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Efficacy of a Second Brain Biopsy for Intracranial Lesions after Initial Negativity

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Background and Purpose The rationale for performing a second brain biopsy after initial negativity is not well evaluated in the literature. This study was designed to 1) assess the efficacy of a second brain biopsy when the first biopsy was nondiagnostic, 2) identify possible factors associated with an increased diagnostic rate in the second biopsy, and 3) analyze additional morbidity induced by the second biopsy.

Methods We performed a retrospective cohort study from 2009 to 2019, during which 1,919 patients underwent a brain biopsy, including 30 who were biopsied twice (1.6%). The specific histological diagnosis rate, diagnosis-associated factors, and complication rate were assessed for the 30 twice-biopsied patients.

Results The second biopsy allowed a specific histological diagnosis in 86.7% of the patients who had initially undergone a nondiagnostic brain biopsy [odds ratio (OR)=7.5, 95% confidence interval (CI)=3.0−18.7, $p<0.001$]. The multivariate analysis showed that only prebiopsy corticosteroid administration (OR=2.6, 95% CI=1.1−6.0, $p=0.01$) was an important factor in predicting a nondiagnostic biopsy. None of the patients developed a symptomatic complication after the first biopsy, while two (6.0%) patients experienced a transient complication after the second biopsy ($p=0.49$).

Conclusions Performing a second brain biopsy in patients who have an initial nondiagnostic biopsy is effective in most cases. We advocate that a second biopsy be systematically considered in the diagnosis algorithm of these patients after it has been verified that molecular testing cannot help to obtain a diagnosis. Corticosteroid administration can lead to nondiagnostic biopsies and should be avoided when possible during the prebiopsy period.

Key Words brain tumor, corticosteroids, diagnosis, neuropathology, neurosurgery, neoplasms.

INTRODUCTION

A brain biopsy is an established method for obtaining a histopathological diagnosis and for guiding the management of cerebral lesions. Between 2% and 9% of needle brain biopsies performed in patients with a suspected brain tumor are reportedly nondiagnostic.[1,2] For these negative cases, an additional biopsy can be proposed that will not provide absolute certainty of obtaining a specific histological diagnosis while exposing patients to additional morbidity.[3] The rationale for performing a second biopsy after initial negativity is not well evaluated in the literature. The main purpose of this study was to determine the efficacy of a second biopsy when the first biopsy was nondiagnostic. The secondary endpoints were to identify possible factors associated with an increased diagnostic rate in the second biopsy and determine the associated additional morbidity.

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METHODS

Patients

We retrospectively reviewed the medical records and histology reports of all adults who underwent a brain biopsy at La Pitié-Salpêtrière University Hospital between January 1, 2009 and December 31, 2019. Patients who underwent two distinct brain biopsies for histological analyses of the same lesion—where the first biopsy was nondiagnostic—were included in the analysis. Patients with incomplete data were excluded.

Study variables and outcomes

The main outcome variables were 1) obtaining a specific histological diagnosis and 2) brain-biopsy-related complications. The other analyzed variables included demographic characteristics, medical history, clinical manifestations, laboratory findings, and brain MRI findings before performing the initial and second brain biopsies.

The histological results of the brain biopsies were categorized into three groups: specific histological diagnosis, nonspecific histology, and normal brain. Obtaining a specific histological diagnosis was defined as the brain-biopsy findings of a specific lesion being sufficient by themselves to make a diagnosis and to modify the therapeutic management.

A multidisciplinary discussion involving neurosurgeons, pathologists, neuroradiologists, neurologists, and internists determined whether a brain biopsy of a nonspecific lesion(s) contributed to the final diagnosis or whether a second biopsy was required to obtain a specific histological diagnosis. The participants in these discussions systematically and comprehensively reviewed the following aspects for each patient: medical history, neurological and extraneurological findings, less-invasive diagnostic workup, and initial brain-biopsy histological results. Two senior neuroradiologists analyzed all of the imaging findings, including available MRI data [T1-weighted fluid-attenuated inversion-recovery (FLAIR) sequences, T2-weighted FLAIR sequences, T1-weighted sequences with gadolinium injection, gradient-echo T2*-weighted sequences, and diffusion-weighted sequences] and multiparametric imaging data. Two senior neuropathologists examined all of the histological slides. A second biopsy was proposed if no consensus was reached during the multidisciplinary discussion about whether the results obtained from the first brain biopsy contributed to a diagnosis.

We attempted to classify the reason why the first biopsy was nondiagnostic into three categories: target error, interpretation error, or sample-size error. The location of the biopsy target was assessed by merging the images from the postbiopsy CT scan with those from prebiopsy MRI.

Brain-biopsy-related complications were defined as occurring during the month following the procedure. We recorded the symptomatic complications as well as the asymptomatic hemorrhages that were visible only on a postoperative CT scan.[4,5]

Surgical procedures and postoperative management

The patients who required corticosteroids before the biopsy initially received methyl prednisone at 2 mg/kg/day for 2 days, and then the daily dose was reduced by half every 2 days until the day on which the biopsy was performed. A stereotactic biopsy was used for deep-seated lesions according to a previously described procedure.[6] Six to eight biopsy samples (~10 mm) were collected for both the primary and secondary stereotactic procedures. Biopsy samples for cortical lesions were obtained via an open craniotomy or a burr hole. We considered a gold-standard diagnostic open-biopsy sample to comprise 1 cm^3 of tumoral cortex.

The collected tissue samples were sent for histopathological analyses. When the differential diagnosis included infection, tissue was set aside for microbiology investigations. Patients were monitored for at least 6 h in the recovery unit. Prior to transfer to the neurosurgery department, a postoperative CT scan was systematically obtained to rule out immediate complications.

Statistical analyses

Results expressed as number and percentage values were compared using χ^2 tests, while continuous variables expressed as mean±SD or median (interquartile range) values were compared using Student's *t*-test. The demographic, clinical, radiological, and biological characteristics of the patients were tested in univariate analyses for their associations with obtaining a specific histological diagnosis, based on intraindividual comparisons between the first and second biopsies. Thereafter, multiple logistic-regression analyses using backward stepwise variable elimination were performed, with the variable-exit threshold set at $p>0.10$. Factors for which $p\leq0.10$ in our univariate analyses were entered into the multivariate model. Statistical significance was defined as $p<0.05$. Analyses were performed using IBM SPSS Statistics software (version 21, IBM Corp., Armonk, NY, USA).

Standard protocol approvals, registrations, and patient consents

The database utilized in this study is registered with the Commission Nationale de l'Informatique et des Libertés (no. 2214386). In accordance with the ethical standards of the Institutional Review Board of our hospital (8610Z-MR3), the Committee for the Protection of Human Subjects, and French law,

written informed consent was not needed for the current demographic, physiological, and hospital-outcome data analyses because this observational study did not modify existing diagnostic or therapeutic strategies; however, all of the patients were informed about their inclusion in the study. The manuscript was prepared in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology statement.

Data availability statement

Anonymized data will be shared upon request from any qualified investigator.

RESULTS

Study population

During the study period, 1,919 patients underwent a brain biopsy, and the 30 who were biopsied twice (1.6%) were included in the analysis (Fig. 1). The male-to-female ratio was 0.76. The age on the first biopsy day was 53.9±16.1 years (range=22.5–73.6 years), the median time interval between the two biopsies was 63 days (range=12–1,064 days, and the follow-up after the first biopsy had a duration of 32±41 months (range=2–180 months).

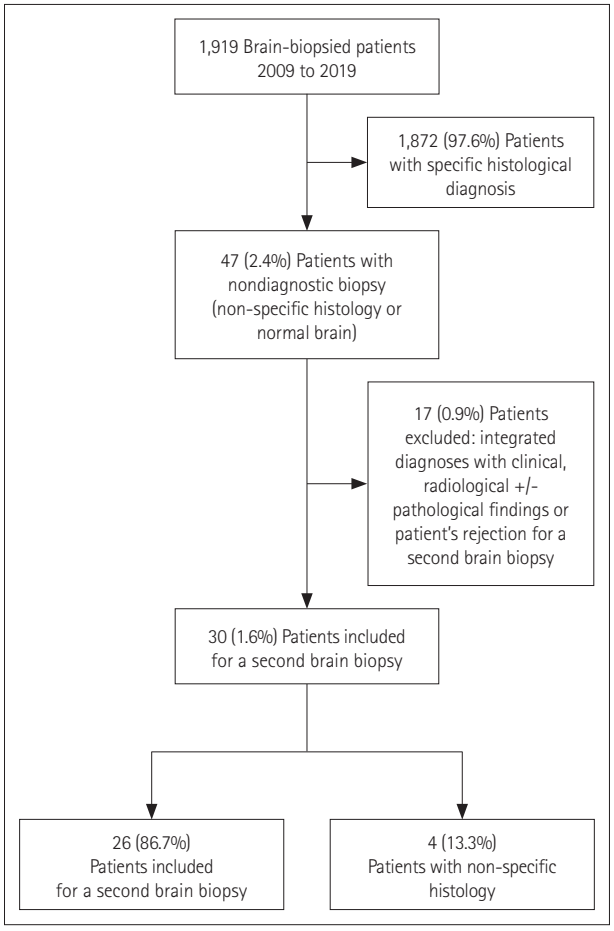

Fig. 1. Flow chart of patient inclusion in this study of the contribution to the diagnosis of a second brain biopsy after a nondiagnostic first biopsy.

The general characteristics of the 30 analyzed patients and their brain biopsies are presented in Table 1. The initial clinical manifestations included neurological deficit (50.0%), extra-neurological symptoms (10.3%), seizures (13.8%), and fever (10.3%). Most patients had unifocal (73.3%) lesions. The biopsy-targeted initial lesions were predominantly supratentorial (93.3%), deep-brain-seated (86.7%) with a largest diameter >1 cm (96.7%), and gadolinium-enhanced (73.3%) lesions. All of the initial biopsies were performed stereotactically, with MRI guidance performed in 80.0% of them.

Diagnoses

All of the 30 patients analyzed in this study had initially undergone a nondiagnostic brain biopsy, and the second biopsy obtained a specific histological diagnosis for 26 (86.7%) of them [odds ratio (OR)=7.5, 95% confidence interval (CI)=3.0–18.7, $p<0.001$]. These 26 patients comprised 16 (61.5%) with glioma, 4 (15.4%) with lymphoma, 4 (15.4%) with metastasis, 1 (3.8%) with nocardiosis, and 1 (3.8%) with radionecrosis (Table 2). The negative result of the first biopsy was attributed to a target error in ten (38.5%) patients, a sample-size error in ten patients (38.5%), and an interpretation error in six (23.0%) patients.

The detailed clinical, radiological, and histological features of the patients are presented in Table 3. Fig. 2 illustrates the differences between the nondiagnostic first biopsy and the diagnostic second biopsy in four representative cases.

Factors associated with the diagnostic yield

Intraindividual comparisons of the demographic, clinical, radiological, and biological characteristics between the initial nondiagnostic biopsy and the second biopsy that resulted in a histological diagnosis are reported in Table 1. More than one-third (36.7%) of the patients had been taking corticosteroids before the initial biopsy, while 3.8% had been taking them before the second biopsy ($p=0.003$). The largest lesion diameter was significantly greater at the second biopsy (35.6 mm vs. 31.6 mm, $p=0.005$). The logistic-regression model used in the multivariate analyses showed that biopsy samples obtained from patients treated with corticosteroids during the prebiopsy period were more often nondiagnostic (OR=2.6, 95% CI=1.1–6.0, $p=0.01$). The diseases associated with nondiagnostic biopsies affected by corticosteroids were lymphoma (66.7%), glioma (16.7%), and nocardiosis (16.7%). Three (75.0%) of the four patients who had undergone a nondiagnostic second biopsy had still been taking corticosteroids before the second biopsy (Table 3). Apart from corticosteroids, there were no ma-

Table 1. Patient and biopsy characteristics

Characteristic	First biopsy (nondiagnostic biopsy, *n*=30)	Second biopsy (specific diagnosis, *n*=26)	Univariate analysis *p*	Multivariate analysis *p*
Medical history				
Autoimmune diseases	8.3 (2/24)	11.5 (3/26)	0.770	
Immunocompromised	3.8 (1/26)	7.7 (2/26)	0.640	
Treatment before biopsy				
Corticosteroids	36.7 (11/30)	3.8 (1/26)	0.003	0.01
Clinical findings before biopsy				
Neurological defect	50.0 (15/30)	50.0 (13/26)	1.000	
Seizure	13.8 (4/29)	16.0 (4/25)	0.820	
Fever	10.3 (3/29)	4.2 (1/24)	0.400	
Extraneurological symptoms	10.3 (3/29)	12.5 (3/24)	0.810	
Altered consciousness (GCS score <15)	0 (0/30)	0 (0/26)	1.000	
Laboratory finding before biopsy				
C-reactive protein, >10 mg/L	0 (0/14)	6.7 (1/15)	0.330	
MRI findings before biopsy				
Multifocal lesions	26.7 (8/30)	34.6 (9/26)	0.520	
Largest lesion diameter, mm	31.6±16.0	35.6±17.6	0.005	
Largest lesion diameter <10 mm	3.3 (1/30)	0 (0/26)	0.350	
Largest lesion diameter >50 mm	13.3 (4/30)	20.0 (5/25)	0.510	0.65
Meningeal involvement	3.3 (1/30)	0 (0/26)	0.350	
Hydrocephalus	6.7 (2/30)	3.8 (1/26)	0.640	
Biopsy-targeted lesion characteristics				
Subcortical	6.7 (2/30)	19.2 (5/26)	-	
Deep brain	86.7 (26/30)	80.8 (21/26)	0.170	
Cortical	6.7 (2/30)	0 (0/26)	-	
Supratentorial	93.3 (28/30)	92.3 (24/26)	0.880	
Gadolinium-enhanced	73.3 (22/30)	80.8 (21/26)	0.510	
Biopsy techniques				
Stereotactic	100.0 (30/30)	96.2 (25/26)	0.280	
MRI-guided	80.0 (24/30)	80.8 (21/26)	0.940	

Patient and biopsy characteristics compared between the first nondiagnostic biopsy and the second biopsy used to obtain a specific histological diagnosis. Results of univariate and multivariate logistic-regression model analyses indicating factors associated with achieving a diagnosis after a second biopsy when the first biopsy was nondiagnostic. Continuous variables are expressed as mean±SD values and were compared using Student's *t*-test; categorical variables are expressed as percentage and number values and were compared using χ^2 tests.
GCS: Glasgow Coma Scale.

jor changes in the medications taken by patients between the first and second biopsies that could have influenced the biopsy results.

Postbiopsy complications

None of the patients developed symptomatic complications after the first biopsy, while two (6.0%) patients experienced transient complications after the second biopsy (p=0.49) (Table 4). One patient experienced a generalized epileptic seizure a few minutes after the intervention, and another patient presented with postbiopsy hemiparesis that resolved fully after corticosteroid treatment. Asymptomatic hemorrhages related to biopsy procedures that were diagnosed only in systematic postbiopsy imaging were observed in 6 (20.0%) patients after the first biopsy and in 13 (43.3%) patients after the second biopsy (p=0.10).

DISCUSSION

Key results

We found that performing a second brain biopsy in patients who had undergone an initial nondiagnostic biopsy was effective in 87% of cases. Prebiopsy corticosteroid treatment appears to be a predictor of a nondiagnostic biopsy.

Predictors of nondiagnostic biopsies

Needle biopsies can lead to diagnostic errors due to the presence of existing hemorrhagic products or necrosis, or when

Table 2. Histological diagnoses obtained from the first and second brain biopsies

	First biopsy	Second biopsy
Specific diagnosis	0 (0)	86.7 (26)
Grade IV glioma	0 (0)	40.0 (12)
Grade III glioma	0 (0)	6.7 (2)
Grade II glioma	0 (0)	6.7 (2)
Lymphoma	0 (0)	13.3 (4)
Metastasis	0 (0)	13.3 (4)
Nocardiosis	0 (0)	3.3 (1)
Radionecrosis	0 (0)	3.3 (1)
Nonspecific histology	93.3 (28)	13.3 (4)
Gliosis	50.0 (15)	10.0 (3)
Inflammation	20.0 (6)	3.3 (1)
Necrosis	16.7 (5)	0 (0)
Other	6.7 (2)	0 (0)
Normal brain	6.7 (2)	0 (0)
Total	100.0 (30)	100.0 (30)

Categorical variables are expressed as percentage and number values. The second biopsy contributed significantly more to a specific diagnosis than did the first biopsy (86.7% vs. 0.0%, odds ratio=7.5, 95% confidence interval=3.0–18.7; χ^2 test: $p<0.001$).

the biopsy fails to target the contrast-enhancing lesion.[7] Therefore, performing an open biopsy rather than a needle biopsy should be the first step when it is possible, in order to avoid a nondiagnostic biopsy. For lesions of concern with a necrotic center, the biopsy should target the area of fine parietal peripheral contrast enhancement. For such cases we recommend performing multiple biopsies at different depths along the same trajectory in order to maximize the probability of success.

Many factors can lead to a nondiagnostic result. Lu et al.[8] considered that prior lesion treatment (surgery or radiation) is strongly negatively associated with the biopsy diagnostic yield. However, because none of our patients had received treatment prior to the biopsy, we cannot comment on this previous finding.

Precision is the ultimate aim of a stereotactic biopsy, and its usefulness is dependent on minimizing errors at every step of the procedure, including frame application, image acquisition, image manipulation, surgical planning of the target and trajectory, patient positioning, and the surgical procedure itself. The neurosurgeon should be familiar with the principles of stereotactic techniques. Errors in target calculation can also occur due to image distortion;[9] however, near-complete distortion correction can be reliably achieved with modern devices.[4] Moreover, several studies have underlined the importance of the experience of the neurosurgeon in obtaining a histological diagnosis and reducing postbiopsy complications.[1,2,10,11] Lastly, the biopsy method (stereotactic or open) applied in our study was chosen according to the location of the lesion, and it did not influence the histological results.

Prebiopsy corticosteroid therapy is known to increase apoptosis,[12-16] and it is considered responsible for misdiagnosing primary lymphomas of the central nervous system.[17-19] This concept has recently been challenged by study results suggesting that the diagnostic yield for lymphoma patients receiving corticosteroids is comparable to those for biopsies performed without prebiopsy corticosteroid therapy.[20,21] Moreover, data obtained from in vitro experiments suggest that mineralocorticoids exert a variable, time-dependent inhibitory effect on the proliferation of glioma cells.[22] Indeed, some authors have reported the regression of glial tumors in patients receiving corticosteroids.[23-28] However, the molecular mechanisms underlying the effects of corticosteroids on tumor cell regulation are still poorly understood.

In our series, prebiopsy corticosteroid therapy was the only risk factor for a nondiagnostic biopsy. In the light of our results and experience, we recommend performing brain biopsies in patients without corticosteroid therapy, even if this means planning them urgently in cases requiring corticosteroid administration without delay. In cases of suspected lymphoma, we consider that a 1-week corticosteroid-free therapeutic window is sufficient to avoid the risk of performing a nondiagnostic biopsy. However, this recommendation depends on the clinical condition of the patient, including since in some cases it can be difficult to wait 1 week without administering corticosteroids. Tailored management should therefore be developed that considers the trade-off between the risk of performing a nondiagnostic biopsy and the risk of clinical worsening by withdrawing corticosteroids.

Methods for enhancing biopsy efficacy

Various methods have been reported for reducing the rate of nondiagnostic biopsies. Mathon et al.[6] applied intraoperative smears, which decreased the rate of nondiagnostic biopsies from 2.6% to 0%. Preoperative 5-ALA administration and the intraoperative assessment of fluorescence could improve the diagnostic yield of needle biopsies, especially for glioma and lymphoma patients.[29,30] Akshulakov et al.[31] reported innovative intraoperative techniques for identifying viable pathological tissue, which included optical and molecular detection methods.

Avoiding a second biopsy by performing molecular testing of the first nondiagnostic sample

Intratumoral necrosis, hemorrhage, and peripheral gliosis are considered the main causes of nondiagnosing biopsies, and recent studies have shown that *IDH1* and pTERT mutations can be detected in a high proportion of nondiagnostic biopsies

Table 3. Clinical, radiological, and histological features of the included patients

Case no.	Age, years	Sex	Interval between the two biopsies, days	First biopsy				Second biopsy		
				Prebiopsy corticosteroids	Largest lesion diameter, mm	Histological diagnosis	Suspected reason for nondiagnostic biopsy	Prebiopsy corticosteroids	Largest lesion diameter, mm	Final histological diagnosis
1	24	F	50	No	58	Gliosis	Sample-size error	No	62	Grade IV glioma
2	69	F	15	Yes	35	Gliosis	Target error	No	50	Grade IV glioma
3	73	F	34	No	45	Normal brain	Target error	No	50	Grade III glioma
4	64	M	20	No	50	Gliosis	Target error	No	51	Grade IV glioma
5	70	F	1,064	Yes	8	Inflammation	Interpretation error (corticosteroids?)	No	15	Lymphoma
6	41	M	444	Yes	14	Inflammation	Interpretation error (corticosteroids?)	No	15	Nocardiosis
7	66	M	28	No	47	Gliosis	Target error	No	49	Grade IV glioma
8	70	M	24	No	50	Inflammation	Unknown	Yes	55	None (inflammation)
9	28	F	63	Yes	15	Inflammation	Interpretation error (corticosteroids?)	No	25	Grade III glioma
10	59	F	97	Yes	15	Lymphocyte infiltrate	Interpretation error (corticosteroids?)	No	15	Lymphoma
11	58	M	265	No	28	Lymphocyte infiltrate	Sample-size error	No	21	Radionecrosis
12	47	M	71	No	40	Gliosis	Unknown	Yes	75	None (gliosis)
13	22	F	884	No	14	Gliosis	Sample-size error	No	30	Grade IV glioma
14	65	F	22	No	25	Gliosis	Target error	No	32	Grade IV glioma
15*	63	F	19	No	25	Normal brain	Target error	No	40	Metastasis
16	58	M	67	Yes	24	Gliosis	Target error	No	30	Metastasis
17	70	F	64	Yes	17	Inflammation	Interpretation error (corticosteroids?)	No	20	Lymphoma
18*	68	M	25	Yes	30	Inflammation	Interpretation error (corticosteroids?)	No	35	Lymphoma
19	64	M	19	No	47	Gliosis	Target error	No	51	Grade IV glioma
20	49	M	15	Yes	73	Necrosis	Sample-size error	No	80	Grade IV glioma
21	42	F	205	Yes	24	Necrosis	Sample-size error	Yes	28	Metastasis
22	73	M	110	No	30	Gliosis	Unknown	Yes	30	None (gliosis)
23	27	F	82	No	60	Gliosis	Sample-size error	No	68	Grade II glioma
24	51	F	165	No	30	Necrosis	Sample-size error	No	35	Metastasis
25*	63	M	45	No	25	Necrosis	Sample-size error	No	40	Grade IV glioma
26	34	M	12	No	25	Gliosis	Target error	No	30	Grade IV glioma
27	52	F	112	No	35	Gliosis	Unknown	No	35	None (gliosis)
28	46	F	135	No	15	Gliosis	Target error	No	21	Grade IV glioma
29	28	F	161	No	20	Gliosis	Sample-size error	No	21	Grade II glioma
30*	57	F	21	Yes	25	Necrosis	Sample-size error	No	30	Grade IV glioma

*Case detailed in Fig. 2.
F: female, M: male.

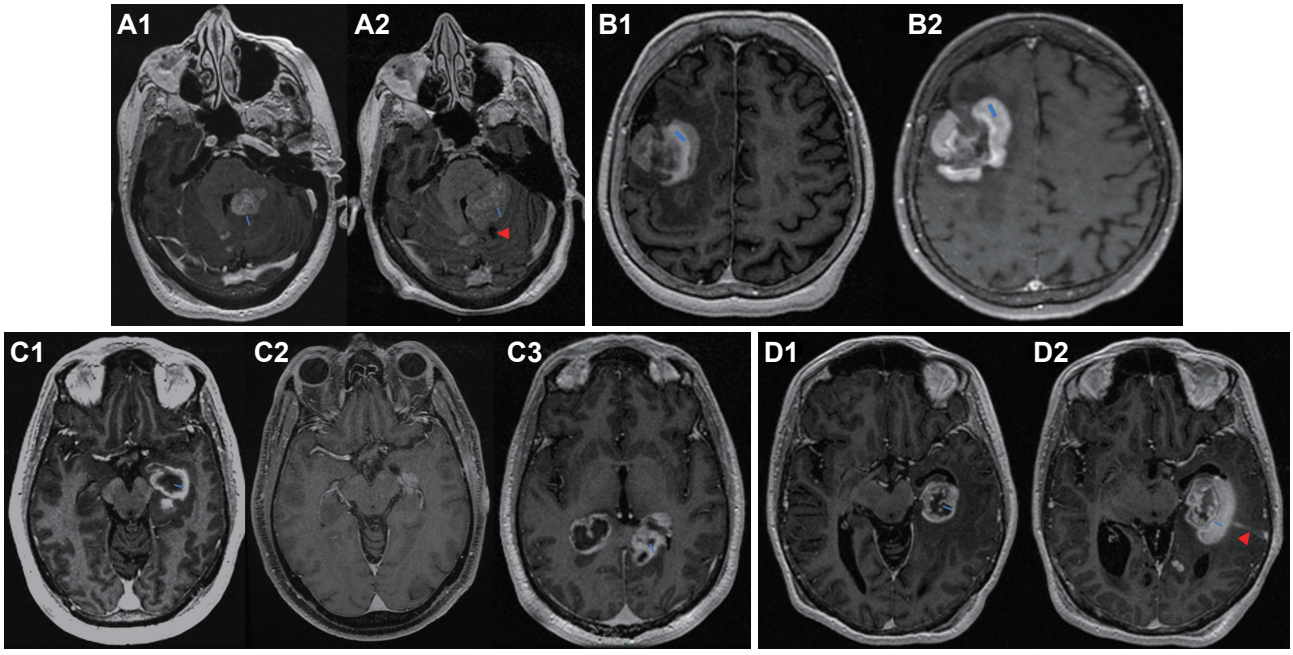

Fig. 2. Four example cases illustrating the differences between the nondiagnostic first biopsy and the diagnostic second biopsy. The blue line indicates the biopsy target obtained by merging postoperative CT scan and preoperative MRI. Case #15. A 63-year-old female underwent a stereotactic brain biopsy for a left middle cerebellar peduncle lesion. The initial neuropathological examination found only normal cerebellar tissue. A postoperative CT scan showed a target error (A1). The neuropathological examination of the second stereotactic biopsy performed 19 days later was consistent with breast cancer metastasis (A2). The red arrowhead shows the target of the first biopsy (A2). Case #18. A 68-year-old male presented with left hemiparesis. Brain MRI showed a right frontal "flaky" contrast-enhanced lesion. Corticosteroids were introduced and then stopped 3 days before performing the stereotactic biopsy. The neuropathological analysis revealed inflammatory lesions with macrophage infiltration (B1). This noncontributory result led to a second biopsy being performed 25 days after withdrawing the corticosteroids, which led to a diagnosis of a B-cell primary lymphoma in the central nervous system (B2). Case #25. A 63-year-old male was admitted due to suspected left medial temporal tumor. The neuropathological examination of the stereotactic biopsy sample revealed nonspecific necrosis (C1). Corticosteroids were introduced after the biopsy, and tumor regression was found in brain MRI performed 20 days later (C2). Corticosteroid therapy was therefore stopped, and follow-up imaging revealed increases in the size and spread of the lesion (C3). A second brain biopsy performed 45 days after the first biopsy disclosed a grade IV glioma. Case #30. A 57-year-old female underwent a stereotactic brain biopsy due to suspected left medial temporal tumor (D1). The neuropathological examination revealed nonspecific necrosis. The second stereotactic biopsy performed 3 weeks later was consistent with a grade IV glioma (D2). The red arrowhead shows the particularly interesting finding of the trajectory of the first needle biopsy (D2).

Table 4. Postbiopsy complications

	First biopsy	Second biopsy	*p*
Symptomatic complication	0 (0/30)	6.0 (2/30)	0.49
Asymptomatic hemorrhage	20.0 (6/30)	43.3 (13/30)	0.10

Categorical variables are expressed as percentage and number values.

from *IDH1* and pTERT-mutant glioma patients,[7,32] which can help to avoid the need to perform an additional biopsy. The efficacy of this type of molecular analysis has already been demonstrated for biopsies of indeterminate thyroid nodules[33] and when interpreting bronchoscopy findings in patients with suspected lung cancer.[34] Moreover, genomic next-generation sequencing of brain tissue performed over the last few years has enabled diagnoses that were not possible using routine histological and microbiological testing.[35] These recently reported novel techniques pave the way to further improve the diagnostic yield of brain biopsies.[36]

Limitations

This study had both limitations and strengths. First, it had a retrospective, monocentric, observational design, but intraindividual comparisons made it possible to eliminate most of the bias. Second, the patient population was quite heterogeneous regarding type of brain lesions, but this reflects the real-world situation of biopsied patients in a tertiary referral center.

Conclusion

Performing a second brain biopsy in patients who have undergone an initial nondiagnostic biopsy is effective in most cases. Given the significant difficulties in managing patients without a definitive diagnosis, we advocate that a second biopsy be systematically considered in the diagnosis algorithm of these patients after it has been verified that molecular testing cannot help to obtain a diagnosis. Corticosteroid administration can lead to nondiagnostic biopsies and should be avoided when possible during the prebiopsy period.

Author Contributions

Conceptualization: Mohamed Chabaane, Bertrand Mathon, Aymeric Amelot. Data curation: Mohamed Chabaane, Bertrand Mathon, Aymeric Amelot, Franck Bielle, Karima Mokhtari, Maximilien Riche. Formal analysis: Mohamed Chabaane, Bertrand Mathon, Aymeric Amelot, Maximilien Riche. Investigation: Mohamed Chabaane, Bertrand Mathon, Aymeric Amelot, Franck Bielle, Karima Mokhtari, Maximilien Riche. Methodology: Mohamed Chabaane, Bertrand Mathon, Aymeric Amelot. Project administration: Bertrand Mathon, Aymeric Amelot, Alexandre Carpentier. Supervision: Bertrand Mathon, Mehdi Touat, Alexandre Carpentier. Validation: all authors. Visualization: all authors. Writing—original draft: Mohamed Chabaane, Bertrand Mathon, Aymeric Amelot. Writing—review & editing: Mehdi Touat, Alexandre Carpentier, Bertrand Mathon, Franck Bielle.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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