Child's Nervous System (2021) 37:1515–1523
https://doi.org/10.1007/s00381-021-05101-2

FOCUS SESSION

Use of intra-operative stimulation of brainstem lesion target sites for frameless stereotactic biopsies

Jason Labuschagne[1,2] · Denis Mutyaba[1,2] · Jacques Nel[3] · Claudia Casieri[4]

Received: 21 January 2021 / Accepted: 24 February 2021 / Published online: 8 March 2021

Abstract

Introduction Frameless stereotactic navigation is used to direct the trajectory and biopsy site of target lesions. We report on a novel intra-operative stimulating (IOS) probe that is integrated into a commercially available stereotactic biopsy needle with the rationale that stimulation of the intended biopsy site should predict functional tissue thus preventing inadvertent biopsy of eloquent tissue.

Methods Patients undergoing brainstem biopsies for atypical lesions were offered the additional stimulation procedure. The IOS probe was used to deliver stimulation in an attempt to determine the proximity of eloquent tissue. Once the desired location of the biopsy needle was achieved, the IOS probe was inserted down the centre of the biopsy needle and the stimulus applied. If no action potential was recorded, biopsies from four quadrants of the lesion were taken. If however a compound action potential was recorded, a new target was selected.

Results Nine patients had the biopsy and stimulation procedure performed. The median age was 36 months. A minimum of 8 samples were obtained from each patient. Biopsy material was adequate to obtain a diagnosis in all 9 patients. In 2 cases use of the device influenced the insertion trajectory or biopsy site. No patients experienced any complications directly attributable to either the biopsy procedure or application of the stimulation.

Conclusions Use of the IOS probe for intra-operative stimulation of the intended brainstem biopsy site was found to be safe and feasible. The addition of stimulation using the IOS probe can be done with minimal change in workflow.

Keywords IONM · Brainstem biopsy · DIPG · Midline glioma

Introduction

Stereotactic brain biopsy is a minimally invasive procedure used to obtain tissue for histological diagnosis. Frameless stereotactic navigation, guided by preoperative imaging, is used to direct the biopsy trajectory to sample the target lesion, while avoiding vasculature and eloquent brain structures [10, 74]. The accuracy of stereotactic navigation is however dependent on multiple factors, including the quality of the preoperative imaging, accuracy of the image to patient registration, mechanical error of the trajectory guide and accuracy of the intra-operative probe tracking [76]. Additionally, brain shift of deep structures [39] and displacement of the brainstem cranial nerve nuclei by intrinsic brainstem lesions [50] may, despite accurate presurgical planning, result in inadvertent injury to eloquent brain structures during stereotactic biopsy.

Given the above inaccuracies of stereotactic biopsy alone, we developed an intra-operative stimulating (IOS) probe that could be integrated into a standard commercially available neurosurgical stereotactic biopsy needle with the rationale that stimulation of the intended biopsy site should predict functional tissue within a 2–5-mm radius and thus prevent inadvertent biopsy of eloquent tissue.

✉ Jason Labuschagne
Jason.labuschagne@icloud.com

1 Department of Neurosurgery, University of the Witwatersrand, Johannesburg, South Africa

2 Department of Paediatric Neurosurgery, Nelson Mandela Children's Hospital, 6 Jubilee Rd, Parktown, Johannesburg 2193, South Africa

3 Jacques Nel and Associates, Atterbury Estate, Pretoria, South Africa

4 Department of Neurophysiology, Nelson Mandela Children's Hospital, Johannesburg, South Africa

Methods

Patient selection

Patients younger than 16 years presenting with a newly diagnosed, untreated brain stem mass that was atypical in nature that required histological diagnosis for a management decision were offered a stereotactic biopsy as per our normal unit protocol. The addition of intra-operative stimulation was offered as an adjuvant to the standard frameless stereotactic guided biopsy. Following an explanation of the experimental nature of the procedure and the lack of safety and efficacy data, written informed consent was obtained on behalf of the children from their parents or guardians. The Human Research Ethics Committee of the medical faculty of the University of the Witwatersrand approved the scientific analyses of these cases.

Device design

We developed a miniaturised hand-held intra-operative stimulating device integrated into a standard neurosurgical brain biopsy needle (Passive Biopsy Needle Kit, Medtronic, Minneapolis, USA) (Fig. 1). The IOS probe is interchangeable with the inner stylet of the biopsy needle. The IOS probe has three contact points, each 1mm by 1mm in diameter. Two stimulation points are placed 2mm apart and serve to deliver bipolar stimulation. The additional stimulating contact point is used to deliver monopolar stimulation.

Stimulation protocol

Recording wire electrodes were inserted under anaesthesia into the orbicularis oculi, orbicularis oris and mentalis muscles for cranial nerve VII monitoring, into the posterior pharynx wall for cranial nerve IX/X monitoring and into the tongue for cranial nerve XII monitoring, according to standard protocol [60, 65, 67]. Vocal cord responses were recorded by a commercially available EMG embedded endotracheal tube device used to detect vocal cord responses (Medtronic NIM® Flex, EMG Tube, Minneapolis, USA). Subdermal needles were placed into the deltoid, biceps brachii, extensor digitorum and abductor pollicis brevis referred to abductor digiti minimi to monitor upper limb electromyographic activity along with tibialis anterior and abductor hallucis pedis to monitor lower limb electromyographic activity as previously described [55, 75]. The presence or absence of spontaneous motor activity on EMG was communicated to the surgeon during advancement of the biopsy needle.

The integrated probe was used to deliver a single monopolar stimulus of 0.2ms duration, at a rate of 1–4 Hz. Stimulation intensity was initiated at 0.1mA and gradually increased until a compound muscle action potential was elicited in one of the monitored muscles, or to a maximum of 2 mA. An additional stimulus delivered at 60Hz of 1-ms pulse length with a biphasic waveform was delivered after completion of the monopolar stimulation. Bipolar stimulation was likewise initiated at 0.1mA and gradually increased until a compound muscle action potential was elicited in one of the monitored muscles, or to a maximum of 2 mA. If EMG activity was elicited, stimulation was repeated to ensure the accuracy of the response. All stimulations and recordings were performed with a commercial stimulator (Medtronic NIM® Eclipse, Minneapolis, USA).

Operative protocol

Anaesthesia was induced and maintained with total intravenous anaesthesia (TIVA) using a propofol target control anaesthesia

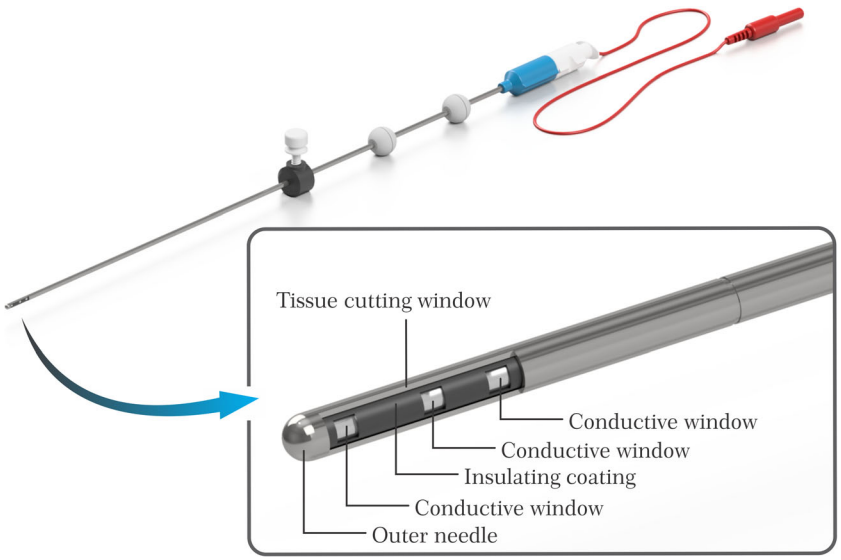

Fig. 1 Diagram of intra-operative stimulating probe integrated in neuronavigation biopsy needle with details of active stimulation area

model (Paedfusor), remifentanil and dexmedetomidine infusions. No muscle relaxants were used throughout the procedure. After induction of anaesthesia and placement of the monitoring electrodes, all patients were placed in the prone position. The patient's head was fixed in a three-point Mayfield clamp secured to the operating table. In children under the age of 2 years, an additional horseshoe headrest was used to support the weight of the patient's head, allowing the pin fixation device to be safely used with minimal force for immobilisation purposes only. Patient registration to the neuronavigation system (STEALTH, Medtronic, Minneapolis, USA) was achieved using surface fiducial markers. The neuronavigation system software was used for surgical planning. A suboccipital, trans-cerebellar surgical approach through the middle cerebellar peduncle was used in all cases (see Fig. 2 of surgical plan and typical trajectory and Fig. 3 of a typical intra-operative configuration). A trajectory was selected, where possible, to pass through the largest dimension of the lesion to allow for multiple biopsies via one needle pass. A standard neurosurgical brain biopsy needle (Passive Biopsy Needle Kit, Medtronic, Minneapolis, USA) with a side cutting window was used to perform the biopsies. The centre of the lesion, along with any enhancing region was targeted. Once the desired location of the biopsy needle was achieved, the IOS probe was inserted down the centre of the biopsy needle and the stimulus applied. The biopsy needle was rotated 360 degrees while the stimulus was delivered. If no compound action potential was recorded then the IOS probe was withdrawn, the inner cannula of the biopsy device inserted and biopsies from four quadrants, each 90 degrees apart, were taken. The biopsy needle was then advanced beyond the centre of the lesion in the same trajectory and the process was repeated such that a minimum of 8 biopsy specimens per trajectory were obtained. If however a compound action potential was recorded then biopsies were not taken from this site, the biopsy needle was advanced, or withdrawn, to a new target point and the stimulation protocol was reapplied. All patients were extubated directly post-operatively and were observed in the PICU for 24 h.

Fig. 3 Intra-operative image of stimulating probe, in use with standard neuronavigation system

Clinical and radiological assessment

Patients were examined clinically during their post-operative course to assess for new neurological deficits or surgical complications. Routine post-operative MRI scans were not obtained. Following integrated histopathological and molecular tumour classification, the children were referred for either adjuvant radiation and/or chemotherapy or formal surgical resection of the lesion if surgery was deemed feasible with acceptable risk.

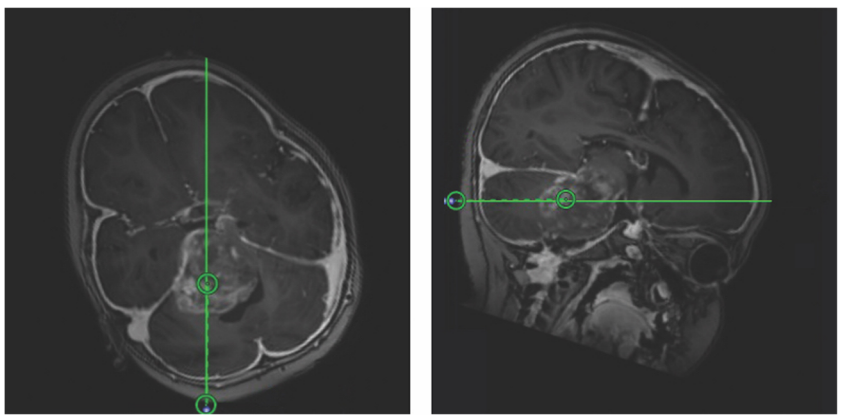

Fig. 2 Images of intra-operative neuronavigation system with typical trajectory and biopsy target site planning for an atypical brainstem tumour which on biopsy revealed an embryonal tumour NOS, in a 2-year-old female patient who was subsequently referred for chemo/radiotherapy

Results

Demographics

A total of 9 patients had the procedure performed. Six of the patients were male (66%) and 3 were female (33%). The median age was 36 months (range 6 months to 11 years). There were 8 tumours located ventrally in the pons and one middle cerebellar peduncle tumour (see Table 1 for a summary of the demographic, histological and clinical findings of the cohort).

Histology analysis

A minimum of 8 samples were obtained from each patient. The biopsy material was adequate to obtain an integrated molecular and histological diagnosis in all 9 patients (100%). Integrated analysis demonstrated two diffuse midline gliomas (WHO IV, H3 mutant), one anaplastic astrocytoma (WHO III, H3 mutant negative), three diffuse astrocytomas (WHO II), one ganglioglioma (WHO I), one pilocytic astrocytoma (WHO I) and one CNS embryonal tumour not otherwise specified (WHO IV).

Results of intra-operative stimulation

The integrated device was used in all 9 cases. In 7 cases, the device did not alter or influence the insertion trajectory or biopsy site, with no evidence of disturbances in the free running EMG, or elicitation of compound action potentials in the monitored cranial nerves or peripherally monitored myotomes. In one case, on advancement of the biopsy guide into a deeper section of the tumour for an additional biopsy, abnormal EMG activity was detected from the vocal cord. It was decided to rather withdraw the biopsy needle and sample a more superficial aspect of the mass. In a second case, on stimulation of the centre of the pontine mass lesion at a stimulation intensity of 1.5mA, a compound action potential was evoked from cranial nerve VII. In this case, it was decided to withdraw the biopsy needle and biopsy the peripheral aspect of the lesion only and not the central core.

Adverse events, neurological sequelae and outcome following the biopsy procedure

No patients experienced any complications directly attributable to either the biopsy procedure per se or the application of the stimulation.

Follow-up care and outcomes

Following histological diagnosis, six of the patients were referred for resective surgery. Of these six patients, one patient declined surgery and is undergoing surveillance only. The other five children had resective surgery performed, with

Table 1 Demographics, histological diagnosis and management

Number	Age/gender	Integrated diagnosis	Intra-operative stimulation findings	Further treatment
1	11 years, female	Diffuse astrocytoma, IHD-1 wild, BRAF +Ve, H3 K27M mutant negative. WHO grade II.	No change in EMG or elicitation of compound action potential	Referred to surgery for resection. Gross total resection achieved.
2	18 months, male	Diffuse astrocytoma. BRAF +Ve. H3 K27M testing not available at the time. WHO grade II	No change in EMG or elicitation of compound action potential	Resective surgery was offered but parents refused additional surgery.
3	6 months, male	Pilocytic astrocytoma. WHO grade I.	No change in EMG or elicitation of compound action potential	Referred to surgery for resection. Subtotal resection achieved
4	1 year, male	Anaplastic astrocytoma. IDH1 wild, H3 K27M mutant negative. WHO grade II.	No change in EMG or elicitation of compound action potential	Referred to surgery for resection. Subtotal resection achieved.
5	3 years, female	Diffuse astrocytoma. IDH1 wild, H3 K27M mutant negative. WHO grade II.	No change in EMG or elicitation of compound action potential	Referred to surgery for tumour resection. Gross total resection achieved.
6	5 years, male	Ganglioglioma, WHO grade I.	No change in EMG or elicitation of compound action potential	Referred to surgery. Gross total surgical resection achieved.
7	5 years, male	Diffuse midline glioma, H3 K27M mutant. WHO grade IV.	No change in EMG or elicitation of compound action potential	Referred for radiotherapy
8	2 years, female	CNS embryonal tumour NOS. WHO grade IV.	Abnormal EMG activity detected from vocal cord monitoring with biopsy needle advancement	Referred for chemotherapy
9	4 years, male	Diffuse midline glioma, H3 K27M mutant. WHO grade IV.	Compound action potential elicited at 1.5mA from CN VII	Referred for radiotherapy

gross total resection (GTR) in three and subtotal resection (STR) in two being achieved. The two patients harbouring the diffuse midline gliomas were referred to the oncological service for radiation therapy and the patient with the embryonal CNS tumour NOS underwent chemotherapeutic treatment according to the "head start" protocol. Median follow-up time was 15 months, range 3 to 24 months.

Discussion

Herein, we introduce a novel IOS device for delivering stimulation to an area of interest before performing a biopsy of the area. The hypothesis being that if eloquent tissue could be identified before a biopsy is taken it may decrease the morbidity and mortality of stereotactic biopsies. To our knowledge, no equivalent IOS probe is available for use with frameless, neuronavigation devices and biopsy needles. The application of monopolar stimulation during computer tomography–guided, frame-based systems has previously been described [7] for supratentorial lesions located in eloquent regions, with a reported reduction in operative morbidity due to the stimulation. The novel IOS probe we describe was developed primarily for use during brainstem biopsies, but it could be utilized for any area in which eloquent tissue is situated within close range to a desired biopsy target.

Since the publication of the manuscript of Albright et al. [2] on behalf of the Children's Cancer Group, in which they posited that "magnetic resonance scans are highly specific for diagnosing brain stem gliomas and obviate the need for histological confirmation", the biopsy of brainstem lesions has been controversial [54] with many neurosurgical units being reluctant to perform biopsies. This reluctance stems from the perception that the procedure is unsafe and that it offers little direct benefit to the patient in terms of management.

The morbidity associated with brainstem biopsy in the recently reported literature [1, 8, 12, 14, 19, 42, 47, 53, 59, 63, 68, 73] ranges from 0 to 30% and the procedure related mortality ranges from 0 to 5%. A metanalysis by Hamish et al. [36] of 735 cases of paediatric brainstem tumours revealed a 6.7% overall morbidity, 0.6% risk of permanent morbidity and 0.6% risk of mortality. Likewise, in a meta-analysis of 1480 cases in both the adult and paediatric groups, Kickingereder et al. [41] found a 7.8% risk of overall morbidity, 1.7% for permanent morbidity and 0.9% risk of mortality.

Until recently, we followed the treatment algorithm outlined by Pincus et al. [53] in dealing with brainstem mass lesions; i.e. based on MRI imaging, focal tumours that are believed to be resectable with acceptable risk are tackled surgically, lesions that are found to be consistent with diffuse pontine gliomas are treated empirically with radiation therapy while atypical lesions have a stereotactic biopsy and histological examination performed, whereupon further decision-making is based. Although by no means not universally accepted [71], the utility and efficacy of obtaining a histological diagnosis in atypical lesions has been validated by several centres [18, 20, 51, 57].

Recently, however, our indication for an upfront biopsy of brain stem lesions has broadened. In up to 35% of tumours not considered to be a typical DIPG on MRI imaging, the H3K27M mutation can be found [11]. Since the presence of the H3K27M mutation carries a uniformly fatal prognosis independent of tumour grade [6], location or extent of tumour resection [40], stereotactic biopsy of both focal and diffuse lesions may be warranted to direct clinical decision-making [31, 33, 38]. Additionally, recent advances in molecular characterisation of brainstem gliomas have revealed several potential targets for molecular based therapies [5, 13, 15, 34, 37, 38, 45], many of which would require tissue for an individualised, directed, precision medicine approach based on genetic or epigenetic information [13, 33]. For these reasons, we now offer upfront brainstem biopsy for all newly diagnosed brainstem mass lesions and anticipate that as a precision medicine–based approach for these lesions becomes more commonplace, the need for brainstem biopsies will become more frequently performed.

When designing the biopsy stimulation probe, we elected to have the ability to incorporate both bipolar as well as monopolar stimulation. The monopolar component was included to localise the vicinity of the cranial motor nerve nuclei (CMN). Monopolar stimulation of the brainstem nuclei has proven to reliably predict the location of CMN in open surgery [16, 48, 49, 69], and despite anatomical distortion of the brainstem by expanding space occupying lesions, monopolar stimulation reliably detects [16, 48] the location of the CMN. Charge from a monopolar electrode spreads radially from the tip towards a distant reference electrode [52] (Fig. 4). This spread allows the surgeon to modulate the stimulator current to estimate the distance to the CMN [29]. The intensity of stimulation required to elicit a CMAP is inversely proportional to the distance from the stimulus to the CMN [62]. The stimulation parameters for this technique (stimulation intensity initiated at 0.1mA, consisting of a single monopolar stimulus of 0.2-ms duration, at a rate of 1–4 Hz) have been well described in open surgery [16, 48, 49, 69] and has been used and validated in the paediatric population [60]. Importantly, the monopolar stimulus delivered should be cathodal as it is more reliable and requires a lower stimulus to elicit an action potential of nerve fibres than anodal stimulation does [9, 70].

Mapping the corticospinal tract (CST) at the level of the pons is not well described; however, corticospinal tract stimulation has been well described to map motor pathways at the level of the internal capsule [22], cerebral peduncle [16, 56] and the midbrain [24, 25] and at the level of the spinal cord [17, 28, 30, 55, 61]. Both monopolar [16] and bipolar [23–25, 56] techniques have been used to map the CST. When using

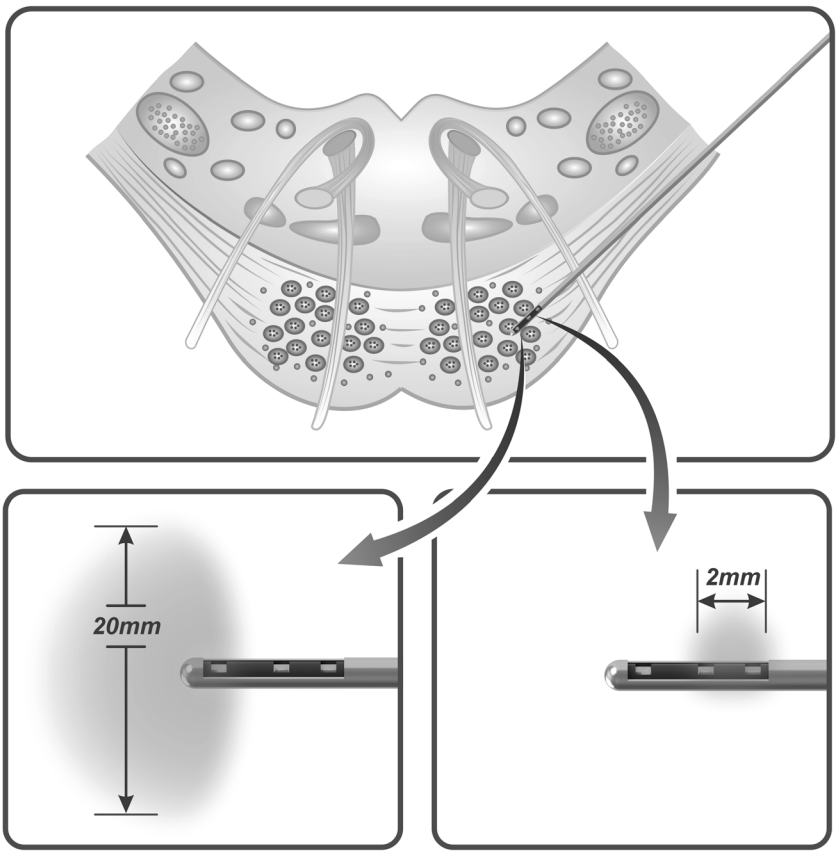

Fig. 4 Top image: Typical trajectory through the middle cerebral peduncle and potential eloquent areas. Bottom left: Monopolar simulation with resultant wide spread of charge from monopolar electrode. Bottom right: Bipolar stimulation charge is transmitted from one arm of the bipolar probe to the other, with rapid dissipation of the electrical field beyond the probe

bipolar stimulation, the distance between the tips of the bipolar probes have ranged from less than 2mm [56] up to 5mm, with several authors, however, favouring a narrower distance between probe points as this allows for better accuracy of the stimulation [24, 28, 56] (Fig. 4). Since bipolar charge is transmitted from one arm of the bipolar probe to the other, the electrical field rapidly dissipates beyond the probe with little electrical diffusion [35], thus activating tissue between the arms of the probe only [52]. In theory, this should answer the binary question of whether the tissue to be biopsied is in close proximity to the corticospinal tract [29] with a high degree of specificity. For this reason, when designing the integrated stimulating probe, we opted to space the bipolar "arms" 2mm apart to minimise the area of tissue activation and thus potentially decrease the risk of false positive stimulation sites. The stimulation parameters for this technique (biphasic square wave pulses, with a pulse frequency of 60Hz a pulse width of 1 ms and a stimulation intensity ranging from 0.1 to 1.0 mA) have been well described and validated in open surgery [23, 25].

The potential for morbidity and mortality following a biopsy in highly eloquent areas may be due to direct parenchymal injury to eloquent tissue, worsening oedema, ischemic injury or haemorrhage [3, 21, 26, 27, 32, 36, 41, 44, 54, 59]. The aforementioned complications may arise from either direct injury due to passage of the biopsy needle, or from the tissue cutting action of the biopsy performed through the side cutting window [58]. There are no direct statistical comparisons of the risk of complications following tissue cutting versus needle insertion alone; however, if one extrapolates the risk of haemorrhagic complications alone in procedures where no tissue cutting is performed, such as in deep brain stimulation, compared to the to the risks of haemorrhagic complications in the brainstem biopsy group, the risk ranges from 0.5 to 2.1% [4, 64, 72, 77] vs 1.7 to 8.5% [32, 43, 44, 46], respectively, implying a significant degree of the parenchymal trauma, is due to the tissue cutting action.

In our case series, 2 of the 9 cases had their surgical procedure modified by the addition of the intra-operative monitoring. The addition of intra-operative stimulation of the intended biopsy site using the IOS probe can be done with minimal change in workflow as the IOS probe is readily interchangeable with the inner stylet of the standard brain biopsy needle. The IOS device can potentially avoid direct parenchymal injury thereby reducing the significant morbidity associated with performing biopsies in the brainstem.

To minimise potential vascular injury during biopsy procedures, the use of optical coherence tomography [58] to intra-operatively detect vessels at risk of intracranial haemorrhage has been proposed. These devices are similarly placed down the biopsy sheath of commercially available biopsy devices and could be used interchangeably with the IOS probe, thus

potentially avoiding both vascular/haemorrhagic and parenchymal disruption injuries. Likewise, previously developed miniaturised probes integrating optical modalities such as Raman spectroscopy and 5-aminilevoleinic acid fluorescence [66] could be incorporated into the IOS probe system, allowing for a "multimodality" needle, potentially maximising biopsy sampling and diminishing parenchymal injury.

Limitations

The current study is limited by a very small sample size. Larger studies with bigger sample sizes are needed in the future to validate these results and truly determine if intra-operative stimulation of target sites in eloquent regions can improve safety.

Conclusion

Using the IOS probe for intra-operative stimulation and neuromonitoring of the intended brainstem biopsy site was found to be safe and feasible. The addition of stimulation of the intended biopsy site with the IOS probe can be done with minimal change in workflow as the IOS probe is readily interchangeable with the inner stylet of a standard brain biopsy needle. With the advent of molecular based therapies for brainstem gliomas, the more ubiquitous requirement for brainstem biopsies is likely. Whether IOS of the intended biopsy site will improve safety and efficacy for patients is still unclear and can only be truly answered with a comparative study.

Acknowledgements The authors would like to acknowledge the assistance of Dr C Lee and Dr S Taylor in the preparation of this manuscript. The authors would like to thank Jamie Colyn for the preparation of the illustrations and images found within the manuscript.

Declarations

Ethical approval The Human Research Ethics Committee of the University of the Witwatersrand approved the research protocol and analysis of these cases (reference number M201108).

Conflict of interest Jason Labuschagne declares that he has a patent pending on the minimally invasive probe described in this manuscript.

References

1. Abernathey CD, Camacho A, Kelly PJ (1989) Stereotaxic suboccipital transcerebellar biopsy of pontine mass lesions. J Neurosurg 70:195–200
2. Albright AL, Packer RJ, Zimmerman R, Rorke LB, Boyett J, Hammond GD (1993) Magnetic resonance scans should replace biopsies for the diagnosis of diffuse brain stem gliomas: a report from the Children's Cancer Group. Neurosurgery 33:1026–1029
3. Arocho-Quinones EV, Pahapill PA (2016) Non-infectious perielectrode edema and contrast enhancement following deep brain stimulation surgery. Neuromodulation 19:872–876
4. Ben-Haim S, Asaad WF, Gale JT, Eskandar EN (2009) Risk factors for hemorrhage during microelectrode-guided deep brain stimulation and the introduction of an improved microelectrode design. Neurosurgery 64:754–762
5. Braunstein S, Raleigh D, Bindra R, Mueller S, Haas-Kogan D (2016) Pediatric high-grade gliomas: current molecular landscape and therapeutic approaches. J Neuro-Oncol 134:541–549
6. Buczkowicz P, Bartels U, Bouffet E, Becher O, Hawkins C (2014) Histopathological spectrum of pediatric diffuse intrinsic pontine glioma: diagnostic and therapeutic implications. Acta Neuropathol 128:573–581
7. Bullard DE, Makachinas TT, Nashold BS (1988) The role of monopolar stimulation during computed-tomography-guided stereotactic biopsies. Appl Neurophysiol 51:45–54
8. Cartmill M, Punt J (1999) Diffuse brain stem glioma. A review of stereotactic biopsies. Childs Nerv Syst 15:235–237
9. Cedzich C, Pechstein U, Schramm J, Schäfer S (1998) Electrophysiological considerations regarding electrical stimulation of motor cortex and brain stem in humans. Neurosurgery 42:527–532
10. Chen SY, Chen CH, Sun MH, Lee HT, Shen CC (2011) Stereotactic biopsy for brainstem lesion: comparison of approaches and reports of 10 cases. J Chin Med Assoc 74:110–114
11. Chiang J, Diaz AK, Makepeace L, Li X, Han Y, Li Y, Klimo P Jr, Boop FA, Baker SJ, Gajjar A, Merchant TE, Ellison DW, Broniscer A, Patay Z, Tinkle CL (2020) Clinical, imaging and molecular analysis of pediatric pontine tumors lacking characteristic imaging features of DIPG. Ac Neuropathol Commun 8:57
12. Chico-Ponce de León F, Perezpeña-Diazconti M, Castro-Sierra E, Guerrero-Jazo FJ, Gordillo-Domínguez LF, Gutiérrez-Guerra R, Salamanca T, Sosa-Sainz G, Santana-Montero BL, DeMontesinos-Sampedro A (2003) Stereotactically-guided biopsies of brainstem tumors. Childs Nerv Syst 19:305–310
13. Clymer J, Kieran MW (2015) The integration of biology into the treatment of diffuse intrinsic pontine gliomas: a review of the North American Clinical trial perspective. Front Oncol 28:169
14. Coffey RJ, Lunsford LD (1985) Stereotactic surgery for mass lesions of the midbrain and pons. Neurosurgery 17:12–18
15. Cohen KJ, Jaboda N, Grill J (2017) Diffuse intrinsic pontine gliomas – current management and new biologic insight. Is there a glimmer of hope? Neuro-oncol 19:1025–1034
16. Deletis V, Fernández-Conejero I (2016) Intraoperative monitoring and mapping of the functional integrity of the brainstem. J Clin Neurol 12:262–273
17. Deletis V, Seidel K, Sala F, Raabe A, Chudy D, Beck J, Kothbauer KF (2018) Intraoperative identification of the corticospinal tract and dorsal column of the spinal cord by electrical stimulation. J Neurol Neurosurg Psychiatry 89:754–761
18. Dellaretti M, Câmara BB, Ferreira PH, da Silva Júnior JB, Arantes RM (2020) Impact of histological diagnosis on the treatment of atypical brainstem lesions. Sci Rep 10:11065
19. Dellaretti M, Reyns N, Touzet G, Dubois F, Gusmão S, Pereira JL, Blond S (2012) Stereotactic biopsy for brainstem tumors: comparison of transcerebellar with transfrontal approach. Stereotact Funct Neurosurg 90:79–83
20. Dellaretti M, Touzet G, Reyns N, Dubois F, Gusmão S, Pereira JL et al (2011) Correlation among magnetic resonance imaging findings, prognostic factors for survival, and histological diagnosis of intrinsic brainstem lesions in children. J Neurosurg Pediatr 8:539–543

21. Downes AE, Pezeshkian P, Behnke E, Bordelon Y, Tagliati M, Mamelak A, Pouratian N (2016) Acute ischemic stroke during deep brain stimulation surgery of globus pallidus internus: report of 5 cases. Oper Neurosurg (Hagerstown) 12:383–390
22. Duffau H (2000) Intraoperative direct subcortical stimulation for identification of the internal capsule, combined with an image-guided stereotactic system during surgery for basal ganglia lesions. Surg Neurol 53:250–254
23. Duffau H, Capelle L, Sichez J (1998) Direct spinal cord electrical stimulations during surgery of intramedullary tumoral and vascular lesions. Stereotact Funct Neurosurg 71:180–189
24. Duffau H, Lopes M, Sichez JP, Bitar A, Capelle L (2003) A new device for electrical stimulation mapping of the brainstem and spinal cord. Minim Invasive Neurosurg 46:61–64
25. Duffau H, Sichez J (1998) Intraoperative direct electrical stimulation of the lamina quadrigemina in a case of a deep tectal cavernoma. Acta Neurochir 140:1309–1312
26. Fenoy AJ, Conner CR, Withrow JS, Hocher AW (2020) Case report of hyperacute edema and cavitation following deep brain stimulation lead implantation. Surg Neurol Int 11:259
27. Fenoy AJ, Simpson RK (2014) Risks of common complications in deep brain stimulation surgery: management and avoidance. J Neurosurg 120:132–139
28. Gandhi R, Curtis CM, Cohen-Gadol AA (2015) High-resolution direct microstimulation mapping of spinal cord motor pathways during resection of an intramedullary tumor. J Neurosurg Spine 22:205–210
29. Gogos AJ, Young JS, Morshed RA, Avalos LN, Noss RS, Villanueva-Meyer JE, Hervey-Jumper SL, Berger MS (2020) Triple motor mapping: transcranial, bipolar, and monopolar mapping for supratentorial glioma resection adjacent to motor pathways. J Neurosurg 5:1–10
30. Gonzalez AA, Shilian P, Hsieh P (2013) Spinal cord mapping. J Clin Neurophysiol 30:604–612
31. Grill J, Puget S, Andreiuolo F, Philippe C, MacConaill L, Kieran MW (2012) Critical oncogenic mutations in newly diagnosed pediatric diffuse intrinsic pontine glioma. Pediatr Blood Cancer 58:489–491
32. Grossman R, Sadetzki S, Spiegelmann R, Ram Z (2005) Hemorrhagic complications and the incidence of asymptomatic bleeding associated with stereotactic brain biopsies. Acta Neurochir 147:627–631
33. Gupta N, Goumnerova LC, Manley P, Chi SN, Neuberg D, Puligandla M, Fangusaro J, Goldman S, Tomita T, Alden T, DiPatri A, Rubin JB, Gauvain K, Limbrick D, Leonard J, Geyer JR, Leary S, Browd S, Wang Z, Sood S, Bendel A, Nagib M, Gardner S, Karajannis MA, Harter D, Ayyanar K, Gump W, Bowers DC, Weprin B, MacDonald TJ, Aguilera D, Brahma B, Robison NJ, Kiehna E, Krieger M, Sandler E, Aldana P, Khatib Z, Ragheb J, Bhatia S, Mueller S, Banerjee A, Bredlau AL, Gururangan S, Fuchs H, Cohen KJ, Jallo G, Dorris K, Handler M, Comito M, Dias M, Nazemi K, Baird L, Murray J, Lindeman N, Hornick JL, Malkin H, Sinai C, Greenspan L, Wright KD, Prados M, Bandopadhayay P, Ligon KL, Kieran MW (2018) Prospective feasibility and safety assessment of surgical biopsy for patients with newly diagnosed diffuse intrinsic pontine glioma. Neuro-Oncology 20:1547–1555
34. Gwak HS, Park HJ (2017) Developing chemotherapy for diffuse pontine intrinsic gliomas (DIPG). Crit Rev Oncol Hematol 120:111–119
35. Haglund MM, Ojemann GA, Blasdel GG (1993) Optical imaging of bipolar cortical stimulation. J Neurosurg 78:785–793
36. Hamisch C, Kickingereder P, Fischer M, Simon T, Ruge MI (2017) Update on the diagnostic value and safety of stereotactic biopsy for pediatric brainstem tumors: a systematic review and meta-analysis of 735 cases. J Neurosurg Pediatr 20:261–268
37. Huang T, Garcia R, Qi J, Lulla R, Horbinski C, Behdad A, Wadhwani N, Shilatifard A, James C, Saratsis AM (2018) Detection of histone H3 K27M mutation and post-translational modifications in pediatric diffuse midline gliomas via tissue immunohistochemistry informs diagnosis and clinical outcomes. Oncotarget 9:37112–37124
38. Infinger LK, Stevenson CB (2017) Re-examining the need for tissue diagnosis in pediatric diffuse intrinsic pontine gliomas: a review. Curr Neuropharmacol 15:129–133
39. Ivan ME, Yarlagadda J, Saxena AP, Martin AJ, Starr PA, Sootsman WK, Larson PS (2014) Brain shift during burr hole-based procedures using interventional MRI. J Neurosurg 121:149–160
40. Karremann M, Gielen GH, Hoffmann M, Wiese M, Colditz N, Warmuth-Metz M, Bison B, Claviez A, van Vuurden DG, von Bueren AO, Gessi M, Kühnle I, Hans VH, Benesch M, Sturm D, Kortmann RD, Waha A, Pietsch T, Kramm CM (2018) Diffuse high-grade gliomas with H3 K27M mutations carry a dismal prognosis independent of tumor location. Neuro-Oncology 20:123–131
41. Kickingereder P, Willeit P, Simon T, Ruge MI (2013) Diagnostic value and safety of stereotactic biopsy for brainstem tumors: a systematic review and meta-analysis of 1480 cases. Neurosurgery 72:873–881
42. Kratimenos GP, Nouby RM, Bradford R, Pell MF, Thomas DG (1992) Image directed stereotactic surgery for brain stem lesions. Acta Neurochir 116:164–170
43. Kreth FW, Muacevic A, Medele R, Bise K, Meyer T, Reulen H-J (2001) The risk of hemorrhage after image guided stereotactic biopsy of intra-axial brain tumours -a prospective study. Acta Neurochir 143:539–546
44. Kulkarni AV, Guha A, Lozano A, Bernstein M (1998) Incidence of silent hemorrhage and delayed deterioration after stereotactic brain biopsy. J Neurosurg 89:31–35
45. Lulla RR, Saratsis AM, Hashizuma R (2016) Mutations in chromatin machinery and pediatric high-grade glioma. Sci Adv 2:1–9
46. Malone H, Yang J, Hershman DL, Wright JD, Bruce JN, Neugut AI (2015) Complications following stereotactic needle biopsy of intracranial tumors. World Neurosurg 84:1084–1089
47. Manoj N, Arivazhagan A, Bhat DI, Arvinda HR, Mahadevan A, Santosh V, Devi BI, Sampath S, Chandramouli BA (2014) Stereotactic biopsy of brainstem lesions: techniques, efficacy, safety, and disease variation between adults and children: a single institutional series and review. J Neurosci Rural Pract 5:32–39
48. Morota N, Deletis V (2006) The importance of brainstem mapping in brainstem surgical anatomy before the fourth ventricle and implication for intraoperative neurophysiological mapping. Acta Neurochir 148:499–509
49. Morota N, Deletis V, Epstein FJ, Kofler M, Abbott R, Lee M, Ruskin K (1995) Brain stem mapping: neurophysiological localization of motor nuclei on the floor of the fourth ventricle. Neurosurgery 37:922–929
50. Morota N, Deletis V, Lee M, Epstein FJ (1996) Functional anatomic relationship between brain-stem tumors and cranial motor nuclei. Neurosurgery 39:787–793
51. Ogiwara H, Morota N (2013) The efficacy of a biopsy of intrinsic brainstem lesions for decision making of the treatments. Childs Nerv Syst 29:833–837
52. Pallud J, Mandonnet E, Corns R, Dezamis E, Parraga E, Zanello M, Spena G (2017) Technical principles of direct bipolar electrostimulation for cortical and subcortical mapping in awake craniotomy. Neurochirurgie 63:158–163
53. Pincus DW, Richter EO, Yachnis AT, Bennett J, Bhatti MT, Smith A (2006) Brainstem stereotactic biopsy sampling in children. J Neurosurg 104:108–114
54. Puget S, Beccaria K, Blauwblomme T, Roujeau T, James S, Grill J, Zerah M, Varlet P, Sainte-Rose C (2015) Biopsy in a series of 130

pediatric diffuse intrinsic Pontine gliomas. Childs Nerv Syst 31: 1773–1780
55. Quinones-Hinojosa A, Gulati M, Lyon R, Gupta N, Yingling C (2002) Spinal cord mapping as an adjunct for resection of intramedullary tumors: surgical technique with case illustrations. Neurosurgery 51:1199–1206
56. Quinones-Hinojosa A, Lyon R, Du R, Lawton MT (2005) Intraoperative motor mapping of the cerebral peduncle during resection of a midbrain cavernous malformation: technical case report. Neurosurgery 56:E439
57. Rachinger W, Grau S, Holtmannspötter M, Herms J, Tonn JC, Kreth FW (2009) Serial stereotactic biopsy of brainstem lesions in adults improves diagnostic accuracy compared with MRI only. J Neurol Neurosurg Psychiatry 80:1134–1139
58. Ramakonar H, Quirk BC, Kirk RW, Li J, Jacques A, Lind CRP, McLaughlin RA (2018) Intraoperative detection of blood vessels with an imaging needle during neurosurgery in humans. Sci Adv 19:4
59. Roujeau T, Machado G, Garnett MR, Miquel C, Puget S, Geoerger B, Grill J, Boddaert N, Di Rocco F, Zerah M, Sainte-Rose C (2007) Stereotactic biopsy of diffuse pontine lesions in children. J Neurosurg 107:1–4
60. Sala F, Coppola A, Tramontano V (2015) Intraoperative neurophysiology in posterior fossa tumor surgery in children. Childs Nerv Syst 31:1791–1806
61. Sala F, Lanteri P, Bricolo A (2004) Motor evoked potential monitoring for spinal cord and brain stem surgery. Adv Tech Stand Neurosurg 29:133–169
62. Sala F, Manganotti P, Tramontano V, Bricolo A, Gerosa M (2007) Monitoring of motor pathways during brain stem surgery: what we have achieved and what we still miss? Neurophysiol Clin 37:399–406
63. Samadani U, Judy KD (2003) Stereotactic brainstem biopsy is indicated for the diagnosis of a vast array of brainstem pathology. Stereotact Funct Neurosurg 5-9
64. Sansur C, Frysinger R, Pouratian N, Fu KM, Bittl M, Oskouian R et al (2007) Incidence of symptomatic hemorrhage after stereotactic electrode placement. J Neurosurg 107:998–1003
65. Schlake HP, Goldbrunner R, Siebert M, Behr R, Roosen K (2001) Intra-operative electromyographic monitoring of extra-ocular motor nerves (Nn. III, VI) in skull base surgery. Acta Neurochir 143:251–261
66. Scolaro L, Lorenser D, Madore W-J, Kirk RW, Kramer AS, Yeoh GC, Godbout N, Sampson DD, Boudoux C, McLaughlin RA (2015) Molecular imaging needles: dual-modality optical coherence tomography and florescence imaging of labeled antibodies deep in tissue. Biomedical Optics Express 6:1767–1781
67. Singh R, Husain AM (2011) Neurophysiologic intraoperative monitoring of the glossopharyngeal and vagus nerves. J Clin Neurophysiol 28:582–586
68. Steck J, Friedman WA (1995) Stereotactic biopsy of brainstem mass lesions. Surg Neurol 43:563–567
69. Strauss C, Romstöck J, Nimsky C, Fahlbusch R (1993) Intraoperative identification of motor areas of the rhomboid fossa using direct stimulation. J Neurosurg 79:393–399
70. Szelényi A, Senft C, Jardan M, Forster MT, Franz K, Seifert V, Vatter H (2011) Intra-operative subcortical electrical stimulation: a comparison of two methods. Clin Neurophysiol 122:1470–1475
71. Tejada S, Aquilina K, Goodden J, Pettorini B, Mallucci C, van Veelen ML, Thomale UW (2020) Biopsy in diffuse pontine gliomas: expert neurosurgeon opinion-a survey from the SIOPE brain tumor group. Childs Nerv Syst 36:705–711
72. Videnovic A, Metman LV (2008) Deep brain stimulation for Parkinson's disease: prevalence of adverse events and need for standardized reporting. Mov Disord 23:343–349
73. Wang ZJ, Rao L, Bhambhani K, Miller K, Poulik J, Altinok D, Sood S (2015) Diffuse intrinsic pontine glioma biopsy: a single institution experience. Pediatr Blood Cancer 62:163–165
74. Woodworth GF, McGirt MJ, Samdani A, Garonzik I, Olivi A, Weingart JD (2006) Frameless image-guided stereotactic brain biopsy procedure: diagnostic yield, surgical morbidity, and comparison with the frame-based technique. J Neurosurg 104:233–237
75. Yingling CD, Ojemann S, Dodson B, Harrington MJ, Berger MS (1999) Identification of motor pathways during tumor surgery facilitated by multichannel electromyographic recording. J Neurosurg 91:922–927
76. Zrinzo L (2012) Pitfalls in precision stereotactic surgery. Surg Neurol Int:S53–S61
77. Zrinzo L, Foltynie T, Limousin P, Hariz MI (2012) Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review. J Neurosurg 116:84–94