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EVALUATION OF NEURONAVIGATION ASSISTED INTRAOPERATIVE ULTRASONOGRAPHY IN GLIOMA SURGERY

Neurosurgery

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ABSTRACT

Background: Maximizing extent of resection (EOR) and reducing residual tumor volume (RTV) while preserving neurological functions is the main goal in the surgical treatment of gliomas. Navigated intraoperative ultrasound (N-ioUS) combining the advantages of ultrasound and conventional neuronavigation (NN) allows for overcoming the limitations of the latter. **Objective:** To evaluate the impact of real-time NN combining ioUS and preoperative contrast enhanced CT on maximizing EOR and minimizing RTV in glioma surgery compared to standard NN. **Methods:** We Prospectively reviewed a series of 50 cases bearing tumor-like brain masses which were deemed surgically resectable. 25 operated under the guidance of N-ioUS and 25 resected with standard NN. Age, location of the tumor, EOR, RTV, and, if any, postoperative complications were evaluated. **Results:** We obtained an Extent of Resection average of 84.6% in the group 1 statistically significant than 78.3% in the group 2 [P-value- 0.014]. The rate of GTR in the group 1 was 84% whereas in group 2 ,60% GTR rate was obtained which was significantly lower . Mean residual tumour volume in group 1 was 4.07cm which was significantly lower than mean residual tumour volume in group 2 which was 5.10.[p= 0.04]. **Conclusion:** Neuro-navigation using intraoperative US integrated with preoperative CECT images is reliable, accurate and user-friendly. Moreover, the adjustments are very helpful in correcting brain shift and tissue distortion. This integrated system allows true real-time feedback during surgery and is less expensive and time-consuming than other intraoperative imaging techniques, offering high precision and orientation.

KEYWORDS

Extent of resection, Navigated Intraoperative ultrasound, Neuronavigation, Residual tumor volume

INTRODUCTION

Neuronavigation or stereotaxy are techniques designed to help neurosurgeons precisely localize different intracerebral pathological processes by using a set of preoperative images (USG, CT, MRI, fMRI, PET, SPECT etc).[1] Neuronavigation glioma surgeries may have several advantages, including reduced length of surgery, lower incidence of wound infections, and shorter length of hospital stay. Neuronavigation can improve orientation within brain tissue at the time of surgery and assist in determining the margins of solid tumor tissue with surrounding infiltrated brain should improve the safety and efficacy of these procedures.[2]

Neuronavigation systems are valuable tools of routine use in neurosurgery, but they suffer from various limitations [3]. The most prominent is that they are based on preoperative images. Therefore, they have to be considered as being not true real-time systems. It is mandatory to remember that the accuracy of such systems during surgery is maximal before the craniotomy and decreases significantly with the progress of surgical manipulation. System accuracy reduction related to parenchymal and vascular structure changes is severe and inevitable, and it is due to two main factors: the first is "brain shift" caused by the effect of gravity on the brain, brain swelling, as well as the escape of cerebrospinal fluid (CSF); the second is due to brain parenchyma deformation caused by surgical manoevers and tumor removal.[4-6]

To make neuronavigation truly effective, an intraoperative imaging system is required which will further push up its benefits. A new era in ultrasound imaging based neuronavigation began with the advent of tracked ultrasound.[7] With this technology, the position and orientation of the ultrasound probe can be known in real-time during glioma neurosurgeries.

The idea to leverage on point-of-care devices is that it can offer real-time imaging of any structure in the surgical field and help surgeons to correlate intraoperative anatomical images with those embedded preoperatively into neuronavigation systems.[8]

Also, the costs for acquisition and maintenance of IoUS suites are significantly cheaper when compared to any other intraoperative imaging tool for selective visualization of blood vessels or tumor residuals during glioma removal neurosurgeries. Besides, IoUS comes across as a more flexible surgical companion since it serves many more purposes: identification of the CSF and blood flow, appreciation of the consistency, tissue density, peripheral infiltration or other physical properties of the lesions excised, and immediate visualization of complications, such as a hematomas and can be repeated as many times as necessary in order to overcome the errors produced by brain shift.[9]

With this background, the present study was planned to evaluate and compare Intraoperative Neuronavigation with ultrasound Versus Neuronavigation alone in Glioma surgery with respect to precision of approach and the extent of resection among all the patients with both high grade and low grade gliomas admitted to Dept. of Neurosurgery, IMS, BHU, Varanasi.

MATERIALS AND METHODS

Patient Population And System Architecture:

We evaluated all 50 patients bearing tumor-like brain masses which were deemed surgically resectable. 25 Patients of group 1 underwent surgery for brain lesion removal with image guidance using a US system equipped with Virtual Navigator allowing fusion imaging for neuronavigation and other 25 patients of group 2 underwent surgery using conventional neuronavigation alone. All patients were thoroughly informed regarding the procedure they were going to undergo and written consent was obtained.

To acquire the preoperative reference images, contrast-enhanced CT images is generally used. We used a last generation US device (Sonosite, M-turbo, U.S.A) equipped with a corresponding software application for Virtual Navigation (Navigation stealth station S-8,Medronic, U.S.A). The probe employed is C11x,a variable band linear array with an operating bandwidth of 50 Hz, covered with a sterile probe cover (Civco, USA), as the intraoperative US scanner. The tracking system consists of a magnetic transmitter positioned on a dedicated support next to the patient's head, a receiver to be attached to the US probe during navigation, and a tracked pointer also equipped by a magnetic receiver used during the initial registration . The Virtual Neuronavigation system provides the position and orientation of the US probe and the pointer in relation to the transmitter in the 3 D coordinate system of the transmitter, where an oblique plane generated by free-hand moving of the probe in a 3 D space is displayed as an oblique cut through the co-registered 3 D CECT dataset in order to calculate virtual 2 D CECT images, which are coplanar to the current US imaging plane.

GROUP-1[NEURONAVIGATION WITH ULTRASOUND]

In this group, we used an US system equipped with Fusion Imaging for

Virtual Navigator to obtain the fusion of 2D US images with the coplanar preoperative CECT images.

Preoperative Procedure And Initial Registration

The first step is to scan the patient with the reference modality . Contrast CT scans are transferred to the navigation system in DICOM format through CD. The VN unit processes every slice, taking into account the (sometimes unequal) slice thickness and spacing, and generates a homogeneous 3 D volume out of them, showing the three orthogonal planes on which the surgical planning is performed as with any navigation system.(Fig 1)

The patient is positioned on the surgical table and the head is fixed with a three-pin head-holder. The transmitter is then mounted on a static support bonded to the surgical table. The transmitter, whose position is considered the origin of the reference system, is kept stationary oriented toward the patient head by a proper fixation support, while the actual position and orientation of the US probe and/or the pointer, moving freely in the generated three-dimensional (3 D) space, is provided by the receiver attached on the instrument. This tracking system generates an electromagnetic field, which is strongest at the transmitter site and attenuates with distance. The total operative range is 70 cm. However, since the highest accuracy is achievable close to the transmitter, the transmitter is placed 15 – 20 cm away from the head of the examined subject . In contrast to optical tracking systems, free line-of-sight is not requested when using electromagnetic tracking. On the other hand, some care has to be taken to avoid the presence of large metallic objects between the transmitter and tracked instruments. This requirement can be typically fulfilled easily.

The registration procedure of the CT volume and the real-time US scan consists of two phases: initial registration and fine-tuning.

The initial rigid registration is performed before sterile patient draping. Since we are not yet in a strictly sterile environment, the surgeon or an assistant performs this procedure. It is based on the identification of external anatomical landmark correspondences, whereas anatomic or external fiducials can be used. Fiducial markers are very easy to identify, but have to be fixed to the skin before radiographic examination and must remain there until the day of operation. This is neither comfortable for the patient nor always possible, in addition the skin can move in relation to the skull, or the fiducials themselves might move. Therefore, fiducials are not commonly used and NN systems typically use eight anatomical landmarks selected on the skull surface (tip of the nose and glabella on the midline; lateral canthus, tragus, ear attachment bilaterally). For this purpose the receiver of the tracking system is attached to the registration pen and is used to click on the anatomical landmarks on the patient's skin matching them with the same points defined on the CECT volume rendering on the US system . This procedure, performed only at the beginning of the operation, is completed typically within 1 – 2 minutes.

The aim of this initial registration, performed with closed skull and using only one imaging modality (CECT), is to align both the current patient's position and orientation and the 3 D CT dataset in relation to the fixed reference coordinate system .[Fig- 2,3]

When all anatomical landmarks, defined on the CECT reconstructed surface, are paired with the corresponding points on the patient, acquired with the pointer tool, the system calculates a so-called "rigid registration matrix". Rigid registration is eligible before craniotomy, since the skull bone behaves like a rigid body. Using this matrix, it is possible now to correlate the oblique transducer spatial position (and the corresponding US image) with the related reference imaging modality. For this purpose the receiver is now mounted on the US probe.

Before performing the craniotomy, we usually check the accuracy of the initial registration and of the system probe-receiver by using the US probe temporarily as "pointer" matching some external anatomical landmarks on the patient with the same points on the volume surface created by the system. To do this, we use the midpoint of the linear US probe as the "tip of an NN pointer". Once the accuracy of the system has been verified, either the navigated US probe or the pointer itself can be used as a drawing instrument in order to navigate and plan the craniotomy .[Figure 4 ,5]

Intraoperative Fine-tuning Procedure And Data Analysis

The second level of the registration phase (fine-tuning) is carried out during surgery. The patient is draped and sterile conditions are set, the US probe is covered with sterile plastic probe cover coupled with ultrasound gel (Civco, USA) and the craniotomy is performed under navigation guidance. The dials of the ultrasound device are also covered with a transparent plastic sheath and can be operated directly by the surgeon, in order to obtain an adequate ultrasound image. After bone flap removal but before opening the dura mater, we might expect brain shift to occur, but no brain deformation yet. The brain is changing its location with respect to the skull as seen in the preoperative images. However, the brain shape as a whole remains de facto unchanged. The initial registration was performed on external skull landmarks, thus this brain shift effect results in a registration misalignment.

For compensating this misalignment, fine-tuning registration is now performed. By placing the US probe directly on the dura, the brain and the lesion are scanned with a standard B-mode US modality and anatomic details from the interior of the brain become clearly visible. [Figure-6,7]

Based on the initial registration, the US imaging and the correspondent preoperative CECT are displayed on the screen of the Virtual Navigation system and are merged together by means of over-blending . The main task here is to identify some visible brain structures both on US and CECT images and visually evaluate on the superimposed image if the corresponding structures are aligned, indicating a perfect match. Again, we do not require a perfect US image here, and it is sufficient to visualize some characteristic landmarks. Thanks to this feature, it is possible to visually evaluate the accuracy of the initial registration looking for misalignment of major anatomical structures such as ventricles, vessels, mid-brain, dural structures between the CECT image and the real-time US image. If a location difference between the real position of a structure (assessed by US image) and the position of the same anatomic detail according to the Virtual Navigation system is observed, the error is measured and might be corrected in two ways:

-In-plane Correction:

If the same characteristic landmark is visible on both images, freeze the displayed US and CECT images on the screen, then drag/shift/rotate one image with the mouse to the correct position over the other.

- Out-of-plane Correction:

If no common landmarks are visible, select one or more clearly visible anatomic landmark(s) on one of the modalities, freeze said image and move the probe until the other (still moving) modality displays the same information as the frozen one; clicking on the same anatomic landmark in both images automatically matches both modalities .

This fine-tuning step is performed whenever needed, typically several times during the operation. During the resection of the mass, additional brain distortions appear. Such distortions can be visually detected on US and corrected any time by repeating one of the two above-mentioned possibilities. The proximity of other structures and the surgical cavity can be visualized as well . Fine-tuning is intuitive and fast. The surgeon operates the transducer and performs the corrections on the US console. In-plane correction is trivial and can be performed within a few seconds. Out-of-plane correction takes longer, since the surgeon has to move the probe until the requested anatomic landmark, which is already visible on CECT, becomes visible also on US. Nevertheless, this task is also completed typically within less than a minute. Once fine-tuning is completed, navigation is started. On the screen the image from the US probe merged with the corresponding oblique co-planar preoperative CECT is visualized, helping to recognize structures .

1.

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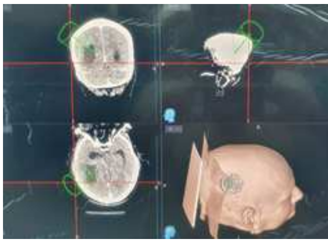
2.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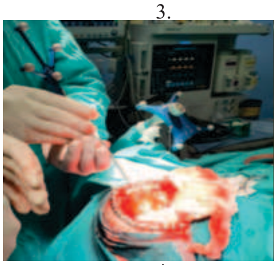
6.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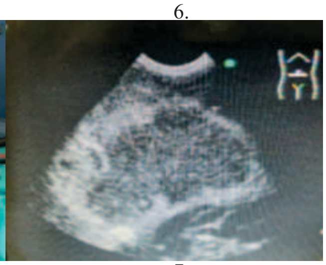
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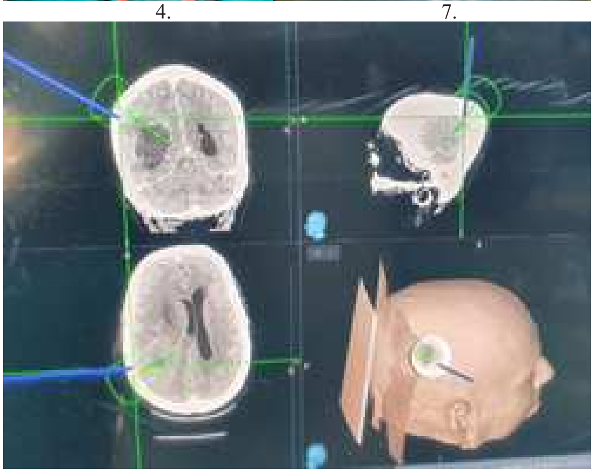
5.

GROUP 2 [NEURONAVIGATION]

All patients in the group 2 were operated on with the guidance of standard NN.

All craniotomies were planned and tailored to the lesion according to NN. At the end of the intradural part of the intervention NN, we used to perform a last control of resection margins and check their accordance to preoperative CECT images.

RESULTS AND OBSERVATIONS

A total of 50 patients were included alternatively [31 males, 19 females] with mean age of 41-50 years in 2 groups.

GROUP 1 - This group includes 25 patients who underwent both neuronavigation with intraoperative ultrasound during glioma surgery.

GROUP 2- This group includes 25 patients who underwent only neuronavigation during glioma surgery.

In all cases, the craniotomy was correctly positioned, showing no differences between the 2 groups. In all 25 cases studied with neuronavigation with ultrasound, fine-tuning was performed immediately after the removal of bone and/or during resection, in order to correct the displacement between the images caused by brain shift. No complications in the operative field have been reported in both groups.

The 2 patient groups (NN and N-ioUS) were comparable for age, sex, tumor localization , preoperative tumor volume, and preoperative clinical deficits.

Extent Of Resection [EOR] And Residual Tumour Volume

We obtained an Extent of Resection average of 84.6% in the group 1 statistically significant than 78.3% in the group 2 [Table no-1].

The rate of GTR in the group 1 was 84% whereas in group 2 ,60% GTR rate was obtained which was significantly lower.[Table 2] .

Collectively these data indicates that neuronavigation with intraoperative ultrasound could be particularly useful in minimizing residual tumour volume along with increasing the extent of resection than conventional navigation alone in glioma surgery.

Table No. 1: Extent Of Resection In Both The Groups

Extent of resection	Group 1	Group 2
Mean	84.6736	78.3136
Median	85.9800	81.7000
Std. Deviation	8.23656	13.53385
Minimum	64.90	46.79
Maximum	100.00	100.00

p-value<0.05 is significant

Table No. 2: Distribution Of Study Subjects According To Resection Classification In Both The Groups

Resection classification	Group 1		Group 2	
	Frequency	Percentage	Frequency	Percentage
GROSS TOTAL RESECTION	21	84.0	15	60.0
PARTIAL RESECTION	2	8.0	2	8.0
SUBTOTAL RESECTION	2	8.0	8	32.0
Total	25	100.0	25	100.0
Chi square	12.642			
p-value	0.011*			

***p-value<0.05 is significant**

A postsurgical Residual Tumour Volume is one of the most important predictors of patient outcome in glioma surgery.

The rate of Residual tumour volume was significantly lower in group 1 compared compared to group 2. [Table 3]

Table No. 3 : Residual Tumour Volume (cm^2) In Both The Groups

Residual tumour volume (cm^2)	Group 1	Group 2
Mean	4.0700	5.1060
Median	2.9000	2.7600
Std. Deviation	2.74236	8.12543
Minimum	1.01	1.01
Maximum	9.90	41.70

GP 1 VS 2	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Residual tumour volume (cm^2)	-1.03600	7.81622	1.56324	-4.26238	2.19038	-.663	24	.044*

***p-value<0.05 is significant**

COMPLICATIONS AND OUTCOME

Intra-operative complications were observed in none of the two groups. However immediate post-operative neurological worsening were found in both the groups which were statistically insignificant and improved transiently with time. [Table 4]

Table No. 4: Distribution Of Study Subjects According To Neurological Worsening In Both The Groups

Neurological Worsening	Group 1		Group 2	
	Frequency	Percentage	Frequency	Percentage
Mild Damage Of L Ext Proprireception, Not Interf With Gait	1	4.0	0	0
Mild Brocas Aphasia	0	0	1	4.0
Total	25	100.0	25	100.0
Chi square	2.651			
p-value	0.180*			

***p-value>0.05 is insignificant**

DISCUSSIONS

Conventional neuronavigation systems are a standard tool in the planning and performing of a craniotomy . Neuronavigation is based on preoperative images[CT ,MRI] with all its positive features: spatial resolution, width of field, absence of anatomic limitations, and the familiarity of neurosurgeons with this imaging technique.

Its main limitation is due to the fact that it is based on preoperative imaging that cannot be updated intra-operatively, so it does not take into account dynamic phenomena such as brain shift, brain deformation (retractors, spatula, and surgical manueuvers), tissue resection and parenchyma re-expansion. Once the bone flap has been removed, brain shift takes place, affecting neuronavigation references and making it less accurate for fine recognition of anatomical landmarks. Even if it would be possible to correct initial brain shift over and over again during surgery, it is not possible to fix the brain deformation that inevitably takes place through surgical manipulation.

Consequently, these factors cause the preoperative images to be inadequate in describing the real anatomic situation during surgery. The advantages of adding intra-operative ultrasound to neuronavigation is that it is a repeatable, fast, cheap, generally available, manually free moving, real-time imaging modality. Nevertheless, its limited field of view, the unusual plane of insonation, its image quality, and the dependency on operator skill and training make it difficult to interpret.

Fusion imaging is a particularly useful tool since it combines the benefits of two imaging modalities, thus overcoming the limitations of both. Coupling these two techniques exceeds the limitations of each technique alone and introduces a new approach to surgery. An increasing number of studies have reported the usefulness of intraoperative ultrasonography in identifying glial lesions and guide their resection.

RESIDUAL TUMOUR VOLUME AND OUTCOME

Mean residual tumour volume in group 1 was 4.07cm which was significantly lower than mean residual tumour volume in group 2 which was 5.10.[p= 0.04]

Intra Operative USG has excellent diagnostic accuracy in identifying residual tumors, especially in patients with low-grade tumors, improving the prognosis and quality of life. IOUS is an effective, safe, inexpensive tool to optimize the extent of cerebral glioma resection.

The ultrasound finding that characterizes residual tumors consists of an irregular and hyperechoic area, greater than 5 mm in thickness, extending to the brain tissue adjacent to the resection cavity. The use of IOUS does not lead to significant increases in total operative time or have any negative consequences for patients.

Precise localization of the tumor and identification of its boundaries are crucial to improve surgical strategies. Real-time imaging with intraoperative ultrasound (IOUS) is a relatively simple and reproducible method that is widely used for tumor localization, monitoring of residual disease, aspiration biopsy guidance, and imaging of intracranial glioma blood flow.

In recent years, the use of residual tumor detection devices has led to radical excisions and a consequent decrease in the rate of malignant degeneration, as well as an increase in mean and progression-free survival.

Extent Of Resection Along With Resection Rates

We obtained an Extent of Resection average of 84.6% in the group 1 statistically significant than 78.3% in the group 2 .[P-value- 0.014]

The rate of GTR in the group 1 was 84% whereas in group 2 ,60% GTR rate was obtained which was significantly lower. Rates of partial resection and subtotal resection were 8% both in group 1 while in group 2, rates of partial resection was 8% and subtotal resection was 32%.This shows there was statistically significant difference between two groups [p-value- 0.011]. Collectively these data indicates that neuronavigation with intraoperative ultrasound could be particularly useful in minimizing residual tumour volume along with increasing the extent of resection than conventional navigation alone in glioma surgery.

Moiraghi et al. proved that real-time Navigational USG promoted better extent of resection (EOR) and neurological outcomes during resection of noneloquent HGGs compared with conventional neuronavigation (NN).

Meanwhile, extent of resection is of great importance for the treatment of gliomas given that it hinders malignant transformation and improves patient survival. However, under conventional conditions, distinguishing gliomas from normal brain tissue has always been challenging.

Unsgård and Lindseth revealed that the improved tumor control obtained during intra-operative ultrasound guided glioma resection was not achieved at the expense of patient quality of life.

Rygh et al. demonstrated that before resection, intra-operative ultrasound was able to describe the tumor boundary with high specificity and sensitivity (both 95%).

Distribution Of Study Subjects According To Neurological Worsening In Both Groups

Post- operatively there was mild worsening of left external proprioception in group 1 and mild broca's aphasia. However both these changes were statistically insignificant and improved transiently with time within next 3-4 months.

Technical Considerations

Neuronavigation with intra-operative USG was employed for surgical planning and craniotomy placing, to identify the lesion before dural opening and during tumor resection, for brain-shift correction, and for the detection of any residual tumor at the end of surgery. For all 25 cases of Neuronavigation with intra-operative USG group , it was necessary to use fine-tuning during the operation, after the removal of the operculum bone, and, subsequently, during intradural surgery in order to correct the discrepancies between ioUS and pre-operative images caused by brain shift. In all these cases relying on US images, the surgeon was always able to correct navigation misalignment. Recalibration and fusion of US imaging and pre-operative imaging has demonstrated an excellent ability to compensate the loss of accuracy due to brain shift.

On the other hand, at the end of most of the surgeries, a substantial distortion and deformation of brain parenchyma often makes it impossible to have a precise overlap between images. In this case, the surgeon relies exclusively on US images.

In cases of important parenchymal deformation, it would have been impossible to complete any intervention relying solely on images from the initial registration because of the increasing navigation loss of accuracy, possibly emphasizing the drawbacks of the classical neuronavigation.

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