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The Utility of CEUS as an Intraoperative Tool for Residual Brain Tumors: An Overview

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Abstract

Brain and other CNS tumors are the eight most common cancers in adults older than 40. This article reviews the main methods used to assess residual brain tumors, such as conventional ultrasound, magnetic resonance imaging (MRI), and contrast-enhanced ultrasound (CEUS). This opinion article points out the effectiveness of CEUS, compared to conventional ultrasound and MRI, as an intraoperative tool for residual brain tumors. Ultrasound (US) is a well-known imaging test that has been used for many years. This technology enables neurosurgeons to resect brain tumors more safely and preserve brain function without exposing the brain to ionizing radiation. Another vital tool frequently used is the MRI. This is a non-invasive imaging technology that produces three-dimensional detailed anatomical images. The most reliable imaging tool for brain tumors is gadolinium-enhanced resonance imaging. However, neurosurgeons have a postoperative time frame of 24-48 hours to perform an MRI with gadolinium enhancement; beyond that time frame, postoperative changes along the operative margins could be misinterpreted as residual enhancing tumors. Currently, the CEUS method is gaining popularity in the imaging field as a new radiological tool. CEUS has been effectively used to assess various organ afflictions, such as liver and renal tumors. However, there is limited evidence regarding its role in the central nervous system (CNS). The use of CEUS in brain tumors has shown to be more accurate in solid tumors when compared to cystic lesions. According to our research, contrast-enhanced ultrasound over conventional ultrasound in the US suggests a better outcome for patients undergoing neurosurgical procedures by reducing brain damage that could result from surgical removal of tumors. Therefore, CEUS should be considered in different operative stages for surgical brain tumor removal and postoperative clinical evaluation to ensure a better outcome for these patients.

Keywords: CEUS; Contrast-Enhanced Ultrasound; Residual Brain Tumor

Abbreviations: CEUS: Contrast-Enhanced Ultrasound; MRI: Magnetic Resonance Imaging; US: Ultrasound; CNS: Central Nervous System; ioUS: Intraoperative Ultrasound; CSF: Cerebrospinal Fluid; LGG: Low-grade Glioma; HGG: High-grade Glioma; BBB: Blood-brain Barrier; PWI: Perfusion-weighted Imaging; MRS: Magnetic Resonance Spectroscopy; DTI: Diffusion Tensor Imaging; fMRI: Functional Magnetic Resonance Imaging; rCBV: Relative Cerebral Blood Volume; Cho/NAA: Choline/N-acetyl-aspartate; BOLD: Blood Oxygen Level Dependent

Introduction

Contrast-enhanced ultrasound (CEUS) is an imaging technique that involves intravenous injection or installation into body cavities of agents that contain gas or air microbubbles that can be transported into the smallest capillaries, allowing visualization of the arterial system following venous injection. Since they are excreted from the lungs and liver, they are safe for patients with decreased renal function. CEUS provides a real-time view into the vascularization and blood flow distribution patterns within an organ or tumor, which may enhance the resolution, sensitivity, and specificity of ultrasound imaging and estimate the degree of tumoral resection [1,2]. This imaging modality can depict the targeted organ's micro and macro circulation, which may include the brain, liver, gallbladder, bile duct, pancreas, kidney, spleen, breast, thyroid, and prostate resulting in improved performance in diagnosis. CEUS consists of two essential elements: an ultrasound contrast agent and a contrast-specific imaging technique. An ultrasound contrast agent circulates within the body and interacts with the ultrasound beam based on the energy of the insonation. Low acoustic powers cause the microbubbles to reflect ultrasound and increase the echo. As the acoustic power increases, the bubbles develop nonlinear resonance, resulting in the generation of harmonic signals. As the power increases, bubble destruction occurs, producing an intense signal. Generally, contrast-specific imaging techniques, such as phase and pulse inversion, discriminate between nonlinear harmonic responses from microbubbles and tissue responses, thereby enabling the detection of microbubble signals in gray-scale images [3].

According to the American Cancer Society, brain and other CNS tumors are the eighth most common cancer in adults older than 40. Most CNS tumors diagnosed in adults are non-malignant (age-adjusted incidence of 22.38 per 100,000 people). Gliomas are the most common type of malignant histology found in adults, while meningiomas and tumors of the pituitary are the most common types of non-malignant tumors. Additionally, malignant brain and other CNS tumors are the sixth leading cause of cancer death in adults older than 40 in the USA [4]. This review analyzes the primary methods for assessing residual brain tumors: conventional ultrasound, magnetic resonance imaging (MRI), and contrast-enhanced ultrasound (CEUS). This opinion article aims to highlight the effectiveness of CEUS when compared to conventional ultrasound and MRI.

Conventional Ultrasound

Ultrasound (US) is a well-known imaging test that has been used for many years. Although US has many advantages, such as low cost, non-invasive, and low radiation exposure, it also has drawbacks, such as high operator dependence and a demanding technique [5-7]. The classic gray-scale brightness mode is the most common type, called B-mode. This simple US imaging method helps identify anatomical structures by sending and receiving sound waves at high frequencies to create a two-dimensional image [5,6]. Over the past few years, ultrasound has proven helpful in the intraoperative setting, especially neurosurgery [5,6]. Due to its complexity, resectioning brain tumors is one of the most challenging procedures for neurosurgeons. The tumor often invades delicate brain tissues, making it difficult to remove it entirely and prevent brain damage. Intraoperative ultrasound (ioUS) has aided neurosurgeons in improving tumor resection rates and preserving brain function without ionizing radiation exposure. The use of ioUS has been widely employed to assist in resecting brain tumors, especially gliomas, the most common primary brain malignancy, which is highly invasive and has a poor prognosis. ioUS has been used primarily during tumor resection to localize and characterize tumors, plan the surgical approach, and delimit the extent of the resection. However, ioUS has been limited by a phenomenon referred to as brain shift, which occurs when the anatomy of the brain changes due to craniotomy, swelling, drainage of the cerebrospinal fluid (CSF), or cavity formation. This brain shift destroys a necessary contact surface between the brain and the probe, disrupting the clarity of the image [5,6].

In a US image, the brightness of anatomical structures shines back the magnitude of the reflected sound waves, which can have strong (hyperechoic), weak (hypoechoic), or neutral (isoechoic) acoustic gradients [5,6]. Typical brain structures may exhibit any acoustic gradient [1,2,5,6]. Tumors often appear hyperechoic, particularly at their margins, but the edema surrounding them can be hypoechoic [5,6,7]. There is a need to emphasize this since the edema surrounding the tumor is often mistaken for residual tumor tissue during resection, resulting in brain damage [5,6,7]. Complications of this nature often arise with conventional B-mode US, which further limits the usefulness of this technique. In addition, the tumor's echogenic appearance depends on its grade. For instance, low-grade gliomas (LGGs) appear slightly hyperechoic relative to normal brain tissue with homogenous and blurred margins. In contrast, high-grade gliomas (HGGs) appear heterogeneously echogenic with hypoechoic central necrotic areas, hyperechoic margins, and surrounding edema [6,7]. Multiple studies showed that US has high sensitivity and specificity in identifying brain tumors, especially gliomas. When identifying residual tumoral tissue after a glioma resection, sensitivity and specificity may be up to 75% and 88%, respectively. In LGG, specificity appears to be higher (94%) than in HGG (77%). While some studies have demonstrated high specificity (85%), they have also shown a low sensitivity (46%) for detecting small residues compared to postoperative MRI [6,7]. Although ioUS exhibits favorable results before tumor resection, its effectiveness gradually decreases due to brain shift phenomena as the surgery progresses [6].

Magnetic Resonance Imaging

MRI is a non-invasive imaging technology that produces three-dimensional detailed anatomical images. It is commonly used for disease detection, diagnosis, and therapeutic

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monitoring. MRI scanners are appropriate for imaging non-bony parts or soft tissues of the body, such as the brain, spinal cord, and nerves. MRI is the method of choice when frequent imaging is required for diagnosis or therapy, especially in the brain [8]. In addition, this technology allows visualization of parenchymal areas, where contrast agents have leaked out through defects in the blood-brain barrier (BBB), a characteristic feature of brain tumors [8,9].

The most reliable imaging tool to assess brain tumors is gadolinium-enhanced resonance imaging [8]. However, no specific imaging characteristic can distinguish a metastatic lesion, the most prevalent form of brain tumor, from those of primary origin [9]. The main goal of tumor resection is to preserve brain function, which is often accomplished using pre-surgical advanced MRI techniques such as perfusion-weighted imaging (PWI), MR spectroscopy (MRS), and diffusion tensor imaging (DTI), and functional MRI (fMRI) [8,9]. These advanced techniques provide valuable information, including the relative cerebral blood volume (rCBV), a marker of tumor angiogenesis, and the metabolite choline/N-acetyl-aspartate (Cho/NAA) ratio, which helps identify and grade gliomas. Blood oxygen level-dependent (BOLD) functional MRI has been used during preoperative planning and intraoperative navigation to map sensory, motor, language, and memory areas. Tumoral brain tissue often exhibits a decreased BOLD signal and alterations in cerebral blood volume in tumor-affected areas [8]. Another application of MRI is to assess changes that represent the progression of a tumor after treatment, such as the presence of contrast enhancement [8]. While serial imaging by gadolinium-enhanced MRI is considered the most reliable imaging technique for assessing disease activity after treatment, it must be performed within 48 hours following surgery. Otherwise, postoperative changes along surgical margins may be misinterpreted as residual tumors [10].

Contrast-Enhanced Ultrasound

Contrast-enhanced ultrasound (CEUS) is a relatively novel radiological tool that has rapidly gained popularity in the imaging field. During CEUS, an intravenous contrast agent is used to expose the venous and arterial systems, allowing a clear view of the vascular structure of the targeted organ [11-13]. Contrast agents used during this modality differ from other imaging techniques. Microbubbles injected during CEUS do not diffuse on the adjacent tissue, allowing the contrast agent to remain in the vessels for a more extended time [14-16]. This method allows a more accurate assessment of the intravascular space while minimizing the risk of contrast-induced cellular toxicity [17,18]. Among the disadvantages of CEUS are its operator-dependency, equipment costs, and availability [19-21].

CEUS has been effectively used in the assessment of various organ afflictions, such as liver and renal tumors, but there is limited evidence regarding its role in the CNS. The use of CEUS in brain tumors has shown to be more accurate in solid tumors when compared to cystic lesions. This accuracy is because solid tumors such as gliomas, glioblastomas, and hemangioblastomas are highly vascularized [22]. In gliomas, CEUS has proven highly sensitive in detecting hypervascularity, even in low-grade tumors. Due to its vascularity, this tumor demonstrates a hyperechoic pattern, which may help detect small lesions even when the surrounding tissue appears normal. In more complex solid tumors such as glioblastomas, peripheral edema and other features might impair the image clarity and complete identification of the remaining affected brain tissue [23,24]. One other application of CEUS has been its use in monitoring patients following brain tumor resection. Due to its ability to distinguish between tumor-free and residual brain tissue based on the density of blood vessels within the tissue, this imaging modality is used to optimize the evaluation of solid brain tumor removal [24].

Conclusion

A complete understanding of the physics, contrast media variability, and technical expertise essential for the Contrast-enhanced ultrasound (CEUS) technique, ensures a high-performance study. Our group recognizes the current need for more sophisticated approaches involving vascular imaging diagnosis and therapeutic assessment for patients with different tumors and vascularization patterns of the targeted organ. According to the data obtained, the election of Contrast-enhanced ultrasound over the Conventional US in the intraoperative setting suggests a better outcome for patients undergoing neurosurgical procedures by limiting the possible brain tissue damage caused by the surgical removal tumors. No overall cellular toxicity is present in either of these methods, as well as significant repeatability and a relatively low cost. However, CEUS offers significant precision when distinguishing between residual tumoral tissue and expected postoperative edema. Therefore, CEUS and its intraoperative application could constitute a more clinically relevant new neuroimaging standard and be successful in routine clinical practice. Although MRI and its different modalities apply to detailed anatomical imaging and a serial assessment of the post-treatment status of the brain parenchyma as a non-invasive procedure, CEUS does not seem to have a specific postoperative evaluation period. Moreover, Contrast-enhanced ultrasound provides added value for multimodality imaging practice, and its role in modern medicine might outperform the conventional techniques reviewed in this article. Accordingly, we believe that contrast-enhanced ultrasound should be considered in different stages of brain tumor removal and postoperative clinical evaluation to ensure a better outcome for these patients.

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