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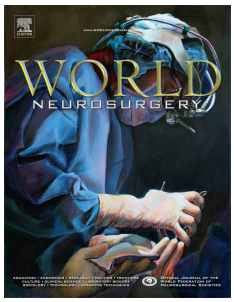

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Intraoperative ultrasound (IoUS) guided resection of Gliomas: A Meta-analysis and review of the literature.

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Abstract:

Introduction: Image guided surgery has become standard practice during surgical resection, using preoperative MRI. Intraoperative-ultrasound has attracted interest, because of its perceived safety, portability, and real-time imaging. This is a meta-analysis of intraoperative-ultrasound in gliomas.

Methods: Critical literature review and meta-analyses, using MEDLINE/PubMed service. The list of references in each article was double-checked for any missing references. We included all studies that reported the use of ultrasound to guide glioma-surgery. The meta-analyses were conducted according to statistical heterogeneity between the studies using Open MetaAnalyst Software. If there was no heterogeneity, fixed effects model was used for meta-analysis; otherwise, a random effect model was used. Statistical heterogeneity was explored by χ^2 and inconsistency (I^2) statistics; an I^2 value of 50 percent or more represented substantial heterogeneity.

Results: Casting a wide-net search caught 19,109 studies that might be relevant, of which 4,819 were ultrasound in neurosurgery. 756 used ultrasound in cranial surgery, of which 24 studies used intraoperative ultrasound to guide surgical resection and 74 to guide biopsy. Fifteen studies fulfilled our stringent inclusion criteria, giving a total of 739 patients. The estimated average gross total resection rate was 77%. Furthermore, the relationship between extent of surgical resection and study population was not linear. GTR was more likely under IoUS when the lesion was solitary, subcortical, and no past history of surgery or radiotherapy. IoUS image quality, sensitivity, and specificity, positive & negative predictive values deteriorated as surgical resection proceeded.

Conclusion: IoUS guided surgical resection of gliomas is a useful tool for guiding the resection and of value in improving the extent of resection. IoUS can be used in conjunction with other complementary technologies that can improve anatomical orientation during surgery. Real-time imaging, improved image quality, small probe sizes, repeatability, portability, and relatively low cost made IoUS a realistic cost effective tool that complements any existing tools in any neurosurgical operating environment.

Keywords: Glioma, Image guided surgery, neuronavigation, Intraoperative ultrasound.

Introduction:

Gliomas are the commonest primary brain tumours and their prognosis is dependent upon the grade of glioma [1]. Maximum safe surgical resection, when possible, has been accepted as the primary therapy in most cases and the extent of surgical resection has been established as an independent prognostic factor. Following gross total resection (GTR) the 5 and 10 year survival rates for low-grade gliomas (LGG) have improved to 97% and 91% respectively [2]. However, the prognosis of high-grade gliomas (HGG), though have improved significantly in recent years, remains bleak with a median survival of merely 16 months [3]. To achieve maximum safe surgical resection, image guided surgery (IGS) has been deployed in the last three decades and advances in neuroimaging, stereotaxy, and computer technology, have permitted neurosurgeons to plan and execute surgical approaches with greater accuracy and precision.

Several technologies have been developed to aid neurosurgeons to plan and execute maximum safe surgical resection of gliomas. In the forefront of these techniques the use of image guided surgery (IGS), Intraoperative MRI (IoMRI), Intraoperative Ultrasound (IoUS), and Fluorescence image guided surgery (FIGS). The biggest drawback of IGS is its dependence on preoperatively acquired images to navigate during surgery. Brain shift that occurs when the dura is opened due to CSF drainage, tissue removal, and gravity introduces significant inaccuracies that render IGS useless intra-operatively. Furthermore, without further imaging there is no way of real-time feedback about the extent of surgical resection. Hence, IoMRI, FIGS and IoUS were introduced. IoMRI restricts the environment of surgery because of ferromagnetic interference, interruption of the workflow each time an MRI is performed and its expensive upkeep. FIGS, using 5-aminolevulinic acid (ALA) induced

fluorescence, is cost effective in HGG. However, it cannot be used in LGG surgery where it is most needed [4]. IoUS was put forward as a complementary technology to overcome some of the aforementioned limitations of IGS. Therefore, we reviewed the literature to realize the benefits and constraints of IoUS during surgical resection.

Materials and Methods:

The medical literature was searched extensively, beginning with basic searches of the MEDLINE/PubMed service of the US National Library of Medicine, using the MeSH (medical subject heading) terms "ultrasound," "image guidance," "glioma," "brain," "high grade glioma," "low grade glioma" "neurosurgery," and "surgery" in various combinations. Furthermore, Web of Knowledge database, BIOSIS Previews, Cochrane library, and Web of Science were searched.

Each article of interest was screened and its reference list was double checked to make sure that no relevant article was missed. The Internet itself was searched for leads to articles appearing in journals not indexed in these databases. We restricted the literature review to the last 10 years (2005 to 2015) based on SIGN (Scottish Intercollegiate Guidelines Network) review criteria [5]. Studies with information about diagnosis, intended extent of resection and postoperative evaluation of extent of resection by neuroimaging were considered. We included all studies that fulfilled the following inclusion criteria: glioma surgical resection, IoUS was used as a guidance tool, study population was 10 patients or more, and assessment of the extent of surgical resection was confirmed by postoperative imaging. Studies that reported mixed series of patients were included as long as the number of glioma patients in the series was ten or more and we included data for the glioma patients only. We excluded studies that were not in English, duplicate publications or failed one or more of our inclusion criteria. The remaining studies were assessed objectively against SIGN criteria [5].
The meta-analyses were conducted according to statistical heterogeneity between the studies using Open MetaAnalyst Software version 0.1 for Mac. If there was no heterogeneity, fixed effects model was used for meta-analysis; otherwise, a random effect model was used. Statistical heterogeneity was explored by χ^2 and inconsistency (I^2) statistics; an I^2 value of 50 percent or more represented substantial heterogeneity. Furthermore, GTR rate was analysed to determine the success of the surgery, and to ascertain the reliability of the results and determine whether the number of patients involved in each study was related to the overall GTR rate, a correlation coefficient was calculated. The average GTR rate and correlation coefficient were calculated using Microsoft Excel 2010.

Results:

The initial wide-net search produced a total of 19,109 publications dealing with surgical ultrasound (Figure 1). Restricting the search to neurosurgical applications reduced the number of publications to 4,819 studies. The main focus of 4,063 publications was on extracranial applications and the remaining 756 focused on cranial applications, of which 98 were dedicated to IoUS guided glioma surgery. IoUS was used to guide biopsy in 74 studies and to guide surgical resection in twenty-four studies. These 24 publications were reviewed critically against our inclusion criteria. Only fifteen studies fulfilled our inclusion criteria. Table 1[6-12] details the reasons of exclusions of nine studies and Table 2[13-27] details summaries of the included fifteen studies in this meta-analysis.

Insert Figure 1 and Tables 1 & 2 here

IoUS and gross total resection (GTR):

The GTR was defined as the absence of any residual enhancement on postoperative volumetric enhanced MRI performed within 72 hours of the surgical resection. The total number of patients included in this review was 739 patients. The meta-analyses demonstrated an estimated average GTR rate of 77% (95% CI was 67.1 to 86.9). The studies by their nature were very heterogeneous ($I^2 = 92.598$, $p < 0.001$) (Figure 2). The correlation coefficient between GTR rate and study population was -0.2464, which indicated non-linear relationship, suggesting that GTR rate was not greatly improved by increasing the number of operations. Postoperative MRI

in all included studies was used to assess the extent of surgical resection; the concordance rate between IoUS and postoperative MRI was 82%, the false positive rate of IoUS was 9% and the false negative rate was also 9%.

Insert Figure 2 here

There were differences in the GTR rates of IoUS in HGG and LGG; enough details of HGG was reported in six studies with an estimated average GTR rate of 71.9% (95% CI was 64-79.7). Heterogeneity in these studies was not statistically significant (I^2 = 49.778, p 0.052) (Figure 3A). The GTR rate was 88% in resectable lesions; single supratentorial in non-eloquent brain. The GTR rate in LGG was reported less frequently (three studies); the estimated average GTR rate in LGG was 78.1% (95%CI 67.1-89.1). These studies were not heterogeneous (I^2 = 0, p 0.380) (Figure 3B). Furthermore, in 59% of procedures, IoUS prompted surgeons to remove residual tumour tissue from the resection cavity.

Insert Figures 3A & 3B here.

IoUS and lesion-localization, sensitivity & specificity:

Six studies reported the percentage of procedures, where IoUS was successful in identifying the exact location of the intradural lesion after craniotomy; the mean localization rate in these studies was 100%. However, image quality was considered poor in 8% of procedures. The sensitivity of IoUS was defined as the number of times IoUS identified residual tumour tissue and subsequent resection and histopathology confirmed the tissue was in fact tumour. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of IoUS were best before the start of surgical resection (95%, 95%, 98%, and 90% respectively). All four values deteriorated as surgery proceeded; a sensitivity of 88%, specificity of 42%, PPV of 73% and NPV of 67% during surgery was reported and at the end of surgery the corresponding values were 26%, 88%, 62%, and 62% respectively.

Clinical outcome of patients, who underwent surgery under IoUS guidance:

Survival data was not reported in most of the studies included in our analyses, and when reported other confounding factors played a significant role such as; patient selection, small sample size, lack of controls, and varied adjuvant therapies. One study reported a 6-month survival of LGG matched controls (IoUS was not used) as 96.7%, the 1-year survival was 73.3%; and 2-year survival was 53.3%. In the study LGG-group, where IoUS was used to navigate and guide surgical resection, survival rates at 6 months, 1-year, and 2-years were 98.0%, 96.1%, and 88.2%, respectively. In the same study the control and study HGG-groups, survival rates at 6 months, 1-year, and 2-years were 83.3% versus 93.4%, 43.3% versus 59.2%, and 13.3% versus 32.8% respectively. There was no significant difference in survival rates between study and control groups at 6-months ($p > 0.05$). However, the 1-year, and 2-years survival rates of the study groups of LGG and HGG, where IoUS was used, were significantly better than the survival rates of the controls ($P < 0.05$). Worsening neurological status in patients, where IoUS was used, was reported in 11.3% (8% to 13%). The majority of patients were unchanged neurological postoperatively and 19% were better off.

Type of IoUS used:

Most studies used 3D mode IoUS such as the SonoWand® (SonoWand, Mison,Trondheim, Norway), equipped with a 5 MHz probe with tracking, which can be used in 2D mode in conjunction with preoperative MRI-based IGS system[14,15,21,23]. Other systems used included high-frequency (5-10 MHz) ultrasound probes with a 180 Plus system (SonoSite, Inc, Bothell, WA)[18], an SSD-alpha10 system (Aloka Co, ltd, Tokyo, Japan), Seimens Omnia Sonoline and Capasee II (Toshiba, Japan)[19]. 3D IoUS mode was used in 7 studies, and 2D mode in the rest. The estimated average GTR rate using 2D IoUS was 84.3% compared to 70.9% using the 3D navigated IoUS, the difference was not statically significant (p 0.699).

Discussion:

Ultrasound imaging has been available for years before CT and MRI. However, its use in cranial imaging was

hindered by the rigid bony structure of the skull that impedes ultrasound waves. This limitation is no longer an issue after the craniotomy, and the main limitations during cranial surgery were ultrasound probe-size, which was too big for the size of craniotomy and image quality, which was poor compared to CT or MRI images. In recent decades the quality of ultrasound imaging improved significantly with 3D acquisition and sophisticated computer technology, and the ultrasound probe-size became more user friendly in craniotomies[6-27]. Furthermore, the extent surgical resection in low-grade gliomas (LGG) and high-grade gliomas (HGG) have been shown to be an independent prognostic factor for progress free survival (PFS) and overall survival (OS)[27-37]. Therefore, the aim of surgical treatment of gliomas is to achieve safe maximum surgical resection whenever possible and preserve normal function and good quality of life. However, maximum safe surgical resection remains a challenge because gliomas are locally invasive and tumour cells infiltrate beyond the normal apparent tumour margins. Improvements in Ultrasound technology and accumulating evidence in support of maximum safe surgical resection of gliomas ignited new interest in IoUS, to overcome the limitations of IGS. IoUS was used in conjunction with IGS to correct errors introduced by brain shift. Brain shift varied from 2 mm to 25 mm depending upon the location and size of lesion[24]. The main advance in IoUS technology was the development of small ultrasound probes for superficial lesions (7.5-10 MHz) and for deep lesions (3-5 MHz)[19]. An excellent example of integration of IGS and IoUS technologies is the SonoWand®. The SonoWand® system can be used as an IGS system based on preoperative MRI images and for 2D or 3D IoUS imaging. Real-time 2D IoUS imaging can be performed as with a conventional ultrasound scanner, but with the optional feature of comparison with corresponding slices of preoperative 3D MRI imported into the SonoWand® system. The integration of ultrasound imaging and IGS-navigation technology enabled acquisition of 3D ultrasound volumes, typically generated from 200 to 300 image slices. The ultrasound image volumes can be readily acquired when needed during surgery, and the data are displayed with preoperative MRI data on the navigation monitor when using tracked tools such as a pointer or ultrasound aspirator. 3D navigation may offer easier anatomical orientation due to displays of images in an orthogonal (patient-related slices) or reformatted according to the position of the tracked tool (tool-related slices). The SonoWand® comes with two flat-phased arrays (FPA) ultrasound probes, one FPA 5 (4–7 MHz) and a smaller FPA 10 (5–10 MHz) probe. The newer system (SonoWand® Invite) comes with a third larger FLA (5–14 MHz) probe[21]. A random effect model was used in our study because of heterogeneity ($I^2 > 50\%$, $p<0.05$)), and the estimated overall GTR rate was 77% using IoUS. The estimated average GTR rate of HGG was 71.9% compared to GTR rate of 78.1% in LGG (Heterogeneity was not significant in the HGG and LGG data sets, $I^2 < 50\%$, $p >0.05$). Image quality and the operators' learning curves played an important role in IoUS GTR rates. One study reported IoUS image quality was good enough to delineate the margins of HGG in 83% of cases and poor IoUS image quality was more likely in patients with previous surgery (p-=0.002) or in patients who had previous radiotherapy (p=0.001) [21]. Patient selection therefore played a significant role in the outcome of GTR in these studies, for example the GTR in patients, with single supratentorial enhancing lesions that did not invade the basal ganglia or corpus callosum and had a preoperative Karnofsky performance score of 70 or better, was 2.5 times better than that of the whole group[21]. The predictors of GTR were explored in a multivariate analysis model and four significant prognostic factors were found; aim of surgery was GTR ($p <0.001$), single lesion ($p=0.003$), good or medium quality IoUS images ($p=0.026$), and non-eloquent lesion-location ($p=0.015$). Other factors, which were significant on univariate analysis that dropped out in the multivariate model, included small lesion volume, Karnofsky performance of 70 or better, no prior radiotherapy, primary surgery, and no extension into the basal ganglia or the corpus callosum[21]. Furthermore, the quality and resolution of IoUS images decreased as the surgical resection proceeded because of artefacts introduced by surgical manipulation[22]. With experience, strategies have been developed to overcome the majority of these problems[38]. A much bigger problem with IoUS was getting familiar with anatomical orientation. Traditionally B-mode ultrasound displayed 2D ultrasound images in a planar format dependent on the ultrasound probe used with the view limited to the sector of sonication, which is often oblique rather than axial. Anatomical disorientation was amplified by lack of easily identifiable brain-landmarks within small exposures. However, real-time IoUS imaging during surgery, 3D IoUS and precalibration and integration of IoUS with IGS improved anatomical orientation[4,13-27]. Furthermore, specialised motorised IoUS probes or reconstruction of 2D IoUS images acquired by tracked probes produced good quality 3D images improving anatomical orientation during surgery[5,39-43]. Without good quality intraoperative imaging surgeons often over-estimated the extent of surgical resection. In one study using 3D IoUS feedback, surgeons esimtated the extent of surgical resection correctly in 59%. The main reasons of over-estimates were poor intraoperative image quality[21]. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of IoUS were best before the start of surgical resection (95%, 95%,

98%, and 90% respectively). All four values deteriorated as surgery proceeded; a sensitivity of 88%, specificity of 42%, PPV of 73% and NPV of 67% during surgery was reported and at the end of surgery these figures were 26%, 88%, 62%, and 62% respectively[23]. In our meta-analyses, the estimated the average GTR rates of HGG and LGG were 71.9% and 78.1% respectively, which were comparable to the reported GTR rates using other neuronavigation technologies. A retrospective study compared IGS with standard surgical resection in HGG reported a GTR rate of 64% in the neuronavigation group compared to 38% in the standard surgery group[44]. On the other hand a randomised controlled study reported a GTR rate of 31% using IGS in glioblastoma (GBM) compared to 19% with standard surgery[45]. A multicentre randomised controlled study comparing FIGS with standard IGS in HGG reported 64% GTR rate in the FIGS group compared to 36% in the IGS group. A meta-analysis of FIGS, using ALA- induced fluorescence, in 565 GBM-resections reported a GTR rate of 75.4% (95% CI 67.4-83.5)[47], which is comparable to the findings of this meta-analysis of IoUS. IoMRI using low field and high field magnets have been in use for some time, the results of IoMRI in gliomas varied considerably; GTR rates of 31% using 1.5T system[48], 67% using 0.2T system[49], and 71% using 0.15T system[50] were reported. These varied results were unlikely to be related to the strength of the IoMRI but more likely due to patient selection. One small study compared 2D navigated IoUS to low field IoMRI in 26 patients reported IoMRI was superior[51]. Another study compared high field IoMRI and linear array IoUS in 44 grade II astrocytoma biopsies to evaluate their accuracy and found imaging results of linear-array IoUS significantly correlated to high field IoMRI images (Spearman's Rho $p < 0.009$), the specificity of both modalities was 67%, and the sensitivity of IoMRI was higher than IoUS (83% versus 79% respectively)[52]. Another randomised study of GTR between IGS and IoUS was used to compare GTR of 95% or more in 93 HGG; the IoUS sensitivity and specificity were higher than IGS alone, the sensitivity of IoUS was superior in newly diagnosed HGG compared to recurrent HGG, and there was no significant difference in the GTR rates between IoUS and IGS[53]. One of the major limitations of IoUS was that it cannot assist in the size or location of the skull opening and hence it is best used in conjunction with other IGS technologies. Once the craniotomy was performed, IoUS was very useful in planning and executing the dural opening, the cortical incision, and identifying surrounding critical structures[29]. HGG Forty % of lesions were clearly identifiable with clear margins on ultrasonography,
Furthermore, in 59% of cases where IoUS imaging was performed to guide the extent of surgical resection, IoUS prompted more tumour resection[15]. However, not all gliomas are suitable for GTR, for example in the same study 21% of cases IoUS demonstrated residual HGG and the surgeon decided to stop the resection because of tumour- proximity or invasion of eloquent brain tissue.
The accepted GTR-definition is the absence of residual enhancement in the resection cavity on postoperative enhanced 3D MRI images obtained within 72 hours of surgery[46]. However, from clinical perspective a resection of more than 98% of the enhancing lesion imparts the best survival outcome in HGG[1]. It is also accepted that enhanced MRI scan and almost all imaging modalities do not delineate the full extent of HGG. For example a study compering MRI with ultrasound images in HGG demonstrated agreement between the two modalities in only 40% of lesions with lesions in average 18.9% larger in MRI images[54]. Furthermore, a comparison of FIGS and MRI demonstrated that enhanced 3D MRI images underestimated the size of HGG[55].
Survival data of gliomas undergoing surgery using 3D-IoUS navigation could not be attributed to the surgical technique alone, as tumour grade, location, preoperative performance status, age, and the extent of surgical resection play a significant role. The 6-month survival of LGG matched controls, where IoUS was not used, was 96.7%, the 1-year survival was 73.3%; and the 2-year survival was 53.3%. In the same study LGG-group, where IoUS was used to navigate and guide surgical resection, survival rates at 6 months, 1-year, and 2-years were 98.0%, 96.1%, and 88.2%, respectively. In the same study the control and study HGG-groups, survival rates at 6 months, 1-year, and 2-years were 83.3% and 93.4%, 43.3% and 59.2%, and 13.3% and 32.8%. When comparing survival rates at 6-months, 1-year, and 2-years between the control and study groups, there were no significant difference at 6-months ($P > 0.05$), but survivals at 1- and 2-years were significantly different ($P < 0.05$), with those undergoing surgery with 3D navigated IoUS faired better[18]. The overall neurological functional outcome in patients undergoing GTR using IoUS was reported as; 8%- 13% worse, 19% better and the rest were unchanged from preoperatively[14,21]; the risk factors for bad outcomes were previous surgery or previous radiotherapy (8% in primary surgery versus 22% in reoperations)[21]. However, worsening neurological function could not be attributed entirely to the use of IoUS as similar incidence of side effects were reported with standard surgery, IGS, or FIGS alone. Although, scientists, economists, and healthcare policy makers would like to see prospective studies comparing IoUS with IoMRI, FIGS and IGS, these studies are difficult to undertake because these technologies are complementary to each other and often used in combination.
Our meta-analysis is as good as the underling studies upon which it was based, however, a key benefit of meta-

analyses is the aggregation of information leading to a higher statistical power and more robust point estimate than is possible from the measure derived from any individual study on its own. The limitations of the selected studies included; some studies had small sample sizes with less than 20 patients, short follow up, lack of controls and detailed outcome assessments, and varied adjuvant therapies, IoUS imaging lacked full-head display making anatomical orientation more tricky without the complement of IGS, the 3D IoUS images were not in real-time, image quality may have deteriorated due to surgical-field movement, surgical manipulation, surgical-cavity collapse, and tissue trauma, and IoUS interpretation by enlarge was operator dependent.

Conclusion: IoUS guided surgical resection of gliomas is a useful tool for guiding the resection and of value in improving the extent of resection. IoUS can be used in conjunction with other complementary technologies that can improve anatomical orientation during surgery. Real-time imaging, improved image quality, small probe sizes, repeatability, portability, and relatively low cost made IoUS a realistic cost effective tool that complements any existing tools in any neurosurgical operating environment.

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Figure legends:

Figure 1: Flow chart of the literature search of IoUS in glioma surgery.

Figure 2: Forest plot demonstrating meta-analysis model with all fifteen studies included, with GTR rate of 77% (95%CI 67.1%- 86.9%), Heterogeneity was significant (I^2 >50, p <0.05).

Figure 3: Forest plot demonstrating meta-analysis model; A= in HGG, GTR 71.9% (95%CI 64%- 79.9%), Heterogeneity was not significant (I^2 <50, p >0.05), B= in LGG, GTR 78.1% (95%CI 67.1%- 89.1%), Heterogeneity was not significant (I^2 <50, p >0.05) .

Table 1: Excluded Studies:

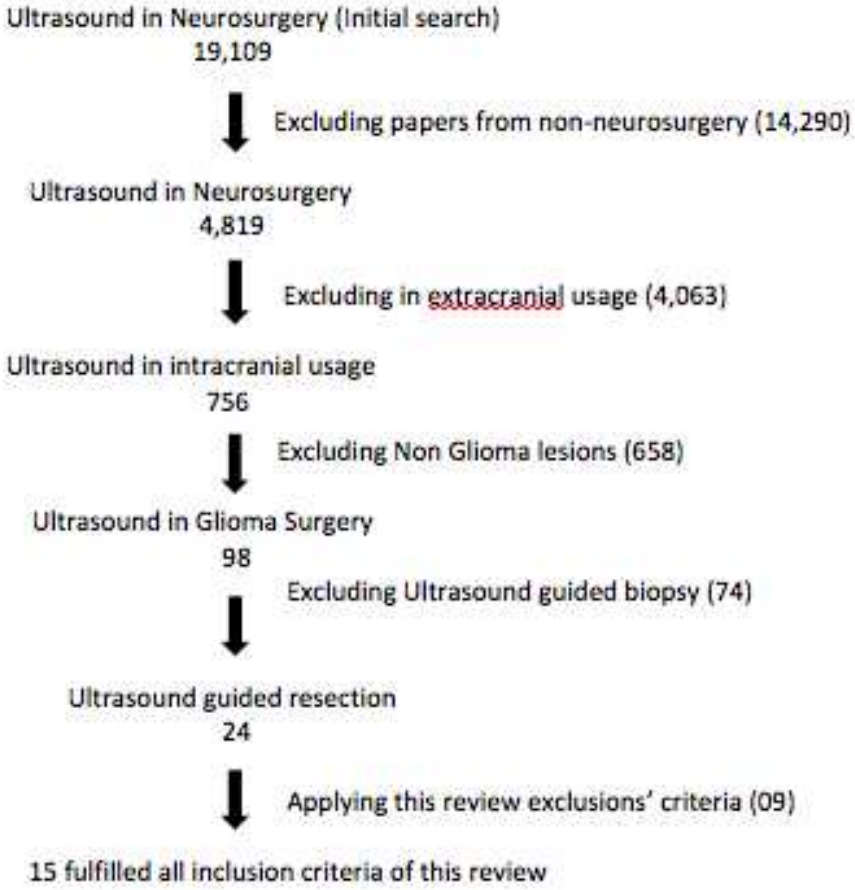
Author	Year of Publication	Reason for exclusion
Chacko AG et al [6]	2003	Less than 10 gliomas
Gulati S et al [7]	2009	Incomplete data.
Enchav Y et al [8]	2006	Incomplete data.
Steno A et al [9]	2012	Less than 10 gliomas
Wang YQ et al [10]	2012	Technical report.
Saether CA et al [11]	2012	Incomplete data.
Erdogan N et al [12]	2005	Incomplete data.

Two more studies were excluded because they were technical in nature.

Table 2: Studies that fulfilled the inclusion criteria:

Reference	Total	GTR % Estimates			Reported details of IoUS in each series					
		Mean	Lower	Upper	Location	HGG*	LGG*	Sen%	Sp%	SuD%
Coburger J et al[13]	15	73.3	51	95.7						
Moiyadi A et al [14]	67	82.2	73.9	90.4	100%	47%				59
Liang SQ et al [15]	80	86.2	79.4	92.9	100%					
Peredo-Harvey et al [16]	18	85.6	79.7	91.6						
Serra C et al [17]	14	86.9	81.7	92						
Wang J et al [18]	137	81.8	73	90.6	100%	67.2%	70.6%			
Moiyadi A et al [19]	41	82	71.6	89.5	100%					
Rohde V et al [20]	16	80.7	73.3	88.1				71	60	
Solheim O et al [21]	142	74.5	60.6	88.5		37%				
Tian YJ et al [22]	88	76.7	63.8	89.6				80.1	69.8	
Rygh OM et al [23]	19	76.9	64.8	89.1				95	95	
Lindner D et al [24]	23	77	65.6	88.5	100%					
Zhao P et al [25]	35	78.2	67.7	88.8	100%					
Renner C et al [26]	22	76.2	65.7	86.6		76.2%				
Unsgard G et al [27]	22	76.6	66.6	86.5						
Overall results of model	739	77	67.1	86.9	100	56.8	70.6	82	74.9	59

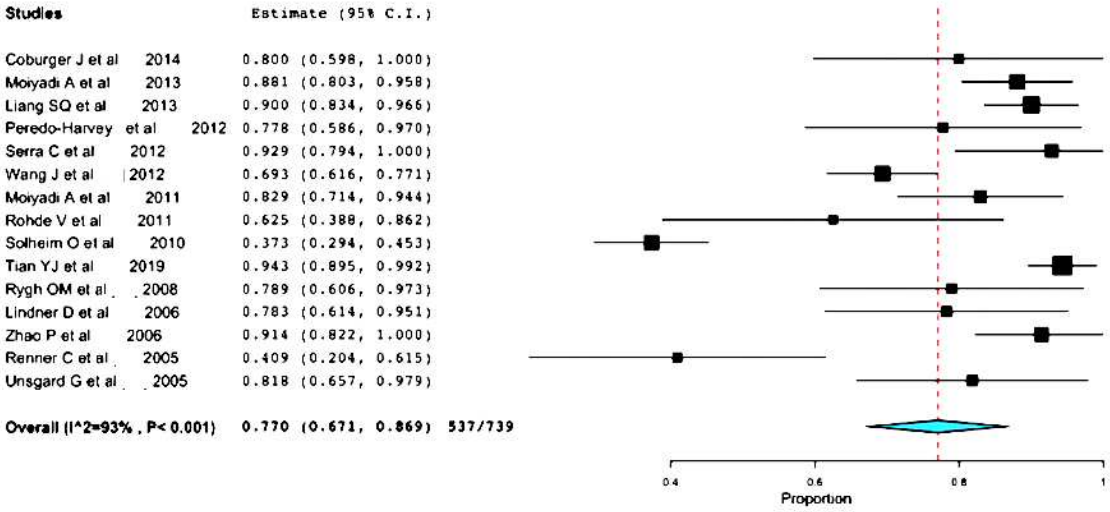
IoUS= Intraoperative ultrasound, HGG=high grade glioma, LGG=low grade glioma, * values are GTR %, Sen%=sensitivity %, Sp%=specificity %, SuD%=% of procedures where IoUS had changed the surgical decision or led to further resection.


Ultrasound in Neurosurgery (Initial search)
19,109
Excluding papers from non-neurosurgery (14,290)
Ultrasound in Neurosurgery
4,819
Excluding in extracranial usage (4,063)
Ultrasound in intracranial usage
756
Excluding Non Glioma lesions (658)
Ultrasound in Glioma Surgery
98
Excluding Ultrasound guided biopsy (74)
Ultrasound guided resection
24
Applying this review exclusions' criteria (09)
15 fulfilled all inclusion criteria of this review

Heterogeneity

tau^2	Q(df=14)	Het. p-Value	I^2
0.033	189.145	< 0.001	92.598

Forest Plot



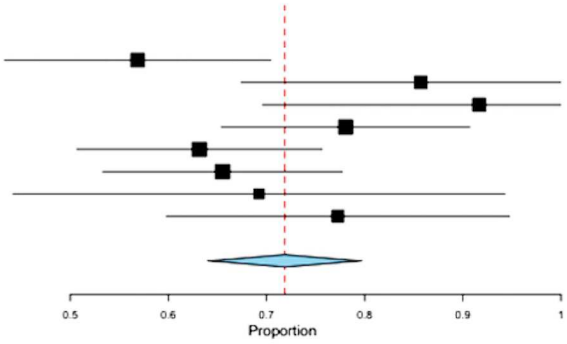
Heterogeneity

tau^2	Q(df=7)	Het. p-Value	I^2
0.006	13.938	0.052	49.778

Forest Plot

A

Studies	Estimate (95% C.I.)
Moiyadi et al 2013	0.569 (0.433, 0.705)
Serra et al 2012	0.857 (0.674, 1.000)
Peredo-Harvey et al 2012	0.917 (0.696, 1.000)
Moiyadi A et al 2011	0.780 (0.654, 0.907)
Solheim et al 2010	0.632 (0.506, 0.757)
Tian et al 2009	0.655 (0.533, 0.777)
Rygh et al 2008	0.692 (0.441, 0.943)
Renner et al 2005	0.773 (0.598, 0.948)
Overall (I^2=50% , P=0.052)	**0.719 (0.640, 0.797)**

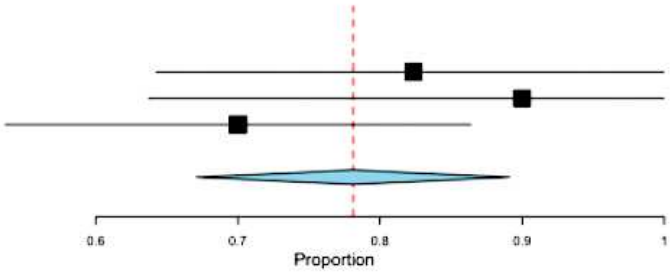


Heterogeneity			
tau^2	Q(df=2)	Het. p-Value	I^2
0.000	1.936	0.380	0

Forest Plot

B

Studies	Estimate (95% C.I.)
Moiyadi et al	0.824 (0.642, 1.000)
Peredo-Harvey et al	0.900 (0.637, 1.000)
Tian et al	0.700 (0.536, 0.864)
Overall (I^2=0% , P=0.380)	**0.781 (0.671, 0.891)**



List of abbreviations:

ALA= 5-aminolevulinic acid.
AVM= areteriovenous malformation.
CSF= cerebrospinal fluid.
FIGS= fluorescence imaged guided surgery.
GTR= gross total resection.
HGG= high grade gliomas.
IGS= image guided surgery.
IoUS = intropertaive ultrasound.
IoMRI= intraoperative magnetic resonance imaging.
LGG= low grade gliomas.
MRI= magnetic resonance imaging.
OS= overall survival.
PFS= progression free survival.
PpIX= protoporphyrin IX.
SIGN= Scottish Intercollegiate guidelines network.

Highlights:

- Maximum safe surgical resection is the aim of glioma surgery.
- The extent of surgical resection of gliomas affects the prognosis.
- Image guided surgery including intraoperative MRI, fluorescence and ultrasound are used to enhance the resection.
- Intraoperative ultrasound is safe, reliable and offers high gross total resection rate.