A SIOPE Registry for Diffuse Intrinsic Pontine Glioma (DIPG)

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1. INTRODUCTION AND RATIONALE

1.1 Relevance

Malignant brainstem glioma represents 10 to 15% of all paediatric central nervous system tumors. Eighty percent of these brainstem gliomas occur in the pons\(^1\). From the patients with pontine glioma (PG), few have a focal pontine tumor, and the majority (80-90%) of patients have a diffuse intrinsic pontine glioma (DIPG)\(^2\). Children suffering from DIPG face a dismal prognosis, with a median overall survival (OS) of approximately nine months and a two-year OS of less than 10%.

*Figure 1. MR-image of a focal\(^3\) (left panel) and diffuse intrinsic\(^4\) (right panel) pontine glioma.*

In children suspected of a pontine tumor, the diagnosis can generally be made on the basis of clinical presentation and MR-imaging (Figure 1). Because of this, and due to the perceived risk of morbidity, biopsy is rarely employed in these patients. However, the resulting scarcity of tumor samples has hampered research on the genetics and biology of DIPG. In the recent years, more insight was gained on molecular aberrations in these tumors, which resulted in the discovery of histone 3 mutations in DIPG and paediatric high-grade gliomas (HGG)\(^5,6\). The evolving knowledge about the true nature of these tumors results in a constant adjustment of classification systems and an ongoing debate about inclusion-, exclusion- and response criteria used in clinical trials. Thus far, no prospectively gathered large data sets are available that define prognostic clinical and biological markers in DIPG.

The current consensus regarding the radiographic definitions is as follows:

*Classical DIPGs*  
- Arise from the pons, and occupy its majority (typically 2/3 or more);  
- are infiltrative in nature: they readily extend superiorly into the midbrain, even the cerebral
peduncles, and beyond; posteriorly into the cerebellar peduncles and cerebellar hemispheres; and less commonly inferiorly into the medulla;
- can grow in an exophytic fashion; either anteriorly (where it can surround the basilar artery); laterally (into the CP angle cistern); less commonly posteriorly (bulging into the fourth ventricle);
- have features of hypocellular tumors, with lower proliferative rates and angiogenesis than is observed in high grade gliomas and glioblastomas (GBM);
- show hypointensity on T1 images;
- show hyperintensity on T2 / FLAIR images, unlike cellular tumors (e.g. GBM or PNET);
- usually (not always) do not show bright signal on diffusion images (baseline ADC values consistent with hypocellular tumors);
- have MRS findings suggestive of proliferative rates (modest increases in choline, decreases of NAA);
- appear hypoperfused (low relative cerebral blood volume) when studied with perfusion MRI, consistent with limited angiogenesis observed in lower grade glial tumors;
- do not show prominent enhancement (involving from zero to 25% of the tumor volume in on average);
- rarely show cysts and necrosis at presentation.

Consequently, focal/atypical DIPGs
- Have prominent enhancement characteristics;
- show extreme homogenous hyperintensity;
- have cysts, which can be seen in high grade gliomas, GBM, PNET, but also pilocytic astrocytomas);
- have low T2/FLAIR signal, and/or high signal on diffusion images (restricted diffusion, elevated ADC), encountered in the higher grade gliomas, GBM, also PNET;
- have significant cystic components (often seen in pilocytic astrocytoma).

The exact incidence of DIPG in Europe is unknown. Information regarding epidemiology is scant and mostly based on research conducted in USA and Canada. With an incidence of 100-150 DIPG patients per year in the USA (0.32 - 0.48 per million)^7, it is estimated that in Europe (with 739.2 million residents; 2011) 240-355 children are diagnosed each year. In line with this estimation, a recently conducted retrospective analysis in the Netherlands confirms the expected incidence of 5-8 patients each year^8.

Treatment options for children with DIPG are limited. The persistent dismal perspective comes from both the unresectability of these tumors, due to its delicate location in the pons, and an alleged resistance to chemotherapy, possibly due to an intact blood-brain barrier. Radiotherapy therewith remains the primary treatment approach, although this can only temporarily improve symptoms.

Despite several new treatment strategies that have been applied, the prognosis of children suffering from DIPG remained unchanged in the past thirty years^1-7. New treatment strategies, however, are mostly not applied in the setting of a (randomized) controlled clinical trial. In our recently conducted retrospective evaluation of the current approach of children suffering from DIPG in The Netherlands,
we observed a wide variety of single patient, hospital based treatment schedules instead of treatment in the setting of an official clinical trial.

We believe there are three components that contribute to the current “heterogeneous” state of affairs instead of the application of randomized controlled trials:

- First, the limited number of clinical trials could very well be a result of the low incidence of DIPG. When diagnosing only one patient each year, one might be less inclined to work at the development of clinical trials. Also, in (single center) trials, the low incidence probably results in low inclusion rates, long duration and a limited power of the trial.

- Second, the rarity, but also the severity of the disease, plus the fact that it mainly affects children, makes it ethically less attractive to perform randomization. The trials conducted in this field of research are therefore mostly single arm trials.

- Third, through the varied use of inclusion-, exclusion-, and response criteria, studies conducted in different centers and countries are incomparable.

To conclude, we believe these components may be partly responsible for the emergence of a wide variety of single center and single arm studies, which are difficult to compare.

- We therefore developed a DIPG registry, the SIOPE DIPG Registry, allowing for collaboration in the conduct of substantiated international prospective clinical trials. Also, data of trial and non-trial patients is collected in a collaborative and structured way.

- This collaborative database will enable reliable, matched-pair analyses in future single arm studies to provide an alternative to randomized studies. In fact, the Paediatric Committee (PDCO) of the European Medicines Association (EMA) has stated that it encourages the development of a database to improve statistically valid comparisons of studies in rare diseases such as DIPG.

- Finally, the SIOPE DIPG Registry allows for the analysis of data concerning baseline characteristics, clinical presentation, radiological characteristics, tumor biology and response, to create international consensus on criteria used in clinical trials, and to retro- and prospectively ascertain clinical and biological parameters that are predictors of therapy response. In retrospect we might even be able to (better) differentiate successful from less successful treatment options.

1.2 Aim

The aim is to provide a comprehensive dataset to allow for international collaborative research in the field of DIPG. The SIOPE DIPG Registry was developed based on international agreements, made by a Network of experts studying and treating DIPG; the SIOPE DIPG Network.

Main objectives and goals of creating the SIOPE DIPG Registry are:
- Collecting data from local hospitals, national registries and multiple clinical trials
- Better understanding the biology and clinical features of DIPG
- Developing new approaches to diagnosis, response assessment, multidisciplinary treatment and follow-up
- Developing more effective therapies that will improve survival

The work of the SIOPE DIPG Registry will therefore include:
- Recruiting all patients diagnosed with DIPG, both in and outside trials
- Collecting data from all patients enrolled in the registry
- Establish and support research collaborations
- Conduct hypothesis-driven international clinical trials

We believe that the SIOPE DIPG Registry will be of great importance for conducting joint trials. These joint trials are necessary to differentiate between successful and less successful treatment options, in the hope to eventually improve treatment options for children suffering from this rare, but devastating, disease.
2. DEVELOPMENT OF THE SIOPE DIPG REGISTRY

2.1 Background

In 2011, a group of paediatric oncologists, paediatric neurologists, radiotherapists, biologists and others, motivated to carry out excellent clinical and biological research in the field of DIPG and to collaborate with colleagues around the world, created a collaboration, the SIOPE DIPG Network. The SIOPE DIPG Network is a sub-committee of the high-grade glioma (HGG) working group of the Brain Tumour Group (BTG) of the International Society of Paediatric Oncology Europe (SIOPE), committed to supporting and fostering the mission of the Society. The Network, initiated in VU University Medical Center (VUmc) in Amsterdam, was initially composed of participants from the Netherlands, UK, Belgium, France, Germany, Italy and Spain. Over the years more and more countries joined the SIOPE DIPG Network. The Network now encompasses 23 European and 3 non-European countries (in green, Figure 2), and has the ultimate ambition to extend its activities to Eastern European countries in the near future.

![Figure 2. The SIOPE DIPG Network](image)
Within the SIOPE DIPG Network, the objectives for a SIOPE DIPG Registry and website were defined:

1. **From research perspective:**
   - To create a resource for those interested in research into DIPG by sharing knowledge and experience and by collecting comprehensive data on all DIPG patients.
   - To initiate biological studies.
   - To initiate collaborative clinical trials with uniform inclusion and exclusion criteria, response criteria and endpoints.
   - To disseminate information to physicians, patients, and parents.

2. **From clinical perspective (i.e., medical professionals / treating physicians / parents / patients):**
   - To create a resource concerning diagnosis, second opinions, treatment options, ongoing clinical trials and additional care for DIPG patients.
   - To create the opportunity to include patients in the Registry and share comprehensive data for research.

Since the first SIOPE DIPG Network international meeting in 2011, a lot of effort was made to develop uniform international agreements for collaborative research purposes. The agreements do not only concern what data are collected and how it will be done, but also responsibility and ownership, as addressed in Appendix 1 (Bylaws) and 2 (Regulatory document). In the beginning of 2012, standardized Case Report Forms (CRFs) with minimal required data were created in order to allow the inclusion of uniform data. The CRFs were developed in parallel and in consultation with the International DIPG Registry (covering the registry of DIPG patients from the USA, Canada, and Australia). In July 2012, DCOG/SKION, KPMG and several ICT specialists offered their help to coordinate the actual development of the SIOPE DIPG Registry, funded by Stichting Semmy and The Cure Starts Now Foundation. To secure each party’s rights and responsibilities during the development and use of the SIOPE DIPG Registry, international legal counsels attended DIPG registry development meetings and critically reviewed the SIOPE DIPG Registry Regulatory Document and SIOPE DIPG Network Bylaws. Together, these parties have developed the infrastructure and therewith a solid basis of an online SIOPE DIPG Registry, which is now ready for use. Ongoing financial support from Stichting Semmy and the DIPG Collaborative has secured full operationality of the SIOPE DIPG Registry already up to 2019.

### 2.2 The SIOPE DIPG Registry

The SIOPE DIPG Registry consists of two entities:

- **An online CRF-structured web application and database for clinical data (www.dipgregistry.eu):**
  Clinical data will be collected by use of standardized Case Report Forms (CRFs). The CRFs have been developed by the SIOPE DIPG Network in close collaboration with colleagues from the USA and Canada. No personal identifiers are included in these CRFs.
- **An imaging repository and analysis system for radiological images**

  MRI images will be uploaded in the imaging repository via a secure FTP server or via CD’s. No personal identifiers are included in these images. Review of these images is performed by a team of international neuroradiologists for definitive review in the Registry. Banked images can furthermore be used for research and educational purposes, improving radiology diagnostics of these tumors.

In the future, the clinical database and Images Repository are to be linked to databases that contain biological data from tumor samples (biopsy and/or autopsy) and data from an online Quality of Life Survey System.

### 2.3 Population

All paediatric patients with focal and diffuse intrinsic pontine gliomas are eligible for the SIOPE DIPG Registry. In order to be able to classify patients, a minimum of diagnostic criteria is required; i.e. clinical and radiological data (MRI images) and, if available, pathology data.

**Inclusion criteria:**
- Patients with Diffuse Intrinsic Pontine Glioma (DIPG)
- Patients with Focal Intrinsic Pontine Glioma (fPG)
- Age between 0 and 21 years
- Informed consent (in case of prospective registration - Paragraph 2.4)

**Exclusion criteria:**
- Pilocytic (grade 1) astrocytomas
- Neurofibromatosis type I

### 2.4 Project phases

The start and future use of the SIOPE DIPG Registry has two phases:

1. **A retrospective cohort.** In this “pilot” phase we aim to include all patients diagnosed between 1990 and 2015. This will provide data of (mostly deceased) patients, which are added to the Registry anonymously. For this, no informed consent is mandatory.

2. **A prospective registration.** Once in a particular country/hospital all legal and ethical agreements are approved, Local Coordinators are encouraged to prospectively include all patients diagnosed with DIPG after he/she has informed parents (and patients), after he/she provided the Patient Information Form and requested for Informed Consent (Appendix 3; English PIF for parents and patients aged 12-18 years).
All physicians treating children with DIPG are asked to inform their patients about the SIOPE DIPG Registry. Patients, however, may reject participation. In that case we do ask Local Coordinators to report the patients and obtain a unique Registry number via the DIPG Registry website. The Registry number and (minimal) registration data will be used for epidemiologic studies only.

2.5 Number of expected registered patients

In the retrospective phase, we expect to include about 150-200 patients per year, diagnosed with DIPG between 1990 and today, potentially resulting in a total number of 3750 – 5000 retrospective cases.

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<thead>
<tr>
<th>Country</th>
<th>DIPG / year</th>
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<tr>
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Figure 3. Estimated incidence of DIPG per country and by countries currently (2015) included in the SIOPE DIPG Network, indicated by ‘e’.

The number of inclusion in the prospective phase is more difficult to indicate. Based on the projected incidence of 100-150 patients per year in the USA (0.32-0.48 per million), it is estimated that each year 267-400 children in Europe, Turkey and Russia are diagnosed with DIPG. Based on the estimated DIPG incidence in participating countries in the SIOPE DIPG Network (83%, 222 – 332 per year, Figure 3), we expect to include 110-165 (50%) per year in the first years. In the future we expect to expand the Network and prospectively include even more patients per year in the Registry.
2.6 What data will be collected?

2.6.1 Medical data in the online CRF-structured web application

Complete data collection will include: demographics (country, referring center, age, gender, date of initial diagnosis, time from first presenting symptoms, relevant past medical history & family history, etc.), symptoms & signs at diagnosis and their duration, MRI features at diagnosis and during disease (including, if available, advanced imaging techniques), treatment regimen, and clinical and radiological response to treatment. All items, some of which mandatory, are included in web-based CRFs.

A SIOPE DIPG Registry Data Entry Manual will be available and sent to every participating site. This manual will provide extensive guidelines for data entry.

2.6.2 Data concerning “Imaging assessment”

Data from the original radiologic reports (MRI a/o MRS/PET) at time of diagnosis and data concerning radiological response evaluation will be collected in the appropriate sections of the online CRF-structured web application.

In addition, all MRI will be uploaded in the imaging repository. No personal identifiers are included in these images.

An international Radiology Review Board will be assembled to conduct imaging review of submitted cases. The Radiology Review Board consist of (neuro-)radiologists, from multiple countries, who have considerable knowledge, expertise and experience in the evaluation of images concerning diffuse intrinsic pontine glioma (DIPG). The neuro-radiologists will be provided access to view the anonymized images. Their review will be entered as a definitive review report in the SIOPE DIPG Registry.

2.7 Safety of data

The SIOPE DIPG Registry’s framework provides a stable, secure and generic basis in many of its products. Experts in the field of sensitive data transfer and access rights have been consulted to certify issues concerning data anonymization, -collection, and -safety. The SIOPE DIPG Registry therewith meets European standards.
3. ETHICAL CONSIDERATIONS

The SIOPE DIPG Registry will be conducted according to the principles of the Declaration of Helsinki. Each participating site will therefore pledge to uphold the principles of Good Clinical Practice and follow all necessary regulatory requirements.

All data of DIPG patients will be submitted anonymized.

In the prospective registration, patients ages 12-18 and/or parents will sign informed consent (Appendix 3).

Registration will do no harm to the individual patient. Patients will undergo planned treatment provided by their personal physician. A single patient has no benefit from centralized data collection, but provides the needed data in aim to cure DIPG in the future.

4. REFERENCES


Appendix 1

Bylaws of the SIOPE DIPG Network
Appendix 2

DIPG Registry and Imaging Repository Regulatory Document
Appendix 3

Patient Information Sheets & Informed Consent Forms