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ORIGINAL ARTICLE - BRAIN TUMORS

Frame-based stereotactic biopsy of deep-seated and midline structures in 511 procedures: feasibility, risk profile, and diagnostic yield

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Abstract

Objectives We evaluated the feasibility, safety, and diagnostic yield of frame-based stereotactic biopsies (SB) in lesions located in deep-seated and midline structures of the brain to analyze these parameters in comparison to other brain areas.

Patients and methods In a retrospective, tertiary care single-center analysis, we identified all patients who received SB for lesions localized in deep-seated and midline structures (corpus callosum, basal ganglia, pineal region, sella, thalamus, and brainstem) between January 1996 and June 2015. Study participants were between 1 and 82 years. We evaluated the feasibility, procedural complications (mortality, transient and permanent morbidity), and diagnostic yield. We further performed a risk analysis of factors influencing the latter parameters. Chi-square test, Student *t* test, and Mann-Whitney rank-sum test were used for statistical analysis.

Results Four hundred eighty-nine patients receiving 511 SB procedures (median age 48.5 years, range 1–82; median Karnofsky Performance Score 80%, range 50–100%, 43.8% female/56.2% male) were identified. Lesions were localized in the corpus callosum (29.5%), basal ganglia (17.0%), pineal region (11.5%), sella (7.8%), thalamus (4.3%), brainstem (28.8%), and others (1.1%). Procedure-related mortality was 0%, and permanent morbidity was 0.4%. Transient morbidity was 9.6%. Histological diagnosis was possible in 99.2% (low-grade gliomas 16.2%, high-grade gliomas 40.3%, other tumors in 27.8%, no neoplastic lesions 14.5%, no definitive histological diagnosis 0.8%). Only the pons location correlated significantly with transient morbidity ($p < 0.001$).

Conclusion In experienced centers, frame-based stereotactic biopsy is a safe diagnostic tool with a high diagnostic yield also for deep-seated and midline lesions.

Keywords Stereotactic biopsy · Midline structures · Deep-seated structures · Feasibility · Safety · Diagnostic yield

Christina A. Hamisch and Jana Minartz contributed equally to this work.

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Strengths and limitations of this study:
□ The current series is the largest in English medical literature analyzing frame-based CT- and/or MR-based biopsies of deep and midline brain lesions.
□ We evaluated our clinical standards and discussed them with regard to other reported techniques.
□ We demonstrated that biopsies of unclear inoperable lesions in deep-seated and midline structures can be performed in experienced centers with a high diagnostic yield and low morbidity.
□ This study is a retrospective investigation including all the limitations of a retrospective design.

This article is part of the Topical Collection on *Brain Tumors*

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Introduction

Brain tumor diagnostics and treatment depend on histopathological and increasingly on molecular diagnostics [1, 3, 10, 29, 30, 33]. A main aspect of the 2016 updated WHO classification is based on molecular markers to establish a definite diagnosis [16]. Thus, tissue diagnosis samples are indispensable for classifying brain lesions. Especially for midline tumors, H3F3A-K27M or H3F3A-G34 mutations are relevant negative prognostic markers in patients with pediatric glioblastoma and diffuse midline gliomas. The detection of new mutations increasingly influences development of new epigenetic tumor therapies [5, 11].

While stereotactic biopsy (SB) is well established for obtaining tumor tissue with low morbidity and mortality, especially in deep and midline structures, it is assumed to carry a higher procedural risk [2, 6, 14, 19, 25, 28]. However, large series analyzing factors for risk minimization are lacking.

Here we assess the risk profile as well as the diagnostic accuracy of SB for lesions located in supra- und infratentorial deep and midline structures in a large cohort, and discuss these parameters with regard to the biopsy technique used in comparison to data reported in the literature to analyze possible options to minimize procedural risk in biopsy of lesions in these localizations.

Patients and methods

Patients

Patients with lesions in deep and midline structures who had received stereotactic biopsy at the Department of Stereotaxy and Functional Neurosurgery of Cologne, between January 1996 and June 2015, were retrospectively identified and included in this study. Exclusion criteria were a stereotactic biopsy of a lesion in a structure other than the corpus callosum, basal ganglia, pineal region, sella, thalamus, intraventricular, or brainstem.

Clinical and histological findings were obtained from patient records. Morbidity was classified into temporary deficits, which resolved completely within 10 days, and permanent deficits, persisting thereafter. The reason for choosing this time point was our routine re-evaluation of the patient for wound control, to discuss the result of the biopsy and to determine future therapeutical steps. Complications were retrospectively analyzed by assessing the documented pre- and postoperative neurological status in patients' records as well as following medical reports.

This retrospective analysis was approved by the local ethical committee (reference numbers 16-476 and 16-477).

Stereotactic biopsy

Indications for a stereotactic biopsy

In all cases, SB was indicated by an interdisciplinary team. Since 1993, all patients suffering from brain tumors have been discussed in a weekly tumor board together with stereotactic and general neurosurgeons, neuroradiologists, and (neuro)oncologists.

One reason to indicate a stereotactic biopsy is an inoperable localization (brainstem, midline tumor) of the lesion.

Other reasons to indicate a stereotactic biopsy are as follows:

- Confirmation of a histological diagnosis before (re-)starting a therapy
- Exclusion/verification of secondary tumor malignization, tumor recurrence, or radiation necrosis following previous irradiation
- Requirement for a histological diagnosis prior to seed implantation for stereotactic brachytherapy

Preoperative preparation and surgical procedure

In all patients, informed consent was obtained from the patient, the legal guardian, or both parents in patients younger than 18 years of age. In eligible cases, an open biopsy/resection was discussed as an alternative.

Stereotactic biopsy was performed under general anesthesia in every patient using a standard protocol for the surgical procedure. While some patients were already on corticosteroids prior to biopsy due to edema, the majority received 20 mg perioperatively after removal of the tissue. All biopsies were frame-based using a modified Riechert-Mundinger stereotactic frame.

In detail, the stereotactic frame was fixed on the patient's head with four finger-tight screwed pins (two in the frontal bone, two in the occipital bone). Afterwards, an intraoperative CT scan was performed. Before January 1996, entry and target points were defined on the CT images only. Thereafter, the intraoperative CT scans were co-registered with images from MRI (1 mm slice thickness), which the patient had undergone prior to the biopsy, using specialized software (STP3; until February 1996, STP2 was used: Stryker, Leibinger, Freiburg, Germany). Usually, axial T1- and T2- and FLAIR-weighted MR images were used. This procedure was performed by a medical physicist and was checked by the surgeon.

Supra- or infratentorial approaches were used for the stereotactic biopsies, and the trajectories were planned to avoid penetrating cortical veins, brain sulci, and the lateral ventricle. The stereotactic arc was adjusted according to the preoperative calculated coordinates and then mounted on the stereotactic frame.

After placement of an 8-mm burr hole, the stereotactic biopsy was taken. In our department, we use the backlund needle (BN) to take the tissue specimens (Fig. 1). The BN has a diameter of 2.1 mm and comprises an outer cannula needle with a sharp edge and an inner rod as well as the spiral needle. The outer cannula and the inner rod had to be inserted to the target point. After removing the inner part of the needle, a Doppler examination was performed to identify vessels that were not recognized in the CT and MRI. In the next step, the spiral needle was inserted and representative stereotactic serial biopsies are taken by screwing the backlund needle into the tissue. Depending on the tumor size and location of risk structures, various tumor samples with a minimum size of 2 × 2 × 1 mm were taken. The duration of the pure surgical procedure ranged from 30 to 60 min.

In all patients where several tumor samples could be obtained, intraoperative frozen tissue sections were assessed during

the operation in order to ensure that the biopsy was representative for the lesion. Thereafter, for all patients, tissue sections were analyzed in detail by neuropathologists in our institute.

Target selection and biopsy approach

Target points and trajectories were planned on the basis of a standard imaging protocol, which was performed in the days before the biopsy in the Radiological Department of the University Hospital of Cologne. Over the years, imaging modalities have been extended so that the current protocol includes the intraoperative contrast enhanced CT as well as preoperative T1-, T2-, and FLAIR-weighted MR images. In contrast-enhancing lesions, target selection was mainly based on T1-weighted images with contrast agents. In lesions without contrast enhancement, T2- and FLAIR-weighted MR images were mainly used to plan the biopsy and select the target point for tissue sampling. Since 2014, fluoroethyl-tyrosine positron-emission tomography (FET-PET) was routinely integrated for patients with noncontrast-enhancing lesions.

The supratentorial approach for the biopsy is preferred due to the less complicated supine position of the patient. However, for cerebellar and some occipital, parietal, or temporomesial targets, a prone positioning approach is used.

Postsurgical management and follow-up

All patients were monitored in a high-care or intensive care unit for 24 h after the biopsy and received corticosteroids in declining doses. The dosage and length of drug administration depend on the preoperative corticosteroid regime, brain swelling, and tumor edema. Patients who had taken no preoperative corticosteroids and with low brain as well as tumor swelling received 8 mg for the first postoperative day and 4 mg daily for 2–3 days. Patients with a diagnosis of lymphoma in the intraoperative frozen tissue or in the final histological diagnosis section received high-dose corticosteroids until the start of oncological treatment.

In cases of postoperative neurological deterioration, a CT was performed.

All patients were closely followed up, and control imaging was usually performed at intervals of 3 months or in cases of clinical deterioration by appointment, as decided on between the treating physicians.

Patients where the biopsy provided an inconclusive pathological finding received a postoperative MRI three months after the biopsy to verify the path of the trajectory. In cases with assumed high-grade glioma, we performed a second biopsy procedure, or in a case-by-case decision an early postoperative MRI.

Statistical analysis

Descriptive statistics and frequencies are provided as mean and standard deviation and/or median and range. Different groups were compared using the Student *t* test for normally distributed variables, otherwise a non-parametric (Mann-Whitney *U* test) test and Levene test for variances were used. The chi-square test was used for categorical variables. p values < 0.05 were considered significant. Statistical analyses were performed using SPSS Statistics software (Release 22.0.0, SPSS Inc., Chicago, IL, USA).

Results

Patients

Between January 1996 and June 2015, we performed 511 stereotactic biopsies in 498 adult patients (43.8% female, 56.2% male). The median age was 48.5 years (range 1–82 years) at the time of SB, and the median preoperative Karnofsky performance score (KPS) was 80% (range 50–100%). The lesions were localized supratentorial (71.2%) and infratentorial (28.8%). The detailed localizations of lesions are shown in Table 1.

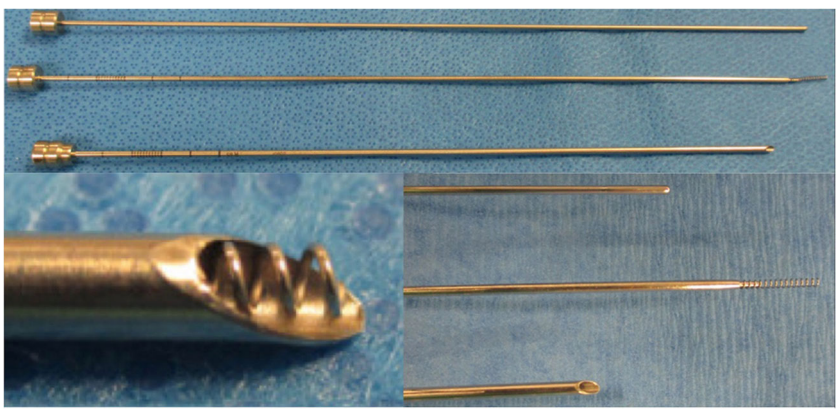

Fig. 1 Backlund spiral needle. The upper and the lower right images show the components (above: inner rod, in the middle: spiral needle, below: outer cannula needle). The lower left image shows the spiral needle in the outer cannula needle

Table 1 Localizations of biopsied lesions

Localizations	
Supratentorial	Thalamus, 22 lesions (4.3%) Sella region, 40 lesions (7.8%) Pineal region, 59 lesions (11.5%) Basal ganglia, 87 lesions (17.0%) Corpus callosum, 151 lesions (29.5%) Others, 5 lesions (1.1%)
Infratentorial	Pons, 139 lesions (27.2%) Mesencephalon, 8 lesions (1.6%)

In 79.8% of the patients, the biopsy was performed to confirm a diagnosis of a primary brain lesion. In 11.9%, detailed information about potential prior therapies or the exact date when the brain lesion was first detected could not be evaluated. The remaining 8.2% of the biopsies were performed in patients with a suspected recurrent or progressed brain tumor or therapeutically induced tissue changes (i.e., radiation necrosis).

Biopsy approach

Supratentorial approaches in a supine position were used in 88.1% ($n = 450$) of cases. Tumor localizations of the tumors biopsied using this approach were corpus callosum ($n = 125$, 27.7%), brainstem ($n = 117$, 26.0%), basal ganglia ($n = 85$, 18.9%), pineal region ($n = 58$, 12.9%), sella region ($n = 40$, 8.9%), thalamus ($n = 22$, 4.9%), and others ($n = 3$, 0.7%).

The remaining biopsies ($n = 61$, 11.9%) were performed by supra- or infratentorial approaches in a prone position. Tumor localizations of these tumors were brainstem ($n = 30$, 49.2%), corpus callosum ($n = 26$, 42.6%), others (n = 2, 3.3%), basal ganglia ($n = 2$, 3.3%), and pineal region ($n = 1$, 1.6%).

Diagnostic yield of stereotactic biopsy

In 99.6% of the patients, a stereotactic biopsy was feasible and quantitative as well as qualitative tissue could be obtained for further histological evaluation. In two patients (0.4%), the biopsy was canceled due to intraoperative bleeding.

In 97.1% of cases, serial tissue samples could be obtained within a single trajectory, while in 2.9% of the patients planning a second trajectory was necessary. The reasons for a second biopsy were (I) cancelation of the biopsy procedure due to an intraoperative hemorrhage, or (II) the harvested tissue that showed no conclusive pathological alterations.

Depending on the size of the tumor and location of risk structures, in 94.7% of the patients, two to eight tissue samples of 3 to 10 mm were taken. In the other cases (5.3%), one tissue sample could be obtained.

Histological diagnosis was obtained in 99.2% of the 99.6% cases. Tumors were detected in 84.3% and were diagnosed based on the WHO classification valid at the time of biopsy into low-grade gliomas ($n = 83$, 16.2%), high-grade gliomas ($n = 206$, 40.3%), and other tumors ($n = 142$, 27.8%). No neoplastic lesions encompassed infectious, reactive, and degenerative disease as well as radionecrosis and were diagnosed in 14.5% ($n = 74$). In the remaining 0.8% ($n = 4$) of the biopsies, no definitive histological diagnosis could be made. In two patients with suspected radionecrosis, one could be verified and one was diagnosed as a recurrent tumor.

Since 2007, all state-of-the-art molecular, immunological, and histopathological examinations were possible in all patients with a histopathologically proven tumor.

Procedural morbidity and mortality

No treatment-related mortality occurred. Permanent and transient morbidity was 0.4% ($n = 2$) and 9.6% ($n = 49$), respectively. One of the two patients with a postoperative permanent deficit presented with a hemiparesis and oculomotor nerve palsy due to a contrast enhancement in the internal capsule. After an uncomplicated stereotactic biopsy, the patient showed deterioration of his hemiparesis and a newly arising aphasia. In the CT scan, a hemorrhage was detected at the target point of the biopsy in the area of the internal capsule. The other patient received a biopsy for a progredient contrast-enhancing tumor in the pons. After an also uneventful biopsy, a new ataxia and left-sided hemiparesis occurred. The CT scan showed neither swelling, hemorrhage, or another cause for the new symptoms. After rehabilitation, the symptoms partially regressed.

Transient complications occurred in 49 patients: in 18 patients (3.5%), preexisting symptoms worsened after stereotactic biopsy, and 31 patients (6.1%) presented new symptoms (cranial nerve palsy (21 patients, 4.1%), peripheral paresis (16 patients, 3.1%), epileptic seizures (4 patients, 0.8%), disturbance of consciousness (3 patients, 0.6%), and hydrocephalus (1 patient, 0.2%)). Impaired wound healing was mentioned in 4 patients (0.8%).

Transient complications were significantly associated with the localization of the biopsied lesion in the pons ($p < 0.001$), but not associated with the patients' age, gender, KPS, or tumor entity (Table 2).

Procedure-related hemorrhage

A postoperative CT scan was performed in all patients with intraoperative bleeding, postoperative deterioration of the known symptoms or new symptoms. A hemorrhage could be demonstrated in four patients (0.8%). Two of these patients suffered from intraoperative bleeding resulting in cancelation of the biopsy but without any hemorrhage-associated clinical symptoms. The other two patients suffered from postoperative deterioration of their clinical symptoms with a permanent

Table 2 Correlation of transient complications and different possible influencing factors

Parameter	*p* value
Pons localization	< 0.001
Patients' age	0.369
Sex	0.445
KPS	0.653
Tumor entity	0.907

deficit in one and a transient deficit in the other patient. In the latter patients, the CT scan showed a hemorrhage at the target point of the biopsy.

Since we do not routinely perform postoperative CT scans, in patients with an inconspicuous postoperative clinical course the percentage of clinically inapparent hemorrhages cannot be determined.

Length of hospital stay

In general, the minimal length of hospital stay is three days after the biopsy. We could analyze the precise hospital stay in 393 of the 511 patients; five patients receiving a biopsy came from another hospital department. The median hospital stay of the remaining patients was five (1–29) days.

Discussion

Modern treatment regimens are increasingly based on molecular findings, and the importance of neuropathological analysis of tumor tissue is growing. Recently, molecular factors especially for deep and midline tumors have been detected [12, 27, 35], and targeted therapies are under development [5, 11]. Therefore, histological diagnostics are necessary for the classification of all brain tumors.

Complications

For superficial lesions, SB is a safe tool to obtain tumor tissue [7, 17, 20–23]. A meta-analysis of 7471 cranial stereotactic biopsies reported a diagnostic yield of 91% as well as morbidity and mortality rates of 3.5% and 0.7%, respectively [7]. However, for deep-seated lesions, indication for SB is pursued more reluctantly, allegedly because complication rates are higher due to the eloquent location and long trajectories [2, 6, 14, 19, 25, 28]. This assumption is not sufficiently substantiated by data in the literature.

For brainstem biopsies, a recent meta-analysis demonstrated that histological diagnosis could be obtained in 96.2% of the biopsies [13]. Overall and permanent morbidity were 7.8% and 1.7%, respectively, with a mortality rate of 0.9% [13]. In children, brainstem location seems to be a factor for a higher complication rate [8], but diagnostic success, overall morbidity, and permanent deficits are comparable with results obtained from adults and other tumor locations [9].

Kongkham et al. reported a cohort of 614 biopsied patients with an increased overall morbidity and mortality rate for an unknown number of patients with deep-seated lesions [14]. Another study found a significant correlation between increased morbidity and thalamic or basal ganglia localization with a morbidity rate of 27% for these patients [19]. Similar morbidity or mortality rates were reported by other authors [2, 6, 25, 28].

In the current series, which is the largest analyzing CT- and/or MR-based biopsies in English medical literature, mortality was zero and the morbidity rate was far lower than in most reported studies. Regarding transient complications, this was only associated with location in the pons. However, even in this location, rates for transient and permanent deficits were only slightly higher than with superficial lesions [7, 14, 15, 24–26, 31].

One reason for our low complication rate could be our dedicated stereotactic department providing specialized neurosurgeons as well as high technical expertise and equipment. Furthermore, due to a diagnostic yield of 99.2%, surgical risks of SB are justifiable. Especially in the context of the growing need for molecular diagnostics that enable individualized treatment regimens, tissue diagnostics is mandatory.

Postoperative CT scan

Biopsy of deep-seated or midline structures implicated long trajectory distances, and in many cases, crossing eloquent brain regions. Therefore, intra- or postoperative hemorrhage at the target point or along the needle track can be associated with serious neurological deficits. While a potentially increased risk of silent hemorrhage in high-grade gliomas may be missed in our cohort due to the lack of routine postoperative CT scans, the clinical status made significant intracerebral hemorrhage highly improbable. Furthermore, recent studies show no benefit of routine postoperative imaging after craniotomy procedures in clinically inapparent patient courses [26]. Therefore, from our point of view, routine postoperative CT scans need not be performed in biopsied patients with deep or midline tumors if the patient can be clinically observed for 2–3 days after SB.

Biopsy technique

In our department, we only used a frame-based technique. Trajectory planning is based on integrating different imaging techniques (e.g., CT scan, different MRI sequences, metabolic based imaging), and intraoperative Doppler sonography is used to avoid vessel damage.

In recent studies, modern neuro-navigational methods for endoscopic, frameless, or open biopsies were analyzed for many things including efficacy, safety, and diagnostic yield for biopsy of brain lesions [2, 4, 32, 34]. A prospective randomized study compared the frameless fiducial-less and frame-based biopsy [4]. They included 56 patients (frame-less 28 patients, frame-based 28 patients), and the study gave equally efficacious and safe results with both groups. The overall duration of the frame-less method was shorter, but the overall time spent was equal to the frame-based biopsy. The authors mentioned that the frame-less technique is associated with several advantages compared with the frame-based technique: no frame that must be fixed to the patient's head, avoiding a preoperative MRI, more flexibility to change targets intraoperatively. Nevertheless, in this study, tumors of only six (frame-based) and nine (frame-less) patients were located in deep-seated structures. The other tumor locations were superficial.

A recently published review of robot-assisted stereotactic brain biopsy described 15 studies [18]. All studies were non-randomized and included one retrospective cohort study and 14 case series or reports including 323 patients. The authors mentioned that the review is restricted by the few studies with variable size and quality and inconsistent reporting of surgical outcomes. Furthermore, only 115 of the biopsied tumors were located in deep or midline structures. In other studies describing a frame-less biopsy technique, patients with deep-seated tumor locations are also rare (e.g., [2, 20]).

Although the studies mentioned above and others published in the literature do not indicate that endoscopic, frameless, or open biopsies are inferior to SB, data for such frameless methods in deep-seated lesions are very sparse. Therefore, further studies are necessary to confirm the equivalence of the frameless techniques compared with frame-based ones.

In conclusion, stereotactic biopsy of unclear inoperable lesions in deep and midline structures can be performed in experienced centers irrespective of the patient's age, preoperative KPS, or tumor localization with low morbidity and mortality.

Conclusion

Stereotactic biopsy of unclear inoperable lesions in deep and midline structures can be performed in experienced centers irrespective of the patient's age, preoperative KPS, or tumor localization with low morbidity and mortality. Also for this localization, it proves to be a safe diagnostic tool with a high diagnostic yield.

Contributors CAH, JM, TB, VH, DR, and AH extracted the data. CAH, JM, SG, and MIR analyzed the data and wrote the manuscript. All authors read, revised, and approved the final version of the paper.

Data Availability No additional data was available.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This retrospective analysis was approved by the local ethical committee (reference numbers 16-476 and 16-477).

Patient consent for publication Not required.

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Comments

The authors review their single-institution series of stereotactic biopsies for deep-seated or midline lesions in adults and children, between January 1996 and June 2015. In all, they report on 489 patients undergoing 511 stereotactic biopsy procedures. There was no mortality. Permanent and transient morbidity were 0.4 and 9.6 %, respectively. Definitive histological diagnosis was obtained in 99.2%. A pontine location of the lesion correlated significantly with transient morbidity. In two cases, biopsy was cancelled because of intra-operative bleeding. The authors conclude that stereotactic frame-based biopsy is safe and effective for biopsy of these lesions.

Although there are now several similar studies detailing experience and outcome of stereotactic biopsy of deep/ midline lesions, this is a large and well-presented series from an experienced group. This study underlines the continued importance of traditional frame-based stereotactic biopsy, despite the availability of other techniques, such as frameless navigation and robot-assisted biopsy. In the context of the increasing relevance of molecular diagnosis to neuro-oncological practice, obtaining tissue safely is now more essential than ever.

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