Update on the diagnostic value and safety of stereotactic biopsy for pediatric brainstem tumors: a systematic review and meta-analysis of 735 cases

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OBJECTIVE Recent studies have shed light on the molecular makeup of diffuse intrinsic pontine gliomas and led to the identification of potential treatment targets for these lesions, which account for the majority of pediatric brainstem tumors (pedBSTs). Therefore, stereotactic biopsy–driven molecular characterization of pedBSTs may become an important prerequisite for the management of these fatal brain tumors. The authors conducted a systemic review and meta-analysis to precisely determine the safety and diagnostic success of stereotactic biopsy of pedBSTs.

METHODS A systematic search of PubMed, EMBASE, and the Web of Science yielded 944 potentially eligible abstracts. Meta-analysis was conducted on 18 studies (including the authors' own institutional series), describing a total of 735 biopsy procedures for pedBSTs. The primary outcome measures were diagnostic success and procedure-related complications. Pooled estimates were calculated based on the Freeman-Tukey double-arcsine transformation and DerSimonian-Laird random-effects model. Heterogeneity, sensitivity, and meta-regression analyses were also conducted.

RESULTS The weighted average proportions across the analyzed studies were 96.1% (95% CI 93.5%–98.1%) for diagnostic success, 6.7% (95% CI 4.2%–9.6%) for overall morbidity, 0.6% (95% CI 0.2%–1.4%) for permanent morbidity, and 0.6% (95% CI 0.2%–1.3%) for mortality. Subgroup analyses at the study level identified no significant correlation between the outcome measures and the distribution of the chosen biopsy trajectories (transfrontal vs transcerebellar), age, year of publication, or the number of biopsy procedures annually performed in each center.

CONCLUSION Stereotactic biopsy of pedBSTs is safe and allows successful tissue sampling as a prerequisite for the molecular characterization and the identification of potentially druggable targets toward more individualized treatment concepts to improve the outcome for children harboring such lesions.

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KEY WORDS pediatric brainstem tumors; diagnostic yield; meta-analysis; procedural complications; stereotactic biopsy; DIPG; oncology

ALTHOUGH brainstem tumors are extremely rare in adults, they comprise approximately 10%–20% of all pediatric brain tumors.²⁶ Diffuse intrinsic pontine gliomas (DIPGs), the most common subtype of pediatric brainstem tumors (pedBSTs), are associated with an

invariably fatal prognosis, and fewer than 10% of children with these tumors survive 2 years from diagnosis.³⁴ The role of stereotactic biopsy for patients with pedBSTs in general, and DIPG specifically, has been controversial. In 1993, Albright et al. reported the results of the Children's

ABBREVIATIONS AANS = American Association of Neurological Surgeons; ASCO = American Society of Clinical Oncology; BST = brainstem tumor; CNS = Congress of Neurological Surgeons; DIPG = diffuse intrinsic pontine glioma; GMS = German Medical Science; IQR = interquartile range; pedBST = pediatric BST.

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Cancer Group DIPG study and concluded that MRI was adequate in making the diagnosis, since tissue sampling did not alter the treatment or impact outcome.² Based on this conclusion and the presumed risk profile of stereotactic biopsy procedures in the brainstem, referring to studies reporting transient or permanent morbidity rates of up to 28% and 9%, respectively,^{5,7} and mortality rates of up to 4%,³¹ tissue sampling has been rarely performed. Thus, very little information on the molecular biology of DIPG has been available until very recently, when collaborative efforts allowed for the collect of a critical number of specimens, primarily derived from autopsy tissue, for molecular characterization of these tumors.^{4,12} These analyses unraveled a unique genetic makeup of DIPG that is distinct from other pediatric high-grade gliomas or adult high-grade gliomas.²⁸ Moreover, DIPGs were found to constitute a heterogeneous entity with 3 molecularly distinct subgroups (H3-K27 M, silent, and MYCN) identified with whole-genome sequencing with methylation, expression, and copy number profiling.⁴ This complexity needs to be considered when designing new therapeutic approaches, since each subgroup potentially requires a different treatment to improve outcome for these children.⁴ Therefore, stereotactic biopsy-driven molecular characterization may become an important prerequisite for the management of these tumors. We conducted a systematic review and meta-analysis to precisely determine the safety and diagnostic success of stereotactic biopsy for pedBSTs.

Methods

Search Strategy and Study Identification

The study was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines;¹⁸ no protocol for this meta-analysis has been published or registered. Appropriate studies were identified by searching the electronic databases PubMed, EMBASE, and Web of Science. Search terms included: “pediatric” or “paediatric” or “children” or “child” or “adolescent” in combination with “biopsy” or “biopsies” or “stereotactic” and in combination with “brainstem” or “brain stem” or “pons” or “pontine” or “mesencephalon” or “midbrain” or “medulla oblongata” or “posterior fossa” or “infratentorial” or “brain” or “intracranial.” Searches were limited to human studies published in English from 1980 and 2015. Reference lists from publications retrieved were also examined to identify additional studies. The websites of the American Association of Neurological Surgeons (AANS; 1997–2010), the Congress of Neurological Surgeons (CNS; 1997–2012), the American Society of Clinical Oncology (ASCO; meeting abstracts, 2004–2012; educational books, 2002–2012), and German Medical Science (GMS; 2003–2012) were also searched for relevant abstracts that met our inclusion criteria. In addition, we also evaluated our own institutional series on patients undergoing stereotactic biopsy for the diagnosis of pedBSTs over the period of 1994 to 2012 and included the results in the present meta-analysis (Supplementary Table 1 encompasses detailed characteristic and procedural metrics, e.g., diagnostic yield, mor-

TABLE 1. Baseline characteristics of the 18 studies included in the present meta-analysis

Characteristic	Value
Study design, no. of studies	
Prospective	1
Retrospective	17
No. of pts in the individual studies	
Median	24
Range	10–130
No. of biopsy procedures performed/yr in the individual institutions*	
Median	3.1
Range	1.4–10.0
Sex, % of pts†	
Female	48
Male	52
Age in yrs‡	
Mean	8.0
Range	6.0–12.8
Biopsy planning based on	
CT only, no. of studies	8
CT &/or MRI, no. of studies	8
Data not available, no. of studies	2
Applied biopsy trajectory, % of pts§	
Transfrontal approach	
Median	60.0
IQR	6.7–87.7
Transcerebellar approach	
Median	40.0
IQR	12.2–93.3

Pts = patients.

* Information available for 81% of patients (599 patients, 16 studies).

† Information available for 87% of patients (637 patients, 14 studies).

‡ Based on the measure of central tendency (mean or median) used in the individual studies. Information available for 79% of patients (577 patients, 15 studies).

§ Information available for 67% of patients (495 patients, 15 studies).

bidity, mortality) of patients in the local dataset; treatment planning and surgical procedure were performed as described previously²⁷). The institutional review board of the University Hospital Cologne approved this retrospective data evaluation, and the requirement for patient informed consent was waived.

Selection Criteria

Selection of abstracts for full review was conducted by 2 independent investigators (P.K. and M.I.R.) based on predefined inclusion and exclusion criteria. Studies were eligible if they reported original data on stereotactic biopsy of brainstem tumors (defined as tumors located in the midbrain, pons, or medulla oblongata) in pediatric patients (age < 21 years) including details on procedure-related complications (morbidity and mortality) and diagnostic

FIG. 1. Flowchart for search strategy and study selection; n refers to number of studies.

success rates. Studies were excluded if they 1) presented a reanalysis of subpopulations already included in other studies; 2) reported on biopsy procedures unrestricted to a certain location, not separately addressing the outcome for the brainstem subpopulation; 3) reported on a group of less than 10 patients; or 4) were commentaries, technical notes, or review articles summarizing the results of previous series. Furthermore, we excluded those series reporting on nonstereotactic (open) biopsies, since this approach has generally been replaced by stereotactically guided biopsies for diagnosing BSTs.^{1,3,5,6,14,24,30} Each person reviewed the abstracts independently and generated a list of studies to retrieve for full-text review. Lists were then compared and discrepancies resolved by consensus.

Data Extraction

Extraction of data was independently performed by 2 authors (P.K. and M.I.R.) and subsequently verified between the 2 authors, with discrepancies settled through consensus discussion. The following details were extracted: treatment institution, year of publication, duration of study, number of patients, age (mean or median age of the study population), and the applied biopsy trajectory (transfrontal or transcerebellar). Furthermore, diagnostic success rates (number of patients with a valid histopathological diagnosis), detailed histopathological results, and procedure-related (overall and permanent) morbidity and mortality rates were extracted.

In a previously published paper, we also performed a literature review and meta-analysis of stereotactic biopsy for brainstem tumors.¹⁵ The focus of that paper was the diagnostic value and safety of the method in the pediatric and adult population, and the research was limited to the period from 1980 to 2012. In this manuscript, we focused on the pediatric population only, updated the literature (1980–2015) and added data from our own case series.

Statistical Analysis

Statistical analysis was performed as described previously.¹⁵ In brief, study-specific proportions of outcome measures (diagnostic success, overall morbidity, permanent morbidity, and mortality) were transformed using the Freeman-Tukey variant of the arcsine square¹⁰ and then combined using DerSimonian-Laird random-effects meta-analyses. Study heterogeneity was assessed by the I^2 statistic, with values of 25%, 50%, and 75% representing mild, moderate, and severe inconsistency, respectively.¹³ Meta-regression was used for subgroup analysis at the study level. Evidence of publication bias was assessed with funnel plots. Sensitivity analysis was conducted by repeatedly calculating the effect size with 1 study omitted per iteration. All analyses were performed with Stata

TABLE 2. Pooled pathological diagnoses (of 735 patients) from the 18 studies included in the present meta-analysis

Pathology	No. of Pts	%
Neoplastic disease	676	92.0
Glioma	620	84.4
Low grade (WHO Grade I–II)	206	28.0
High grade (WHO Grade III–IV)	169	23.0
Information regarding WHO grade not provided	245	33.3
PNET	22	3.0
Ependymoma	16	2.2
Other tumors	18	2.4
Nonneoplastic disease	33	4.5
Infectious disease	16	2.2
Inflammatory disease	3	0.4
Other nonneoplastic diseases	14	1.9
Nondiagnostic biopsy procedure	26	3.5

PNET = primitive neuroectodermal tumor.

FIG. 2. Forest plot of diagnostic success, as assessed in the present meta-analysis. Squares and horizontal bars indicate point estimates and 95% confidence intervals of weighted proportions in the individual studies. The last line indicates the pooled proportions with 95% confidence intervals calculated with random-effects meta-analysis.

statistical software, release 12 (StataCorp LP). Statistical tests were 2-sided and used a significance level of $p < 0.05$.

Results

Search Results

The search strategy retrieved 945 publications (Fig. 1). Screening of the titles and abstracts showed that 907 articles did not meet criteria for inclusion in the meta-analysis. Full text was retrieved for 38 studies. Review of these studies led to the elimination of 21 for not meeting inclusion criteria for the meta-analysis. Thus, including our own institutional series, a total of 18 studies were included in the present meta-analysis.^{2,5,6,8,9,11,16,17,19–23,25,29,32,33}

Study Population

The key characteristics of the patients and studies ana-

lyzed are listed in Table 1. The studies comprised a sample of 735 patients.^{2,5,6,8,9,11,16,17,19–23,25,29,32,33} The cohorts varied between 10 and 130 patients, with a median of 24 patients per study. Annually, a median of 3.1 patients received stereotactic biopsy for BSTs in the individual institutions (range 1.4–10.0 patients per year). The chosen biopsy trajectory was transfrontal in 60% of patients and transcerebellar in 40%. However, when comparing the biopsy trajectories at a study level it became evident that several institutions almost exclusively performed biopsies with only 1 of these trajectories (interquartile range [IQR] of 7%–88% for the transfrontal approach and 12%–93% for the transcerebellar approach).

Meta-Analysis

The weighted proportions for diagnostic success and procedure-related complications (overall and permanent morbidity and mortality) across the studies are shown in Figs. 2–5. In detail, the weighted average proportion

FIG. 3. Forest plot of mortality, as assessed in the present meta-analysis. *Squares and horizontal bars* indicate point estimates and 95% confidence intervals of weighted proportions in the individual studies. The *last line* indicates the pooled proportions with 95% confidence intervals calculated with random-effects meta-analysis.

calculated by random-effects modeling was 96.1% (95% CI 93.5%–98.1%) for diagnostic success, 6.7% (95% CI 4.2%–9.6%) for overall morbidity, 0.6% (95% CI 0.2%–1.4%) for permanent morbidity, and 0.6% (95% CI 0.2%–1.3%) for mortality. Death was reported for only 1 patient within the analyzed cohort and was attributed to development of progressive brainstem edema.³²

Sensitivity analysis for random-effects models that calculated pooled proportions upon exclusion of single studies in turn showed similar results, indicating that overall estimates were not driven by the findings of single studies (Supplementary Fig. 1). Between-study heterogeneity was absent for mortality ($I^2 = 0.0\%$, 95% CI 0.0%–50.0%) and permanent morbidity ($I^2 = 0.0\%$, 95% CI 0.0%–53.6%), mild for overall morbidity ($I^2 = 48.4\%$, 95% CI 9.5%–70.6%), and moderate for diagnostic success ($I^2 = 56.9\%$, 95% CI 27.1%–74.5%) (Fig. 2–5). Funnel plots of study-specific proportions were approximately symmetrical, and most data points were within the funnel area, indicating

low evidence for presence of publication bias (Supplementary Fig. 2).

Subgroup Analyses

Meta-regression for subgroup analysis at the study level identified no significant correlation between the analyzed outcome measures and the distribution of chosen biopsy trajectories (transfrontal vs transcerebellar), distribution of the mean patient age in the individual studies, the year of publication, or the number of biopsy procedures performed annually in each center (Supplementary Table 2).

Pathological Results

A detailed list of the pathological entities diagnosed throughout the studies included in the present meta-analysis is shown in Table 2. In brief, histopathological evaluation revealed brain tumors in 92.0% of brainstem lesions.

FIG. 4. Forest plot of overall morbidity, as assessed in the present meta-analysis. Squares and horizontal bars indicate point estimates and 95% confidence intervals of weighted proportions in the individual studies. The last line indicates the pooled proportions with 95% confidence intervals calculated with random-effects meta-analysis.

Glial neoplasms were found in 84.4% of biopsy samples, primitive neuroectodermal tumors in 3.0%, and ependymomas in 2.2%. Nonneoplastic lesions—most commonly originating from infectious disease—accounted for 4.5% of biopsy samples. Stereotactic biopsy was nondiagnostic in the remaining 3.5% of patients.

Discussion

Our meta-analysis of 735 patients with pedBSTs indicates that stereotactic biopsy is a safe diagnostic procedure and is associated with a low rate of procedure-related complications (overall morbidity 6.7%, permanent morbidity 0.6%, mortality 0.6%). Furthermore, it allows adequate tissue sampling in 96.1% of cases, which is a prerequisite for histological diagnosis as well as for the molecular characterization of these tumors.

Over the last decade, there has been an increasing understanding of the molecular, biological, and genetic make-up of pedBSTs in general and DIPGs specifically,

which has revealed that these tumors are not a homogeneous entity, but rather comprise several distinct molecular subgroups, and that they are different from other pediatric gliomas and also different from adult gliomas.^{4,12,28} This strongly suggests that effective therapies for pediatric DIPGs may be distinct from effective therapies for other high-grade gliomas in pediatric or adult patients and highlights the problems of the past decades where clinical trials for pediatric DIPG were primarily chosen based on antitumor activity defined in adult high-grade gliomas.²⁸ The latter is nowadays considered to be one of the reasons why no molecularly targeted agent has been shown to significantly improve survival in a clinical trial for pediatric DIPG. Given this demonstration of safety, along with the significant information obtained, the ability to perform molecular testing on small biopsy specimens, the identification of potentially druggable targets, and the heterogeneity of these tumors, stereotactic biopsy may become an important prerequisite for the molecular characterization

FIG. 5. Forest plot of permanent morbidity, as assessed in the present meta-analysis. Squares and horizontal bars indicate point estimates and 95% confidence intervals of weighted proportions in the individual studies. The last line indicates the pooled proportions with 95% confidence intervals calculated with random-effects meta-analysis.

of pedBSTs in general and DIPGs specifically as a crucial first step toward more individualized treatment concepts to improve the outcome for children harboring such lesions.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Kickingeder, Ruge. Acquisition of data: Kickingeder, Hamisch, Fischer, Ruge. Analysis and interpretation of data: Kickingeder, Ruge. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kickingeder. Statistical analysis: Kickingeder. Administrative/technical/material support: Kickingeder. Study supervision: Kickingeder, Ruge.

Supplemental Information

Online-Only Content

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