The diagnostic accuracy and era for improvement for frameless stereotactic brain biopsy: a series of 109 procedures and a systemic review

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Abstract

Purpose

To evaluate the diagnostic accuracy of frameless stereotactic brain biopsy and review the era for improvement.

Methods

This is a prospectively collected cohort study from 2007 to 2020. We reviewed patients who received frameless stereotactic brain biopsy in Prince of Wales Hospital and evaluated the diagnostic accuracy of the frameless stereotactic brain biopsy procedures. The biopsy result was classified into conclusive, inconclusive or negative, based on the pathological, radiological and clinical diagnosis concordance. For inconclusive or negative results, we further evaluated the pre-operative planning and post-operative imaging to review if further improvement could be made. The complication rate of symptomatic hemorrhage and mortality rate was also analyzed.

Results

There were 106 patients with 109 biopsy procedures performed from 2007 to 2020. The conclusive diagnosis was reached in 103 (94.5%) procedures. The inconclusive diagnosis was noted in four (3.7%) procedures and negative diagnosis was yielded in two (1.9%) procedures. Symptomatic hemorrhage was noted in one patient (0.9%). There was no mortality case (0.0%) in our case series. The registration errors occurred in three cases (2.8%), sampling of the non-representative part of the lesion occurred in two cases (1.8%), and one biopsy (0.9%) for lymphoma was negative after the commencement of steroids. Systemic review showed that the diagnostic accuracy under the structurally defined diagnosis criteria was comparable with published literatures in recent ten years.

Conclusion

The stereotactic biopsy is a safe procedure with high diagnostic accuracy only if meticulous pre-operative planning and careful intra-operative registration is performed. The common pitfalls precluding a conclusive diagnosis are errors during registration and non-representative biopsy sites.

Background

The stereotactic brain biopsy is a widely used diagnostic neurosurgical procedure, especially for intracranial lesions that are not amenable to open surgery. Both frame-based and frame-less procedure have been validated for their efficacies in neurosurgical patients. Previous research has showed that there was no significant difference in diagnostic yields and complication rates for frame-based or frame-less procedures. [5] The efficacy of stereotactic brain biopsy has been reported to be 86.6% – 100%. [5] The post-operative hemorrhage is the most common complication after the stereotactic brain biopsy procedure, and it is reported to range from 2.4–17.8%. [5] In our unit, we have been using frameless stereotactic biopsy since 2007. We have previously reported a lower hemorrhagic rate using 1.8mm diameter biopsy needle comparing with 2.5mm diameter biopsy needle in a cohort of 54 procedures. [26] We have been continued the same protocol of frameless stereotactic biopsy since then. In this paper, we reviewed the accumulative 106 procedures performed in a 13-year interval. The aim is to identify the aspects for improvement with emphasis on the diagnostic accuracy.

Patients And Methods

All patients underwent frameless stereotactic brain biopsy from 2007 to 2020 in our institute were included. Patients with frame-based stereotactic biopsy or patients with intra-operative ultrasound guided biopsy were excluded. Patient demographics, including age at operation, gender, medical comorbidities including hypertension, diabetes mellitus, renal failure, liver cirrhosis and bleeding tendency were recorded.

Surgical indication and pre-operative preparations

The clinical history, physical signs, investigations and imaging findings of all biopsy cases were discussed in the pre-operative meeting together with neuroradiologists and neurologists for the indications of biopsy. The indications for brain biopsy were lesion in the brain that pathological diagnosis would be essential to the subsequent treatment selection. For neoplastic lesion, biopsy was indicated if the lesion cannot be treated by surgical excision, including deep-seated lesions, infiltrative lesions without margin or lesions in eloquent cortex, where gross total resection without neurological deficit was impossible and survival was not improved by partial resection. [16] For lesions with imaging findings not suggestive of neoplastic lesion, biopsy was indicated for representative sampling for further microbiological investigations for any infection or pathological delineation for any demyelination process. [16] Patients undergoing biopsy were admitted to neurosurgical unit for pre-operative preparation including blood test, chest X-ray, electrocardiogram, and other relevant investigations for general anesthesia. Antiplatelets and anticoagulation therapy were discontinued prior to the operation.

Target planning

The target planning had been described previously by Yuen et al. [26] Pre-operative images including computerized tomography (CT) and magnetic resonance imaging (MRI) of brain were fused. In general, the target of biopsy was set at the center of the lesion. Various factors were considered in setting the target including contrast enhancement, location of the lesion and possible vasculature. Spectroscopy study was also used for reference if available. If there were multiple lesions, the most representative lesion with the lowest possibility of causing post-biopsy neurological deficit was chosen for biopsy. The entry site and trajectory were planned considering the following factors: (1) gyral entry, (2) shortest distance to the target, (3) avoid sulci, vessels, ventricles and critical functional areas such as the motor cortex and the internal capsule, (4) aligning the biopsy window along the long axis of the lesion, especially for small oval

shape lesions. The ‘target lesion size’ was defined as the dimension of the lesion measured on probe view at the target level. This was grouped under ≤ 10 mm or > 10 mm. The target locations were classified into (1) cerebrum, (2) insula, basal ganglia and thalamus, (3) pineal and brainstem and (4) cerebellum.

Operation

The procedures had also been described previously by Yuen et al.[26] All the biopsies were performed under general anesthesia using frameless stereotaxy. BrainLAB navigation (BrainLAB AG, Feldkirchen, Germany) together with the instrument holder, VarioGuide system (BrainLAB AG, Feldkirchen, Germany) were used for majority of the case except 4 cases in whom the Fiagon navigation system (Fiagon GmbH, Hennigsdorf, Germany) were used. Prophylactic antibiotic was routinely given. Majority of the patients were positioned in supine or supine-oblique (with ipsilateral shoulder raised by a pad plus head rotation to the contralateral site) position while few cases were performed in lateral position.

The registration method was surfacing matching. Either spiral computerized tomography (CT) 0.625 per slide or T1-3D magnetic resonance imaging (MRI) less than 1mm per slide were used for the image source for registration. The accuracy of registration was checked meticulously using the software’s function and at the anatomical landmarks including nasion, lateral and medial orbital canthi, tragus, and scalp surface.

After a burr hole was made, the dura was opened to confirm gyrus entry. The biopsy needle was then inserted through the instrument holder towards the target under navigation guidance. Upon reaching the planned target, a syringe was applied to the inner cannula of the biopsy needle, and the side window was opened. Negative pressure was applied through a 2.5ml syringe routinely, unless it was insufficient to obtain the specimen. In contrast, a 1ml syringe was used for targets located in the brainstem. To obtain adequate amount of tissue and to increase the sampling area, specimens were taken at different directions by rotating the needle plus minor moving the needle back and forth along the same trajectory.

In all the cases, the specimen was sent for intra-operative frozen section or smear. Direct communication was made intra-operatively with the neuropathologist to discuss the histological result as well as the amount of specimen adequate for subsequent pathological study. Additional specimen would be obtained from different depth and orientation if the intra-operative histological result was uncertain. Additional amount of specimen would also be obtained if the remaining specimen after frozen section was anticipated insufficient for subsequent pathological study, provided that no intraoperative post-biopsy haemorrhage was encountered, i.e. blood was aspirated or came out from the lumen of biopsy needle. From 2007 to 2010, a Sedan-type side-cutting biopsy needles of 2.5 mm diameter (Elekta AB, Stockholm, Sweden) was used and after 2010, we changed to a 1.8mm diameter biopsy needle (BrainLAB AG, Feldkirchen, Germany) [26].

Postoperative Imaging

A CT scan of brain was performed within 12 hours postoperatively in each case to assess the presence of haemorrhage. The postoperative raw CT data was fused to the pre-operative imaging for correlation of the biopsy site by the presence of postoperative change such as air bubbles or evidence of haemorrhage. Spiral CT scanning with 0.625mm/slide was used for examination of the presence of haemorrhage for all the cases.

Diagnostic accuracy

The final diagnosis was discussed in a regularly held combined meeting with neuropathologist, radiologists and neurologists. According to the final pathological results, the pathological diagnosis was classified into (1) conclusive, (2) inconclusive and (3) negative. Diagnostic accuracy represented the percentage of cases with a conclusive diagnosis. The criteria for each diagnostic category was shown in Table 1.

Table 1
Criteria for diagnostic category adopted in the current study.

	Tissue	Histological	Radiological	Clinical
Conclusive	Pathological	Tumor ¹	Accurate	Consistent
		Infection ²	Accurate	Consistent
		Neurological disorder ³	Accurate	Consistent
Inconclusive	Abnormal	Non-specific descriptive diagnosis	Accurate	Consistent
Negative	Non-diagnostic	Normal brain, blood clots etc.	Not specified	Contradicting
Notes: 1. Tumor - histological type and grading confirmed. 2. Infection – microorganism identified or confirmed by characteristic histological findings. 3. Neurological disorder – characteristic abnormal tissue obtained.				

A *conclusive diagnosis* was defined as: (1) tumour, i.e. confirmed tumour type and grading; (2) infection, i.e. confirmed infection and micro-organism by histology and/or microbiology; (3) neurological disorders, i.e. characteristic abnormal tissue was obtained, the target site was accurate on postoperative imaging, and the histological findings were consistent with other systemic investigations and the clinical course of the neurological disorders. In cases where no characteristic abnormal tissues were obtained but only a descriptive histological diagnosis such as necrosis, it would remain ‘conclusive’ if subsequent open biopsy confirmed the same result.

An *inconclusive diagnosis* was defined as: abnormal tissue was obtained but only a non-specific descriptive diagnosis could be made, in spite of the fact that the biopsy site was accurate on postoperative imaging and was consistent with the clinical diagnosis.

A *negative biopsy* was defined as: only normal brain tissue was obtained and/or the histological diagnosis was contradicted to a subsequent biopsy, other investigation or clinical course of the disease.

Diagnosis of Postoperative Haemorrhage

Same as describe previously, any visible new hyperdense signals were strictly documented as haemorrhages, and the largest diameter was measured on the CT images.[26] The size of the haemorrhage was classified to nil, less than 5mm, 5 to 10mm and more than 10mm. The haemorrhage was also classified clinically into symptomatic and asymptomatic according to whether associated neurological deterioration was present or not.

The pre-operative planning, the operations and the postoperative imaging analysis were supervised by the same senior consultant (Dr. C.X.L. Zhu) for all procedures and cases. All biopsy specimens were evaluated by our neuropathologist (Prof. HK Ng).

Literature search and selection

A systemic literature review was performed using PubMed and Medline from OvidSP for diagnostic accuracy or diagnostic yield of frameless stereotactic brain biopsy for patients with intracranial lesions. We aimed to evaluate the original studies with case numbers for more than one hundred. The detailed syntaxes were shown in Table 2.

Table 2
The searching method and syntax for systemic review for diagnostic yield of frameless-stereotactic biopsy

Date of query	26 Aug 2021	Database	
Field	Syntax	Pubmed	Ovid MEDLINE
Domain	#1 Brain OR Intracranial OR cerebral	All fields	Keyword (Map Term to Subject Heading)
Determinant	#2 Frameless stereotactic brain biops* or Frameless stereotactic biops* or Image-guided brain biops* or image guided biops* or stereotactic brain biops* or stereotactic biops*	Title/Abstract	Keyword (Map Term to Subject Heading)
Outcome	#3 Diagnostic yield or Diagnostic rate or Diagnostic accuracy or Accuracy or Nondiagnostic yield or Diagnostic error or Nondiagnostic biops*	Title/Abstract	Keyword (Map Term to Subject Heading)
Search		#1 AND #2 AND #3	#1 AND #2 AND #3
Filter		Publication date 10 years	From 2011 to 2021

Statistical analysis

The statistical analyses were calculated by IBM SPSS Statistics Version 25.0. (Armonk, NY: IBM Corp). Continuous variables were reported by mean and standard deviation. Percentages of distribution were calculated for categorical data.

Results

There were 106 patients with 109 biopsy procedures performed, including two patients with two biopsy procedures at two different sites in one operating session and one patient with a second biopsy performed for a previous negative biopsy. There were 54 male patients and 52 female patients. For biopsy procedures, the mean age at operation was 49.1 years old (standard deviation 19.7, range 4.0–80.0). The locations of the lesions were lobar in 59 cases (54.1%), insula / basal ganglia / thalamus in 34 cases (31.2%), pineal / brain stem in 13 cases (11.9%), and cerebellum in 3 cases (2.8%). Eighteen (16.5%) target lesions were less than 10mm in diameter, while 91 (83.4%) target lesions were equal to or larger than 10mm in diameter, as shown in Table 3. The 2.5mm biopsy needle was used for 30 biopsy procedures from 2007 to 2009 and afterwards 1.8mm needle was used for the other 79 biopsy procedures. In 105 procedures, BrainLab navigation system was used and in 4 procedures Fiagon system was used.

Table 3
Case numbers by distribution of lesion location and size

Location	Size of the lesion				Total	Percentage
	≥ 10mm	%	< 10mm	%		
Lobar	47	43.1%	12	11.0%	59	54.1%
Insular, basal ganglia, or thalamus	33	30.3%	1	0.9%	34	31.2%
Pineal, brainstem	8	7.3%	5	4.6%	13	11.9%
Cerebellum	3	2.8%	0	0.0%	3	2.8%
Total	91	83.5%	19	16.5%	109	100%

Of the 109 procedures, the diagnostic accuracy was conclusive in 103 (94.5%) procedures, inconclusive in 4 (3.7%) procedures and negative in 2 (1.8%) procedures. Under the inconclusive diagnosis, there were three cases with brain metastasis and one glioma case. Under the negative diagnosis, there were one out of 31 primary central nervous system lymphoma (PCNSLP) cases and one out of eight other primary brain tumors. The distribution of pathologies and the diagnostic accuracy among different pathologies are shown in Table 4.

Table 4
The diagnostic accuracy for different histological categories and subtypes.

Category		Diagnostic status				
		Number of cases	Conclusive	Inconclusive	Negative	Percentage of conclusive diagnosis
Neoplasm	Glioma	51 (46.8%)	50 (45.9%)	1 (0.9%)	0 (0.0%)	98.0%
	Primary CNS Lymphoma	31(28.4%)	30 (27.5%)	0 (0.0%)	1 (0.9%)	96.8%
	Other primary brain tumour	8 (7.3%)	7 (6.4%)	0 (0.0%)	1 (0.9%)	87.5%
	Brain metastasis	6 (5.5%)	3 (2.8%)	3 (2.8%)	0 (0.0%)	50.0%
Infection	Brain abscess	4 (3.7%)	4 (3.7%)	0 (0.0%)	0 (0.0%)	100.0%
	Encephalitis	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	100.0%
	Tuberculosis	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	100.0%
	Cysticercosis	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	100.0%
Others	Progressive multifocal leukoencephalopathy	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	100.0%
	Auto-immune disease	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	100.0%
	Demyelination	3 (2.8%)	3 (2.8%)	0 (0.0%)	0 (0.0%)	100.0%
	Radiation necrosis	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	100.0%
Total		109 (100%)	103 (94.5%)	4 (3.7%)	2 (1.8%)	94.5%

The details of the four inconclusive and two negative results were studied (Table 5, Fig. 1 to Fig. 4). Factors leading to the diagnostic error were various. Among the six biopsy procedures without conclusive results, there were three cases where the biopsy sites were deviated from the planned target with reference to the post-operative CT scans. In these three cases, the lesions were in the parieto-occipital region. In one of these three cases, the lesion was small the near ventricular wall in the trigone region. The biopsy needle went into the ventricle and CSF was aspirated before a tissue could be obtained. Another two biopsies were taken at the non-representative part of the lesions, including the non-enhancing part in the center of one lesion, and another biopsy at the cystic part of the lesion. One biopsy was taken while the steroid treatment was started, and subsequent stereotactic biopsy after steroid discontinuation confirmed primary CNS lymphoma.

Table 5
Details of the inconclusive and negative biopsy cases with error types analyzed.

Case	Year	Age	Lesion location	Biopsy pathology	Diagnosis	Final Diagnosis	Final diagnosis by	Biopsy site	Target selection	Target lesion size (mm)	Error Type
1	2007	52	Basal ganglia	Macrophage and chronic inflammation	Negative	Lymphoma	Secondary biopsy after withholding steroid	Accurate	Appropriate	32	Timing of surgery
2	2008	61	Lobar, Trigon	Gliosis	Inconclusive	Brain metastasis	Lung FNAC ¹ : non-small cell carcinoma Intracranial Cyst fluid aspiration: carcinoma cell present	Deviated	Appropriate	25	Inaccurate targeting
3	2013	54	Lobar, Trigon	Necrotic tissue With a small number of highly atypical cells and endothelial proliferation, suggestive of tumour.	Inconclusive	Brain metastasis	Craniotomy biopsy and excision	Deviated	Appropriate	26	Inaccurate targeting
4	2016	63	Insular	Necrotic tissue	Inconclusive	Brain metastasis	Craniotomy cyst drainage and biopsy	Accurate	Non-representative ²	45	Target selection
5	2016	12	Lobar, Trigon	blood clot & crushed brain tissue only	Negative	Germinoma	Based on the history and subsequent response to radiation therapy	Deviated	Appropriate	7	Inaccurate targeting, small target size flushing the ventricle
6	2017	62	Insular	Cyst fluid without tumour cell, Tissue: Gliosis	Inconclusive	Pilocytic astrocytoma	Craniotomy biopsy and excision	Accurate	Non-representative	46	Target selection
Notes: 1. FNAC – Fine needle aspiration cytology. 2. Biopsy was taken accurately as planned but at the hypointense part of the lesion instead of the enhancing part. 3. The biopsy was taken at the cystic part of the lesion. 4. Biopsy taken while was taken steroid											

Post-operative hemorrhage was noted in 50 patients, with the mean diameter of 9.07mm, standard deviation of 5.32mm and a range from 3.00mm to 24.00mm. The distribution of post-operative haemorrhage between the 1.8mm biopsy needle and 2.5mm biopsy needle was shown in Table 6. Symptomatic haemorrhage was noted in one patient (0.9%) with 2.5mm biopsy needle, who developed right hemiparesis after biopsy of left basal ganglia lesion with power down to grade 4 by Medical Research Council Scale and a post-operative hematoma diameter of 11mm. [20]

Table 6
Comparison of diagnostic accuracy and hemorrhage risk by different biopsy needle

Needle diameter (mm)	Number of procedures	Diagnostic accuracy				Haemorrhage			Size of haemorrhage			
		Conclusive	Inconclusive	Negative	P	Asymptomatic	Symptomatic	P	< 5mm	5-10mm	> 10mm	P
2.5mm	30 (27.5%)	28 (25.7%)	1 (0.9%)	1 (0.9%)	0.769	21 (19.2%)	1* (0.9%)	0.431	3 (2.8%)	8 (7.3%)	10 (9.2%)	0.1
1.8mm	79 (17.4%)	75 (68.8%)	3 (2.8%)	1 (0.9%)		29 (26.6%)	0 (0.0%)		12 (11.0%)	9 (8.3%)	8 (7.3%)	
Notes: Value are presented as the number (%) in each needle type. *The haemorrhage size in this case was 11mm.												

Among the 109 cases, there were 11 cases received craniotomy after biopsy. In 9 (82%) cases, the histological diagnosis was in complete agreement with the diagnosis from biopsy. The remaining two cases were non-diagnostic from the biopsy result (case 1 and case 4 in Table 3) and subsequent open biopsy provided the final diagnosis.

Immunohistochemical and molecular studies were all performed in this cohort except three cases due to insufficient tissue occurred in 2014, 2015 and 2017 respectively, and all insufficient cases were Glioblastoma Multiforme (GBM).

We have identified 12 relatively large sample original studies evaluating the diagnostic accuracy or yield of frameless stereotactic brain biopsy within the recent ten years. The literature research result and selection criteria were illustrated in Fig. 5.

Discussion

This paper was preceded by our previous publication by Yuen et al in 2014, with an emphasis on the diagnostic accuracy and an aim for improvement.[26] We previously reported a diagnostic accuracy of 93.0% (50/54) and symptomatic haemorrhage of 1.9% (1/54) in a series of 54 frameless stereotactic brain biopsy procedures. The current study was a continuation of the previous study with an accumulation of 109 procedures with same criteria for diagnostic accuracy. In our current study, the diagnostic accuracy was 94.5% (103/109) with a symptomatic hemorrhage rate of 0.9% (1/109). The diagnostic accuracy of frameless stereotactic brain biopsy among the relatively large case series with procedure numbers more than 100 in the recent 10 years were shown in Table 7. The diagnostic yield of 94.5% in this study was within the range of 72.8–99.7% and the accuracy was pronounced considering the structurally defined criteria for diagnostic accuracy in the current study. [23, 8, 2, 22, 18, 13, 24, 17, 14, 1, 10, 7]

Table 7
Comparison of Frameless brain biopsy results from different neurosurgical centers with frame-less stereotactic biopsy performed

Author	Center	Year	Number of biopsy/patients	Navigation	Diagnostic Accuracy	Symptomatic hemorrhage	Mortality
Current study	Hong Kong	2021	109	BrainLab, Fiagon	94.5%	0.9%	0.0%
Ungar et al [23]	Israel	2021	130	Medtronic StealthStation	96.9%	1.6%	0.8%
Giamouriadis et al [8]	United Kingdom	2019	371	Medtronic AXIEM	94.1%	0.9%	1.1%
Æbeløa et al [2]	Denmark	2019	111	Medtronic Stealthstation	98.2%	3.6%	1.8%
Sciortino et al [22]	Italy	2019	140	BrainLab	93.6%	2.1%	0.0%
Mader et al [18]	Germany	2018	119	BrainLab	92.4%	1.7%	0.8%
Kellermann et al [13]	Germany	2017	229	Stryker STP3	91.7%	0.4%	0.4%
Verploegh et al [24]	Netherlands	2015	247	Medtronic StealthStation, BrainLab	94.6%	1.2%	0.8%
Lu et al [17]	USA	2015	113	GE Healthcare	89.4%	N/A	N/A
Khatab et al [14]	Netherlands	2014	235	Medtronic StealthStation, Zeiss-MKM,	72.8%	2.1%	0.9%
Air et al [1]	USA	2012	284	Medtronic StealthStation, BrainLab	89.2%	N/A	N/A
Harrisson et al [10]	United Kingdom	2012	150	Medtronic StealthStation AxiEM	96.7%	4.7%	2.7%
Fрати et al [7]	Italy	2011	296	Medtronic StealthStation	99.7%	1.0%	N/A
Notes: N/A – Not available from the published journal.							

The goal of the current study was to seek improvement in the future biopsy procedures. In our case series, there were four inconclusive pathological results and two non-diagnostic pathological results. With respect to Yuen et al in 2014, while no more symptomatic haemorrhage case occurred, there were one inconclusive and one negative results encountered after 2014.[26] We further analyzed all the six procedures in detail with reference to the target selection, trajectory planning, intra-operative navigation, aspiration technique, and post-operative biopsy tract verification. The identified causes for inconclusive or negative diagnosis included two inappropriate target selection, three inaccurate targeting and one incorrect timing, as shown in Table 5. All these errors have been described previously and the question to the neurosurgeons is how to avoid these errors.[16, 19, 9]

One of the inconclusive pathology results in 2007 was due to incorrect time to biopsy (Table 5, Case 1). It was a case of primary central nervous system lymphoma (PCNSLP) who received steroid prior to the biopsy (Fig. 1). It was well known that PCNSLP was very sensitive to steroid. For patients with brain lesion undergoing biopsy with steroid therapy commenced, an updated imaging is very important. If there is significant shrinkage of the lesion, one important differential diagnosis is lymphoma and in such case, the biopsy should be withheld.[4] We learned the lesson and no similar error occurred in the subsequent 30 cases of suspected primary CNS lymphoma.

There were two inconclusive pathologies occurred in 2016 and 2017 respectively due to error in target selection (Table 5, Case 4 and 6). In one procedure, the target was the central necrotic area and the other was inside the tumour cyst. Retrospectively, the error might have been avoided if we paid more attention to the characteristic of the imaging finding (Fig. 2 and Fig. 3).

There were three nondiagnostic procedures with inaccurate targeting evidenced on the post-operative CT. All lesions were in the parietal lobe near the trigone area. In one of the cases the error could also be contributed to its small size and the proximity to the trigone of the lateral ventricle (Fig. 4). Birski et al reported nondiagnostic yield of 5/85 intraventricular or periventricular lesions.[3] Our experience was that using facial recognition for registration, special attention

should be paid to the accuracy in the parieto-occipital region. The accuracy can be checked by the function of the navigation software and improved by adding registration points to the parieto-occipital scalp during the registration procedure. Firmly fixed skull pins and the refractory array are also important points in order to avoid the inaccuracy in targeting.

Reviewing the six cases without a diagnostic pathology result, we believed that the error could be definitively avoided in the timing of biopsy for lymphoma and could likely to be avoided in cases with inaccurate targeting. For the two cases with target selection error, avoidance remained possible.

Apart from a positive histological diagnosis for tumour type and grading, further immunohistochemical and molecular evaluations were increasingly important in the diagnosis and prognosis of certain types of brain tumors. For patients with GBM, the absence of TERT mutation and the presence MGMT promoter methylation had better prognosis.[6, 11] Mader et al reported the nondiagnostic rate of 1.5% (1 in 67 cases) for MGMT promoter methylation among GBM cases in 2018.[18] We have three GBM cases where immunohistochemical staining was incomplete due to insufficient tumor sampling, including two GBM cases with TERT mutation detection not performed and one GBM case while test for IDH1 mutation was negative, other immunohistochemical test was incomplete. Weise et al suggested that the tangential trajectory planning along the long axis of the lesion would enhance the MGMT promoter methylation detection.[25] Our experience was that a minimum of four aspirations with appropriate size tissues together with a good communication with the pathologist intra-operatively for the quality and quantity of the biopsied tissue, were necessary for an adequate pathological and immunohistochemical diagnosis.

Another important topic for stereotactic brain biopsy was to examine the agreement of pathological diagnosis between the biopsy and open surgery. Discrepancy between stereotactic biopsy and open surgery had been reported to be 38% in Jackson et al, 24% in Reithmeier et al and relatively low (3.3%) in Kim et al.[12, 21, 15] The reason for discrepancy between stereotactic biopsy and open surgery was that the biopsied site might not be fully representative of the entire lesion and the true diagnosis might not be reached, which would affect the subsequent disease course and treatment.[12] Among the 11 cases that received both biopsy and open surgery in our case series, there were two cases with discrepancy in the biopsy and subsequent excision result and thus the reliability rate was 82%. These two cases were known to be non-diagnostic after the stereotactic biopsy. We believed that appropriate target selection and post-operative auditing could improve the reliability and avoid this discrepancy.

The symptomatic hemorrhage rate in our study was 0.9% due to one hemorrhage that occurred in 2009 when we used 2.5mm diameter biopsy needle. Our current study enhanced the believe that the rate of symptomatic haemorrhage was low without compromising the diagnostic accuracy with the 1.8mm diameter biopsy needle.

There were certain limitations in our research. Firstly, this was not a prospective study though stereotactic brain biopsy procedure was collected based on the operating protocol at the time of surgery for each procedure. Considering a study of 14 years interval, experience accumulation over time might weaken the comparability between early and recent results. Nevertheless, our analysis for the diagnostic accuracy and illustration on the nondiagnostic cases provided insights for further improvements for frameless stereotactic brain biopsy.

Conclusion

The key factors for a successful stereotactic brain biopsy include an appropriate target selection for the representative area of the lesion with reference to the imaging characteristics, accurate registration together with rigid instrument holder and the precise trajectory alignment, adequate tissue sampling under controlled aspiration, and intra-operative communication with the pathologist for provisional diagnosis and tissue adequacy. The diagnostic accuracy was 94.5% in our case series with 0.9% symptomatic hemorrhage rate. Periodic review and vigorous auditing of each biopsy results are indispensable in order to avoid pitfalls, to evaluate the errors and ultimately to improve the surgical outcomes.

Declarations

Part of the result was presented in oral format in the Annual Scientific Meeting of the Hong Kong Neurosurgical Society on Dec 18, 2020 by Dr. He Zhexi and in video format in the 7th World Federation of Neurosurgical Societies (WFNS) Foundation Asian Congress of Neurological Surgeons (ACNS) Winter Web Seminar on Feb 20, 2021, by Dr. He Zhexi.

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Conflict of Interest Statement

The authors listed in this study have no conflict of interest to disclose.

Availability of data and material

The data that support the findings of this study are available upon request from the corresponding author, under the regulations from the Joint Chinese University of Hong Kong - New Territories East Cluster Clinical Research Ethics Committee.

Code available

Not applicable

Author Contributions Statement

Dr. He Zhexi performed the data collection, analysis and interpretation, and drafted the manuscript.

Dr. Zhu Xian Lun Cannon conceived the concept of this study, built the protocol for data collection, and collected the data, and analyzed the surgical outcome and errors occurred for the biopsy procedures, and editing and reviewing the manuscript.

Dr. Chan Tat Ming Danny provided editing suggestions and ethical review, access to the research resources and governed the patient's privacy and safety.

Dr. Cheung Chi Yan Tom, provided access to the imaging, provide neuroradiological diagnosis and provided editing suggestions.

Prof. Ng Ho-Keung provided crucial access to the neuropathological diagnosis, immunohistochemical staining results, and critically reviewed this manuscript.

Dr. Mok Chun Tong Vincent provided important neurological diagnosis and differential diagnosis for this case series, and critically reviewed this manuscript.

Prof. Poon Wai Sang provided research resources, governed the patient's privacy and safety and critically reviewed this paper manuscript.

Ethical approval

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol was reviewed and approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CREC Ref. No. 2021.354).

Consent to participate

As this is a retrospective study with a long study interval, a large proportion of patients deceased due to malignant brain tumor and thus consent for individual patient is impossible. The study protocol was reviewed and was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CREC Ref. No. 2021.354) with the patient consent waived.

Consent to publish

There are no patient-identifiable or patient-specific information contained in this manuscript.

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Figures

Figure 1

52 years old male presented with cognitive decline (Table 4, Case 1). He was put on dexamethasone 4mg four times per day. 1a: CT at presentation. 1b: CT 16 days after steroid treatment. The biopsy was performed on day 17. 1c: CT on the same day after biopsy. Arrow: a dot of haemorrhage indicating the biopsy site. 1d: CT at one month after the 1st biopsy with steroid stopped. The lesion reappeared. 1e: CT after the 2nd biopsy. Arrow: the small air bubble indicating the biopsy site (CT – Computerized tomography)

Figure 2

63 years old female presented with progressive lethargy and dysarthria (Table 4, Case 4). 2a and 2b: Pre-operative MRI T1 with contrast in sagittal and coronal views. Red line: the planned biopsy trajectory. 2c and 2d: post-operative plain CT co-registered to the pre-operative MRI. The air bubble (short arrow) inside the lesion indicating that the biopsy was accurate. During the operation, frozen section result was necrotic tissue. Further biopsies were performed at 6mm deep to and 8mm superficial to the planned target point. However, the final pathological result remained necrotic tissue only. Craniotomy for open biopsy and excision 2 weeks later confirmed the diagnosis to be metastatic carcinoma. Retrospectively, if the biopsy trajectory was from low temporal towards the thick part of the enhanced rim of the tumour (long arrow), a diagnostic specimen might have been obtained. (MRI – Magnetic Resonance Imaging, CT – Computerized tomography)

Figure 3

62 years old female presented with right side weakness and slurring of speech (Table 4, Case 6). 3a and 3b pre-operative MRI T1 with contrast and 3c pre-operative CT in oblique views aligned to the biopsy trajectory. The red line was the planned trajectory targeting the junction between the cyst and the solid components of the lesion. All images were co-registered. 3d: post-operative CT: the cyst of the lesion collapsed after cyst fluid aspiration. However, no diagnostic tissue was obtained. The pathological diagnosis was pilocytic astrocytoma on subsequent open biopsy and tumour excision two years later. Retrospectively, after cyst fluid aspiration, we might be able to obtain the diagnostic tissue by rotating the window of biopsy needle inferiorly towards the solid part of the lesion. In addition, intra-operative imaging would be helpful for this case. (MRI – Magnetic Resonance Imaging, CT – Computerized tomography)

Figure 4

12 years old girl with known history of germinoma received chemotherapy (Table 4, Case 5). New lesions were found on follow-up MRI with tumour spread suspected. The lesion was small and located in the parietal lobe closed to the trigone of the lateral ventricle. 4a-4d: pre-operative biopsy plan on MRI 3D reconstruction (red line: trajectory). 4a showed the position of the patient for facial matching registration during the operation. 4e-4h: Post-operative CT 3D was fused to pre-operative imaging, which showed that the biopsy tract was medially deviated from the planned trajectory. Air bubbles were present in the ventricle (arrow) and were consistent with the cerebrospinal fluid aspiration during the biopsy procedure. Pathological diagnosis of the biopsy was mainly blood clot with some crushed brain tissue. The patient received radiotherapy subsequently and the lesions disappeared (MRI – Magnetic Resonance Imaging, 3D – Three dimensional, CT – Computerized tomography)

Figure 5

The literature research flowchart for the diagnostic accuracy of frameless stereotactic brain biopsy.