CHAPTER 9

Palliative and end-of-life care for children with diffuse intrinsic pontine glioma: Results from a London cohort study and international survey

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ABSTRACT

INTRODUCTION More than 90% of patients with diffuse intrinsic pontine glioma (DIPG) will die within 2 years of diagnosis. Patients deteriorate rapidly during the disease course, which severely impairs their quality of life. To date, no specific research on this clinically important subject has been conducted. This study aimed to compile an inventory of symptoms experienced, interventions applied, and current service provision in end-of-life care for DIPG. **METHODS** We performed a retrospective cohort study of children with DIPG, aged 0–18 years, who received treatment under the care of 2 London hospitals. Symptoms, interventions, and services applied during the 12 weeks before death were analyzed. In addition, we conducted a global questionnaire-study among health care professionals. **RESULTS** In more than 78% of DIPG patients, problems concerning mobility, swallowing, communication, consciousness, and breathing arose during end-stage disease. Supportive drugs were widely prescribed. The use of medical aids was only documented in 15% of patients. Palliative and end-of-life care was mostly based on the health care professional's experience; only 21% of the questionnaire respondents reported to have a disease-specific palliative care guideline available. **DISCUSSION** This research assessed the current state of palliative and end-of-life care for children with DIPG. Our results show the variability and complexity of symptoms at end-stage disease and the current lack of disease-specific guidelines for this vulnerable group of patients. This first descriptive paper is intended to act as a solid basis for developing an international clinical trial and subsequent guideline to support high-quality palliative and end-of-life care.

INTRODUCTION

Despite decades of clinical research, the dismal prognosis and inevitable neurological decline has not changed for patients suffering from diffuse intrinsic pontine glioma (DIPG) [1,2]. Tumor growth and associated peritumoral edema lead to serious dysfunction of internal pontine and brainstem structures. The pons regulates vital autonomic functions, contains nuclei of the cranial nerves, and serves as a bridge for neuronal tracts from the brain to the spinal cord. Local disturbance results in symptoms that severely affect the child's daily functioning and quality of life, especially at end-stage disease. To the best of our knowledge, no data have been published that describe the symptoms in DIPG patients at end-stage disease and, most importantly, the associated specific needs for palliative and active end-of-life care.

Eighty-nine percent of parents whose child died of cancer report at least one distressing symptom in the last month of life [3]. Since DIPG is a rapidly progressive and severely disabling disease, it is important to examine the disease-specific distressing symptoms and their evolution over time to optimally anticipate the interventions and services needed for holistic palliative and active end-of-life care as defined by the World Health Organization (WHO) [4]. Currently, radiotherapy may temporarily reduce symptoms for DIPG patients, but premature death remains inevitable. This raises the important questions of when to introduce the concept of palliative care and when a more active end-of-life phase is indicated. The aim of this first study was therefore (*i*) to investigate DIPG-specific symptoms and their evolution during the 12 weeks before death, (*ii*) describe the current palliative and end-of-life care approach, including the timing of initiation and the use of clinical guidelines, and (*iii*) evaluate the potential need for uniform international disease-specific palliative and end-of-life care guidelines for DIPG.

METHODS

To obtain disease-specific data, a retrospective cohort study was performed. This study was supplemented with an online international questionnaire among health care professionals to ascertain information on the (multi-)institutional and (multi-)national approach to palliative care for DIPG patients, availability of clinical guidelines, and possible gaps in the current organization of care.

Retrospective cohort study

This study was approved by the institutional review boards of the Royal Marsden Hospital and Great Ormond Street Hospital. A retrospective chart review was performed for children with DIPG who were diagnosed between 1996 and 2011. Eligible patients

were those aged 0–18 years receiving palliative care following the diagnosis of a typical DIPG on MR-imaging, defined as a T1-weighted hypointense and T2-weighted hyperintense tumor with at least 50% involvement of the pons on T2 as confirmed by the local radiologist [5].

For each patient, demographics and clinical data, including all symptoms and applied interventions, covering the period of the last 12 weeks (i.e. 3 months) until death, were extracted from case notes for further analysis. In addition, data on the disease course (i.e. progression-free survival [PFS] and overall survival [OS]) were obtained. The date of diagnosis was defined as the date of the first MRI. Progressive disease was defined as clinical disease progression (i.e. increase of symptoms or new symptoms) and/or radiological tumor progression as obtained from the patient records and radiology reports. When available, the dates of treatment and date of initiation of active end-of-life care were obtained. In both institutions, poor-prognosis patients and their families were introduced to the pediatric oncology outreach and palliative care team at the time of diagnosis. This team provides oncology outreach and symptomatic supportive care from diagnosis; as disease progresses, the focus of care shifts to active palliation and end-of-life care. Following identification of disease progression, the date at which the palliative care team renewed patient contact was defined as the point of initiation of active end-of-life care.

Online international questionnaire

In addition to the analysis of patient data, an online questionnaire was conducted among health care professionals specializing in DIPG (Supplementary Material; available from: https://www.ncbi.nlm.nih.gov/pubmed/26459800). The questionnaire provided information about the local approach to palliative care, including interventions and clinical guidelines, and the expert's experience of acknowledged anticipated signs and symptoms in DIPG patients. The questionnaire was primarily distributed via the International Society of Paediatric Oncology (SIOPE), Europe's DIPG Network, which currently includes 20 of the 28 European Union member states, and three non-EU-member states (Iceland, Russia, and Turkey). Via this Network, the questionnaire was distributed worldwide using electronic mailing lists from SIOPE, the International Society of Pediatric Neuro-oncology (ISPNO), and the International Brain Tumour Alliance (IBTA).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp). Patient data regarding demographics, symptoms, and interventions were first analyzed by descriptive statistical methods. Subsequently, for each of the 6 most

prevalent symptoms, their weekly presence from week 12, and daily presence in the last week prior to death were scored. With these data, logistic generalized estimating equation (GEE) analyses were run to display the evolution over time at end-stage disease. As a result of the logistic GEE analyses, the probabilities of having a symptom at different time points were calculated. PFS and OS were estimated using the Kaplan-Meier method. For the questionnaire study, descriptive statistics were conducted.

RESULTS - RETROSPECTIVE COHORT STUDY

Patient population

Sixty-three patients met the criteria for inclusion in the study from the Great Ormond Street and Royal Marsden Hospital cohorts (Table 1).

TABLE 1 | Demographics.

Characteristic	
Number of DIPG patients	63
Age (SD in years)	7.2 (3.6)
Gender (male/female)	35 / 28
PFS (Q1 - Q3[a] in months)	5.7 (3.6 - 8.1)
Median OS (Q1 - Q3 in months)	7.9 (5.3 - 10.7)

DIPG: diffuse intrinsic pontine glioma; OS: overall survival; PFS: progression-free survival; SD: standard deviation. [a]Quartile 1 – Quartile 3.

DIPG-specific symptoms at end-stage-disease

Patients experienced an average of 13 symptoms (range: 5–19) during the 12 weeks prior to death. The most common symptoms were impaired mobility, dysphagia, dysarthria, communication difficulties, loss of consciousness, and breathing difficulties (Table 2). The results from the GEE analyses on these symptoms display their evolution over time during the 12 weeks before death (Fig. 1A and B). The trajectory and duration of DIPG-related problems varied according to the individual deficits, with mobility problems occurring 3 months before death in many patients. Problems with speech, swallowing, and (nonverbal) communication started to arise around 8 weeks prior to death, and in the days immediately preceding death there was a steep increase in the incidence of breathing difficulties and loss of consciousness.

TABLE 2 | Occurrence of symptoms in diffuse intrinsic pontine glioma patients during last 12 weeks of life.

Symptoms	% of patients
Impaired mobility (e.g. paresis)	90
Dysphagia	83
Dysarthria	79
Communication difficulties (i.e. verbal and non-verbal)	79
Unconsciousness	79
Breathing difficulties	78
Nutrition problems	63
Headache	45
Visual impairment	45
Vomiting	39
Spasticity	39
Nausea	29
Constipation	26
Pyrexia	26
Behavior abnormalities	25
Urinary retention	23
Posturing (e.g. decorticate/decerebrate)	22
Neuropathic pain	21
Dehydration	21
Urinary incontinence	20
Seizures	17
Coughing	15
Pneumonia	10
Diarrhea	10
Decubitus (confined to bed)	9
Hearing loss	4
Depression	4

Interventions at end-stage-disease

Analysis of the patient charts showed a wide variety of prescribed drugs and applied interventions (Table 3). Analgesics were prescribed in all DIPG patients, antiemetics in 94%, and antisecretory drugs in 81%. Other commonly prescribed medications included steroids (57%) and anticonvulsants (47%). Medical aids to support communication, vision, or hearing were not commonly recorded as being used. The use of aids to support mobility problems (e.g. wheelchairs, commodes, etc.) or feeding (e.g. nasogastric tubes or gastrostomy) were not specifically documented in the patients' charts but were known to have been used.

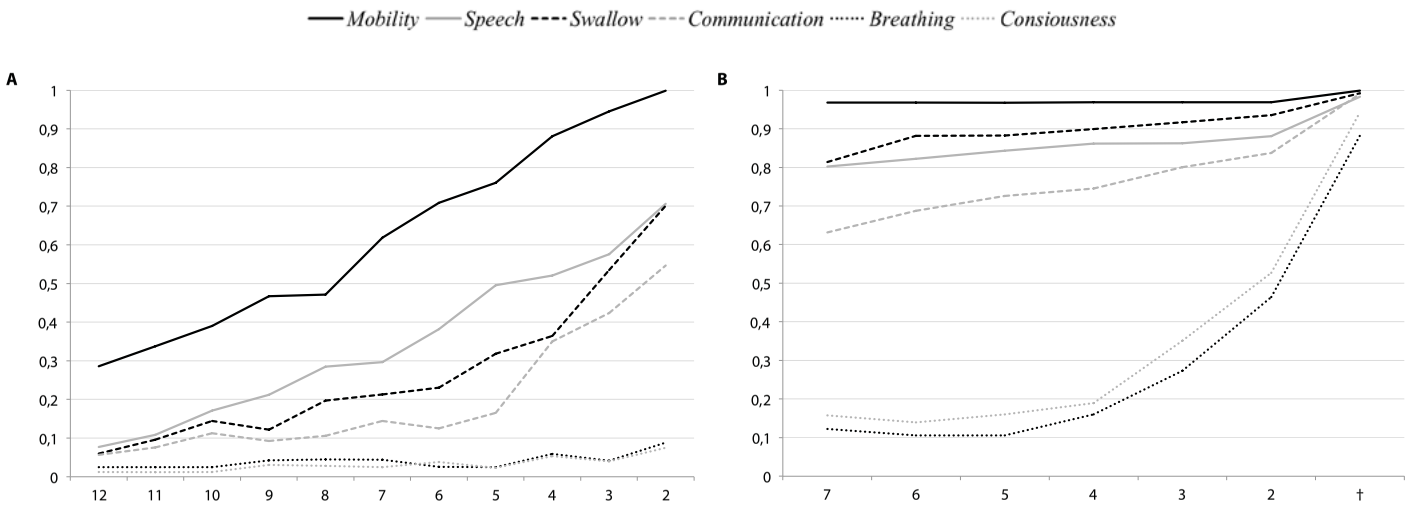

FIGURE 1 | Estimated probabilities of the 6 most frequent symptoms as a result of logistic generalized estimated equation analysis. Evaluation of symptoms in diffuse intrinsic pontine glioma patients during the last 12 weeks **(A)** and last days **(B)** prior to death.

TABLE 3 | Interventions applied during last 12 weeks of life.

Interventions	% of patients
Analgesics	100
Antiemetics	94
Antisecretory drugs	81
Steroids	57
Anticonvulsants	47
Laxatives	45
Nasogastric feeding	29
Sedatives	26
Communication aids	15
Visual aids	11
Antidepressants	3
Hearing aids	0

Timing of palliative care

Figure 2 shows the relationships between the disease course, the timing of anticancer treatment, and the commencement of palliative care and the active end-of-life phase. In 52 patients (83%), active anticancer treatment was given up to a median of 5.4 months (i.e. 22 weeks) before death. Disease progression started at a median of 2.5 months (i.e. 10 weeks) before death in 60 patients (95%). The time at which active end-of-life care was initiated was only recorded in 29 charts. There was a median duration of 0.8 months (i.e. 24 days) between the formal initiation of active end-of-life care and the date of death.

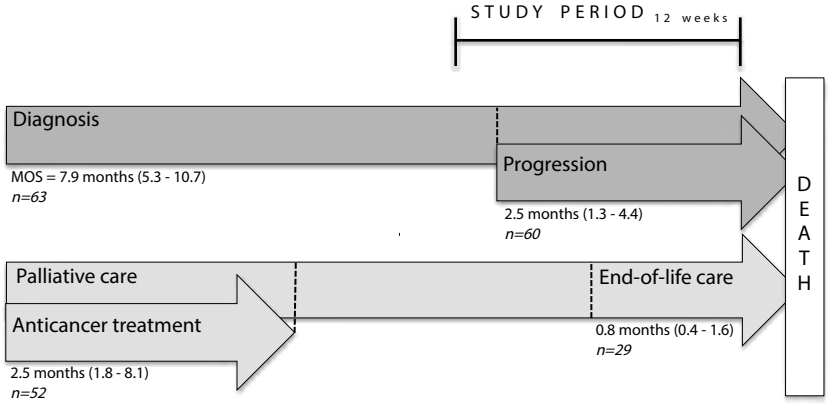

FIGURE 2 | Disease course and treatment.

MOS: median overall survival in months (Quartile 1 – Quartile 3); n: number of patients with data available.

ONLINE INTERNATIONAL QUESTIONNAIRE

One hundred health care professionals specializing in DIPG completed the online questionnaire. Sixty-eight respondents had a clinical practice based in Europe, and 32 were outside Europe (Fig. 3). In total, 26 countries were represented: 18 European and 8 non-European. Most respondents were pediatric oncologists (82%), while others included pediatric neurologists (6%), radiotherapists (5%), and nurses (3%) (Supplementary Data).

Responses indicated that European health care professionals each treat a median of 2 DIPG patients per year (range: 1–10 patients); while the median is 4 patients per year (range: 1–25) outside of Europe. There were 6 centers in which physicians treat 10 or more DIPG patients each year. These centers are located in the United States (n = 3), Argentina (n = 1), and Italy (n = 2) (data not shown).

FIGURE 3 | Geographical distribution of respondents to the international online survey.

DIPG-specific symptoms at end-stage-disease

Respondents reported ataxia, motor deficits, immobility, speech and communication problems (i.e. verbal and nonverbal), swallowing difficulties, and feeding problems as the most prevalent symptoms (>90%), followed by nausea and vomiting, headache, and constipation (+/-70%), urinary difficulties and behavioral problems (+/-50%), backache, neuropathic pain, and seizures (20%–35%).

Interventions at end-stage disease

The most prevalent interventions reported were the use of analgesics (100%), laxatives and steroids (85%–95%), followed by sedative medication (75%) and the prescription of antisecretory medication and the commencement of nasogastric feeding (+/-60%). Only a minority of respondents (32% and 20%, respectively) stated that they use chemotherapy and re-irradiation with the aim of relieving symptoms at end-stage disease.

Timing of palliative care and current approach

Seventy-two percent of the respondents stated that they often mention palliative care at the time of diagnosis (45% always, 27% frequently).

Seventy-nine percent of health care professionals reported they did not have access to institutional guidelines for palliative care in DIPG patients. No difference was seen in the use of guidelines between centers with higher or lower numbers of DIPG patients.

According to the respondents, palliative care is predominantly organized by pediatric oncology teams (76%) and less frequently by multidisciplinary pediatric palliative care teams (37%). These specialized palliative care teams, however, are mainly seen in Germany, United Kingdom, Canada, and United States. Specialists involved in palliative care are the pediatric oncology or palliative care physician (96% and 63%, respectively), the child's family doctor (64%), a social worker (80%), a psychologist (78%), physiotherapist (63%), pediatric oncology outreach nurse (62%), and spiritual input (65%). In 62% of cases, these health care specialists come together in a specific palliative care meeting.

The most common place for children with DIPG to die is at home (77%). Children die less frequently in the hospital (19%) or a hospice (5%). Brain or whole-body autopsy is rarely routinely discussed (21% and 10%, respectively). Almost all respondents (90%) stated that parents receive bereavement support and/or follow-up. This is mostly carried out by the pediatric oncology physician (55%), social worker (42%), psychologist (37%), outreach nurse (29%) or pediatric palliative care physician (22%).

DISCUSSION

In this study, we surveyed the reported symptoms during the 12 weeks before death in a cohort of typical DIPG patients with the aim of (*i*) investigating DIPG-specific symptoms and their evolution at end-stage disease. A number of studies have been published specifically describing the most common symptoms of children with a progressive (non-DIPG) brain tumor [6–11]. There is one literature review that describes symptoms in DIPG patients, but this review only addresses symptoms at diagnosis and not during disease progression [12]. At this time during the disease course, DIPG patients often present with a classic triad of cranial neuropathies, long tract signs, and ataxia. These symptoms are described in almost all studies published on DIPG. Our current study is the first to describe the many additional symptoms experienced by patients with DIPG as the disease progresses and during end-stage disease. Our results, from both the cohort study and questionnaire, show that DIPG patients suffer a high number of symptoms that could severely affect their quality of life in the last 12 weeks (e.g. impaired mobility and problems with swallowing, communication, consciousness, and breathing.) Seizures and neurocognitive decline, however, were less commonly reported in DIPG than in studies of other types of brain tumors [13]. The high prevalence of symptoms experienced in children with DIPG, who often remain cognitively intact while their disease evolves to a locked-in-syndrome with total motor impairment, including the inability to swallow or speak [14,15] confirms the importance of high-quality palliative care for these patients.

In addition to the high number of symptoms that occur at end-stage disease, our study demonstrates the pattern in which the 6 most prevalent symptoms arise, illustrating the trajectory by which patients deteriorate as a consequence of increasing brainstem dysfunction. Taking into account the rapid decline, our aim was to (*ii*) describe the current palliative and end-of-life care approach, including the timing of initiation and use of clinical guidelines. By presenting the relationship between the disease course (i.e. the date of diagnosis, disease progression, and death), the treatment approach (i.e., the date of last anticancer treatment), and the supportive care approach (i.e. commencement of palliative and active end-of-life care), together with the trajectory by which patients deteriorate during the last 12 weeks (i.e. 3 months) of life, we have demonstrated a role for palliative care from the time of diagnosis rather then the phase of rapid symptom escalation in the last few days of life (Fig. 1 and 2).

Based on the results from our study, we recommend a model in which palliative care begins at diagnosis and continues throughout the child's life and into bereavement. In the 2 London hospitals included in this study, all DIPG patients are introduced to the pediatric oncology outreach and palliative care team at the time of diagnosis. This team is

composed of pediatric palliative care nurse specialists and medical or nurse consultants who work in partnership with the pediatric oncology teams. They provide supportive palliative care, including symptom management, from diagnosis throughout treatment, in addition to care through the end-of-life phase and bereavement. The advantage of this model is that specialist symptom management and supportive care can be provided from the time of diagnosis, along with anticancer treatments, rather than just through disease progression or the end of life. It avoids the need to transfer care or introduce, a new team during the child's last days because it promotes seamless continuation of the already-existing partnerships between the family and the oncology and palliative care teams. This model also allows for anticipatory prescribing and preparing families for what may occur (e.g. with written information or early referral to occupational therapy services). When introducing palliative care, it is important that families and clinicians understand that it does not refer to end-of-life care only but rather includes the whole spectrum of symptoms and family support needs from diagnosis throughout the disease trajectory.

The survey among health care professionals investigated the worldwide approach of palliative and end-of-life care in our aim to (*iii*) evaluate the potential need for uniform international disease-specific palliative and end-of-life care guidelines for DIPG. The results of the survey show a wide variety of applied interventions as well as the diversity in the ways palliative care is organized, which could potentially lead to less efficient or less effective care. An example includes mobility and communication difficulties, both of which cause major problems for patients progressing with DIPG and for which specific interventions should be employed in time to support the physical dysfunction. Standardized protocols for these interventions and the best supportive care plans (e.g. to teach children how to use communication aids before they decline) should be developed to minimize possible delays. This not only applies to the frequently observed symptoms but also to symptoms that occur less frequently, such as nausea (present in 29% of patients) and/or vomiting (present in 39%). Interventions for vomiting could, for example, range from prescribing antiemetics to placement of a drain to reduce intracranial pressure - although vomiting may also occur from less common causes (for which interventions are still limited), such as disturbance of vagus nerve projections to the esophagus [16–18]. A final example is pyrexia (present in 26% of patients), which could be caused by tumor disturbance of autonomic brainstem structures and thus does not always indicate an infection requiring diagnostics and antibiotics. More knowledge and standardized protocols may avoid under- or overtreatment. With these examples, and the described diversity in the way palliative care is currently organized, we emphasize the need to develop evidence-based, standardized disease-specific (multi-) institutional and (multi-)national palliative care guidelines for DIPG patients.

This is underlined by our observation that currently only a few countries have regionally or nationally organized palliative care for these patients and that many centers treat only small numbers of patients.

A limitation of our study is the fact that the data from the patient cohort were retrieved retrospectively and from one city in the United Kingdom. The results rely on the completeness of historical records for symptoms and interventions. Although the patient charts were generally well documented, our study could represent an underestimation of the true number of symptoms at end-stage disease since the records did not have any validated prospective scoring of symptoms or quality of life.

Finally, we were unable to correlate interventions to targeted symptoms, in order to determine their effect, because of the limited patient numbers and the variation of observed effects over time. The international survey among health care professionals could have been influenced by recall bias as clinicians were not required to look back at notes. Future studies should therefore include prospective registration of DIPG-specific symptoms, from diagnosis and throughout the disease trajectory, and accurate recording of applied interventions and their effect on symptoms and quality of life. Such studies should also include clear definitions for the curative, palliative, and active end-of-life phases as the timing of initiation of each phase will be an important focus when developing a clinical guideline.

With this first inventory of symptom prevalence during DIPG patients' disease trajectory and the palliative and end-of-life care approach, we are able to describe the current state of affairs and its gaps. We have proposed a list of focus points that could be used to develop an international prospective clinical study. Such a trial can be easily conducted within the recently developed European DIPG registry (www.dipgregistry.eu) by the SIOPE DIPG Network and International DIPG Registry (www. dipgregistry.org) [19]. Our current study, exploratory and descriptive in nature, is a first step towards the development of a collaborative clinical study and subsequent evidence-based disease-specific (multi-) institutional and (multi-) national palliative care guidelines for patients suffering from DIPG.

SUPPLEMENTARY DATA

What is your profession?	(%)
* Pediatric Oncologist	82
* Radiotherapist	6
* Pediatric Neurologist	5
* Nurse	3
* Pediatric Surgeon	1
* Neuro-Oncologist	1
* Consultant pediatric palliative medicine	1
* Psychiatrist	1

Number of DIPG patients each year	Overall
* Median (Q1-Q3)	2 (1-4)
* Min - Max	1-25

Which of the following symptoms do you encounter during end of life care for patients with DIPG?	(% Yes)
* Motor deficits	99
* Feeding problems	96
* Ataxia	96
* Immobility	96
* Swallow difficulties	96
* Speech/communication difficulties	94
* Headache	71
* Constipation	71
* Nausea & Vomiting	70
* Behavioral problems	56
* Urinary difficulties	49
* Backache	33
* Neuropathic pain	30
* Seizures	18

Which of the following interventions do you offer during end of life care for patients with DIPG?	(% Yes)
* Opiate analgesics (e.g. morphine, fentanyl etc.)	94
* Non-opiate analgesics (e.g. non-steroidals, paracetamol)	91
* Oral analgesics	89
* Laxatives	88

* Steroids	87
* Sedative medication (e.g. midazolam)	74
* Anti-secretory drugs (e.g. hyoscine, glycopyrrolate)	60
* Nasogastric feeding	59
* IV analgesics	53
* Anti-consultants	39
* IM analgesics	36
* Chemotherapy	32
* Irradiation	20

At what time point is palliative care mentioned in your DIPG patients?	**(% Yes)**
* Diagnosis	94
- Always	*45*
- Often	*27*
- Sometimes	*22*
* During Therapy	98
- Always	*39*
- Often	*37*
- Sometimes	*22*
* Relapse	100
- Always	*90*
- Often	*9*
- Sometimes	*1*

Questions regarding the use of palliative care guidelines for DIPG:	**(% Yes)**
* Do all children with DIPG have an individualized palliative care guideline	63
* Do you use a specific palliative care guideline in your institution?	21
* If so, would you be willing to share your guideline with the SIOPE DIPG Network?	23

Who leads on palliative care for DIPG patients in your center?	**(% Yes)**
* Pediatric oncology team	76
* Pediatric palliative care team	37
* Adult palliative care team	3
* Childs pediatric team	1
* Childs family doctor	1
* Neurology	1

Please tick all of those involved in palliative care for DIPG patients in your center?	(% Yes)
* Pediatric oncology physician	96
* Social worker	80
* Psychologist	78
* Spiritual (Religious or Faith) input	65
* Childs family doctor	64
* Pediatric palliative care physician	63
* Physiotherapist/Occupational therapist	63
* Pediatric oncology outreach nurse	62
* Play therapy	51
* Dietician	49
* Speech and language therapist	39
* Children's Hospice team	39
* Community children's nurse	37
* Childs pediatric team	27
* Counselor	19
* Adult palliative care physician	17

Are all children with DIPG discussed in a specific palliative care meeting? / If yes who attends this palliative care meeting?	(% Yes)
* Yes	61
* Pediatric oncology physician	58
* Pediatric oncology nurse	51
* Social worker	48
* Pediatric palliative care physician	43
* Psychologist	43
* Physiotherapist/Occupational therapist	25
* Play therapy	20
* Children's Hospice team	18
* Dietician	16
* Spiritual (Religious or Faith) input	15
* Community children's nurse	12
* Speech and language therapist	11
* Childs pediatric team	8
* Childs family doctor	8
* Adult palliative care physician	7
* Counselor	5

Please list in your experience/opinion the most common place of death for children with DIPG in your area?	(% Yes)
* Home	77
* Hospital	19
* Hospice	5

Is (brain/whole-body) autopsy routinely discussed as an option for patients/ families with DIPG at your center?	(% Yes)
* Brain	21
* Whole body	10

Do all families have bereavement support/ follow up? If yes who conducts this?	(% Yes)
* Yes	90
* Pediatric oncology physician	55
* Social worker	42
* Psychologist	37
* Pediatric oncology outreach nurse	29
* Pediatric palliative care physician	22
* Bereavement specialist	13
*Childs family doctor	9
* Childs pediatric team	5
* Community children's nurse	3
* Adult palliative care physician	2

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