Resection of Pediatric Brain Tumors: Intraoperative Ultrasound Revisited

Aliasgar V. Moiyadi, Prakash Shetty, Amol Degaonkar

Background: Extent of resection is a very important prognostic marker in most pediatric brain tumors. Intraoperative imaging facilitates resection control. Intraoperative ultrasound (IOUS) is a cost-effective alternative to intraoperative magnetic resonance, but scant literature addresses its utility in this context.

Methods: We retrospectively reviewed all pediatric brain tumors operated at our center using navigated three-dimensional ultrasound (US). The utility of the US in resection control was recorded and extent of resection evaluated. Results: IOUS was used in 20 cases (3 for frameless biopsy and 17 for tumor resection control). It was 100% accurate in localizing all tumors and yielded 100% diagnosis in the biopsy cases. Technical limitations precluded its use in 2 of the 17 cases of tumor resection. In the remaining 15, it correctly predicted the residual tumor status in 13 cases (87%). A gross total resection was achieved overall in 12 cases (80%) with postoperative morbidity in only one case. Conclusions: IOUS is a useful tool to localize intracranial tumors and guide the resection reliably. Widespread use can improve its applicability and make it an effective intraoperative imaging tool in pediatric brain tumors.

Keywords: Intraoperative imaging, intraoperative ultrasound, pediatric brain tumors, utility

INTRODUCTION

Radical resection remains the primary aim of surgery in most pediatric tumors.[1-5] Given the limitations of conventional microscopic visualization of tumor-brain interface, a suitable intraoperative adjunct to enhance this information is increasingly used. Intraoperative magnetic resonance (IOMR) remains the gold standard for visualization of tumors and tumor-brain interface with superior multiplanar resolution. Intraoperative computed tomography (CT) is limited by the poor image contrast (with respect to brain tumors) and risk of ionizing radiation, especially when repeated image updates are required. Intraoperative ultrasound (IOUS) may not be able to match the resolution of the MR, but with rapid strides in technological advancements and improvements in image resolution over the years, has come to be acknowledged as a very useful intraoperative imaging tool.[6] Its advantage over the IOMR stems from the ease of use, safety, and widespread availability in most settings. The addition of navigation and three-dimensional US (3DUS) technology has narrowed the gap between IOMR and IOUS and positioned the IOUS as a very useful alternative to IOMR. Despite a lot of published literature in adult brain tumors, few reports focus on its utility in pediatric tumors. Our report aims to objectively assess the utility of IOUS in a select cohort of pediatric brain tumors.

METHODS

This was a retrospective analysis. We have been using a navigated US system (SonoWand, SONOWAND AS, Trondheim, Norway) since 2011 and operated over 250 tumors using it. From the prospectively...
maintained database we selected all cases <18 years for the present analysis. As part of this database, demographic, clinical, radiological, and intraoperative details are recorded. These were reviewed to extract the relevant data. Specifically the details about the use of the IOUS (mode, number of scans, and the intraoperative impression regarding tumor residue) were noted. Histology was recorded from the hospital database. Extent of resection was classified as gross total resection (GTR) if there was no documented residue on the immediate postoperative MRI (n = 15) or CT (n = 6). Concordance between the postresection US and postoperative imaging was calculated. Descriptive statistics were used for most of the variables. Chi-square test was used to assess statistical significance (with a P < 0.05 cutoff). SPSS ver 20.0 (SPSS, IBM Inc, NY, USA) 0 was used for the statistical analysis.

**RESULTS**

A total of 158 pediatric brain tumors were operated at our institute in the time between June 2011 and June 2016. The navigated US system was used in 21 cases (16 males and 5 females) ranging in age from 5 to 18 years (mean age 11.9 years). There were 17 supratentorial (including one pineal tumor) and 4 infratentorial tumors. Six children had undergone prior surgery (with one case having received radiotherapy additionally) before presenting to us. Radical surgery was intended in 17 and tissue sampling alone (biopsy) in four cases. 14 of the cases were either close to (11 cases) or involving (3 cases) eloquent areas. There were 13 glial tumors (six low grade, and seven high grade gliomas) and eight nonglial tumors (2 primitive neuroectodermal tumors, and one each of medulloblastoma, atypical teratoid rhabdoid tumor, pineoblastoma, schwannoma, cavernoma, and ganglioglioma). Figures 1–3 depict the spectrum of cases where the US was used.

The navigated 3DUS system we use can function as a standalone navigation (using preoperative MRI) as well as a navigated intraoperative 3DUS system (“so called “direct 3DUS mode”). Both these modes can be combined into a “combined sononavigation” mode too. In the 21 pediatric tumors where we used the system, the navigation mode alone was used in a single case. This was a case of a thalamic tumor which was planned for a biopsy only. In all the other 20 cases, the navigated 3DUS was used (14 as “direct 3DUS" and 6 as “combined sononavigation” mode). In these 20 cases, the US was used for the purpose of frameless biopsy in three cases and resection control of the tumor in 17. A phased-array probe (5–10 MHz, 15 mm × 13 mm footprint) was used in 18 cases as most of the tumors were deep seated. The linear probe (6–12 MHz, 32 mm × 11 mm footprint) was used in the remaining two superficial lesions. Tumor was identified by the US in all the cases where it was used (100% localization). The tumor delineation was reported as good in 13 cases and fair or moderate in 6 others. In one case, the tumor was very ill-defined (a case of medulloblastoma). The image resolution on US was neither influenced by the prior treatment, nor the location (supratentorial versus infratentorial) of the tumor [Table 1]. Nonglial tumor histology was associated with better US image resolution, but this was not statistically significant.

**Utility of the intraoperative ultrasound**

In all three cases where a frameless biopsy was planned, positive histological proof was obtained as guided by the US (100% yield). In 15 of the 17 cases where a resection control was planned, multiple intermediate scans were obtained to guide the resection, prompting additional resection in six cases. In the other two cases, due to technical problems in obtaining optimal US images after the resection commenced (both due to position of the patient resulting in inadequate filling of the cavity with saline precluding optimal acoustic coupling, as well as artefacts induced by proximity to skull base bone), the US could not be used after the initial scan. In the 15 cases where it was used for resection control, the US predicted GTR in 12 cases and showed residual tumor in three (further resection intentionally aborted due to the proximity to eloquent areas). Based on postoperative imaging, GTR was achieved overall in 12 of the 15 cases (80%). In the 15 cases where the US was used for resection control, we calculated the concordance with postoperative imaging. The US correctly predicted residual disease status in 13 cases (concordance of 87%; in 11 cases no residue and in 2 cases residual tumor was correctly predicted). There was one case each where the US was false-positive as well as false-negative.

Neurological worsening was seen in only one case. All the others either remained neurologically stable (16) or
A case of the left trigeminal schwannoma. Screenshot from the SonoWand system showing the preoperative magnetic resonance (in a dual surgical plane view) on the left, and the same magnetic resonance overlaid with ultrasound and power Doppler angiogram. Note the well-delineated hyperechoic tumor on the ultrasound images and the well depicted circle of Willis surrounding it. The angiogram helped landmark the critical vascular anatomy during the surgery.

The well-delineated hyperechoic tumor on the ultrasound images and the well depicted circle of Willis surrounding it. The angiogram helped landmark the critical vascular anatomy during the surgery.

Figure 1: A case of the right frontal recurrent PNET. (a) The preoperative T1-contrast magnetic resonance images. (b) The postoperative T2 (upper row) and T1-contrast magnetic resonance images (lower row) shows complete excision of the tumor with persistent edema surrounding the cavity. (c) The intraoperative screenshot from the SonoWand system. On the left panel is the presection ultrasound images in dual plane view. Note the similarity in image morphology of the ultrasound images with the preoperative magnetic resonance images depicted in (a). On the right panel is the postresection ultrasound image. Persistent edema which is less hyperechoic than the tumor itself is seen clearly and correlates with the postoperative magnetic resonance in (b).

Figure 2: A case of the right frontal recurrent PNET. (a) The preoperative T1-contrast magnetic resonance images. (b) The postoperative T2 (upper row) and T1-contrast magnetic resonance images (lower row) shows complete excision of the tumor with persistent edema surrounding the cavity. (c) The intraoperative screenshot from the SonoWand system. On the left panel is the presection ultrasound images in dual plane view. Note the similarity in image morphology of the ultrasound images with the preoperative magnetic resonance images depicted in (a). On the right panel is the postresection ultrasound image. Persistent edema which is less hyperechoic than the tumor itself is seen clearly and correlates with the postoperative magnetic resonance in (b).

Discussion

Intraoperative adjuncts are increasingly used during resection of brain tumors. Intraoperative MR remains the gold standard for such image guidance. The use of IOMR in pediatric neurosurgery in general, and pediatric tumors specifically, has been reported with good results.[7] Both, low-field and high-field IOMR solutions have been used with mildly differing results.[8-10] Low-field IOMR is probably more suited for cyst drainage, neuro-endoscopy guidance and catheter placement procedures whereas high-field solutions are preferred for tumor surgery considering the better image resolution required.[11] However, logistical challenges and cost-implications preclude the widespread use of IOMR technology.

In this scenario, IOUS has emerged as a useful cost-effective alternative to IOMR. In tumor surgery, it is a very useful tool for localizing lesions as well as following the resection and assessing residual status in real-time. Navigated 3DUS is a specialized tool which combines the benefits of real-time image updates of the US with navigation technology.[11] This has been proven in numerous reports mainly in the adult population.[12-15] Its use in the pediatric population has however not been widely reported. Considering that the extent of resection is probably as important (if not more) in many of the pediatric brain tumors, it is surprising that more importance has not been accorded to the role of adjuncts facilitating resection control in this population.

Though not a prospective study, our analysis was based on consecutive cases where the operating surgeon felt the need for some sort of intraoperative guidance during tumor resection. This was a small proportion of all pediatric tumors operated in the same time period (13%). However, of note is the fact that when image guidance was needed, pure navigation was used only in 1 of the 21 cases. In all the others, updated intraoperative imaging (in the form of navigated 3DUS) was preferred. Moreover, in 14 of the 20 cases (70%) the US was sufficient by itself, without the need for combined preoperative MR. Combined sononavigation (using preoperative MR overlaid with updated IOUS) is very useful in orienting the plane of the US images and especially beneficial for new and inexperienced users. In our practice, with increasing experience with US, we have moved away from using the preoperative MR and gravitated toward using the 3DUS directly. This eliminates the need for an additional preoperative MRI (which in the case of smaller children may entail an additional anesthesia), reduces the time (which would have otherwise been required for MRI registration) and also eliminates the error involved in MRI to patient registration intraoperatively. Even for the cases where we planned only a frameless biopsy, except for the one case where preoperative MR based navigation was employed, we preferred the “direct” US mode. The IOUS was extremely accurate in localizing the tumor (100% localization). When used for targeting tumors for diagnostic biopsies, it had a 100% yield. Further, in cases where it was used for controlling the extent of resection, it correctly predicted the residual disease status in 87% of cases. Thus overall, it was an extremely useful intraoperative tool.

Few studies have specifically addressed the role of IOUS in the pediatric brain tumor population. Babcock et al. included in the list.
reported probably one of the earliest series of IOUS in pediatric brain tumors in the early 1990s. More than a decade later, Vougioukas et al. described 22 cases of pediatric tumors operated using 3DUS assistance. This report however did not provide much objective information. Roth et al. reported a series in 2007 describing 16 cases operated using navigated-3DUS (the same SonoWand system we have used) and achieved GTR in 14 of 16 cases. They did not report on accuracy objectively but mentioned that the IOUS was correct and useful in all cases. Our present results reconfirm these findings. El Beltagy et al. reported a study of 25 cases. They used 2DUS technology and found 100% accuracy in localizing and detecting residue. They can achieve GTR rate 56% in their cohort. This lower GTR rate may have been a result of using 2DUS. However without a direct comparison with 3DUS it may be difficult to say which is better. Subsequently, the same group reported results for posterior fossa tumors. In this study, they compared navigated US with conventional microsurgery (and navigation) and found that the navigated US group had better GTR rates and lesser mutism postoperatively.

Ulrich et al. described 22 cases where real-time 3DUS was used achieving complete resection in 82%. The US correctly predicted this in 18 of 19 cases. There was no additional morbidity with these extended resections. The authors concluded that IOUS was extremely useful in resection control. More recently, Singhal et al. (central nervous system 2015) reported a large series of 58 cases using 2DUS which had a positive predictive value of 100%, negative predictive value of 98% and overall accuracy of 98% with kappa agreement value of 0.956 between US and MR. Table 2 summarizes these main studies related to the use of US in pediatric brain tumor surgery.

A limitation of these series (and ours) is the retrospective nature of these studies and the possibility of selection bias whereby tumors with better US delineation and therefore more amenable to resection could have been selected for undergoing IOUS guided resections. Nonetheless, even in these cases, the IOUS was very useful in guiding the resection and thereby achieving the main goal of the surgery with no added morbidity. In resource constrained settings where more expensive adjuncts like IOMR may be only a distant dream, the IOUS can be a very effective tool for guiding the resection. Its use should be encouraged and promoted.

**Conclusions**

IOUS is a very reliable and useful adjunct during respective surgery in pediatric brain tumors. User experience is essential, but is easily acquired over a period of time. Navigation technology and 3DUS developments have tremendously expanded the scope and utility of IOUS. Early adoption and regular use of IOUS can improve tumor resections and provide for better outcomes.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**Table 2: Overview of various studies reporting the role of intraoperative ultrasound in pediatric brain tumors**

| n (ST: IT) | Type of IOUS | GTR rates (%) | Localization accuracy (%) | Predictive value of IOUS for residual disease (%) |
|-----------|--------------|---------------|---------------------------|-----------------------------------------------|
| Vougioukas et al. | 22 (NA) | 3DUS | NA | NA |
| Roth et al. | 16 (16:0) | 3DUS | 87.5 | 100% | NA |
| El Beltagy et al. | 25 (8:17) | 2DUS | 56 | NA | NA |
| Ulrich et al. (2011) | 22 (12:10) | 3DUS | 82 | NA | 95 |
| Singhal et al. | 58 (20:38) | 2DUS | 72.5 | NA | 98 |
| Moiyadi et al. (2016), present | 21 (17:4) | 3DUS | 80 | 100 | 87 |

NA: Not available, ST: Supratentorial, IT: Infratentorial, GTR: Gross total resection, 3DUS: Three-dimensional ultrasound, 2DUS: Two-dimensional ultrasound, nUS: Navigated ultrasound, IOUS: Intraoperative ultrasound
REFERENCES

1. Souweidane MM. The evolving role of surgery in the management of pediatric brain tumors. J Child Neurol 2009;24:1366-74.

2. Sun MZ, Ivan ME, Clark AJ, Oh MC, Delance AR, Oh T, et al. Gross total resection improves overall survival in children with choroid plexus carcinoma. J Neurooncol 2014;116:179-85.

3. Ullrich NJ, Pomeroy SL, Kapur K, Manley PE, Goumnerova LC, Loddenkemper T. Incidence, risk factors, and longitudinal outcome of seizures in long-term survivors of pediatric brain tumors. Epilepsia 2015;56:1599-604.

4. McCrea HJ, Bander ED, Venn RA, Reiner AS, Iorgulescu JB, Puchi LA, et al. Sex, age, anatomic location, and extent of resection influence outcomes in children with high-grade glioma. Neurosurgery 2015;77:443-52.

5. Kumar LP, Deepa SF, Moinca I, Suresh P, Naidu KV. Medulloblastoma: A common pediatric tumor: Prognostic factors and predictors of outcome. Asian J Neurosurg 2015;10:50.

6. Vougioukas VI, Hubbe U, Hochmuth A, Gellrich NC, van Velthoven V. Perspectives and limitations of image-guided neurosurgery in pediatric patients. Childs Nerv Syst 2003;19:783-91.

7. Mutchnick I, Moriarty TM. Intraoperative MRI in pediatric neurosurgery—an update. Transl Pediatr 2014;3:236-46.

8. Avula S, Mallucci CL, Pizer B, Garlick D, Crooks D, Abernethy LJ. Intraoperative 3-Tesla MRI in the management of paediatric cranial tumours – initial experience. Pediatr Radiol 2012;42:158-67.

9. Moriarty TM, Titsworth WL. The evolution of iMRI utilization for pediatric neurosurgery: A single center experience. Acta Neurochir Suppl 2011;109:89-94.

10. Lam CH, Hall WA, Truwit CL, Liu H. Intra-operative MRI-guided approaches to the pediatric posterior fossa tumors. Pediatr Neurosurg 2001;34:295-300.

11. Unsgård G, Solheim O, Lindseth F, Selbekk T. Intra-operative imaging with 3D ultrasound in neurosurgery. Acta Neurochir Suppl 2011;109:181-6.

12. Moiyadi AV. Intraoperative ultrasound technology in neuro-oncology practice-current role and future applications. World Neurosurg 2016;93:81-93.

13. Jakola AS, Myrme KS, Kloster R, Torp SH, Lindal S, Unsgård G, et al. Comparison of a strategy favoring early surgical resection vs. a strategy favoring watchful waiting in low-grade gliomas. JAMA 2012;308:1881-8.

14. Sæther CA, Torsteinsen M, Torp SH, Sundstrøm S, Unsgård G, Solheim O. Did survival improve after the implementation of intraoperative neuronavigation and 3D ultrasound in glioblastoma surgery? A retrospective analysis of 192 primary operations. J Neurol Surg A Cent Eur Neurosurg 2012;73:73-8.

15. Jakola AS, Unsgård G, Solheim O. Quality of life in patients with intra cranial gliomas: The impact of modern image-guided surgery. J Neurosurg 2011;114:1622-30.

16. Babcock DS, Barr LL, Crone KR. Intraoperative uses of ultrasound in the pediatric neurosurgical patient. Pediatr Neurosurg 1992;18:84-91.

17. Roth J, Biyani N, Beni-Adani L, Constantini S. Real-time neuronavigation with high-quality 3D ultrasound SonoWand in pediatric neurosurgery. Pediatr Neurosurg 2007;43:185-91.

18. El Beltagy MA, Aggag M, Kamal M. Role of intraoperative ultrasound in resection of pediatric brain tumors. Childs Nerv Syst 2010;26:1189-93.

19. El Beltagy MA, Atteya MM. The benefits of navigated intraoperative ultrasonography during resection of fourth ventricular tumors in children. Childs Nerv Syst 2013;29:1079-88.

20. Ulrich NH, Burkhardt JK, Serra C, Bernays RL, Bozinov O. Resection of pediatric intracerebral tumors with the aid of intraoperative real-time 3-D ultrasound. Childs Nerv Syst 2012;28:101-9.

21. Singhal A, Ross Hengel A, Steinbok P, Doug Cochrane D. Intraoperative ultrasound in pediatric brain tumors: Does the surgeon get it right? Childs Nerv Syst 2015;31:2353-7.