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Clinical Article

Intraoperative ultrasound in determining the extent of resection of parenchymal brain tumours – a comparative study with computed tomography and histopathology

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Summary

Background. Radical excision of parenchymal brain tumours is generally associated with a better long-term outcome; however, it is difficult to ascertain the extent of resection at surgery. We used intra-operative ultrasound [IOUS] to help detect residual tumour and define the tumour-brain interface.

Methods. Thirty-five patients with parenchymal brain lesions including 11 low-grade and 22 high-grade tumours and 2 inflammatory granulomata were included in the study. The IOUS was used to localize tumours not seen on the surface, define their margins and assess the extent of resection at the end of surgery. Multiple samples from the tumour-brain interface which were reported as tumour or normal tissue on IOUS were submitted to histopathology. The IOUS findings were compared with a postoperative contrast enhanced computed tomogram [CT] and with histopathology.

Results. All tumours irrespective of histology were hyperechoic on IOUS. IOUS was useful in localizing those tumours not seen on the surface of the brain. In 71.4% of cases IOUS was useful in defining their margins, however in the remaining cases the margins were ill-defined. The tumour margins were ill-defined in those treated previously by radiation. With regard to the extent of excision, after excluding the cases who were irradiated, it was found that in the 28 patients who had parenchymal neoplasms, there was concordance between the ultrasound findings and the postoperative CT scan in 23 cases. Of the 79 samples taken from the tumor-brain interface which were reported as tumour on ultrasound, 66 had histopathological evidence of tumour while 13 samples were negative for tumour. On the other hand, in the tissue sent from 17 sites where the IOUS showed no residual tumour, 2 were positive for tumour on histopathology while 15 were negative.

Interpretation. In conclusion, IOUS is a cheap and useful real-time tool for localizing tumours not seen on the brain surface, for defining their margins and for determining the extent of resection.

Keywords: Intraoperative ultrasound; glioma; brain neoplasm; computed tomography.

Introduction

It is generally accepted that the most effective management of primary and secondary brain tumours is maximal surgical resection followed by radiation and chemotherapy [9, 10, 14]. The likelihood of excising an intraparenchymal brain tumour depends on the surgeon's ability to localize the tumour, define its margins and recognize the presence of residual tumour. The tumour-brain interface may be difficult to define intraoperatively and the surgeon relies on a change in tissue colour and consistency. Although intra-operative MRI and CT scans are useful, they are expensive and available in only a few centres. Several studies have shown that intra-operative ultrasound is a reliable real-time tool for assessing tumour volume, defining tumour margins and for detecting residual tumour [7, 11, 15].

This prospective study was designed to evaluate the usefulness of intra-operative ultrasound (IOUS) in the detection of residual tumour compared with a postoperative computed tomogram and with histopathology.

Material and methods

We prospectively studied 35 patients with parenchymal brain tumours undergoing surgery using intra-operative ultrasound between July and December 2000. All patients had a CT scan and 11 had

magnetic resonance imaging in addition. At surgery, the operating field was kept horizontal so that saline could fill the tumour bed for appropriate ultrasound usage. All the intra-operative ultrasound studies were done with the same machine (Pie Medical Scanner 200). The transducer frequencies used were 5.0 and 7.5 MHz and the probe draped in a sterile manner. The dural opening was tailored to the ultrasound localization of the tumour. The brain was insonated to localize masses that were not seen on the surface and the echogenicity of the tumour noted. The margins of the tumour were considered well defined on IOUS when they could be clearly differentiated from normal brain, and poorly defined when the margins could not be seen or separated from normal brain. The surgeon then proceeded to excise the tumour and the ultrasound used periodically whenever the surgeon felt he had reached normal brain tissue. A final ultrasound assessment was made when the surgeon felt that the tumour was completely excised to determine the presence of residual tumour. Tissue samples taken from these marginal zones were submitted to histopathology making a note of whether the IOUS reported the areas as tumour or normal tissue. Surgery usually proceeded until the sonologist declared that there were no residual hyperechoic areas suggestive of tumour. There were 12 cases in which tumour was intentionally left behind in an eloquent area. The pathologist was not informed of the findings on intra-operative ultrasound. Photographs were taken with a digital camera directly off the screen of the ultrasound machine and stored in a database. All patients underwent a hyperacute plain and contrast CT scan immediately after the surgery.

Results

There were 24 males and 11 females. Six patients were less than 18 years of age. Five patients had been operated on and irradiated previously while the remaining were operated on for the first time. Of the five tumours in patients with prior irradiation, four had poorly defined margins on the CT scan while one had ill-defined margins on MRI with no enhancement on gadolinium. Thirteen patients had intratumoral cysts.

Table 1 shows the pathological diagnosis in 35 patients undergoing craniotomy and excision with intra-operative ultrasound. All lesions were hyperechoic in relation to normal brain. The high-grade gliomas exhibited a non-homogenous hyperechoic pattern with areas of necrosis and cystic degeneration being hypoechoic (Fig. 1). When there was haemorrhage within the tumour these areas were intensely hyperechoic. The low-grade tumours were also hyperechoic, and were however, more homogenous in appearance (Fig. 2).

Table 1. *Pathological diagnosis in 35 patients undergoing surgery with ultrasound guidance*

Tumour pathology	Number
Primitive neuro-ectodermal tumours	1
High grade gliomas	23
– Glioblastomas	20
– Anaplastic oligodendrogliomas	2
– Anaplastic astrocytoma	1
Low grade gliomas	6
– Diffuse Astrocytoma	3
– Oligodendroglioma	1
– Mixed Astrocytoma-Oligodendroglioma	1
– Pleomorphic Xantho-astrocytoma	1
Neuronal tumours	5
– Dysembryoplastic Neuro-epithelial tumour	2
– Ganglioglioma	3
Inflammatory	2
– Tuberculoma	1
– Cysticercus granuloma	1

Table 2 is a comparison between CT and intra-operative ultrasound [IOUS] in defining the margins of the 35 parenchymal brain tumours. Ten tumours had poorly defined margins on IOUS and the tumour-brain interface was also ill defined at surgery indicating that the tumour was more extensive than the CT-enhancing margins would suggest. These 10 cases included four who had undergone prior radiation and two who had low-grade gliomas.

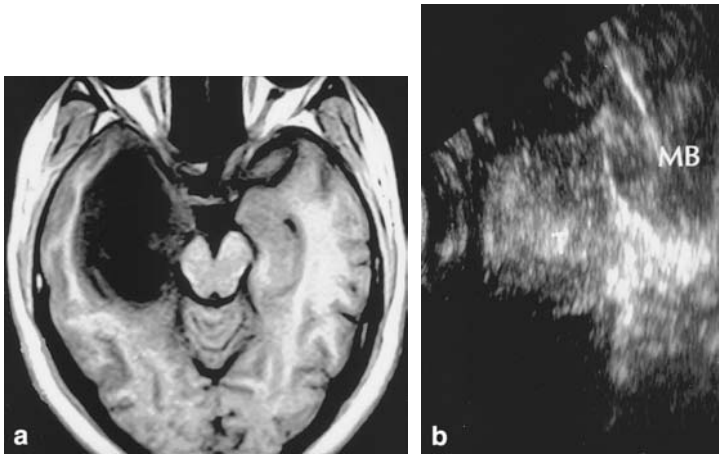

Fig. 1. (a) The axial T1-weighted post-gadolinium MRI scan of a low grade glioma, showing a uniformly hypointense, non-enhancing mass in the right temporal lobe with well defined margins. (b) The axial IOUS done soon after opening the dura. Note the hyperechoic tumour (*T*) with well-defined margins abutting the middle incisural space and midbrain (*MB*)

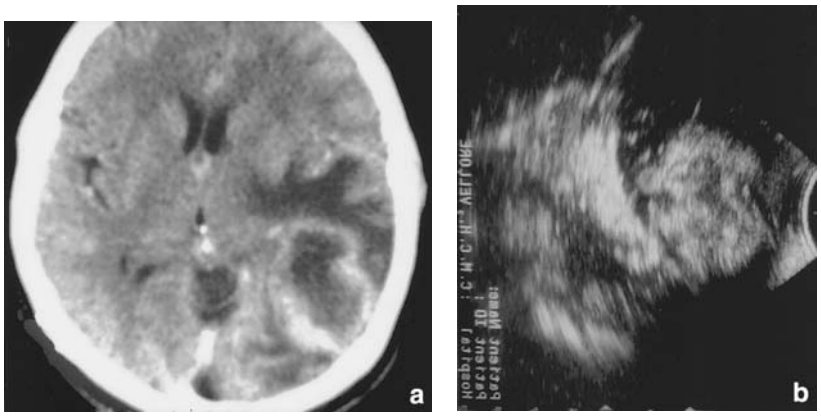

Fig. 2. (a) An axial contrast enhanced CT scan of a high grade glioma showing a peripherally enhancing mass in the posterior parietal region with central necrosis and marked peripheral oedema. (b) The axial IOUS done soon after opening the dura. The mass is hyperechoic with a central hypo-echoic area corresponding to the central necrosis seen on the CT scan. The margins are well defined

Table 2. *A comparison between computed tomography and intra-operative ultrasonography in defining the margins of 35 parenchymal brain tumours*

		Computed tomography	
		Well defined	Poorly defined
Intra-operative ultrasound	Well defined	24	1
	Poorly defined	7	3

Table 3. *The postoperative CT findings correlated with the corresponding intra-operative ultrasound findings in 28 patients with intraparenchymal tumours (5 patients who had received prior RT and the 2 inflammatory granulomas were excluded)*

		Computed tomography	
		Residual tumour seen	No residual tumour seen
Intra-operative ultrasound	Residual tumour seen	10	1
	No residual tumour seen	4	13

Table 4. *A comparison of IOUS and histopathological findings in 96 samples from the parenchymal tumours in low-grade tumours*

		Histopathology	
		Tumour positive	Tumour negative
Intra-operative ultrasound	Tumour positive	66	13
	Tumour negative	2	15

Table 3 is a comparison between the IOUS findings and the postoperative CT scan findings in the 28 patients with parenchymal tumours. Five patients who had received prior radiation and 2 inflammatory granulomas were excluded from the analysis. There was concordance between the ultrasound findings and the postoperative CT scan in 23 of 28 cases. However, in 4 cases the IOUS failed to report tumour that was detected on the postoperative CT scan and in one case the IOUS reported residual tumour that was not seen on the postoperative CT scan. Table 4 compares the ultrasound findings with the histopathology reports in 96 tissue samples taken from the tumour margins in 28 patients with parenchymal tumours. These samples were taken from the tumour margin when the surgeon felt that the tumour had been completely removed. In 79 samples presumed to be tumour on ultrasound, 66 had histopathological evidence of tumour while 13 samples were negative for tumour. On the other hand, in the tissue sent from 17 sites where the IOUS showed no residual tumour, 2 were positive for tumour on histopathology while 15 were negative.

Discussion

Radical surgical resection of parenchymal brain tumours is largely limited by the surgeon's ability to localize tumours not seen on the surface, define their margins and to differentiate residual tumour from normal brain. In this prospective study of 35 patients, we used intra-operative ultrasound to assess the extent of resection of parenchymal brain tumours and compared the findings with that of histopathology and an immediate postoperative CT scan.

Our findings show that most parenchymal tumours, irrespective of histopathology are hyperechoic on ultrasound. Therefore, lesions that are not seen on the

surface can be accurately localized by IOUS and we found this especially useful during tumour excision. With regards to estimation of extent of excision, in comparison with postoperative CT, there was a concordance with the IOUS findings in 23 of 28 cases (82%) and a discordance in 18% when the IOUS failed to detect or falsely reported residual tumour.

This study is unique in that we have histopathological correlates for the IOUS findings at the end of surgery. We compared the ultrasound findings, when the surgeon felt that the tumour was completely excised, to histopathology on samples taken from the tumour margins. In the majority of samples there was a concordance between IOUS and histopathology, however, there were instances (16%) when the ultrasound reported tumour while the biopsies were negative.

While, we acknowledge that there are limitations in any study using imaging modality for the detection of residual tumour, in our study, the tumour margin was well delineated by IOUS in 25 of 35 cases. It needs to be borne in mind that current imaging techniques may not fully reflect the biological extent of the tumour. That is, the detection of microscopic tumour cell migration into the surrounding parenchyma may not be feasible and hence the aim of intra-operative image guidance would be to achieve the optimal extent of resection keeping this limitation in mind. The utility of ultrasound is limited only to cases where a margin can be well defined. The number of cases in our study is small and a larger series with a greater number of patients in each histopathological subgroup would enable us to draw firm conclusions regarding the efficacy of IOUS in low or high-grade tumours. Most ultrasound studies have shown that the margins of parenchymal brain tumours are readily differentiated from surrounding brain [6, 11]. Some studies have even reported the ability of ultrasound to differentiate oedema from solid tumour that is difficult on both CT and MR imaging [5]. However, two studies using ultrasound reported that the tumour borders were less clear as compared to CT [1], and that on occasion the borders of low-grade gliomas were not definable [24]. Hammoud *et al.* [7] found that ultrasound was able to clearly define tumour margins in most tumours, except for those that had undergone prior radiation.

At present, the preferred method of estimating residual tumour postoperatively is by MR imaging. Hammoud *et al.* [7] used postoperative MR imaging for measuring post excision tumour volumes and established that intra-operative ultrasound was able to define well the extent of resection in 18 patients with gliomas, four of five patients with recurrent gliomas and in all 34 patients with metastatic tumours. However, the extent of resection was poorly defined in all patients who had radiation-induced lesions.

One study reported that IOUS imaging for the detection of residual tumour towards the end of operation was unreliable [24]. Blood clots in the tumour cavity, despite irrigation with saline, can result in a hyperechoic band on ultrasound that may be interpreted as tumour. This may have contributed to the false positives on IOUS in the low-grade and high-grade tumours in this study. Irregularities of the tumour-bed created during the excision possibly create multiple interfaces that result in the increased echotexture, indistinguishable from the tumour echotexture. Acoustic enhancement is another phenomenon that can explain the low specificity but we were well aware of this fact [22]. Sound waves traversing a cyst are less attenuated as compared to those passing through solid tissue. Therefore, a hyperechoic rim is created on the far side of the cyst cavity. A tumour cavity filled with saline acts in a similar fashion to a cyst and the non-attenuated sound waves results in a hyperechoic rim in the tumour bed resembling tumour. The presence of blood in the tumour bed and contrast enhancement in the disrupted blood-brain-barrier may be other, confounding factors. In a comparison of ultrasound, CT and histological findings from stereotactic biopsies, Becker *et al.* [3] found that the 32 of 33 contrast enhancing areas on CT were hyperechogenic on ultrasound and 29 of 32 [91%] contained tumour tissue. Hyperechogenic areas always represented solid tumour (23/23 patients), even when CT showed low density non-enhancing lesions. Interestingly, biopsies obtained from parenchyma with normal echogenicity revealed tumour in 3 of 16 specimens.

Stereotactic localization techniques, intra-operative MR and IOUS

Frame-based and frameless stereotactic techniques, making use of CT or MR imaging, are routinely used to help surgeons accurately localize lesions, plan the site of craniotomy and identify critical structures for preservation [2, 17, 26]. These have inherent problems related to loss of accuracy resulting from unpredictable distortions, shifts and deformations after a craniotomy and tissue removal. Furthermore, using these

techniques it is not possible to track surgical instruments as they pass through brain tissue to cysts or tumours; residual tumour still has to be recognized by gross visual inspection and hyperacute tumour-bed, epidural or subdural hematomas cannot be detected until a postoperative imaging is performed. Intra-operative imaging techniques, such as, ultrasound, CT and MR, therefore, have a role to play in providing periodic updating during the surgery. IOUS has been employed in neurosurgery for almost 2 decades, [18] does not have the drawbacks that the frame-based or frameless stereotactic methods have and has several advantages over intra-operative CT and MR imaging. The intra-operative examinations are real-time, allowing surgeons to immediately correct the trajectory to deep-seated lesions [16, 25]. Moreover, ultrasound scans are inherently stereotactic, in that the frame of reference is always the transducer itself, that is located at the craniotomy site. This makes biopsy and guidance of procedures very simple obviating the need for additional computers or stereotactic frames to map the co-ordinates from the frame of reference of MR imaging to that of the operator [20]. Recently, Unsgaard *et al.* [23] have combined a pre-operative MRI with intra-operative ultrasound in an attempt to provide the surgeon with an updated image. These authors integrated the 3-D ultrasound imaging device into a navigation system thereby enabling the position of the ultrasound probe to be detected by the navigation camera. This allows a spatial correction of the 3-D MR scan of the lesion when brain shifts occur during surgery. They subjectively felt that residual tumour was discovered on the last 3-D ultrasound scan in 53% of cases in which the resection was considered complete.

The principal advantage of IOUS is that the significant expense and difficulties involved in making the operating room ''MR compatible'' do not exist. The advantages of intra-operative MR imaging include helping in marking the craniotomy flap, precise delineation of the tumour margin on T2-weighted scans and in the detection of hemorrhage [21]. Although conventional US machines cannot help in planning the craniotomy, transcranial ultrasound can identify brain tumours through the skull albeit in areas where the bone is thin [3, 4]. Furthermore, early tumour-bed haematomas have a characteristic appearance on US and have been documented at routine diagnosis and in the operating theatre [8, 13, 19].

In conclusion, intra-operative ultrasound is a cheap and useful real-time tool for determining the extent of resection in parenchymal brain tumours when intra-operative MRI and CT are not available.

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Comment

The authors of this paper have operated 35 patients with parenchymal brain tumors, using intraoperative ultrasound to localize tumors not seen on the surface, define margins of the tumors and assess the extent of the resection at the end of surgery. The paper indicates that ultrasound has the same ability as CT in defining tumor margins and detecting residual tumor, which is an important observation in itself. But we know that postoperative CT is "kind" to the surgeon by not showing residual tumors that the surgeon himself knew was left behind. The comparison to histopathology is therefore more important. The correlation between ultrasound image and histopathology is very good. It would have been nice to have some illustrations from the biopsy sampling to see the image quality at that stage of the operation, but an instant image is not necessarily fair to the method, because ultrasound is dynamic, making it possible to follow the progress of the operation, and thus providing the surgeon with information that an outside observer do not have. This paper adds important data to the growing literature that indicates that intraoperative ultrasound is a reliable tool for imaging during brain tumor operations.

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