J Neurosurg Pediatrics 11:704–709, 2013

Safety and diagnostic accuracy of neuroendoscopic biopsies: an international multicenter study

Clinical article

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Object. Analysis of the safety and morbidity of neuroendoscopic biopsies (NEBs), as well as the reliability in obtaining an accurate diagnosis, has until now been based on studies with relatively small sample sizes. Through the cooperative efforts of several international medical centers, authors of the present study collected data on a large number of patients to obtain better insight into this issue. When possible, they compared pathology obtained through an NEB with the "gold-standard" pathology obtained in open surgery.

Methods. Thirteen randomly chosen medical centers in 9 countries collected data for patients who had undergone NEB, which were then analyzed for universal complications, bleeding, navigation technique, pathology, mismatch between biopsy results and final diagnosis, and a number of other potentially influential factors.

Results. Data for 293 patients were analyzed. Sixty percent of the patients were male, and patient ages ranged from 0.1 to 78.7 years (median age 20.4 years). The most common tumor locations were pineal (33.1%), thalamic (16.7%), tectal (13%), and hypothalamic (4.4%). Fifty percent of the tumors were larger than 20 mm, 36% were between 10 and 20 mm, and 14% were smaller than 10 mm. Intraoperative bleeding was seen in 275 patients (94%). The amount of blood was noted as mild in 75%, moderate in 13%, and severe in 6%. Infection occurred in 8 patients (3%). Death occurred in 1 patient (0.3%), which was caused by severe intraoperative bleeding. Biopsies were informative in 265 patients (90.4%). Seventy-eight patients (26.6%) had open surgery following the NEB. For these patients, the pathology results from the NEB were compared with those from the open surgery that followed. In 14 cases (17.9%) there was disagreement on the pathology. Of these cases, a meaningful mismatch, in which the erroneous NEB pathology could have led to an inappropriate management decision, occurred in 9 cases (11.5%). Most of these meaningful mismatches were lesions diagnosed as low-grade or pilocytic astrocytoma on the NEB and later proved to be high-grade astrocytoma (4 cases) and 1 case each of meningioma, cavernoma, primitive neuroectodermal tumor, neurocysticercosis, and pineocytoma.

Conclusions. In experienced hands, NEBs can be performed with low morbidity and mortality, providing meaningful pathological data for the majority of patients with a wide range of tumor types, locations, and presentations. These biopsies also offer other advantages, such as the ability to perform concomitant endoscopic third ventriculostomy and septum pellucidotomy. However, due caution must be maintained, since pathology obtained from an NEB, as with stereotactic biopsies, may be subject to sampling errors, especially when the results seem to indicate a low-grade glial tumor.
(http://thejns.org/doi/abs/10.3171/2013.3.PEDS12416)

Key Words • **endoscopy** • **neuropathology** • **brain tumor** • **stereotactic biopsy** • **neuroendoscopic biopsy**

Neuroendoscopic biopsies are performed routinely. However, the safety and accuracy of this surgical methodology has only been studied in relatively small numbers of patients in single-center reports. The aim in our current multicenter study was to collect data on large numbers of NEB patients at several international medical centers. We focused on analyzing two aspects of the procedure: safety and diagnostic accuracy. When taking a biopsy with an endoscope, we are relatively lim-

Abbreviations used in this paper: NEB = neuroendoscopic biopsy; SNB = stereotactic needle biopsy.

ited in our technical abilities to control bleeding. When bleeding occurs, vision is usually severely hampered, further limiting our coagulation ability. Would these factors negatively impact the safety level of NEB procedures? Establishing the correct pathological diagnosis based on the tiny specimens harvested through an NEB can be challenging. Tissue retrieved from the tumor periphery, a sampling error, and an occasional inability to see the pathological structure are all potential sources for histopathological inaccuracies. In the large cohort in this study, we had the opportunity to compare the pathology obtained from an NEB with the "gold-standard" pathology obtained during open surgery. Would the NEB results provide a lower level of diagnostic accuracy?

Methods

Retrospective data were collected from 13 randomly chosen medical centers that routinely performed NEBs between January 1998 and December 2009. Each center had completed a minimum of 15–20 endoscopic biopsies. While individual centers may have contributed very small numbers of NEB patients to the current study, all participating centers had expressed a strong academic and clinical interest in neuroendoscopy and were routinely performing a wide range of endoscopic procedures in addition to the NEBs.

Each medical center had its own criteria for performing the procedure. Patient data had to include detailed pathological information. All information collected was entered into a database (FileMaker Pro 6, FileMaker, Inc.). We used SPSS software (SPSS Institute, Inc.) to analyze data and check for any statistical correlations between demographic, anatomical, or technical variables, and morbidity, feasibility, or biopsy accuracy. Both Pearson and Spearman correlation coefficients were calculated for the complete range of variables, including universal complications, bleeding, pathology, mismatch between biopsy results and final diagnosis, tumor location, surgical technique and equipment, tumor size, number of samples, and use of navigational aids.

Results

We analyzed data for 293 patients from 13 centers (Table 1). Patients had a mean age of 28.3 ± 22.2 years (range 0.1–78.7 years), and 60% were male.

Upon presentation, 196 patients (67%) had elevated intracranial pressure. Tumor anatomy spanned a wide range of locations and sizes (Table 2). The most common tumor locations were pineal (33.1%), thalamic (16.7%), tectal (13%), and hypothalamic (4.4%). Fifty percent of the tumors were larger than 20 mm, 36% were between 10 and 20 mm, and 14% were smaller than 10 mm.

Approach side, number of bur holes, and type of scope were among the technical variables documented (Table 3). Navigation devices were used 15.4% of the time, and continuous rinsing was used in 47% of the procedures. The average number of specimens per procedure was 4.2.

Note that we collected and analyzed a wide range of surgical parameters, including universal complications, bleeding, pathology, mismatch between biopsy results and final diagnosis, anatomical site of origin, surgical technique, type of equipment (biopsy forceps and endoscope), tumor size, number of samples, and use of navigational aids. However, most of the factors analyzed were found to have no statistically significant bearing on the diagnostic yield, morbidity, or correlation between NEB and final results. For example, we found that the use of navigation had no effect on the complication rate or diagnostic yield, and neither did surgical technique, choice of implements, use of irrigation, and any other variable examined. These decisions, specific to each participating medical center, simply reflected individual surgeon preferences and were not shown to have any statistically significant impact on the study results.

TABLE 1: List of participating centers and their contributions to the sample of 293 patients

City	Investigator	No. of Patients
Bangalore, India	Mohanty	43
São Paulo, Brazil	Zymberg/Cavalheiro	40
Liverpool, UK	Mallucci	36
Marburg, Germany	Hellwig	34
Izmir, Turkey	Ersahin	33
Niigata, Japan	Mori	20
Bologna, Italy	Mascari	19
Nova Lima, Brazil	Costa Val	18
Tel Aviv, Israel	Constantini/Beni/Roth	16
Mainz, Germany	Wagner	13
Toronto, Canada	Kulkarni	9
Birmingham, UK	Sgouros	6
Tokyo, Japan	Oi	6

Complications during and after NEB are summarized in Table 4. The amount of intraoperative bleeding was noted as mild in 75%, moderate in 13%, and severe in 6%. Infection occurred in 8 patients (3%). One patient (0.3%) died because of severe intraoperative bleeding. Four cases of CSF leakage were reported with no infection.

Tumor (paraffin) pathology details are provided in Table 5. Biopsies were informative in 90.4% of the patients. Results included low-grade astrocytoma (21.5%), high-grade astrocytoma (12.6%), germ cell tumor (12.3%), juvenile pilocytic astrocytoma (10%), other (8.5%), and unknown (9.6%).

Intraoperative frozen sections were analyzed in 34% of the patients (100 patients). The frozen sections were proven accurate in 57.6%, questionable in 17.2%, and noninterpretable in 25.2%.

Seventy-eight patients (27%) had open surgery following the NEB. The reason for subsequent open surgery after NEB was attributable to oncological considerations, in most cases following resolution of hydrocephalus. All 78 patients had completed NEB procedures that provided meaningful pathological results.

We compared the pathology results from the NEBs with those from the subsequent open surgeries (Table 6). Pathology was inconsistent to some degree (significant

TABLE 2: Location and size of tumors

Tumor Location	No. (%)			
	All Tumors	<10 mm	10–20 mm	>20 mm
pineal	97 (33.1)	9 (3.1)	44 (15.0)	44 (15.0)
intraventricular*	66 (22.5)	12 (4.1)	23 (7.8)	31 (10.6)
thalamic	49 (16.7)	5 (1.7)	9 (3.1)	35 (11.9)
tectal†	39 (13.3)	5 (1.7)	20 (6.8)	14 (4.8)
hypothalamic	13 (4.4)	2 (0.7)	3 (1.0)	8 (2.7)
suprasellar‡	9 (3.1)	1 (0.3)	2 (0.7)	6 (2.0)
parenchymal§	9 (3.1)	5 (1.7)	2 (0.7)	2 (0.7)
posterior fossa¶	5 (1.7)	0	1 (0.3)	4 (1.4)
other	6 (2.0)	2 (0.7)	2 (0.7)	2 (0.7)
total	293 (100)	41 (14.0)	106 (36.2)	146 (49.8)

* Includes septal region, foramen of Monro, caudate nucleus, mesencephalic region, and corpus callosum.
† Includes midbrain and tegmental region.
‡ Includes pituitary adenoma.
§ Includes cortex, frontal lobe, frontoparietal region, parietooccipital region, parietal right region, and gliomatosis cerebri.
¶ Includes cerebellar region, fourth ventricle, and vermis.

or insignificant) in 14 cases (17.9%). Insignificant (nonmeaningful) mismatch, in which the erroneous NEB pathology would not have altered the management decision, occurred in 5 cases (6.4%). Significant (meaningful) mismatch, in which the erroneous NEB pathology could have led to an inappropriate management decision, occurred in 9 cases (11.5%). Six (43%) of the 14 mismatches, which included both meaningful and nonmeaningful instances, were actually found to be low-grade astrocytomas. Three (21%) of the other mismatches were actually found to be juvenile pilocytic astrocytomas. In no instance was a tumor mistaken for a high-grade tumor after the NEB, reevaluated, and changed to a low-grade category.

Discussion

This is the largest available multicenter study evaluating the safety and accuracy of NEBs for brain tumor. Previous information on this subject has been reported mainly for single-center experiences, with significantly smaller numbers of patients.[2–5,12,15,16,19] The large number of patients included in our cohort, spanning a wide range of ages and pathologies, allowed us to examine many variables relevant to the NEB's clinical implications. The large number of participating centers enabled us to identify factors that are common across different surgeons and different departments, and therefore may be more relevant for other surgeons who are active in this field. Thus, this study effectively demonstrates the advantages of shared data and international multicenter studies.

Based on information in this cohort, NEBs are relatively safe. We report a fairly low and mostly reversible complication rate of < 13% (in 293 procedures), with almost no long-term morbidity and only a single death due to severe intraoperative bleeding. (Apparently, during this procedure, significant venous bleeding led to procedure abortion and the need for a ventricular drain, with gradual deterioration of the patient's condition within 2 days to a state of brain death.) Despite these encouraging numbers, one must remember that all of our data came from experienced centers. It is important to keep in mind that, in general, NEBs are advanced procedures requiring a learning curve and the appropriate technology.

Neuroendoscopic biopsies provided meaningful pathological data for over 90% of the patients, for a wide range of tumor types, locations, and presentations. This number is comparable with the pathological validity of SNBs.[6–8,10,13,14,18] The SNB diagnostic yield is heavily dependent on the patient population studied. For example, SNBs of smaller lesions with deeper locations offer lower accuracy compared with SNBs of larger, peripherally based tumors. This is why SNB diagnostic yields have been found to range from 62% to 100%.[6,8,18] Parreño et al.[13] reported usable diagnostic specimens in 100% of pediatric patients, whereas Jackson et al.[7] noted a very low diagnostic yield of 62% with SNBs of tumors located in or near eloquent brain areas. The overall diagnostic yield and safety of NEB and SNB seem to be comparable, with the reliability of NEB results, as demonstrated by the current study, less dependent on tumor location.

There are many advantages to NEB as compared with SNB. Neuroendoscopic biopsies are the preferred technique for tumors with an epicenter within the ventricular walls. Such lesions may be more hazardous to "blind" biopsy with stereotaxy, as the needle may not be surrounded by tissue and the anatomy may change upon fluid aspiration. Neuroendoscopic biopsies offer clear visibility, enable the surgeon to select a specific point for the biopsy, and provide an opportunity to examine the biopsy site and verify that there is no active bleeding. In addition, this type of biopsy procedure can easily be extended to include additional procedures such as relieving CSF pressure through endoscopic third ventriculostomy and septum pellucidotomy.[1,2,9,17] As such, we conclude that for lesions whose epicenter lies within a ventricle or those with concomitant hydrocephalus, NEB is to be preferred

TABLE 3: Variables of surgical technique in 293 NEBs*

Variable	No. (%)
side of approach	
rt	243 (82.9)
lt	50 (17.1)
no. of bur holes	
1	238 (81.2)
2	24 (8.2)
3	30 (10.2)
6	1 (0.3)
navigation	
yes	45 (15.4)
no	248 (84.6)
type of scope	
Storz	93 (31.7)
Aesculap	89 (30.4)
Codman	50 (17.1)
Rudolf	34 (11.6)
PSMed	19 (6.5)
other	8 (2.7)
ETV	172 (58.7)
septum pellucidotomy	41 (14.0)
continuous rinsing	139 (47.4)
external ventricular drain	39 (13.3)
biopsy taken	293
no. of specimens	
mean	4.2 ± 2.5
range	1–15

* ETV = endoscopic third ventriculostomy.

over a needle biopsy, provided that the experience and technology are available.

Our large cohort also made it possible for us to look at a unique group of 78 patients who first underwent an NEB and later had an open surgical procedure. The reason for open surgery after NEB was attributable to oncological considerations, in most cases following resolution of hydrocephalus. All 78 patients had completed NEB procedures that provided meaningful pathological results. Patients taken to open surgery were mostly those with presumably low-grade pathology, in whom it was decided that resection would provide a better prognosis. Most open surgeries were not performed for germ cell tumors and/or other malignant lesions that should be treated with radiochemotherapy and not resection. We were able to compare the NEB pathological results with the "gold-standard" open surgery histopathology, thereby identifying the exact rate of mismatches and determining the clinical situations in which the pathological results of NEB should be accepted with caution. The factors identified as significant were classic sampling errors and the significant difficulties that even the most experienced neuropathologist can encounter when interpreting tiny tissue pieces obtained during NEBs.[11]

TABLE 4: Complications during and after NEB

Complication	No.
intraop bleeding	
none	18
mild	221
moderate	38
severe	16
infection (meningitis/ventriculitis)	8
CSF leakage*	4
postop hematoma†	3
hyponatremia	2
temporary memory deficit	1
cardiac arrest‡	1
pulmonary embolism	1
fixed cranial neuropathy	1
death	1

* No infections.
† Operations required for 2 instances, resolved through insertion of a ventriculoperitoneal shunt. The extradural hemorrhage resolved itself.
‡ Postoperative Day 5.

Pathology was inconsistent to some degree in 14 cases (17.9%). However, it is important to distinguish between inconsistent pathologies that were insignificant, meaning inconsistencies that did not make any difference in terms of treatment decisions, and significant mismatches, in which the erroneous NEB pathology could have led to an inappropriate treatment decision.

We encountered 9 (11.5%) of 78 cases with significant

TABLE 5: Tumor pathology from NEB paraffin cut

Tumor Pathology	No. (%)
low-grade astrocytoma	63 (21.5)
high-grade astrocytoma	37 (12.6)
germ cell tumor	36 (12.3)
non-secreting germinoma	28 (9.6)
secreting germinoma	5 (1.7)
teratoma	3 (1.0)
primitive neuroectodermal tumor	32 (10.9)
juvenile pilocytic astrocytoma	29 (9.9)
metastases	12 (4.1)
craniopharyngioma	9 (3.1)
pineocytoma	8 (2.7)
lymphoma	6 (2.0)
ependymoma	5 (1.7)
oligodendroglioma	3 (1.0)
other*	25 (8.5)
unknown	28 (9.6)

* Includes cavernous angioma, granuloma/tuberculoma, choroid plexus papilloma, dysembryoplastic neuroepithelial tumor, meningioma, neurocytoma, pituitary adenoma, inflammatory, infection, hematoma, and cyst.

TABLE 6: Matching of pathological results for NEB and open surgery

Match Type	No./Total (%)	NEB	Open Surgery
complete match	64/78 (82.0)		
mismatch, nonmeaningful (erroneous NEB pathology would not have altered management decision)	5/78 (6.4)	low-grade astrocytoma*	ganglioglioma
		low-grade astrocytoma*	ganglioglioma
		juvenile pilocytic astrocytomas*	low-grade astrocytoma
		pineocytoma/low-grade astrocytoma*	benign teratoma
		germinoma/teratoma	teratoma
mismatch, meaningful (erroneous NEB pathology could have led to inappropriate management decision)	9/78 (11.5)	low-grade astrocytoma*	high-grade astrocytoma
		low-grade astrocytoma*	high-grade astrocytoma
		low-grade astrocytoma*	high-grade astrocytoma
		low-grade astrocytoma*	high-grade astrocytoma
		juvenile pilocytic astrocytomas*	cavernoma
		juvenile pilocytic astrocytomas*	meningioma
		germ cell	primitive neuroectodermal tumor
		inflammatory	neurocysticercosis
		inflammatory	pineocytoma

* Correlation between low grade and mismatch ($p = 0.001$).

pathological mismatches that could have led to a mistaken clinical decision. In most cases, the mismatches occurred in tumor cases that appeared to be low grade but were actually a higher grade, as seen in the open procedure pathology. (Note that the shift from low- to high-grade pathology remained within the same histopathological family, meaning, for example, that a low-grade glial tumor was reclassified as a high-grade glial tumor. No low-grade glial tumors were reclassified as germ cell tumors.)

This pattern of low-grade/high-grade mismatches is certainly an important factor when making treatment decisions following an NEB that reveals a low-grade pathology. In such cases, it must be acknowledged that about 1 in 5 such patients may, in fact, harbor a higher-grade pathology.

With this understanding, it is clear that at the end of the day NEB provided a valid working diagnosis approximately 90% of the time. This reliability rate is essentially comparable to the rate seen with stereotactic biopsies, which suffer from a similar vulnerability to sampling error and have a similar risk of higher-grade tumors appearing to be lower grade. The overall diagnostic yield and safety of NEB and SNB seem to be comparable, with the reliability of NEB results less dependent on tumor location.

Conclusions

Neuroendoscopic biopsies can be performed with low morbidity and mortality, providing meaningful pathological data for the majority of patients with a wide range of tumor types, locations, and presentations. Neuroendoscopic biopsies also offer other advantages, such as the ability to perform concomitant endoscopic third ventriculostomy and septum pellucidotomy. Note, however, that pathological results obtained from NEBs can be misleading, especially those that seem to indicate a low-grade glial tumor.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Constantini. Acquisition of data: all authors. Analysis and interpretation of data: Constantini. Drafting the article: Constantini. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Constantini. Study supervision: Constantini.

Acknowledgments

The authors thank Dorit S. Jacobson and Adina Sherer for invaluable assistance writing the manuscript. This project was performed under the auspices of the International Federation of Neuroendoscopy.

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Manuscript submitted August 15, 2012.
Accepted March 8, 2013.
Please include this information when citing this paper: published online April 12, 2013; DOI: 10.3171/2013.3.PEDS12416.

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