

# CHAPTER

General discussion and  
future prospects

# 16



This thesis addresses various aspects of DIPG, ranging from its definition to its historical perspective, etiology, treatment options, palliative care, and its impact on patients and their family. Here, the findings and implications of the research are discussed against the background of current knowledge. From this perspective, recommendations for future research are presented.

DIPG is the leading cause of brain tumor-related death in children. DIPG, to this day, is still incurable and therapeutic options have not improved. Mid twentieth century, less than 10 percent of children with cancer were cured, whereas nowadays, nearly 80 percent will survive. Nevertheless, none of the survivors are DIPG patients, which is why DIPG is called “*one of the most formidable challenges in pediatric oncology*” [1].

Four major factors have impeded basic and translational DIPG research:

1. First and foremost, DIPG is extremely rare, qualifying as an orphan disease<sup>1</sup>. By means of a retrospective cohort study (**Chapter 7**), the absolute incidence of DIPG in the Netherlands was determined to be nine patients per year (0.54 per 1,000,000; 2.32 per 1,000,000 aged 0-20 years), with annual variations ranging from 5-13. This extreme rarity has hampered adequate patient enrollment, both for clinical trials and epidemiological studies. Also, most research initiatives have been relatively small-scaled, mono-centered and therefore, scattered. Consequently, it was difficult to distinguish patterns in existing research cohorts.
2. Second, DIPG is diagnosed particularly in children and very rarely in (young) adults [3] so it can almost exclusively be investigated by studying children. Research in children is an ethical balance between the protection of seriously ill patients, thereby avoiding harm of research on the one hand and allowing patients to benefit from innovation from research on the other hand. Research in children is very strictly regulated in the Netherlands [4], narrowing down the possibilities of early phase clinical trials for DIPG.
3. Third, DIPG tumor material was scarcely studied up to 2012. For decades, the approach to the diagnosis had been non-uniformly descriptive, based on clinical symptoms and characteristic imaging findings. On MR-imaging, certain features were considered pathognomonic for the diagnosis of DIPG, so the need for histological confirmation was not felt. In addition, earlier studies showed that biopsy of DIPG yielded inconsistent results with respect to WHO grading of tumor samples [5]. This left the underlying biological patterns hidden, and introduced bias through inter-observer variation, misclassification and heterogeneous use of inclusion criteria in

<sup>1</sup> Rare diseases are defined as life-threatening or chronically debilitating conditions that affect no more than 5 in 10.000 people in the European Union [2]

clinical trials.

4. Finally, DIPG remains incurable. Patients deteriorate rapidly and severely, but with great inter-patient variation. The Dutch retrospective cohort study (**Chapter 7**) showed that between 1990 and 2010 only a minority of patients (18%) was included in clinical trials. This may be a direct result of rapid deterioration in the majority of patients, or a preference for individualized therapy. It may also reflect a lack of trial-oriented attitude, possibly due to the limited number of patients treated per center and the dismal prognosis. It has, however, resulted in a large heterogeneity of applied treatment schedules and incomparability of data.

Analysis of the impeding factors, as addressed above, suggested that research into DIPG could benefit from (i) international, standardized, and centralized collection of data, (ii) the formation of consensus on the diagnostic-, treatment- and supportive care approach to these patients, and (iii) the conduction of international collaborative clinical trials designed in a way to allow individual patient-centered adjustments, to fit the clinical reality of DIPG and avoid unnecessary drop-out [6]. In the past four years our efforts have been aimed at achieving these goals.

## **STANDARDIZED AND CENTRALIZED COLLECTION OF DATA**

To overcome the lack of data and to improve the DIPG research infrastructure, the concept of collaboration and data sharing was applied within the recently established SIOPE DIPG Network. This enabled the development of the SIOPE DIPG Registry and Imaging Repository (**Chapter 14**).

Initially, the DIPG registry harbored mainly retrospective data. As of September 2016, prospective registration has been initiated. Based on the incidence, determined in the Dutch retrospective study (**Chapter 7**), and the number of countries united in the SIOPE DIPG Network (with a total number of about 600 million residents aged 0-19 years; August 2016), it is estimated that over 350 DIPG patients are diagnosed each year in Europe. It is of the highest importance to register all these DIPG patients, both in- and outside of trials, as it provides the opportunity to analyze 'real-life' DIPG patient data.

With retrospective registration alone, the SIOPE DIPG Registry thus far retrieved comprehensive data of  $\approx 700$  DIPG patients from six of the 27 countries that are united in the SIOPE DIPG Network. The remaining 21 countries are currently awaiting Medical Ethical Committee and IRB approval. The availability of DIPG patient data was further increased by establishing a close collaboration with the International DIPG Registry (Fig.1).



**FIGURE 1** | Geographic representation of current collaboration in DIPG research.

Dark gray - SIOPE DIPG Registry, Light gray International DIPG Registry; AT: Austria, AU: Australia, BE: Belgium, CA: Canada, CH: Switzerland, CZ: Czech Republic, DE: Germany, DK: Denmark, EL: Greece, ES: Spain, FI: Finland, FR: France, HR: Croatia, HU: Hungary, IE: Ireland, IS: Iceland, IT: Italy, LT: Lithuania, MX: Mexico, NL: Netherlands, NO: Norway, NZ: New Zealand, PL: Poland, PT: Portugal, RU: Russia, SE: Sweden, SI: Slovenia, SK: Slovakia, TR: Turkey, UK: United Kingdom, US: United States of America

Merging of the registries was considered, but the choice was made to maintain two separate registries because of geographic differences in rules and regulations, and to allow for external cross-validation of data. The inclusion of uniform data in both registries, which was secured by developing standardized case report forms, resulted in the largest ever published cohort of >1100 DIPG patients when data were combined (**Chapter 15**).

## THE STRENGTH OF BIG DATA

Having a large comprehensive reference cohort of DIPG patients is a huge step forward compared to 2012, when the only references available from the literature were (selection- or publication-biased) data from small-scaled Phase I/II clinical trials.

Big data analysis allows for a better study of similarities and differences among patients who are currently uniformly classified as having a “DIPG”. This increases the likeliness of identifying patterns, which may otherwise remain unnoticed. Big data analysis will not only allow for disease-related subgroup comparisons, but also for the study of potential epidemiological differences (i.e., inter-country, inter-ethnicity, inter-age group, etc.). In this respect, it is important to keep in mind that the biggest breakthroughs in the discovery of cancer risk factors have come from epidemiological studies, and were unexpected, such as the identification of the causal relationship between tobacco smoking and lung cancer [7], radiation exposure and leukemia or skin- and female breast cancer [8], *Helicobacter pylori* infection or dietary factors and distal gastric cancer, and gastro-esophageal reflux disease or obesity and proximal gastric cancer [9], human papillomavirus infections and cervical cancer [10], and hepatitis B or C virus and liver cancer [11].

Big data analysis furthermore enables retrospective meta-analysis of benefits, or risks, associated with different levels and types of exposure (such as to different treatment strategies). With qualitative measurements (i.e., the comparison of additional chemotherapy vs. radiotherapy alone, or radiotherapy vs. best supportive care), as well as quantitative measurements (i.e., the comparison of different dose levels of a certain chemotherapeutic agent, or different (re-)irradiation schedules) patterns of potentially effective treatment modalities, as well as treatment toxicity, can be elucidated.

Such meta-analyses require comparability of data. In our Dutch retrospective cohort study (**Chapter 7**), we showed that 103 DIPG patients all underwent essentially different treatment schedules, making it difficult to analyze the effectiveness of particular treatment strategies. This emphasized the need for international consensus on the diagnostic approach, treatment and supportive care of patients, and the need for well-designed and well-monitored standardized clinical trials. The strength of creating big data in the SIOPE and International DIPG Registries lies in the fact that it allows for individualization, fitting the clinical reality of DIPG, and permitting individual patient-based treatments provided those treatment schedules are meticulously recorded. By up-scaling the patient numbers via central registration, beneficial or harmful effects of certain treatments will be more easily identified. Also, small effects will be more easily noticed. Finally, registered data from patients who cannot, or choose not to, undergo treatment, will contribute essential information on the natural course of the disease where before, they were excluded from all research efforts.

## THE FIRST STUDIES USING BIG DATA: SHOWING PATTERNS

The first DIPG studies in which big data were created, determined the prognostic value of multiple clinical and radiological disease characteristics. In the first study (**Chapter 11**), all patients (n=316; now included in the SIOPE DIPG Registry) were centrally reviewed and confirmed to be “typical DIPG”, based on the classification by Barkovich et al. [12]. The DIPG survival prediction model that was developed in this study, showed the potential to discriminate patients with short, average, and increased survival, based on one radiological and three clinical variables. External validation of this model in the second study (**Chapter 12**) was performed in a cohort of patients from the International DIPG Registry (n = 249) and showed adequate discriminative and calibration abilities, confirming the hypothesis that subgroups exist.

In the third study, the first in which the SIOPE and International DIPG Registry collaborated, data from >1100 centrally-reviewed and radiologically-confirmed DIPG patients were combined to analyze characteristics of DIPG patients with longer survival (e.g.,  $\geq 24$  months) versus those with shorter survival (**Chapter 15**). Complementing the above-described studies, this study included biological, as well as clinical and radiological, disease characteristics. The results of this study offer the most accurate survival data of DIPG patients to date, and offers unique insight into 103 long-term survivors (including 17 very long-term survivors (e.g. patients with survival  $\geq 60$  months). Median survival for the entire cohort was 11 months (range 0-167 months), and 1-, 2-, 3-, 4- and 5-year OS were 42.3%, 9.6%, 4.3%, 3.2%, and 2.2%, respectively. Univariate and multivariate analysis confirmed (or contrasted) some previously described factors that correlate with survival, including age  $< 3$  [13–17] or  $> 10$  years [18], longer symptom duration [15,16], lack of CN palsy [19–21], receipt of chemotherapy at diagnosis [14,22–25], smaller cranio-caudal tumor dimension and absence of extra-pontine extension (contrasting [26]), necrosis, or ring enhancement on diagnostic MRI [16,26–29], and presence of *HIST1H3B* mutation [30,31]. This study herewith added confirmation of biological characteristics that very likely underlie DIPG subgroups, which implicates that selection bias might have influenced results obtained in small-scaled clinical studies in the past. And, although historically the consensus among the pediatric neuro-oncology community has been that the use of neoadjuvant or adjuvant chemotherapy with radiotherapy does not improve survival, an important finding of this study is that (neo)adjuvant chemotherapy at diagnosis correlated with long-term survival in both uni- and multivariate analyses ( $p = 0.005$  and  $p = 0.01$ , respectively). This finding requires further research.

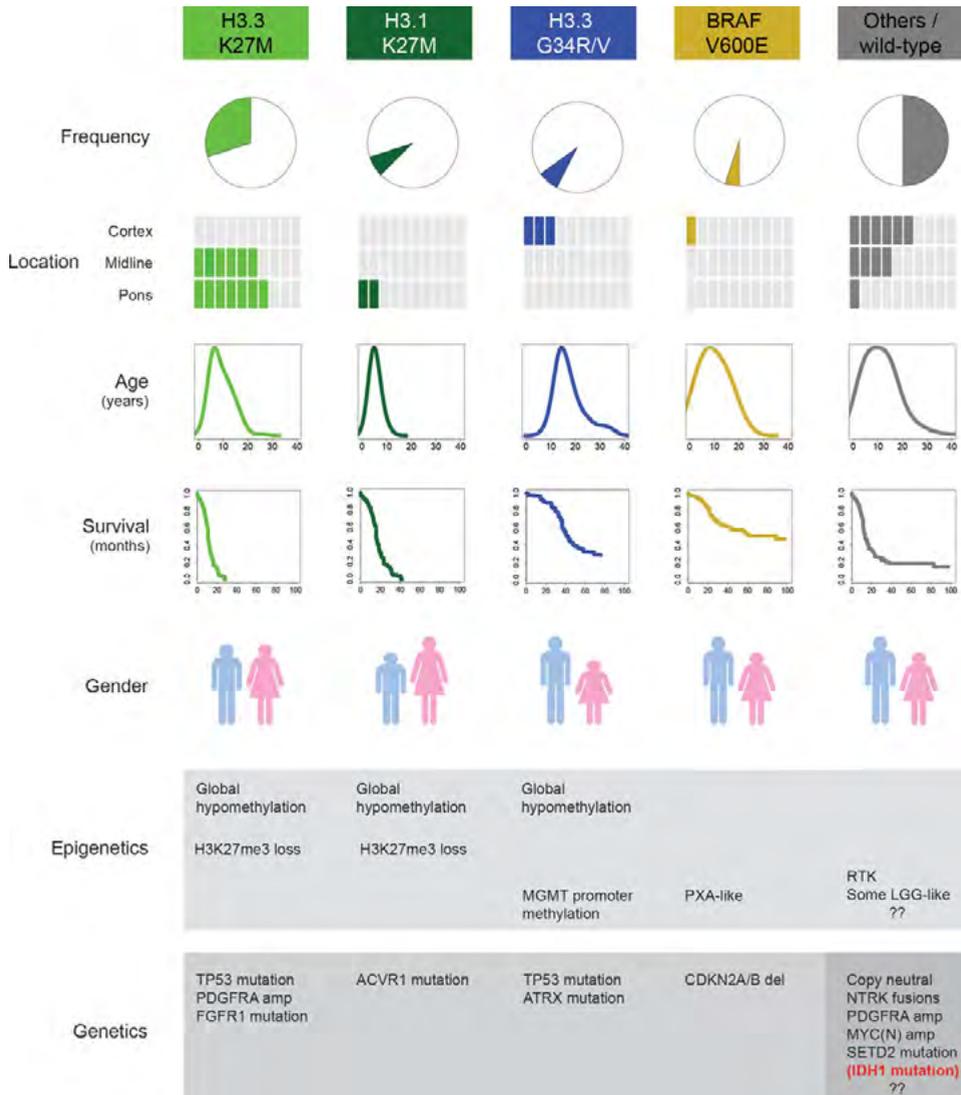
## NOVEL BIOLOGICAL INSIGHTS, PATIENT SUBGROUPS AND DISEASE CLASSIFICATION

In recent years, tumor biopsies and autopsy studies have been re-introduced, increasing the availability of biological data. The opportunity to actually investigate DIPG tumor tissue led to the discovery of unique mutations in histone H3, and a fundamental re-classification of DIPG patients.

In 2012, high-recurrent and mutually exclusive mutations were discovered in the genes encoding histone H3.3 (*H3F3A*), H3.2 (*HIST2H3C*), and histone H3.1 (*HIST1H3B* and *HIST1H3C*) variants [31–33]. These mutations lead to either a lysine-27-to-methionine (p.Lys27Met; K27M) or a lysine-to-isoleucine (K27I) amino acid substitution, resulting in global reduction in trimethylation (H3 K27me<sub>3</sub>), or a glycine-34 to arginine (p.Gly34Arg; G34R), or valine (p.Gly34Val;G34V) substitution. The discovery of histone mutations was a landmark in DIPG research. Histone H3 mutations had thus far never been described in any other type of cancer and were found to occur in up to 90% of DIPG tumors. Moreover, it was shown that the different types of histone H3 mutations show strong associations with primary tumor site: K27M mutations are very specific for diffuse gliomas occurring in the pons (i.e., DIPGs), but interestingly, were also found in a subset of other gliomas, such as thalamic and spinal diffuse gliomas. H3.3 G34R/V-mutations on the other hand, have only been found in high-grade glioma outside the midline. The different types of histone H3 mutations are also significantly associated with clinical characteristics, such as age, gender and survival (Fig. 2), and different types of histone H3 mutations have shown to underlie mutually exclusive oncogenetic pathways and phenotypic changes [34,35]. Recent evolutionary reconstruction studies have shown conserved spatial and temporal homogeneity of histone H3 mutations throughout the tumor and its spread, suggesting these aberrations to be an early event in DIPG tumorigenesis [36,37]. Histone mutations are therefore interesting potential targets for treatment, for instance by histone deacetylase (HDAC) inhibitors such as panobinostat [38–40].

Based on these discoveries, in May 2016, the World Health Organization published a new classification of Central Nervous System tumors as an update of the 2007 edition [41,42]. For the first time, 'K27M-mutated diffuse midline gliomas' (WHO grade IV) are classified as a separate entity [42]. This classification no longer differentiates diffuse pontine tumors (i.e., DIPGs) from diffuse thalamic and medullary tumors when harboring a K27M mutation, creating new paradigms with consequences at different levels. For one, it is likely that the DIPG survival prediction model (**Chapter 11 and 12**) will have to be updated in the near future with inclusion of (these) biological disease characteristics. The recent WHO re-classification also implies that the inclusion criteria for the SIOPE DIPG Registry may need to be adjusted to also include patients with non-pontine diffuse

midline gliomas, thereby dropping the anatomical boundary of the reigning definition. It also implies that our diagnostic approach will move from a solely clinico-radiological diagnosis to also, or possibly rather, a biology-based diagnosis. And since it was shown that underlying mutations, and subsequent events, are not reflected in histology (**Chapter 5**), the biology-based approach must move from a solely morphology-based to an integrated, morphology-molecular-based approach.



**FIGURE 2 |** Biologically and clinically defined subgroups of DIPG; copy from [34].  
With permission.

In our collective aim to cure DIPG patients, it is very encouraging that a lot of effort goes out to finding treatments based on these recent discoveries, which hopefully will result in actual survival. We must keep in mind, however, that this will not yet cover the whole field. In our autopsy study (**Chapter 5**), 22% percent of MRI-based ‘typical DIPG patients’ fell outside of the K27M category and were classified as diffuse astrocytoma “not otherwise specified” (NOS), even though they (interestingly) did show (focal) loss of histone trimethylation, and, most importantly, faced the same dismal prognosis. This implies that there are other, as yet undiscovered, biological characteristics to unravel.

## EVOLUTION OF IDEAS CONCERNING THERAPEUTIC STRATEGIES

As mentioned before, a remarkable finding of the “long-term survivor study” (**Chapter 15**) is the fact that neoadjuvant or adjuvant chemotherapy is significantly associated with long-term survival in both univariate and multivariate analyses. This finding contrasts long-standing dogma in the DIPG research community that chemotherapy provides no survival benefit. This dogma was based on the fact that no significant improvement in survival has been established in over 250 clinical trials executed over the past decades, unlike the spectacular increase in survival of childhood leukemia patients from <10% to over 80%. First, this was blamed to a supposed resistance of DIPG tumor cells to cytotoxic agents. Pre-clinical studies, however, showed that primary cultures derived from DIPG patients are actually not resistant to a number of traditionally used cytotoxic drugs and novel targeted chemotherapeutics [38,43]. But as these agents showed no survival benefit in clinical trials, the hypothesis of a possible delivery problem of chemotherapeutics across the blood-brain-barrier (BBB) arose, a paradigm that dominated DIPG research in the past decades.

In our molecular imaging study (**Chapter 3**), the first to have been performed in children, we challenged the reigning hypothesis of a drug delivery problem through the assumedly intact BBB. The results showed that indeed there is considerable heterogeneity among patients, and within tumors, in drug uptake of zirconium-89 (<sup>89</sup>Zr)-labelled bevacizumab. The overall limited uptake of <sup>89</sup>Zr-bevacizumab could explain the lack of effect in clinical trials [44–47]. With only seven patients in this pilot study, however, more extensive studies are needed to determine the correlation between <sup>89</sup>Zr-bevacizumab-uptake and response, or survival, upon bevacizumab treatment. Also, linking molecular imaging studies to biopsy data, enabling direct correlation between the displayed drug uptake and tumor characteristics, as done in our case report (**Chapter 6**), should be considered in future studies. Although this latter study concerned a single case, the results showed that vascular proliferation is an important, yet not the only, determinant of intralesional heterogeneity in <sup>89</sup>Zr-bevacizumab uptake. Current case, unfortunately, did not allow for one-on-one analysis of BBB integrity.

With our  $^{89}\text{Zr}$ -bevacizumab PET study we aimed to encourage other research groups to develop molecular imaging studies since these type of studies can be helpful in any clinical trial investigating chemotherapeutic agents, in any type of childhood cancer. Our pilot study has already been expanded to include pediatric non-pontine HGG. Moreover, the possibility of labeling other, seemingly promising, monoclonal antibodies and tyrosine kinase inhibitors, which are currently tested in clinical trials for DIPG, is being explored. Future studies may also be directed at investigating drug-uptake concomitant to radiotherapy, since radiation is known to increase the permeability of the BBB [48]. By showing that the procedures are feasible in children, we have paved the way for other groups (also those investigating other types of pediatric solid tumors) to develop molecular imaging studies. And by determining the optimal moment of scanning, a first step has been made towards optimization of the study procedures and decrease of the patient's burden, both in time, and in terms of mean effective radiation dose. In this respect, future  $^{89}\text{Zr}$ -bevacizumab PET studies will only require one PET-low dose CT of the brain, instead of three full-body scans, as performed in this first pilot.

In the aim to overcome a possible delivery problem of chemotherapeutics, several strategies have been explored in the field of DIPG research. These strategies were aimed at overcoming the (largely intact) BBB by using high-dose chemotherapy with stem cell support, by modifying drugs to enhance their permeability, by temporarily disrupting the BBB, by altering the efflux transporters, or by using local delivery methods, such as convection enhanced delivery (CED) [49–51]. Especially the latter has received considerable attention in the field of DIPG research and seems a promising approach to enhance the potential of chemotherapy. To identify potential drug candidates for CED, we developed a theoretical model including all physicochemical properties that influence passive diffusion (upon systemic drug delivery) or active drug distribution (upon CED) (**Chapter 8**). This study shows that carmustine, etoposide, tacrolimus, temsirolimus, cabazitaxel, cytarabine, gemcitabine, carboplatin and cisplatin are potential candidates for CED. Moreover, the model shows that the majority (i.e., 85%) of drugs that historically have been administered systemically are not likely to cross an intact BBB. Although the study was primarily aimed at creating awareness for the influence of physicochemical properties of anti-cancer drugs on drug-uptake and the potential of alternative drug delivery techniques, we encourage the use of this model to support choices in the design of high-throughput screening studies of candidate therapies in patient-derived DIPG cell cultures and xenograft models, as well as future clinical trials. Especially when combinations of systemic and local drug delivery techniques are envisioned, the model may support the selection of the right drug for the right treatment modality.

## IMPLICATIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Based on the research described in this thesis, a number of implications for future DIPG research are summarized here.

- Until the etiology and pathophysiology of DIPG are fully unraveled, the inclusion criteria for epidemiological registration in the SIOPE DIPG Registry should be as broad as possible. It is tempting to jump to conclusions, for instance about common patient subgroups, and to proceed to exclude patients who do not seem to fit today's pattern. But the key to unraveling this disease may still present itself in an unexpected, as yet unidentified, form. On the other hand, in clinical trials, we must take into account that evidence is now available on the existence of patient subgroups, and we must acknowledge that evidence has been acquired in other cancers that different subgroups may have specific sensitivities to certain therapies. It is therefore paramount to establish international consensus on specific inclusion criteria for clinical trials, in order to prevent heterogeneous application, leading (again) to incomparability of data.
- It is important to realize that the current content of the variables included in the SIOPE DIPG Registry is based on contemporary knowledge. It is likely that new discoveries will be made and that variables will have to be modified or added. The Registry will therefore need to be actively adjusted based on increasing knowledge. This applies especially to biological variables. The Registry might also be extended to the registration of patients with non-pontine diffuse midline gliomas or adult patients with DIPG. And, with the ever-advancing modalities in imaging of brain tumors, the Imaging Repository will likely be adjusted to include novel imaging techniques or sequences.
- Clinical research into DIPG should be primarily focused at efficient use of the valuable information that can be obtained from this vulnerable group of patients. Consistency in research protocols may contribute to this purpose. Also, alternative methods, other than the traditional controlled trials, should be designed with the intent of minimizing the number of patients, or time needed for recruitment and conduction of clinical trials, and maximizing the statistical efficiency of study analyses [52–57]. In this respect, trials may be more efficiently expedited by using the recently established multi-national setting of the SIOPE DIPG Network or the DIPG Registries. At the same time, research into DIPG should be designed to allow for the rapid and severe deterioration of patients. To not miss out on information of patients who become clinical trial dropouts, all patients should be offered registration in the SIOPE DIPG Registry.

- Clinical trials should offer standard biopsy procedures by specialized neurosurgical teams. This will serve multiple goals. First, for the majority of patients it will serve as diagnostic confirmation of the type of histone H3 K27M mutation and further genetic characterisation, possibly leading to a more specified classification and potentially even subgroup-specific therapies in the future. Secondly, it will lead to more tumor material for the development of representative, possibly subgroup-specific, cell cultures and animal models, which enable high-throughput screening of candidate therapies. It should, however, be taken into account that currently, biopsies are not possible in all situations (especially in non-academic centers, less-developed countries, or in severely ill patients). Although we advocate centralization of DIPG patient care in a limited number of specialized pediatric cancer centers, the condition of the patient may result in a preference for treatment close to home. Biopsies should be encouraged, but it is debatable whether biopsies should be mandatory for the inclusion in clinical trials, as it would reduce the eligible research population resulting in bias due to selective inclusion. We are currently investigating the sensitivity and specificity of alternative, blood-based “liquid biopsy” techniques, aimed at harvesting free circulating or tumor-exosome-derived RNA and/or DNA. If proven to adequately reflect the genetic make-up of DIPG tumors, this technique is much less invasive, and might therefore drastically increase the number of eligible patients. Also, it may allow for serial biopsies and thus longitudinal molecular analysis of DIPG [58].
- Ideally, all clinical trials, in which chemotherapeutic agents are administered to DIPG patients, should be primarily directed at obtaining information on drug distribution (providing information on potential toxicity) and actual tumor targeting (providing information on potential efficacy). In current practice, such information is mostly obtained from adult studies and directly translated to the pediatric setting. Information on drug potential may be obtained by conventional Phase 0 pharmacokinetic (PK)/ pharmacodynamic (PD) studies [59]. However, since PK/PD studies usually start with low doses of the drug, these studies are not expected to benefit the patients personally. In that case Medical Research Ethics Committees require minimal objectives for patients that consent to participate. A less invasive option to assess target expression, drug distribution and actual tumor targeting is now provided by the successful introduction of molecular drug imaging in children (**Chapter 3**), introducing for the first time a potential imaging biomarker to investigate drug toxicity and efficacy. Molecular drug imaging studies might in the future also facilitate easy selection of the right drug for the right patient with any type of brain- or solid tumor. The introduction of on-therapy biopsies combined with molecular imaging studies may even enable direct correlation between the observed drug uptake, drug concentration and local tumor characteristics.

- An important necessity in clinical DIPG research is the establishment of reliable markers for response. Currently, clinical trials mostly use endpoints based on time-to-event, such as progression free survival (PFS) and overall survival (OS) (**Chapter 2**). These however, do not directly reflect the effect of the applied treatment. Both PFS and OS are, among other things, influenced by the natural course of the disease (i.e., by the potentially confounding effects of prognostic factors). Especially OS is also influenced by subsequent second- or third-line treatments, and possibly by the use of steroids (i.e., by potential confounding effects of additional therapies). Moreover, determination of PFS and OS may require a long follow-up. And finally, PFS and OS may change over the course of decades, based on improved general health status or supportive care, which limits their usefulness in retrospective meta-analysis. The development of more direct (bio)markers for response may be facilitated by the implementation and integration of improved technology, such as advanced imaging techniques (**Chapter 3 and 4**) or by the previously discussed liquid biopsy technique.
- More prospective studies should be employed into the use of steroids, quality of life, and palliative care in DIPG patients. Our first studies, described in **Chapter 9 and 10**, provide a list of focus points to be addressed in working towards the development of evidence-based, disease-specific, multi-institutional and multi-national guidelines. First, more precise data should be obtained to enable further study of the current needs of DIPG patients and families. To this aim, web-based quality of life assessments will be integrated into the SIOPE DIPG Registry, using the Quality of Life Childhood Oncology (QLIC) application ([www.hetklikt.nl](http://www.hetklikt.nl)). The QLIC application is a tool to monitor and identify Health Related Quality of Life (HRQOL) issues in children via standardized questionnaires. In working towards evidence-based information and clinical guidelines on the optimal use of steroids, collaborative clinical studies will very likely need to be developed. In this respect, steroid alternatives, such as boswellic acids, osmotic diuretics, mannitol, acetazolamide, celecoxib, bevacizumab, spironolactone, losartan and high-dose bicarbonate also need further research [60].
- Finally, there are dilemmas to be taken into account in future clinical research. Considering the rapid developments in the field of DIPG research, we have to ask ourselves how many concurrent and even conflicting trials we may offer to DIPG patients and their parents. On the one hand, having a range of trial options provides patients and families with the opportunity to make choices based on the child, the situation, family status, lifestyle or work- and financial considerations. Trials in which the investigated treatment modality and the patient burden greatly differ (i.e., a (re-)irradiation trial versus systemic chemotherapy versus CED) provide

families with these choices. On the other hand, trials that are largely similar (i.e., radiotherapy and temozolomide, radiotherapy and thalidomide, radiotherapy and etc.) complicate parents' choices because the scientific evidence on possible benefit is currently lacking. Treating physicians can never decide what is best for a family. We must therefore ensure that we optimally inform patients and parents about the possibilities, both locally and abroad, together with evidence-based considerations on possible benefits and disadvantages. In a first aim to support patient and parents' decisions concerning informed cost-benefit choices, the DIPG Registry website ([www.dipgregistry.org](http://www.dipgregistry.org)), which was created by the International DIPG Registry team, may serve as a common resource to families and medical professionals from around the world, providing a quick conduit for asking scientific, or treatment-related, questions, or for requesting formal neuro-oncological consultation. Especially in DIPG treatment and research, it is very important to stay close to the patients' wishes and to those of his or her parents.

## CLOSING REMARKS

For decades, DIPG research has stagnated through lack of tumor tissue and limited number of patients in heterogeneous clinical trials. In recent years, progress has been made thanks to new technical possibilities and increased availability of data, leading to enhanced knowledge on patient subgroups. Uncovering mysteries, however, simultaneously leads to a large number of new questions and it feels as if we are still a long way off from the day that we can cure a child who is struck by this disease. Nevertheless, over the past four years, with the establishment of the SIOPE DIPG Network, the SIOPE DIPG Registry and Imaging Repository and Interantional DIPG Registry, the foundation has been laid for an efficient, multi-disciplinary research-infrastructure to facilitate the design and execution of high-quality laboratory and clinical studies. This infrastructure will also allow for research transparency, international collaboration and the elimination of duplication of research efforts. Joining forces within an international research-infrastructure stimulates the initiation of, and active accrual in, international multicenter trials, with sufficient power to address the many, yet unanswered, questions. This, together with the recent evolution of ideas concerning therapeutic strategies, should facilitate the identification, and selection, of novel tolerable and effective therapies. All of this with one aim: a cure for children with DIPG.

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