Original Article

Frame-based versus frameless stereotactic brain biopsies: A systematic review and meta-analysis

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ABSTRACT

Background: Stereotactic brain biopsy techniques have been a focus of rapid technological innovation. The recent advent of frameless stereotaxy has invited the question of whether it can provide the same diagnostic yield as frame-based techniques, without increasing risk of harm to patients. The goal of this meta-analysis was to compare each of these techniques in terms of yield and safety.

Methods: We independently searched four databases for English studies comparing frameless and frame-based stereotactic brain biopsies. Our primary outcome was biopsy diagnostic yield. Our secondary outcomes included mortality, morbidity (e.g., symptomatic postbiopsy intracranial hemorrhage, asymptomatic postbiopsy intracranial hemorrhage, new postbiopsy neurological deficit, and postbiopsy seizure), and frequency of repeat biopsy. We calculated pooled estimates and relative risks for dichotomous outcomes using Review Manager 5.3, with corresponding 95% confidence intervals.

Results: A total of 3256 stereotactic brain biopsies (2050 frame based and 1206 frameless), from 20 studies, were included in our final analysis. The results did not demonstrate any significant difference between the two stereotactic systems in terms of diagnostic yield (risk ratio [RR] 1.00, 95% confidence interval [CI] 0.99–1.02, $P = 0.64$, $I^2 = 0\%$). The only significant difference was the increased frequency of asymptomatic hemorrhages in the frameless group (RR 1.37, 95% CI 1.06–1.75, $P = 0.01$, $I^2 = 0\%$). Application of Grading of Recommendations Assessment, Development, and Evaluation to the results yielded very low quality of all outcomes.

Conclusion: Based on very low-quality evidence, both frame-based and frameless stereotaxy are safe and effective for biopsy of intracranial tumors. Further study of patient preference and cost comparing analysis is required to identify if either modality should be preferred.

Keywords: Brain biopsy, Frame-based brain biopsy, Frameless brain biopsy, Stereotactic biopsy, Stereotactic brain biopsy, Stereotaxy

INTRODUCTION

Brain biopsy is a surgical procedure whereby a small amount of intracranial tissue is obtained for pathological analysis. It is conducted for diagnostic purposes on which treatment recommendations are based. While the basic procedural principles (e.g., need of imaging for target visualization and definition of spatial reference points for targeting) have remained

largely unchanged, the specific methods of obtaining samples of brain tissue have evolved overtime from freehand craniotomy procedures into minimally invasive stereotactic techniques. Modern approaches, aided by further evolving medical imaging modalities, allow for the sampling of very small and even deep-seated intracranial lesions with safety, accuracy, precision, and reliability.[1,11] The pathological entities most commonly biopsied are tumors, but the technique is suitable for other lesions including those caused by infection, inflammation, demyelinating diseases, and neurodegenerative diseases.[4]

In general terms, stereotactic techniques allow for the brain to be mapped onto a three-dimensional (3D) coordinate system by utilizing preoperative imaging, typically magnetic resonance imaging (MRI) or computed tomography (CT), in conjunction with a radiopaque fiducial set or fixed frame. Suitable target coordinates are then selected based on the reference system to guide a biopsy needle through a small burr hole toward the intended target point.[14] Current stereotactic systems can be divided into two main methods: rigid frame-based systems with skeletal fixation or frameless stereotaxy. In the former, a rigid frame is mounted onto the patients' skull before image acquisition immediately before surgery. In the latter, image acquisition is scheduled separately from the surgical time.

a) Frame-based techniques have been considered the gold standard for many years, due to their superiority over freehand biopsy.[11] Various systems have been developed to this end, but the common feature of this technique is that it utilizes a rigid frame, firmly attached to the head of the patient before surgery. The frame is secured using skeletal pins at multiple points on the scalp which are infiltrated with local anesthesia. The patient may be awake or under general anesthesia during this process, before transfer for image acquisition and subsequent surgery. The frame-based technique employs a 3D coordinate system, in which any target point in the brain is given a corresponding coordinate point relative to a reference point that is defined on the frame's orientation on preoperative imaging.[14] Although technological advancements have allowed for the development of many versions of the stereotactic frame, frame-based techniques remain limited by the complexity to assemble and maintain a frame, the required length of a combined imaging and surgical time, and patient discomfort.[7]

b) Frameless neuronavigation systems utilize a pointer system, a digitizer, a work station, and fiducials. The fiducials are placed on the scalp for preoperative imaging and then used as reference to allow for the definition and calibration of the surgical space relative to the patient's head on these images. The digitizer registers and then transfers this spatial information to a workstation, which allows a registered pointer and the biopsy probe to be projected onto the preoperative images. This provides accurate intraoperative navigation and targeting of lesions using the preoperative images.[8] Surgery can be done under local or general anesthesia and specimen acquisition can be done entirely frameless through electromagnetic guidance systems. As previously mentioned, neuronavigation systems allow for imaging and planning to be separated from surgery in time and location. For example, the patient can undergo MRI or CT the morning of surgery or even days prior. This may shorten procedural time otherwise needed to apply a rigid frame and makes operative planning more flexible while improving patient comfort, as patients are able to move freely with fiducials in place.[20]

Conventionally, rigid frame-based biopsy is considered to convey greater precision when compared to frameless options, particularly when targeting small deep-seated lesions. This is due to the hypothesis that frameless techniques require more complex hand-eye coordination and, therefore, may be more prone to drift and tremor.[20] Very few studies have compared the two methods, demonstrating similar results for diagnostic yield and morbidity.[18] This review systematically examines frame-based and frameless biopsy techniques in the context of diagnostic yield and procedural complications.

The primary outcome for this meta-analysis is biopsy diagnostic yield, with a secondary focus on associated complications, with outcomes including mortality, postbiopsy intracranial hemorrhage, new postbiopsy neurologic deficit, postbiopsy seizure, and frequency of a repeat biopsy.

MATERIALS AND METHODS

Search strategy and study selection

This systematic review and meta-analysis are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis[12] and the Cochrane Handbook for Systematic Reviews of Interventions.[10] A detailed search was conducted with MEDLINE, EMBASE, and CINAHL in July 2017, without date, language, or publication type restrictions. In addition, Web of Science was searched on September 2017. The search strategies were developed in consultation with a McMaster University librarian with expertise in systematic reviews. Keywords and medical subject headings terms related to stereotactic, frameless or frame-based, biopsy, or excision of intracranial tissue were used. The search strategy employed for each database is provided in Online Resource 1. Studies were eligible for inclusion if they reported histological yield or clinical outcomes of brain biopsies performed under frame-based and frameless techniques. Papers that only reported on one of the techniques were excluded. *In vitro* studies, review articles, correspondences, and studies published in languages

other than English were also excluded. Two investigators independently evaluated studies for eligibility. Disagreements between reviewers concerning the decision to include or exclude a study were resolved by consensus, and if necessary, consultation with a third reviewer.

Data collection

Data regarding patient and study characteristics, details of the specific biopsy apparatus and other operative details, lesional characteristics, histological yield, postbiopsy bleeding rates, postbiopsy clinical complications, and length of hospital stay were abstracted. The primary outcome investigated in our study is histopathological yield. Diagnostic yield was defined as the proportion of biopsies performed with either stereotactic technique that yielded a definitive diagnosis. The secondary outcomes included incidence of mortality, symptomatic postbiopsy intracranial hemorrhage, asymptomatic postbiopsy intracranial hemorrhage, neurological deficit, seizure, and frequency of repeat biopsy. Mortality included all-cause mortality events postbiopsy, and not necessarily related to the biopsy. Asymptomatic postbiopsy intracranial hemorrhage was defined as hemorrhage noted on imaging, but without any clinical consequences. The data abstraction table is provided in Online Resource 2.

Data analysis

Histological yield and risks of frame-based versus frameless intracranial brain biopsies were pooled using Review Manager (version 5.3, Cochrane Collaboration) by the inverse variance method and random effects analysis model. The pooled results of the seven dichotomous outcomes were presented as risk ratio (RR) with corresponding 95% confidence interval (CI). The statistical significance was defined as $P < 0.05$. Quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[9] Evidence was ranked as being of very low quality, low quality, moderate quality, and high quality, based on the risk of bias, inconsistency, indirectness, imprecision, and publication bias.

RESULTS

Our search identified 13,580 records with 5234 of these representing duplicate publications and 8280 excluded after screening of title and abstract. In total, 66 full-text articles were assessed in detail for eligibility. Of these remaining articles, 30 were excluded as they did not compare the two stereotactic techniques being assessed with this study, eight papers were repeat publications, six lacked the complete set of desired clinical outcomes for this study, and two were published in languages other than English. In total, 20 studies

were included for quantitative synthesis consisting of 19 observational studies and one randomized control study [Figure 1]. All studies were full-text articles except for one conference abstract. Study characteristics, outcomes, and references of all 20 studies are provided in Online Resource 2. The final analysis consisted of 3256 stereotactic brain biopsies; 2050 frame based and 1206 frameless.

For frame-based brain biopsy, the mean age of participants was 50.1 years (SD 8.5), of whom 41.6% were women. The majority of frame-based biopsies were performed under local anesthesia 68.8%, while only 31.2% employed general anesthesia, with the average total procedure time being
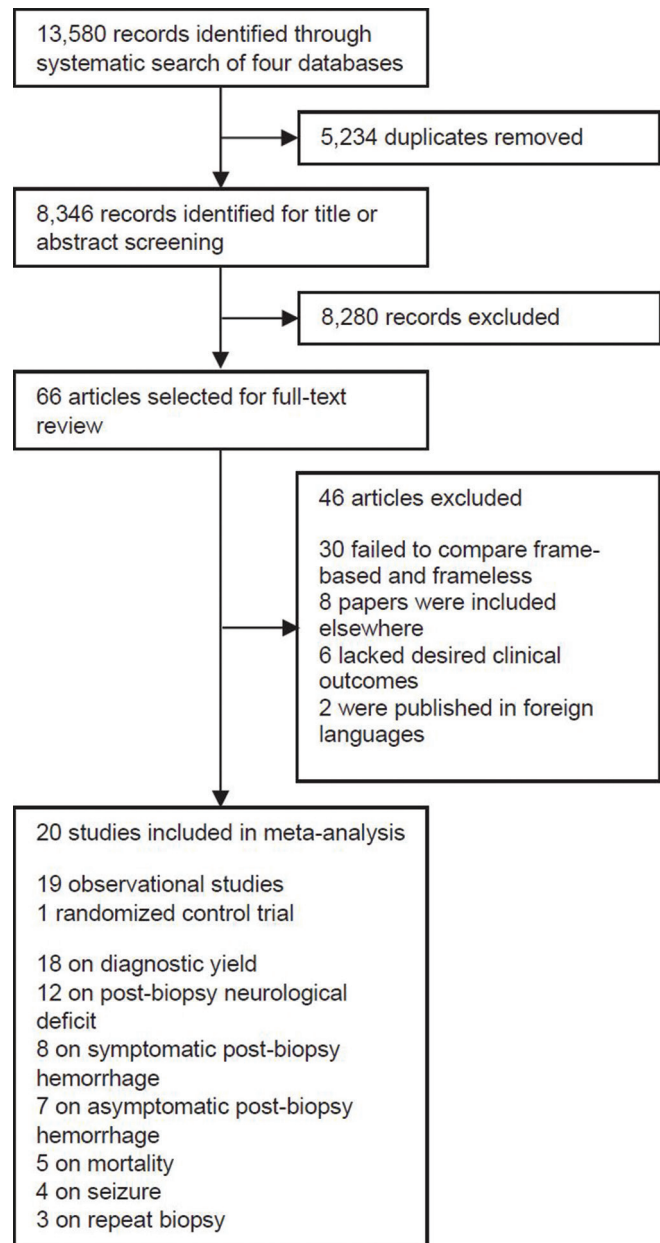

Figure 1: Flowchart of study selection.

125.5 min (SD 34.2). The nature of the lesions targeted by frame-based biopsies composed of high-grade glioma 45.5%, low-grade glioma 20.7%, ungraded glioma 1.6%, other tumors 2.6%, metastasis 5.9%, lymphoma 11.8%, and other 11.9%. The location of the lesions targeted included lobar 63.2%, midline 33.5%, cerebellum 1.3%, multiple locations 1.5%, and other 0.5% [Table 1]. Midline targets included brainstem, diencephalon, basal ganglia, and ventricles.

For frameless brain biopsy, the mean age of participants was 51.5 years (SD 8.6), of whom 44.0% were women. Almost all biopsies were performed under general anesthesia 97.4%, with only 2.6% of frameless biopsies performed under local anesthesia. The average total procedure time was 98.2 min (SD 44.8). The lesions targeted with the frameless technique included high-grade glioma 53.8%, low-grade glioma 14.7%, ungraded glioma 2.2%, other tumors 2.0%, metastasis 5.0%, lymphoma 10.3%, and other 12.0%. The lesions targeted were lobar 56.9%, midline 39.1%, cerebellar 2.1%, and multiple 1.9% [Table 1]. Biopsies performed with frameless stereotaxy targeted a significantly higher percentage of midline lesions (39.1% vs. 33.5%, $P = 0.04$) and were significantly more likely to be performed under general anesthesia (97.4% vs. 31.2%, $P < 0.05$) when compared to frame-based biopsies.

In terms of the primary outcome, diagnostic yield, 18 studies were analyzed with a total of 2678 stereotactic brain

Table 1: Baseline characteristics of participants, biopsies, and target lesions.

	Frame-based biopsy	Frameless biopsy
Age (years)	50.1 (SD 8.5)	51.5 (SD 8.6)
Gender (%)	*n*=488	*n*=364
Female	41.6	44.0
Male	58.4	56.0
Anesthesia (%)	*n*=1332	*n*=684
General	31.2	97.4
Local	68.8	2.6
Lesion location (%)	*n*=993	*n*=476
Lobes	63.2	56.9
Midline	33.5	39.1
Cerebellum	1.3	2.1
Multiple	1.5	1.9
Other	0.5	0
Lesion nature (%)	*n*=849	*n*=641
High-grade glioma	45.5	53.8
Low-grade glioma	20.7	14.7
Ungraded glioma	1.6	2.2
Other tumors	2.6	2.0
Metastasis	5.9	5.0
Lymphoma	11.8	10.3
Other	11.9	12.0
Procedure time (min)	125.5 (SD 34.2)	98.2 (SD 44.8)

Data are represented as mean (SD) or %.

biopsies. There were 1063 biopsies in the frameless group (from which diagnostic tissue was obtained in 990 biopsies, 93.1%) and 1615 biopsies in the frame-based group (from which diagnostic tissue was obtained in 1494 biopsies, 92.5%). Ultimately, there was no significant difference between frameless and frame-based diagnostic yield in any of the studies included or the pooled analysis (RR 1.0, 95% CI 0.99–1.02, $P = 0.64$, $I^2 = 0\%$) [Figure 2]. In keeping with these data, studies reporting cases in which repeat biopsy was required were analyzed as well. Three studies were included, analyzing 401 biopsies in total. In the frameless group, 7/150 biopsies were repeated (4.7%), compared with 13/251 in the frame-based group (5.2%). There was no significant difference in repeat biopsy rate between frameless and frame-based stereotaxy in either of the three included studies or in the pooled analysis (RR 0.84, 95% CI 0.35–2.05, $P = 0.70$, $I^2 = 0\%$) [Figure 2].

Secondary outcomes included measures of morbidity and mortality. The analysis for postbiopsy mortality included a total of five studies, with 1108 biopsies in total. Of 457 biopsies in the frameless group, there were 10 instances of mortality (2.2%). This compares with 13 cases of mortality in the frame-based group in 651 cases (2.0%). This difference was not found to be significant in either the pooled data (RR 1.06, 95% CI 0.47–2.39, $P = 0.89$, $I^2 = 0\%$) [Figure 2] or any of the included studies. Measures of morbidity included asymptomatic postbiopsy hemorrhage, symptomatic postbiopsy hemorrhage, postbiopsy neurological deficit, and postbiopsy seizure. The first of these considered radiologically identified bleeding with no detected clinical change. Seven studies were included in this analysis, consisting of 1032 biopsies. There were a total of 420 biopsies in the frameless group, with 84 of those exhibiting postoperative hemorrhage on imaging of no clinical significance (20.0%). The frame-based group included 612 biopsies, 96 of which had radiologic evidence of hemorrhage postoperatively with no clinical change (15.7%). There was a significant difference between these groups in the pooled analysis in that there were more radiologically detected postbiopsy bleeds in the frameless stereotaxy group (RR 1.37, 95% CI 1.06–1.75, $P = 0.01$, $I^2 = 0\%$) [Figure 2]. This was the only significant difference between the two stereotactic methods assessed in our study; incidences of symptomatic postbiopsy hemorrhage (RR 0.65, 95% CI 0.33–1.28, $P = 0.21$, $I^2 = 0\%$), postbiopsy neurologic deficit (RR 0.79, 95% CI 0.51–1.22, $P = 0.29$, $I^2 = 0\%$), and postbiopsy seizure (RR 1.04, 95% CI 0.45–2.37, $P = 0.93$, $I^2 = 0\%$) showed no differences between the groups [Figure 2]. Individual forest plots for each outcome are available in Online Resource 3.

The overall quality of available evidence for this meta-analysis was rated as very low using the GRADE approach [Figure 3].
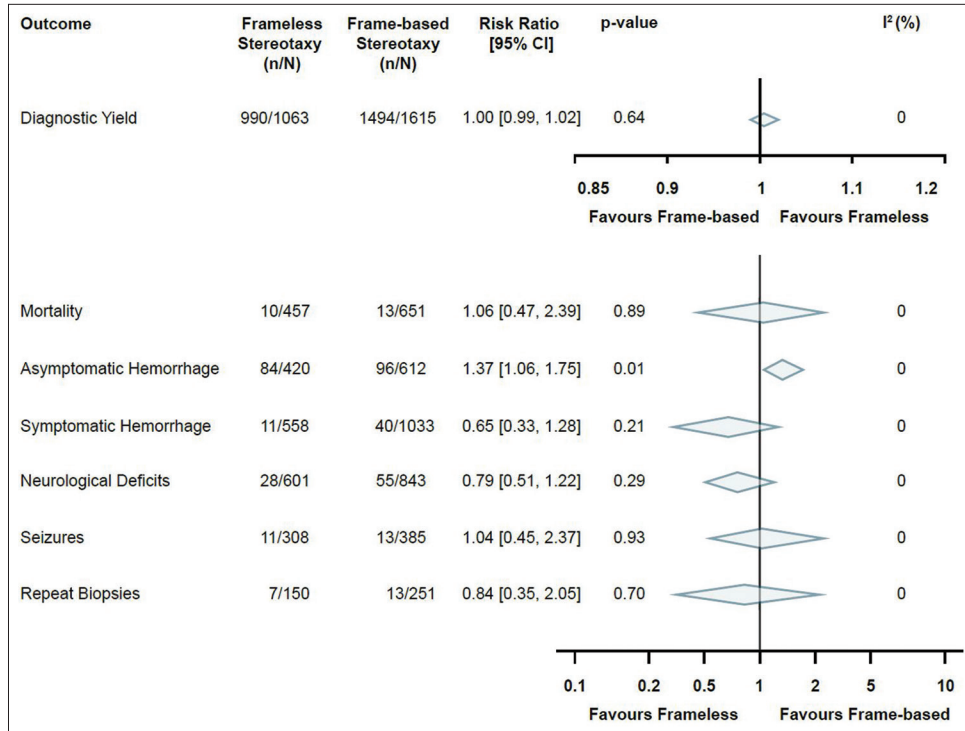
Figure 2: Pooled analysis of risk ratios of measured outcomes.

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Frameless	Risk with Frame-based			
Diagnostic yield	925 per 1,000	925 per 1,000 (916 to 944)	RR 1.00 (0.99 to 1.02)	2678 (17 observational studies, 1 RCT)	■ ⬚ ⬚ ⬚ VERY LOW
Post-biopsy mortality	20 per 1,000	21 per 1,000 (9 to 48)	RR 1.06 (0.47 to 2.39)	1108 (5 observational studies)	■ ⬚ ⬚ ⬚ VERY LOW
Post-biopsy asymptomatic hemorrhage	157 per 1,000	215 per 1,000 (166 to 275)	RR 1.37 (1.06 to 1.75)	1032 (6 observational studies, 1 RCT)	■ ⬚ ⬚ ⬚ VERY LOW
Post-biopsy symptomatic hemorrhage	39 per 1,000	25 per 1,000 (13 to 50)	RR 0.65 (0.33 to 1.28)	1591 (8 observational studies)	■ ⬚ ⬚ ⬚ VERY LOW
Post-biopsy neurological defects	65 per 1,000	52 per 1,000 (33 to 80)	RR 0.79 (0.51 to 1.22)	1444 (11 observational studies, 1 RCT)	■ ⬚ ⬚ ⬚ VERY LOW
Post-biopsy seizures	34 per 1,000	35 per 1,000 (15 to 80)	RR 1.04 (0.45 to 2.37)	693 (4 observational studies)	■ ⬚ ⬚ ⬚ VERY LOW
Repeat Biopsy	52 per 1,000	44 per 1,000 (18 to 106)	RR 0.84 (0.35 to 2.05)	401 (3 observational studies)	■ ⬚ ⬚ ⬚ VERY LOW

CI: Confidence Interval, RR: Risk Ratio, RCT: Randomized Controlled Trial

Figure 3: Grading of Recommendations Assessment, Development, and Evaluation summary of findings.

DISCUSSION

This systematic review of literature and subsequent meta-analysis did not demonstrate any significant clinical difference between reported frame-based and frameless stereotactic brain biopsy techniques. Postbiopsy asymptomatic hemorrhage incidence was the only outcome displaying a significant difference between the two groups.

This analysis showed that biopsies performed with frame-based techniques, contrary to general belief, did not have a higher diagnostic yield. Some of the confounding factors that may have biased this result to be nonsignificant when comparing the two systems include the indications of using either technique as well as the size and depth of lesions in relation to the number of samples taken. With the potential bias of neurosurgeons preferentially using the frame-based apparatus for deeper seated lesions,[6,19] it is conceivable that a surgeon who uses a frameless system for a large low-risk lesion has a better yield with several samples taken than a surgeon using a frame-based system for a small deeper lesion for which fewer samples could be obtained due to risks intrinsic to the lesion and its location. That being said, in this analysis, frameless biopsies actually had a significantly higher proportion of midline versus lobar targets when compared to frame-based biopsies ($P = 0.03$). However, the mean size and depth of the target lesions, along with the number of samples taken, were not analyzed. Another factor that could have influenced the diagnostic yield comparison is the experience of the cited institutions with these stereotactic methods. Seven of the 18 studies[3,4,13,17,19,21,22] which were included in the diagnostic yield analysis transitioned to frameless stereotactic biopsy during their own study period. The learning curve of using the frameless system may have worsened results for the frameless group and skewed the data in favor of the frame-based system. However, this also implies that some of the frame-based systems used in these studies were of older generations, which may have skewed the data in the opposite direction.

Among all publications included in the postbiopsy asymptomatic hemorrhage analysis, the study by Michaud *et al.*[15] carried 82.8% of the weight, driving the significant difference found and favoring frame-based over frameless stereotaxy. In fact, when this study was excluded, the difference between the stereotactic systems became insignificant ($P = 0.78$). Michaud *et al.* also stated that the difference in postbiopsy hemorrhage in their study could be accounted for by the fact that the frame-based patients underwent their CT scan sooner after surgery compared to the frameless group.[15] We are aware of the fact that the observed hemorrhage rate is highly dependent on timing of postoperative imaging. Only by implementing a rigid time stamped postoperative imaging algorithm would a proper comparison of postbiopsy hemorrhage be possible.

In the absence of any difference in terms of histologic diagnostic yield or clinically significant complication rates, it is worthwhile considering factors that do differentiate these techniques. Here, in an effort to improve patient experience and operative efficiency, surgeon and patient experience may influence the decision to favor one method over the other. Frameless techniques carry advantages to patients in terms of comfort. Frame-based approaches require fixation of the frame to the patient's head, and the patient must wear the rigid apparatus for imaging before being taken to the operating room. Although many studies report frame placement as "well tolerated," there have been a number of reports in functional neurosurgery that provides evidence that frame fixation is quite uncomfortable for patients[2,16] if experienced over a significant period of time. The widespread use of intraoperative MRI, however, can minimize the duration the frame is fixed and restrict it to the operating room. Alternatively, one major advantage of frame-based techniques is offsetting the need for general anesthesia. In this analysis, 31.2% of frame-based biopsies required general anesthesia while 97.4% of frameless biopsies required general anesthesia ($P < 0.05$). This is clinically relevant, particularly for the elderly, frail patients who require tissue diagnosis for further management, but cannot tolerate general anesthesia.

Limitations of our study

The first limitation of this review pertains to the restriction of our study to the four large existing databases and to studies published in the English language. Second, the level of evidence available on the topic was deemed poor, with reported outcomes of very low-quality evidence per the GRADE method. Nineteen of the 20 articles included in this analysis were observational studies, significantly lowering the quality of evidence. This meta-analysis included significantly more frame-based ($n = 2050$) than frameless ($n = 1206$) biopsies, which could be a reflection of a lower comfort level with frameless systems in the reporting institutions. It should also be considered that several articles had differing criteria with respect to what was considered a diagnostic specimen. This could have significantly altered the pooled data. In addition, several confounding variables may have impacted whether a specimen was diagnostic, including underlying pathological entity, size of the specimen retrieved, number of samples acquired per surgery, and number of separate tracts and trajectories acquired. However, given that we included published studies from multiple institutions, these factors cannot be well controlled for, unless one performs a controlled trial with a unified tissue acquisition protocol as well as central pathological review of all specimens. There was also a significant difference in the number of studies included in each outcome analysis, ranging from three for repeat biopsies to 18 for diagnostic yield; further limiting the quality of our data. The fewer number of included studies also allowed for

individual articles to have a substantial weight percentage in outcome analysis. This is illustrated by the previous example of how Michaud *et al.*[15] attributed to 82.1% weight in the analysis of postbiopsy asymptomatic hemorrhage. Another example would be how Dammers *et al.*[4] held 64.4% weight of the analysis of postbiopsy mortality. It solely accounted for the high mortality rate cited in this analysis; 2.2% for frameless and 2.0% for frame-based biopsies. When this article was excluded from the analysis, mortality rates dropped to 1.35% and 0.93%, respectively. Finally, this study did not evaluate economic analysis between groups. This may, however, be a deciding factor in some centers to determine which particular stereotactic biopsy technique will be chosen in the absence of any other clinically significant difference between techniques. This is one outcome requiring further research to determine difference between the two techniques.

To the best of our knowledge, there is only one previously reported meta-analysis comparing frame-based versus frameless stereotactic biopsy.[5] Based on 15 included studies, Dhawan *et al.* concluded that the available evidence supported the noninferiority of frameless versus frame-based stereotactic brain biopsies in respect to diagnostic accuracy and adverse clinical outcomes. Our meta-analysis includes five additional studies with a more comprehensive search strategy, corroborating their findings.

CONCLUSION

This meta-analysis provides evidence of noninferiority for frameless biopsy methods when compared to frame-based brain biopsy techniques. There was no significant difference in either biopsy diagnostic yield or the presence of negative clinical outcomes between techniques. As such, we argue that practical considerations, particularly patient experience, should be taken into consideration as a guiding factor in deciding between these two techniques in cases where technical or procedural challenges do not exclude either one of the methods.

In the absence of any evidence to suggest that frameless techniques are less likely to yield the correct histopathological diagnosis, and based on emerging evidence that these techniques are not more likely to cause harm to patients, we suggest to consider this method in routine practice. Further study with granular outcomes such as efficiency, cost-effectiveness, and patient experience as outcomes may mitigate this consideration and are required to develop a comprehensive recommendation of which method to use. However, our study identifies that surgeons should feel confident in both biopsy yield and patient safety regardless of modality used.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Conflicts of interest

There are no conflicts of interest.

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