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# 3D ultrasound-augmented image guidance for surgery of high-grade gliomas – A quantitative analysis focused on the extent of resection

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## ABSTRACT

**Background:** We have retrospectively reviewed our series of brain tumor patients operated on using 3D IntraOperative UltraSound (IOUS) to report technical advantages and areas of improvement.

**Methods:** Clinical and radiological data of patients with a diagnosis of high-grade glioma IV operated with and without IOUS were retrieved and analyzed.

**Results:** We have found 391 patients operated using IOUS coupled with neuronavigation and 257 using neuronavigation standalone. We have selected a pool of 60 patients with a diagnosis of GlioBlastoma (GB), comparing two equally sized groups operated with and without IOUS, respectively. The average extent of resection (EOR) in the IOUS group was 93%, while in the control group, it was 80%. IOUS was significantly associated with improved EOR ($P < 0.0004$), even when accounting for other factors affecting EOR. The average overall survival (OS) was 13.4 months, and the average progression-free survival (PFS) was 7.4 months. The Cox proportional hazard model showed an advantage in OS on patients operated using the IOUS. No statistically significant effect was observed on PFS.

**Conclusion:** Intraoperative ultrasound coupled with image guidance is associated with an improved EOR and possibly an improved OS. While we are aware of several limitations related to the present analysis, these data support the routine use of IOUS as a safe and reliable technology. Larger, prospective series with updated IOUS technology are desirable to verify the accuracy of these results.

**Keywords:** 3D ultrasound, High-grade glioma, Intraoperative ultrasound, Neuro-oncology, Ultrasound

## INTRODUCTION

The research on new intraoperative devices to improve brain tumor resection is an ever-developing field in neurosurgery. Traditional neuronavigation systems use preoperative computer tomography (CT) or magnetic resonance imaging (MRI) data to plan surgical procedures and guide surgeons to tumor margins, allowing a greater degree of precision, safer surgery, and a more complete tumor resection that correlates with clinical outcomes.[1,7,13,28,32,34] They are, however, limited by their failure to compensate for the anatomical changes of the brain during surgery.

Intra operative ultrasound (IOUS) is an appealing solution, offering a cheaper, faster, and more accessible alternative to intraoperative MRI (iMRI). However, it is still not considered the imaging modality of choice by many surgeons. In the past, IOUS has been criticized for its poor spatial resolution, and the loss of image quality to surgical artifacts (air, blood, and instruments) detracts from its usefulness in tumor resection surgery.[14] Furthermore, most commercial ultrasound (US) scanners only provide a 2D cross-sectional view, often in the oblique orientation, which is difficult to interpret.

The image fusion of IOUS and preoperative MRI has improved the quality of tumor resection and the clinical outcome of surgery[12,18], and preliminary work has shown that the introduction of IOUS has coincided with an improvement in survival following glioblastoma resection in Trondheim (Norway).[29] Moreover, the more defined resolution and the development of new software allowing the surgeon to perform a 3D reconstruction have substantially improved the performance of current IOUS devices.[16]

The present study is a retrospective review of our experience using intraoperative 3D-IOUS. We have performed a subgroup analysis on a cohort of patients affected by high-grade gliomas grade IV (HGG-IV) who underwent IOUS-aided surgical resection and compared them with a control group operated using a standard, standalone neuronavigation system.

### Aims

This study retrospectively examines data from a series of HGG-IV surgeries. We investigated whether combining 3D intraoperative ultrasound (3D IOUS) with neuronavigation improves the extent of resection (EOR) compared to standard neuronavigation alone. In addition, we sought to discern any survival benefits in terms of overall survival (OS) and progression-free survival (PFS).

## MATERIALS AND METHODS

### Neuronavigation systems – technical features

This study utilized the data from surgeries assisted by two primary neuronavigation systems. Ethical clearance for data usage was granted by the Health and Research Authority – Bloomsbury Research Committee, London. REC reference: 19/LO/1763, Integrated Research Application System project ID 265404.

As mentioned, two specific devices were considered for this purpose.

#### *SonoWand*©

A combined 3D-IOUS neuronavigation device, Sonowand, was used to retrieve the data for the exposure group of this study - see Lindseth *et al.* detailed technical specifications.[18] The device is an infrared-based neuronavigation system combined with two differently sized US probes. It operates independently or in tandem with 3D US. The optical neuronavigation tracker links the 3D US through a specialized tracking mechanism [Figure 1]. After the standard preparatory steps and the application of the Mayfield clamp, fiducial landmarks are preset on the patient and registered based on the preoperative

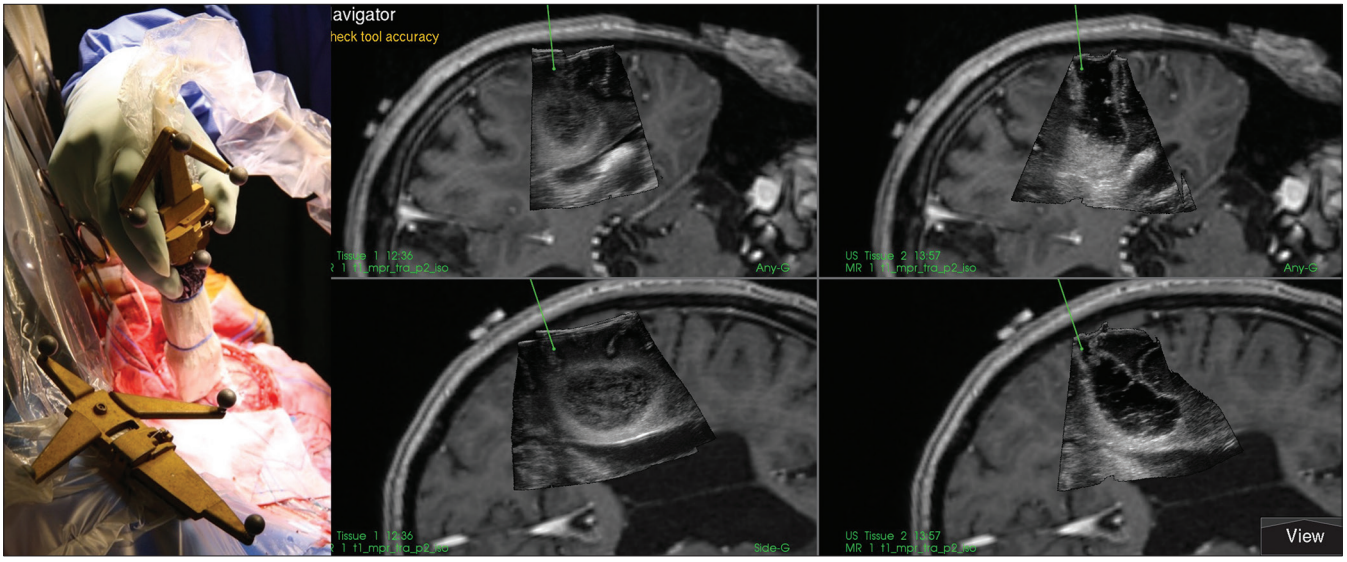


**Figure 1:** 3D-IOUS intraoperative scanning. Left: Intraoperative picture showing the dedicated tracking device coupled with the probe during and IntraOperative UltraSound (IOUS) acquisition, which links the intraoperative magnetic resonance imaging scan with the IOUS images. Center and right: A case showing two IOUS acquisitions, one performed after exposing the cortical surface (center), the other at the end of the resection (right), showing the resection cavity.

volumetric MRI scan. Neuronavigation is utilized during the operation. Postcraniotomy, the US probe encased in a sterile cover, is synchronized with the tracking system using a dedicated tracking device coupled to the IOUS [Figure 1]. The device then captures 3D intraoperative ultrasound images and aligns them with the volumetric MRI registration. This capture focuses on a single spatial plane, and the system automatically generates images for the other two planes, thus providing axial, sagittal, and coronal projections (hence the "3D" definition). The surgeon can use the IOUS either use the IOUS either freehand or perform multiple IOUS registrations during tumor removal to monitor the resection progress in real time.

### *Medtronic© neuronavigation*

Medtronic stealth neuronavigation, a globally recognized neuronavigation system known for its accuracy and reliability, was used to retrieve the data for the control group of this study. Unlike SonoWand , it does not incorporate IOUS, making it ideal for the purposes of our comparison. The device utilizes an infrared tracking system and offers registration through fiducial or anatomical landmarks. It also features a surface tracer option [Figure 2].

The process of image registration for both devices is similar, but aside from the obvious difference of the IOUS coupling or lack thereof, the SonoWand system allows for multiple intraoperative reads and acquisitions, thus providing a real-time image at any point of surgical resection and partially adjusting for imaging shift [Figure 3]. All cases coming from the present series were operated using either of these two neuronavigation devices.

### Data collection

Population samples have been selected from the data stored on three neuronavigation devices. Collected cases were divided into two categories:

### *Exposure group*

Patients operated using the 3D-IOUS-neuronavigation integrated system. Two identical and interchangeable 3D-IOUS-stealth coupled devices (marked 51 and 55) were used to extract data.

### *Control group*

Patients operated using the standalone neuronavigation system (Medtronic© Neuronavigation).

Regarding the inclusion criteria, we have collected all HGG-IV cases where the surgeon was planning to achieve

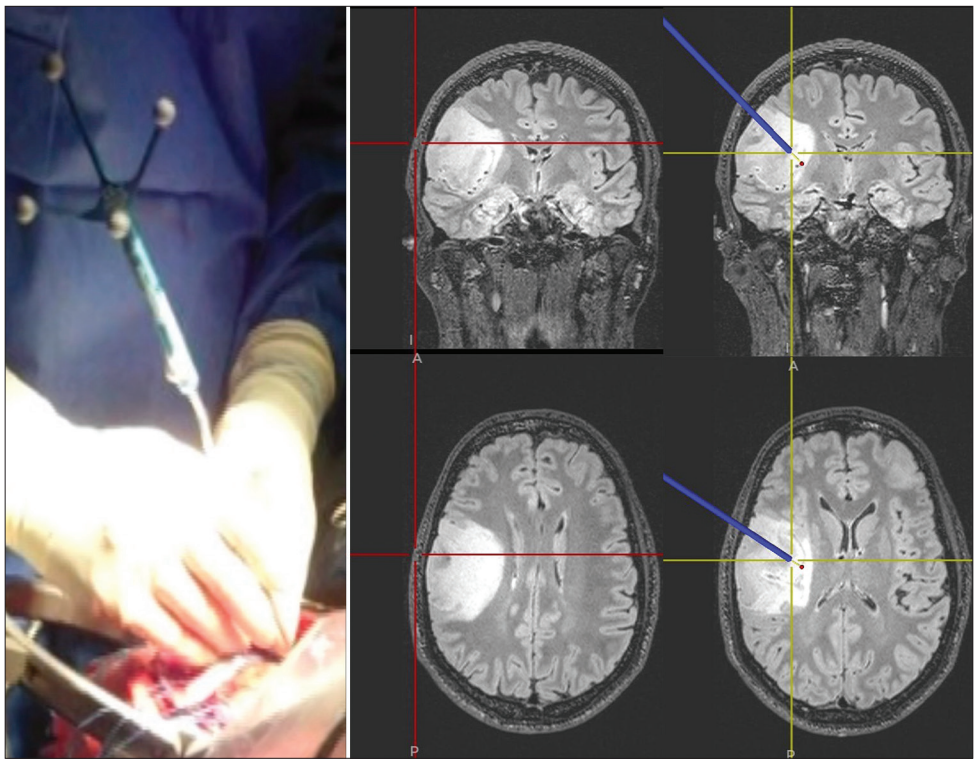

**Figure 2:** A case (not included in the present series) showing a standard neuronavigation deployment during surgery for an anaplastic astrocytoma. Left: Intraoperative picture showing the probe. Center: Snapshot at the beginning of the case. Right: Snapshot toward the end of the resection.

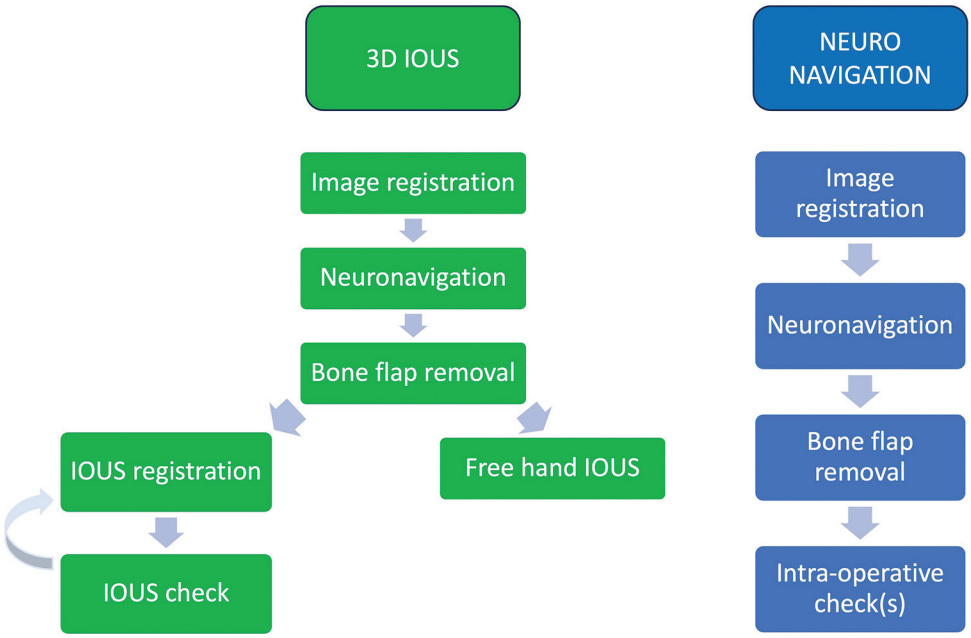


**Figure 3:** Flow chart showing the different acquisition techniques. Aside from the obvious difference that the SonoWand© can be coupled with an IntraOperative UltraSound (IOUS) probe, it allows for multiple acquisitions at any point during tumor resection, thus providing different views even during and at the end of the resection. IOUS probes can also be used free hand, without coupling with neuronavigation.

a gross total resection (GTR) (100%) or at least a near total resection (NTR) (>90%) of the tumor, as per the operative note record entry and excluded all cases where a partial debulking or a biopsy was intentionally performed. Cases were selected by matching the intraoperative stealth and IOUS scan details and those into the operative notes where a surgeon clearly documented that, in his/her opinion, GTR or NTR was achieved. Patients undergoing surgery without the use of any neuronavigation devices were also excluded. Cases were selected based on a homogeneous timeframe, meaning all patients included were operated during the same period. Six senior surgeons were equally involved in the treatment of patients from the two groups. Out of this group of consultants, three anonymized surgeons (C1, C2, and C3) were dedicated neuro-oncology surgeons, and most of the cases of the present series were treated under their care. All selected patients had a preoperative and an early postoperative (<48 h) volumetric MRI scan T1 weighted (T1w) with gadolinium (Gd). Patients without volumetric images were omitted. Patients undergoing postoperative CT scan as a radiological method to check for the EOR were also excluded. The selection of cases was randomly performed by a research fellow (author GA), who operated on a random selection of all patients with a diagnosis of HGG-IV and with the appropriate inclusion criteria. Specifically, once the inclusion criteria screening was performed, the cases were randomly selected from the available pool by removing all identifiable data, assigning a random number using a randomization function on the dedicated database, and subsequently extracting an equal number of cases from the exposure and control group for transfer to the software for statistical analysis (see below). All the senior surgeons were kept blind to the results.

The following clinical data have been collected from both groups: age at diagnosis, sex, comorbidities, consultant neurosurgeon responsible for the procedure, adjuvant treatment, OS, PFS, and performance status (PS). Pre and postoperative radiological data in the form of pre and postoperative volumetric MRI scans have been collected for each patient to establish tumor volume and the presence of postoperative residual. Pre and postoperative volumetric calculations on tumor volumes and postoperative residuals (when present) have been performed on the sequences mentioned above by a dedicated neuroradiology team. GTR was defined as the absence of enhancing residual on an early (<48 h) postoperative volumetric T1w with a Gd MRI scan. Blind imaging data were provided to the radiology team (authors IS, OC, and AW) so that they were not aware of which group the patient was extracted from (exposure vs. control) to limit confirmation bias. The location of the tumors in terms of depth and proximity to cortical and subcortical eloquent areas has also been considered in our analysis.

The primary outcome considered for the present study was the EOR in the two groups in terms of both volume reduction

and the presence/absence of the residual. The secondary outcomes were the OS and PFS in the two groups.

### Statistical analysis

Statistical analysis was performed using RStudio (version 2021.09.2) running R (version 4.1.2). A linear regression model was built to test the effects of each variable on the EOR in R. The following variables were considered: use of IOUS, sex, age at diagnosis, depth of the most superficial and deepest point of the tumor, tumor size, proximity to an eloquent area, surgeon operating, and whether the case was a recurrent HGG-IV or not. Regarding the secondary outcomes (OS and PFS), a Cox proportional hazard model was built to weigh different factors' roles. In addition to the previously mentioned fields, the following ones were considered: peri-operative PS, percentage of volume resected, MethylGuanine MethylTransferase (MGMT) and Isocitrate DeHydrogenase (IDH) status, postoperative chemoradiotherapy (CRT), and the presence of peri-operative complications. Kaplan–Meier curves were built to compare OS and PFS for the following variables: use of IOUS (Y vs. N), peri-operative complications (Y vs. N), and postoperative treatment (no CRT, palliative CRT, or radical CRT). Plots were generated in GraphPad Prism (ver. 9.3.1). Statistical significance was determined using the Mann–Whitney U-test (box-and-whisker plots) or log-rank (Mantel-Cox) test for Kaplan–Meier curves.

## RESULTS

We have retrieved 391 tumor patients operated using either of our two 3D-IOUS-stealth coupled machines (numbered 55 and 51) and 257 operated using stealth neuronavigation. The remaining patients were operated using different neuronavigation devices or without neuronavigation.

Thirty HGG-IV cases operated using IOUS-stealth coupled devices, and thirty operated using Medtronic were randomly selected from the pool of cases fitting the inclusion criteria. All cases included in the analysis had surgery between the 1st of January 2014 and the 31st of December 2017. Those cases' clinical and radiological features are summarized in Table 1 – a more detailed summary, including a more precise location of the tumors, is listed in Supplementary material. The mean age of the patients at diagnosis was 55 years (±15); 21 patients were females, and 39 were males (M:F ratio = 1.8).

The average tumor volume for the whole pool of cases was 91.16 cm$^3$ (±72.69). Tumor volume was higher in the IOUS group (mean 118 cm$^3$, ±86 cm$^3$) compared to the control group (mean 64.14 cm$^3$, ±42 cm$^3$, p = 0.007) [Figure 4a], Depth points of the tumors were comparable between the two groups: the average most superficial point was 1 cm in both groups (min 0 cm, max 3, standard deviation ± 0.8), while the average deepest point was 5 cm deep (±1.29 and

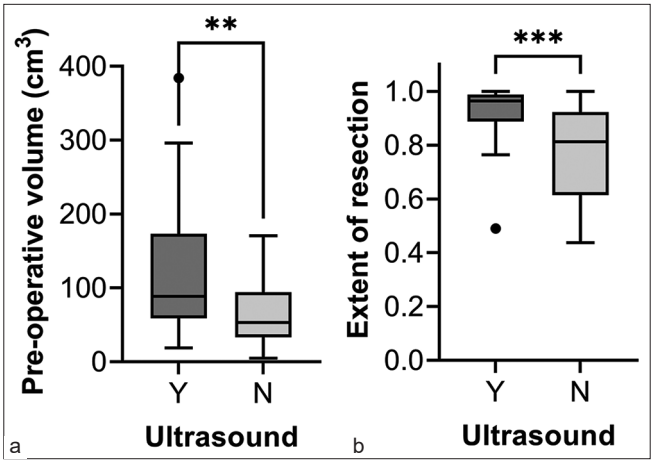


**Figure 4:** (a) Box-and-whisker plot of preoperative volumes. Cases included in the 3D-IOUS group were found to have larger volumes compared to those included in the control group. (b) Box-and-whisker plot showing the differences in extent of resection between the group where 3D-IOUS was used, and the one where it was not (Mann–Whitney U-test was used, $P < 0.0004$). IOUS: Intraoperative ultrasound This correlation was found to be independent from other variables. Y = Yes. N = No; ** and *** = strength of the p value expressed in decimals (example: *** meaning p = 0.000x).

±1.44 in the IOUS group and the control group, respectively). Six and seven cases were in proximity of eloquent areas in the 3D-IOUS group and the control group, respectively. All cases located near an eloquent area were operated using neurophysiological monitoring, awake surgery, or a combination of the two, depending on the indications.

Five patients overall were operating using 5-aminolevulinic acid (5-ALA), 2 in the 3D-IOUS group and 3 in the control group. The routine use of 5-ALA in HGG-IV surgery was introduced as standard in clinical practice in the UK only in 2018. This was not part of our routine practice before that date, and given the exiguous number of patients treated using 5-ALA, this factor was not included in our final analysis.

As expected, EOR was found not to be normally distributed, with two clear peaks seen in the density distribution, separating a large population with optimal resection ($n$ = 51, mean 92% ± 8%) and a small population with suboptimal resection ($n$ = 9, mean 55% ± 6%). The average EOR in the IOUS group was 93% (±10%), while in the control group, it was 80% (±17%). There was a significant increase in EOR in the IOUS group compared to the control group, independent of other variables [Figure 4b], (p = 0.0004) known to affect resection, such as tumor depth and location near an eloquent area. Superficial access to the tumor was also linked to an improved EOR ($P < 0.03$). Interestingly, a weak association between consultants not normally performing neuro-oncological surgery and an improved EOR has also been found ($P = 0.05$).

**Table 1:** Summary of HGG-IV cohort characteristics. For a more detailed list, check "Supplementary Material."

| | IOUS | Stealth | Total |
|---|---|---|---|
| Age (years) | 58 (±14.8) | 53 (±14.4) | 55 (±14.6) |
| Sex | 23 M, 7 F | 16 M, 14 F | 49 M, 21 F |
| Tumor volume ($cm^3$) | 118 (±86) | 64 (±42) | 91.16 (±72.69) |
| Tumor location | | | |
| Frontal | 9 | 8 | 17 |
| Temporal | 11 | 13 | 24 |
| Parietal | 8 | 6 | 15 |
| Occipital | 0 | 2 | 2 |
| Proximity with eloquent areas | 6 | 7 | 13 |
| Performance Status preoperative | 0 in 29 pts; 1 in 1 pt | 0 in 14 pts; 1 in 15 pts; 2 in 1 pt | 0 in 42 pts, 1 in 17 pts, 2 in 1 pt |
| Performance Status postoperative | 0 in 27 pts; 1 in 1 pt; 4 in 2 pts | 0 in 13 pts; 1 in 10 pts; 2 in 2 pts; 3 in 5 pts | 0 in 40 pts; 1 in 11 pts; 2 in 2 pts, 3 in 5 pts and 4 in 2 pts |
| IDH1 Status | | | |
| Wildtype | 21 | 23 | 44 |
| Mutant | 6 | 3 | 9 |
| NOS | 3 | 4 | 7 |
| MGMT | | | |
| Unmethylated | 16 | 14 | 30 |
| Methylated | 7 | 1 | 8 |
| NOS | 5 | 9 | 14 |
| Consultant operating (years of experience) | | | |
| C1 (23) | 17 | 5 | 22 |
| C2 (23) | 4 | 19 | 23 |
| C3 (26) | 2 | 4 | 6 |
| Other (NOS) | 5 | 2 | 7 |

NOS: Not otherwise specified, C1, C2, and C3: Consultant 1, Consultant 2, and Consultant 3, HGG-IV: High-grade glioma IV. IOUS: IntraOperative UltraSound; IDH: Isocitrate DeHydrogenase, MGMT: MethylGuanine MethyTransferase.

The IDH1 gene has been reported as wildtype in 44 cases, mutant in 9, and was not analyzed in the remaining 7 cases. The MGMT gene was unmethylated in 33 cases, methylated in 12 cases, and was not analyzed in the remaining 15 cases.

The preoperative PS was 0 in 42 patients, 1 in 17 patients, and 2 in one patient. Immediate postoperative PS was 0 in 40 patients, 1 in 11 patients, 2 in 2 patients, 3 in 5 patients, and 4 in 2 patients. Four patients experienced significant postoperative complications: Two in the form of severe postoperative cognitive and neurological impairment (PS 4), and two developed acute hydrocephalus postoperative, treated with ventriculoperitoneal shunting. One of the patients with hydrocephalus also developed aspiration pneumonia, which was successfully treated with antibiotics. We did not observe postoperative ischemic complications in either of the groups. Where observed, the worsening postoperative status was in all cases related to postoperative edema.

The average OS was 13.4 months (±8), and the average PFS was 7.4 months (±7).

The Cox proportional hazard model showed a significant advantage in OS on patients operated using the 3D-IOUS, with a hazard ratio (HR) = 0.196 and $P = 0.017$. As expected, administration of radical CRT was also associated with improved OS (HR = 0.199, $P = 0.006$). The presence of postoperative complications significantly affected survival (HR = 15.612, $P = 0.002$). We also observed differences in OS based on the presence of the tumor near an eloquent area (HR = 0.349, $P = 0.013$), the tumor volume (HR = 1.007, $P = 0.047$), and the surgeons performing the operations, both the "other" group (HR = 11.729, $P = 0.004$) and surgeon C3 (HR = 7.703, $P = 0.013$). However, only the peri-operative complications and application of CRT had independent effects on survival times [Figure 5a]. Only the administration of radical CRT was significantly associated with increased PFS (HR = 0.242, $P = 0.013$), and this association was seen as independent of other factors [Figure 5b].

## DISCUSSION

### Historical background and 3D IOUS development

The first ever reported application of the US in neurosurgery was on a postmortem case of a 54-year-old woman.[10] Since then, several intraoperative imaging devices have been developed to help neurosurgeons to localize the tumor

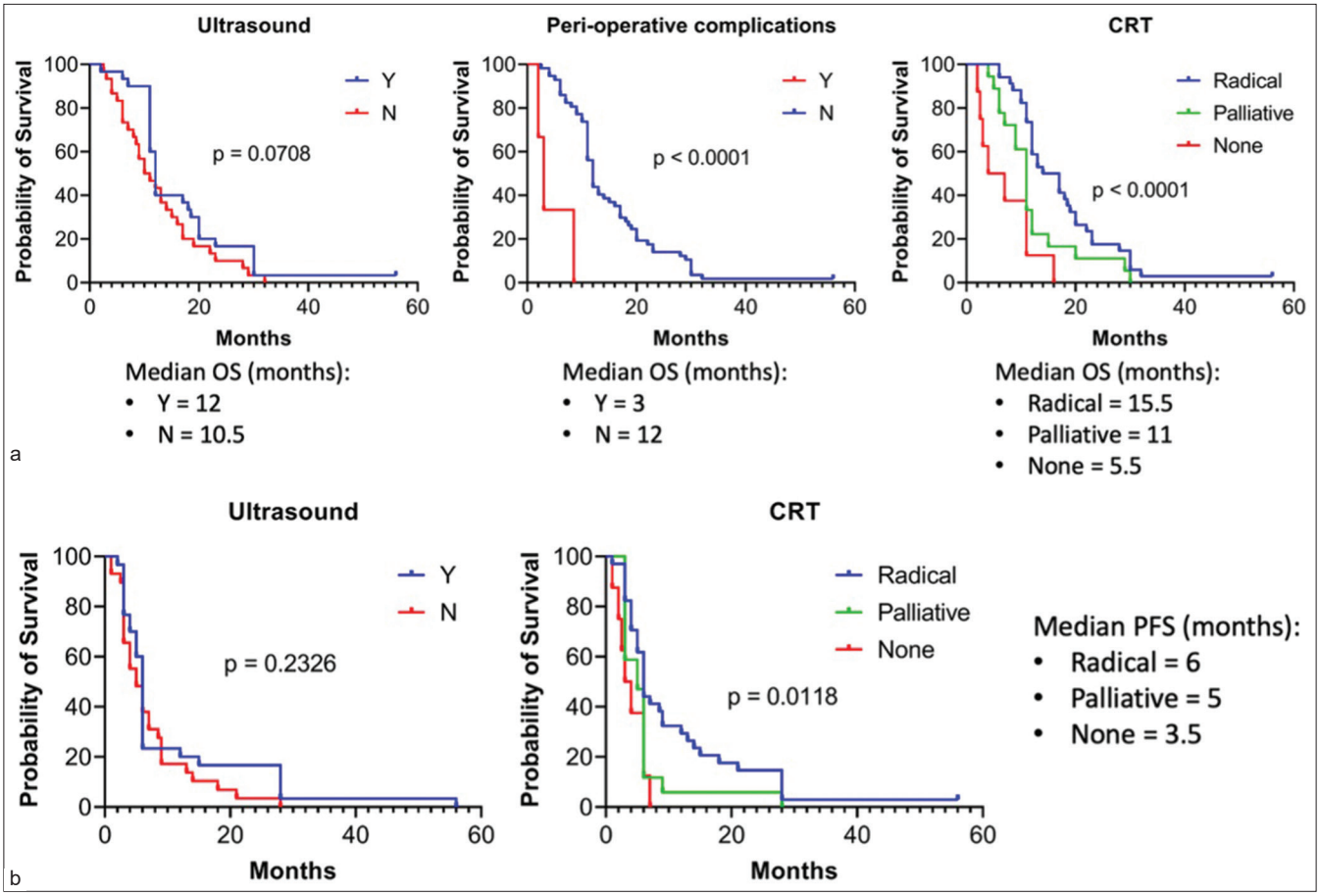


**Figure 5:** (a) While not independently significant, we have found a shift toward longer survival in the 3D- IOUS cohort. Perioperative complications were found to have a highly significant impact: three patients showed markedly shorter overall survival. Radical chemoradiotherapy (CRT) also significantly extends survival times, in keeping with the results of the known literature. *P*-values were determined by log-rank (Mantel-Cox) test. (b) Overall, progression-free survival (PFS) is poor in all patients, and we found that the differences between groups are not substantially significant. 3D-IOUS does not appear to be significantly associated with significantly improved PFS. Radical CRT promotes longer PFS, as expected. *P*-values determined by log-rank (Mantel-Cox) test. IOUS: IntraOperative Ultrasound, Y: Yes, N: No, OS: Overall Survival, CRT: ChemoRadioTherapy, PFS: Progression Free Survival.

before surgery. CT and MRI scans, introduced in clinical practice during the 70s and in the 80s, respectively, were two of the major technological advancements that allowed neurosurgeons to localize the target lesion more accurately inside the brain. Neuronavigation frameless devices were introduced during the 90s, and they were the first tools allowing intraoperative localization of the tumor,[9] although they did rely on preoperative images rather than real-time acquisition. IOUS appeared to solve the problem of real-time imaging technology. The preliminary reports showed successful intra-operative tumor identification.[7] Interestingly, in several cases, the signal obtained from IOUS was different when compared to that obtained using traditional imaging technologies (CT or MRI scan), thus suggesting that the IOUS could be used not only as an intra-operative aid but also as a complementary tool for those lesions of unclear nature or margins.[7] Moreover, coupling the IOUS with neuronavigation has greatly improved the possibility of midline shift adjustment during surgery[17,23,27,35] and has been proven useful to improve tumor demarcation when close to eloquent areas.[26] In more recent years, further technological advancement has led to the development of 3D IOUS.[30,31] The 3D reconstruction is automatically generated by the neuronavigation software after an intraoperative acquisition through a single spatial plane. The images can be integrated with Doppler angiography when required so that vessel encasement by an intracranial mass or aneurysm can also be detected.[30,31] Recent research has also focused on the possibility of integrating IOUS with contrast[1] or, more importantly, planning surgical resection based on IOUS.[23] As discussed in the following sections, the system we have used is also partially oriented toward the same goal, which is to provide a cost-contained and more reliable and real-time option to improve EOR.

An extensive systematic review and meta-analysis focused on IOUS has shown an average GTR of 77%, an 82% concordance rate between IOUS and postoperative MRI scan, and high sensitivity/specificity at the beginning of surgical resection (>90%).[19] The same study failed to find a significant correlation between the use of IOUS and a significant impact on survival, which is the reason why we have attempted a quantitative analysis on a subgroup of relatively homogeneous patients.

**Our results**

Our study delves into the utility of 3D-IOUS in HGG-IV surgeries. In general, HGG-IV and anaplastic gliomas grade III presented diverse IOUS results. While anaplastic astrocytomas and oligodendrogliomas were hard to discern due to mixed boundaries with surrounding edema, necrotic and cystic areas were typically discernible. For this study, HGG-IV was chosen due to its prevalence and because there is consensus on defining the EOR by looking at the enhancing component. On IOUS, HGG-IVs mirrored MRI features: the enhancing capsule was hyper-echogenic, whereas the necrotic core was hypoechogenic. Recurrent HGG-IV and recurrent anaplastic grade III are more challenging tumors to visualize on 3D-IOUS, in our experience [Figure 6]. As highlighted by other authors,[19] the intraoperative imaging quality varies based on the stage of surgical resection. Superficial, small-sized lesions were typically very well visualized by the acquisition and during resection. However, even a modest-to-moderate amount of bleeding causes a visible artifact that can hamper surgical view beyond the limits of resection [Figure 7].

We have included two comparable groups of HGG-IVs operated by a heterogeneous pool of surgeons. This selection aimed at choosing a homogeneous group of patients, tumors, and treatment groups to address how much the EOR would change with or without the IOUS and whether there could be an impact on OS and PFS. The tumors included had different locations, sizes, and proximity to the surface. However, the number of tumors located near eloquent areas was similar between the exposure and the control group (6 vs. 7, respectively). Moreover, the average depths of the tumors were comparable between the two groups in terms of the most superficial and the deepest portions. On the other hand, preoperative tumor volumes were higher in the 3D-IOUS group than in the control group, which was presumably a stochastic effect. Despite the average larger tumor volume pointing toward a potentially more challenging surgical resection, the EOR was still more generous in the 3D-IOUS group, thus suggesting that IOUS makes a difference in the quality of EOR regardless of tumor size. Our results show that, when all possible factors are considered, the EOR is increased when IOUS is used. This result aligns with those from the international literature [21,25,31] and the evidence, although not consensual, seems to point toward the direction of a clear advantage in using IOUS to improve EOR.[2] In that regard, some authors stressed the fact that IOUS is an operator-dependent technology, needing a learning curve and without a standardized training pathway.[6] Such limiting circumstances could easily explain the lack of homogeneous results and point toward the necessity of further studies and a more defined educational and professional pathway for the application of IOUS in different centers. Interestingly,

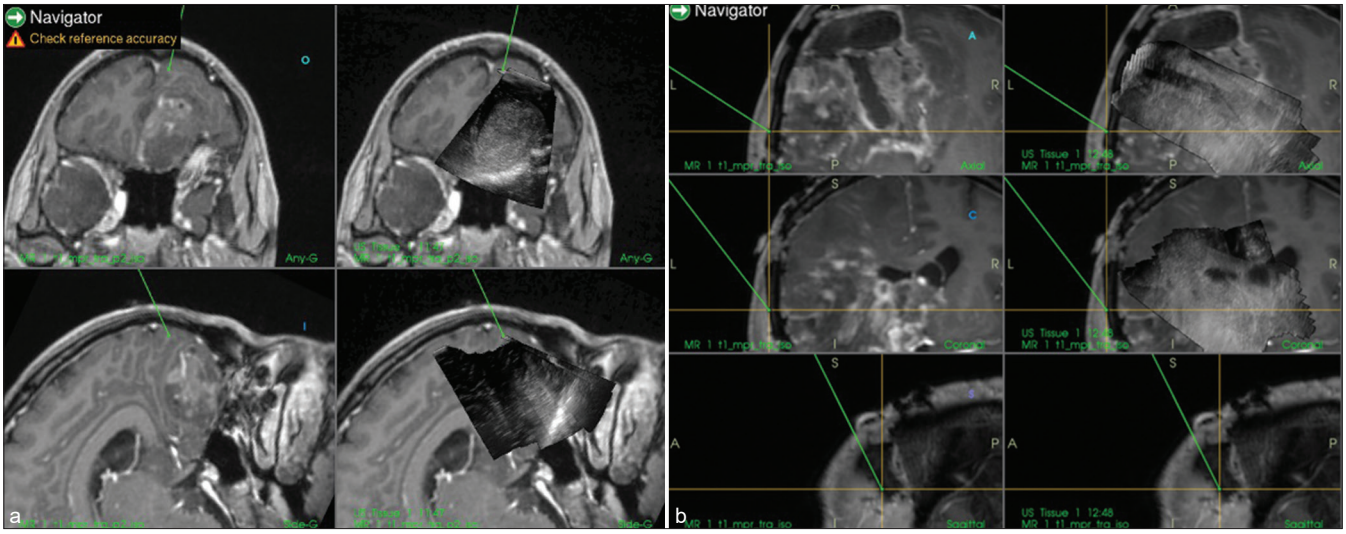


**Figure 6:** (a) A right frontal high-grade glioma as seen on the SonoWand neuronavigation sequence alone (left) and with the same sequence co-registered with 3D-IOUS. Visualization of tumor boundaries is adequate, although the lesion often appears homogeneously hyperechogenic, with no clear distinction between the tumor capsule and the necrotic core. (b) A case of left frontal recurrent glioblastoma. Apart from the size of the lesion requiring multiple acquisitions and therefore causing linear artifacts, the tumor appears challenging to define on IOUS due to the relatively homogeneous hyperechogenic signal. IOUS: Intraoperative ultrasound

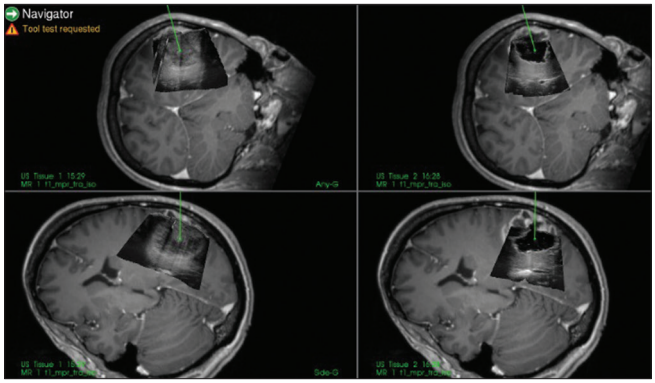


**Figure 7:** Intraoperative picture of right posterior temporal glioblastoma before (left) and after resection (right). In this case, the necrotic core was well visualized. On the right side, note the presence of a partial shift of the brain surface and a cone of hyperechogenic material due to the deposit of blood products at the bottom of the cavity.

in our series, the use of IOUS also resulted in a borderline statistically significant improvement of OS, although the advantage was not massive. This finding seems consistent with what some other groups have recently reported.[4,15,21,22,33] While most of these series are retrospective and often mix different histological subtypes,[33] one relatively small randomized controlled trial also confirmed these results.[15] In our series, the small number of patients included and the numerous confounding variables suggest that this outcome should be taken cautiously. A potential prospective study enrolling a more conspicuous pool of patients, with stratification based on tumor location, size, and depth, might be helpful to verify this finding. A more recent systematic review compared IOUS with other intraoperative imaging techniques, including iMRI, fluorescence, and tractography. [2] the authors were also cautious regarding the survival benefit of IOUS. While the compound evidence toward an improvement of EOR seems to be adequately supported, the effect on OS is still debatable, and it needs to be clarified, accounting for several confounding factors. A promising, more extended randomized controlled trial is currently in the recruitment phase in the UK.[24] It is also worth stressing that the same finding did not apply to PFS in the present series, and it is not entirely clear why this should be the case. Several authors pointed out that PFS and OS are not always linearly correlated in cancer series and PFS is actually an approximated metric, which might benefit from more refined and updated versions.[3,5] Assuming the OS finding is significant in our series, PFS might not be as accurately represented, given that the follow-up scan time points were less homogeneous between different patients. It is still possible, however, that the observed effect on OS is random, and the PFS results truly reflect the overall trend, implying that IOUS deployment might not have a real survival effect. The Cox proportional hazard model highlighted the impact of CRT on OS, an expected finding already known from the international literature.[11,20] Postoperative complications' impact seems significant on the log-rank test [Figure 5a, middle graph] and the Cox proportional hazard model ($P$ = 0.002). On a closer analysis of the results, all these patients but one showed a poor PS postoperative and were not offered a postoperative radical CRT regimen. We observed no major complications significantly affecting OS or PFS related to the CRT regimen itself, despite temozolomide having been interrupted in 3 cases due to blood toxicity. Another interesting finding concerns the stratification of patients according to the surgeon operating on them. We have purposely decided to include this variable in the analysis to consider the inevitable inter-operator variability: different surgeons have different approaches and techniques when resecting a tumor. As expected, most patients were operated by dedicated neuro-oncology consultants, with a few being operated by general neurosurgeons (grouped and marked as "others"). EOR did not show significant differences among the three neuro-oncology surgeons operating, although the confidence interval (CI) was broader in C2 compared to C1 and C3. Differences in resection technique, patient PS, comorbidities, and proximity to eloquent areas could account for the discrepancy. However, even more interesting, the differences in EOR did not translate directly into differences in OS and PFS, with C1 being the consultant with the highest associated survival but EOR comparable with that of C3. Furthermore, C1 has operated on a lower number of cases included, which might have skewed the analysis. Tumor depth has not significantly affected EOR, OS, or PFS. Still, this effect is likely to be linked to preoperative case selection: deeply located lesions are unlikely to be selected for GTR to start with. This is also true for the PS, MGMT, and IDH1 status and their impact on OS and PFS. Finally, both groups demonstrated an equal distribution of complications and deteriorating postoperative neurological outcomes. Upon examining the subset of patients who experienced significant postoperative impairment, it was noted that only a single patient had a glioma situated in an eloquent region, specifically the occipital cortex. In the two postoperative hydrocephalus cases, the tumors were positioned in the hippocampal and trigonal regions, respectively. This suggests that the likelihood of postoperative hydrocephalus was anticipated. Notably, in this series, the influence of complications appeared to have statistical significance exclusively concerning OS. However, there seemed to be no correlation with any other factor, barring the anticipated statistical variances.

## Limitations

The present data collection and relative analysis have been conducted to the best of our knowledge without selection

biases and limiting access to nonblind data to all the authors involved in the analysis. However, we are aware that the present study still has several limitations. First, this is a retrospective review based on data previously collected. We have, therefore, excluded a great number of cases due to incomplete or missing pools of data. For example, many patients have not been scanned within 48 hours postoperative, and in many others, we found a lack of a volumetric T1 with Gd scan, either pre or postoperative. We believe that it was crucial for homogeneous data to retrieve only those cases where all the inclusion criteria were strictly followed. Still, this decision has inevitably reduced the number of cases we could include. Second, the dataset is quite heterogeneous, and some of the surgeons clearly preferred using the 3D-IOUS to start with because of the integration between neuronavigation and the US. This is the main reason why we have included the operating surgeon as a possible confounding variable in the statistical analysis. Still, given the small pools of cases analyzed, this factor might have impacted more than shown. Third, the small sample included in the analysis did not allow for a more precise stratification of the data, meaning that tumors similar in locations and size could not be precisely compared. In our analysis, we have partially tried to solve this problem by accounting for tumor location in terms of eloquence proximity, preoperative size, and depth. However, ideally, it would have been more adequate to compare outcomes from pools of tumors in similar locations. It is also worth noting that eloquent area proximity is an outdated concept [8], and therefore, a more precise stratification is desirable for future studies. With this being a retrospective series, it was logistically challenging to stratify tumor locations more accurately. Fourth, most of these patients were operated on at a historical moment when the 5-ALA was not used as a standard of care in the UK, so unfortunately, we have a limited number of cases where this agent was used and a comparison analysis between that, and the IOUS was not performed. It is important to stress this point, as 5-ALA has also been found to be superior to iMRI in one study.[4] However, we do not believe that this has significantly impacted our results as most of the surgeons involved were senior and experienced enough to assume that the difference in their performance would have been negligible. Finally, we have relied on the clinical notes to include patients in the statistical analysis, meaning that we have assumed that the aim of the surgeon to achieve a GTR or NTR of the enhancing component was not biased. A relatively wide CI on EOR suggests that a degree of error was present in some cases. This is also the case when analyzing the impact of the tumor molecular profiles in relationship with OS and PFS: MGMT and IDH statuses were missing in a significant minority of cases because the present series dates to 2014, and molecular profiling was not fully included in the WHO classification yet, so their real impact was difficult to determine with the data available.

## CONCLUSION

The present statistical analysis on HGG-IV cases shows an advantage in EOR using IOUS compared to the cases where IOUS is not used. This is in keeping with the more recent results from the international literature and highlights the possibility that an improved EOR is achieved when IOUS is deployed by an experienced team. Our analysis also suggests a potential advantage in OS in those cases where IOUS is used, and this holds even when considering other factors known to affect survival, such as complications, administration of postoperative radical CRT, PS, and tumor size. The OS finding needs further studies to be confirmed, as PFS seems to be unaffected by IOUS. Finally, IOUS and tumor resections remain heavily operator-dependent, suggesting that the results of the present analysis might have been affected by the limitations mentioned above. A prospective analysis of a broader pool of patients, stratified according to a more precise tumor location, surgical technique, and preoperative planning, is desirable to verify these findings.

### Ethical approval

The research/study approved by the Institutional Review Board at Research Authority – Bloomsbury Research Committee, number 19/LO/1763, dated October 17, 2019.

### Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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