Child's Nervous System
https://doi.org/10.1007/s00381-020-04523-8

ORIGINAL ARTICLE

Biopsy in diffuse pontine gliomas: expert neurosurgeon opinion—a survey from the SIOPE brain tumor group

Sonia Tejada[1] · Kristian Aquilina[2] · John Goodden[3] · Benedetta Pettorini[4] · Conor Mallucci[4] · Marie Lise van Veelen[5] · Ulrich-W. Thomale[6]

Received: 29 July 2019 / Accepted: 25 January 2020

Abstract

Introduction The prognosis of diffuse intrinsic pontine glioma (DIPG) is poor. The role of biopsy in DIPG remains controversial since the diagnosis may be established with imaging alone. Recent advances in understanding molecular biology and targeting of brain tumors have created a renewed interest in biopsy for DIPG. The Neurosurgery Working Group (NWG) of the SIOP-Europe Brain Tumor Group (BTG) undertook a survey among international pediatric neurosurgeons to define their current perceptions and practice regarding DIPG biopsy.

Methods The NWG developed a 20-question survey which was emailed to neurosurgeons in the International Society for Pediatric Neurosurgery (ISPN). The questionnaire included questions on diagnosis, indications, and techniques for biopsy, clinical trials, and healthcare infrastructure.

Results The survey was sent to 202 neurosurgeons and 73 (36%) responded. Consensus of > 75% agreement was reached for 12/20 questions, which included (1) radiological diagnosis of DIPG is sufficient outside a trial, (2) clinical trial–based DIPG biopsy is justified if molecular targets are investigated and may be used for treatment, and (3) morbidity/mortality data must be collected to define the risk:benefit ratio. The remaining 8/20 questions proved controversial and failed to reach consensus.

Conclusions Routine DIPG biopsy continues to be debated. Most neurosurgeons agreed that DIPG biopsy within a clinical trial should be supported, with the aims of defining the procedure risks, improving understanding of tumor biology, and evaluating new treatment targets. Careful family counseling and consent remain important.

Keywords Diffuse intrinsic pontine gliomaStereotactic biopsy · Frameless stereotaxy · Neuronavigation

The results of this survey have been presented at the annual meeting of the SIOP-European Brain Tumor Group in April 2019.

✉ Sonia Tejada
stejadasolis@yahoo.es

[1] Department of Neurosurgery, IIS-Fundación Jimenez Diaz-UAM, Hospital Fundación Jiménez Díaz, Grupo Quirón, Madrid, Spain

[2] Neurosurgery Department, Great Ormond Street Hospital, London, UK

[3] Neurosurgery Department, Leeds General Infirmary, Leeds, UK

[4] Neurosurgery Department, Alder Hey Children's NHS Foundation, Liverpool, UK

[5] Neurosurgery Department, Erasmus University Medical Center, Rotterdam, Netherlands

[6] Department of Pediatric Neurosurgery, Charité Universitätsmedizin, Berlin, Germany

Introduction

Brain tumors are the leading cause of cancer death in children, with 10–15% occurring in the brainstem. More than 50% of pediatric brainstem tumors are gliomas. They are classified into four categories on the basis of anatomic location and radiographic appearance: diffuse, focal intrinsic, focal exophytic, and cervicomedullary. Diffuse intrinsic pontine glioma (DIPG), accounts for > 75% of pediatric brainstem glioma and is usually terminal.

As DIPG grow, the tumor cells slowly compress brainstem nuclei and tracts, leading to progressive neurological symptoms and deficits. The most common symptoms are (1) impaired balance and coordination, (2) long-tract impairment with weakness or sensory deficit in the limbs or trunk, and (3) cranial nerve palsies, especially affecting CN VI and VII. Headaches, altered level of

Published online: 04 February 2020

consciousness, and other cranial nerve deficits due to obstruction of cerebrospinal fluid (CSF) pathways are also common.

The peak incidence of DIPG occurs between 6 and 9 years of age. Patients typically present with rapidly progressive symptoms. Since the 1990s, diagnosis has usually based on typical radiological characteristics on MRI, without biopsy [1]. Fredstein and Constantini [2] defined the MRI characteristics for DIPG as diffuse expansion of the pons > 50%, hypo-intensity of the tumor on T1-weighted images and hyper-intensity on T2-weighted imaging, and minimal or absence of contrast enhancement. It was recommended that a biopsy would not be required in these circumstances.

Diagnostic biopsy has rarely been performed on a routine basis, except in cases where the radiological appearance is atypical [3]. Biopsy and post-mortem specimens have revealed histological characteristics typical of high grade glioma (WHO Grade III or IV), including microvascular proliferation, cellular necrosis, and the presence of mitotic figures but low grade glioma histology is also common. The prognosis is poor for all histological patterns.

In 2009, Frazier et al. [4] reviewed DIPG treatment strategies and recommended that decision-making regarding biopsy required an assessment of the risks versus benefits in relation to the potential treatment options resulting from the biopsy findings.

Currently, there is no effective treatment for these tumors. Due to their eloquent location, they are not amenable to surgical resection. Chemotherapy and radiotherapy have only had limited success, potentially delaying symptomatic progression but not providing a cure. As a result, the median overall survival is 8–11 months, with overall survival at 1, 2, and 5 years of 35%, 9%, and < 2%, respectively [5].

Due to a historical lack of biopsy tissue, the molecular biology of DIPG remains poorly understood, resulting in difficulties identifying potential treatment targets. More recently, mutations have been identified in H3-K27M, PDGFRA, and ACVR1, prompting Grill et al. [6] to urge neurosurgeons to once again consider performing biopsies to enable genomic profiling to identify possible therapeutic targets.

Since that time, the INFORM Registry and BIOMEDE Trial have commenced, with the aim of identifying DIPG molecular genetic alterations, through biopsy tissue samples. However, it remains unclear how to handle the risk/benefit balance optimally for those patients on a routine basis since the benefit is yet not well-defined. As a result, the Neurosurgery Working Group (NWG) of the SIOP-Europe Brain Tumor Group (BTG) conducted an international survey to define current opinion and practice among neurosurgeons on the management of these tumors.

Methods

The SIOP-E BTG NWG developed a survey with 20 questions. This was emailed to consultant members of the International Society for Pediatric Neurosurgery (ISPN). The survey was performed online with *SurveyMonkey.com*® over a period of 2 months (2/2019–4/2019). The approximate time required to answer the survey was 5 min. Non-responders were re-contacted up to five times. The questions addressing DIPG biopsies were structured into five main topics, including (1) the diagnosis of DIPG, (2) indications for biopsy, (3) biopsy techniques, (4) clinical trials, and (5) infrastructure required. The results were recorded with *SurveyMonkey.com*® and were presented and discussed for interpretation in the NWG meeting of the SIOP-E BTG in April 2019 (Table 1).

Results

The survey was sent to 202 neurosurgery consultants, with responses obtained from 73 (36%).

Radiological diagnosis

Forty-five respondents (62%) agreed that, in patients without neurofibromatosis, the MRI characteristics of DIPG where the tumor occupies > 50% pons are T1-hypointense and T2-hyperintense, and with minimal or no contrast enhancement. Fifty-five (75%) said radiological diagnosis alone is sufficient for standard treatment of DIPG outside a clinical trial. Thirty-four (46%) felt that central MRI review was essential prior to any treatment of DIPG in the absence of biopsy.

Indications for biopsy

Sixty-three neurosurgeons (86%) stated that a biopsy was not needed to diagnose a DIPG in every case. Forty-two (57%) would only perform a biopsy within the context of a prospective clinical trial. Forty-eight (65%) stated that biopsies are justified if the trial investigated molecular biological targets without planning to use its outcome directly for treatment. However, if these molecular targets were to be used to guide treatment, the number agreeing to biopsy increased to sixty-eight (93%). There was unanimous agreement (100%) regarding the consent process—that this should be jointly performed by specialists in neurosurgery and neuro-oncology, with sufficient time for the family to consider the options prior to surgery. The youngest patient considered for DIPG biopsy was 6 months for 36%, 1 year for 54%, and 2 years for 79% (presented as cumulative result).

Table 1 Questions and answers

Questions	Answers		
	Yes	No	Others
1. Would you agree on the following criteria being sufficient for diagnosis DIPG without biopsy: Diffuse intrinsic pontine lesion with hyperintense signal in T2 and hypointense signal in T1, occupying at least 50% of the pons in non-neurofibromatosis patients.	45 61.64%	26 35.62%	2 (2.74%) -Depends on age -Accompanied by rapid clinical history
2. Is radiological diagnosis alone sufficient for standard treatment of DIPG outside a trial?	55 75.34%	18 24.66%	
3. Is central review of the MR images outside of a clinical trial an essential component prior to any treatment of DIPG without biopsy?	36 49.32%	34 46.58%	3 (4.11%) -By Neuroradiology -Yes-If diagnosis and treatment is planned outside an experienced pediatric oncology and neurosurgery left -Should be
4. Is biopsy needed to diagnose DIPG in all cases (inside and outside of a trial)?	9 12.50%	63 86.30%	-1 missing answer
5. Should DIPG biopsies only be performed within the context of a prospective clinical trial?	42 57.53%	29 39.73%	2 (2.74%) -Depends on certainty of diagnosis, family, etc. -Atypical
6. Are DIPG biopsies justified in the context of a clinical trial if molecular biological targets are investigated and used as a treatment target?	68 93.15%	3 4.11%	1 (1.41%) -Only if they are reliable with good specificity 1 no answer
7. Are DIPG biopsies justified in the context of a clinical trial if molecular biological targets are investigated but NOT used as a treatment target?	48 65.75%	21 28.7%	4 (5.48%) -Not sure -I would address this on a case by case basis. -Only after well-informed consent by the parents -Always need a biopsy
8. Is it mandatory to perform trial-specific training in brainstem biopsy techniques in a left before taking part in the trial?	37 51.38%	28 38.89%	6 (8.33%) -Depends on experience and general caseload in stereotactic procedures. -Biopsy techniques have been established -Most academic hospitals have expertise for this procedure -Depends on previous experience of the left -Not necessary If left can show expertise in routine stereotactic procedure like DBS and non-brain stem eloquent biopsies -It is not mandatory, but if a new drug therapy isnvolved the Regulation Bodies often require this training-much to the dismay of neurosurgeons …
9. The trial must include morbidity and mortality data acquisition in order to prospectively evaluate the risk/benefit ratio of DIPG biopsies.	70 97.22%	2 2.78%	1 no answer
10. Should the trial define the neurological state of a patient in order to be eligible for a biopsy?	54 73.97%	15 20.83%	2 (2.73%) -The neurological state of any patient undergoingsurgery should always be documented -Yes, this data should be captured; but it should not be an exclusion criteria
11. The consent from the parents for a DIPG biopsy should be taken after collectively discussing it with a neurosurgeon and oncologist in a sufficient time prior to intervention?	73 100%		
12. For (frameless) stereotactic biopsies, what instruments would be acceptable?	Side-cutting needle: 56 76.71%	Forceps needle: 9 12.32%	Not sure 1 (1.36%) No answer 7 (9.58%)
13. Should the minimum required volume of tissue be defined in the trial?	54 73.97%	17 23.28%	No answer 2 (2.73%)
14. The targeted region for biopsy should include contrast-enhancing parts of the DIPG, if present?	57 78.01%	9 12.32%	No answer 2 (2.73%)

Table 1 (continued)

Questions	Answers		
	Yes	No	Others
			Others 5(6.84%): 2 not mandatory, 1 if not too risky, 1 if possible, 1 include also the rim with normal brain.
15. Post-operative imaging with high-resolution thin-sliced MRI is required in order to verify the correct region of biopsy?	59 80.82%	10 13.69%	3 (4.16%) -Not if anesthesia needed -CT can be enough -Unless pathology is clear cut
16. The institution performing the biopsy must offer the infrastructure for immediate tissue processing for fresh tissue processing?	63 86.3%	8 10.95%	1 (1.36%) -Depends on the reason 1 no answer
17. The treating team should offer the full range of treatment including palliative care for the patients?	66 90.41%	5 6.84%	1 (1.36%) -Possibly 1 no answer
18. What is the lowest age of a patient being included for a DIPG biopsy?	6 months, 35.62% (26) 1 year, 19.18% (14) 2 years, 24.66% (18) 3 years, 5.48% (4) 4 years, 5.48% (4)		7 Others: 9.59% No limits in 4 responders, 1 should be case basis, 1 before 3 years is unusual and it is difficult to use stereotaxy.
19. What are the accepted approaches for DIPG biopsies? (multiple answers possible)	Transfrontal 57.75% (41) Transcerebellar 90.14% (64) Trans-4th-ventricle 40.85% (29) Endoscopic 49.44% (28)		7.04% (5) Depends on the side of the tumor, trans-4th-ventricle seems to be open surgery?
20. The accepted techniques for DIPG biopsies are: (multiple answers possible)	Frame-based stereotaxy 88.73% (63) Frameless stereotaxy 83.10% (59) Microsurgical 59.15% (42) Endoscopic 46.48% (33)		5.63% (4) Robotic biopsy

Biopsy technique

Accepted techniques for biopsy were frame-based stereotaxy (88%), frameless stereotaxy (83%), microsurgery (59%), endoscopy (46%), or robot-assisted (6%) biopsies (multiple answers possible). The commonest tool for stereotactic biopsy was the side-cutting needle (77%). The approaches used were transcerebellar (90%), transfrontal (58%), trans-fourth-ventricular (41%), and endoscopy (together with ETV; 49%). The contrast-enhancing part of a DIPG, where present, is targeted by 78%. Post-operative imaging with high-resolution thin-slice MRI was utilized by 82% to verify the biopsy site. Sixty-three respondents (86%) stated that the institution performing the biopsy must offer the infrastructure for immediate processing of fresh tissue.

Biopsy in clinical trials

In the context of a clinical trial, 51% (37) respondents agreed that trial-specific training in brainstem biopsy techniques should occur. Fifty-four (74%) stated that a patient's neurological state should be defined as part of the trial eligibility criteria. Ninety-seven percent stated that the trial should include collection of morbidity and mortality data. Seventy-four percent agreed that the minimum required tissue volume should be defined in the trial. Finally, 91% stated that the

treating team should offer the full range of treatment, including palliative care.

Discussion

The aim of the survey was to generate a better understanding regarding neurosurgical opinion of pediatric DIPG biopsy.

Historically, there have been different opinions about the risks and benefits of biopsy, due to the perceived risks of surgery and the poor prognosis despite advances in oncological therapy. In 1983, Albright et al. [7] suggested that DIPG biopsy could identify patients with a worse prognosis (e.g., those with increased mitoses), to potentially justify more aggressive treatment. In 1993, the same group concluded that these tumors can be identified reliably by radiological criteria alone, differentiating them from focal tumors or medullary or midbrain tumors [1]. As a result, they concluded that it has no benefit to DIPG biopsy and that "routine biopsy should be relegated to neurosurgical history" [1]. This is subsequently supported by Epstein and Constantini [2], who defined MRI characteristics for the diagnosis of DIPG without the need for biopsy [8]. In this survey, 26 (36%) respondents considered that MRI characteristics alone were insufficient for DIPG diagnosis, with 2 respondents specifying that other criteria such as age and symptom onset should also be considered. There was no agreement as to whether central review of the images should be mandatory outside a clinical trial.

With the advent of molecular profiling [9] and improvements in safe biopsy techniques [10], the option of DIPG biopsy at diagnosis has been reconsidered—with the aims of identifying molecular alterations, performing biological-based research, and evaluating new treatment options. In addition, biopsy could provide further information to guide the development of pre-clinical models and may lead to targeted therapies for these tumors in the future [11].

As we prepared this neurosurgery-focused survey for publication, another oncology-focused DIPG survey was published [12]. Their stated primary objective was to describe the current situation in Europe with the aim of developing international consensus guidelines. The survey was organized and disseminated by pediatric oncologists. The authors focus on the diagnosis and therapeutic strategies for these tumors, and the vast majority (87.8%) of respondents were pediatric oncologists, and only 6.8% respondents were neurosurgeons. In contrast, the survey we present in this paper was directed to pediatric neurosurgeons with the primary objective of providing a detailed analysis of the neurosurgical attitudes to DIPG biopsy.

In the El-Khouly et al. survey, there was an interesting analysis of treatment decision-making. With respect to tumor biopsy, 41.9% stated that all or most patients should have a biopsy (all 13.5%; most 28.4%), although 16.2% never consider a biopsy (Fig. 1). Some of the reported variation was felt to stem from concerns over the potential relevance and benefit of biopsy as this rarely influences treatment modality decisions.

The responses demonstrated that there is still a lot of diversity in terms of type and intensity of treatment options. In summary, 54.1% use radiotherapy monotherapy and 44.6% combine radiation with chemotherapy. The option of no therapy increases significantly from the time of diagnosis (1.4%) to the first (9.5%) and second recurrence (77%).

Another interesting finding from El-Khouly was that even though 73% respondents reported to have ongoing clinical trials in their hospital or country, the majority of respondents (51.4%) recruit less than 25% of their patients to clinical trials. Overall, therefore, the El-Khouly paper demonstrates that there is still variation in attitudes to biopsy, with the majority not considering a biopsy, and great heterogeneity in the treatment regimes, especially upon disease progression.

The goal of the current survey was to assess the acceptability of DIPG biopsy within an international neurosurgical community. The ISPN membership list was chosen since it

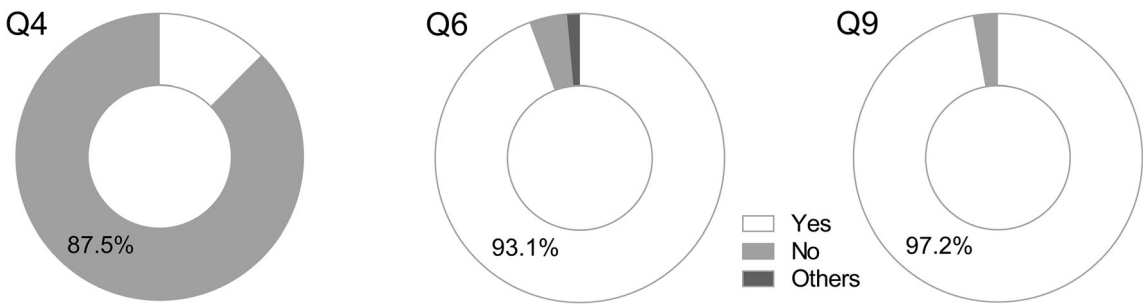

Fig. 1 Rate of answers given in percentage from questions no. 4: Is biopsy needed to diagnose DIPG in all cases (inside and outside of a trial)?; no. 6: Are DIPG biopsies justified in the context of a clinical trial if molecular biological targets are investigated and used as a treatment target?; no. 9: The trial must include morbidity and mortality data acquisition in order to prospectively evaluate the risk/benefit ratio of DIPG biopsies

allowed access to a wide distribution of international neurosurgeons with a breadth of experience and resources.

Our survey confirmed that DIPG biopsy is still controversial and there remains no consensus about its routine use. A low percentage of responders from our survey (14%) biopsied all these tumors routinely, which is in line with the El-Khouly survey (13%) [12]. Our neurosurgical survey demonstrated an almost unanimous agreement that a biopsy should be performed in the setting of a clinical trial where molecular profiling is included and could be used for targeted treatment. The El-Khouly survey also showed that a significant proportion of patients were not recruited to clinical trials, with the conclusion that these patients are unlikely to undergo tumor biopsy. The clear neurosurgical willingness to undertake DIPG biopsy in the context of clinical trials is important to recognize when considering trial design. Neurosurgeons appear willingly to perform the surgery, so now we need well-designed trials of appropriately targeted therapeutics. As we write this, however, we are also aware that one of the current trials with biopsy-related targeted therapy (BIOMEDE) has recently stopped recruiting due to lack of efficacy on interim analysis. This highlights the ongoing challenge that DIPG poses to the pediatric neuro-oncology community.

In our survey, there was a clear desire to better understand the morbidity and mortality risks associated with DIPG biopsy—the vast majority of neurosurgeons agreed that this data should be collected as part of a clinical trial. In turn, this risk:benefit data would allow improvements in informed consent processes. The favored surgical technique involved frame-based or frameless stereotaxy, using a side-cutting needle via a transcerebellar transpeduncular approach.

One area that proved controversial was the actual site of the biopsy. When asked whether "the contrast-enhancing area of the tumor should be targeted during biopsy when present," there was no consensus opinion. One of the reasons for this may be that the enhancing region is variably located, and may be in a deep area of tumor such as the anterior pons, making it a more dangerous target. Puget and Grill [13] recommended the transitional zone at the middle cerebellar peduncle as the optimal target, since this is representative of the deeper tumor mass and was considered to be relatively safe.

Currently, there are 36 clinical trials on DIPG registered in clinicaltrials.gov, which are actively recruiting patients. Of those, 5 trials include the collection of tissue samples for molecular profile studies. Two trials are observational (NCT03101813 and NCT01106794). Three trials are interventional, one using a H3.3K27M peptide vaccine [14], another using Erlotinib/Everolimus/Dasatinib treatment depending on the molecular profiling (BIOMEDE) [15], and the third using an oncolytic virus [16]. However, only one of the trials [15] includes the collection of biopsy-related morbidity data. In addition to the clinical trials, Germany has a cancer registry which includes DIPG biopsy (INFORM—INdividualized Therapy FOr Relapsed Malignancies in Childhood) and has the intention of developing personalized therapies [17].

A clear majority of respondents supported on-site fresh tissue processing for DIPG biopsy, which is something that the authors also agree with. Trials such as BIOMEDE have highlighted the need to consider more fragile research targets such as RNA—which rapidly degrades after a biopsy has been obtained. Therefore, if we are to advance our understanding of the molecular biology of these tumors and develop new treatments, it is important to process the fresh tissue in a short timeframe after it has been obtained. It is also important to ensure that adequate tissue samples are obtained, and surgeons need to ensure that enough cores of tissue are taken at each biopsy, with a minimum recommendation of 2-cores of tissue [18].

The role of trial-specific training in DIPG biopsy proved controversial in this survey, with only 37 respondents (51%) in favor. This probably relates to a number of factors. There will be a body of neurosurgeons who are familiar with frame-based and frameless biopsy techniques and therefore feel that additional training on these matters is not required. However, this has to be balanced against the trial-specific protocols that cover the amount of tissue needed, and how it is to be handled, the drug being tested (if any) and sponsor/research governance requirements. While the expertise of individual neurosurgeons may not be at question in such trial-specific training, the authors acknowledge that research governance protocols will frequently require trial-specific training to occur. Therefore, perhaps the real outcome from this question is that there is a need for improved communication about the development of DIPG clinical trials and related protocols. As mentioned in the previous published survey about DIPG diagnosis and treatment [12], international guidelines or recommendations should be developed based in data registration (via DIOPE DIPG Registry as an example).

Conclusions

Our survey has found that DIPG biopsy is viewed as acceptable by the majority of responding neurosurgeons, as long as it is in the context of clinical trials that include molecular profiling and potential targeted treatment. Prospective multi-center DIPG trials that include biopsy would present an opportunity to improve understanding of these tumors, and would potentially be able to offer novel therapeutic options. Trial protocols need to include analysis of the risks associated with biopsy, and underline the importance of multidisciplinary collaboration. Until then, we recommend that all DIPG biopsies are recorded in an International registry to provide data on tumor biology and procedure-related risk.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Albright AL, Packer RJ, Zimmerman R, Rorke LB, Boyett J, Hammond GD (1993) Magnetic resonance scans should replace biopsies for the diagnosis of diffuse brain stem gliomas: a report from the children's cancer group. Neurosurgery 33(6):1026–1030
2. Epstein F, Constantini S (1996) Practical decisions in the treatment of pediatric brain stem tumors. Pediatr Neurosurg 24(1):24–34
3. Fisher PG, Breiter SN, Carson BS, Wharam MD, Williams JA, Weingart JD, Foer DR, Goldthwaite PT, Tihan T, Burger PC (2000) A clinicopathologic reappraisal of brain stem tumor classification. Identification of pilocystic astrocytoma and fibrillary astrocytoma as distinct entities. Cancer 89(7):1569–1576
4. Frazier JL, Lee J, Thomale UW, Noggle JC, Cohen KJ, Jallo GI (2009) Treatment of diffuse intrinsic brainstem gliomas: failed approaches and future strategies. J Neurosurg Pediatr 3(4):259–269
5. Jansen MH, van Zanten SEV, Aliaga ES, Heymans MW, Warmuth-Metz M, Hargrave D, van der Hoeven EJ, Gidding CE, de Bont ES, Eshghi OS, Reddingius R, Peeters CM, Meeteren AY S-v, Gooskens RH, Granzen B, Paardekooper GM, Janssens GO, Noske DP, Barkhof F, Kramm CM, Vandertop WP, Kaspers GJ, van Vuurden DG (2015) Survival prediction model of children with diffuse intrinsic pontine glioma based on clinical and radiological criteria. Neuro Oncol 17(1):160–166
6. K.J. Cohen, N. Jabado, and J. Grill, "Neuro-oncology and new biologic insights. Is there a glimmer of hope ?," vol. 19, no. December, pp. 1025–1034, 2017
7. Albright AL, Price RA, Guthkelch AN (1983) Brain stem gliomas of children. A clinicopathological study. Cancer 52(12):2313–2319
8. Constantini S, Epstein F (1996) Surgical indication and technical considerations in the management of benign brain stem gliomas. J Neuro-Oncol 28(2–3):193–205
9. Grill J, Puget S, Andreiuolo F, Philippe C, MacConaill L, Kieran MW (2012) Critical oncogenic mutations in newly diagnosed pediatric diffuse intrinsic pontine glioma. Pediatr Blood Cancer 58(4): 489–491
10. N. Gupta, L.C. Goumnerova, P. Manley, S.N. Chi, D. Neuberg, M. Puligandla, J. Fangusaro, S. Goldman, T. Tomita, T. Alden, A. DiPatri, J.B. Rubin, K. Gauvain, D. Limbrick, J. Leonard, J.R. Geyer, S. Leary, S. Browd, Z. Wang, S. Sood, A. Bendel, M. Nagib, S. Gardner, M.A. Karajannis, D. Harter, K. Ayyanar, W. Gump, D.C. Bowers, B. Weprin, T.J. MacDonald, D. Aguilera, B. Brahma, N.J. Robison, E. Kiehna, M. Krieger, E. Sandler, P. Aldana, Z. Khatib, J. Ragheb, S. Bhatia, S. Mueller, A. Banerjee, A.L. Bredlau, S. Gururangan, H. Fuchs, K.J. Cohen, G. Jallo, K. Dorris, M. Handler, M. Comito, M. Dias, K. Nazemi, L. Baird, J. Murray, N. Lindeman, J.L. Hornick, H. Malkin, C. Sinai, L. Greenspan, K.D. Wright, M. Prados, P. Bandopadhayay, K.L. Ligon, M.W. Kieran, "Neuro-oncology prospective feasibility and safety assessment of surgical biopsy for patients with newly diagnosed diffuse intrinsic pontine glioma," vol. 20, no. May, pp. 1547–1555, 2018
11. T. J. MacDonald, "Diffuse intrinsic pontine glioma (DIPG): time to biopsy again?" Pediatr Blood Cancer, vol. 58, no. 4. United States, pp. 487–488, 2012
12. El Khouly FE, Van Zanten SEMV, Santa V, Lopez M (2019) Diagnostics and treatment of diffuse intrinsic pontine glioma: where do we stand? J Neurooncol 145(1):177–184
13. Puget S, Beccaria K, Blauwblomme T, Roujeau T, James S, Grill J, Zerah M, Varlet P, Sainte-Rose C (2015) Biopsy in a series of 130 pediatric diffuse intrinsic pontine gliomas. Childs Nerv Syst 31(10): 1773–1780
14. Chheda ZS, Kohanbash G, Okada K, Jahan N, Sidney J, Pecoraro M, Yang X, Carrera DA, Downey KM, Shrivastav S, Liu S, Lin Y, Lagisetti C, Chuntova P, Watchmaker PB, Mueller S, Pollack IF, Rajalingam R, Carcaboso AM, Mann M, Sette A, Garcia KC, Hou Y, Okada H (Jan. 2018) Novel and shared neoantigen derived from histone 3 variant H3.3K27M mutation for glioma T cell therapy. J Exp Med 215(1):141–157
15. Castel D, Barret E, Picot S, Plessier A, Le Dret L, Nysom K, Huybrechts S, Capolino P, Le Deley MC, Vassal G, Puget S, Varlet P, Grill J, Debily MA (2017) DIPG-21. Genomic landscape of the first 100 tumors registered in the biological medicine for DIPG eradication (BIOMEDE) trial. Neuro Oncol 19(suppl_4): iv9–iv9
16. Tejada S, Alonso M, Patino A, Fueyo J, Gomez-Manzano C, Diez-Valle R (2017) Phase I trial of DNX-2401 for diffuse intrinsic pontine glioma newly diagnosed in pediatric patients. Neurosurgery
17. Pfaff E, El Damaty A, Balasubramanian GP, Blattner-Johnson M, Worst BC, Stark S, Witt H, Pajtler KW, van Tilburg CM, Witt R, Milde T, Jakobs M, Fiesel P, Frühwald MC, Driever PH, Thomale UW, Schuhmann MU, Metzler M, Bochennek K, Simon T, Dürken M, Karremann M, Knirsch S, Ebinger M, von Bueren AO, Pietsch T, Herold-Mende C, Reuss DE, Kiening K, Lichter P, Eggert A, Kramm CM, Pfister SM, Jones DTW, Bächli H, Witt O (2019) Brainstem biopsy in pediatric diffuse intrinsic pontine glioma in the era of precision medicine: the INFORM study experience. Eur J Cancer 114:27–35
18. Rutkowski S, Modena P, Williamson D, Kerl K, Nysom K, Pizer B, Bartels U, Puget S, Doz F, Michalski A, von Hoff K, Chevignard M, Avula S, Murray MJ, Schönberger S, Czech T, Meeteren AYN S-v, Kordes U, Kramm CM, van Vuurden DG, Hulleman E, Janssens GO, Solanki GA, van Veelen MC, Thomale U, Schuhmann MU, Jones C, Giangaspero F, Figarella-Branger D, Pietsch T, Clifford SC, Pfister SM, Van Gool SW (2018) Biological material collection to advance translational research and treatment of children with CNS tumours: position paper from the SIOPE Brain Tumour Group. Lancet Oncol 19(8):e419–e428