Emerging Strategies and Future Perspective in Neuro-Oncology Using Transcranial Focused Ultrasonography Technology

Giada Toccaceli[1,5], Roberto Delfini[2], Claudio Colonnese[3,4], Antonino Raco[1], Simone Peschillo[5]

Key words
- Blood-brain barrier
- Brain tumors
- Focused ultrasonography
- High-intensity focused ultrasonography
- Mininvasive neurosurgery
- Nanoparticles
- Neuro-oncology

Abbreviations and Acronyms
BBB: Blood-brain barrier
BTBB: Blood-tumor-brain barrier
CNS: Central nervous system
NP: Nanoparticle
FUS: Focused ultrasonography
IL: Interleukin
MR: Magnetic resonance
MRgFUS: Magnetic resonance—guided focused ultrasonography
PEG: Polyethylene glycol

From the [1]NESMOS Department—Division of Neurosurgery, [2]Department of Human Neurosciences, Neurosurgery, and [3]Department of Human Neurosciences, Neuroradiology, University of Rome, "Sapienza", Rome; [4]IRCCS INM Neuromed, Pozzilli, Italy; and [5]Endovascular Neurosurgery, Policlinico Umberto I, Rome, Italy

To whom correspondence should be addressed: Simone Peschillo, M.D., Ph.D. [E-mail: simone.peschillo@gmail.com]

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BACKGROUND: **Despite the progress achieved in recent years, the prognosis of patients with primary brain tumors remains poor. Research efforts have therefore focused on identifying more effective and minimally invasive treatment methods. Magnetic resonance—guided transcranial focused ultrasonography (MRgFUS) is a consolidated minimally invasive therapeutic technique, which has recently acquired a role also in the treatment of some nononcologic intracranial diseases.**

METHODS: **We reviewed the latest studies to take stock of the potential of MRgFUS.**

RESULTS: **The objective of the research in the last decade was to apply FUS also to the treatment of intracranial neoplastic diseases, using both the thermal effects (thermal ablation) and, above all, the ability to permeabilize the blood-brain barrier and modify the tumor microenvironment. This strategy may allow the use of drugs that are poorly active on the central nervous system or active selectively at high doses, minimize the side effects, and substantially modify the prognosis of patients affected by these diseases.**

CONCLUSIONS: **In the future, targeted drug delivery, immunotherapy, and gene therapy will probably become main players in the treatment of brain neoplasms, with the aid of MRgFUS. In this way, it will be possible to directly intervene on tumor cells and preserve healthy tissue.**

INTRODUCTION

The treatment of primary and secondary brain neoplasms represents a neurologic challenge. The intracranial region often restricts the possibility of total or supramarginal surgical removal, at times implying severe neurologic functional damage; the blood-brain barrier (BBB) isolates it from the rest of the organism, acting as a filter not only for harmful substances but also for drugs.

In recent years, several studies have therefore focused on 2 basic problems: the treatment of lesions located in nonsurgical sites (deep or eloquent areas) and overcoming the BBB for the targeted administration of anticancer drugs.

Focused ultrasonography (FUS) could represent a response to both needs, providing promising results in the ablative treatment of neoplasms of difficult surgical access and also proving the only effective method that can permeabilize the BBB.

In this article, the main advances in the use of FUS transcranial are discussed, starting from the latest clinical trials in progress to FUS-mediated gene therapy (Table 1).

FUS

FUS is a noninvasive therapeutic procedure that conveys an ultrasound beam at target points at certain frequencies; the acoustic energy, released in the form of thermal and mechanical energy, facilitates the destruction or the alteration of the involved tissue (Table 2).

The use of ultrasound for this purpose is now a consolidated strategy in the thermoablative treatment of neoplasms such as prostatic cancer, breast carcinoma, uterine fibroma, and bone tumors.[1-3]

In the neurologic field, transcranial magnetic resonance (MR)-guided FUS (MRgFUS) has been approved by the U.S. Food and Drug Administration for the treatment of the first line of essential tremor and also as a second-choice therapy of chronic neuropathic pain, parkinsonism, and Parkinson syndrome. MRgFUS has also been used with good clinical results in cases of obsessive-compulsive disorders and depression.[4-11]

On the other hand, in neuro-oncology, FUS has not yet entered clinical practice; several clinical trials (Table 3) are investigating the possibility of using FUS for thermoablative purposes or as an

Table 1. Applications of Focused Ultrasonography Technology in Neuro-oncology

	Thermoablation	Drug Delivery	Nanoparticles	Immunotherapy	Gene Therapy
Characteristics	High/medium frequencies—high intensity	Low frequencies—low intensity			
Status	Clinical trial	Clinical trial	Preclinical studies	Preclinical studies	Preclinical studies
Purpose	Thermocoagulation of the target tissue inducing coagulative necrosis, protein denaturation, and apoptosis	To increase the permeability of the blood-brain barrier, favoring the drug delivery processes within the limited areas of the brain	To amplify and make more effective the use of nanoparticles as vectors for drug delivery at intracellular level	Delivery of drugs with immune action in the site of interest, and stimulation of the endogenous antitumor immune response	To induce cellular apoptosis or modifying tumor cells sensitivity to drugs
Administration	Microbubbles Conveying a magnetic resonance—guided ultrasound beam at target points	Microbubbles Systemic e.v. drug delivery i.a. drug delivery	Microbubbles Systemic e.v. or superselective i.a. administration	Microbubbles Systemic e.v. or superselective i.a. administration	Systemic e.v., local or superselective i.a. administration
Advantages	Mininvasive and nonsurgical ablation of deep tumors	Use of drugs that are currently poorly active on the central nervous system or active at high doses, minimizing the side effects	Intracellular administration and diffusion in extracellular tumor space of currently unused chemotherapy drugs avoiding their systemic toxicity and bypassing the blood-brain barrier	Application of immunotherapy principles to brain tumor treatment	Bypassing the undesirable effects of the intracranial administration of genetic material
Limits	Treatment limited by the cranial morphology and by the possibility to treat only deep lesions; hemorrhagic risk	Treatment limited by the cranial morphology and by the possibility to treat only deep lesions; risk of inertial cavitation and irreversible tissue damage	Treatment limited by the cranial morphology and by the possibility to treat only deep lesions; risk of inertial cavitation and irreversible tissue damage; currently available only preclinical studies	Treatment limited by the cranial morphology and by the possibility to treat only deep lesions; risk of inertial cavitation and irreversible tissue damage; currently available only preclinical and in vitro studies	Treatment limited by the cranial morphology and by the possibility to treat only deep lesions; risk of inertial cavitation and irreversible tissue damage; currently available only preclinical and in vitro studies

i.v. intravenous; i.a., intra-arterial.

instrument for temporarily permeabilizing the BBB and allowing the targeted passage of chemotherapies at the site of the lesion.[4-8,12]

Clinical Application of MRgFUS in Oncology

Thermal Effects of FUS. At medium-high frequencies (650 kHz) and high intensity, FUS acts on the target tissue, releasing, after repeated applications, thermal energy. Higher than 55°C, the phenomena of coagulative necrosis, protein denaturation, and cell apoptosis occur.[8,13-15]

As already stated, if MRgFUS has already entered clinical practice in neurology, the ablation of brain tumors has been tested in vivo and on patients in only a few official series and with conflicting results.

Ram et al. in 2006[16] used MRgFUS for the first time on 3 patients with glioma; in all cases, there was evidence of thermocoagulation of the target tissue, but the treatment included the need for a craniectomy to overcome the bone barrier and, in 1 case, neurologic damage occurred. The first attempts on noncraniectomized patients were made by McDannold et al. in 2010[17]; in this series of 3 patients with glioma, it was shown that there was a possibility of collimating the ultrasound beam in the target area and controlling the temperature reached by means of MR imaging, although it failed to reach therapeutic temperatures. The first case of thermoablation of a deep glial lesion with MRgFUS in the absence of periprocedural complications was reported by Coluccia et al. in 2014[18]; in this case, the thermoablation was successful but the procedure was interrupted at an early stage, because of the onset of sensations of heat in the patient.

Subsequently, the obstacles encountered in the clinical application of the FUS have been partially overcome by using intracranial temperature measurement systems (two-dimensional and three-dimensional MR thermometry),[12,19,20] software for the correction of phase aberration caused by cranial irregularities, and devices for circumventing the skull delivering FUS via an intracranial catheter delivery system,[21] minimizing overheating of the bone.[22,23]