A COMPARISON OF INTRAOPERATIVE ULTRASOUND AND POST-OPERATIVE MRI IN PAEDIATRIC INTRA AXIAL TUMOURS

by

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Dissertation Submitted in Partial Fulfilment of the Requirements

for the degree of

Masters of Surgery (Neurosurgery)

This dissertation is prepared in accordance with the format required by

Journal of Korean Neurosurgical Society

UNIVERSITI SAINS MALAYSIA
NOVEMBER 2022

ACKNOWLEDGEMENTS

This study became a reality with the kind support and help of many individuals. Foremost, I want to offer this endeavour to our God Almighty for the wisdom He bestowed upon me, the strength, peace of mind and good health in order to finish this study.

I would like to express my gratitude to my family for their encouragement. My beloved and supportive husband, for keeping me focused and tirelessly helping out to ensure this study was completed on time.

I am highly indebted to my supervisors and senior colleagues, both in Hospital Tunku Azizah, Hospital Kuala Lumpur and Universiti Sains Malaysia. My deepest gratitude to Mr. (Dr.) Azmi Alias, Mr. (Dr.) Fadzlishah Johanabas, Professor Mr. (Dr.) Zamzuri Idris, Professor Dato' Dr. Jafri Malin Abdullah and Professor Dato' Mr. (Dr.) Abdul Rahman Izani Ghani. Their invaluable advice, guidance and constructive criticism has taught me a lot in the journey of this study, and gave a huge impact to the final product.

This study would not be possible without the active participation and support from my co-investigators, Dr. Rohazly binti Ismail and Dr. Adi Afiq bin Md Anour, paediatric radiologists of Hospital Tunku Azizah, Kuala Lumpur. Their brilliant ultrasound knowledge and extreme patience in performing IOUS during our long surgery hours were invaluable.

Finally, my deepest appreciation to everyone whose names were not mentioned here but has guided or lent a hand to me. This study is dedicated to all of you.

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LIST OF ABBREVIATIONS AND SYMBOLS

Abbreviation	Description
CNS	Central Nervous System
IOUS	Intraoperative Ultrasound
CT	Computerised Tomography
GCS	Glasgow Coma Scale
GoF	Goodness of Fit
GOS	Glasgow Outcome Scale
H-L	Hosmer-Lemeshow $\hat{C}$ statistic test
MRI	Magnetic Resonance Imaging
ATRT	Atypical teratoid rhabdoid tumour
GTR	Gross total resection
IOMR	Intraoperative MRI
IOCT	Intraoperative CT
κ	Kappa

ABSTRAK

Latar Belakang: Barah Sistem Saraf Pusat (CNS) adalah barah pediatrik kedua paling kerap, selepas barah hematologi. Barah CNS amat bergantung kepada tahap reseksi tumor. Dalam dekad yang lalu, ultrasound intraoperatif (IOUS) telah berkembang sebagai alat pengimejan neuro meluas yang menawarkan panduan pembedahan secara langsung, dan merupakan modaliti pengimejan yang boleh dicapai secara meluas dengan risiko dikenal pasti minima, tiada masa operasi tambahan, dan juga kos yang lebih rendah. Kajian terkini mendapati korelasi kuat antara IOUS dan penemuan MRI selepas pembedahan apabila menilai tahap reseksi tumor dalam populasi dewasa yang menunjukkan bahawa IOUS mungkin mempunyai implikasi klinikal yang ketara, namun tidak banyak kajian yang melibatkan populasi pediatrik. Objektif kajian kami adalah untuk membandingkan korelasi dan kebolehpercayaan ultrasound berbanding dengan MRI untuk reseksi tumor dalam populasi pediatrik. Kami juga menilai IOUS sebagai alat navigasi secara langsung semasa pembedahan tumor intra paksi dalam pesakit kanak-kanak.

Kaedah Kajian ini merupakan kajian pemerhatian prospektif yang dilakukan di Hospital Tunku Azizah, Kuala Lumpur. Pesakit berumur kurang daripada 12 tahun, yang dimasukkan ke wad antara 1 Disember 2019 hingga 30 November 2021 dengan diagnosis MRI pra-operasi tumor otak intra-paksi telah diambil untuk kajian ini. IOUS dilakukan secara intraoperatif, dan MRI pasca operasi dilakukan dalam masa 24-72 jam selepas operasi. Penilaian utiliti IOUS dilakukan secara intraoperatif.

Keputusan Kami telah menganalisis sejumlah 25 pesakit kanak-kanak yang memenuhi kriteria kemasukan. Analisis konkordans antara penilaian IOUS dan MRI menunjukkan

persetujuan yang baik (kappa = 0.527). Analisis regresi logistik *multivariate* telah dilakukan untuk mencari sebarang faktor percanggahan yang ketara, dan didapati tiada pembolehubah signifikan yang menyebabkan percanggahan. Ujian kesesuaian *Hosmer and Lemeshow* telah dilakukan, dan menunjukkan bahawa model kami adalah padanan yang baik, dengan nilai ramalan yang baik 0.497.

Kesimpulan Penggunaan IOUS boleh menjadi modaliti pengimejan intra operasi yang dipercayai untuk mencapai reseksi kasar tumor otak yang lebih baik untuk pesakit pediatrik.

ABSTRACT

Background Malignant tumours of the Central Nervous System (CNS) is the second most common paediatric malignancy, following haematological malignancy. CNS tumours depend significantly on the extent of tumour resection. In the past decade, intraoperative ultrasound (IOUS) has evolved into a widespread neuroimaging tool that offers real-time surgical guidance, and is a widely accessible imaging modality with minimal identified risk or additional operative time, and also lower economic investment. Recent studies found a strong correlation between IOUS and post operative MRI findings when evaluating extent of tumour resection in adult population suggesting that IOUS might have significant clinical implications, however not many studies involved the paediatrics population. The objective of our study was to compare correlation and reliability of the ultrasound as compared to MRI for tumour resection in paediatric population. We also evaluated IOUS as a real-time navigation tool during surgical resection of intra axial tumours in paediatric patients.

Methods This was a prospective observational study done in a Hospital Tunku Azizah, Kuala Lumpur. Patients aged less than 12 years old, admitted between 1st December 2019 to 30th November 2021 with preoperative MRI diagnosis of intra-axial brain tumour were recruited in this study. IOUS was performed intraoperatively, and post-operative MRI performed within 24-72 hours post-op. IOUS utility assessment scoring was performed intraoperatively.

Results We analysed a total of 25 paediatric patients that met the inclusion criteria. Concordance analysis between IOUS evaluation and MRI showed good agreement (kappa = 0.527). A multivariate logistic regression analysis was performed to look for any significant factors of discordance, and none of the variables were found significant for discordance. Hosmer and Lemeshow goodness of fit test was performed, and showed that our model is a good fit, with a good prediction value of 0.497.

Conclusion The use of IOUS allowed reliable intra operative imaging modality to achieve more successful gross total resection of brain tumours in paediatrics.

INTRODUCTION

Malignant tumours of the CNS is the second most common paediatric malignancy, following haematological disorders. It is generally accepted that positive outcomes in paediatric CNS tumours depend significantly on the extent of tumour resection. In light of this, techniques to improve resection results have significant clinical implications in the paediatric population. [10-11] In the past decade, few methods of intraoperative adjuncts to aid in tumour resection have been applied. Amongst them are neuro-navigation, intraoperative ultrasound, intraoperative CT/ MRI and 5-aminolevulinic acid. These methods help to localise and identify tumour borders, as well as aiding in maximum tumour resection. [2] In recent years, intraoperative ultrasound has evolved into a widespread neuroimaging tool that offers real-time surgical guidance, and is a widely accessible imaging modality with minimal identified risk or additional operative time. [1,10] In this study, we would like to observe the accuracy of intraoperative ultrasound performed pre and post resection. Post resection ultrasound is then compared with postoperative MRI. This study is primarily aimed to evaluate the correlation between findings in IOUS with postoperative MRI to provide further support for the role of IOUS in enhancing tumour surgery especially in paediatric population. Most of the IOUS applications in brain tumours derive from adult series, hence our study is aimed to replicate the positive results in the paediatric population instead. However, in this particular study, our paediatric population is of 12 years and below due to reasons that our paediatric patients in this Woman and Child’s Hospital would only accommodate this age range. The goal of cerebral glioma surgery is not only maximal but also safe tumour resection, in which the maximum neurologically permissible tumour volume should be resected, but eloquent areas must be spared and neurological damage minimised. [1,4]

Image-guided surgery based on neuronavigation is widely used and has become an essential tool in this recent decade. [9] The accuracy of neuronavigation systems are based on pre operative data limited to intraoperative changes. These limitations can be addressed by intraoperative MRI and CT however both modalities require long acquisition time and enormous economic investment. These intraoperative modalities significantly lengthen operating time, require additional staff to run the scanners, increase the risk of breaks in sterility, and have much higher overhead and running costs. Contrast is required for tissue demarcation, and ionising radiation is emitted in the case of intraoperative CT. Furthermore, intraoperative CT is rarely acceptable for paediatric patients due to the ionising radiation. [3,27,28] In a review of IOUS as effective neuronavigation in paediatric tumour surgery, safe maximal tumour resection can be achieved through accurate localization and intraoperative mapping of eloquent areas required for functions such as language, sensation, or movement. [3] The main advantage of IOUS in brain tumour surgery lies in its real time property. It can generate a complete overview of the tumour and the surrounding structures within seconds. IOUS also can repeatedly evaluate the extent and location of residual tumour tissue at any stage of the surgery. The ability to depict real time anatomic data during a surgical procedure is very useful for surgical decision making. [4,5,7] IOUS is an effective way to localise and characterise lesions and to assist with the monitoring of the surgical field for the improvement of resectability and reduction of the risk of parenchymal injury. [4] In a retrospective study of 260 patients by Sweeney et al., treated for brain tumour with IOUS performed and post operative MRI done within 1 week, authors reported an intended gross tumour resection rate of 81% across diverse cases. IOUS was able to correctly identify residual tumour in 100% of cases. [1] IOUS provided useful intraoperative information, allowing the surgeon to visualise the extent of residual tumour when making the decision to proceed or conclude the resection based on the benefit/risk ratio. [3] In cases of deep-seated tumours, IOUS helps in finding a cleavage plane for resection. In epilepsy surgery, it is difficult for the surgeon to distinguish dysplastic lesions from normal cortex. In cases like this, IOUS can depict cortical dysplasia with high resolution. Post resection, IOUS can be used to identify tumour residuals. [15-18] Roth et al., reported that the majority of glial tumours in paediatric patients are low-grade tumours. In this group of tumours (e.g. pilocytic astrocytoma), prognosis is directly related to the extent of resection. Quite frequently, low grade tumours include a subtle component, which may be hard to differentiate from the normal surrounding brain tissue. In addition, during surgery of deep-seated ventricular lesions, as well as periventricular lesions, a large amount of cerebrospinal fluid may be removed. Thus, a real-time imaging modality combined with navigational capabilities may be helpful. [5] Also, precise skin incisions, smaller craniotomies and easy localization of intracranial pathologies are fundamental applications of neuronavigation systems in neurosurgery in general and paediatric neurosurgery in particular. [10,21]

The neuro-oncological paediatric population has several peculiarities when compared to adults, including a larger variety of histological subtypes and lesions are frequently located in the posterior fossa. As most studies are derived from the adult population, therefore there is a gap in evaluation of the IOUS usefulness for paediatric intra axial tumour resection. [28] The pivotal role of accurate assessment of residual tumour in paediatric patients is underlined by the International Society for Paediatric Oncology of a new scale to quantify both the operator's assessment and the postoperative imaging data. This new scale has guided us to objectively compare our IOUS resection evaluation with early postoperative MRI findings. [33] In our practice, IOUS is used routinely in adult and paediatric patients with intra axial tumours, but we acknowledge that IOUS has some limitations. A practical limitation is user dependency. As with many aspects of neurosurgery, user dependency is subject to a steep learning curve, but this limitation can be overcome readily over time. IOUS is therefore an essential adjunct in modern neurosurgery.

METHODS AND MATERIALS

RESEARCH DESIGN

This is a prospective observational study, based in Hospital Tunku Azizah Kuala Lumpur whereby data was collected from 25 patients who were admitted to the paediatric Neuroscience ward between 1 December 2019 and 30 November 2021 for elective surgery. These patients are <12 years old, with intra axial brain tumours of the supra tentorial and infra tentorial region, that was earlier diagnosed on preoperative MRI. IOUS will be performed during tumour resection surgery and postoperative MRI will be done within 24-72 hours. Findings of IOUS and post operative MRI will be compared and tabulated. This study was approved by the Malaysian Medical Research and Ethics Committee (MREC). [NMRR ID: NMRR-20-2608-55443 (IIR)]

RESEARCH LOCATION AND DURATION

This study was conducted in a single neurosurgical centre in Hospital Tunku Azizah, Kuala Lumpur. Our centre is one of the main paediatric neurosurgery referral centre in Klang Valley. Thus, our centre receives a substantial amount of paediatric neurosurgery brain tumour cases. Patients who fulfil the inclusion and exclusion criteria were selected and included in this study. The total study duration was over a span of 2 years, from 1 December 2019 - 30 November 2021.

METHOD OF RESEARCH

This prospective observational study involves paediatric patients aged <12 years old who were admitted to neuroscience ward 11C, diagnosed with intra axial axial tumours from preoperative MRI, and undergoing elective surgery for tumour resection. Children admitted to the paediatric wards in Hospital Tunku Azizah are of age 12 and below. Sample size estimation was calculated using a single correlation formula. Prior data by Sweeney et al. in Efficacy of intraoperative ultrasonography in neurosurgical tumour resection, indicate that the correlation coefficient between IOUS and post operative MRI was 0.693. Thus, a minimum sample size of 14 samples to be able to reject the null hypothesis with probability (power) 0.8. The general research objective is to compare the correlation and reliability of the ultrasound as compared to MRI for tumour resection in paediatrics population. We also evaluate intraoperative ultrasound as a real-time navigation, as an adjunct in surgical excision of intra axial tumours in paediatric patients and we observe findings in post resection IOUS with early postoperative MRI that is performed within 24 -72 hours in paediatric intra axial tumours.

Patients who fulfil the inclusion and exclusion criteria will be recruited for this study. Patients recruited must be < 12 years old, have intra axial brain tumours located in the supra tentorial or infratentorial region, undergoing elective tumour resection and have postoperative MRI within 24-72 hours post surgery. Patients undergoing emergency tumour resection and postoperative MRI performed >72 hours post surgery, were not recruited in this study. All recruited patients were consented by their parents and assent form was also provided for the patients.

All children underwent craniotomy and microsurgical resection of tumour. Intraoperative ultrasound (Hitachi Aloka MP-2450) equipped with micro convex linear transducer, with frequency range of 4-10 Mhz was used before and after dura opening to confirm relationship of the tumour to the brain landmarks, during resection at surgeon's discretion, at the end of the resection to confirm microsurgical impression of reaching the planned resection. Post-operative imaging was performed on a 3T Siemens MRI machine. Extent of resection was evaluated according to the latest recommendation of the International Society of Pediatric Oncology (SIOP), which integrates a surgical grading with a MRI grading. Surgical impression on resection was graded from SR0 to SR3. Radiological assessment was graded MR0 to MR3. To reduce interrater variability, surgery performed by three surgeons, intraoperative ultrasound performed by two experienced paediatric radiologists, and postoperative MRI were reviewed by 2 different paediatric radiologists; and subsequently analysed using Cronbach's alpha inter rater reliability.

The radiologist accompanied the neurosurgeon during each procedure and in each of the cases, the insonation was performed prior to and after dural opening. The selected probe was draped in a sterile cover filled with sterile jelly and all air bubbles were ensured to be eliminated. Throughout the insonation procedure, sterile irrigation with saline was performed as well to ensure optimal coupling. The radiologist would adjust the probe frequency using the variable frequency probe to suitably insonate both superficial and deep structures as required. The best image showing the whole lesion was measured and the length, width, and height of the lesion measured and written down on the data collection sheet. Prior to closure as well, the resection cavity will be assessed to see any suspicious residual tumour or bleed. Once the surgeon is satisfied with the resection, the final assessment will be done and any residual tumour if any will be documented as well. Utility scoring system was also employed prior to our procedure whereby we identified various parameters to reflect different aspects of the perceived utility of the IOUS. These parameters were then assessed and documented in our surgical notes.

STATISTICAL ANALYSIS

The statistical analysis employed was Statistical Package for Social Sciences for Windows (SPSS, Chicago, IL, USA). The data generally comprises demographic information, site of the tumour, tumour diameter, tumour histology, extent of intraoperative resection and post-operative contrast enhanced MRI assessment. Categorical variables are shown as frequency (with percentages) and continuous variables are shown as mean ±standard deviation or median (interquartile range) unless otherwise stated.

Data collected was compared between intraoperative ultrasound and postoperative MRI in which would be measured using Fleiss Kappa agreement. Multivariate logistic regression analysis was performed to identify predictors for discordance between intraoperative ultrasound evaluation and MRI. The variables which would be used as predictors include age, sex, size, location of tumour, volume of tumour and tumour histology. The H-L GoF tests the null hypothesis that the model's estimates fit the observed data. The subjects are divided into deciles based on the predicted probabilities, and then computes χ^2 observed and expected frequencies. Then, a p-value is calculated from the χ^2 distribution, if the p-value of H-L GoF test is > 0.05, we fail to reject the null hypothesis that there is no statistical difference, hence implying that the model's estimates fit the observed data.

RESULTS

Our study included 25 patients, the mean age was 5.68 years, with a median of 5 years. Average tumour volume was 94.65cm^3. The most frequent tumour site was in the infratentorial region (52%); posterior fossa (48%), pineal (4%). Tumours in the supratentorial region (48%) comprising of ; hemispheric (24%), intraventricular (4%), sellar (8%) and thalamus (12%). Among the histologies obtained were; pilocytic astrocytoma (12%), craniopharyngioma (4%), choroid plexus papilloma (4%), ganglioma (8%), low grade diffused glioma (4%), cortical tuber (4%), diffused astrocytoma (8%), ependymoma (8%), germinoma (4%), medulloblastoma (28%), pineoblastoma (4%), Atypical teratoid rhabdoid tumour (ATRT) (4%), CNS embryonal tumour (ETMR) (4%) and glioblastoma (4%). (Table 1)

Table 1: Study population

Features of patient population and disease			
Age	Years	5.68	
Sex	M	15	60.0%
	F	10	40.0%
Pre-operative Tumour Volume	cm^3	94.65	
Histological Diagnosis	Pilocytic astrocytoma	3	12.0%
	Craniopharyngioma	1	4.0%
	Choroid plexus papilloma	1	4.0%
	Ganglioglioma	2	8.0%
	Low grade diffused glioma	1	4.0%
	Cortical tuber	1	4.0%
	Diffused astrocytoma	2	8.0%
	Ependymoma	2	8.0%

	Germinoma	1	4.0%
	Medulloblastoma	7	28.0%
	Pineoblastoma	1	4.0%
	Atypical teratoid rhabdoid tumour	1	4.0%
	CNS embryonal tumour (ETMR)	1	4.0%
	Glioblastoma	1	4.0%
Tumour Site	Supratentorial	12	48.0%
	Infratentorial	13	52.0%

Utility scoring system was employed intraoperatively (Table 2). Seven parameters were used to assess IOUS utility and were documented. Based on this utility assessment, the median score was 5 and the mean overall utility score was 5.8. There were no scores less than 4, and from this it is deemed that the IOUS was useful in all cases (Table 3).

Table 2: Scoring system for assessing the utility of intraoperative ultrasound (IOUS)

Parameter	**Interpretation**	**Score**
Lesion Identification	Lesion discernible	1
	Not discernible on IOUS	0
Lesion delineation	Well defined margins	1
	Poorly defined margins but discernibly distinct from normal brain	1
	Imperceptibly diffuse. No use of IOUS	0
Utility in craniotomy modification	IOUS prompted a modification/extension in the craniotomy	1
	No modification of bone removal needed	0
Use in durotomy planning	Useful/helped optimise the durotomy site and extent	1

	Not needed/useful	0
Use in corticectomy/ myelotomy planning	Useful to plan the entry site	1
	Not needed/useful	0
Use for assessment of extent of resection	Used for assessing extent of resection/residue	1
	Not needed/useful	0
Visualisation of adjacent structures	Useful and needed	1
	Not needed/useful	0

Table 3: Overall IOUS utility scores

Overall Score	**Number of Cases**	**Percentage**
1	0	0
2	0	0
3	0	0
4	4	16
5	11	44
6	2	8
7	8	32

Based on the 25 cases, surgical and radiological evaluation of resection was done according to the latest recommendation from the International Society of Paediatric Oncology (SIOP). (Table 4) From this evaluation, we found that complete surgical resection as evaluated on IOUS (SR0) was 56% (14/25) and “near total” resection (SR1) was 20% (5/25). However we also had cases that achieved SR2 at 20% (5/25) and SR3 at 4% (1/25). This will be explored further in the discussion. In our postoperative MRI assessment of these 25 cases, MR0 36% (9/25), MR1 44% (11/25), MR2 16% (4/25), MR3 4% (1/25). (Table 5) From these data, we found that the IOUS under estimated tumour resection in 24% of cases.

Table 4: Extent of resection as evaluated intraoperatively and on postoperative contrast-enhanced MRI to be performed within 48h (max 72h) after surgery (according to SIOP)

SR 0	Total resection, no residue
SR 1	Suspected residue, possible local invasion
SR 2	Sold residuum (to be defined by postoperative MRI)
SR 3	Tumour volume unchanged, biopsy
MR 0	No visible tumour
MR 1	Rim enhancement or signal abnormality (matching the tumour) at the operation site only (“Rim”), ≤ 3mm in any of the dimensions and equivocal for tumour residue
MR 2	Residual tumour measuring > 3mm in all 3 dimensions (greater than MR1, less than MR3)
MR 3	No significant change to preoperative tumour size (“minimal change”)

Table 5: Tabulation of IOUS and MRI evaluation of tumour resection.

		Postoperative MRI				Total
		MR0	MR1	MR2	MR3	
Intraoperative IOUS	SR0	8	5	1	0	14
	SR1	0	5	0	0	5
	SR2	1	1	3	0	5
	SR3	0	0	0	1	1
Total		9	11	4	1	25

Concordance analysis between IOUS evaluation and MRI showed good agreement (kappa = 0.527) (Table 6). In this cohort of paediatric brain tumours, IOUS when used to assess the extent of resection as compared to early postoperative MRI, was found to have 89% sensitivity. We further analysed our data to look for any confounding factors that could cause discordance, therefore multivariate logistic regression analysis was performed. The factors that we analyzed include age, sex, site (supratentorial versus infratentorial), largest volume of lesion (in cm^3) and tumour histology. In this analysis, we did not find any of the variables to be a significant factor of discordance (Table 7). Among the limitations to this is the sample size. The initial sample size was calculated based on our main objective, which is to see the agreement between IOUS evaluation with post operative MRI, which is achieved within our 25 samples. Hosmer and Lemeshow goodness of fit test was performed, and showed that our model is a good fit, with a good prediction value of 0.497 (Table 8). Cronbach's Alpha inter rater reliability performed and showed p=0.785 which shows no inter rater biasness (Table 9).

Table 6: Cohen's κ agreement between IOUS and MRI (κ = 0.527)

Symmetric Measures

		Value	Asymptomtic Standard Error[a]	Approximate T[b]	Approximate Significance
Measure of Agreement	Kappa	.389	.126	3.566	.000
N of Valid Cases		25			

Note: Cohen's κ was run to determine if there was agreement between the two IOUS and MRI scorings by two different raters in 25 individuals. There was good agreement between the two raters, κ = 0.389 (95% CI, .126 to 3.566), $p < .001$.

Table 7: Multivariate regression analysis based on patient's age, sex, site, volume of tumour and histology

Variables	p-value	OR	95% C.I.
Age	.173	1.209	0.920 – 1.590
Sex	.236	3.535	0.438 – 28.506
Site	.822	1.287	0.144 – 11.501
Volume of tumour	.528	1.003	0.994 – 1.012
Histology	.305	3.185	0.348 – 29.126

Note: Multivariable regression analysis shows that there is a statistically proven **no discordance** between the two imaging modalities

Table 8: Hosmer and Lemeshow Goodness of Fit Test (p=0.497)

Step	Chi-square	df	Sig.
1	5.372	6	.497

Note: H-L goodness of fit test is used to show that the model is good for prediction value with a p value of 0.497 (p>0.005)

Table 9: Cronbach's Alpha inter rater reliability

Reliability Statistics	
Cronbach's Alpha	N of Items
.785	2

Note: Cronbach's Alpha inter rater reliability shows there was no inter rater biasness by two different raters in 25 individuals. p= .785 (95% CI, 0.70 to 0.95)

DISCUSSION

In neurosurgery, neuronavigation has improved patient outcomes given its enhanced accuracy and safety intraoperatively, making it a standard for pre-resection initial localisation and evaluation of tumour boundaries in many hospitals. [34] Common intraoperative diagnostic imaging techniques include intraoperative magnetic resonance (IOMR), intraoperative computed tomography (IOCT), intraoperative ultrasound (IOUS) and dyes (fluorescence). [35] The use of IOMR has verified that resection control and extent of resection promote longer survival. However, the complicated surgical arrangements, increased costs and prolonged operative durations associated with IOMR have limited its application. [34]

Recently, ultrasonography has become a widely used medical imaging modality with numerous clinical applications. Intraoperative ultrasound is an emerging tool in the era of modern neurosurgery with a growing body of evidence to support its advantages for lesion targeting and extent of resection evaluation.[3,10,15] In the previous decades, among the main limitations of IOUS during cranial surgery were the ultrasound probe size was too big for the craniotomy size and image quality was poor in comparison with CT or MRI images. In recent decades, the quality of ultrasound imaging has improved significantly with 3D acquisition and sophisticated computer technology, and the ultrasound probe sizes are also more user-friendly for craniotomies.[15,34] In cases of glioma, extent of surgical resection is the independent prognostic factor for progression-free survival and overall survival.[10,33] In the setting of paediatric neurosurgical oncology, control over the extent of resection is essential. The neuro-oncological paediatric population has several peculiarities when compared to adults, including a larger variety of histological subtypes and lesions are frequently located in the posterior fossa.[28] As most studies are derived from the adult population, therefore there is a gap in evaluation of the IOUS usefulness for paediatric intra axial tumour resection. Hence, our study was aimed at evaluating the feasibility and benefits of IOUS in paediatrics population in hopes of reproducing a similar positive outcome found in most adult studies; our study demonstrated a sensitivity of 89% in IOUS versus post operative MRI in the extent of tumour resection as compared to various adult studies where the rate of gross total resection estimated via IOUS, ranges from 57-95% based on a meta-analysis by Mahboob et al. [13]

IOUS is a reliable real time navigation tool and has become a standard practice in many neurosurgical centres including ours. This neuronavigation tool enhances accuracy and safety during tumour resection. [9,10] For each case recruited, we performed an objective utility assessment in which we found IOUS was reliable in localising lesions, determining tumour boundaries and surrounding essential structures, and most importantly, real time monitoring of brain shift without having to change patient's position or increase operative time. [15,34]

However, in our study, IOUS underestimated 6 out of 25 of tumour resection. In these 6 cases, 5 were suggested complete resection on IOUS, while MRI showed residual smaller than 3mm in diameter. These 6 cases were noted to be posterior fossa tumours , and they were among the first few cases that we performed IOUS and postoperative MRI evaluation. We attributed this underestimation to artifacts produced during surgery that were difficult to distinguish from residual tumours. Brain contusions or blood clots also caused strong echoes at the bottom of the resected tumour cavity in which were also difficult to distinguish with residual tumours. We also found that peritumoral edema produces similar echoes to the surrounding brain tissue and this is also an attributable cause. Another possible consideration would be that there was difficulty in delineating the residual tumours post resection due to the image quality and anatomical orientation especially in the posterior fossa whereby most of the tumours tend to infiltrate or have close proximity to the brainstem. However, this could be overcome with the recent advancements in ultrasound technologies such as the introduction of 3D IOUS imaging whereby the reconstructed images are clear and intuitive, can be easily used to measure the size and volume of lesions, while displaying the 3D shape and spatial location of the lesion with reduced tumour artifacts.[34] Traditionally, 2D ultrasound images are displayed in a planar format which is dependent on the ultrasound probe used, and often the view is limited to the sector of sonification which is often in oblique rather than true axial. Therefore, anatomical disorientation could easily happen and this affects the image quality, especially during assessment of residual during post resection. However, recently with the advancement of IOUS as real-time imaging during surgery, a 3D IOUS and precalibration and integration with image guided surgery (IGS), has improved anatomic orientation and identification of artifacts versus residual tumours in real-time. In a study with 3D IOUS was used, surgeons were able to estimate the extent of surgical resection correctly in 59% of cases in their study, and found that among the main reasons for overestimation was poor intraoperative image quality, which was improved by 3D IOUS.[13] Throughout our study duration, our fellow radiologist colleagues have also significantly gained the necessary training and experience, and hence with time, explains the drastic improvement in our extent of tumour resection as recommended by SIOP with reduction of underestimation.

Study limitations and Recommendations

In our study, one of the main limitations includes the lack of skills and experience in performing IOUS amongst neurosurgeons; therefore resulting in poor ultrasound images and difficulties in anatomical orientation. The absence of known anatomical landmarks makes it hard to determine orientation, especially when attempting to observe small areas of residual tumour. This is further compounded by a limited craniotomy exposure in most of our tumour resection cases at the beginning of our study. To overcome this limitation and improve skills in intraoperative ultrasonography, each case of our study was done by two radiologists with the presence of neurosurgeons. Another limitation that we tend to observe is the inaccuracies in placing the tip of the surgical tool causing inaccurate insonation planes resulting in difficulties in image interpretation. Therefore, one of the suggested solutions include miniaturisation of probes to improve the resolution of images and to allow our neurosurgeons to undergo abundant ultrasound training and related processes in order to improve our learning curve especially for the young neurosurgeons and fellow radiology colleagues.

CONCLUSION

The use of IOUS may allow reliable intra operative imaging modality that improves lesion detection and localization which contributes to a successful gross total resection of brain tumours in paediatrics. We have successfully performed a study that compares the correlation and reliability of the ultrasound as compared to MRI for tumour resection in paediatric population and found a good agreement between the two modalities. However, due to the aforementioned limitations, we would need to increase our study size which includes multi-centres while incorporating the latest ultrasonography advancements in order to fully extract the benefit of IOUS and be used routinely in all paediatric tumour resections; which in turn helps improve tumour resection, promote more radical resection, and ultimately enhance patient survival and quality of life.

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APPENDIX

APPENDIX A - Ethical Approval

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(MEDICAL RESEARCH & ETHICS COMMITTEE)
KEMENTERIAN KESIHATAN MALAYSIA
MINISTRY OF HEALTH MALAYSIA
Kompleks Institut Kesihatan Negara (NIH)
No.1, Jalan Setia Murni U13/52,
Seksyen U13 Bandar Setia Alam,
40170 Shah Alam, Selangor.
Tel.: +(6)03-33628888/ 33628205

Ref. : KKM/NIHSEC/P20-2521(12)
Date : **20-April-2021**

DR. NADIAH BINTI AHMAD FUAD
HOSPITAL TUNKU AZIZAH (HOSPITAL WANITA DAN KANAK-KANAK KUALA LUMPUR)

Dear Dato'/ Dr/ Sir/ Madam,

LETTER OF ETHICAL APPROVAL:

NMRR-20-2608-55443 (IIR)
A COMPARISON OF INTRAOPERATIVE ULTRASOUND AND POST OPERATIVE MRI IN PAEDIATRIC INTRA AXIAL TUMOURS

This letter is made in reference to the matter above.

2. The Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH) has provided ethical approval for this study. Please take note that all records and data are to be kept strictly **CONFIDENTIAL** and can only be used for the purpose of this study. All precautions are be taken to maintain data confidentiality. Permission from the District Health Officer / Hospital Administrator/ Hospital Director and all relevant heads of departments /units where the study will be carried out must be obtained prior to the study. You are required to follow and comply with their decision and all other relevant regulations including the Access to the Biological and Benefit Sharing Act 2017.

3. The investigators and sites involved in this study are:

Hospital Tunku Azizah (Hospital Wanita Dan Kanak-Kanak Kuala Lumpur)
Dr. Nadiah Binti Ahmad Fuad (Principal / Coordinating Investigator)
Prof Madya Zamzuri Idris
Dr. Azmi Alias
Dr. Fadzlishah Johanabas Bin Rosli
Dr. Rohazly Binti Ismail

4. The following study documents have been received and reviewed with reference to the above study:

Documents received and reviewed with reference to the above study:

1. Cover letter to MREC (Version 3, dated 16-04-2021)
2. Declaration of Conflict of Interest (COI) (Version 1, dated 13-11-2020)
3. Protocol (Version 3, dated 26-03-2021)
4. English: Parental Information Sheet/ Informed Consent Form (Version 2, dated 26-03-2021)
5. Malay: Parental Information Sheet/ Informed Consent Form (Version 2, dated 26-03-2021)
6. Data Collection Form (Version 1, dated 23-10-2020)
7. English: Patient Information Sheet/ Assent Form (Version 1, dated 26-03-2021)
8. Malay: Patient Information Sheet/ Assent Form (Version 1, dated 26-03-2021)
9. Follow-up Review Report (Version 1, dated 09-03-2021)
10. IA-HOD-IA, CV and GCP Certification of:
    - Dr. Nadiah Binti Ahmad Fuad
    - Prof Madya Zamzuri Idris
    - Dr. Azmi Alias
    - Dr. Fadzlishah Johanabas Bin Rosli
    - Dr. Rohazly Binti Ismail

…/2-

Ref : KKM/NIHSEC/P20-2521(12)

5. Please note that the approval is valid until **19-April-2022**.The following are to be reported upon receiving ethical approval. Required forms can be obtained from the National Medical Research Registry (NMRR) website.

i. **Continuing Review Form** has to be submitted to MREC within 2 months (60 days) prior to the expiry of ethical approval.
ii. **Study Final Report** upon study completion to the MREC.
iii. Ethical approval is required in the case of **amendments/ changes** to the **study documents/ study sites/ study team**. MREC reserves the right to withdraw ethical approval if changes to study documents are not completely declared.
iv. **Applicable for Clinical interventional Studies only:** Report occurrences of **all Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reaction (SUSARs)** and **Protocol Deviation/Violation** at all MREC approved sites to MREC. SAEs are to be reported within 15 calendar days from awareness of event by investigator. Initial report of SUSARs are to be reported as soon as possible but not later than 7 calendar days from awareness of event by investigator, followed by a complete report within 8 additional calendar days.

6. There will be **14 subjects/ patients/ respondents** targeted to be enrolled in this study within Malaysia.

7. Please take note that the reference number of this letter must be stated in all future correspondence related to this study to facilitate the administrative processes.

Project Sites:
HOSPITAL TUNKU AZIZAH (HOSPITAL WANITA DAN KANAK-KANAK KUALA LUMPUR)

Decision by Medical Research & Ethics Committee:
(√) Approved
(   ) Disapproved

Date of Approval : **20-April-2021**

…………………………………………
DR. HJH SALINA BINTI ABDUL AZIZ
Chairperson
Medical Research & Ethics Committee
Ministry of Health Malaysia
(MMC No: 27117)

c.c:

HRRC Hospital Wanita Dan Kanak-Kanak

C/MMREC_Share\Approval 2020\Expedited by Primary Reviewer\April 2021\55443

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Appendix B - Annual Ethical Renewal for 2022

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(*Medical Research & Ethics Committee*)
KEMENTERIAN KESIHATAN MALAYSIA
d/a Kompleks Institut Kesihatan Negara
Blok A, No 1, Jalan Setia Murni U13/52,
Seksyen U13, Bandar Setia Alam,
40170 Shah Alam, Selangor.
Tel: 03-3362 8888/8205

Ruj.Kami: KKM/NIHSEC/ P20-2521
Tarikh: 05-April-2022

DR NADIAH BINTI AHMAD FUAD
HOSPITAL TUNKU AZIZAH (HOSPITAL WANITA DAN KANAK-KANAK KUALA LUMPUR)

Dato'/ Tuan/ Puan,

Annual Ethical Renewal for 2022

NMRR-20-2608-55443 (IIR)
Protocol No :
A Comparison of intraoperative ultrasound and post operative MRI in paediatric intra axial tumours

With reference to the 'Continuing Review Form' submitted 04-April-2022, we are pleased to inform that the conduct of the above study has been granted approval (via Expedited Review by Chairperson) for a year by the Medical Research & Ethics Comittee, Ministry of Health Malaysia. To renew the approval, a completed 'Continuing Review Form' has to be submitted to MREC **within 2 months** before the expiry of the approval.

The Medical Research & Ethics Committee, Ministry of Health Malaysia operates in accordance to The International Council for Harmonization of Technical Requirement for Pharmaceutical for Human Use (ICH) dan Malaysia Guidelines for Good Clinical Practice.

Effective date: 20-April-2022 Until 19-April-2023

Comments (if any): NIL

"WAWASAN KEMAKMURAN BERSAMA 2030"

"BERKHIDMAT UNTUK NEGARA"

Yours sincerely,

(DR HJH SALINA ABDUL AZIZ)
Chairman
Medical Research & Ethics Committee
Ministry of Health Malaysia