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Frameless stereotactic neuronavigated biopsy: A retrospective study of morbidity, diagnostic yield, and the potential of fluorescence
A single-center clinical investigation

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ABSTRACT

Objective: The primary objective of this retrospective study was to evaluate the diagnostic yield and morbidity/mortality associated with frameless stereotactic neuronavigated intracranial biopsies with and without the use of fluorescein.

Patients and methods: Patient cases from January 2007 to December 2017 were identified using the ICD-10 procedure code AAG00. Relevant clinical data, including histological diagnosis, were collected retrospectively from the electronic patient charts and independently reviewed by two authors.

Results: 111 biopsies obtained from 103 patients were identified. Of these, 109 biopsies yielded a diagnosis and resulted in a diagnostic yield of 98.2%. Fluorescein was used in 13 biopsies (11.7%). Twelve patients (10.8%) experienced postoperative complications, and the mortality attributed to the surgery was 1.8%. In 12.6% of cases, the biopsies showed inflammation or nonspecific reactive changes. No statistically significant differences were observed in diagnostic yield or number and severity of complications according to whether intraoperative histological examination was used or not.

Conclusion: Although direct comparisons between studies are difficult due to lack of consensus about the definition of diagnostic yield, the present study reports a similar diagnostic yield to other studies. Intraoperative histopathological analysis appeared to give little extra benefit.

1. Introduction

Intracranial biopsy is a relatively safe and effective way for diagnosing intracerebral pathologies. The diagnostic yield (DY) has in recent studies ranged from 72.8% to 99.3%, while morbidity and mortality rates vary, ranging from 0 to 12.9% and 0–2%, respectively [1,2,4,6,7,11,14,15]. Biopsies in eloquent brain areas are as safe and effective as those in non-eloquent areas [1]. In brain stem tumors, a large meta-analysis with 1480 cases has documented the safety, with an overall morbidity of 7.8% and mortality of 0.9%, and DY of 96.2% for biopsies [8].

Although the preferred surgical management of most brain tumors is removal of all or as much as possible of the tumor tissue, surgical removal is sometimes not possible mostly due to the location of the brain pathology. In other cases, the suspected brain pathology warrants biopsy instead of resection (i.e. cerebral lymphoma and certain inflammatory diseases).

At the Neurosurgical Department at Odense University Hospital, Denmark, intracerebral biopsies are obtained using the frameless stereotactic neuronavigational method. This is combined in some cases with intraoperative histopathological assessment, which can improve the diagnostic yield [4]. As of 2016, all biopsy procedures have included the use of fluorescein.

The present study reports on the diagnostic yield and morbidity associated with frameless stereotactic neuronavigated intracranial biopsies with and without the use of fluorescein performed at our

Abbreviations: ASA, American Society of Anaesthesiologists; CSF, cerebral spinal fluid; DY, diagnostic yield; GCS, Glasgow Coma Scale; ICU, intensive care unit; PTCL, peripheral T-cell lymphoma

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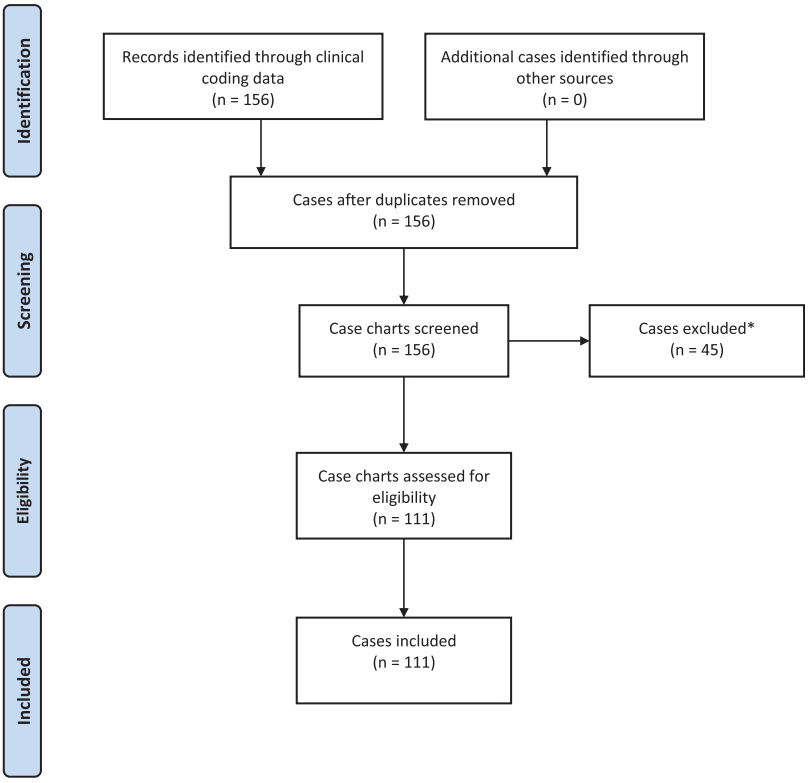

Fig. 1. PRISMA 2009 Flow Diagram.

institution from 2007 to 2017.

2. Materials and methods

The study was approved by the Danish Patient Safety Authority and the Danish Data Protection Agency.

Patients undergoing frameless stereotactic brain biopsy at our center in the period from January 2007 to December 2017 were identified using the ICD-10 code (AAG00).

2.1. Biopsy procedure

A total of 111 needle biopsy cases in 103 patients were identified (Fig. 1).

One biopsy attempt failed due to problems with calibration of the equipment and was excluded from the study.

Based on a preoperative MRI, T1 with contrast (< three days old), a biopsy plan was made avoiding eloquent brain areas. In general anesthesia, the patient head was fixed in a Sugita head frame. The Medtronic Stealth equipment was mounted and the patient head registered according to the manufacturers recommendation. According to the predefined surgical biopsy plan, a linear incision with underlying burr hole was made. Dura was opened and a Medtronic biopsy needle attached to the Medtronic guiding steer or Navigus system (from 2010) was inserted toward the predefined biopsy target. After the procedure, the wound was sutured.

If a new biopsy was obtained within three months of the primary one, it was categorized as a repeat biopsy.

Fluorescein was used for biopsies in 2016 and 2017 by administering 200 mg fluorescein (Anatera ®, Novartis) prior to anesthesia. These biopsies were validated by the presence of fluorescein seen perioperatively in a Zeiss® Pentero microscope with a dedicated filter (560 nm).

2.2. Patient and operative characteristics

Data on the following parameters were obtained from the electronic patients files: gender, age at time of surgery, date(s) of surgery, smoking habits and alcohol consumption (defined as alcohol usage exceeding the limit defined by the national health guidelines [5]), comorbidity, presenting symptoms, location of biopsy, biopsy method, number of biopsies, use of intraoperative histological examination, intraoperative complications, postoperative complications (morbidity), biopsy-related death (mortality), residual lifetime if deceased, duration of surgical procedure (defined as time from skin incision to wound closure), American Society of Anesthesiologists (ASA) score, and duration of stay in the neurosurgical ICU.

The histopathological diagnosis was obtained and subsequently used to calculate DY.

All data was independently reviewed by two authors (AMAE) and (VRN), and consensus was reached in case of disagreement.

2.3. Diagnostic yield and complications

DY was defined as described in McGraw-Hill Concise Dictionary of Modern Medicine from 2002 [12]: “The likelihood that a test or procedure will provide the information needed to establish a diagnosis”.

Complications were defined as minor or major in accordance with Sawaya et al. [15]. Minor complications were defined as not life-threatening, not prolonging the ICU stay, and resolving within 30 days of surgery. Other complications were defined as major. Both minor and major complications were categorized as either neurological, regional, or systemic in nature.

2.4. Statistical analysis

The data were analyzed using IBM SPSS version 24.0 for MAC and Windows. Fisher´s exact test was used to investigate any differences in patient characteristics between subgroups. Spearman's rho was used to

Table 1
Characteristics of 103 patients having 111 frameless stereotactic brain biopsies.

Numbers are presented as percentage or Mean ± SD (range)		
Male		57.66%
Age (years)		62.6 ± 12.4 (23–83)
Smoking		21.6%
Alcohol		6.3%
Comorbidity:		
	Hypertension	28.8%
	Cancer[a]	18.9%
	Hypercholesterolemia	9.0%
	Diabetes	8.1%
Presenting symptoms:		
	Motor impairment[b]	55.9%
	Headache	25.2%
	Dizziness	24.3%
ASA score		2.21 ± 0.65 (1-3)
Number of biopsies taken[c]		5.6 ± 2.49 (1–13)
Use of intraoperative histopathology		83.8%
Use of fluorescence		11.7%
Duration of surgery (min.)		63.2 ± 32.28 (20–170)

[a] Includes previous and ongoing illness.
[b] Includes paralysis and paresis of extremities and face.
[c] Calculated from 76 cases due to missing data.

calculate correlations between ASA score and patient age and residual lifetime. All data was collected in the period from October of 2016 to June 2018. Significance level $p < 0.05$ was considered statistically significant.

3. Results

Table 1 summarizes patient and operative characteristics.

A total of 103 patients underwent a total of 111 frameless stereotactic brain biopsies. Six patients had a repeat biopsy within three months. In two cases, further biopsies were performed after approximately four years. Fluorescein was administered prior to surgery in 11.7% of cases.

ASA score was noted in 109 of 111 cases prior to the operative procedure; 52.3% had an ASA score of 2, 12.6% had ASA score of 1, and 33.3% had an ASA score of 3.

ASA score was positively linked to increasing age, as could be expected. Spearman's rho shows a correlation of coefficient of 0.35 ($p < 0.05$). It was also negatively correlated with shorter survival and may represent a selection bias, as patients with worse ASA score might be better suited for biopsy than for surgical resection.

There was a statistically significant correlation of −0.312 between higher ASA scores and decreased residual lifetime ($p < 0.05$)

The number of sample biopsies per case varied from 1 to 13, with a mean of 5.6 biopsies per patient case.

Intraoperative histopathological examination on fresh frozen cryostat sections was used in 93 of the 111 biopsies (83.8%). In the remaining cases, no intraoperative histopathological examination was performed due to sparse amount of available tissue.

Intraoperative histopathological examination was not used in any of the cases where fluorescein was administered.

No statistically significant differences were observed in diagnostic yield whether intraoperative histological examination was used or not.

Duration of surgical procedure varied from 20 to 170 min.

3.1. Diagnostic yield

For an overview, see Table 2.

Table 2
Histopathological diagnosis of the 111 frameless stereotactic brain biopsies.

	Diagnose	n
Glial Tumor:		71 (64%)
	Glioblastoma	29
	Anaplastic astrocytoma	21
	Diffuse astrocytoma	13
	Gliomatosis cerebri	2
	Glioma	3
	Glioma, OBS PRO	1
	Oligoastrocytom, relaps	1
	Oligodendroglioma	1
Lymphoma:		14 (12.6%)
	Diffuse large B-cell lymphoma	9
	Diffuse large B-cell lymphoma, relapse	1
	Diffuse large B-cell lymphoma, anaplastic variant	1
	B-cell lymphoma	1
	Intravascular large B-cell lymphoma	1
	Burkitt's lymphoma	1
Metastases:		3 (2.7%)
	Metastasis, carcinoma	1
	Metastasis, adenocarcinoma	1
	Metastasis, planoepithelial carcinoma	1
Others:		2 (1.8 %)
	Inflammation	1
	Progressive multifocal leukoencephalopathy (PML)	1
Non-diagnostic:		21 (18.9%)
	Nonspecific reactive changes	9
	Inflammation	5
	Necrosis	4
	No sign of malignancy	1
	Gliosis	1
	Normal brain tissue	1
Total		111

Of the 111 biopsies, 109 yielded a diagnosis in accordance with our chosen definition of DY, resulting in a DY of 98.2%. Fluorescein was used in 13 of the 111 biopsies (11.7%), and all these were given a diagnosis, resulting in a DY of 100%. There was no statistical difference in DY between the fluorescein group and the non-fluorescein group (where 96 of 98 biopsies were given a diagnosis, resulting in a DY of 97.9%; $p > 0.05$).

3.2. Complications

Postoperative complications were observed in 12 of the 103 patients (11.6%). Of these, eight were minor complications and four were major, see Table 3.

Although there was no statistically significant difference in overall survival time for patients with (110.6 days) and without postoperative complications (305.2 days; $p > 0.05$), the 30-day mortality rate was significantly higher among patients experiencing postoperative complications ($p < 0.01$).

Patients with postoperative complications also had a longer ICU stay

Table 3
Number and severity of postoperative complications among the 103 patients.

Complication	Location	Major (n)	Mnor (n)	n (total)
Bleeding	Central	2	2	4
Bleeding	Frontal Lobe	2	0	2
Aphasia	Frontal Lobe	0	1	1
Epilepsy	Frontal Lobe	0	1	1
Infection	Frontal Lobe	0	1	1
Diplopia	Frontal Lobe	0	1	1
Edema	Thalamus	0	1	1
Prolonged latency	Thalamus	0	1	1
Total:		4	8	12

(mean of 7.55 days compared to 2.15 days for patients without complications; $p < 0.01$).

The mean survival time for patients where fluorescein was used was 229 days compared to 290 days in the group without fluorescein ($p > 0.05$).

In the fluorescein group, one patient (7.7%) experienced postoperative complications. In the non-fluorescein group, 11 patients (11.2%) experienced postoperative complications ($p > 0.05$).

3.3. Mortality

One patient experienced both intraoperative and postoperative hemorrhage and died within the first week after surgery. The patient's Glasgow Coma Scale score worsened within hours of the procedure, and a GSC of 3–4 was reported the following morning. A computer tomography of the head revealed a small bleeding at the site of biopsy and a large cerebral edema.

Another patient died due to a complication associated with the care at the ICU and the death was not related to the biopsy procedure itself. Thus, two deaths, one directly and one indirectly was related to the operation.

In the twelve people who died within 30 days of operation, the biopsy revealed glioblastoma, anaplastic astrocytoma, necrosis, or nonspecific reactive changes. None of the patients in the fluorescein group die within 30 days and no statistical significant difference was observed when compared with the biopsies acquired without the help of fluorescein. ($p > 0.05$).

4. Discussion

4.1. Diagnostic yield

We found a DY of 98.2% which is comparable to previously published data. Table 4 lists eight studies from 2009 to 2015 investigating the safety and DY of the frameless stereotactic method. DY was obtained directly from the studies or re-calculated for comparative reasons in accordance with the definition used in this study [12], and ranged from 72.8 to 99.3% based on analysis of 1267 cases [1,2,4,6,7,11,14,15]. Direct comparison of these studies is difficult, however, due to the lack of consensus regarding definitions, including the definition of DY. This is noted by Khatab et al. [7] in their comparison of DY across 16 studies from 2003 to 2013. They found an average DY of 93.8% in 1628 patients, but the data were based on papers that investigated both the frameless technique and other biopsy methods. DY was obtained from the studies or calculated for comparative reasons in accordance with the definition used in this study [12].

While Khatab et al. [7] reported a DY of 72.8%, Verploegh et al. [15] reported a DY of 93.5%. These authors defined DY differently and categorized their pathological findings as a) conclusive biopsy/full diagnosis, b) inconclusive biopsy/partial diagnosis, and c) non-diagnostic biopsy, based on World Health Organization (WHO) 2007 classification of tumors of the central nervous system [9]. Khatab et al. [7] used their own definition of DY to encompass tumor type and grading: "the likelihood that a test or procedure will provide the information needed to establish a diagnosis which is certain and precise according to the WHO CNS tumor classification system".

Although our study showed a diagnostic rate of 98.2%, we found that in about 19% of cases the pathological diagnosis was of limited value in planning treatment. These diagnoses were mostly inflammation, nonspecific reactive changes, or necrosis.

Table 4
Comparison with previous studies reporting on frameless stereotactic biopsies.

Authors	Year	N of Cases	Diagnostic Yield	Morbidity[a]	Mortality[b]
Air et al.	2009	284	89.8%	6.7%	2%
Dammers et al.	2010	160	98.2%	8.5%	0.6%
Shooman et al.	2010	134	99.3%	2.2%	1.5%
Quinn et al.	2010	33	87.9%	0.0%	0%
Gempt et al.	2012	96	93.8%	2.1%	0%
Burkhardt et al.	2013	78	97.4%	1.3%	0%
Khatab et al.	2014	235	72.8%	8.5%	0.9%
Verploegh et al.	2015	247	93.5%	12.9%	0.8%
Average:			91.6%	5.3%	0.73%
Present Study	2017	111	98.2%	10.8%	1.8%

[a] Complications were not well defined; either as transient/permanent or major/minor.

[b] Mortality: either within 30 days or not specified.

4.2. Non-diagnostic biopsies

In two cases (1.8%), the biopsies revealed either normal brain tissue or no signs of malignancy.

As Lu et al. [10] note in their article, it is difficult to know whether these 'negative biopsies' represent the clinical situation or underlying disease.

The patient with a normal brain tissue biopsy had a repeat biopsy a week later, which showed metastasis from squamous cell carcinoma. This suggests that repeated biopsy is warranted if the initial biopsy is inconclusive. The patient with a biopsy showing no sign of malignancy was later diagnosed with relapse of diffuse large B-cell lymphoma through analysis of the CSF acquired via lumbar puncture.

4.3. Complications and mortality

The present study found an overall complication rate of 10.8%, which is in line with other studies reporting a mean of 5.3% and ranging from 0 to 12.9% [1,2,4,6,7,11,14,15].

In the present study, we defined mortality as death occurring within 30 days and being directly or indirectly related to the operation. We thus reported two deaths, one directly and one indirectly, related to the operation, resulting in an overall procedure-related mortality of 1.8%.

Eight previous studies [1,2,4,6,7,11,14,15] describe a mortality rate related to the procedure ranging from 0% to 2%. Three of these studies defined a postoperative time period of 30 days from which death would be considered related to the procedure [1,4,15]. Only Dammers et al. [4] defined their criteria for an operational related death as "death occurring within 30 days as a result of symptomatic postoperative haemorrhage or oedema".

In the present study, 6 of the 12 patients who died within 30 days of operation were diagnosed with glioblastoma, while the other 6 had anaplastic astrocytoma, necrosis, and nonspecific reactive changes.

Anaplastic astrocytomas and glioblastomas are aggressive brain tumors and are not surprising causes for two-thirds of the patients dying within 30 days [13]. In addition, the patients selected for biopsy on suspicion of primary brain tumor (and not tumor resection) often have a worse preoperative performance score and/or have pathology in areas where resection is not possible.

When comparing residual lifetime across the different pathological diagnoses, necrosis was associated with the shortest time between biopsy and death (23 days).

4.4. Patient characteristics

The patients in the present study were aged 23–83 years and suffered a wide array of neurological deficits. We used the ASA score in an effort to compare patients, but this approach focuses on physical status and does not encompass all the differences observed between the patients. The ASA score was documented in 98.2%, and the mean score was 2.2 (where ASA 1: A normal healthy patient, ASA 2: A patient with mild systemic disease, and ASA 3: A patient with severe systemic disease [3]).

4.5. Improving diagnostic yield

Previous studies have investigated possible means of improving yield from cerebral biopsies. Dammers et al. [4] in a single center study increased their DY from 89.4% to 98.2% with the use of intraoperative histopathological examination. The surgeon would macroscopically examine the tissue and only request frozen section examination when it was uncertain if the biopsy represented pathological tissue.

In contrast, Shooman et al. [14] found no correlation between intraoperative frozen section examination of a biopsy and DY, as in the present study. In the present study, intraoperative frozen section examination was used in 93 cases (83.8%). In a few cases, the surgeon obtained more tissue for examination if the intraoperative histopathological examination was inconclusive, but mostly refrained from doing so due to the risk of complications.

The diagnostic yield was slightly higher after implementation of preoperative fluorescein (irrespective of intraoperative histopathological examination of samples), but this was not statistically significant presumably due to a low number of fluorescein cases. The use of preoperative fluorescein, however, gives the surgeon more confidence that biopsies have been sampled from the intended contrast-enhancing target. We suggest, therefore, that fluorescein can replace intraoperative histopathological tissue sample examinations in standard biopsy procedures of contrast-enhancing intracerebral processes.

4.6. Study limitations

There are several limitations to this study. The number of biopsies was relatively low especially in the fluorescein group. The study was retrospective, and some patients were sent to peripheral hospitals where access to clinical follow-up data was limited.

A prospective design would probably provide a more accurate assessment of DY and the complications of frameless brain tumor biopsies.

5. Conclusions

This study showed that the procedure of obtaining and diagnosing a biopsy is precise and associated with relatively few complications. However, it is difficult to compare the diagnostic yield with the results from previous studies due to lack of consensus regarding definitions.

We found that the diagnostic yield of biopsies does not reflect the usefulness of the procedure. In 19% of cases, a diagnosis was obtained from the biopsy, but did not result in postoperative treatment. Furthermore, we found limited use of intraoperative histological tissue examination. The usefulness of intraoperative fluorescein technique needs to be investigated in larger scaled studies.

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Conflict of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study, formal consent was not required.

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