Intraoperative Ultrasound-Guided Resection of Gliomas: A Meta-Analysis and Review of the Literature

Syed Mahboob[1], Rachael McPhillips[2], Zhen Qiu[3], Yun Jiang[4], Carl Meggs[4], Giuseppe Schiavone[5], Tim Button[4], Marc Desmulliez[5], Christine Demore[2], Sandy Cochran[6], Sam Eljamel[7]

■ BACKGROUND: **Image-guided surgery has become standard practice during surgical resection, using preoperative magnetic resonance imaging. Intraoperative ultrasound (IoUS) has attracted interest because of its perceived safety, portability, and real-time imaging. This report is a meta-analysis of intraoperative ultrasound in gliomas.**

■ METHODS: **Critical literature review and meta-analyses, using the 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% or more represented substantial heterogeneity.**

■ RESULTS: **A wide search yielded 19,109 studies that might be relevant, of which 4819 were ultrasound in neurosurgery; 756 studies used ultrasound in cranial surgery, of which 24 studies used intraoperative ultrasound to guide surgical resection and 74 studies used it 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. Gross total resection was more likely under IoUS when the lesion was solitary and subcortical, with no history of surgery or radiotherapy. IoUS image quality, sensitivity, specificity, and positive and negative predictive values deteriorated as surgical resection proceeded.**

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

INTRODUCTION

Gliomas are the most common primary brain tumor, and the prognosis depends on the grade of glioma.[1] Maximum safe surgical resection, when possible, has

Key words
- Glioma
- Image-guided surgery
- Intraoperative ultrasound
- Neuronavigation

Abbreviations and Acronyms
2D: Two-dimensional
3D: Three-dimensional
CI: Confidence interval
FIGS: Fluorescence imaged-guided surgery
GTR: Gross total resection
HGG: High-grade gliomas
IGS: Image-guided surgery
IoMRI: Intraoperative magnetic resonance imaging
IoUS: Intraoperative ultrasound
LGG: Low-grade gliomas
MRI: Magnetic resonance imaging
NPV: Negative predictive value
PPV: Positive predictive value
SIGN: Scottish Intercollegiate Guidelines Network

From the [1]Division of Neuroscience, University of Dundee and Ninewells Hospital; [2]Division of Cancer Research, University of Dundee; [3]Institute of Medical Science and Technology, University of Dundee, Dundee; [4]Applied Functional Materials Ltd, University of Birmingham, Birmingham; [5]Research Institute in Signals, Sensors and Systems, Heriot Watt University, Edinburgh; [6]Division of Imaging and Technology, University of Dundee, Dundee; and [7]Department of Neurosurgery, University of Dundee and Ninewells Hospital, Dundee, United Kingdom

To whom correspondence should be addressed: Prof. Sam Eljamel, M.B.B.Ch., M.D., F.R.C.S.(Ir), F.R.C.S.(Ed), I.F.R.C.S.(SN), I.F.A.A.N.S.
[E-mail: professor.ms.eljamel@gmail.com]

Citation: World Neurosurg. (2016) 92:255-263.
http://dx.doi.org/10.1016/j.wneu.2016.05.007

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

1878-8750/$ - see front matter

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 (LGGs) have improved to 97% and 91%, respectively.[2] Conversely, the prognosis of high-grade gliomas (HGGs) has improved significantly in recent years, but still 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 IGS, intraoperative magnetic resonance imaging (IoMRI), IoUS, and fluorescence IGS (FIGS). The main drawback of IGS is its dependence on preoperatively acquired images to navigate during surgery. Brain shift that occurs when the dura is opened because of cerebrospinal fluid drainage, tissue removal, and gravity introduces significant inaccuracies that render IGS useless intraoperatively. Without further imaging, there is no way to obtain real-time feedback regarding 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 that magnetic resonance imaging (MRI) is performed and its expensive upkeep. FIGS, using 5-aminolevulinic acid—induced fluorescence, is cost effective for HGGs; 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 U.S. 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 ensure that no relevant article was missed. The Internet 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 Scottish Intercollegiate Guidelines Network (SIGN) 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 used as a guidance tool, study population of 10 patients or more, and assessment of the extent of surgical resection 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 10 or more and we included data for the glioma patients only. We excluded studies that were not in English, were 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, a fixed-effects model was used for meta-analysis; otherwise, a random-effect model was used. Statistical heterogeneity was explored with χ^2 and inconsistency (I^2) statistics; an I^2 value of 50% or more represented substantial heterogeneity. Furthermore, GTR rate was analyzed to determine the success of the surgery, and a correlation coefficient was calculated to ascertain the reliability of the results and to determine whether the number of patients involved in each study was related to the overall GTR rate. The average GTR rate and correlation coefficient were calculated using Microsoft Excel 2010.

RESULTS

The initial wide-net search produced 19,109 publications addressing surgical ultrasound (Figure 1). Restricting the search to neurosurgical applications reduced the number of publications to 4819 studies. The main focus of 4063 publications was 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 24 studies. These 24 publications were reviewed critically against our inclusion criteria. Only 15 studies fulfilled our inclusion criteria. Table 1[6-12] details the reasons of

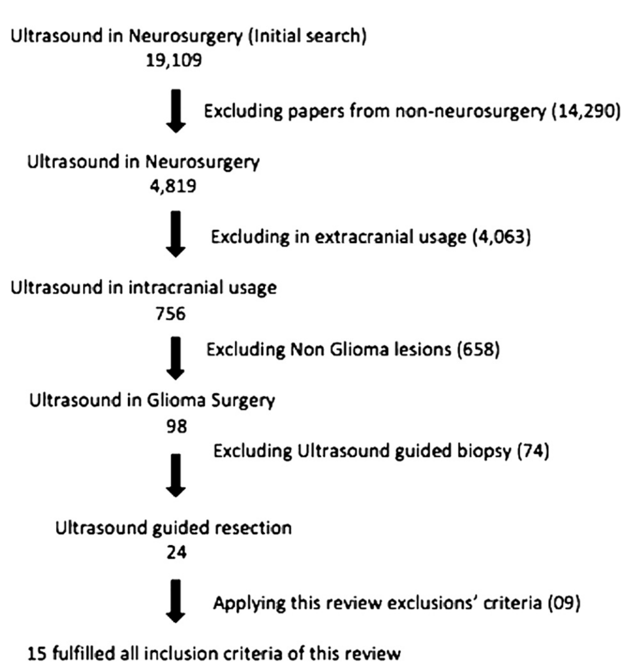

Figure 1. Flow chart of the literature search of intraoperative ultrasound in glioma surgery.