Frame-based Stereotactic Biopsy: Description and Association of Anatomical, Radiologic, and Surgical Variables with Diagnostic Yield in a Series of 407 Cases

Monica Lara-Almunia[1] Javier Hernandez-Vicente[2]

[1] Department of Neurosurgery, Son Espases University Hospital, Palma, Spain
[2] Department of Neurosurgery, University Hospital of Salamanca, Salamanca, Spain

Address for correspondence Monica Lara-Almunia, MD, PhD, Department of Neurosurgery, Son Espases University Hospital, Palma, Mallorca 07010, Spain (e-mail: mnclr23@gmail.com).

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Abstract

Background and Study Aims Stereotactic biopsy is a versatile, minimally invasive technique to obtain tissue safely from intracranial lesions for their histologic diagnosis and therapeutic management. Our objective was to determine the anatomical, radiologic, and technical factors that can affect the diagnostic yield of this technique. We suggest recommendations to improve its use in clinical practice.

Methods This retrospective study evaluated 407 patients who underwent stereotactic biopsies in the past 34 years. The surgical methodology changed through time, distinguished by three distinct periods. Different stereotactic frames (Todd-Wells, CRW, Leksell), neuroimaging tests, and planning programs were used. Using SPSS software v.23, we analyzed a total of 50 variables for each case.

Results The series included 265 men (65.1%) and 142 women (34.9%) (average age 53.8 years). The diagnostic yield was 90.4%, morbidity was 5.65% ($n = 17$), and mortality was 0.98% ($n = 4$). Intraoperative biopsy improved accuracy ($p = 0.024$). Biopsies of deep lesions ($p = 0.043$), without contrast enhancement ($p = 0.004$), edema ($p = 0.036$), extensive necrosis ($p = 0.028$), or a large cystic component ($p = 0.023$) resulted in a worse diagnostic yield. Neurosurgeons inexperienced in stereotactic techniques obtained more nondiagnostic biopsies ($p = 0.043$). Experience was the clearest predictive factor of diagnostic yield (odds ratio: 4.049).

Conclusions Increased experience in stereotactic techniques, use of the most suitable magnetic resonance imaging sequences during biopsy planning, and intraoperative evaluation of the sample before finalizing the collection are recommended features and ways to improve the diagnostic yield of this technique.

Keywords
- stereotactic biopsy
- diagnostic yield
- stereotactic techniques
- brain tumor

Introduction

Stereotactic biopsy is a simple and precise procedure that neurosurgeons have used for more than a century.[1–4] Since its emergence, the technique has combined and adapted its essential principles using the current technological advances. Today it constitutes the least invasive strategy to obtain a histologic sample for diagnosis and therapeutic evaluation of patients with intracranial lesions.

Stereotactic biopsy has a high percentage of accuracy and a low percentage of complications. Its accuracy was demonstrated in numerous studies, with an average diagnostic yield of ~ 90 to 95%.[5–7] The large published series reflect an estimated morbidity of 1 to 6.5%, along with an estimated

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mortality of 0 to 1.7%.[8,9] The most frequently reported procedure-related complication is intracranial hemorrhage, with an overall occurrence of 1.4 to 9.6%.[5–16]

Despite the wide use of stereotactic biopsy, statistical analyses of the factors associated with its diagnostic yield are few, and even fewer have included large patient series. Consequently, their results are controversial, disparate, and occasionally even remarkable (i.e., sex and diagnostic yield).

We present our ample experience with stereotactic biopsy. This retrospective study provides a detailed statistical analysis with the aim of identifying specific reasons that could affect the histopathologic diagnoses obtained by the procedure. We also suggest ways to optimize the daily clinical practice of stereotactic biopsy.

Materials and Methods

Patients and Data Collection

The clinical histories and neuroimaging tests of 407 patients who underwent stereotactic biopsy in the past 34 years between 1982, when this technique was first used in our institution, and 2016 were retrieved and evaluated.

Fifty baseline patient and case variables were entered into a database and analyzed. The variables included the demographic and clinical characteristics of the patients, the anatomical and radiologic characteristics of the brain lesions,[17–20] the surgical technique, the diagnosis and therapeutic course, and the prognosis.

Surgical Planning

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria considered when determining whether a patient was a candidate for stereotactic biopsy were previously described.[5,6,8,10,12,14,15,21]

Surgical Technique

The surgical methodology used throughout the decades was determined by the equipment available in the hospital at the time. We identified three methodological periods.

Period 1 (1982–1991)

During this first stage, the Todd-Wells stereotactic device (Integra Radionics, Burlington, Massachusetts, United States),[22] and the Backlund spiral needle,[8] the first unit made by the senior author (J.H.V.), were used. As a peculiarity of this period, it is worth mentioning the use of an impedance meter (Integra Radionics , Burlington, Massachusetts, United States) to estimate tissue resistance throughout the selected trajectory.

The radiologic equipment included portable radiographic devices (C- arm; Philips, Amsterdam, The Netherlands) to which a 16-slice CT scanner (Siemens, Berlin, Germany) was added in 1985.

Initially, an angiogram was used to perform the calculations to reach the target, but after the acquisition of CT, the calculations were performed by super positioning between the radiographic images and the brain CT scan. The coordinates were obtained by locally developed MS-DOS application (►**Fig. 1a**, **1b**).

Period 2 (1991–2011)

During period 2, the Cosman-Roberts-Wells stereotactic guide (CRW; Integra Radionics, Burlington, Massachusetts, United States)[23,24] was used along with various other instruments such as the Sedan-Nashold biopsy needle.[25]

A CT scan, both 16 slice (Siemens, Berlin, Germany) and 40 slice (Philips, Amsterdam, The Netherlands), replaced conventional radiography beginning in 2002.

Until 1998, targets were established on CT images and calculated by CT software. Then a workstation with the Target 1.19 planning program was adopted (Brainlab, Munich, Germany) (►**Fig. 2a**, **2b**).

Period 3 (2011–2016)

During this most recent period, the Leksell stereotactic system (Elekta Instruments, Inc., Stockholm, Sweden)[26] and a Sedan/Nashold biopsy needle (Elekta Instruments, Stockholm, Sweden)[25] were used.

The hospital had a 64-slice CT scan (General Electric, Boston, Massachusetts, United States) and a 3T MRI (General Electric, Boston, Massachusetts, United States).

In most cases, targets were established on the most suitable MRI sequence, which was later fused with a stereotactic CT scan. The coordinates were obtained with Framelink and the Cranial v.3.0 planning program (Medtronic, Minneapolis, United States) (►**Fig. 3a**).

The most experienced stereotactic neurosurgeon retired during this period.

During all three periods, the biopsy technique consisted of making a drill or a burr hole and obtaining tissue samples comprising three or four cylinders at different depths of the trajectory of the needle on its way across the target, or targets, on the lesion.

Patients were monitored in the intensive care unit or recovery room for 24 hours after the biopsy was obtained. During the first two periods, postoperative control brain CT scans were only performed if there was a clinical deterioration of the patient, whereas in period 3, brain CT scans were ordered routinely 24 hours after the intervention.

Anesthetic Technique

Local anesthesia (bupivacaine 0.25% plus epinephrine) and light sedation were used during the surgical intervention. Exceptionally, general anesthesia was used in some pediatric patients or in patients with clinically significant mental alteration.

Histopathologic Evaluation

Intraoperative histologic evaluation was performed on tissue smears. If there was no evidence of abnormal tissue, additional samples were obtained. The definitive histopathologic evaluation was performed on fixed and stained tissue.

The World Health Organization's *Classification of Tumours of the Central Nervous System* (2007) was used,[27] not the recent 2016 classification,[28] due to the period in which the biopsies were performed and the pathologic diagnoses were made.

Nondiagnostic biopsies were classified as either inconclusive or negative following previously described criteria.[29] A biopsy was considered inconclusive if the samples included

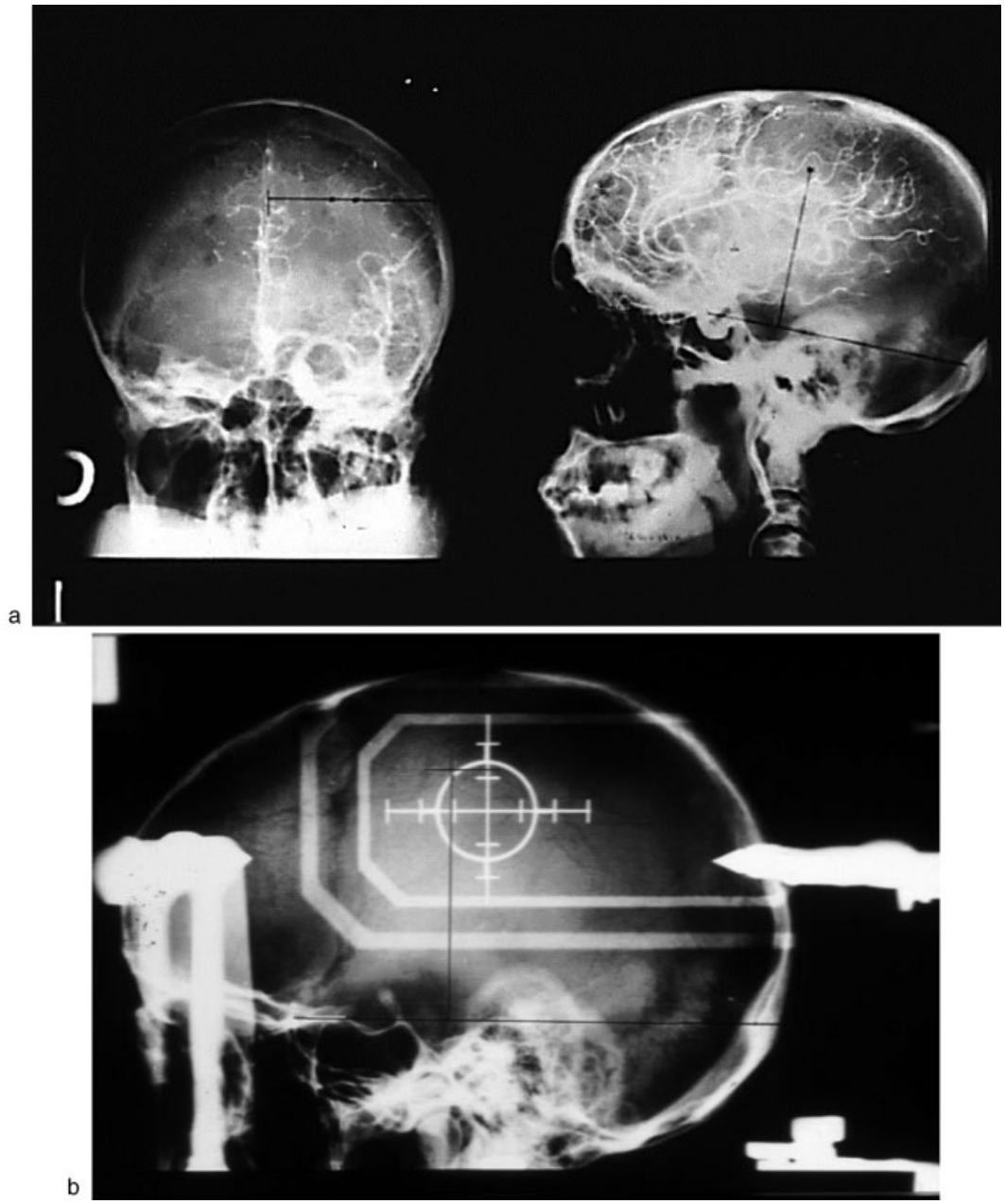

Fig. 1 Period 1 (1982–1991) surgical planning. (**a**) Angiography calculations. (**b**) Radiography calculations on Todd-Wells stereotactic guide.

tissue representative of the lesion but a definite diagnosis could not be made. Negative biopsies failed to indicate the nature of the mass.

Statistical Analysis

Statistical analysis was performed with SPSS v. 23 for Windows (SPSS Inc., Chicago, Illinois, United States) using parametric tests. Descriptive statistics were reported for qualitative and quantitative variables. The tests used for the study of the statistical association between two independent variables were the chi-square test, with correction by means of the Fisher exact test when necessary, for the qualitative variables, and the Student *t* test and analysis of variance, with the Bonferroni test, for the analysis of the association between qualitative and quantitative variables with two or more than two categories, respectively. The association of two or more independent variables was tested by binary logistic regression (multivariate analysis). The results were considered statistically significant for $p < 0.05$.

Results

Demographic Characteristics: Patients and Pathologies

We analyzed a total of 407 patients who had undergone stereotactic biopsy in our department, 143 in period 1 (35.2%), 213 in period 2 (52.3%), and 51 in period 3 (12.5%).

The average age of the patients in the series was 53.8 years. Most of the patients were in the fifth and sixth decades of life (47.6%; $n = 194$), with an average of 57 years of age

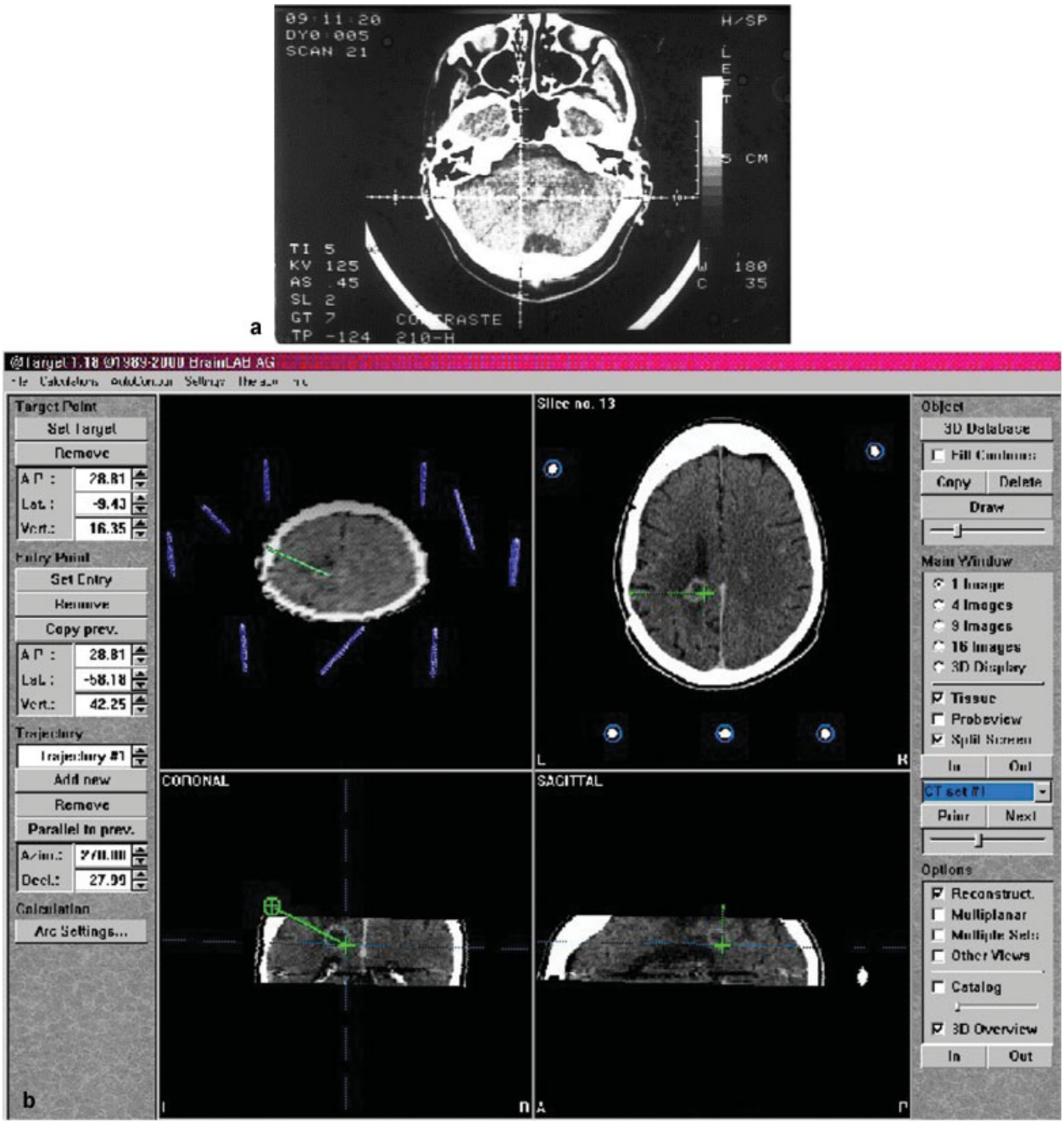

Fig. 2 Period 2 (1991–2011) surgical planning. (**a**) Computed tomography software calculations. (**b**) Calculations with Target v.1.19 program (Brainlab).

(range: 3–86 years). Fourteen (3.4%) were pediatric (patients ≤ 16 years of age). The sex ratio was 1.8:1, with 265 men (65.1%) and 142 women (34.9%).

The most frequent presenting symptoms were seizures in 24.6% ($n = 100$), motor deficit in 24.3% ($n = 99$), and intellectual function disorders in 14.3% ($n = 58$). Neurologic examinations found a motor deficit in 31.2% ($n = 127$), followed by the absence of findings in 27.8% ($n = 113$), intracranial hypertension in 16.2% ($n = 66$), and intellectual functioning disorders in 11.5% ($n = 47$).

Most lesions were on the left side (41.8%; $n = 170$). The frontal region was the most frequently biopsied anatomical region (24.8%; $n = 101$), and the cerebellum (1%; $n = 4$) and brainstem (1%; $n = 4$) were the least.

After histologic evaluation, the most frequently diagnosed pathologies were tumor in 78.8% ($n = 321$), followed by vascular pathology (i.e., hemorrhagic or ischemic stroke) in 5.4% ($n = 22$), radionecrosis in 0.5% ($n = 2$), and neurologic pathology (multiple sclerosis) in 0.2% ($n = 1$). The most frequently diagnosed tumor was a high-grade glioma (42.8%; $n = 174$); the biopsies were nondiagnostic in 9.6% ($n = 39$).

Forty patients (9.8%) had symptomatic intracranial hemorrhages (worsened the level of consciousness and/or

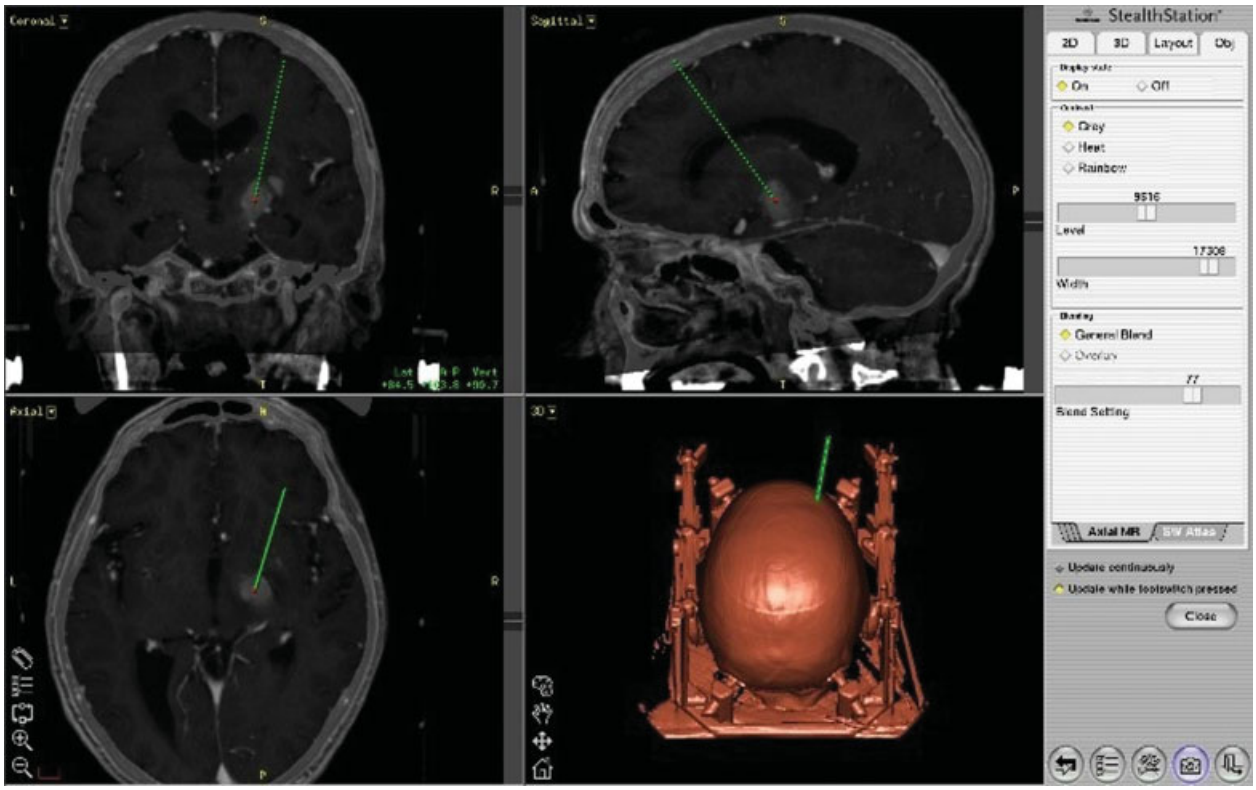

Fig. 3 Period 3 (2011–2016) surgical planning. Calculations with Framelink program (Medtronic).

produced new neurologic deficits after the biopsy). Most of those patients improved significantly in the following days. Twenty-three of the patients (57.5%) were discharged with a Karnofsky performance status > 80. The procedure-associated mortality was 0.98% ($n = 4$).

►**Table 1** shows the demographic characteristics of the patients and pathologies in the series, and according to the methodological period.

Diagnostic Yield and Related Variables

The overall diagnostic yield of our stereotactic biopsies was 90.4%, and there were no statistically significant differences in the diagnostic yields among the three methodological periods ($p = 0.864$).

Lesion Topography

Biopsies performed on deep lesions, specifically lesions located in diencephalic structures, had a worse diagnostic yield ($p = 0.043$). In contrast, the biopsies of brainstem lesions (1%; $n = 4$) reached a 100% diagnostic yield.

Radiologic Characteristics of the Lesion

Biopsies of hypodense lesions without contrast enhancement (18.9%; $n = 77$), biopsies of lesions with patent and extensive edema (45.4%; $n = 185$), patent and extensive necrosis (1%; $n = 251$), or biopsies of largely cystic lesions (21.6%; $n = 88$) showed a lower diagnostic yield ($p < 0.05$).

Multivariate logistical regression analysis showed that both the absence of contrast enhancement, with an odds ratio (OR) of 0.313 ($p = 0.002$), and the presence of a large cystic component, with an OR of 0.396 ($p = 0.014$), were configured as predictor variables of a worse diagnostic yield of the biopsy.

Surgical Procedure Peculiarities

On the one hand, and in relation to the number of targets, because we obtained between three and four cylinders in each target routinely, we decided to analyze whether the establishment of one or more targets with their respective trajectories on different lesion points affected the diagnostic yield of the technique. In the series, we found no statistical significance ($p = 0.054$). However, during period 1, we observed a greater diagnostic yield if the samples were obtained from two or more targets ($p = 0.021$).

On the other hand, the performance of an intraoperative biopsy was requested on 92.1% of the procedures ($n = 375$). We obtained 7.2% of nondiagnostic biopsies if the intraoperative smear was made compared with 37.5% of nondiagnostic biopsies if it was not made ($p = 0.024$).

Neurosurgeońs Experience

In this series, the biopsy tissue was obtained from 80.8% of the patients ($n = 329$) by a neurosurgeon with experience in stereotactic techniques. The percentages were 80.4% ($n = 115$) in period 1, 89.6% ($n = 191$) in period 2, and 70.6% ($n = 36$) in period 3.

The analysis showed that 16.6% of the nondiagnostic biopsies were obtained by an inexperienced neurosurgeon compared with 6.9% obtained by an experienced

Table 1 Descriptive profiles of patients and pathology

	Series ($n = 407$)	Period 1 ($n = 143$)	Period 2 ($n = 213$)	Period 3 ($n = 51$)
A. Patients				
Age, y				
Mean	53.8	49.9	55.1	59.6
Median	57	55	58	64
Range	3–86	3–86	4–82	15–81
Sex, *n* (%)				
Men	265 (65.1)	90 (62.9)	144 (67.6)	31 (60.8)
Women	142 (34.9)	53 (37.1)	69 (32.4)	20 (39.2)
Symptomatology, *n* (%)				
Intellectual disorders	58 (14.3)	12 (8.4)	32 (15)	14 (27.5)
Seizures	100 (24.6)	35 (24.5)	62 (29.1)	3 (5.9)
Intracranial hypertension	97 (23.8)	46 (32.2)	41 (19.2)	10 (19.6)
Motor	99 (24.3)	41 (28.7)	45 (21.1)	13 (25.5)
Sensory	6 (1.4)	0 (0)	6 (2.8)	0 (0)
Others	47 (11.5)	9 (6.2)	27 (12.6)	11 (21.5)
Signs, *n* (%)				
None	113 (27.8)	24 (16.8)	69 (32.4)	20 (39.2)
Intellectual disorders	47 (11.5)	9 (6.3)	30 (14.1)	8 (15.7)
Intracranial hypertension	66 (16.2)	49 (34.2)	17 (7.9)	0 (0)
Motor	127 (31.2)	48 (33.6)	62 (29.1)	17 (33.3)
Sensory	10 (2.4)	2 (1.4)	7 (3.3)	1 (2)
Others	44 (10.8)	11 (2.7)	28 (13.1)	5 (9.8)
B. Pathology, *n* (%)				
Side				
Right	154 (37.8)	59 (41.2)	71 (33.3)	24 (47.1)
Left	170 (41.8)	66 (46.2)	88 (41.3)	16 (31.3)
Bilateral	83 (20.4)	18 (12.6)	54 (25.4)	11 (21.6)
Region				
Telencephalon	307 (75.5)	114 (79.1)	160 (75.3)	33 (64.7)
Diencephalon	49 (12)	19 (13.3)	18 (7.5)	12 (23.5)
Cerebellum	4 (1)	2 (1.4)	2 (0.9)	0 (0)
Brainstem	4 (1)	2 (1.4)	1 (0.5)	1 (2)
Multiple	43 (10.5)	6 (4.2)	32 (15)	5 (9.8)
Diagnosis				
Tumoral pathology	321 (78.6)	109 (76.3)	169 (79.4)	43 (84.2)
Vascular pathology	22 (5.4)	16 (11.2)	6 (2.7)	0 (0)
Infectious disease	22 (5.4)	5 (3.5)	15 (7.1)	2 (4)
Radionecrosis	2 (0.5)	0 (0)	2 (0.9)	0 (0)
Neurologic pathology	1 (0.2)	0 (0)	0 (0)	1 (2)
Nondiagnostic biopsy				
Inconclusive	8 (2)	3 (2.1)	4 (1.9)	1 (2)
Negative	31 (7.6)	10 (7)	17 (8)	4 (7.8)
Hemorrhagic complications: Karnofsky performance status ≤ 70 at discharge	17 (5.6)	7 (4.8)	8 (3.7)	2 (3.9)
Mortality	4 (0.98)	0 (0)	1 (0.24)	3 (5.8)

Table 2 Diagnostic yield and related variables

	Series ($n = 407$) p^*	I Period ($n = 143$) p^*	II Period ($n = 213$) p^*	III Period ($n = 51$) p^*	Predictive Factor (OR)
A) Lesion					
Anatomical Variables					
Location	$p = 0.043^*$	$p = 0.493$	$p = 0.086$	$p = 0.043^*$	–
Radiological variables					
Contrast	$p = 0.004^*$	$p = 0.008^*$	$p = 0.072$	$p = 0.634$	0.313
Edema	$p = 0.036^*$	$p = 0.255$	$p = 0.160$	$p = 0.271$	–
Necrosis	$p = 0.743$	$p = 0.059$	$p = 0.807$	$p = 0.040^*$	–
Cyst	$p = 0.023^*$	$p = 0.258$	$p = 0.072$	$p = 0.051$	0.396
B) Surgery					
Procedure					
Number of targets	$p = 0.054$	$p = 0.021^*$	$p = 0.690$	$p = 0.739$	–
Intraoperative biopsy	$p = 0.024^*$	$p = 0.521$	$p = 0.045^*$	$p = 0.013^*$	–
Operator's experience	$p = 0.001^*$	$p = 0.521$	$p = 0.005^*$	$p = 0.014^*$	4.049

*The results were considered statistically significant if $p < 0.05$.

neurosurgeon ($p = 0.001$). Surgeon experience was also associated with ordering an intraoperative biopsy. Nonexpert neurosurgeons requested an intraoperative biopsy in 52.5% of the cases; expert neurosurgeons asked for it in 87.2% of the procedures ($p = 0.001$).

Finally, the multifactorial analysis showed that experience in stereotactic techniques, with an OR of 4.049 ($p = 0.001$), was the strongest predictor of diagnostic yield.

►**Table 2** shows the analytical results, in the series and according to the methodological period.

Nondiagnostic Biopsies

Overall, 39 of the biopsies (9.6%) were nondiagnostic. Of those, 2% ($n = 8$) were inconclusive, and 7.6% ($n = 31$) were negative.

In these patients, the stereotactic biopsy was repeated once in 71.7% of the cases ($n = 28$) and twice in 10.2% of the cases ($n = 4$).

In this series of 407 patients, 82 (20.1%) underwent craniotomies after the biopsy. The main reasons were either surgical resection of the lesion was considered the best treatment strategy after histologic results (64.7%; $n = 53$) or there were doubts about these histologic results because of the clinical condition and the neuroimaging tests of the patient (26.8%; $n = 22$). In seven patients (8.5%), the indication for surgery was based on not obtaining a diagnosis by stereotactic methods.

Discussion

Since the mid-20th century, stereotactic techniques have been used as one of the first minimally invasive strategies adapted to the field of neurosurgery.[2,30–35] Today stereotactic procedures are very versatile and used in diverse surgical procedures including brain tissue biopsy, production of lesions in the brain parenchyma, stimulation of brain regions, or the administration of intracranial treatments, all with extreme precision.

Diagnostic Yield of Stereotactic Biopsy

Successful histologic diagnosis of tissue obtained by stereotactic biopsy depends on the correct performance of the procedure, the suitability of the biopsy technique, and the adequacy of the samples obtained. In our hands, 9.6% of the biopsies were nondiagnostic. Our result is consistent with previous reports (►**Table 3**).[36–63]

Among its diverse indications,[5,6,8,10,12,14,15,21] stereotactic biopsy is especially useful for reaching lesions located in deep territories, areas that normally belong to the diencephalic structures of the human brain. In those areas, the need for careful planning and increased possibility of mistakes or complications may affect the diagnostic yield. However, the data are not conclusive. An evaluation of 351 cases by Livermore et al found that the percentage of nondiagnostic biopsies was higher if they were performed in deep lesions ($p = 0.011$).[12] Kim et al, in a series of 308 patients,[53] and Tsermoulas et al, with 124 patients,[64] did not find that the depth influenced the diagnostics ($p > 0.05$). However, studies such as those by Jain et al, in a series of only 86 cases, found that the diagnostic yield was greater in tissue obtained from the thalamus or the basal ganglia (85.4%), compared with tissue from the cerebral hemispheres (75%).[65] Our results show that increased depth of the lesion was associated with a decreased diagnostic yield ($p = 0.043$), and we believe the large sample size facilitated obtaining this result.

In relation to deep locations, brainstem biopsies should be mentioned, due to the high eloquence of the area. Both the large published series made up of pediatric and adult patients (Kickingereder et al[66] or Samadani et al)[67] and those

Table 3 Review of frame-based biopsies, large series diagnostic yield, complications, and mortality

Study	Patients, *N*	Intraoperative biopsy	Nondiagnostic biopsy, *N* (%)	Morbidity, *N* (%)	Mortality, *N* (%)
Ostertag et al[36] (1980)	302	Yes Smear	26 (8.7)	10 (3.3)	7 (2.3)
Edner[37] (1981)	345	Yes Smear	–	10 (2.9)	3 (0.9)
Sedan et al[38] (1984)	318	–	27 (8.5)	15 (4.7)	2 (0.6)
Mundinger[39] (1985)	815	Yes Smear	–	33 (3)	8 (0.6)
Davis et al[40] (1987)	439	–	–	17 (0.4)	9 (0.2)
Apuzzo et al[5] (1987)	500	Yes Smear	22 (4.4)	5 (1)	1 (0.2)
Blaauw and Braakman[41] (1988)	243	–	29 (11.9)	10 (4.1)	1 (0.4)
Thomas and Nouby[42] (1989)	300	Yes Smear	21 (7.2)	13 (4.4)	1 (0.3)
Wild et al[43] (1990)	200	–	12 (6)	17 (8.5)	2 (1)
Kellyl[44] (1992)	547	–	10 (1.8)	16 (2.9)	2 (0.3)
ÓNeill et al[45] (1992)	259	Yes Smear	17 (6.5)	17 (6.5)	8 (3.3)
Heilbrun et al[46] (1993)	357	–	11 (3.1)	23 (6.4)	6 (1.7)
Gomez et al[47] (1993)	501	Yes Frozen section	8 (3.7)	23 (10.8)	0 (0)
Ranjan et al[29] (1994)	407	Yes Smear	29 (7.1)	–	–
Bernstein and Parrent[48] (1994)	300	Yes Frozen section	14 (4.7)	14 (4.7)	5 (1.7)
Regis et al[49] (1996)	370	Several centers	22 (6)	6 (1.6)	5 (1.5)
Sawin et al[50] (1998)	225	–	–	12 (5.3)	1 (0.4)
Hall[51] (1998)	7471		672 (9)	261 (3.5)	52 (0.7)
Yu et al[52] (2000)	550	–	19 (3.4)	42 (7.8)	0 (0)
Field et al[15] (2001)	500	–	28 (5.6)	46 (9.2)	1 (0.2)
Kreth et al[16] (2001)	345	Yes Smear	7 (2)	11 (3.1)	0 (0)
Kim et al[53] (2003)	300	Yes Frozen section	25 (8.3)	12 (3.9)	2 (0.6)
Grossman et al[54] (2005)	355	No	22 (6.1)	25 (7)	2 (0.6)
McGirt et al[55] (2005)	270	Yes Frozen section	–	36 (14)	3 (1)
Tilgner et al[56] (2005)	5000	Yes Smear	230 (4.6)	65 (1.3)	35 (0.7)

Table 3 (*Continued*)

Study	Patients, *N*	Intraoperative biopsy	Nondiagnostic biopsy, *N* (%)	Morbidity, *N* (%)	Mortality, *N* (%)
Dammers et al[57] (2008)	227	Yes Frozen section	23 (10.3)	28 (12.5)	9 (4)
Kongkham et al[58] (2005)	622	Yes Frozen section	10 (1.6)	43 (6.9)	8 (1.3)
Ersahin et al[59] (2011)	290	Yes Smear	13 (4.5)	12 (4.1)	2 (0.8)
Eibach et al[60] (2014)	315	–	–	19 (6.3)	–
Waters et al[61] (2013)	267	–	18 (6.7)	1 (0.5)	0 (0)
Livermore et al[12] (2014)	302	Yes Smear	14 (5.5)	9 (3.7)	5 (1.7)
Kellermann et al[62] (2017)	230	–	7 (3)	8 (3.5)	1 (0.4)
Hamisch et al[63] (2017)	285	Yes Smear	7 (2.5)	2 (0.7)	0 (0)
Lara-Almunia and Hernandez-Vicente (2018)	407	Yes Smear	39 (9.6)	17 (5.6)	4 (0.98)

with pediatric patients (Rajshekhar et al[68] or Puget et al)[69] showed diagnostic yield figures for the technique close to 100%. The consistency of diagnostic yield from this location might result from established standardized stereotactic techniques to perform the biopsies in this region and from the relatively limited pathologic differential diagnosis of brainstem lesions, especially in children.

Selecting the appropriate biopsy site is an important determinant of obtaining an adequate histologic sample for evaluation. The choice of biopsy site could be influenced by the morphology of the lesion in the neuroimaging tests.

Previous studies found that biopsies performed on hypodense lesions and/or those with scarce or no contrast enhancement were the most likely to be nondiagnostic.[29,64,70–72] However, none of these reports were statistically significant ($p > 0.05$). Nevertheless, in our work we have been able to demonstrate statistically what was only a perception in those studies ($p = 0.004$). In this patient series, biopsies of lesions without contrast enhancement, with an OR of 0.313, were 23.8% more likely to be nondiagnostic. This could be explained by the fact that most hypodense lesions without contrast uptake are generally tumors with a low degree of differentiation, and they are difficult to distinguish by other histologic findings such as gliosis.

Unlike many other studies, we included other radiologic features of the pathology in the evaluation, finding that significant edema ($p = 0.036$) or necrosis ($p = 0.040$) was associated with nondiagnostic biopsies. This could have resulted from difficulties in defining the lesion boundaries and consequently establishing the most appropriate biopsy site.

Biopsies of lesions with a large cystic component also had a reduced diagnostic yield ($p = 0.023$). This feature, with an OR of 0.396, is also a predictive factor for diagnostic yield, such that the biopsies performed on lesions with a large cystic component had a 28.3% probability of being nondiagnostic. This result might be explained by the limited amount of histologically useful tissue that is generally obtained from such lesions. It may also have resulted from changes in the preplanned target after nonintentional drainage of the cystic component during the first acquisition of the histologic material. Those changes should be avoided.

The study findings stress the importance of systematic evaluation of suitable MRI sequences during the surgical planning of the biopsy to obtain a detailed map of the brain anatomy that shows the actual limits of the lesion and provides a three-dimensional image of the target, especially for deep locations.

In recent years, the routine integration of positron emission tomography (PET) with 18F-labeled fluorodeoxyglucose (FDG) in the planning of stereotactic brain biopsy has increased the technique's diagnostic yield.[73–75] Fourteen procedures in period 3 used ^{18}F-FDG PET/CT guidance. The patients had multiple intracranial lesions or a controversial differential diagnosis on conventional neuroimaging techniques. A diagnostic yield of 100%, transitory morbidity of 7.1% ($n = 1$), and 0% mortality was obtained in the 14 patients.

The number of biopsy samples should be enough to arrive at a diagnosis. Jain et al[49] and Brainard et al.[76] suggested that diagnostic yield increased with the number of samples obtained, but the difference did not achieve statistical significance ($p > 0.05$). Obtaining samples from more than one target could facilitate determining the degree of histologic differentiation, especially in heterogeneous lesions, and could improve diagnostic yield. In this series, the overall association of the

number of samples and diagnostic yield was not significant ($p = 0.054$). Period 1 was an exception, possibly because of the degree of heterogeneity in the number of targets (two or more targets were established in 16.1% of the cases). We could see a greater diagnostic yield if various samples, between three and four cylinders, were obtained from two or more targets ($p = 0.021$). Currently available planning software and the use of drills instead of burr holes facilitates obtaining several tissue samples from different targets.

In addition to adequate size, the histologic sample should also have adequate quality, which means that intraoperative assessment of the sample is highly relevant. Frozen sections[77,78] and tissue smears[79,80] are quick and simple ways to achieve this. Previous studies confirmed that intraoperative assessment decreased the number of nondiagnostic samples ($p < 0.05$)[12,45,81] and coincided with the definitive pathologic diagnosis in 90.3% of cases.[56] The results obtained in this series were consistent with previous reports, with a higher percentage of diagnostic biopsies in procedures that included an intraoperative evaluation ($p = 0.024$). The agreement of the intraoperative and definitive histologic diagnosis was 90.7%.

Close collaboration with the pathology laboratory is essential, and the pathologist should be aware of the clinical history of the patient, the radiologic features of the lesion, and the most probable differential diagnosis.

The selection of the target and the trajectory directly depend on the neurosurgeon. In work by authors such as Ranjan et al, it is appreciated that experienced neurosurgeons in stereotactic techniques obtained approximately half the number of nondiagnostic biopsies (2.4%) as inexperienced neurosurgeons did (5.7%).[29] Other studies did not make the same observation.[43,45] None of these studies achieved statistical significance ($p > 0.05$). Nevertheless, in our study we found that inexperienced neurosurgeons obtained nearly three times more nondiagnostic biopsies (16.6%) compared with experienced neurosurgeons (6.9%), which was statistically significant ($p = 0.001$). This fact was more remarkable in period 3 in which we had the greatest number of biopsies performed by inexperienced neurosurgeons ($n = 15$; 29.4%). As an example, in this last period, 12 biopsies were performed on diencephalic structures. A total of 4 (33.3%) were performed by inexperienced neurosurgeons. All these biopsies were nondiagnostic. We think this result determined a worse diagnostic yield if the stereotactic biopsy was performed on diencephalic structures in this series ($p = 0.043$). In addition, inexperienced neurosurgeons only requested intraoperative biopsies in 52.5% of the cases compared with the 87.2% requested by experienced neurosurgeons ($p = 0.001$). Finally, with an OR of 4.049, we found that the neurosurgeon's experience was the most clear predictive factor of diagnostic yield. There was an 80.1% higher probability that the biopsy was diagnostic if it had been performed by a neurosurgeon experienced in stereotactic techniques.

We believe that experience significantly influenced the period 3 results and explains why technical advances and sophistication of the equipment used did not result in statistically important improvements in the reliability and safety of the stereotactic biopsies in this period. The appropriate and thorough management of stereotactic biopsy techniques requires neurosurgeons to have a special interest in neuroradiology, to select the most useful radiologic tests before surgery, and in neuro-oncology, to possess the knowledge and clinical judgment that allows them to connect with the different specialties involved in the treatment of patients with intracranial lesions. They should also have adequate stereotactic training that provides them with in-depth knowledge of the principles of stereotactic neurosurgery, the technology related to the procedures, the use of the available instruments, as well as how to plan meticulously and carefully carry out the technique. The training would ensure fully exploiting the benefits and minimizing the risks of an extremely powerful surgical tool.

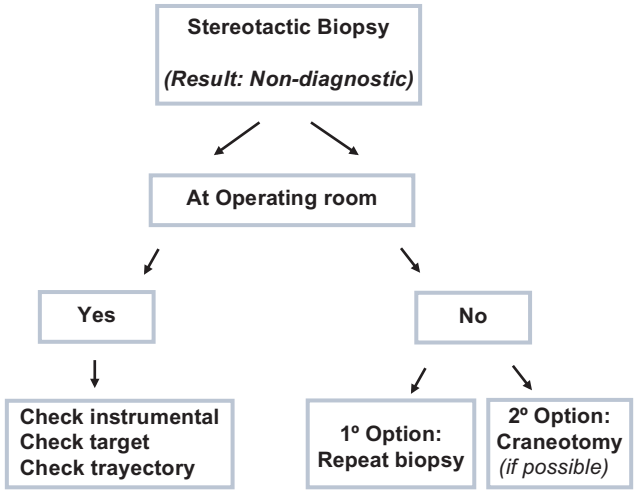

Fig. 4 Postbiopsy patient handling.

Postbiopsy Patient Management

Obtaining a nondiagnostic biopsy is an unfavorable result that should be taken into account before indicating a stereotactic biopsy. If the neurosurgeon suspects this during surgery, intraoperative biopsy, the precision of the stereotactic instruments, and the suitability of the planned target and trajectory should be evaluated and/or adjusted.[82]

If the surgical intervention has been completed and the final histologic diagnosis is inconclusive or ambiguous, we believe there are various management possibilities based on the clinical situation of the patient and the neuroimaging findings.

Because a stereotactic biopsy was initially considered the most suitable technique, it is reasonable to consider offering the patient a repeat biopsy. This was the course followed in 81.9% of our nondiagnostic biopsies.

If the patient refuses this option or if the lesion is located in a relatively accessible anatomical region, a craniotomy to obtain tissue for histologic study can be offered. This was the course followed in the remaining 18.1% of cases with nondiagnostic biopsies (►**Fig. 4**).

Conclusions

Stereotactic biopsy constitutes a perfectly consolidated procedure in neurosurgical departments. It is a versatile technique that allows a safe and effective histologic diagnosis and therapeutic planning in patients with intracranial lesions.

Our findings confirm that obtaining more than one tissue sample and performing an intraoperative study help ensure the quality of the histologic material and thus improve the diagnostic yield of this technique. Similarly, the use of the most suitable MRI sequences during biopsy planning is required to obtain a detailed map of the lesion and its relation to the brain anatomy. This facilitates establishing the target and the most appropriate trajectory.

Technological advances achieved in the previous decades and their integration into stereotactic biopsy procedures have placed increasingly manageable instrumentation and simpler planning tools at our disposal. This has clearly made it easier to perform this neurosurgical intervention. Nevertheless, to obtain the best results, it is necessary to optimize each neurosurgeon's experience and interest in stereotactic techniques, neuroradiology, and neuro-oncology. These features are essential to determine the indication for stereotactic biopsy, the establishment of the best targets and their trajectories, and the appropriate intraoperative management of the histologic samples obtained.

Conflict of Interest
None declared.

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