Neurosurgical Forum LETTERS TO THE EDITOR

Identification of residual glioma using ultrasound miniprobes

TO THE EDITOR: We read with great interest the paper written by Prada et al.⁹ (Prada F, Del Bene M, Fornaro R, et al: Identification of residual tumor with intraoperative contrast-enhanced ultrasound during glioblastoma resection. *Neurosurg Focus* 40(3):E7, March 2016) describing the benefits of contrast-enhanced ultrasound (CEUS) use during glioblastoma surgery. The authors should be commended for popularizing this technology among neurosurgeons. In fact, our interest in CEUS was triggered after reading the important study by Prof. DiMeco's group,¹¹ and we started to perform this technique at our department this year. CEUS appears to be undoubtedly very promising in oncological as well as in vascular neurosurgery.

Nevertheless, we would like to comment on the authors' discussion concerning identification of residual glioma tissue using CEUS versus identification using a miniature US probe inserted into the resection cavity—a technique we presented in 2012.¹⁵ Prada et al. correctly pointed out the fact that small probes have a limited field of view.⁹ However, we cannot agree with the statement that it is not possible to obtain an overview of the anatomy and residual mass entity by using miniprobes. Indeed, the limited field of view of miniprobes is a significant limiting factor predominantly when these probes are used with a 2DUS system; in that case the anatomical orientation certainly may be difficult.^{2,7} In contrast, when miniature probes are used with navigated 3DUS systems, which allow rendering of the US image in orthogonal planes (axial, coronal, and sagittal) and automatic fusion with preoperative MRI sequences, the anatomical orientation and residual tumor identification is usually not a major challenge.^{2,7,12,13,15,16} These systems use US probes equipped with reflective marker reference frames; the 3DUS data are acquired by freehand probe movement, tracking the position and orientation of the probe by means of a navigation camera system. After scanning (i.e., 3DUS data acquisition), 3DUS systems enable surgeons to visualize and navigate the whole volume of normal and pathological tissue that was scanned; thus the narrow field of view of miniprobes is not a significant limiting factor, because the volume of tissue scanned and subsequently visualized can be relatively large (Fig. 1). In addition, the 3DUS data acquired during several scanning sessions can be fused into a single image.

This might be helpful in situations in which a superficial vessel crosses the resection cavity and hinders sufficient movement of an inserted miniprobe, and thus precludes scanning of the whole bottom of the resection cavity during a single scanning session. Of note, the whole process of rendering the US image in 3 dimensions and the automatic fusion with preoperative MRI sequences (or other US data) takes only few seconds.

A significant benefit of the use of mini-probes is the fact that their insertion into the resection cavity enables distinct visualization of both normal and pathological structures at the resection cavity bottom (Fig. 1).^{12,13,15,16} When the resection cavity is scanned using a US probe placed on the brain surface, its bottom is often depicted indistinctly^{3,4,8} due to the acoustic enhancement artifacts (AEAs); these are the most common and dominant image artifacts in intraoperative US imaging of brain tumors.¹² The AEAs appear when US penetrates a higher column of water (saline) as a result of the large difference between a very low attenuation of acoustic waves in water (saline) and high attenuation in brain tissue.^{5,12} By inserting the miniprobe into the resection cavity, the column of saline between the tip of the probe and scanned tissue at the bottom of the resection cavity gets smaller (or is even absent if the tip of the miniprobe touches the bottom); shortening the column of saline reduces the AEAs and enables better visualization of the structures at the resection cavity bottom (Fig. 1). Additional use of the 3DUS power-Doppler mode (Fig. 2) further facilitates the surgeon's anatomical orientation and contributes to the safety of the procedure.¹⁴ Moreover, integration of all updated data into a single comprehensible image is possible by performing a fusion of the US image obtained with a probe placed on the brain surface (showing the whole resection cavity and adjacent tissue) and the image data obtained with a miniprobe distinctly visualizing the medial part of the resection cavity (Fig. 3).

Importantly, considering the specificities of both methods, identification of residual lesion by using miniprobes might be superior in some glioma types to use of CEUS. Besides imaging of various lesions, small US probes inserted into the resection cavity generally enable direct visualization of residual mass also in Grade II astrocytomas (Figs. 1–3); these tumors are most often hyperechoic.^{6,17} The role of CEUS in visualization of residual Grade II astrocytomas needs to be determined, considering the facts that these tumors often have limited vascularity¹ and that

FIG. 1. Visualization of a right-sided insulo-opercular Grade II astrocytoma before and during resection. The yellow lines and the center of their intersection are placed on all images at an identical point of the cranial cavity. **A:** Preoperative 3D FLAIR MRI axial and coronal sequences. **B:** Preresectional intraoperative 3DUS image performed with large version of a flat linear array (FLA-L) probe, frequency range 6–12 MHz (SONOWAND AS) fused with navigation MRI sequence. Red arrows designate the medial tumor border, and black arrows the superior periinsular sulcus. **C:** A 3DUS scan performed from the brain surface during the resection using an FLA-L probe. White line designates the virtual position of the probe during the scanning. Note that due to AEAs (white arrows) the hyperechoic area extends far more medially than was the position of the medial tumor border, which cannot be reliably recognized because it is overlapped by AEAs; blue arrowhead points to the superficial vein crossing the resection cavity. **D:** A 3DUS image acquired via scanning with a minicraniotomy (MC) probe, frequency range 5–10 MHz (SONOWAND AS), inserted within the resection cavity; the AEAs are minimized. Note distinct visualization of the medial tumor border (red arrows). Two scanning sessions were performed and fused; black and white lines depict the virtual position of the miniprobe during the scanning. Note that a large area of brain could be visualized using the miniprobe.

FIG. 2. Use of 3DUS power-Doppler mode. **A:** Preresectional 3DUS image performed with a 12-FLA-L probe fused with navigation MRI FLAIR sequence and 3DUS power-Doppler data; 3DUS angiography was performed using a flat phased array (8-FPA) probe, frequency range 3–8 MHz (SONOWAND AS). Note that one of the lenticulostriate arteries (arrow) is just medial to the medial tumor border. **B:** A 3DUS scan performed from the brain surface during the resection using a 12-FLA-L probe fused with 3DUS power-Doppler data; note that the lenticulostriate artery (arrow) is now within the hyperechoic area of the AEAs, and the medial margin of tumor is not identifiable. **C:** A 3DUS image acquired via scanning with an MC probe inserted within the resection cavity fused with 3DUS power-Doppler data. Note that the medial tumor margin and its anatomical relationship with the lenticulostriate artery (arrow) is distinctly depicted, and the AEAs are minimized.

FIG. 3. Integration of 3DUS data obtained with a large probe and a miniprobe into a single comprehensible image. Intraoperative visualization of residual tumor (**A**) during the resection using a fusion of the US image acquired via scanning from the brain surface using an FLA-L probe with the US image acquired via scanning with the MC probe inserted within the resection cavity and preoperative MRI FLAIR sequence. Note that the MC probe was used for visualization of the medial tumor border and the 12-FLA-L probe was used for the rest of the tumor. The center of the intersection of the yellow lines is within the resection cavity. All margins of the residual tumor are distinctly depicted (arrows). The image is easier to interpret when comparing to preresectional 3DUS images (**B**) and preoperative MRI (**C**) rendered in corresponding orthogonal planes.

the agents used for CEUS are purely intravascular.⁹ As previously reported by Prada et al., the enhancement of low-grade gliomas using US contrast agents is only mild,¹⁰ and their borders are not always clearly distinguishable from healthy brain tissue.¹¹ Using miniprobes might represent a plausible solution enabling detection of residual tissue in tumors that are not distinctly visualized by CEUS. Future studies are necessary to determine possibilities for the utilization of both techniques; in addition, further development of high-end US systems as well as development of new standard US probes and miniprobes is necessary to get optimal image quality. Potential integration of miniprobes and CEUS into a single 3DUS system should be considered, because the benefits of both techniques could be provided during the surgery and could contribute to better visualization of normal and pathological parenchymal and vascular structures.

Andrej Šteňo, MD, PhD
Viktor Matejčík, MD, PhD
Juraj Šteňo, MD, PhD

Comenius University, University Hospital Bratislava, Bratislava, Slovakia

References

1. Cha S, Tihan T, Crawford F, Fischbein NJ, Chang S, Bollen A, et al: Differentiation of low-grade oligodendrogliomas from low-grade astrocytomas by using quantitative blood-volume measurements derived from dynamic susceptibility contrast-enhanced MR imaging. *AJNR Am J Neuroradiol* **26**:266–273, 2005
2. Coburger J: Linear array ultrasound: a dedicated tool for a dedicated application. *Acta Neurochir (Wien)* **157**:959–960, 2015 (Letter)
3. Gerganov VM, Samii A, Giordano M, Samii M, Fahlbusch R: Two-dimensional high-end ultrasound imaging compared to intraoperative MRI during resection of low-grade gliomas. *J Clin Neurosci* **18**:669–673, 2011
4. Hentschel SJ, Lang FF: Surgical resection of intrinsic insular tumors. *Neurosurgery* **57** (1 Suppl):176–183, 2005
5. Jakola AS, Jørgensen A, Selbekk T, Michler RP, Solheim O, Torp SH, et al: Animal study assessing safety of an acoustic coupling fluid that holds the potential to avoid surgically induced artifacts in 3D ultrasound guided operations. *BMC Med Imaging* **14**:11, 2014
6. Le Roux PD, Berger MS, Wang K, Mack LA, Ojemann GA: Low grade gliomas: comparison of intraoperative ultrasound characteristics with preoperative imaging studies. *J Neurooncol* **13**:189–198, 1992

7. Moiyadi AV: Linear intraoperative ultrasound probes and phased-array probes: two sides of the same coin. **Acta Neurochir (Wien)** **157**:957–958, 2015 (Letter)
8. Petridis AK, Anokhin M, Vavruska J, Mahvash M, Scholz M: The value of intra-operative sonography in low grade glioma surgery. **Clin Neurol Neurosurg** **131**:64–68, 2015
9. Prada F, Del Bene M, Fornaro R, Vetrano IG, Martegani A, Aiani L, et al: Identification of residual tumor with intraoperative contrast-enhanced ultrasound during glioblastoma resection. **Neurosurg Focus** **40**(3):E7, 2016
10. Prada F, Mattei L, Del Bene M, Aiani L, Saini M, Casali C, et al: Intraoperative cerebral glioma characterization with contrast enhanced ultrasound. **Biomed Res Int** **2014**:484261, 2014
11. Prada F, Perin A, Martegani A, Aiani L, Solbiati L, Lamperti M, et al: Intraoperative contrast-enhanced ultrasound for brain tumor surgery. **Neurosurgery** **74**:542–552, 2014
12. Selbekk T, Jakola AS, Solheim O, Johansen TF, Lindseth F, Reinertsen I, et al: Ultrasound imaging in neurosurgery: approaches to minimize surgically induced image artefacts for improved resection control. **Acta Neurochir (Wien)** **155**:973–980, 2013
13. Šteňo A, Guissani C, Riva M: Multimodal imaging in glioma surgery, in Prada F, Solbiati L, Martegani A, et al (eds): **Intraoperative Ultrasound (IOUS) in Neurosurgery - From Standard B-mode to Elastasonography**. Cham, Switzerland: Springer, 2016, pp 81–97
14. Šteňo A, Jezberová M, Holý V, Timárová G, Šteňo J: Visualization of lenticulostriate arteries during insular low-grade glioma surgeries by navigated 3D ultrasound power Doppler: technical note. **J Neurosurg** [epub ahead of print February 5, 2016. DOI: 10.3171/2015.10.JNS151907]
15. Šteňo A, Karlík M, Mendel P, Čík M, Šteňo J: Navigated three-dimensional intraoperative ultrasound-guided awake resection of low-grade glioma partially infiltrating optic radiation. **Acta Neurochir (Wien)** **154**:1255–1262, 2012
16. Šteňo A, Matejčík V, Šteňo J: Intraoperative ultrasound in low-grade glioma surgery. **Clin Neurol Neurosurg** **135**:96–99, 2015 (Letter)
17. Unsgaard G, Selbekk T, Brostrup Müller T, Ommedal S, Torp SH, Myhr G, et al: Ability of navigated 3D ultrasound to delineate gliomas and metastases—comparison of image interpretations with histopathology. **Acta Neurochir (Wien)** **147**:1259–1269, 2005

Disclosures

The authors report no conflict of interest.

Response

We thank Prof. Andrej Šteňo and colleagues for their interest in our article and for their additional comments, with which we largely agree, and we are pleased to have the opportunity to further clarify our point of view. It is well known that the main drawback of B-mode US in glioma surgery is the arduous discrimination between residual tumor, surgically induced artifacts, and tumor-induced edema, especially at the latter stages of resection.^{1,5–7} In our article we report our experience with CEUS during glioblastoma (GBM) resection, the necessity of which had been raised precisely to highlight residual tumor, trying to overcome the aforementioned limitations. The use of contrast agents to highlight GBM tissue is in fact already well established for other imaging modalities such as CT and MRI. Furthermore, the use of CEUS has become a recognized solution to highlight tumoral tissue in other organs such as the liver.² With these considerations in mind

it seemed reasonable to us to attempt residual GBM visualization with CEUS.

In our paper we also analyze the major existing alternatives to overcome artifact-induced limitations. Particularly in regard to miniprobess, it is well known that, due to their physical construction and technical aspects, they suffer from a limited field of view, lateral resolution, and US penetration compared to larger linear array probes.^{1,5} Moreover, it takes time to scan the entire surface with such a limited array and also, despite the small proportions, the probes have a limited freedom of movement, especially when dealing with deep-seated lesions approached through narrow corridors (Fig. 1).

Šteňo and colleagues rightly point out all these limitations, advocating the use of navigated miniprobess to fuse the 3D data sets obtained with miniprobess to those obtained with standard linear probes placed on the brain surface. Fusion imaging between these modalities permits the investigator to obtain a complex data set that overcomes the drawbacks of both US probes. Even recognizing the value of this solution, we would like to discuss some aspects: further imaging processes are necessary to perform fusion imaging between a large 3D volume acquired with a linear array probe and the volume acquired with the miniprobe, because the miniprobe alone is insufficient for a correct orientation and comprehension of the surgical cavity. Another consideration regards the acquisition of a 3D volume to navigate on the 3 orthogonal planes. We believe that from a neurosurgical perspective this is a familiar image representation and also a practical tool for navigation, but in a certain sense it is counterproductive from a purely echographic point of view: it annuls the effect of real-time 2D evaluation, reducing the proprioceptive/eye-hand coordination information obtained while moving the probe to perform the US scan, making the mental reconstruction of the relationships, spatial position, and orientation of the structures under examination more difficult.

We believe that intraoperative US should be (at least initially) approached with a radiological clinical mindset, using the 2D feature as in other corporeal regions, thus taking advantage of the proprioceptive feedback, and of eye-hand coordination to reconstruct a mental representation of the surgical field. Interpretation of the US image might be facilitated by the use of fusion imaging between preoperative MRI and intraoperative 2D US, which allows for a continuous real-time comparison of the 2 modalities by using a familiar imaging method such as MRI to better understand US images (Fig. 2). On the other hand, the use of real-time 2D US permits one to overcome the limits of navigation based on preoperative data sets.⁴ The freehand acquisition of a 3D volume in which it is possible to navigate, in our opinion, is really useful and facilitates the identification of a given area within the surgical field but is at the same time less informative.

Nevertheless, the use of CEUS has several advantages: the US contrast agent's signal is highly specific and is poorly affected by artifacts and therefore is highly desirable to detect GBM remnants (Fig. 1). As demonstrated in our paper, CEUS was able to show tumor remnants in all cases in which a suspicious hyperechoic area on B-mode was found after gross-total removal, either on the walls or

FIG. 1. Sagittal B-mode and CEUS scan of a surgical cavity (arrowheads) obtained during the resection of a frontomesial GBM. The maximum width of the cavity is 2.5 cm, thus making tilting and sweeping of the miniprobe difficult. The cavity is crossed by the callosomarginal artery (A), which is highlighted in CEUS. Note that the CEUS is not affected by artifacts and provides images that are more clearly understandable.

at the bottom of the surgical cavity, even if artifacts on B-mode are present. Furthermore, CEUS allows one to study the surgical field numerous times during surgery with both 2D and 3D views provided by just 1 probe, allowing a real-time mental reconstruction of the volume. Moreover, it must be said that the information obtained with CEUS

highlights the more viable areas of the tumor, not just describing its morphological-echogenicity features.

Another interesting point raised by Steño and colleagues regards the identification of residual mass in low-grade glioma (LGG). In our article we report only on the use of CEUS in GBM because these tumors, due to their

FIG. 2. Screenshot of the US system during surgery for a GBM. Note how the continuous comparison between US and preoperative MRI helps in the understanding of US images. C = cerebellum; L = lesion; M = midbrain; T = tentorium.

biology, present a clearer interface between the core of the lesion and the surrounding parenchyma. As demonstrated in other papers from our group, in LGG, CEUS depicts the metabolically active tumor as an area of mild enhancement invading the healthy brain tissue and not always clearly distinguishable from the surrounding parenchyma.⁴ This seems to be especially true when the LGG is in proximity to the basal ganglia, which present a different contrast enhancement pattern on US compared to lobar parenchyma, similar to that of LGG. In other words, the CEUS pattern in LGG reflects the biology and the behavioral phenotype of these tumours.

In conclusion, we largely agree with Šteňo and colleagues in regard to the utility of miniproboscopes, especially in LGG remnant identification. However, we believe that this technique is somewhat cumbersome, in terms of time of acquisition and complexity of data visualization. We prefer (also in agreement with other authors) to check for residual tumor using linear array probes with a larger field of view to obtain a comprehensive representation,^{1,3} and we look forward to further improvements such as the fluid proposed by Selbekk and colleagues, which will help in reducing artifacts.⁵

Regarding GBM surgery, we found CEUS to be a good solution to overcome the insurgence of artifacts, and we strongly advocate its intraoperative use in neurosurgical procedures, as has already happened for other interventional procedures.

Francesco Prada, MD¹
Massimiliano Del Bene, MD¹
Francesco DiMeco, MD^{1,2}

¹Fondazione IRCCS Istituto Neurologico C. Besta, Milan, Italy

²Johns Hopkins Medical School, Baltimore, MD

References

1. Moiyadi AV: Linear intraoperative ultrasound probes and phased-array probes: two sides of the same coin. *Acta Neurochir (Wien)* **157**:957–958, 2015
2. Piscaglia F, Nolsøe C, Dietrich CF, Cosgrove DO, Gilja OH, Bachmann Nielsen M, et al: The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): update 2011 on non-hepatic applications. *Ultraschall Med* **33**:33–59, 2012
3. Prada F, Del Bene M, Mattei L, Lodigiani L, DeBeni S, Kolev V, et al: Preoperative magnetic resonance and intraoperative ultrasound fusion imaging for real-time neuronavigation in brain tumor surgery. *Ultraschall Med* **36**:174–186, 2015
4. Prada F, Mattei L, Del Bene M, Aiani L, Saini M, Casali C, et al: Intraoperative cerebral glioma characterization with contrast enhanced ultrasound. *BioMed Res Int* **2014**:484261, 2014
5. Selbekk T, Jakola AS, Solheim O, Johansen TF, Lindseth F, Reinertsen I, et al: Ultrasound imaging in neurosurgery: approaches to minimize surgically induced image artefacts for improved resection control. *Acta Neurochir (Wien)* **155**:973–980, 2013
6. Šteňo A, Karlík M, Mendel P, Čik M, Šteňo J: Navigated three-dimensional intraoperative ultrasound-guided awake resection of low-grade glioma partially infiltrating optic radiation. *Acta Neurochir (Wien)* **154**:1255–1262, 2012
7. Šteňo A, Matejčík V, Šteňo J: Intraoperative ultrasound in low-grade glioma surgery. *Clin Neurol Neurosurg* **135**:96–99, 2015

INCLUDE WHEN CITING

DOI: 10.3171/2016.5.FOCUS16180.

©AANS, 2016