Diffuse intrinsic pontine gliomas (DIPG) represent 75–80% of the brainstem tumors occurring in children, with the highest incidence between the ages of 5 and 10 years (1). The diagnosis is based on clinico-radiological findings and biopsies have historically been reserved for atypical cases, or performed in the context of clinical trials (2). Standard treatment is based on palliative radiotherapy (1,2). Multiple studies over past decades evaluating a myriad of chemotherapeutic and targeted agents have not shown any significant improvement in the survival outcomes compared to standard radiotherapy alone (1,2). The estimated median progression-free survival (PFS) and overall survival (OS) for DIPG patients are 6 and 11 months, respectively (3). In this context, DIPG constitutes the most challenging pediatric brain tumor, given the dismal outcomes and the scarcity of effective therapies.

The European Society for Pediatric Oncology DIPG Registry (SIOPE-DIPGR) and the International DIPG Registry (IDIPGR) were set up in 2011 and 2012, respectively, as a result of the joint efforts of international multi-stakeholder networks to improve the diagnosis, treatment and outcomes of DIPG patients (3,4). Notably, these registries embodied a paradigm shift towards collaborative research into DIPG. Hoffman et al. have recently reported the first joint study of the SIOPE-DIPGR and the IDIPGR which constitutes the largest cohort of DIPG patients published to date (5).

The study evaluated the characteristics of long-term survivors (LTSs) of DIPG, defined as those with OS ≥2 years from diagnosis. Out of 1,008 centrally-reviewed DIPG cases, 101 (10%) were LTSs. Several aspects of this report are to be highly commended. Firstly, it gathers a colossal sample size, which is a truly exceptional feature for a study focused on a pediatric brain tumor. This illustrates a major change in pediatric neuro-oncology from small single-centre case series to large multi-centric centrally-reviewed cohorts of patients with rare tumors. Secondly, the study provides comprehensive insight into DIPG and expands the body of knowledge adding valuable clinical, radiologic, pathologic and molecular data. Lastly, and very importantly, the study is the result of a major collaboration between the two leading DIPG networks worldwide providing a role model for future international collaborations to address major challenges in pediatric oncology.

Similarly, to that reported in previous studies, the median OS for the whole cohort of DIPG patients was 11 months (interquartile range, 7.5 to 16 months); and their 1-, 2- and 5-year OS [95% confidence interval (CI)] were 42.3% (38.1–44.1%), 9.6% (7.8–11.3%) and 2.2% (1.4–3.4%), respectively. The OS for the subset of LTSs ranged from 24 to 156 months (5). Compared with short-term survivors (STTs), LTSs more commonly presented at age <3 or >10 years, as well as longer symptom duration (i.e., >24 weeks); and LTSs less commonly presented with cranial nerve palsy, ring enhancement, necrosis and extrapontine...
extension. LTSs were also more likely to harbor a \textit{HIST1H3B} mutation and had more commonly received systemic therapy at diagnosis.

The study constitutes a major breakthrough with regards the understanding of longer-term survival in DIPG. Notwithstanding, the following issues should also be taken into consideration when interpreting these results:

(I) The study describes very elegantly the main features of LTSs with DIPG. But the fact that some features occur more frequently in LTSs or STSs does not allow us to infer that those characteristics can discriminate between the two subgroups. This might be partly related with the large sample size of the study which allows for small differences to appear as statistically significant. For instance, age <3 years at presentation was more frequently associated with long-term survival; but the rates of children aged <3 years were 11% among LTSs versus 3% in STSs (P<0.001). Presentation with cranial nerve palsy was significantly less frequent in LTSs than in STSs: 73% versus 83%, respectively (P=0.008); although this was not significant in the multivariate analysis. Additionally, extrapontine extension was associated with worse outcomes, but differences were modest: 86% in LTSs versus 92% in STSs (P=0.04) (5). Therefore, in routine practice it is still not possible to identify upfront which patients will become LTSs, and thus caution should be excised when managing parental expectations.

(II) With regards the molecular biology, when compared to H3.3 K27M and H3 wild-type tumors, the detection of H3.1 K27M mutation was associated in the multivariate analysis with improved median OS: 10.4, 10.5 and 15 months, respectively (5). Notwithstanding, the survival of patients with H3.1 K27M is still very low. This is also illustrated by the Kaplan-Meier curves of patients with H3.1 K27M and H3.3 K27M tumors crossing over beyond 3 years of diagnosis (5). Therefore, as opposed to other brain tumor types with molecularly-defined subsets which clearly carry better survival outcomes, such as Wnt medulloblastomas in children aged <16 years (6) or YAP1 and PFB ependymomas (7), in the case of DIPG no molecular subtypes appear thus far substantially more favorable than the rest.

(III) As regards therapy, two surprising findings were reported concerning the use of reirradiation and systemic therapies. Firstly, patients who had been reirradiated presented better 1-year PFS than those who had not: 74% versus 88%, respectively (P=0.007). The authors suggest that this might be explained by a combination of clinician bias when recommending reirradiation to patients with a more indolent disease course, as well as greater sensitivity to initial radiotherapy in patients who ultimately received reirradiation. However, it must be noted that only a minority of patients (7%) received reirradiation (5). Secondly, systemic therapy at diagnosis was associated with longer survival: 88% in LTSs versus 75% in STSs (P=0.005). This finding challenges the historical perception that systemic treatment does not influence survival outcomes and the authors suggest that this might be explained in part by inconsistent eligibility criteria between trials hampering cross-cohort comparisons (5). Interestingly, the authors showed that some targeted therapies, such as epidermal growth factor receptor (EGFR) inhibitors and bevacizumab, were significantly associated with long-term survival (5). These results should be cautiously regarded, since no randomised clinical trials have yet backed up this finding. However, they are encouraging enough so as to not disregard the use of systemic therapy in forthcoming clinical trials for DIPG. Overall, although patient registries are not methodologically devised to confirm causal relationships, they constitute powerful tools to validate diagnostic criteria, to describe the natural history of a particular disease and to generate hypotheses for future research studies.

The authors acknowledged the possibility of enrolment bias on the part of the participant institutions and the patients/families who self-refer, as well as variations in the standard of care between countries/institutions and overlap of registry patients with cases previously reported elsewhere, as other limitations of the study. Another issue which is particularly relevant for DIPG patients is the quality of life associated with any given treatment strategy. However, due to the retrospective nature of this study, data on quality of life was not available and had it been, may have added value.

On the other hand, significant strengths of this study include the use of standardized case report forms and the central review of diagnostic neuroimaging with cross-validation between pediatric neuroradiologists.

In summary, this study is the largest and most
comprehensive cohort of radiologically confirmed DIPG ever published to date. This research constitutes a major contribution to the field of DIPG and will become a reference framework for future studies. Importantly, it should also be regarded as a role model for worldwide collaboration to address this and other major challenges in pediatric oncology. No doubt there is still a long way to go to improve the course of this disease. But initiatives like this reported by Hoffman et al. pave the way towards that goal.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Xian-Xin Qiu [Shanghai Proton and Heavy Ion Center (SPHIC), a.k.a. the Proton and Heavy Ion Center of Fudan University Shanghai Cancer Center (FUSCC), Shanghai, China].

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.03.12). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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