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Biopsy of the Superficial Cortex: Predictors of Effectiveness and Outcomes

BACKGROUND: Brain biopsies of superficial cortex are performed for diagnosis of neurological diseases, but preoperative predictors of successful diagnosis and risks are lacking.

OBJECTIVE: We evaluated effectiveness and outcomes of superficial cortical biopsies and determined preoperative predictors of diagnosis, outcomes, morbidities, and mortality.

METHODS: A single-institution retrospective analysis of 170 patients who underwent open brain biopsies of superficial cortex was performed. Clinical predictors of effectiveness and outcomes were determined using univariate/multivariate analyses and a system for risk-benefit stratification was created and tested.

RESULTS: Brain biopsies led to successful diagnosis in 122 of 170 (71.8%) and affected management in 97 of 170 (57.1%) cases. Factors increasing the odds of diagnostic pathology included age older than 45 years (odds ratio [OR]: 2.67, 95% confidence interval [CI]: 1.34-5.27, $P < .01$), previous cancer diagnosis (OR: 3.64, 95% CI: 1.69-7.85, $P < .001$), focal (OR: 3.90, 95% CI: 1.91-8.00, $P < .001$) and enhancing (OR: 5.03, 95% CI: 2.41-10.52, $P < .001$) lesions on magnetic resonance imaging, biopsy of specific lesions on magnetic resonance imaging (OR: 9.34, 95% CI: 4.29-20.33, $P < .001$), and use of intraoperative navigation (OR: 6.59, 95% CI: 3.04-14.28, $P < .001$). Brain biopsies led to symptomatic intracranial hemorrhage, seizures, other significant morbidities, and perioperative mortality in 12.4%, 16.2%, 37.1%, and 8% of cases, respectively. Risk of postoperative intracranial hemorrhage was increased by a history of aspirin use (OR: 2.51, 95% CI: 1.23-5.28, $P < .05$) and age older than 60 years (OR: 2.66, 95% CI: 1.36-5.18, $P < .01$).

CONCLUSION: Effectiveness and risk of morbidity/mortality can be estimated preoperatively for patients undergoing open brain biopsies of the superficial cortex. Older age and specific imaging characteristics increase the odds of diagnostic biopsy. Conversely, older age and aspirin use increases the risk of postoperative complications.

KEY WORDS: Brain tumor, Dementia, Efficacy, Hemorrhage, Open brain biopsy, Outcomes, Pathology

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Brain biopsy of the superficial cortex is a commonly performed procedure for the diagnosis of neurological illness. However, the decision to pursue an open brain biopsy is not always straightforward. One patient may present with a neurological deficit and a corresponding lesion on brain magnetic resonance image (MRI). Intuitively, biopsy of this lesion would likely produce a successful diagnosis to affect management. Meanwhile, biopsy of a patient with neurological deterioration such as cognitive decline and no specific lesion on imaging may have lower diagnostic yield.

ABBREVIATIONS: AUC, area under the curve; **CI,** confidence interval; **ICH,** intracranial hemorrhage

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Numerous studies have evaluated the use of both stereotactic and frameless brain biopsies for malignancy and human immunodeficiency virus infection (HIV)–related diseases.[1-4] In patients with discrete intracranial lesions, stereotactic needle biopsies have a reported pathology diagnostic yield of 91.7%.[4] Frameless needle biopsy techniques

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boast similar diagnostic yields.[3] Complication rates for stereotactic needle biopsies vary from 0 to 10%.[1,5-12] Complications have been associated with hypertension, HIV, biopsy of the pineal region, and thrombocytopenia.[5,7,10,13,14]

In contrast, the utility of brain biopsies in patients with worsening neurological conditions without focal imaging findings remains unclear. Open brain biopsies for dementia and neurological decline produce nondiagnostic pathology including normal tissue and nonspecific changes in 5% to 71% of cases.[15-20] Normal brain tissue is seen in 1% to 45% of biopsy specimens.[15-18] Previous reports show that brain biopsies for cognitive decline affects management in 8% to 12% of patients.[17,20] Complication rates vary from 2% to 14%.[18]

This report details the retrospective analysis of our institution's experiences with brain biopsy of the superficial cortex to develop predictors of diagnostic pathology affecting clinical management, outcomes, morbidities, and mortalities. We specifically studied biopsies of the cortical surface (both lesional and nonlesional) rather than needle biopsies. Through this analysis, we developed models that may help estimate the effectiveness and outcomes for patients being evaluated for possible brain biopsy.

PATIENTS AND METHODS

Database

After approval by Washington University Institutional Review Board, patients who underwent brain biopsies of the superficial cortex at Washington University School of Medicine between 1998 and 2011 were identified through CPT procedure codes. Inclusion criteria included a patient who underwent a craniotomy/craniectomy for biopsy of the cortical surface. Lesions were on the cortical surface and most amenable to superficial biopsy rather than stereotactic needle biopsy of a deeper lesion. Patients who underwent a tumor resection, endoscopic procedure, stereotactic needle biopsy, or any other procedure more complex than a superficial cortical biopsy were excluded. Over 14 years, 265 patients had procedural codes with burr hole/trephine with biopsy or craniotomy/craniectomy for exploration. Of these, 170 patients met the inclusion/exclusion criteria. A total of 698 patients had procedure codes for stereotactic biopsy, aspiration, or excision with burr hole(s) for intracranial lesion. A database with 170 superficial cortical biopsy patients was created for the retrospective analysis. Database included demographics, preoperative symptoms and signs, medications, laboratory values, imaging studies, procedural details, postoperative course, postoperative laboratory test results, pathology details, and follow-up hospital and clinic notes. Long-term clinical outcome data were derived from clinic notes. Postoperative complications included seizures, hemorrhages, and deaths occurring within 31 days of the operation. Radiology reports were assessed for focal lesion on head computed tomography (CT) scans and magnetic resonance imaging (MRI), enhancing lesions on MRI, and T2-hyperintensity signal abnormalities. Angiography reports were examined for vasculitis or vasculopathy (determined by artery caliber changes as determined by the neuroradiologist). Postoperative complications were assessed by evaluating medical records for each individual patient. Postoperative intracranial hemorrhages, seizures, deaths, or significant other life-threatening morbidities were recorded and tabulated. Reports of postoperative CT scans or MRI were evaluated for intracranial hemorrhages (ICHs) including intraparenchymal and extra-axial hemorrhages. Radiology reports demonstrating "postoperative blood products" or "postoperative changes" were not included as ICHs. The size and type of hemorrhage were documented and correlated with medical record notes to assess for clinical changes. When available, all CT scans and MRI were reviewed. A positive effect on clinical management was defined by a documented changed in the treatment plan as a result of the biopsy. Long-term clinical outcome data were derived from outpatient and inpatient medical record notes. The outcome data were collected from follow-up documentation of either the surgeon or neurologist who evaluated the patient at the time of biopsy. Based on the assessments, the status was either recorded as worsened, unchanged, improved, or not documented.

Biopsy Procedure

Brain biopsies were performed to diagnose pathology underlying neurological symptoms or signs and/or abnormal imaging findings. The open brain biopsies were performed using standard operative technique. Unless the location of biopsy-targeted radiographic findings, the biopsy was located in the right frontal lobe (occasionally left frontal lobe) anterior to the coronal suture. For some cases, frameless StealthStation (Medtronic Inc, Minneapolis, Minnesota) image-guided navigation was used to pursue a lesion on imaging. After craniotomy or craniectomy was performed at the biopsy site, the dura was opened and a biopsy specimen was taken of a discrete lesion or 10-mm cube of brain parenchyma was removed en bloc. For some procedures, dura was also collected.

Pathology

Specimens were fixed in formalin, processed in paraffin wax, and sectioned for routine histopathological stains such as hematoxylin and eosin and Luxol blue/cresyl violet, and reviewed by a neuropathologist. Additional histopathological and immunohistochemical stains were performed as determined by the neuropathologist. Information for the database was taken from the official pathology report. Nondiagnostic pathology was defined as normal tissue and nonspecific inflammatory changes. Histological vasculopathy was defined as abnormalities found in vasculature without definitive findings of inflammatory cells (which would connote a vasculitis).

Data Analysis

Patient demographic and clinical characteristics as well as the features and outcomes of brain biopsies were summarized as mean $\pm$ SD, median, or frequency, as appropriate. Exploratory univariate logistic regression was used to assess the association between each predictor and effectiveness or outcome, and the strength of association was described by odds ratio (OR) and its 95% confidence interval (CI). Multivariate models were created by selecting the most clinically relevant factors among those found during the univariate analysis, and the model development was also assisted by backward stepwise selection procedures. To facilitate an easy clinical interpretation, age at biopsy (the only continuous predictor) was categorized and the selection of optimal cutoff values was assisted by receiver-operating characteristic curves. The overall performance of multivariate logistic analyses were measured by the area under receiver-operating characteristic curves (AUC) and the reliability of the models were also assessed using 10-fold cross-validation.[21] AUC measures the ability of a model to correctly classify 2 randomly selected subjects. Its value ranged from 0.5 to 1, with 1 indicating a perfect differentiation. All analyses were

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2 sided and significance was set at a P value of .05. Statistical analyses were performed using SAS version 9.0 (SAS Institute, Cary, North Carolina).

RESULTS

Demographics

Over 14 years, 170 cases met the inclusion criteria. Demographics and case characteristics are detailed in Table 1. The mean age of the patients at the time of biopsy was 48.6 years (SD = 22.2; 1 day-85 years). Fourteen percent of patients were younger than 21 years of age; 17% were 21 to 40 years of age; 34% were 41 to 60 years of age; and 35% were older than 60 years of age. Ninety-nine patients 58.2%) were male. Forty-two patients (25.9%) smoked tobacco, and 21 patients (12.7%) had a history of coronary artery disease. Fifty-three patients (31.7%) had vascular disease, including hypertension. Three patients had a diagnosis of HIV (1.8%). Seventy-seven patients (46.1%) had a previous cancer diagnosis. Patients presented with headaches, cognitive decline, behavioral changes, hallucinations, focal weakness, myoclonus, and seizures, respectively. Forty-one patients (24.6%) were taking aspirin on initial neurosurgical consultation. Fifty-eight percent were taking 81 mg/d, and aspirin was held 1 to 30 days before surgery. Seven (4.2%), 7 (4.2%), 8 (4.9%), and 60 (36.4%) were taking clopidogrel, warfarin, nonsteroidal anti-inflammatory drugs, or steroids, respectively.

TABLE 1. Patient Demographics and Characteristics[a]

Variable	No. (%) of Total
Age, mean ± SD, y	48.6 ± 22.1
Male	99 (58.2)
Comorbidities	
Smoker	42 (25.9)
Coronary artery disease	21 (12.7)
Vascular disease	53 (31.7)
HIV	3 (1.8)
History of cancer	77 (46.1)
Presenting symptoms and signs	
Headaches	68 (40.7)
Cognitive decline	85 (50.3)
Behavioral change	63 (37.5)
Hallucinations	10 (6.0)
Focal weakness	68 (40.5)
Myoclonus	6 (3.6)
Seizures	57 (33.7)
Medications on consultation	
Aspirin	41 (24.6)
Clopidogrel	7 (4.2)
Coumadin	7 (4.2)
NSAIDs	8 (4.9)
Steroids	60 (36.4)

[a]HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs.

Preoperative Evaluation

Before open brain biopsy, each patient underwent an extensive preoperative evaluation (Table 2). Radiological evaluations included a head CT scan, brain MRI, magnetic resonance angiography, CT angiography, catheter angiography, and additional studies such as positron emission tomography and spectroscopy. Fifty-nine of 102 head CT scans (57.8%) revealed a focal lesion. Focal abnormalities on brain MRI were noted in 115 of 167 patients (68.9%). An enhancing lesion on MRI was noted in 93 of 163 patients (57.1%). MRI revealed hyperintense T2 signal changes in 139 of 163 patients (85.3%). Catheter angiography, CT angiography, and MR angiography were performed in select patients and showed signs of vasculitis/vasculopathy in 11 of 169 patients (6.5%). Spectroscopy, positron emission tomography, electroencephalography, basic laboratory studies, bleeding studies, and cerebral spinal fluid (CSF) studies were performed on select patients.

TABLE 2. Preoperative Evaluation[a]

Imaging and Clinical Studies	No. (%) of Total
Focal lesion on CT scan	59/102 (57.8)
Focal lesion on MRI	115/167 (68.9)
Enhancing lesion on MRI	93/163 (57.1)
Catheter angiogram performed	44/169 (26.0)
CT angiogram performed	2/169 (1.2)
MR angiogram performed	26/169 (15.4)
Vasculitis/vasculopathy on angiogram	11/169 (6.5)
PET	21/166 (12.7)
Spectroscopy	18/165 (10.9)
EEG	53/165 (32.1)
Normal	12 (7.2)
Slowing	30 (18.2)
Seizure	11 (6.7)

Laboratory Studies	Mean (SD)	No. of Patients Tested
INR	1.0 (0.1)	152
Platelet count, ×1000 cells/mm^3	270 (105)	160
ESR, mm/h	28.5 (31.0)	73
CRP, mg/L	19.5 (33.3)	40
WBCs, ×100 cells/mm^3	9.8 (8.8)	160
Cerebrospinal fluid studies		
Nucleated cells, cells/μL	60 (224)	92
Protein, mg/dL	132.2 (214)	91
Glucose, mg/dL	68.4 (25.1)	91
IgG index	0.96 (1.7)	30
Platelet function screen		28
Epinephrine, s	147 (76)	
ADP, s	76 (47)	

[a]CT, computed tomography; MRI, magnetic resonance imaging; MR, magnetic resonance; PET, positron emission tomography; EEG, electroencephalography; INR, international normalized ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBCs, white blood cells; IgG, immunoglobulin G, ADP, adenosine diphosphate. Platelet function screen normal values: epinephrine (60-160), ADP (50-110).

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Procedure

Surgeons pursued a discrete lesion on MRI and used image-guided navigation in 67.3% and 65.2% of biopsies, respectively. Biopsies of the right and left hemispheres were performed in 55.9% and 36.1% of cases, respectively (see Table 1, Supplemental Content 1, http://links.lww.com/NEU/A538). An intraoperative complication, a seizure, was noted in 1 of the 170 biopsies.

Pathology

Overall pathology findings are shown in Figure 1 and revealed diagnostic pathology in 70.6% of patients. Forty-nine percent (83/170) of samples were neoplastic. Neoplasms included glioblastoma (32.5%), astrocytoma (22.9%), meningioma (9.6%), oligoastrocytoma (7.2%), oligodendroglioma (7.2%), CNS lymphoma (10.8%), other primary nervous system neoplasms (6.0%), and metastases (3.6%). Open brain biopsy pathology showed non-diagnostic pathology in 29.4% of open brain biopsies: nonspecific inflammatory changes in 18.2% (31/170) and normal tissue in 11.2% (19/170) of cases. Fourteen percent of brain biopsies (24/170) were found to have vascular anomalies including vasculitis (2.9%), vasculopathy (3.5%), vascular malformations (1.2%, a capillary telangiectasia and an arteriovenous malformation), and amyloid angiopathy (6.5%). Infectious etiologies and demyelination were found in 2.4% of open brain biopsies (4/170 and 4/170) each. Degenerative pathology was found in 1.8% (3/170) of open brain biopsies including spongiform changes (1.2%) and Alzheimer plaques (0.6%). Lymphohistiocytic infiltrate and neuronal ceroid lipofuscinosis were found in 2 patients.

Predictors of Diagnostic Pathology and Outcome

We evaluated for preoperative predictors of successful diagnostic pathology using a hypothesis-generated and exploratory univariate analysis (Table 3). Patients older than 45 years of age had 2.67 times the odds of diagnostic pathology than younger patients (95% confidence interval [CI]: 1.34-5.29; $P < .01$). Patients older than 45 years of age at the time of biopsy had diagnostic pathology in 80% of biopsies. Conversely, patients 45 years of age and younger had diagnostic pathology in 60%. History of a cancer diagnosis increased the odds of diagnostic pathology by 3.64 (95% CI: 1.69-7.85; $P < .001$). A focal lesion on CT (OR: 5.54, 95% CI: 2.13-14.43,$P < .001$), a focal lesion on MRI (OR: 3.90, 95% CI: 1.91-8.00, $P < .001$), and an enhancing lesion on MRI (OR: 5.03, 95% CI: 2.41-10.52, $P < .001$) were associated with diagnostic pathology. Biopsy of a discrete lesion on MRI (OR: 9.34, 95% CI: 4.39-20.33, $P < .001$), and use of a frameless image-guided surgical technique (OR: 6.59, 95% CI: 3.04-14.28, $P < .001$) increased the odds of diagnostic pathology. No statistically significant associations were identified with sex, smoking, vascular disease, HIV, headaches, behavioral changes, cognitive decline, hallucinations, myoclonus, seizures, steroid use, T2 signal changes on MRI, findings of vasculitis or vasculopathy on angiograms, white blood cell count, inflammatory markers, CSF studies, or use of positron emission tomography, spectroscopy, or electroencephalography.

An enhancing lesion on MRI altered the diagnoses attained with open brain biopsy (Figure 2). Enhancing lesions on MRI had

TABLE 3. Predictors of Diagnostic Tissue Pathology[a]

Variable	OR	95% CI	*P* Value
Age >45 y	2.67	1.34-5.29	<.01
Male sex	0.78	0.39-1.56	
Comorbidities			
Smoker	0.85	0.39-1.82	
Coronary artery disease	4.28	0.95-19.14	
Vascular disease	0.86	0.42-1.77	
HIV	0.78	0.07-8.81	
Previous cancer diagnosis	3.64	1.69-7.85	<.001
Presenting symptoms and signs			
Headaches	0.66	0.34-1.30	
Cognitive decline	0.72	0.45-1.15	
Behavioral change	0.61	0.31-1.21	
Hallucinations	1.63	0.33-8.00	
Focal weakness	1.00	0.50-1.99	
Myoclonus	0.18	0.03-1.04	
Seizures	2.06	0.95-4.44	
Medications on consultation			
Steroids	0.93	0.47-1.87	
Imaging and clinical studies			
Focal lesion on CT scan	5.54	2.13-14.43	<.001
Focal lesion on MRI	3.90	1.91-8.00	<.001
Enhancing lesion on MRI	5.03	2.41-10.52	<.001
Catheter angiography performed	0.35	0.17-0.72	<.01
CT angiography performed	0.39	0.02-6.39	
MR angiography performed	0.39	0.17-0.93	<.05
Vasculitis/vasculopathy on angiography	0.30	0.09-1.04	
Surgical technique			
Biopsy of specific lesion on MRI	9.34	4.29-20.33	<.001
Image-guided surgery	6.59	3.04-14.28	<.001

[a]OR, odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; CT, computed tomography; MRI, magnetic resonance imaging.

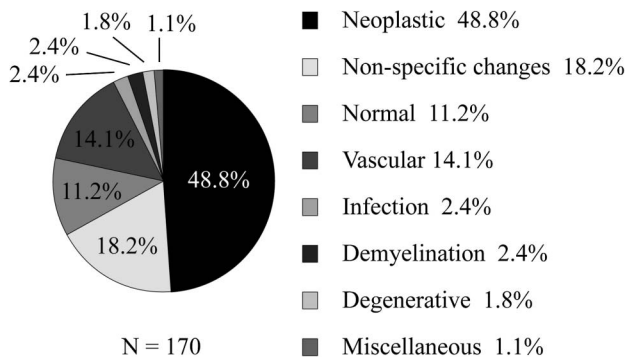

FIGURE 1. *Distribution of pathology results for 170 brain biopsies of the superficial cortex.*

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	Enhancing (+) No. (%)	Non-enhancing (-) No. (%)
Neoplastic	62/93 (66.7%)	17/71 (23.9%)
NS Inflam. changes	13/93 (14.0%)	16/71 (22.5%)
Normal	1/93 (1.1%)	18/71 (25.4%)
Vascular	9/93 (9.7%)	15/71 (21.1%)
Infection	4/93 (4.3%)	0/71 (0%)
Demyelination	4/93 (4.3%)	0/71 (0%)
Degenerative	0/93 (0%)	3/71 (4.2%)
Miscellaneous	0/93 (0%)	2/71 (2.8%)

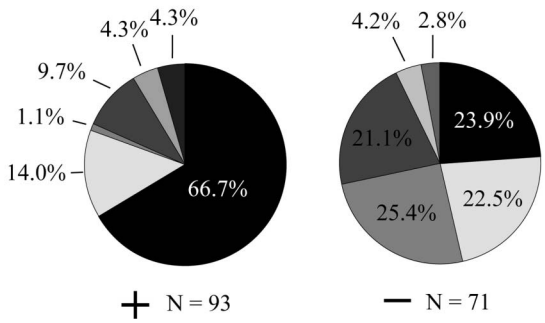

FIGURE 2. *Pathology results for open brain biopsy patients who underwent a preoperative magnetic resonance imaging study including 93 who showed enhancing lesions (+, left) and 71 with no enhancing lesions (−, right). Quantitation and pie charts are shown each subgroup of patients. NS Inflam., nonspecific inflammatory changes.*

a significantly different distribution of diagnoses compared with nonenhancing lesions ($P < .0001$, Fisher exact test). If MRI showed an enhancing lesion, pathology revealed a neoplasm in 66.7% of biopsies. Normal pathology and nonspecific inflammatory changes accounted for 1.1% and 14.0% of biopsies, respectively. The remainder of biopsies showed vascular disease (9.7%), infections (4.3%), and demyelinating disorders (4.3%). Without an enhancing lesion on MRI, pathology showed normal tissue in 25.4% and nonspecific inflammatory changes in 22.5% of biopsies: 47.9% nondiagnostic. Neoplasms (23.9%) and vascular diseases (21.1%) accounted for the majority of other diagnoses.

Biopsy affected the clinical management plan in 97 of 170 patients (57.1%). Biopsy affected management in 75.0% of patients with a cancer history vs 55.4% in patients without a previous cancer diagnosis ($P < .001$). Myoclonus decreased the likelihood that biopsy affected management ($P < .05$). A focal CT lesion ($P < .01$), a focal MRI lesion ($P < .001$), and an enhancing MRI lesion ($P < .001$) increased the probability that biopsy affected management. Biopsy of a discrete MRI lesion and use of intraoperative navigation increased the odds that biopsy affected management ($P < .001$). Patients who had catheter angiography performed were less likely to have a biopsy finding that affected management ($P < .01$). Brain biopsy affected management in 9.1% of patients who had angiographic signs of vasculitis vs 63.7% in other patients ($P < .001$).

Several factors correlated with long-term outcomes after open brain biopsies. Overall, 72 of 149 patients (48.3%) were improved on long-term follow-up after open brain biopsies. Twenty-one patients were lost to follow-up. Median length of follow-up time was 28.0 months (interquartile range, 5.7-57.0 months). Thirty-seven percent of previous cancer patients were improved on follow-up vs 43.6% of patients without a previous cancer diagnosis ($P < .05$). Patients who improved on follow-up were younger (42.9 ± 20.6 years old) than those who did not improve (51.5 ± 22.7 years; $P < .01$). Thirty-seven percent of patients who presented with cognitive decline improved on follow-up compared with 59.5% patients without cognitive decline ($P < .01$). In contrast, presenting with headaches increased the chance of improvement on follow-up from 38.8% to 62.3% ($P < .01$).

Morbidities and Mortalities

Postoperative morbidities and mortalities were recorded for each patient (Table 4). Fifty-five patients (32.5%) had reports of postoperative ICH. Of these, 21 (12.4%) were symptomatic and 34 (20.1%) were asymptomatic. The mean ICH size was 1.5 ± 1.8 cm. A symptomatic ICH was 3.9 times larger than an asymptomatic ICH (3.1 ± 2.3 vs 0.8 ± 0.6 cm, respectively; $P < .01$). Five biopsies (3%) were complicated by ICH requiring surgical intervention. Twenty-seven patients (16.2%) experienced postoperative seizures. Of these, 10 of 27 experienced de novo seizures. Sixty-two (37.1%) experienced significant postoperative morbidities, including major systemic complications, infections, neurological deficits, strokes, and hemorrhages. Thirteen biopsies (8%) were associated with perioperative mortality (within 31 days postoperatively; range, 1-31 days).

TABLE 4. Postoperative Morbidity and Mortality[a]

Morbidity and Mortality	No. (%) of Patients	Size, cm (SD)
ICH	55 (32.5)	1.5 (1.8)
Symptomatic ICH	21 (12.4)	3.1 (2.3)
Asymptomatic ICH	34 (20.1)	0.8 (0.6)[b]
ICH requiring surgical intervention	5 (3.0)	
Seizure	27 (16.2)	
Significant morbidities	62 (37.1)	
Perioperative mortality	13 (8.0)	
Mortality 2°/2 disease progression	3 (1.8)	
Mortality 2°/2 ICH	3 (1.8)	

[a]ICH, intracranial hemorrhage.
[b]Different from symptomatic ICH, $P < .01$; size = mean diameter.

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Three (1.8%) died of postoperative ICH and 3 (1.8%) died of disease progression.

Predictors of Morbidities

Several preoperative variables were associated with postoperative ICH (Table 5). Patients without a postoperative ICH had a mean age of 46.5 ± 24.2 years, whereas postoperative patients with ICH had a mean age of 53.2 ± 21.8 years ($P < .05$). Age older than 60 years at the time of surgery increased the odds of postoperative ICH by 2.66 (95%: CI 1.36-5.18, $P < .01$). Forty-nine percent of patients who took aspirin on initial consultation had a postoperative ICH compared with 27.2% of those who did not take aspirin (OR: 2.51, 95% CI: 1.23-5.28, $P < .05$). Exploratory univariate analysis of risk factors found no associations with postoperative ICH and coagulation studies, platelet count or function tests, surgical technique or diagnosis. Preoperative seizures increased the incidence of postoperative seizures from 9.0% to 39.9% ($P < .001$). Forty-nine percent of patients with a previous cancer diagnosis had a postoperative morbidity compared with 28.4% of patients without previous cancer ($P < .01$).

TABLE 5. Predictors of Postoperative ICH[a]

Variable	OR	95% CI	*P* Value
Age >60 y	2.66	1.36-5.18	<.01
Male sex	1.22	0.63-2.36	
Comorbidities			
Smoker	0.93	0.43-1.98	
Coronary artery disease	0.83	0.30-2.26	
Vascular disease	1.30	0.65-2.59	
HIV	1.07	0.09-12.04	
Previous cancer diagnosis	1.31	0.69-2.51	
Medications on consultation			
Aspirin	2.51	1.23-5.28	<.05
Clopidogrel	0.83	0.16-4.43	
Warfarin	0.84	0.16-4.47	
NSAIDs	0.29	0.03-2.41	
Steroids	1.26	0.64-2.48	
Imaging and clinical studies			
Focal lesion on CT scan	2.19	0.91-5.29	
Focal lesion on MRI	1.33	0.65-2.72	
Enhancing lesion on MRI	2.00	1.01-3.99	
Catheter angiography performed	0.52	0.23-1.14	
CT angiography performed	2.07	0.13-33.8	
MR angiography performed	0.32	0.11-0.99	<.05
Vasculitis/vasculopathy on angiography	0.44	0.09-2.09	
Surgical technique			
Biopsy of specific lesion on MRI	1.87	0.90-3.90	
Image-guided surgery	1.58	0.77-3.24	

[a]ICH, intracranial hemorrhage; OR, odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs; CT, computed tomography; MRI, magnetic resonance imaging.

Models for Predicting Effectiveness and Outcome

Multivariate analyses identified age older than 45 years and biopsy of a discrete lesion on MRI as the 2 independent predictors, and the 10-fold cross-validation[21] demonstrated a reliable prediction of both diagnostic pathology (AUC = 0.82) and surgery (AUC = 0.76) affecting management. Age older than 45 years increased a patient's odds of diagnostic pathology and surgery affecting management to 6.01 (95% CI: 2.38-14.09) and 2.88 (95% CI: 1.35-6.17), respectively (Table 6). Biopsy of a radiographic lesion increased a patient's odds of diagnostic pathology and surgery affecting management to 14.09 (95% CI: 5.57-22.57) and 9.34 (95% CI: 1.35-6.17), respectively (Table 6). Using age and operative plan as variables, the percentages of biopsies that led to diagnostic pathology and affected management were tabulated and presented in numerical (see Table 2, Supplemental Content 2, http://links.lww.com/NEU/A539) and graphic forms (Figure 3A). This model illustrates that in a person 45 years of age or younger and without a discrete lesion on MRI, an open brain biopsy will lead to diagnostic pathology in 22.7% and affect management in 13.6% of patients. Age older than 45 years increases the diagnostic yield of a biopsy to 54.1%, affecting management in 35.1%. A discrete lesion on MRI with age 45 years or younger led to 75.0% diagnostic yield with 65.9% biopsy affecting management. Finally, a person older than 45 years of age and with a discrete lesion on biopsy had a 95.2% chance of diagnostic pathology and an 82.5% chance of biopsy affecting management.

A multivariate model was also created for postoperative ICH risk assessment. Aspirin use at the time of consultation and age older than 60 years were found to increase the risk of a postoperative ICH (AUC = 0.63)[21]. Age older than 60 years and aspirin use increased the odds of an ICH by 2.10 (95% CI: 1.03-4.31) and 2.26 (95% CI: 1.01-5.09), respectively (Table 6). Using these 2 variables, the percentages of biopsies that led to radiographic ICH and symptomatic ICH were tabulated and presented in numerical (see Table 3, Supplemental Content 3, http://links.lww.com/NEU/A540) and graphic forms (Figure 3B). Age older than 60 years and use of aspirin on initial

TABLE 6. Multivariate Analyses of Predictors of Effectiveness and Outcomes[a]

Predictors of Variable	OR	95% CI	*P* Value
Diagnostic pathology			
Age >45 y	6.01	2.38-15.22	<.001
Biopsy of specific lesion on MRI	14.09	5.57-22.57	<.001
Affecting management			
Age >45 y	2.88	1.35-6.17	<.01
Biopsy of specific lesion on MRI	9.34	4.26-20.46	<.001
Intracranial hemorrhage			
Age >60 y	2.10	1.03-4.31	<.05
Aspirin use history	2.26	1.01-5.09	<.05

[a]OR, odds ratio; CI, confidence interval; MRI, magnetic resonance imaging.

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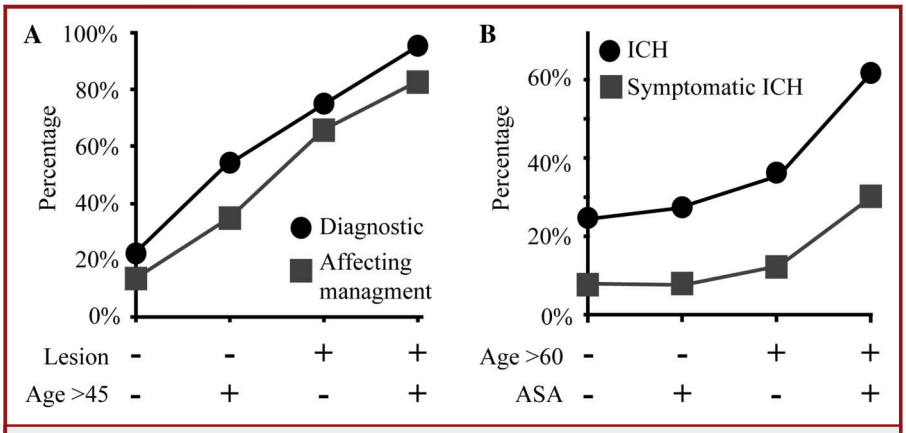

FIGURE 3. *Correlating age, aspirin (ASA) history, and operative plan with effectiveness and outcome for open brain biopsy.* **A**, *percentages of diagnostic pathology (circles) and biopsy affecting management (squares) are plotted relative to predicting variables. Variables included age at the time of operation older than 45 years or 45 years and younger and biopsy of a discrete lesion on magnetic resonance imaging (lesion).* **B**, *percentages of intracranial hemorrhage (ICH) (circles) and symptomatic ICH (squares) are plotted relative to predicting variables. Variables included age at the time of operation older than 60 years or 60 years and older and aspirin use on initial consultation.*

consultation predicted the chance of ICH and symptomatic ICH in 61.5% and 30.8% of patients, respectively.

DISCUSSION

This single-center retrospective analysis of variables can help predict effectiveness and outcomes for brain biopsies of the superficial cortex. We found that, overall, superficial brain biopsies led to neoplastic diagnosis in 49% of cases but were nondiagnostic in 29%. Older age, previous cancer diagnosis, and a focal/enhancing lesion on imaging increase likelihood of diagnostic pathology. Our findings corroborate those of other reports suggesting an association between age and diagnostic yield.[13,20] Our data show that older age correlates with diagnostic pathology. This is similar to Field et al,[13] who showed that in needle biopsies, younger age was associated with a reduced diagnosis rate. In contrast, Burns et al,[20] who included only those with normal or indeterminate imaging findings and excluded immunocompromised patients and those with a previous diagnosis of intracranial neoplasms, showed younger age correlated with diagnostic pathology. Biopsy of a specific lesion on imaging and use of intraoperative image-guided surgery increased the likelihood of diagnostic pathology. Previous reports have indicated that angiography has minimal sensitivity for vasculitis.[22] In our patients, angiographic signs of vasculitis were not associated with diagnostic pathology.

This study highlights the importance of diagnostic imaging to predict effectiveness of the open brain biopsy. As shown in Figure 2, the presence of an enhancing lesion on MRI dramatically reduced the incidence of nondiagnostic pathology from 50% to 15%. Furthermore, in patients without an enhancing lesion, neoplasms still accounted for a large percentage of the diagnostic pathology followed closely by vascular abnormalities.

Predictors of morbidity included older age, aspirin use, preoperative seizures, and a history of cancer. Older age increased the odds of an ICH, possibly due to small-vessel disease and other age-related factors. With clinical details such as patient age, operative plan, and medication list, a clinician can estimate the chances of diagnostic success and hemorrhage for an open brain biopsy. Some patients may be in poor neurological condition without obvious options for treatment, whereby a high risk-benefit ratio may be warranted, but for other patients, observation may be justified. A hemiparetic young woman with an enhancing superficial lesion has a 75% chance of a diagnosis. An elderly man with progressive cognitive decline and no lesion on imaging has a 54% chance of diagnostic pathology. A young, neurologically devastated man without a lesion on imaging has a 23% chance of a diagnosis. The findings shown here and in other studies[2,13,16,17,19,20,23] provide hope for achieving a diagnosis for very ill patients and emphasize that for some patients, the clinical picture may strongly justify the risk of biopsy.

This study carries some inherent limitations such as its single-center retrospective nature. Patient selection was affected by the overlap between patients selected for resection and open biopsy. We excluded needle biopsies, which account for a large number of biopsies and likely excluded many pathologies. The definition of an ICH likely overrepresents this complication. Information regarding transfusions was not available for this study. The analysis was not powered strongly enough to evaluate aspirin dose, time held, or platelet function studies.

CONCLUSION

Preoperative variables can be used to predict the potential risks and benefits of performing an open brain biopsy. Variables that

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correlated with increased effectiveness include increased age, previous cancer diagnosis, focal lesions, lesions with enhancement, and targeting lesions with surgical navigation. Conversely, older age and history of aspirin are associated with an increased risk of postoperative complications. This single-center, retrospective study suggests that using age, operative plan, and history of aspirin use, the models and concepts presented here can aid a physician's clinical judgment to stratify the risks and benefits for open brain biopsy procedures.

Disclosures

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COMMENTS

The authors present their single-center experience of a large retrospective series of open biopsy procedures of the superficial cortex, white matter, leptomeninges, and/or dura mater. The effectiveness of the procedure, ie, diagnostic yield and its effect on treatment management, was evaluated and related to possible preoperative predictors by multivariate logistic analysis. Their findings might aid in deciding whether to pursue an open brain biopsy in a selected category of patients.

As one might expect, biopsy of a focal and/or enhancing lesion as observed on preoperative imaging increased the odds of diagnostic pathology. In our experience, there is indeed no doubt when all diagnostic measures are exhausted and the diagnosis remains unknown that an open biopsy of the lesion seems justified. As is exemplified in this study, this will provide a high chance on a successful diagnosis (~90%), leading to an altered treatment plan.

More questionable, I believe, are patients with severe neurological disease of unknown etiology and indeterminate brain imaging offered to the neurosurgeon for open biopsy. Earlier studies have shown diagnostic yields of approximately 30% to 45%, most often showing angiopathies, prion disease, inflammatory disease, and primary central nervous system lymphoma.[1-3] In 10% of patients, this resulted in an alteration of treatment plan. These results are corroborated by the current study. Therefore, one might wonder whether these numbers justify exposing the patients to a chance on surgery-related morbidity and even mortality?

I concur with the authors, nevertheless, that in every individual patient, the expected benefits should be weighed against the possible risks. This especially holds true for patients with neurodegenerative disease of unclear origin.[4] These results might further aid the neurosurgeon in this oftentimes troublesome decision-making process because they show that approximately 25% of patients younger than 45 years of age and more than 50% of patients older than 45 years of age with nontargeted biopsy had a diagnostic pathology, leading to approximately a 10% and 30% change in management, respectively.

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The authors present a single-center, retrospective analysis of a cohort of 170 patients who underwent biopsy of the superficial cerebral cortex with the intent of providing a comprehensive picture of the diagnostic yield, effect on subsequent patient management, and complications of the procedure. The study addresses a number of relevant clinical questions regarding brain biopsy and provides useful data that can help guide neurosurgeons and neurologists in their deliberations about whether and how to proceed with biopsy in their patients. The strengths of the study include the relatively large number of included patients and comprehensive assessment of outcomes, including not only diagnosis but also detailed assessment of complications. Conversely, the information that the study provides about overall clinical outcomes is of little value due to the heterogeneity of the patients' underlying diseases and the subjective nature of the outcome data.

Of what value are these data? First, they reinforce the already established utility of brain biopsy in patients with target lesions on neuroimaging. More importantly, they confirm previously published data showing that even in patients without a target lesion on preoperative imaging, the diagnostic yield in selected patients may still be in the vicinity of 20%, taking the procedure out of the realm of futility. Finally, the most important data from this study are those detailing the complications of this procedure, which the authors address in much greater detail than in previously published papers on this topic. The data regarding rates, types, and possible risk factors for postoperative intracranial hemorrhage are of particular practical value. Ideally, the risk model for postoperative intracranial hemorrhage presented in this study would need to be confirmed by at least another study before it is relied too heavily on in clinical decision making. Until then, however, neurosurgeons and neurologists can use these authors' data as a reasonable guide.

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CME QUESTIONS

1. When performing an open brain biopsy in a patient with an enhancing lesion on MRI, what is the chance of a non-diagnostic result?
   a. 5-15%
   b. 15-25%
   c. 25-35%
   d. 35-45%
   e. 45-55%
2. Which patient-related factor is a significant predictor of postoperative ICH following brain biopsy?
   a. Platelet function and number
   b. Cardiac output
   c. Renal function
   d. Karnofsky performance status
   e. History of stroke
3. What demographic factor is most predictive of diagnostic brain biopsy?
   a. Age > 45
   b. Male gender
   c. History of tobacco smoking
   d. History of coronary artery disease
   e. HIV status

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