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Research Article

Extent of Glioma Resection on Intraoperative Ultrasound Correlates Well with Postoperative MRI Results

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ABSTRACT

Background: Maximal surgical resection is thought to confer survival benefit for both high- and low-grade gliomas. Intraoperative imaging assists with achieving maximal surgical resection. Different intraoperative imaging modalities have been implemented, but intra-operative MRI has a high cost that may limit its uptake in resource scarce healthcare systems.

Objectives: This study aims to evaluate intraoperative ultrasound as a surrogate for intra and post-operative MRI for assessing the extent of resection of glioma.

Methods: A partially prospective comparative study, which compares a prospective cohort group with a historical control group. We evaluated 74 glioma patients, who all underwent surgery in a regional UK Neurosurgical centre between October 2013 and October 2017. The study population was divided into 2 groups based on the use of ultrasound to guide the resection. We compared the size of the lesion prior and after excision to evaluate the extent of resection and undertook comparison with post-operative MRI.

Results: The mean extent of resection on the ultrasound images was 96.1 % and 97.7 % on the postoperative MR. Using Spearman's correlation; extent of resection on the ultrasound images was strongly correlated with the extent of resection on the postoperative MR images (P -value < 0.001). The use of intraoperative ultrasound was associated with a significant increase in the number of patients in whom 95% or greater extent of resection was achieved (Fisher's exact test P = value 0.033).

Conclusion: Intra-operative ultrasonography could provide a reliable and cheaper alternative to intraoperative MRI to improve the extent of resection in glioma surgery.

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Introduction

The extent of resection of many intrinsic brain tumours such as gliomas has been identified repeatedly as a positive prognostic factor [1]. As well as allowing neuropathological and molecular diagnosis according to the WHO grading system, respective surgery is also likely to have benefits by reducing mass effect, cyto-reduction of the tumour and by reducing intra-tumour heterogeneity. Establishing demarcation between healthy brain and tumour tissue at surgery is key to achieving maximal safe resection, but can be challenging, as tumour, especially at its periphery, may resemble normal brain. Reliance on preoperative imaging has drawbacks including no real time feedback during tumour removal, and

brain shift occurring during tumour resection [2].

Fluorescence guided surgery using 5 aminolevulinic acid (5ALA) has been shown to significantly increase the rate of complete resection of enhancing tumour in high grade glioma, with an associated increase in progression free survival [3]. This technique allows identification of areas of significant viable high-grade tumour but is less useful for low grade glioma, though it does allow identification of anaplastic foci [4]. However, to utilise 5ALA requires a fluorescence adapted microscope, with costs for the light source and filter of around forty thousand UK pounds, a significant capital investment, with the individual cost per patient of around one thousand UK pounds per case.

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Structural intraoperative imaging has been shown to increase the rate of total tumour resection in some series by as much as from 19% to 69% [5]. Intraoperative Ultrasound (iU/S), Computed tomography (iCT) and Magnetic resonance imaging (iMRI) have been used, each having its own positives and drawbacks. iCT has the obvious disadvantage of potential repeated exposure to ionizing radiation which has limited its adoption and investigation. iMRI gives excellent imaging quality and does not involve ionizing radiation but has high capital cost and can be intrusive to use in theatre. The cost of the installation of an iMRI system varies significantly from unit to unit as much of the capital expenditure is often on building costs e.g. re-enforcing floors to take the weight of a scanner, but the scanner alone will cost in the region of 1.5-3 million UK pounds. iMRI has been shown to increase complete resection rates for brain tumours and post-operative MRI to assess extent of glioma resection is standard practice where available [6].

iU/S was one of the earliest intra-operative imaging techniques to be introduced in neurosurgery in the 1950s, but several problems hampered its utilisation, especially poor image quality [7]. Advances in U/S technology have led in recent years to the resurgence of iU/S. It allows several real-time scans within a few minutes and does not require radiology technicians for routine usage, once the user is experienced in interpreting images. In the last few decades, both 2D and 3D ultrasound have become much more widely used in neurosurgery. 3D ultrasound allows linkage to a conventional image guidance system and real time updating of the pre-operative MR or CT scans. However, the 3D systems come at significant cost as they include an image guidance system. 2D ultrasound machines are very much cheaper (a standard machine is in the region of twenty thousand UK pounds). 2D iU/S has several advantages including reliability, accuracy, ease of use and providing real time anatomical and structural feedback, however, concerns remain about how the iU/S images relate to the 'gold-standard' images generated by MRI [8].

The value of 2D iU/S in assessing extent of resection of intracranial tumour remains unclear due to the absence of large case series and long-term follow-up data. Potentially, it could be used as a cheaper alternative to iMRI and post-operative MRI in resource poor settings, but clarification of whether it gives comparable data to the surgeon on extent of resection is still lacking. In this study, we aim to evaluate iU/S as an adjunct for resection of gliomas, aiming to clarify whether the extent of resection as measured by iU/S is comparable to the extent of resection as measured on the gold standard of a post-operative MRI scan.

Materials and Methods

This was a comparative study, which compared a prospective cohort group in whom ultrasound (Hitachi Aloka "Arietta V60") was used, with a historical control group in whom it was not. Patient recruitment was done in one UK regional Neurosurgical unit (catchment population 3.4 million) between October 2013 and October 2017. We recruited 33 patients in the prospective iU/S group and included 41 matched patients in the retrospective non iU/S group. Primary outcome was the degree of correlation of extent of resection between iU/S images taken intra-operatively and on post-operative MR scans done within 48 hours of resection. Secondary outcome was early postoperative complications (within a month) evaluated by full neurological examination. Inclusion

criteria for patients recruited to the prospective arm of the study included: 1. Patients diagnosed as having glioma of any grade on pre-operative diagnostic MR images. 2. Patients who were a candidate for surgery aiming on pre-operative planning to resect a substantial portion (>50%) of the tumour. 3. Patients older than 16 years old. We excluded: 1. Patients who had multifocal or multicentric disease. 2. Patients who were medically unfit for surgery.

The study population was divided into 2 groups based on the use of ultrasound to guide the resection:

1. Prospective group: resection of the gliomas was done using ultrasound-guided surgery.
2. Retrospective group: resection had been performed without the use of the ultrasound.

All patients were evaluated by being asked for a detailed history followed by full neurological examination. Subsequently Stealth image guidance system compatible post contrast Magnetic Resonance Images (e.g. MPRAGE 1mm volume T1 post-gadolinium) were performed and standard frameless image guidance based on the pre-operative imaging used for all patients in both the historical control and ultrasound groups. A craniotomy was planned using image guidance with the craniotomy flap large enough to provide a sufficient window for use of ultrasound (ultrasound probe head 3cm by 1cm) in the study group. Following craniotomy trans-dural ultrasound images were obtained. Further images were obtained after opening the dura when the application of the probe direct to the brain surface improved image quality. Grey scale B mode was used to define the extent of the tumour in a real time rather than relying on just image guidance / preoperative MRI and iU/S was used after dural opening to evaluate extent of resection as the procedure progressed. The colour flow Doppler integral to the Aloka machine was used to identify vascular structures in the vicinity of the resection e.g. the middle cerebral artery.

Complete excision of the lesion was attempted whenever considered possible in the context of preservation of neurological function, aided by undertaking awake surgery (Table 1) if the lesion was near eloquent areas such as primary speech or motor cortex or tracts. Ultrasound was used throughout the surgery and at the end to compare it with the pre-resection trans-dural iU/S and the postoperative MRI. All procedures were performed by the same surgeon, who had previously undertaken in excess of 50 ultrasound guided cases, thus avoiding a 'learning curve' effect.

MR and Ultrasound images interpretation

Preoperative MRI (including image guidance sequences) was done one month or less before surgery. Tumour volumes were estimated for both modalities using a geometric formula (prolate ellipsoid) based on maximum sagittal, coronal, and anteroposterior diameters:

1. A: greatest dimension in Axial view,
2. B: greatest dimension in coronal view, and
3. C: greatest dimension in sagittal view.

A postoperative contrast MRI was done within 48 hours of the surgery. For high grade tumours, extent of resection was defined as the extent of resection of enhancing tumour, for low grade (non-enhancing) tumours

extent of resection was defined as the extent of resection of high FLAIR signal. Tumour volume was measured on the MRI by taking the 3 directly orthogonal diameters (D1, D2, D3) then estimating volume as: $V = \pi / 6 \times D_1 \times D_2 \times D_3$. We utilised the ellipsoid technique as it is not possible to calculate true volumetric measurements on the 2d ultrasound images, this would require the 3d ultrasound systems linked to an image guidance platform that are correspondingly more expensive and less widely available. This study sort to evaluate a basic 2d i/US system that may be available as a solution in resource poor healthcare systems and thus we utilised the same assessment method for resection volume for both modalities.

A percentage volume comparison was performed between preoperative and postoperative MR images to evaluate the extent of resection of the lesion and to compare such extent with that calculated based on the ultrasound pictures taken at the beginning and end of the tumour

resection. Volumetric measurement by the same method to allow direct comparison was also performed on iU/S images. Abnormalities interpreted as haemorrhage, calcification or surrounding oedema were identified and recorded. iU/S images were recorded at the end of excision before placement of any fibrillar surgical (haemostatic agent) as these agents can potentially be difficult to distinguish from residual tumour or haemorrhage.

Statistical Analysis

Data were analysed with appropriate statistical tests using the Statistical Package for Social Science (SPSS Inc., Chicago, version 21). Continuous variables e.g. age, were analysed using t-test; Chi square or Fishers exact were used for categorical variables and Spearman's test for correlation. Multiple linear regression was used to control for the effects of variables in the overall analysis.

Table 1: Demographics and characteristics of Group A (No i/US) and Group B (i/US) showing percentages and statistical significance of comparisons between the groups.

Variable		No i/US	i/US	P value
Number of patients		41	33	
Sex (male)		20 (48.8%)	19 (57.6%)	0.451 (chi2)
Age (mean)		57.5	52.6	0.163 (t-test)
Co-morbidity present		26 (60.6%)	20 (63.4%)	0.804 (chi2)
Seizures pre-op		23 (56.1%)	13 (39.4%)	0.153 (chi2)
Neurological deficits present pre-op		16 (39.1%)	17 (51.5%)	0.064 (chi2)
Percentage undergoing redo surgery		5 (12.2%)	3 (9.1%)	0.669 (chi2)
5ALA used		8 (19.5%)	16 (48.5%)	0.008 (chi2)
Awake surgery undertaken		1 (2.3%)	3 (9.1%)	0.208 (Fishers)
Histological WHO grade	2	6 (14.6%)	6 (18.2%)	
	3	4 (9.8%)	2 (6.1%)	
	4	31 (75.6%)	25 (75.8%)	0.799 (chi2)
IDH1 R132h status (mutant tumours)		11 (26.8%)	11 (33.3%)	0.543 (chi2)

No iU/S; no use of intraoperative ultrasound, iU/S; intraoperative ultrasound, 5ALA; 5 Aminolevulinic acid, IDH1 R132h; Isocitrate dehydrogenase -1 mutant R132H

Results

Characteristics for the control and ultrasound groups are summarised in (Table 1). The mean age of patients was 55.34 years (range 19-83 years), 39 of 74 (52.7%) patients were male and 72 (97.3%) were right-handed. 66 out of 74 (89.2%) had de novo lesions while 8 (10.8%) had recurrent lesions. 22 tumours were frontal (29.7%), with 19 parietal (25.7%), 14 (18.9%) temporal and 1 cerebellar (1.4%). 36 patients (48.6%) presented with seizure, 20 with headache (27.03%) and 33 (44.6%) with neurological deficit. Speech was affected in 17 patients (23%). 6 patients (8.1%) presented with GCS <15. 24 (32.4 %) had midline shift, and 1 (1.4%) had hydrocephalus.

There were 33 patients (44.6%) in the prospective i/US group and 41 (55.4%) in the retrospective no i/US group. 4 patients (5.4%) had awake surgery because of location of the lesion in a dominant eloquent area. We used 5ALA fluorescence guided surgery in 24 patients out of 74 (32.4%) as they appeared high grade and suitable for maximal resection on the preoperative MR images. Use of 5ALA was the only significantly different variable between groups with a higher proportion of patients in

the ultrasound group receiving 5ALA. All tumours were astrocytomas; 56 (75.7%) were grade 4, 12 (16.2%) were grade 2, and 6 (8.1%) were grade 3. 52 (70.3%) were wild type IDH-1, and 22 (29.7%) were R132H mutated IDH-1. As regards MGMT methylation, 13 (17.6%) were unmethylated, 6 (8.1%) had low level of methylation and 51 (68.9%) were not tested. 28 (37.8%) had intact ATRX gene, 7 (9.5%) had lost expression, and in 39 (52.7%) ATRX testing was not performed.

Using Spearman's correlation test, it was found that extent of resection ascertained on ultrasound images was strongly correlated with the extent of resection as calculated on the postoperative MR images ($P = \text{value} < 0.001$), suggesting that direct comparison between modalities is possible. In 28 out of 33 (84.84%) patients with gliomas, the borders of the tumour were well defined on iU/S with a sharp demarcation between hyperechoic tumour and hypoechoic normal brain. Borders of the tumour on the ultrasound images were poorly defined in 5 (15.1%). Margins were regarded as well defined, if the remnant was delineated exactly and fully corresponded to features on postoperative MR images; and poor, if a suspicious area existed but could not be confidently differentiated from artefacts or from normal brain tissue. Representative

images for pre and post-resection for a low-grade glioma (Figure 1) and a high-grade glioma (Figure 2) are shown to illustrate the typical

appearances gained during the resection and upon which the resection calculations were based.

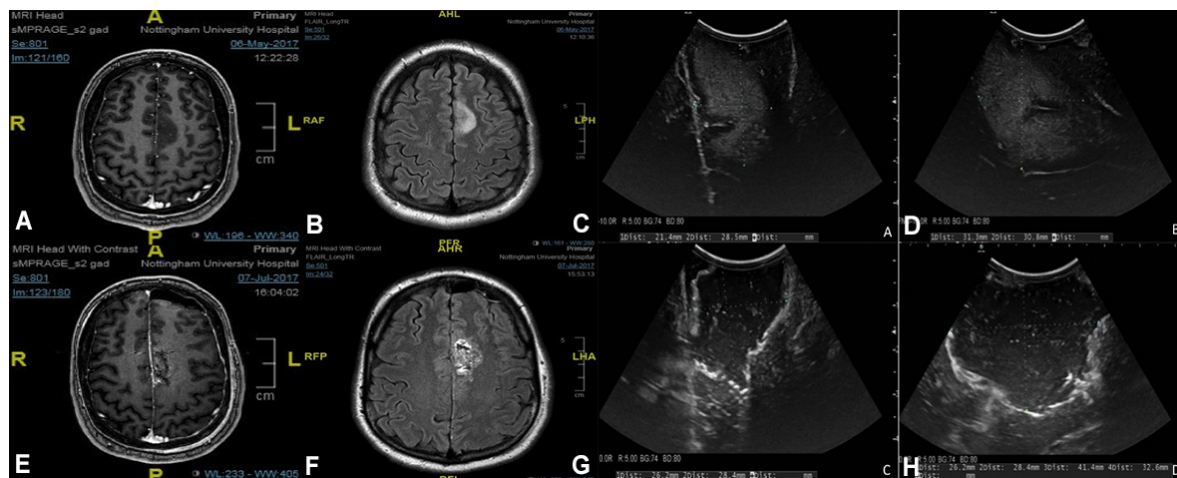


Figure 1: Ultrasound guided resection of a low-grade glioma: (A) axial preoperative T1 sequence with gadolinium contrast showing left parasagittal hypointense lesion. (B) axial preoperative FLAIR sequence showing left parasagittal hyperintense signal lesion. (C) Intra-operative pre-resection ultrasound image showing coronal dimension of the lesion. (D) Intra-operative ultrasound image showing pre-excision sagittal dimension of the lesion and its relation to falx. (E) postoperative T1 sequence with contrast showing complete resection of the lesion with no residual disease. (F) postoperative flair sequence showing resection cavity with complete resection. (G & H) showing post-excision coronal (G) and sagittal (H) views of the resection cavity and hyper echoic signal around edges of the resection cavity representing localized edema and blood products.

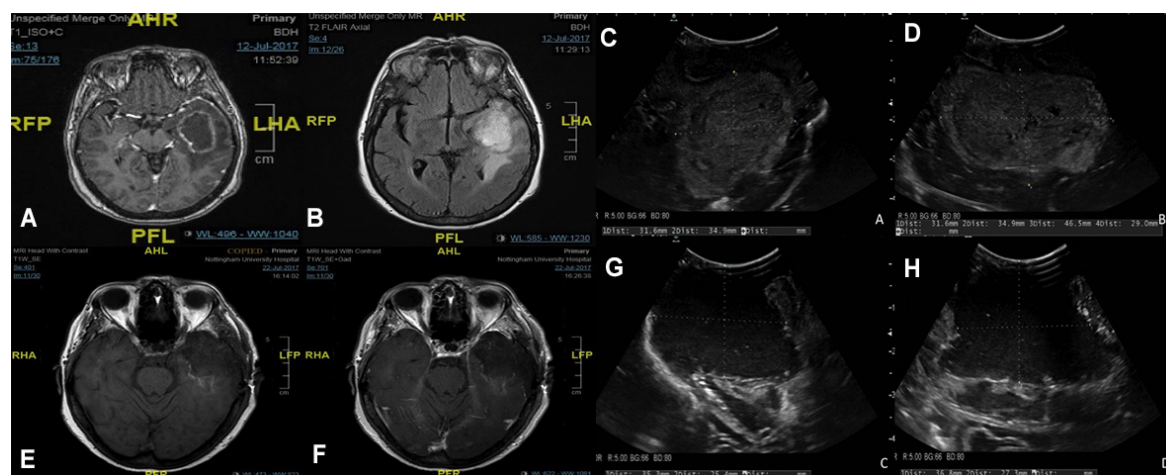


Figure 2: Ultrasound guided resection of a high-grade glioma: (A) axial preoperative T1 sequence with gadolinium contrast showing left temporal cystic lesion with enhancing wall. (B) axial preoperative flair sequence showing left temporal lesion with surrounding edema. (C) intraoperative ultrasound image pre-resection showing coronal view of the lesion and relation to skull base (white line on right of image). (D) intraoperative pre-resection ultrasound image showing sagittal appearance of the lesion. (E&F) – postoperative MRI T1 sequence with gadolinium showing complete resection of the lesion with some blood at posterior edge of the resection cavity but no contrast enhancement. (G&H) – intraoperative ultrasound images post-resection in coronal (G) and sagittal (H) planes showing resection of original lesion and hyperechoic change in surrounding tissue, likely representing surgically induced changes.

The mean extent of resection calculated on the ultrasound images was 96.1% (+/- 1.0% SE). Median extent of tumour resection as assessed on the ultrasound pictures was 99%. Mean extent of resection for all patients as calculated based on the post-operative MRI was 95.7% (+/- 1.2% SE) (range 30.2% to 100%). Mean resection rate in patients who received i/US (calculated on post-op MRI) was 97.7% compared to 93.9% in patients who did not receive i/US, a difference of 3.8%, but the p value for the difference was not significant (0.09 t-test). For the group undergoing ultrasound, thus allowing comparison between ultrasound and MRI post-op images, the mean extent of resection on the

postoperative MR was 97.75%, compared to 96.12% as calculated using i/US images, a mean difference of 1.63% with no significant difference between methods ($p=0.723$ t-test).

Interestingly, the use of intraoperative ultrasound was associated with a significant increase in the number of patients in whom 95% extent of resection was achieved (88% of patients with ultrasound versus 66% of patients without ultrasound) (Fisher's exact test p value 0.033). On multiple linear regression analysis to control for the use of different modalities e.g. 5ALA, iU/S and awake surgery, no significant correlation

between any of these variables alone and the overall extent of resection on the postoperative MR was observed (iU/S $P=0.266$, Awake surgery $P=0.953$, 5ALA $P=0.208$).

5 cases out of 33 (iU/S group) (15.2%) developed complications postoperatively but these were not related to the use of ultrasound, whereas 9 out of 41 (non ultrasound group) (21.9%) developed complications postoperatively. Complications included visual impairment, dysphasia and cognitive impairment, with all morbidity being temporary and self-limiting, with full resolution of all complications by 3 months. We did not find any significant correlation between use of the ultrasound and rate of a complication occurring (Chi squared P -value 0.846). The Doppler function allowed identification of important vascular relations, which could help to avoid injury to such vessels. Proximity to significant vessels and visualization of significant vessels on Doppler flow was identified in 100% of cases.

Discussion

Several groups have studied the accuracy of intraoperative ultrasound in brain tumour resection, from different perspectives. However, drawing conclusions from many of these studies were hampered by limitations, including small sample sizes, short follow up, lack of controls and detailed outcome assessments. One group evaluated ultrasound guided resection by evaluating the preoperative MR images of twenty-two brain tumours and comparing the intraoperative ultrasound images with the surgical and pathological findings [9]. They found that ultrasound estimation of tumour volume agreed well with tumour volume as estimated by T2 pre-operative MRI, and both these techniques appeared superior to estimating volume of low-grade glioma based on T1 sequences alone. Another group examined the cavity borders of 32 tumors after resection with a 7 MHz intraoperative probe. Any echogenic region >5 mm in thickness extending from the surgical cavity into the brain substance was taken as the sonographic criterion for residual tumor. A continuous echogenic rim <5 mm was considered normal. Results were correlated with gadolinium-enhanced MRI obtained within 48 h after surgery [10]. They demonstrated that there was overall good agreement between modalities, but that small volume residuum could be left if the 5mm cut-off was adopted. We found that by resecting to the margin of abnormal ultrasound signal, residuum characteristics were very similar to post-operative MRI. Another group prospectively studied the reliability of ultrasound-controlled tumour resection (36 gliomas and 34 metastases) in comparison with the postoperative MRI, reporting good reliability of iU/S in defining the borders of tumors and in assessing the extent of their resection, with similar levels of ease of definition of tumour borders [11]. In our experience delineation of anatomical landmarks clearly varies depending on the location of the tumour with ventricles and sylvian fissure being the most easily visualized and useful for tumour in their vicinity. Ultimately, visualization of tumour extent is independent of delineation of anatomical landmarks and inability to visualize them did not halt resection in any case.

In our series, the extent of resection on the ultrasound images was strongly correlated with the extent of resection on the postoperative MR images (Spearman correlation P -value <0.001). This suggests that intraoperative ultrasound provides a realistic and accurate alternative to

intra- and post-operative MRI. Extent of resection as visualized by ultrasound intra-operatively can be expected to correspond very closely to that which would be seen on post-operative MRI. We found that the mean extent of resection on the ultrasound images was 96.12 % while on the postoperative MR was 97.75 % with a difference of only 1.63%. In settings lacking access to intra- or post-operative MRI, intra-operative ultrasound will provide a comparable technique to assess extent of resection and as an adjunct to maximize resection. This is in agreement with results published by Erdoğan et al 2005 [10]. They found a strong inter-method agreement between extent of resection on intraoperative ultrasound and postoperative MRI (kappa value=0.72). One important difference with his study is that they looked at different types of lesions, not only gliomas as we did. Hammoud et al also showed in their study that tumour volumes measured post excision using IOUS and MR imaging were significantly correlated for gliomas ($p = 0.97$) [11]. Smith et al 2016 confirmed also the significant correlation of the intraoperative ultrasound results with postoperative MRI results ($\phi = 0.726$; $p = <0.001$). These results match our results with the exception that all the patients recruited by Smith were in the paediatric age group [12]. Moiyadi et al 2016 in their study stated that overall concordance was seen in 64 cases (82.5%) but used direct navigated 3D ultrasound instead of 2D that we used [13]. All these results support the conclusion of a meta-analysis that was published in 2016 [15]. In this the postoperative MR in all included studies was used to assess the extent of surgical resection; the concordance rate between iU/S and postoperative MRI was 82%, the false positive rate of iU/S was 9% and the false negative rate was also 9%.

Interestingly, in our study, the use of iU/S was associated with a significant increase in the proportion of patients in whom 95% extent (i.e. complete or near complete) resection was achieved (T-test p value = 0.033), though this was non-significant on linear regression when controlling for other variables, possibly because overall patient numbers in this study are fairly low and rates of 5ALA usage differed. In a series of 90 patients with intracranial tumours (of which 51 were HGG and 17 were LGG), Moiyadi et al. found that iU/S improved resection in 59% of the patients operated and in 21% iU/S showed residual tumor that was not resected due to vicinity of eloquent tissue [15].

We tried to compare the extent of resection of gliomas achieved with the aid of the intraoperative ultrasound with that with intraoperative MRI by looking at the literature. A small number of studies have suggested that iMRI helps to maximize extent of resection (EOR) in glioma surgery. Hatiboglu et al 2009 recruited 27 GBM patients who were operated on with 1.5T iMRI guidance and found after iMRI that 48% required extended tumor resection. The final gross total resection (GTR) rate was increased from 44% to 89% [16]. The EOR increased from 63% to 100% for patients who had non-enhancing grade 1 gliomas, but there were not enough patients for adequate statistical analysis. Wu et al 2014 conducted a prospective, randomized trial to evaluate the effect of 3.0-T Intraoperative Magnetic Resonance Imaging in cerebral glioma surgery. Intraoperative iMRI updated image guidance led to extended tumour resection in 17 of 44 participants (38.64%) [17]. Senft et al 2011 enrolled 58 patients in a randomized controlled trial. More patients in the intraoperative MRI group had complete tumour resection (23 [96%] of 24 patients) than did in the control group (17 [68%] of 25, $p=0.023$) [6]. The effectiveness of intraoperative ultrasound in the literature in

increasing the extent of resection of gliomas thus seems similar to that reported for intraoperative MRI.

We found the evaluation and interpretation of dynamic ultrasound images far superior to static images. Different angles and scan planes may give differing information and it is important to scan through the whole of the tumour and surrounding brain, in the same way as MRI will scan through in a series of slices and planes. Surgical experience in interpreting images and relating them to pre-operative MRI is required and there is certainly a learning curve involved with interpreting the i/US images in our experience. Despite the fact that the ultrasound was not associated with a significant change in the rate of complications, we felt it provided a valuable tool in detecting important anatomical relation and proximity to the ventricles as well as its Doppler function, which allowed identification of important vascular relations, which could help to avoid injury to such vessels. As more patients achieved complete or near complete resection with i/US, the comparable complication rate suggests that this increased resection can be achieved safely without added risks.

Although we currently do not have iMRI in our unit and were thus unable to perform a direct comparison, it is likely that the length of operation is significantly shorter with i/US compared to iMRI. Each ultrasound scan adds less than 3 minutes to the procedure, and we would typically perform around 5 scans per operation. iMRI scanning in the literature typically adds 60 min to conventional surgery [6]. Ultrasound eliminates the need for shielding, intraoperative transfers and specialized equipment in the operating room.

The limitations of our study include that the number of patients recruited was relatively small and the use of a historical control group, limiting the statistical significance of the increased extent of resection seen with i/US. The i/US group had an increased rate of usage of 5ALA as this technique was introduced to our unit during the duration of the study. Part of the increased rate of greater than 95% resections may be attributable to 5ALA, but this technique was not used for any of the low-grade gliomas resected in this study. Survival benefit was not examined due to the prospective nature of the study (most patients in the prospective arm are still alive) and the limited numbers recruited. It must be noted that in this study, the ultrasound findings were not confirmed by histological sampling but with respect to the postoperative MR imaging. All surgery was performed by the same surgeon, though the learning curve could alter the results of the outcomes in other settings. The operating surgeon was experienced in the use of i/US (greater than 30 cases) prior to the start of the study and had thus likely already completed his learning curve. We tried to match the 2 (prospective and retrospective) groups by matching the population recruited in the study and the surgical tools used apart from the use of ultrasound.

Conclusions

The use of intra-operative ultrasonography could provide a reasonable and less costly alternative to intra and post-operative MRI, by improving the extent of resection in glioma surgery. Our study suggests that i/US can be safely implemented as an effective adjunct to measure and improve resection rates for intrinsic glioma surgery, especially in healthcare settings without easy access to MRI.

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