual crude response criteria, no longer useful in a growing number of tumor types.

Conflict of interest None.

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