

**Reply to “Reporting paediatric brain tumours according to their behaviour code can result in biased survival estimates – A European perspective to Girardi et al.”**

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**Conflict of interest**

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We welcome the remarks of Hoogendijk et al. on our study, which revealed wide international variation in the distribution of histology and behaviour among children and adults diagnosed with a brain tumour. Over 90% of brain tumours diagnosed in children in Europe are histologically verified,<sup>1</sup> and benign tumours are usually included in survival estimates because they can also kill. Hoogendijk et al. simulate the impact of varying the proportion of malignant and non-malignant brain tumours on incidence and survival among 2,705 children and adolescents diagnosed in the Netherlands during 2000-2017. The impact of misclassification of behaviour on survival for malignant tumours appeared remarkable.

Accurate comparison of population-based survival for brain tumours raises complex problems. Global differences in access to care may result in under-diagnosis or under-registration; even in countries with optimal healthcare systems, non-malignant brain tumours, by far the most common type in children, may still not be reported by law. Even if all brain tumours are diagnosed, the pathological diagnosis may be inaccurate, or cancer registration incomplete. The clinical behaviour of brain tumours is also very variable, so categorisation by behaviour alone may be simplistic.

In our study,<sup>2</sup> we devised a classification system for brain tumour histology in children, based on the International Classification of Childhood Cancer (ICCC-3<sup>3</sup>), but more granular for astrocytic tumours. We examined the histology for 67,331 brain tumours in children diagnosed during 2000-2014 in 60 countries participating in CONCORD-3.<sup>4</sup> We included all records with a valid morphology code in the International Classification of Diseases for Oncology (ICD-O-3<sup>5</sup>), regardless of the behaviour code (fifth digit). We identified remarkable variation in the proportion of diagnoses coded as unspecified astrocytoma (0.2-27%), unspecified glioma (0-28.6%) or unspecified neoplasm (0.2-52%). Some tumours in these ill-defined categories were coded as microscopically verified, which is counter-intuitive. Where such discrepancies are particularly marked, the quality of pathology or tumour registration may be questioned. Survival by histology can only be estimated robustly if all tumours of a given histological sub-type are ascertained.

We welcome the European Network of Cancer Network efforts to foster implementation of the guidelines on registration of brain tumours that are diagnosed clinically, without microscopic verification. This should allow more robust comparisons of survival, but accurate registration of brain tumours by histology, not just behaviour, is also crucial. Beyond Europe, this can only be achieved through harmonisation of brain tumour pathology and registration world-wide, as well as improved access to care.

Brain tumour histology is central to the WHO Global Initiative for Childhood Cancer,<sup>6</sup> which includes low-grade glioma among the six cancers for which major improvements in survival are envisaged by 2030. This will require a profound revision of ICC-3, which does not currently include grade for astrocytic tumours, the most common type in children. Our findings indicate that survival estimates for countries where data quality is sub-optimal should be interpreted with caution. Nevertheless, our study shines a light on the global landscape of brain tumour reporting. This may stimulate future studies and, ultimately, improve the lives of patients diagnosed with a brain tumour.

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