Original Research Article

Stereotactic Biopsy for Brainstem Lesions: A Meta-analysis with Noncomparative Binary Data

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Abstract

Objectives: To evaluate the diagnostic yield and safety of brainstem stereotactic biopsy for brainstem lesions.

Methods: We performed a meta-analysis of English articles retrieved from the PubMed, Web of Science, Cochrane Library, and APA psycInfo databases up to May 12, 2021. A binary fixed-effect model, the inverse variance method, or a binary random-effect model, the Dersimonian Laird method, were utilized for pooling the data. This meta-analysis was registered with INPLASY, INPLASY202190034.

Findings: A total of 41 eligible studies with 2792 participants were included. The weighted average diagnostic yield was 97.0% (95% confidential interval [CI], 96.0-97.9%). The weighted average proportions of temporary complications, permanent deficits, and deaths were 6.2% (95% CI, 4.5–7.9%), .5% (95% CI, .2–.8%), and .3% (95% CI, .1–.5%), respectively. The subgroup analysis indicated a nearly identical weighted average diagnostic yield between MRI-guided stereotactic biopsy and CT-guided stereotactic biopsy (95.9% vs 95.8%) but slightly increased proportions of temporary complications (7.9% vs 6.0%), permanent deficits (1.9% vs .2%), and deaths (1.1% vs .4%) in the former compared to the latter. Moreover, a greater weighted average diagnostic yield (99.2% vs 97.6%) and lower proportions of temporary complications (5.1% vs 6.8%) and deaths (.7% vs 1.5%) were shown in the pediatric patient population than in the adult patient population.

Conclusions: Brainstem stereotactic biopsy demonstrates striking accuracy plus satisfying safety in the diagnosis of brainstem lesions. The diagnostic yield, morbidity, and mortality mildly vary based on the diversity of assistant techniques and subject populations.

Keywords

stereotactic biopsy, brainstem lesion, diagnostic yield, safety, meta-analysis

Key Points

(1) Combined with multiple new techniques, brainstem stereotactic biopsy is efficient and safe to diagnose brainstem lesions in adults and children.
(2) CT-guided stereotactic biopsy shows a diagnostic yield similar to that of MRI-guided stereotactic biopsy but with improved safety.
(3) Brainstem stereotactic biopsy reveals more effectiveness and safety to diagnose brainstem lesions in the pediatric patient population than in the adult patient population.
(4) When modifying the combined techniques and/or participant populations, the diagnostic yield, morbidity,

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and mortality of the procedure may be marginally different.

Introduction

Since the advent of stereotactic biopsy for more than 7 decades, its application fields and clinical utilities have been gradually expanded in combination with an increasing body of novel adjunctive tools (e.g., CT, MRI, PET-CT, and robot assistance). With the advantages of accurate positioning, less trauma, and contributions to pathological diagnosis, stereotactic biopsy has become the gold standard for diagnosing brain tumors at the end of the 20th century.[1] Stereotactic localization was first applied to biopsy and radiofrequency treatment of brainstem lesions by Gleason et al. in 1978.[2] Approximately 15% of pediatric and 2% of adult intracranial space-occupying lesions are brainstem lesions.[3] Brainstem stereotactic biopsy is performed through 4 main routes: contralateral extraventricular transfrontal approach, ipsilateral transfrontal approach, transtentorial approach, and suboccipital transcerebellar approach, which appear to have no significant difference concerning the diagnostic yield and total complications.[4,5] Given that the brainstem is the densest distribution area of cerebral nuclei, many neurosurgical teams are concerned about the potential risks of brainstem stereotactic biopsy and discern no direct benefits to patients, thus they are prone to decline the implementation of this procedure. In 1993, the Children's Cancer Group-9882 study[6] demonstrated the high specificity of MRI in diagnosing brainstem glioma and made no alteration to the treatment paradigm because of histological confirmation, thus they suggested obviating the usage of biopsy before radiotherapy. Since then, there has been a paucity of brainstem stereotactic biopsies for nearly 1 decade.

Over time, this operation has been refueled by the following 3 factors. First, a large number of studies together confirm that there are more than 15–20% inconsistent outcomes between preoperative MRI diagnosis and postoperative pathological findings[7-11]; second, many benign brain lesions (e.g., ischemia, demyelination, radionecrosis, vascular malformation, abscess, tuberculoma, granuloma, encephalitis, and cystic lesions)[12,13] and several malignant tumors (e.g., glioma, metastasis, lymphoma, ependymoma, and primitive neuroectodermal tumor)[14] may mimic each other in radiological imaging; and finally, the diagnosis and treatment of brainstem tumors increasingly depend on the molecular diagnostics, for example, the 3 molecularly distinct subgroups (H3-K27 M, Silent, and MYCN) of the diffuse intrinsic pontine gliomas that can be utilized as new therapeutic targets.[15] Therefore, stereotactic biopsy is extremely crucial for the definitive diagnosis of space-occupying lesions of the brainstem, the molecular classification of brainstem neoplasms, and the development of new targeted therapies.

Brainstem stereotactic biopsy can be operated with CT-, MRI-, or PET-CT-guided framed navigation or with robotic frameless assistance.[16-19] Again, thanks to these new techniques, contemporary brainstem stereotactic biopsy shows high diagnostic yield and good safety. Two previous systematic reviews and meta-analyses investigating the diagnostic value and safety of brainstem stereotactic biopsy in brainstem tumors by Dr Ruge's team both found a high weighted average proportion of diagnostic success (96.1-96.2%) coupled with low overall morbidity (6.7-7.8%), permanent morbidity (.6-1.7%), and mortality (.6-.9%).[20,21] However, none of the 2 systematic reviews performed further subgroup analyses in light of populations and biopsy methods. We herein conducted a meta-analysis to explore the diagnostic yield and safety of brainstem stereotactic biopsy for brainstem lesions. Additionally, subgroup analysis of the operation with different biopsy strategies (i.e., CT guidance, MRI guidance, framed navigation, and transcerebellar approach) and in diverse populations (i.e., adults and children) was performed to gauge its clinical utility.

Materials and Methods

Our work abided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[22,23] This meta-analysis was registered with INPLASY, INPLASY202190034. There was no need for Ethical or Institutional Review Board Approval for the study design due to the nature of our work.

Literature Search

We conducted a computerized search in the PubMed, Web of Science, Cochrane Library, and APA psycInfo databases to identify English-language articles up to May 12th, 2021. The following terms were used: ("brainstem lesion [MeSH]" or ((brainstem or (brain stem) or pons or pontine or mesencephalon or midbrain or (medulla oblongata)) AND (tumor or tumor or cancer or neoplasm or glioma or carcinoma)) AND (biopsy or biopsies) AND (diagnosis or diagnostic or diagnose).

Inclusion and Exclusion Criteria

Clinical articles evaluating the diagnostic yield and/or safety of brainstem stereotactic biopsy were considered to be eligible for our purposes. Additionally, potential studies were required to meet the following inclusion criteria: (1) populations—patients with brainstem mass lesions, regardless of age; and (2) reference standards—the ultimate diagnosis was compared with histopathologic results plus clinical assessments. Retrieved citations that met any of the following criteria were removed: (1) article type—reviews, case reports, case series that involved fewer than 10 patients, editorials, letters, comments, and conference papers; (2) diagnostic methods—only radiological images but without pathological examinations; and (3) overlapping study populations.

Data Extraction and Quality Assessment

We extracted the following data from the included studies by using a standardized form: (1) study characteristics—family name of the first author, publication year, study duration, original country or area, study type, number of patients, and tumor/total ratio; (2) demographic characteristics—mean age, patient cohort (i.e., pediatric patient population and adult patient population) and male/female ratio; (3) examination characteristics—guided techniques or assistant methods; and (4) outcome characteristics—diagnostic yield and safety, comprising temporary complications, permanent deficits, and deaths. The overall survival (OS) of the included subjects was also assessed in our study. Two coauthors (Dr Dongjie He and Dr Gaiyan Li) independently assessed the literature search, study selection, and data extraction. If there were any inconsistencies, they were addressed by a third coauthor (Dr Yuhong Qi).

Quality assessment of the analyzed studies was not judged because the noncomparative data did not present any risk of publication bias.

Data Synthesis and Statistical Analysis

The primary outcome was the weighted average diagnostic yield of stereotactic biopsy for brainstem lesions, and the secondary outcomes were the weighted average proportions of temporary complications, permanent deficits, and deaths. The crude proportions with 95% confidence intervals (CIs) in all analyzed studies were independently calculated and then pooled together to the weighted average values. The number of events, if not provided by the publication, was calculated in light of the endpoint percentage or other relevant information. The heterogeneity that implicated the degree of variability in results across the included studies was assessed by Cochran's Q test and Higgins I^2 statistic test[24]; $P < .10$ suggested significant heterogeneity, and different cutoff intervals of I^2 values at 0–25%, 25–50%, 50–75%, and 75–100% corresponded to nonsignificant, moderate, substantial, and considerable heterogeneity, respectively. When the heterogeneity test indicated no statistical significance ($P \geq .1$), a binary fixed-effect model, the inverse variance method, was used to pool data, and if not so, a binary random-effect model, the Dersimonian Laird method, was employed.[25] All statistical analyses were conducted by the software Open Meta-Analyst (http://www.cebm.brown.edu/openmeta/download.html).

Results

Literature Search

A PRISMA flow diagram of the literature screening selection is shown in Figure 1. We obtained 5012 citations from the PubMed, Web of Science, Cochrane Library, and APA psycInfo databases and excluded 303 reduplications, 22

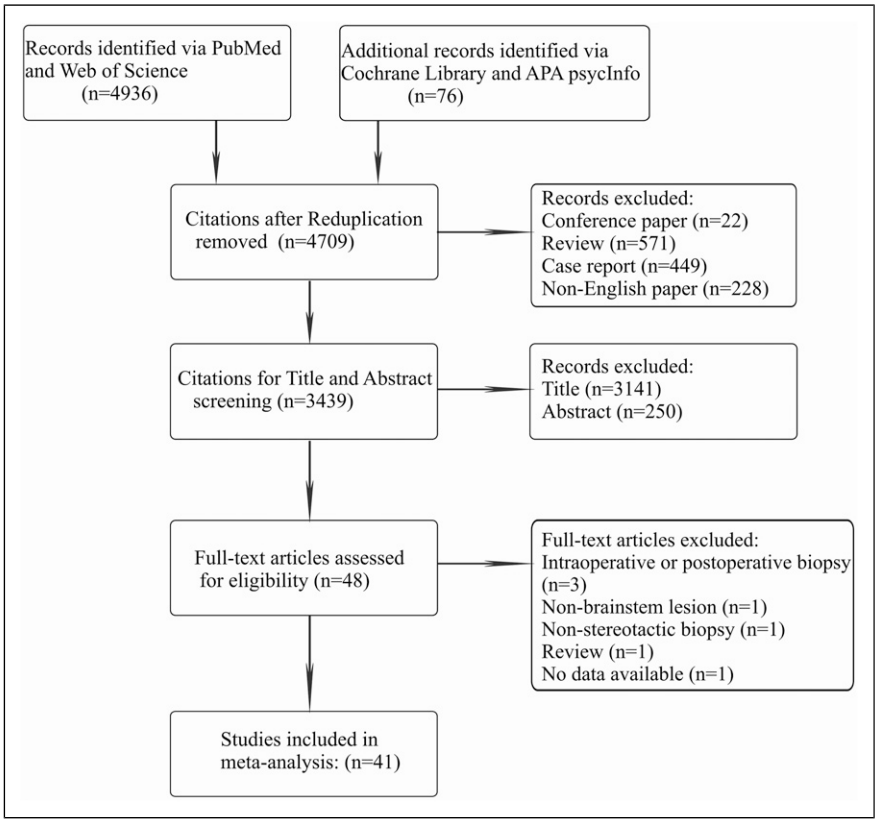

Figure 1. PRISMA flow diagram of study selection.

Table 1. Characteristics of Included Studies in the "Study-Level" Analysis.

Study (Year)	Study Duration	Original Nation	Biopsy technique†	Patient Cohort	Mean Age	Total Sample (n)	Definitive Diagnosis (n)	Permanent Deficits (n)	Temporary Complications (n)	Death (n)	Tumor/ Total*	Ref
Bahrami (2020)	2006–2016	Iran	MRI; F; TC	A+C	35.4	39	38	0	0	0	27/38	26
Shad (2005)	NA	UK	CT; F; TF	A	47.0	13	12	0	3	0	11/12	27
Puget (2015)	2002–2015	France	MRI/CT; F; TC	C	6.7	130	130	0	5	0	130/130	28
Pincus (2006)	NA	USA	3D; F; TF/TC	C	12.8	10	10	0	1	0	10/10	13
Cheng (2020)	2015–2017	China	MRI/CT; F/FL; TF/TC	A+C	32.7	111	106	NA	NA	3	99/106	29
Dellaretti (2011)	1988–2007	France	MRI; F; TF/TC	C	6.0	44	41	0	4	0	41/44	30
Dellaretti (2012)	1988–2007	France	MRI; F; TF/TC	A	41.0	96	92	0	9	1	82/92	31
Cartmill (1999)	1990–1995	UK	CT; F; TT	C	6.0	18	18	0	5	0	18/18	32
Wang (2015)	2001–2012	USA	NA; NA; TC	C	8.8	15	15	0	3	0	15/15	33
Birski (2021)	2007–2018	Poland	MRI/CT; F; NA	A	48.0	85	83	0	10	2	83/83	1
Hamisch (2019)	1996–2015	Germany	MRI/CT; F; TT	A+C	48.5	498	494	2	48	0	431/494	34
Lara-Almunia (2019)	1982–2016	Spain	CT; F; NA	A+C	53.8	407	368	NA	NA	4	321/368	16
Dellaretti (2020)	2008–2018	Brazil	MRI/CT; NA; TF/TC	A+C	29.4	31	26	0	3	0	26/26	14
Ryken (1992)	1985–1990	USA	NA; NA; NA	A+C	43.8	11	9	0	1	0	9/9	35
Puget (2012)	NA	France	NA; F; TC	C	NA	90	90	0	4	0	90/90	36
Akay (2019)	2011–2018	Turkey	MRI; F; TF/TC	A+C	43.8	18	18	0	2	0	16/18	17
Morais (2020)	2008–2018	Brazil	MRI; F; TC	C	8.8	26	22	NA	NA	0	21/22	37
Gupta (2018)	2011–2015	USA	MRI; F; TC	C	6.4	50	46	0	3	0	46/46	38
Kondziolka (1995)	NA	USA	CT; F; TF	A+C	NA	40	38	0	1	0	34/38	39
Pirotte (2007)	1995–2006	Belgium	PET; F; TF/TC	C	8.2	20	20	1	1	0	20/20	18
Gupta (2020)	2015–2020	USA	Robot; F/FL; TC	C	9.1	22	21	0	4	0	20/21	18
Dawes (2019)	2015–2017	UK	Robot; F; TC	C	10.0	11	10	0	0	0	9/10	40
Rachinger (2009)	1998–2007	Germany	MRI/CT; NA; TF/TC	A	43.0	46	46	0	1	0	43/46	41
Rajshekhar (2010)	1987–2008	India	CT; F; TF/TC	C	9.25	106	106	0	11	0	96/106	42
Gonçalves-Ferreira (2003)	1992–2001	Portugal	MRI/CT; F; TF/TC	A+C	43.0	30	28	0	2	0	18/28	43
Dellaretti (2012)	1984–2007	Brazil	MRI; F; TF/TC	NA	NA	123	115	13	13	1	106/115	4
Valdés-Gorcía (1998)	1989–1997	Mexico	MRI/CT; F; NA	C	6.5	30	29	0	0	1	20/29	44
Samadani (2006)	1996–2003	USA	MRI; F; NA	A+C	46.0	12	12	NA	NA	0	10/12	45
Quick-Weller (2016)	1994–2015	Germany	MRI; F; TF/TC	A+C	33.0	26	26	0	5	1	26/26	46
Manoj (2014)	1994–2009	India	MRI/CT; F; NA	A+C	22.11	82	75	2	5	0	61/75	47
Steck (1995)	1983–1993	USA	CT; F; TF/TC	A+C	39.5	24	23	0	2	1	23/23	48
Haegelen (2010)	2004–2006	France	Robot; FL; TF/TC	A+C	32.0	15	13	1	2	0	9/13	49
Coffey (1985)	1982–1984	USA	CT; F; TF/TC	A	56.5	12	12	0	0	0	10/12	8
Parker (1999)	1991–1996	USA	MRI/CT; F; TC	A+C	25.3	18	18	0	2	0	17/18	50
Chico-Ponce de León (2003)	1989–2002	Mexico	MRI/CT; F; TF/TC	C	7.0	50	50	NA	NA	0	50/50	51
Hood (1986)	1984–1985	USA	CT; F; TF/TC	A+C	15.5	12	12	1	0	0	12/12	52
Abernathey (1989)	1984–1988	USA	MRI/CT; F; TC	A+C	34.0	26	26	0	0	0	16/26	7
Mathisen (1987)	NA	Norway	CT; F; TC	A+C	NA	29	28	NA	NA	NA	24/28	53
Sanai (2008)	NA	USA	MRI/CT; F; TC	A	52.0	13	12	1	0	0	10/12	54
Quick-Weller (2018)	2013–2015	Germany	NA; F; NA	A	63.0	43	43	NA	NA	NA	43/43	55
Yu (1998)	1991–1995	China	CT; F; NA	A+C	39.3	310	299	0	5	0	257/299	56

*The calculation of the tumor/total ratio is based on the biopsy results.
†Information on the biopsy techniques details the guided techniques, navigation methods, and biopsy approaches.
Abbreviations: NA, not applicable; MRI, magnetic resonance imaging; CT, computerized X-ray tomography; PET, positron emission tomography; 3D, three-dimensional localization; F, framed; FL, frameless; TC, transcerebellar; TF, transfrontal; TT, transtentorial; A, adults; C, children.

conference papers, 571 reviews, 449 case reports, and 228 non-English publications. The remaining 3439 citations were assessed by title and abstract screening, and 3391 of them were removed; fundamental characteristics of the abstracts were judged with respect to the inclusion and exclusion criteria, and full-length articles were chosen. After full-text scrutinization, 7 of the remaining 48 articles were further omitted for the following reasons: (1) 3 articles investigated intraoperative or postoperative biopsy; (2) 1 article involved space-occupying lesions of non-brainstem; (3) 1 article involved non-stereotactic biopsy; and (4) 1 article presented no available data. Ultimately, 41 articles including 2792 unique patients with brainstem lesions were eligible for the meta-analysis.[1,4,7,8,13,14,16-19,26-56]

Characteristics of the Studies Included for Meta-analysis

The characteristics of the 41 eligible studies in the "study-level" analysis are outlined in Table 1, and those in the "patient-level" analysis are summarized in Table 2. The retrospective cohort studies (n = 32)[1,4,7,8,13,14,16,17,19,26,29-37,42-52,54,56] outnumbered the prospective cohort studies (n = 9)[18,27,28,38-41,53,55]; the publication year ranged from 1986 to 2021 (median: 2010); USA ranked at the first place of all original nations (n = 13)[7,8,13,19,33,35,38,39,45,48,50,52,54]; from all available studies, the median value of the mean age of included subjects was 32.7 (6-63), that of the male/female ratio was 1.3 (.5-4.5), and that of the tumor proportion was 93.2% (61.5-100.0%); and the median OS of included subjects was provided by 11 publications,[7,18,19,28,32,33,35,37,41,42,52] with the median value of 11.0 (7.5-28.0). Additionally, Table 1 summarizes the details of diagnostic yield and safety from all analyzed studies.

Diagnostic Yield

All 41 studies were involved in analyzing the diagnostic yield of brainstem stereotactic biopsy.[1,4,7,8,13,14,16-19,26-56] The pooled result showed a weighted average diagnostic yield of 97.0% (95% CI, 96.0–97.9%) (Figure 2). The subgroup analysis indicated that the weighted average diagnostic yields with the CT-guided technique, MRI-guided technique, framed navigation, and transcerebellar approach were 95.8% (95% CI, 93.0–98.6%), 95.9% (95% CI, 93.7–98.1%), 97.1% (95% CI, 96.1–98.1%), and 99.1% (95% CI, 98.3–99.9%), respectively. The weighted average diagnostic yield in the pediatric patient population (99.2%; 95% CI, 98.5–99.9%) was numerically higher than that in the adult patient population (97.6%; 95% CI, 96.0–99.1%) (Table 3).

Temporary Complications

We collected 34 eligible studies[1,4,7,8,13,14,17-19,26-2830-36,38-44,46-50,52,54,56] to investigate the temporary complications caused by brainstem stereotactic biopsy. The pooled result indicated that the weighted average proportion of temporary complications was 6.2% (95% CI, 4.5–7.9%) (Figure 3). The subgroup analysis indicated that the weighted average proportions of temporary complications with the CT-guided technique, MRI-guided technique, framed navigation, and transcerebellar approach were 6.0% (95% CI, 1.8–10.1%), 7.9% (95% CI, 3.7–12.0%), 6.0% (95% CI, 4.2–7.7%), and 3.6% (95% CI, 1.9–5.4%), respectively. The weighted average proportion in the pediatric patient population (6.8%; 95% CI, 2.4–11.2%) was 1.7% less than that in the adult patient population (5.1%; 95% CI, 3.2-6.9%) (Table 3).

Permanent Deficits

Equivalently, these 34 articles[1,4,7,8,13,14,17-19,26-28,30-36,38-44,46-50,52,54,56] were further included in the analysis of brainstem stereotactic biopsy-caused permanent deficits. The pooled result showed that the weighted average proportion of permanent deficits was .5% (95% CI, .2–.8%) (Figure 4). The subgroup analysis suggested that the weighted average proportions of permanent deficits with the CT-guided technique, MRI-guided technique, framed navigation, and transcerebellar approach were .2% (95% CI, .0–.7%), 1.9% (95% CI, .1–3.7%), .4% (95% CI, .2–.7%), and .7% (95% CI, .0–1.5%), respectively. The weighted average proportion in the pediatric patient population (.6%; 95% CI, .0-1.3%) was similar to that in the adult patient population (.3%; .0-.7%) (Table 3).

Deaths

There was concern regarding brainstem stereotactic biopsy-caused mortality, for which 39 articles[1,4,7,8,13,14,16-19,26-52,54,56] were involved in the analysis. The pooled result in Figure 5 revealed that the weighted average proportion of deaths was .3% (95% CI, .1–.5%). The subgroup analysis indicated that the weighted average proportions of deaths with the CT-guided technique, MRI-guided technique, framed navigation, and transcerebellar approach were .4% (95% CI, .0–.7%), 1.1% (95% CI, .1–2.1%), .3% (95% CI, .1–.5%), and .7% (95% CI, .0–1.5%), respectively. The weighted average proportion in the pediatric patient population (.7%; 95% CI, .1–1.3%) seemed to be safer than that in the adult patient population (1.5%; 95% CI, .2–2.8%), with a .8% decreased proportion (Table 3).

Heterogenicity

The majority of analyses found insignificant heterogenicity across their involved clinical studies, and the minority of analyses showed moderate to considerable heterogenicity as follows: (1) diagnostic yield ($P < .001$, $I^2 = 53.29\%$); (2) permanent deficits ($P < .001$, $I^2 = 57.55\%$); (3) diagnostic yield of CT-guided technique ($P < .001$, $I^2 = 74.61\%$), and framed navigation ($P < .001$, $I^2 = 55.29\%$); (4) temporary

Table 2. Characteristics of Included Studies in the "Patient-Level" Analysis.

Characteristic	Studies, no. (%) (N = 41)	Analyzed Subjects, no. (%) (N = 2792)
Study type		
Prospective cohort	32 (78.0)	382 (13.7)
Retrospective cohort	9 (22.0)	2410 (86.3)
Publication year, median (range), y	2010 (1986–2021)	
Mean age, median (range), y*	32.7 (6–63)	
Male/female ratio, median (range)*	1.3 (.5–4.5)	
Tumor proportion, median (range), %	93.2 (61.5–100.0)	
Original nation		
Iran	1 (2.4)	39 (1.4)
UK	3 (7.3)	42 (1.5)
France	5 (12.2)	375 (13.4)
USA	13 (31.7)	304 (10.9)
China	2 (4.9)	421 (15.1)
Poland	1 (2.4)	85 (3.0)
Germany	4 (9.8)	613 (22.0)
Spain	1 (2.4)	407 (14.6)
Brazil	3 (7.3)	180 (6.4)
Turkey	1 (2.4)	18 (.6)
Belgium	1 (2.4)	20 (.7)
India	2 (4.9)	188 (6.7)
Portugal	1 (2.4)	30 (1.1)
Mexico	2 (4.9)	80 (2.9)
Norway	1 (2.4)	29 (1.0)
Patient cohort		
Adult	7 (17.1)	308 (11.0)
Children	14 (34.1)	622 (22.3)
Adult + children	19 (46.3)	1739 (62.3)
No details	1 (2.4)	123 (4.4)
Guidance technique		
MRI	9 (22.0)	434 (15.5)
CT	10 (24.4)	971 (34.8)
Robot-assistant	3 (7.3)	48 (1.7)
PET	1 (2.4)	20 (.7)
MRI/CT	12 (29.3)	1150 (41.2)
3D	1 (2.4)	10 (.4)
No details	4 (9.8)	159 (5.7)
Navigation methods		
Framed	34 (82.9)	2721 (97.5)
Frameless	1 (2.4)	15 (.5)
Framed/frameless	2 (4.9)	133 (4.8)
No details	4 (9.8)	103 (3.7)
Biopsy approaches		
Transfrontal approach	2 (4.9)	53 (1.9)
Transtentorial approach	2 (4.9)	516 (18.5)
Transcerebellar approach	12 (29.3)	469 (16.8)
Transfrontal/transcerebellar approach	17 (41.5)	774 (27.7)
No details	8 (19.5)	980 (35.1)
Median OS assessment		
Yes	11 (26.8)	432 (15.5)
No	30 (73.2)	2360 (84.5)
Median OS, median (range), m*	11.0 (7.5–28.0)	

*The calculation of the median value is based on the provided data from the included studies.; Abbreviations: MRI, magnetic resonance imaging; CT, Computerized X-ray tomography; PET, positron emission tomography; 3D, three-dimensional graphics workstation; OS, overall survival.

complications of CT-guided technique (P = .009, I^2 = 62.42%), MRI-guided technique (P = .019, I^2 = 60.58%), framed navigation (P < .001, I^2 = 60.72%), and in the adult patient population (P = .084, I^2 = 48.52%); and (5) permanent deficits of MRI-guided technique (P = .051, I^2 = 52.21%).

Discussion

Despite the refined sensitivity and specificity of modern neuroimaging technologies, only relying on imaging results to diagnose brainstem lesions gives rise to a nonnegligible misdiagnosis rate, ranging from 10% to 20%.[7-11] With the popularity of molecularly targeted therapy for cancers, the selection of well-matched targeted agents is dependent on the biologically diagnostic outcome of tumor samples; additionally, the demonstrations of different molecular phenotypes of brainstem tumors require a high level of histological diagnosis for space-occupying lesions. Accurate tissue diagnosis may alter the subsequent treatment intervention and prognosis. However, correct surgical algorithms, appropriate biopsy techniques, and adequate sample acquisition affect the diagnostic yield and safety of brainstem stereotactic biopsy. Involving recently published literature spanning more than 3 decades, our meta-analysis confirms a maximal diagnostic yield plus the minimal morbidity and mortality of brainstem stereotactic biopsy. These optimistic results can obviate the concerns of most neurosurgical teams who consider brainstem stereotactic biopsy to be detrimental to patients and support the successful histologic diagnosis of brainstem lesions.

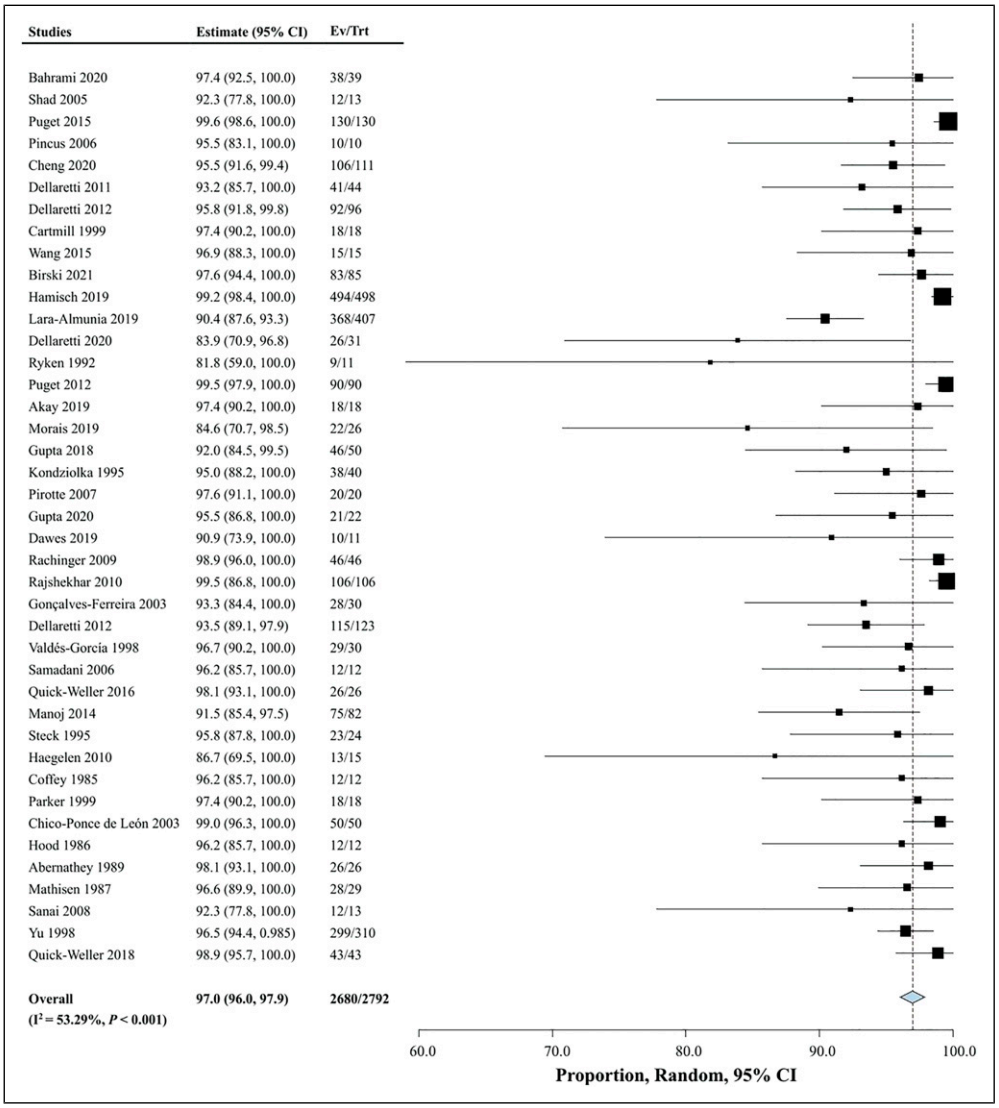

Figure 2. Coupled forest plot of diagnostic yield. A binary random-effect model, the Dersimonian Laird method, was used to pool the data because of substantial heterogeneity.

Table 3. Subgroup Analysis With the Different Assistant Techniques and Patient Populations.

Subgroup Analysis	Weighted Average Proportion (95% CI)	Included Studies (N)	Event/Total (N)	Effect Model	Heterogeneity Test	
					I^2, %	*P* Value
Diagnostic yield						
CT-guided technique	95.8% (93.0-98.6%)	10	916/971	Random	74.61	< .001
MRI-guided technique	95.9% (93.7-98.1%)	8	295/311	Fixed	.00	.615
Framed navigation	97.1% (96.1-98.1%)	31	2444/2541	Random	55.29	< .001
Transcerebellar approach	99.1% (98.3-99.9%)	13	466/479	Fixed	.00	.362
Adult patients	97.6% (96.0-99.1%)	9	344/359	Fixed	.00	.352
Pediatric patients	99.2% (98.5-99.9%)	15	647/663	Fixed	.00	.309
Temporary complications						
CT-guided technique	6.0% (1.8-10.1%)	8	27/535	Random	62.42	.009
MRI-guided technique	7.9% (3.7-12.0%)	7	36/396	Random	60.58	.019
Framed navigation	6.0% (4.2-7.7%)	28	141/1991	Random	60.72	< .001
Transcerebellar approach	3.6% (1.9-5.4%)	11	22/424	Fixed	.00	.433
Adult patients	6.8% (2.4-11.2%)	6	23/265	Random	48.52	.084
Pediatric patients	5.1% (3.2-6.9%)	11	36/528	Fixed	.00	.284
Permanent deficits						
CT-guided technique	.2% (.0-.7%)	8	1/535	Fixed	.00	.854
MRI-guided technique	1.9% (.1-3.7%)	7	13/396	Random	52.21	.051
Framed navigation	.4% (.2-.7%)	28	20/1974	Fixed	.00	.627
Transcerebellar approach	.7% (.0-1.5%)	11	1/424	Fixed	.00	.977
Adult patients	.3% (.0-.7%)	7	1/575	Fixed	.00	.85
Pediatric patients	.6% (.0-1.3%)	12	1/546	Fixed	.00	.99
Deaths						
CT-guided technique	.4% (.0-.7%)	9	5/942	Fixed	.00	.736
MRI-guided technique	1.1% (.1-2.1%)	9	3/434	Fixed	.00	.997
Framed navigation	.3% (.1-.5%)	32	11/2469	Fixed	.00	.982
Transcerebellar approach	.7% (.0-1.5%)	12	0/450	Fixed	.00	.993
Adult patients	1.5% (.2-2.8%)	8	3/316	Fixed	.00	.987
Pediatric patients	.7% (.1-1.3%)	15	1/663	Fixed	.00	.998

Abbreviations: CT, computerized X-ray tomography; MRI, magnetic resonance imaging.

Some clinical studies have revealed the reliability of brainstem stereotactic biopsy for brainstem lesions, with a diagnostic yield of 81.8–100.0%.[17,34,35] The weighted average diagnostic yield of brainstem stereotactic biopsy for brainstem lesions is 97%, which mirrors the outcomes of the 2 aforementioned meta-analyses.[20,21] Brainstem stereotactic biopsy combined with other techniques yields the achievement of tissue samples from children and adults for histopathologic diagnosis. Multiple studies have suggested that the diagnostic yield of brainstem stereotactic biopsy with CT guidance is 90.4–100.0%[16,42] and that with MRI guidance is 84.6–100.0%.[37,46] Furthermore, according to different patient cohorts, other studies noted that the diagnostic yields of brainstem stereotactic biopsy in the pediatric and adult patient populations were 84.6–100.0%[28,37] and 80.0–100.0%,[49,55] respectively. The present subgroup analysis signifies a nearly identical diagnostic yield between CT-guided and MRI-guided stereotactic biopsy and a 1.6% increment in the weighted average diagnostic yield in the pediatric patient population compared to the adult patient population. Our findings suggest that brainstem stereotactic biopsy to definitively diagnose brainstem lesions is somewhat more effective in children than in adults.

Brainstem stereotactic biopsy is safe for the diagnosis of brainstem lesions, with a low proportion of temporary complications (e.g., facioplegia, facial pain, changes in blood pressure and heart rate, and breathing difficulty).[26,36,56] Our study reaffirms the safety of this procedure in that the weighted average proportion of temporary complications is 6.2%. The diverse guided techniques and different analyzed patient cohorts may slightly influence the safety of brainstem stereotactic biopsy. In our subgroup analysis, the imaging technique using MRI guidance manifests a 1.9% higher proportion of the weighted average temporary complications than that using CT guidance, and the adult patient population has a 1.7% higher proportion than the pediatric patient population. Notably, the heterogeneity test of the subgroup analyses of the CT-guided technique, MRI-guided technique,

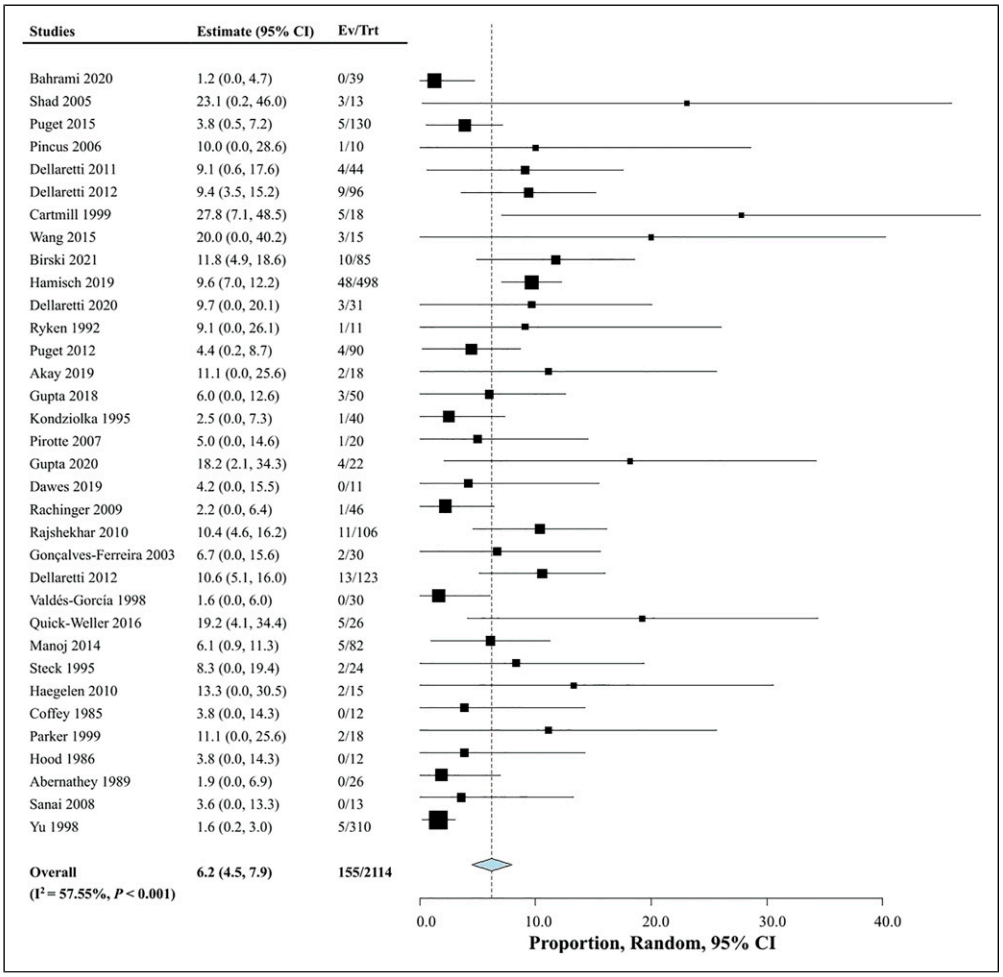

Figure 3. Coupled forest plot of the proportion of temporary complications. A binary random-effect model, the Dersimonian Laird method, was used to pool the data because of substantial heterogeneity.

and the adult patient population shows moderate to substantial heterogeneity.

A lower proportion of permanent deficits (i.e., nonself-limiting damage) than temporary complications occur after the procedure.[14,28,34] The weighted average proportion of permanent deficits was .5% in the present meta-analysis. The subgroup analysis indicates the similarity of weighted average proportion between the pediatric patient population and the adult patient population but an increased proportion in MRI-guided techniques compared to CT-guided techniques. It is worth mentioning the substantial heterogeneity across all studies included in the subgroup analysis of MRI-guided techniques, which is attributed to the study of Dellaretti et al[4] that documents the occurrence of permanent deficits in 13 of 123 included patients.

Successful and safe brainstem stereotactic biopsy demands a set of optimal infrastructures, a highly standardized surgical workflow, and an experienced biopsy neurosurgeon.[41] Nevertheless, procedure-induced mortality is a nonnegligible issue. Indeed, our work demonstrates a very low weighted average proportion of deaths that is merely .3%. The subgroup analysis shows that biopsy with MRI guidance is likely to have larger mortality than biopsy with CT guidance, and biopsy in the adult patient population seems to be more detrimental than biopsy in the pediatric patient population. There may be several reasons why CT-guided biopsy would counterintuitively have lower mortality rates than MRI-guided biopsy. First, CT-guided biopsy may involve larger lesions that do not require MRI and thus are easier to biopsy. Additionally, the CT-guided technique may involve an older series and be more likely to employ framed navigation because frameless navigation is unavailable. Nevertheless, histopathologic biopsy can result in an unequivocal diagnosis and assist in the selection of suitable targeted therapy, indicating that brainstem stereotactic biopsy may optimize the prognosis of patients.

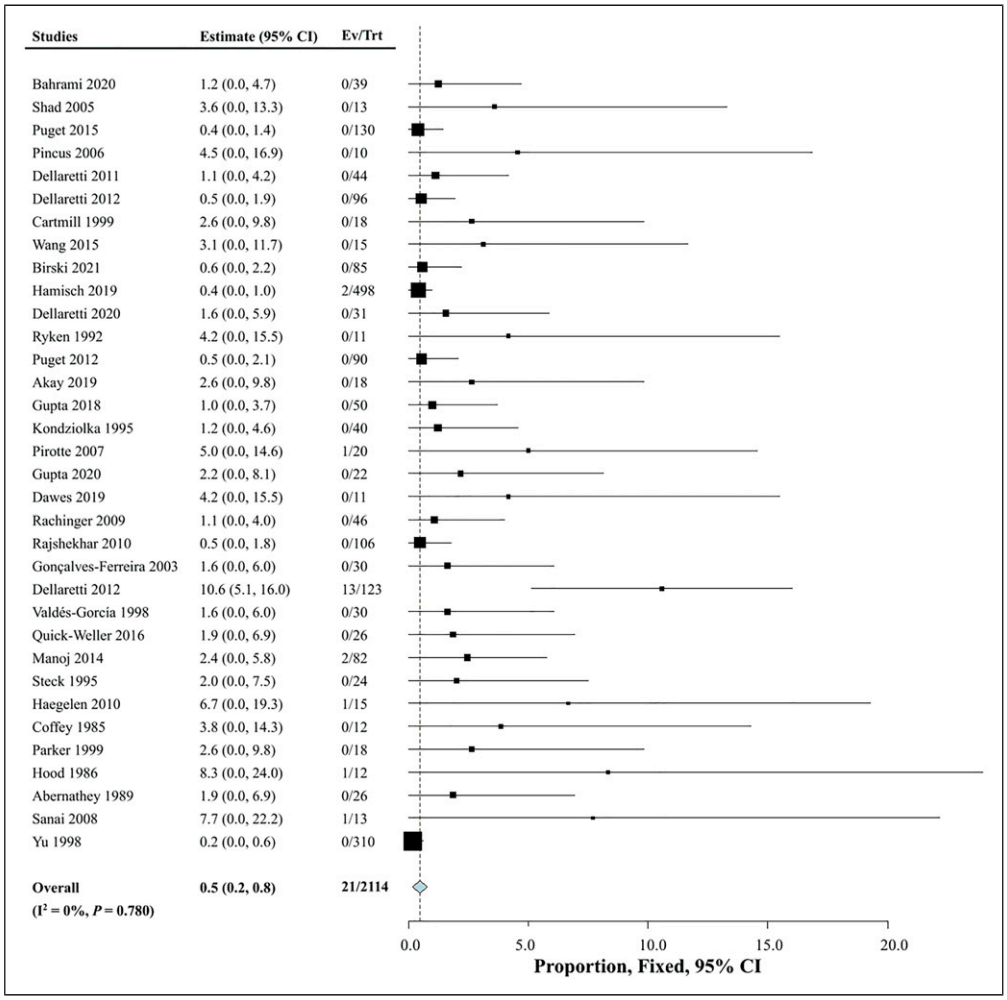

Figure 4. Coupled forest plot of the proportion of permanent deficits. A binary fixed-effect model, the inverse variance method, was used to pool the data because there was no significant heterogeneity.

The importance of framed navigation and biopsy trajectories influencing the diagnostic yield, complications, and mortality cannot be overlooked. Jaradat et al[57] recommended that a supratentorial transfrontal approach was indicated for lesions in the midbrain, upper pons, and medulla oblongata, and an infratentorial transcerebellar approach was suitable for lesions within the lower pons. In contrast, a study by Mathon and coworkers[58] highlighted a greater complication rate in the supratentorial transfrontal approach than in the infratentorial transcerebellar approach. In light of this, they proposed that only midbrain lesions should be used for biopsy with a supratentorial transfrontal approach, whereas lesions located within other parts could be safely attained by an infratentorial transcerebellar approach. The diagnostic accuracy and safety may vary from the supratentorial transfrontal approach to the infratentorial transcerebellar approach and from framed navigation to frameless navigation. However, because of the low number of studies with small sample sizes of participants on frameless navigation, transfrontal approach, and transtentorial approach (Table A1 in Appendix 1, *Page 1*), the diagnostic yield and safety within these subgroups were not available for pooling in our meta-analysis.

Collectively, brainstem stereotactic biopsy is a safe and accurate procedure. CT-guided biopsy has a similar diagnostic yield but low morbidity and mortality to MRI-guided biopsy. The diagnostic accuracy and safety of this procedure are improved in the pediatric patient population compared to the adult patient population. Since the subgroup of 1 single guided technique involves different patient cohorts and vice versa, heterogeneity occurs. Thus, future clinical trials need to validate our findings by comparing the diagnostic yield and safety of CT guidance to that of MRI guidance in the same patient setting and also comparing them in the pediatric patient population

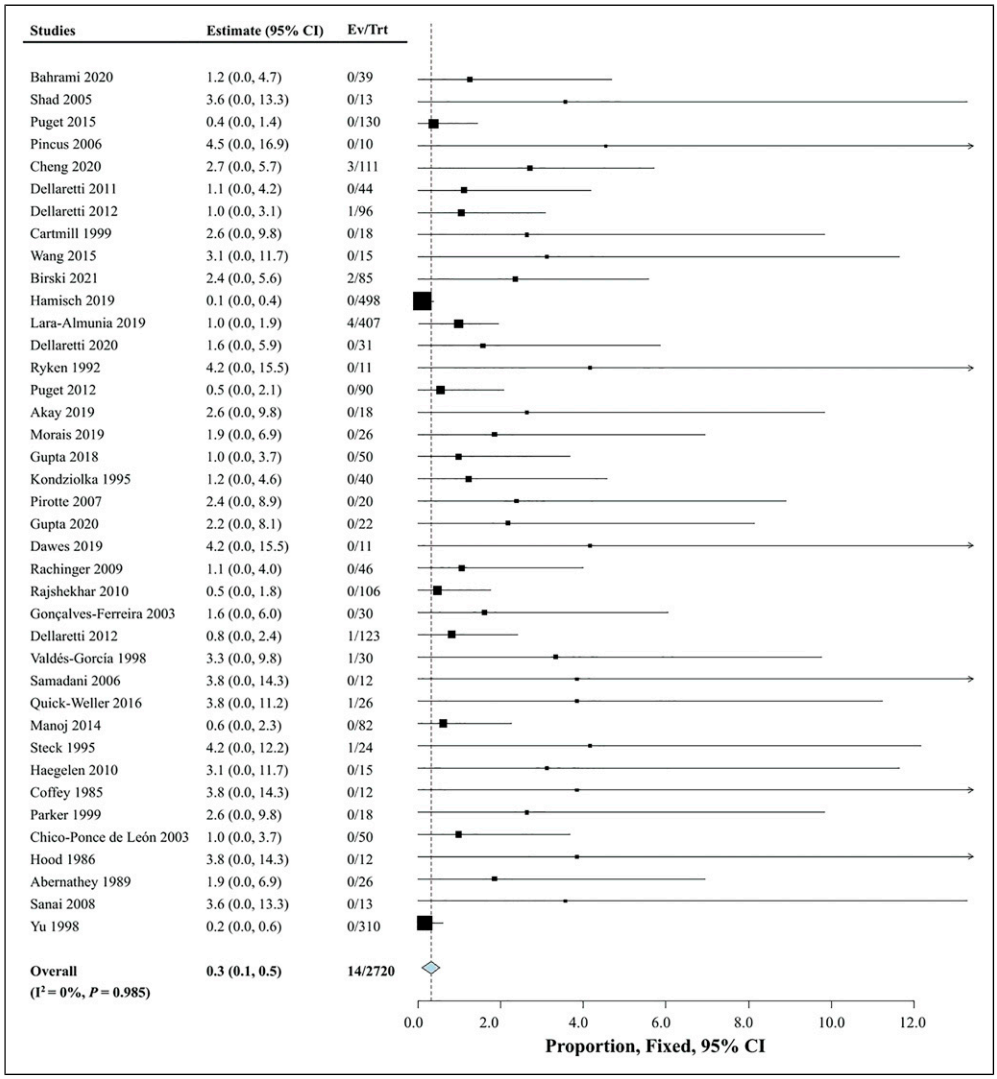

Figure 5. Coupled forest plot of the proportion of deaths. A binary fixed-effect model, the inverse variance method, was used to pool the data because there was no significant heterogeneity.

and the adult patient population using the same biopsy method.

There are some limitations in this article that deserve a mention. First, the analyzed data in this meta-analysis were binary noncomparative variables, as no available methods were used to calculate the publication bias. Second, the majority of analyzed studies (n = 19) involved smaller sample sizes (< 30 participants), which might give rise to important selection bias. Third, the majority of included studies were performed retrospectively, which indicated other biases due to the data collection and subject selection. More importantly, since there were limited numbers of publications included in the subgroup analyses, the data did not allow us to conduct further subgroup analyses according to different patient cohorts with the same combined assistant technique or distinct guided techniques with the same patient cohort.

Conclusions

Brainstem stereotactic biopsy is an accurate and safe procedure for the diagnosis of brainstem lesions. Alterations in assistant techniques and/or patient populations slightly modify the optimal diagnostic yield and safety. Biopsies targeting the brainstem, as a critical function-related structure, may be associated with higher functional complications or mortality. Our findings may help guide treatment options by elucidating the benefits and risks commonly encountered in neurosurgical practice when performing stereotactic brainstem biopsies.

Appendix 1

Table A1. Study details for different stereotactic biopsy methods.

Classifications	Studies (N)	Event/Total (n/N)	Subgroup Analysis
Diagnostic yield			
CT-guidance	10	916/971	Available
MRI-guidance	8	295/311	Available
Frame-based navigation	31	2444/2541	Available
Frameless navigation	1	13/15	Unavailable
Transcerebellar approach	13	466/479	Available
Transfrontal approach	2	50/53	Unavailable
Transtentorial approach	2	512/516	Unavailable
Temporary complications			
CT-guidance	8	27/535	Available
MRI-guidance	7	36/396	Available
Frame-based navigation	28	141/1991	Available
Frameless navigation	1	2/15	Unavailable
Transcerebellar approach	11	22/424	Available
Transfrontal approach	2	4/53	Unavailable
Transtentorial approach	2	53/516	Unavailable
Permanent deficits			
CT-guidance	8	1/535	Available
MRI-guidance	7	13/396	Available
Frame-based navigation	28	20/1974	Available
Frameless navigation	1	1/15	Unavailable
Transcerebellar approach	11	1/424	Available
Transfrontal approach	2	0/53	Unavailable
Transtentorial approach	2	2/516	Unavailable
Deaths			
CT-guidance	9	5/942	Available
MRI-guidance	9	3/434	Available
Frame-based navigation	32	11/2469	Available
Frameless navigation	1	0/15	Unavailable
Transcerebellar approach	12	0/450	Available
Transfrontal approach	2	0/53	Unavailable
Transtentorial approach	2	0/516	Unavailable

Authors' Contributions

LH, Writing manuscript, Statistical analysis DH, Writing manuscript; Data collection YQ, Writing manuscript, Supervision JZ, Table drawing CY, Figure drawing HC, Validity QW, Supervision GL, Data collection QS, Conception/DesignFinal approval of manuscript. All authors reviewed and approved the manuscript prior to submission.

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