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Frame-Based Stereotactic Biopsy - A Single Neurosurgeon Experience of 604 Diagnostic Procedures and Literature Review

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ABSTRACT

AIM: Frame-based stereotactic biopsy (SB) is essential in managing patients with suspected intracranial lesions. This study aimed to evaluate the surgical experience of the senior neurosurgeon to define the lesion, radiology, and technique-related factors that affect the diagnostic yield and complications, along with the literature review.

MATERIAL and METHODS: Documents were examined for consecutively performed frame-based SBs from 1999 to 2021. Procedures that are aimed at nondiagnostic purposes were excluded, thus leaving 604 diagnostic procedures. Diagnostic yield, complication rates, and their relationship with clinical variables were investigated.

RESULTS: The diagnostic yield was 98%, with a symptomatic hemorrhage rate of 1.2%, a total morbidity rate of 4.8%, and a mortality rate of 0.83%. Larger tumors (odds ratio [OR]=1.350), experienced neurosurgeon (OR=1.339), and pathologist (OR=462.743), and prebiopsy examination with both computed tomography and magnetic resonance imaging (MRI) (OR=27.062) were associated with an increased diagnostic yield. None of the parameters were statistically significant for nonhemorrhagic morbidity, whereas the increasing number of specimens (OR=1.395) and glial tumors (OR=3.740) were associated with an increased hemorrhagic risk. Likewise, the increasing number of specimens (OR=2.497) along with the increasing age (OR=14.098) were associated with increased mortality risk.

CONCLUSION: Knowledge of stereotactic techniques and meticulous surgical planning is required to enhance the diagnostic yield and safety of SB. Considering the results of this largest, MRI-guided, single-neurosurgeon SB series, we advocate training neurosurgeons on stereotactic techniques, routine use of intraoperative pathological examination, and working with dedicated neuropathologists when possible.

KEYWORDS: Diagnostic yield, Frame-based, Intracranial lesion, Stereotactic biopsy

ABBREVIATIONS: SB: Stereotactic biopsy, **RT:** Radiation therapy, **TRAMs:** Treatment response assessment maps, **PWI:** Perfusion-weighted imaging, **MRI:** Magnetic resonance imaging, **T1W:** T1-weighted, **T2W:** T2-weighted, **CT:** Computed tomography, **IPE:** Intraoperative pathological examination, **PPE:** Permanent pathological examination, **OR:** Odds ratio, **GBM:** Glioblastoma, **MRS:** Magnetic resonance spectroscopy, **PET:** Positron emission tomography, **18F-FDOPA:** Fluoro-18-L-Dihydroxyphenylalanine, **IH:** intracranial hypertension; **HHGs:** High-grade gliomas.

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INTRODUCTION

"If you know the enemy and know yourself, you need not fear the result of a hundred battles" is a well-known quote by Sun Tzu (67). The metaphor of enemy and battle can be respectively used for intracranial lesions and therapeutic strategies in the neurosurgical armamentarium. Precise diagnosis depends on histological and molecular characteristics, thus adequate representative tissue sampling is critical to know your enemy and win the battle (33,38).

From a neurosurgical standpoint, there are two principal approaches for tissue sampling: open surgery and stereotactic biopsy (SB). Conventional surgery provides copious tissue samples with associated higher perioperative morbidity risk; however, SB is the least invasive approach to tissue sampling (3,28,48,74). Image-guided frame-based SB is the most commonly used technique, and previous studies have reported variable data on planning, technique, diagnostic yield rate, morbidity and mortality rates, and postprocedure management (2,28,56). Previous heterogeneous results were due to the management of study cohorts by several neurosurgeons, and the neurosurgical experience was revealed to significantly impact the outcomes (35,55).

The present study aimed to present a retrospective investigation of 604 consecutively performed diagnostic frame-based SBs by a senior neurosurgeon (SP) and review the literature on a recently published large series of SBs.

MATERIAL and METHODS

This retrospective study was approved by the Institutional Review Board of Koç University (2022.021.IRB1.016). Informed patient consent was obtained from all patients or representatives.

Patients and Data Collection

Data of consecutively performed frame-based SBs between 1999 and 2021 by the senior author were retrieved and evaluated. SBs accompanied by another intervention (cyst fenestration, catheter placement, etc.) were excluded.

Indications

Indications were as follows: (a) a lesion that could not be approached by standard craniotomy (deep-seated lesions, etc.), (b) diffusely infiltrating or multifocal lesions, (c) when medical/radiation therapy was superior to resection, (d) suspected lesions that are not eligible for resection (encephalitis, demyelinating diseases, etc.), (e) patients unfit for resection, (f) diagnosis confirmation before (re-)starting therapy, and (g) exclusion/verification of tumor upgrade, recurrence, or radiation necrosis.

Presurgical Imaging and Planning

For stereotactic planning, minimum requirements include thin-slice, contrast-enhanced T1-weighted (T1W), and T2W magnetic resonance images mainly obtained 1 day before biopsy. The pattern of contrast enhancement is noted as homogeneous, poor, or heterogeneous. In the case of homogenous/heterogeneous contrast enhancement, the enhancing area on MRI is chosen as the biopsy target. Otherwise, the center of the T2W hyperintense lesion serves as a biopsy target. A contrast-enhanced computed tomography (CT) scan is rarely preferred over MRI due to patient-related contraindications. In the case of previous radiation therapy, color-coded treatment response assessment maps and perfusion-weighted imaging are used to define the target. Referencing requires a CT with 1.0 mm slices with the patient's head fixed in a Leksell stereotactic frame (Leksell Stereotactic System; Elekta Instruments, Atlanta, GA). The frame is applied in the CT room under sterile conditions, and screws are tightened with thumb and index finger grip to avoid over-tightening. Once all images are acquired, they are automatically merged. When possible, the trajectory is planned to avoid vessels, sulci, ventricles, and functional areas, controlled in a three-dimensional view, and perpendicular and parallel oblique views of needle trajectory. Finally, stereotactic coordinates are calculated. During the study period, three different planning systems were used, namely Leksell GammaPlan® (1999–2005), Leksell SurgiPlan® (2006–2017), and Brainlab Elements™ (2017–2021).

Procedure

Following the reference CT, the patient is transferred to the operating room and is placed in a supine position with the frame attached to the table. However, patients undergoing posterior fossa biopsy are placed in a semisitting position. The coordinates are then manually transferred to the Leksell Stereotactic System®. The procedures are performed either under general anesthesia or local anesthesia. In general anesthesia, the patient is intubated before applying the frame. The surgical site is not shaved, and a percutaneous twist-drill craniotomy is performed using a hand-operated drill. A Sedan side-cutting needle is inserted into a precalculated depth when the patient is normotensive. Then, multiple specimens are taken from different needle track orientations and depths. With a suspected infectious cause, extra specimens are collected for microbiological examination. At that stage of the surgery, the senior neurosurgeon takes the specimen to a neuropathology laboratory for intraoperative pathological examination (IPE) and examines the tissue along with the pathologist. Without histology abnormality, further samples are obtained at different depths along the same trajectory, and a second trajectory was never needed. With a diagnostic IPE, the frame is removed and a CT scan is postoperatively performed for most patients. Data regarding the operating and overall procedure time is acquired using the hospital's digital database. The overall procedure time included the stereotactic frame application, stereotactic CT acquirement, transportation to the operating room, and the operating time. The experience of the neurosurgeon was evaluated based on the level of expertise during each stereotactic biopsy (SB), as time from the start of neurosurgical practice to the SB date.

Evaluation of Biopsy Results

IPE and permanent pathological examination (PPE) reports were reviewed to ascertain whether the results satisfactorily answered the clinical question. A discordant IPE with PPE or PPE was determined to be nondiagnostic. A PPE was nondiagnostic if (a) the final histologic sample was inadequate or was characterized as nondiagnostic by the pathologic

report, (b) the patient required a second biopsy procedure, or (c) the tissue was characterized as normal or reactive. The experience of the pathologist was evaluated based on the expertise level during each SB, as time from the start of pathologic practice to the SB date.

Statistical Analysis

Our study investigated the primary outcome as diagnostic yield. The secondary outcomes included nonhemorrhagic morbidity, asymptomatic and symptomatic hemorrhage, and mortality. Morbidity was classified into temporary deficits, which were completely resolved within 10 days, and persistent permanent deficits. Asymptomatic postbiopsy hemorrhage was defined as hemorrhage noted on imaging but without any clinical consequences. Mortality included biopsy-related mortality.

The Statistical Package for the Social Sciences version 26 (SPSS Inc., Chicago, Illinois, United States) was used for statistical analysis. Descriptive statistics were used for qualitative and quantitative variables. Associations between variables were analyzed using the Chi-square test or Student t-test and analysis of variance, where suitable. Logistic regression analysis was performed to investigate univariate associations when multivariate logistic regression analysis was impossible. A p-value of <0.05 was considered statistically significant.

RESULTS

General Characteristics

Within 22 years, 600 consecutive patients underwent 604 frame-based SBs, of which 4 patients were re-biopsied due to an inconclusive diagnosis. The male–female ratio was 1.6. The mean age was 50.9 ± 17.87 years. The median Karnofsky performance status score was 80%. The most frequent presenting symptom was paresis (30.1%). SB was done either to make a diagnosis (93.7%) or to elucidate diagnosis in patients with a predisposing factor, namely history of radiation therapy (RT) (n=7), primary cancer (n=23), and others (n=8).

Most tumors were supratentorial (n=569) and the most common localizations were the frontal (27.2%), followed by the thalamic (18.5%) and parietal (13.7%) areas. Most targets showed laterality (70.2%). The majority of lesions were solitary (56.8%), with a median diameter of 2.9 cm (range: 1.0–7.5 cm). The most frequent MRI enhancement pattern was poor/heterogeneous enhancement (75.5%).

Most targets were planned on magnetic resonance imaging (MRI) (97.4%). The most commonly used planning system was Leksell GammaPlan® (52.6%), followed by Leksell SurgiPlan® (36.8%) and Brainlab Elements™ (10.6%). The majority of SBs were performed under local anesthesia (94.5%). All biopsies were performed in a supine position, and the most common route was the transfrontal (85.3%), followed by the transparietal (13.6%) route. A median of 2 samples (range, 2–8) was collected. The mean overall procedure and operating times were 84.7 ± 16.24 min and 34.7 ± 8.82 min, respectively.

Table I displays the general patient characteristics, lesions, biopsies, and pathologies.

Table I: General Characteristics of the Patients, Lesions, Biopsies and Pathologies in the Series

Parameters	Value
Number of patients	600
Number of biopsies	604
Age, median, years	53 (5-89)
Gender, male	366
Karnofsky Performance Status score, median, %	80 (40-90)
Presenting symptoms (%)	
Paresis	30.1
Headache	27.8
Seizure	11.6
Dizziness	6.3
Visual problems	6.3
Personality change	6.1
Speech disorder	4.1
Memory impairment	4.1
Other	3.6
Duration of symptoms, median, weeks	8 (1-208)
Predisposing factors, n	38
Lesion location (%)	
Lobar	57
Subcortical nuclei	21.6
Midline	8.1
Posterior fossa	6
Other	7.3
Lesion characteristic (%)	
Solitary	56.8
Multiple	24.7
Diffuse	18.5
Maximum lesion diameter, median, cm	2.9 (1-7.5)
Contrast enhancement (%)	
Heterogenous	48.7
Poor	26.8
Homogenous	24.5
Planning imaging modality (%)	
CT only	2.6
MRI / CT	97.4
Anesthesia (%)	
General	5.5
Local	94.5
Biopsy samples taken, median, n	2 (2-8)
Duration of the procedure, mean, minutes	
Operative time	34.7 ± 8.82
Overall	84.7 ± 16.24
Lesion nature according to permanent pathological examination (%)	
Glial tumor	67.2
Metastasis	8.5
Lymphoma	8.9
Other tumoral	3
Non-tumoral lesions	10.4
Inconclusive	2

Diagnostic Yield

IPE was performed in all biopsies, and a preliminary diagnosis was achieved in 527 patients providing a diagnostic yield of 87.3%. A definitive diagnosis was achieved in 592 patients providing a diagnostic yield of 98% in PPE. The most frequent diagnosis was glial tumors (67.2%). A good agreement was found between the IPE and PPE, κ=0.749, p<0.001. All discordant cases are detailed in Table II.

Twelve biopsies were found to be inconclusive or nondiagnostic. Of those, eight patients did not consent for additional invasive procedures. Thus, four patients were submitted to a second SB, and a diagnosis could be made in all patients, including metastasis, lymphoma, germinoma, and high-grade glioma (HGG), respectively. Biopsy specimens in seven cases (1.2%) were labeled as perilesional and were in the nondiagnostic group. The subgroup analysis revealed that these specimens were more common in the group with 1–3 biopsy specimens (6 vs. 1, p=0.476), poor/heterogeneous contrast enhancement (5 vs. 2, p=0.682), and GammaPlan® era (6 vs. 1, p=0.125); however, none of these reached statistical significance.

Of the eight predictor variables, only four were statistically significant in the logistic regression including diameter, neurosurgeon and pathologist experience, and the type of radiological examination. Larger tumors (odds ratio [OR]=1.350), the experience of the neurosurgeon (OR=1.339) and pathologist (OR=462.743), and prebiopsy examination with both CT and MRI (OR=27.062) were associated with an increased diagnostic yield (Table III).

Morbidity and Mortality

A postoperative CT scan was performed in 602 biopsies. Overall morbidity and mortality rates were 4.8% (29/604) and 0.83% (5/600), respectively. Asymptomatic hemorrhage was observed in 17 (2.8%) patients. Seven patients (1.2%) had symptomatic intracranial hemorrhage, of which six underwent surgery. Histopathology showed glioblastoma (GBM) in four, pilocytic astrocytoma in one, and metastasis in one patient. One patient who was diagnosed with gliomatosis cerebri had a subdural hematoma that showed spontaneous regression. Procedure-associated mortality was 0.7% (n=4), and all patients were diagnosed with GBM. Five patients, including four with symptomatic intracranial hemorrhage, suffered an epileptic seizure (0.7%) and one (0.17%) occurred without intracranial hemorrhage evidence.

Of the 11 predicted variables, none were statistically significant for nonhemorrhagic morbidity in the logistic regression. Contrarily, the increasing number of specimens (OR=1.395) and glial tumors (OR=3.740) were associated with an increased hemorrhagic risk. Likewise, the increasing number of specimens (OR=2.497) along with the increasing age (OR = 14.098) were associated with increased mortality risk (Table III). Although it did not reach statistical significance (p=0.79), all mortalities were observed before 5 years of neurosurgical expertise of the SP.

DISCUSSION

A series of 604 consecutive frame-based SBs were analyzed. The diagnostic yield was 98%, with symptomatic hemorrhage, total morbidity, and mortality rates of 1.2%, 4.8%, and 0.83%, respectively. Numerous authors have previously published about frame-based SBs, and the assessment of techniques and related risks remains essential. Table IV summarizes the data for frame-based (16,17,20,30-32,36,64) and frameless (12,15,37,39,44,62,71) series, which describe at least 300 and 50 patients, respectively, reported over the last 20 years. This study is the largest MRI-guided biopsy cohort of patients who underwent frame-based SBs by a single neurosurgeon.

Diagnostic Yield

Despite recent developments, the negative biopsy rate approaches 5% in the literature (37). Literature results regarding lesion and surgical technique-related parameters are heterogeneous. We found that only larger tumors (OR=1.350), experienced neurosurgeons (OR=1.339) and pathologists (OR=462.743), and prebiopsy examination with both CT and MRI (OR=27.062) were associated with an increased diagnostic yield.

A smaller lesion unavoidably yields less tissue for examination, which is crucial in the diagnostic yield. Waters et al. analyzed 267 patients and revealed that SB of lesions of <1 cm^3 resulted in a significantly lower diagnostic yield (76.2% vs. 94.8%, p=0.0081) (69). Similarly, Taweesomboonyat et al. reviewed 89 frameless SBs and revealed that lesions of >3

Table II: Discordant Diagnoses Between Intraoperative and Permanent Pathological Examinations

		Intraoperative pathological examination					
		Glial	**Metastasis**	**Lymphoma**	**Other tumoral**	**Non-tumoral**	**Inconclusive**
Permanent pathological examination	**Glial**	386	1	1	1	0	17
	Metastasis	1	46	1	0	0	3
	Lymphoma	2	1	32	1	0	18
	Other tumoral	2	0	0	14	0	2
	Non-tumoral	7	0	0	0	34	22
	Inconclusive	1	0	0	0	0	11

Table III: Logistic Regression Predicting Diagnostic Yield, Morbidity and Mortality Based on Patient, Lesion and Biopsy Parameters

Diagnostic yield			
	B	**p**	**OR**
Lesion location	.909	0.456	-
Lesion diameter	.300	*<0.001*	*1.350*
Number of lesions	-.004	0.995	-
Imaging modality used for planning	3.298	*0.005*	*27.062*
Contrast enhancement pattern	-17.505	0.995	-
Number of specimens	0.297	0.481	-
Experience of pathologist	6.137	*0.008*	*462.743*
Experience of neurosurgeon	.292	*0.042*	*1.339*
Non-hemorrhagic morbidity			
	B	**p**	**OR**
Age	-.025	0.984	-
Gender	-.592	0.615	-
KPS	.068	0.324	-
Lesion location	15.994	0.998	-
Lesion diameter	.042	0.339	-
Number of lesions	-.398	0.700	-
Anesthesia type	15.745	0.998	-
Number of specimens	-1.206	0.237	-
Operative time	-.009	0.886	-
Permanent section diagnosis	.000	1	-
Experience of neurosurgeon	.051	0.996	-
Hemorrhage			
	B	**p**	**OR**
Age	-.052	0.922	-
Gender	-.112	0.808	-
KPS	-.047	0.076	-
Lesion location	-.005	0.997	-
Lesion diameter	.015	0.510	-
Number of lesions	-.516	0.262	-
Anesthesia type	17.998	0.998	-
Number of specimens	*.333*	*0.027*	*1.395*
Operative time	-.025	0.321	-
Permanent section diagnosis	1.319	*0.038*	3.740
Experience of neurosurgeon	-.078	0.100	-
Mortality			
	B	**p**	**OR**
Age	2.646	*0.029*	*14.098*
Gender	-.478	0.697	-
KPS	-.070	0.296	-
Lesion location	14.680	0.998	-
Lesion diameter	-.004	0.951	-
Number of lesions	-.871	0.465	-
Anesthesia type	15.408	0.998	-
Number of specimens	.915	*0.004*	*2.497*
Operative time	-.037	0.581	-
Permanent section diagnosis	.670	0.601	-
Experience of neurosurgeon	-.101	0.478	-

cm were associated with higher diagnostic yield (OR=6.46) (63). Tsermoulas et al. reported that the odds of achieving a diagnosis increased 7-fold with each cm^3 increase in volume (66). Our study detected a 1.307-fold increased diagnostic yield. Frame-based SB is traditionally preferred for maximal targeting precision in smaller lesions (70). Frame avoids the necessity for intraoperative registration, thus increasing the overall precision (40). The overlap of both frame-based and frameless methods should be noted possible due to the newly developed navigation systems. Thus, Owen and Linskey suggested that the mean localization error rises to >3–4 mm in frameless technique depending on the registration technique when similar standards are applied to frameless systems (51). Thus, several neurosurgeons sympathy frame-based SB for lesions of <10 mm (54). Grunert et al. even suggested that frameless biopsy should be restricted to lesions of >15 mm. In addition to the lesion size, the morphology affects the ideal target point selection (21). Former studies revealed that SBs in hypodense and/or poorly enhanced lesions were most likely nondiagnostic. However, none were statistically significant (26,55,66,73). Most hypodense are speculated as low-grade gliomas, and distinguishing these from gliosis can be challenging. Additionally, Tsermoulas et al. stated that enhancement only denotes increased permeability of neo-vessels and no evidence supports the more dominant neoplastic cell proliferation or viability (66). This might elucidate the absence of a relationship between the enhancement and diagnostic yield in these and our study.

Lara-Almunia and Hernandez Vicente revealed that SBs of hypodense lesions without enhancement exhibited lower diagnostic yield (OR=0.313) (35). Recently, in a biopsy series of 208 patients, Chen et al. stated that enhancement was a critical factor for a diagnostic biopsy (11). Several imaging modalities have been proposed to overcome contrast-related shortcomings. T2-weighted/fluid-attenuated inversion recovery sequence guides SB in nonenhancing lesions, but peritumoral edema might hinder the accurate tumoral localization. MR spectroscopy (MRS) can reflect metabolic changes; however, it is prone to artifacts. Moreover, multivoxel MRS is infeasible in multiple lesions, as visualizing all withinside the identical plane is challenging (1). Chen et al. reported using conventional MRI with MRS and perfusion-weighted imaging (PWI) in 17 patients and achieved 100%

Table IV: Large, Single-Center Series of Frame-Based (N≥300) and Frameless (N≥50) Stereotactic Biopsy Series Published in the Last 20 Years

Frame-based biopsy series								
Author, year	**Study design**	**n**	**Technique**	**Diagnostic yield (%)**	**Hemorrhage (%)**	**Morbidity (%)**	**Mortality (%)**	**Procedure time (min)**
Kreth et al., 2001 (32)	Single surgeon*, PS	345	RM	98	0.9	2.9	0	NR
Field et al., 2001 (17)	Multi surgeon, RS	500	CRW	94.4	1.2	9.2	0.2	NR
Kim et al., 2003 (30)	Multi surgeon, RS	300	RM	91.7	NR	6.2	0.6	NR
Grossman et al., 2005 (20)	Multi surgeon, RS	355	CRW	93.8	3.6	7	0.6	NR
Tilgner et al., 2005 (64)	Multi surgeon, RS	5000	RM	95.4	NR	1.3	0.7	NR
Kongkham et al., 2008 (31)	Single surgeon, PS	622	BRW/CRW	98.4	4.8	6.9	1.3	NR
Eibach et al., 2014 (16)	Multi surgeon, PS	315	Leksell	NR	3	6.3	NR	NR
Lara-Almunia et al., 2020 (36)	Multi surgeon, RS	429	Todd-Wells, CRW, Leksell	90.7	9.5	3.9	0.93	NR
Current study, 2021	Single surgeon, RS	604	Leksell	98	1.2	4.8	0.83	84.7 ± 16.24
Frameless biopsy series								
Dorward et al., 2002 (15)	Multi surgeon, RS	76	EGN	98.6	0	14.4	1.3	56.3 ± 23.6
McGirt et al., 2005 (44)	Multi surgeon, RS	110	SS	93**	4**	18.2	1**	NR
Smith et al., 2005 (62)	Multi surgeon, RS	74	SS (88%), BL (7%), ISG (5%)	90.5	0	1.3	1.3	185±6
Woodworth et al., 2006 (71)	Multi surgeon, RS	110	ISG	89	4	15	1	NR
Dammers et al., 2008 (12)	Multi surgeon, RS	164	SS	88.9	2.4	11.5	3.7	127±33
Livermore et al., 2014 (37)	Multi surgeon, RS	95	SS	95.8	3.7**	NR	0.6**	103
Lu et al., 2015 (39)	Multi surgeon, RS	113	GE	89.4	NR	19.6	0	NR

PS: *Prospective,* ***RS:*** *Retrospective,* ***RM:*** *Riechert mundinger,* ***CRW:*** *Cosman-Roberts-Wells,* ***BRW:*** *Brown-Roberts-Wells,* ***EGN:*** *EasyGuide neuro by philips medical systems,* ***SS:*** *Stealth station surgical navigation by medtronic,* ***BL:*** *Brainlab cranial navigation,* ***ISG:*** *ISG viewing wand system,* ***GE:*** *GE Healthcare cranial navigation system.*

**performed or supervised*

***also including frame-based biopsy series.*

diagnostic yield by targeting the regions with high choline/N-acetyl aspartate index and high perfusion (11). In unclear MRI findings, molecular imaging may offer extra data on tumor metabolism. Todeschi et al. reported 20 patients who underwent SB for a nonenhancing tumor but with hypermetabolism on Fluoro-18-L-Dihydroxyphenylalanine positron emission tomography (PET) and achieved 100% diagnostic yield. However, economic burden and radiation exposure should be noted as the main PET limitations (65). Our study revealed that association of prebiopsy examination with both CT and MRI (OR = 24.998) with increased diagnostic yield compared to CT-only examination, and all patients with previous RT also underwent treatment response assessment maps (52) and PWI (Figure 1).

In addition to proper targeting, adequate samples should be obtained. Numerous studies have recommended that the increasing number of samples improves the diagnostic yield. In their study of 86 cases, Jain et al. revealed that diagnostic yield increased from 76.5% for one sample to 84%–88.2% for two and three samples, and 100% for five to six samples (27). Similarly, Brainard et al. revealed that up to four samples enhanced the diagnostic yield by an extra 22% (8). Meanwhile, Lara-Almunia and Hernandez-Vicente suggested that multitarget sampling might determine histologic differentiation in mixed lesions and enhance diagnostic yield and reported a greater diagnostic yield with several samples taken from two or more targets (p=0.021) (35). Our study could not find a relationship between the number of specimens and the diagnostic yield (p=0.481). Additionally, a secondary trajectory was unnecessary in any patients. The biopsy tissue must also have satisfactory quality in addition to the quantity. Former studies established that IPE decreased the number of nondiagnostic samples and agreed with definitive diagnosis in 90.3% of cases (12,13,18,35,37,50,64,75). Our study result is consistent with prior reports, with a 7.561-fold increase in diagnostic yield with IPE. Overall, concordance between IPE and PPE was 95.7%. In our practice, the SP directly brings the specimen to the neuropathologist and examines the specimen together. During the biopsy, we wait for a response from IPE to ascertain whether the specimen established the suspected diagnosis or additional samples are needed. IPE lasts only a few minutes and does not unjustifiably lengthen the procedure. It helps macroscopic and microscopic evaluation by the neurosurgeon and enables the discussion of the clinical picture, radiologic features, and the most probable diagnosis with the neuropathologist. A retrospective study reported that IPE reduced negative biopsy risk from 11.1% to 3.7% (37). Thus, IPE is extremely useful, particularly for small and/or deep location lesions (18). These findings and our experience prove the significance of IPE in the diagnostic yield. Contrarily, Shooman et al. stated that IPE should not be regularly endorsed when multiple tissue samples are taken (61). Supporting this, IPE requirement is questioned with the

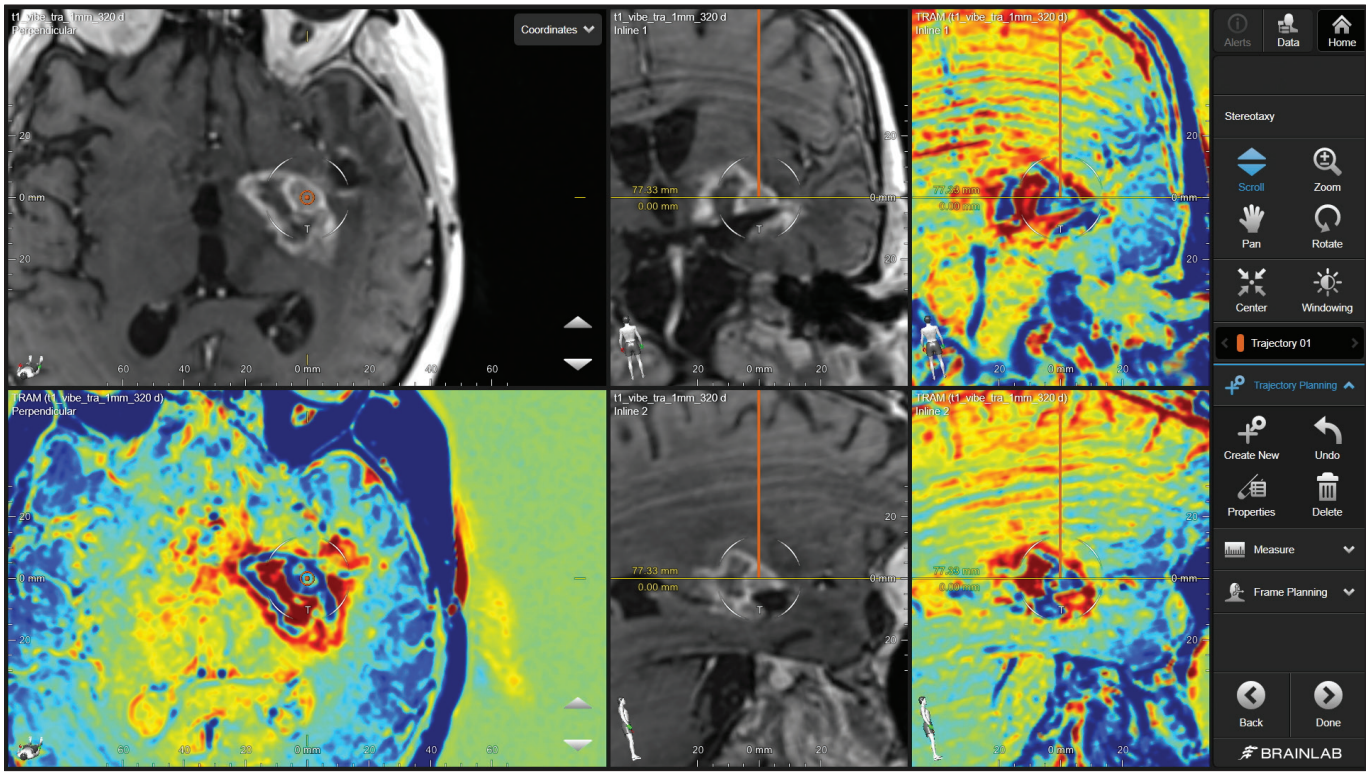

Figure 1: A case of a putaminal mass in a patient with a radiation therapy history for a glial tumor. Contrast-enhanced axial T1-Weighted magnetic resonance images show a heterogeneously enhancing lesion. Color-coded Treatment Response Assessment Maps provided by Contrast Clearance Analysis Module of Brainlab Elements™ (Brainlab AG, Munich, Germany). An anterolaterally located area with a relatively high contrast clearance (depicted in blue) was targeted. A diagnosis of the recurrent tumor was concluded after the biopsy.

emergence of tissue fluorescence-assisted SB. Catapano et al. examined 11 SBs with fluorescence assistance and achieved a 100% diagnostic yield. They reported that the number of samples was the applicable minimum and that eliminating IPE significantly reduced the procedure time (42.09 vs. 69.72 min) (9). Millesi et al. also observed a significantly shorter operating time (41 vs. 77 min) and decreased specimens (3.6 vs. 4.9) with fluorescence-assisted SB in 79 patients (45). However, it should be noted that experienced neuropathologists should conduct both IPE and PPE to obtain a high level of reliability. Our study associated the experience of the pathologist (OR=462.743) with an increased diagnostic yield.

The target and trajectory selection explicitly rely on the neurosurgeon. In their series of 407 cases, Ranjan et al. revealed that the most experienced neurosurgeon had a lower negative biopsy rate (2.4%) than that of others (5.7%). However, the authors concluded that experience is not required to achieve a high yield following specific guidelines on patient and target selection (55). Lara-Almunia and Hernandez Vicente revealed that inexperienced neurosurgeons performed nearly thrice more nondiagnostic biopsies than experienced neurosurgeons (16.6% vs. 6.9%) and concluded that experience was the most obvious predictive factor (OR=4.049) for diagnostic yield (35). Additionally, experienced neurosurgeons were more likely to ask for IPE than inexperienced neurosurgeons (87.2% vs. 52.5%). Other studies did not make the same observation. In a study of 259 CT-guided SBs done by 28 surgeons, O'Neill et al. revealed that experience did not affect the failure and complication rates (50). Our study revealed that the yearly experience of the neurosurgeon (OR=1.339) was associated with an increased diagnostic yield. Additionally, all mortalities were observed before 5 years of neurosurgical expertise of the SP although not statistically significant (p=0.79).

Complications

Frame-based SB has minimal morbidity and mortality than other cranial surgeries. A recent review by Riche et al.(56) revealed the overall morbidity and mortality rates of 3%–13% and 0.7%–4%, respectively. Symptomatic hemorrhage rate was reported as 0.9%–8.6%. The overall morbidity, mortality, and symptomatic intracranial hemorrhage rates of 4.8%, 0.83%, and 1.2%, respectively, in our series were in line with the literature. Of the 11 predicted variables, none were statistically significant for nonhemorrhagic morbidity. Contrarily, the increasing number of specimens (OR=1.395) and glial tumors (OR=3.740) were associated with an increased hemorrhagic risk. Likewise, the increasing number of specimens (OR=2.497) along with the increasing age (OR = 14.098) were associated with increased mortality risk.

Morbidity in SB is primarily due to postbiopsy hemorrhage. However, brain edema and epileptic seizures have also been described (49). Edema is an undervalued but severe complication, as mortality is almost inevitable in most patients (24). It mainly happens in patients who previously suffered from intracranial hypertension (IH) and HGGs that are treated with corticosteroids (22). Neovascularization and abnormal vessel structure were speculated to increase the edema following blind manipulation in high-grade lesions (5). Patients with IH and lesser intracranial compliance cannot tolerate a small volume increase; thus, a slight volume increase by the edema, hemorrhage, or the inserted biopsy device could all precipitate the neurological impairment. Bernstein and Parrent revealed that three patients with large bilateral GBMs died following SB (5). Seizure is also another morbidity. The total postbiopsy seizure incidence is low (0.5%–2%); however, several neurosurgeons closely monitor patients who have prebiopsy seizures. McGirt et al. (44) revealed that patients with prebiopsy seizures were not prone to encounter a postbiopsy seizure than patients without seizures and only 4% of patients with prebiopsy seizures experienced postbiopsy seizures. Yamada et al. revealed a 2.2% postbiopsy seizure rate (72). Dammers et al. revealed comparable results with a rate of 1.3% (12). Chen et al. revealed 4 cases (1.34%) of new-onset seizures without hemorrhage on postoperative CT scan (10). Our study observed postbiopsy seizures in five patients, one without hemorrhage on postbiopsy CT and the remaining with prebiopsy seizures. All patients were well managed with antiepileptic drugs. Postbiopsy permanent neurological impairment has been described in 0%–3.9% of patients in the literature (56). McGirt et al. evaluated the medical records of 270 patients who underwent SB and revealed diabetes mellitus (OR=3.73), thalamic lesions (OR=4.06), and basal ganglia lesions (OR=3.29) as independent risk factors. Pontine biopsy and prebiopsy seizures were not found as risk factors (44). Like McGirt et al., numerous authors also revealed deep-seated lesions as a risk factor for postbiopsy morbidity (44). Kongkham et al. revealed that deep lesion location presented a significant relationship (OR=1.82) with the total complication rate. Regarding the location, SB in the eloquent cortex and brainstem is expected to cause more neurological deterioration (31). Bouvier et al. revealed postbiopsy transient neurological worsening in 26% of patients with perirolandic lesions (6). More than one needle trajectory also increased the neurological deficits by 27% in deep-seated lesions (44). The reported morbidity rates were 6.7% in children (23) to 19.2% in adults in brainstem biopsy (53). Potential complications include cranial nerve deficits, hemiparesis, hydrocephalus, cerebrospinal fluid leak, and wound infection (25). High transient and permanent morbidity and mortality rates have concluded that brainstem biopsy is too risky. However, other investigators established that SBs are related to comparatively lower morbidity. A meta-analysis of 1480 brainstem SBs reported an overall morbidity of 7.8%, a permanent morbidity of 1.7%, and a mortality of 0.9% (29). Likewise, a meta-analysis of 735 SBs reported an overall morbidity of 6.7%, a permanent morbidity of 0.6%, and a mortality of 0.6% (23). Despite relatively higher morbidity risk, SBs of brainstem tumors are still recommended as some patients might receive inadequate therapy with an incorrect radiological diagnosis. Furthermore, the role of molecular markers in possible treatments should not be ignored (53,57). The present series included six infratentorial lesions, of which five were in the brainstem; none of these patients experienced postbiopsy neurological worsening. However, small cohort prevents a significant risk analysis of this subgroup. The present study revealed no relationship between the several other patient and lesion features and increased nonhemorrhagic morbidity risk.

The most common complication in published series is hemorrhage, with varying rates from 0.9% to 8.6% (56). The heterogeneity can be attributed to various definitions of hemorrhage in the studies. Most studies only consider symptomatic hemorrhage, and the rate may be as high as 59.8% when all hemorrhages (symptomatic + asymptomatic) are considered (56). A few risk factors are explained, but none are strongly related to symptomatic hemorrhage (20). The deep-seated location and lymphoma histology were related to postbiopsy hemorrhage (37,42,60). A population-based analysis of 7514 patients by Malone et al. revealed that hemorrhage is related to advanced age (≥60 years, OR=1.90), hydrocephalus (OR=3.02), and cerebral edema (OR= 2.16) and is less likely with a primary malignant neoplasm (OR=0.73). Similar findings were revealed in several studies regarding the SBs of malignant lesions (42). Grossman et al. revealed no significant differences in the complication rates between high and low-grade tumors (20). Konghkham et al. did not find any association between the pathology and total complication rate or risk of hemorrhage (31). Contrarily, Bernstein and Parrent detected that hemorrhagic complication was 6.4% in HGG, 6.3% in lymphoma, and 2.8% in metastasis (5). Kulkarni et al. revealed that 63% of all hemorrhages were HGG biopsies, whereas 35% were due to lymphoma biopsies (34). Comparable results were described by Malikova et al. (41), Dammers et al. (12), Kim et al. (30), Sawin et al. (59), and Livermore et al. (37). In our series, seven patients (1.2%) had symptomatic intracranial hemorrhage, PPE-disclosed GBM in four, pilocytic astrocytoma in one, and metastasis in one. Similar to the literature, glial tumor pathology (OR=3.740) was related to an increased hemorrhagic risk. Therefore, HGGs have a greater tendency to postbiopsy hemorrhage. Procedural features, such as the number of specimens, instrumentation, and neurosurgeon's expertise, were also evaluated in the literature. In our study, approximately all procedural factors were standardized, and their effects were minimized. Additionally, all samplings were performed with the same side-cutting Sedan-type instrument. The literature provides contradictory data regarding the role of increasing biopsy specimens and complication risk. Morbidity was significantly associated with the number of biopsy attempts according to Sawin et al. (59). McGirt et al. (44) revealed a correlation between increased biopsy attempts and neurologic deficits, but only in patients with deep-seated lesions. An increasing number of specimens (OR=1.395) was also associated with hemorrhage in our series. However, Field et al. (17), Grossman et al. (20), Kim et al. (30), and Kreth et al. (32) did not find a correlation between the number of biopsy attempts or the instrument used and adverse events. Importantly, surgical procedures are the leading cause of bleeding, and precautions should be taken to avoid vessel injury (46). Susceptibility-weighted imaging helps detect small veins to avoid hemorrhage in stereotactic techniques (58). Future advancements of SB should include incorporating optical probes for real-time vessel detection (2). Better visualization is essential in preventing vessel injury, thus using planning systems with more targeted functions is a must. Most (91.7%) of the hemorrhagic complications were in the GammaPlan® and SurgiPlan® era, although without statistical significance (p=0.376).

SB has a low complication rate; however, mortality ranges from 0% to 4% and is related to postbiopsy hemorrhagic complication (56). Our study revealed a 0.7% procedure-associated mortality, of which all had a postbiopsy hemorrhage. Several factors for mortality were documented in the literature; however, associative risk factors rather than causative factors were primarily discovered. In our study, as a consequence of hemorrhage, an increasing number of specimens (OR=2.497) along with increasing age (OR=14.098) was associated with increased mortality risk. Older age may be speculated to increase the odds of intracerebral hemorrhage due to small-vessel disease and thus leads to increased mortality; however, age was not a predictor of hemorrhagic complications in our study. Therefore, the effects of age might be due to other age-related factors. However, the age at which we perceive a person to be elderly is changing since patients become fitter and more independent as they age.

Frame-Based Versus Frameless Biopsy

Frame-based and frameless SBs are usually compared in terms of safety, complications, and procedural parameters. The decision to sympathize with one method over another may be influenced by the neurosurgeon's and the patient's experience. The frame-based SB is believed to be associated with several disadvantages. First, a frame must be attached to the patient's head and the patient must wear the frame for reference imaging. These steps were reported as stressful (47). However, Bradac et al. (7) revealed that visual analog scale measurements of anticipated discomfort were not significantly different between frame-based and frameless groups (3.2 ± 2.7 vs. 2.4 ± 1.3, p=0.207). Second, frames make it harder for the anesthesiologist to access the airway if necessary. Third, specimens can only be collected from preoperatively determined targets. Therefore, the time spent with the frame is minimized nowadays since we only perform CT and fuse with MRI that was obtained 1 day before the biopsy. Alternatively, one key advantage of frame-based SB is the elimination of necessary general anesthesia. In their analysis of 2050 frame-based and 1206 frameless SBs, Kesserwan et al. revealed that only 31.2% of frame-based SBs needed general anesthesia compared to 97.4% in frameless SBs. This rate was even lesser (5.5%) in our study (28). This is clinically relevant for elderly or unfit patients who cannot tolerate general anesthesia.

The lesion size remained debatable since most biopsied lesions with the frameless technique are >15 mm. This may help overcome drift, tremor, and registration errors during frameless techniques. However, robot-assisted SB is also an increasing approach in neurosurgical armamentarium as a possible solution for these errors. Robots are limited with geometric inaccessibility and image registration errors (43). Georgiopoulos et al. compared frameless and frame-based SB in 28 patients and speculated that the comparatively large (15–55 mm) lesions in the frameless group were one of the causes for a comparably suited frameless approach (19). Another speculated parameter is the average time required to complete the biopsy. Conflicting results were reported in the literature; however, frameless SB is commonly believed to be

related to a shorter operating room occupancy (15). However, Dhawan et al. revealed a shorter procedure time for a frame-based cohort (p=0.01) in a meta-analysis (14). The authors speculated that this outcome could be skewed because frame-based SBs were more likely to involve local anesthesia. Georgiopoulos et al. revealed no significant difference between the two groups regarding either the operating time (48.1 ± 13.8 vs. 58.7 ± 18.4 min., p = 0.22) or the operating room occupancy (82.1 ± 22.4 vs. 79.1 ± 22.7 min.; p=0.75) (19). These findings are convincing; however, the actual time savings will differ based on institutional workflow. Comparable with the literature, the mean overall procedure duration and operating time were 84.7 ± 16.24 min and 34.7 ± 8.82 min, respectively, in our study.

Postbiopsy Care

The management of postbiopsy patients is disputed, particularly whether patients must receive routine postbiopsy CT. Numerous studies have criticized and recommended postbiopsy CT only in cases of intraoperative hemorrhage, longer times to extubation, or new-onset deficits (16,68). Other studies supported overnight hospitalization because of delayed hemorrhage risk (17,20). Kulkarni et al. revealed that the negative predictive value of postbiopsy CT was 100% in delayed deterioration as no delayed worsening was found in patients who had no new-onset neurological deficit and no hemorrhage on CT scan (34). Similarly, Barkley et al. suggested that any size hemorrhage on postbiopsy CT was related to a higher new-onset deficit and seizure risk (4). Therefore, postoperative CTs should be routine in our current practice.

Limitations

The major limitation of the present study was its retrospective nature. The surgeon-, instrument-, and procedure-related factors were minimized; however, the single-surgeon nature of the study may introduce the possibility of bias. Further, the reported SB cases in this study may not represent the patients who underwent SB at other institutions. Contrarily, the reported cohort is the largest MRI-guided biopsy cohort of patients undergoing frame-based SBs by a single neurosurgeon using the same instruments.

CONCLUSION

SB of intracranial lesions will always be essential in diagnosing and managing patients. SB can seldom result in life-threatening consequences, regardless of the probable pathology. Setting pre-, intra-, and postbiopsy rules and sticking to those rules is of utmost importance. Never forget the well-known quote of Sun Tzu: “The general who wins the battle makes many calculations in his temple before the battle is fought. The general who loses makes but few calculations beforehand.” (67).

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AUTHORSHIP CONTRIBUTION

Study conception and design: YS, SP

Data collection: YS, GA, AHL

Analysis and interpretation of results: YS, GA, AHL

Draft manuscript preparation: YS, GA, AHL

Critical revision of the article: YS, SP

Other (study supervision, fundings, materials, etc...): SP

All authors (YS, GA, AHL, SP) reviewed the results and approved the final version of the manuscript.

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