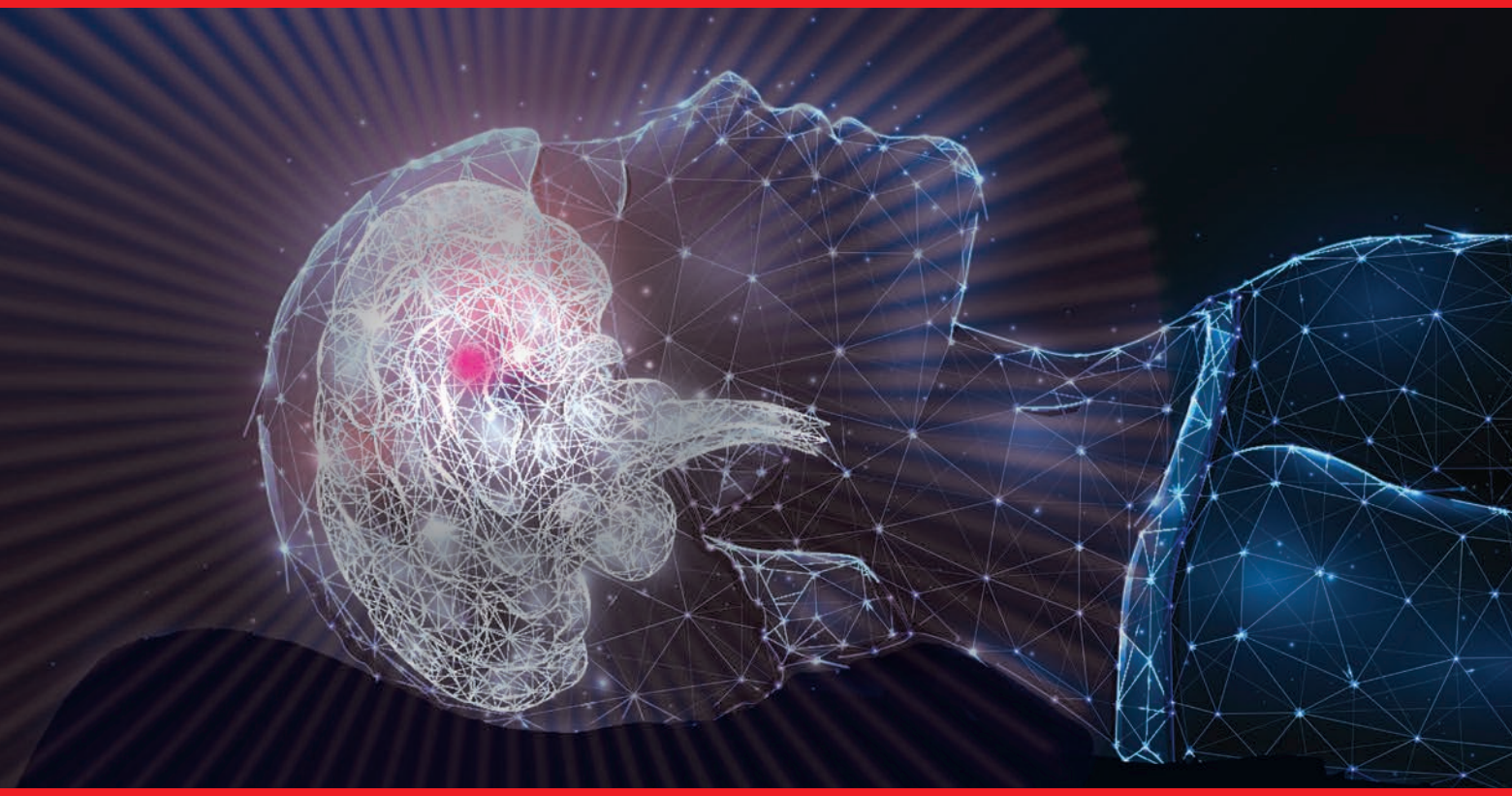
December 2022
Volume 11, Number 4

Applied Radiation Oncology™

10 YEARS



SA-CME
Breaking Barriers: The Past, Present and Future of Focused Ultrasound and Diffuse Intrinsic Pontine Glioma

Review
Focused Ultrasound for Ablation in Neurosurgery: Present Use and Future Directions

Case Report
Radiation Myonecrosis Following Stereotactic Body Radiation Therapy in Metastatic Renal Cell Carcinoma

Case Report
High-Dose-Rate Brachytherapy Followed by Concurrent Chemoradiotherapy for Esophageal Adenocarcinoma

www.appliedradiationoncology.com

Stereotactic precision for any anatomy

Push the boundaries of your stereotactic practice

Stereotactic treatments demand the highest levels of accuracy, precision and efficiency—and we've designed a linac that delivers. Versa HD™ enables high definition dynamic radiosurgery (HDRS)—offering absolute SRS and SBRT reliability with anatomically guided accuracy and efficiency. Empower practice growth. Choose Versa HD.

elekta.com/chooseVersaHD

LADVHD200211

Focus where it matters.

Elekta

Applied Radiation Oncology™

Anderson Publishing, Ltd.
180 Glenside Avenue,
Scotch Plains, NJ 07076
Tel: 908-301-1995
Fax: 908-301-1997
info@appliedradiology.com
ESSN: 2334-5446 (online)

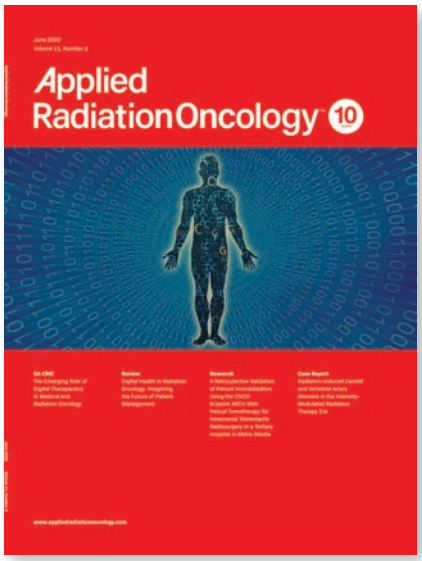
CIRCULATION, COVERAGE and ADVERTISING RATES: Details regarding circulation, coverage, advertising rates, space sizes, and similar information are available to prospective advertisers. Closing date is 30 days preceding date of issue. View our media planner at appliedradiationoncology.com/advertise.

EDITORIAL CONTRIBUTIONS: Applied Radiation Oncology accepts clinical review articles, research papers, and case reports that pertain to radiation oncology and related oncologic imaging procedures that will be of interest to radiation oncologists. Author guidelines are available at https://appliedradiationoncology.com/Author-Guidelines. Every precaution is taken to ensure accuracy, but the publishers cannot accept responsibility for the correctness or accuracy of the information supplied or for any opinion expressed. Before using procedures or treatments discussed or suggested by authors, clinicians should evaluate their patients' conditions, compare the recommendations of other authorities, consider possible contraindications or dangers, and review applicable manufacturer's product information. Review articles and cases should be geared to the practitioner and should reflect practical everyday clinical applications rather than research activity. Articles and cases may pertain to clinical management, administration, fiscal, technical, and medico-legal issues. All review articles, research articles and case reports undergo a double-anonymized peer review process.

Editorial Advisory Board

Applied Radiation Oncology

UPDATE YOUR SUBSCRIPTION PREFERENCES



Launched as an eJournal in 2012, Applied Radiation Oncology (ARO) is now available in print, online or on your mobile device. Published quarterly under the editorial guidance of John Suh, MD, FASTRO, FACR, Chairman of the Department of Radiation Oncology and Associate Director of the Gamma Knife Center at the Brain Tumor and Neuro-Oncology Center at Cleveland Clinic, each issue presents board-reviewed case presentations and clinical review articles that provide practical, actionable information that radiation oncologists can use to enhance the efficiency and quality of radiotherapy.

Editorial coverage targets imaging, contouring, target delineation, treatment planning, patient immobilization, organ tracking, safety and quality, and other timely topics essential to the discipline.

Please take a moment to update your subscription preferences.

appliedradiationoncology.com/subscribe

Applied Radiation Oncology™

December 2022, Vol 11, No 4

FOCUS: FOCUSED ULTRASOUND

Applied Radiation Oncology (ISSN: 2334-5446) is published quarterly by Anderson Publishing, Ltd.,180 Glenside Avenue, Scotch Plains, NJ 07076. Subscription is free of charge to all medical professionals. To update your subscription preferences, visit appliedradiationoncology.com/subscribe. Complaints concerning non-receipt of this journal should be made via email to our publisher, Kieran Anderson at kieran@appliedrradiology.com.

Dr. Suh is the editor-in-chief of Applied Radiation Oncology, and professor and chairman, Department of Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.

Brain Waves: Expanding Treatment Options in Neuro-Oncology and Beyond

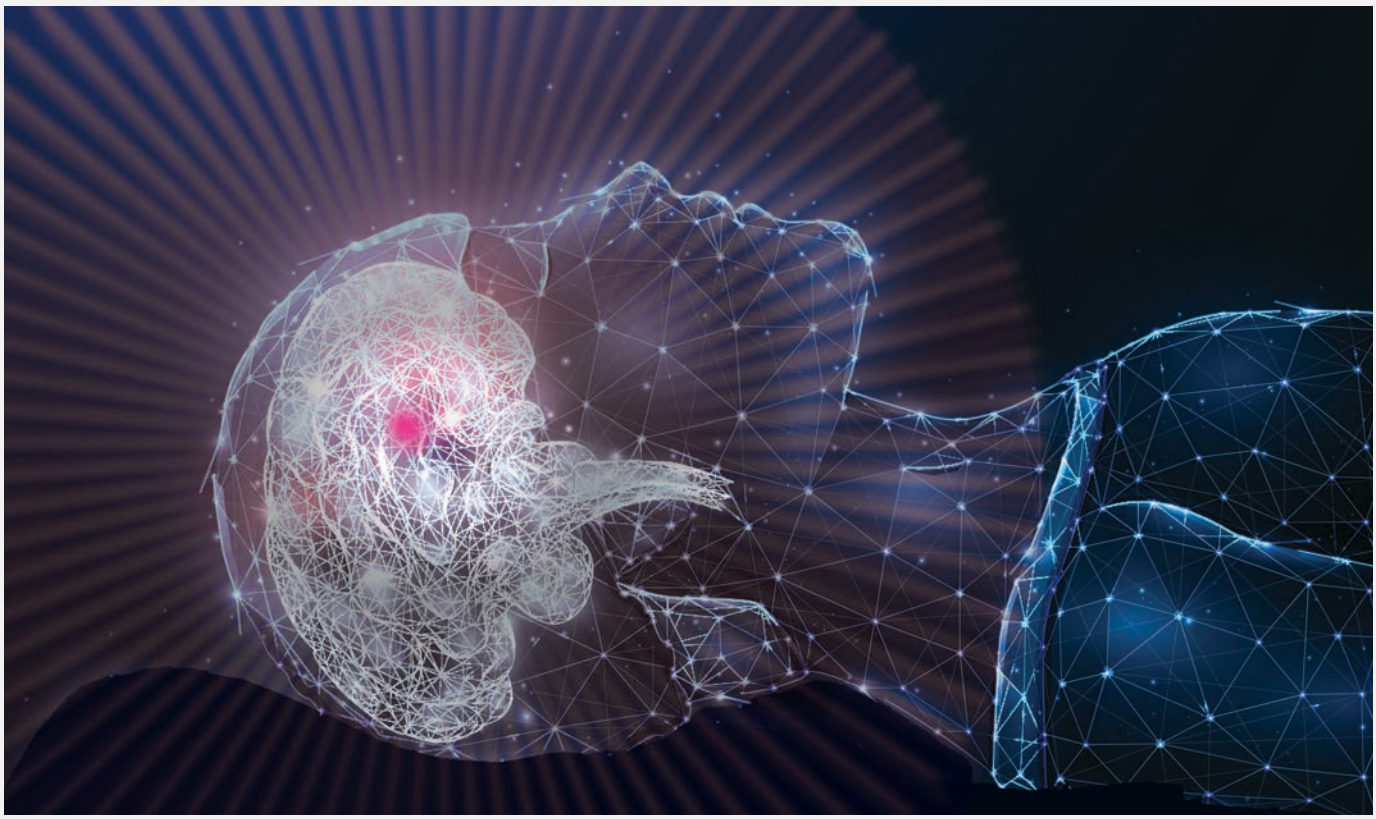
John Suh, MD, FASTRO, FACR

Welcome to the December 2022 issue of *Applied Radiation Oncology*, which focuses on the role of focused ultrasound (FUS) for neurological disease. FUS, while not a traditional tool in the radiation oncology armamentarium, is garnering interest and showing potential as a treatment option to consider for certain patient populations. The review article, *Breaking Barriers: The Past, Present and Future of Focused Ultrasound and Diffuse Intrinsic Pontine Glioma (DIPG)*, offers a comprehensive update on how the advent of FUS-mediated blood brain barrier opening lays groundwork to promising advances in neuro-oncology. Approved for SA-CME credit, the article discusses preclinical studies from the last decade that assess the safety and feasibility of FUS-mediated BBB opening in the brainstem. The authors also review published phase 0-II clinical trials of low-frequency FUS therapy in the adult glioma population, and phase I clinical trials in DIPG that are underway. We hope you enjoy this interesting and timely review of emerging technologies to consider in treating this highly malignant cancer.

A second review article, *Focused Ultrasound for Ablation in Neurosurgery – Present Use and Future Directions*, examines the risk-benefit ratio of MR-guided FUS surgery as a noninvasive ablative therapy for movement disorders such as essential tremor and Parkinson's disease, as well as other indications. The authors describe the science behind ablative action and note that there may be a future role for radiation oncologists in utilizing this form of treatment.

The issue also features two case reports, the first of which is *Radiation Myonecrosis After Stereotactic Body Radiation Therapy (SBRT) for Metastatic Renal Cell Carcinoma (RCC)*. This insightful article details what is believed to be the second reported case of radiation myonecrosis after SBRT and the first reported case in a patient with RCC, as well as the first involving a patient on concurrent immunotherapy. This report adds to the published collection of radiation-induced myonecrosis cases and cautions clinicians on this rare but serious potential side effect of radiation therapy.

The second case report, *High-Dose-Rate Brachytherapy (HDRBT) Followed by Concurrent Chemoradiotherapy for Esophageal Adenocarcinoma*, provides an unusual example of how an upfront 3D HDRBT boost with dose manipulation followed by intensity-modulated radiation therapy showed good tumor response and minimal toxicity in a patient. Additionally, this case illustrates how upfront HDRBT swiftly relieved dysphagia, increasing the patient's acceptance of subsequent treatment with concurrent chemoradiotherapy, and how dose escalation with the aim to improve local control rate is feasible with HDRBT.



Finally, we are delighted to present the Resident Voice editorial, *Resident-Led Education Committee: Fostering Leaders and Impactful Change in Radiation Oncology Education.* Cultivating leadership is a passion of mine and it's exciting to see how residents in radiation oncology and medical physics at UCSF have built a successful program to bolster teaching and leadership training. Through summer internships, journal clubs, a tumor board series and more, this enterprising group is fostering confidence and laying the foundations to exceptional leadership.

In other news, we are delighted to welcome Amishi Bajaj, MD, as the new Association of Residents in Radiation Oncology (ARRO) representative to serve on the *ARO* editorial advisory board for a 1-year term. Dr. Bajaj is a PGY5 radiation oncology resident at Northwestern University, Feinberg School of Medicine; chair of ARRO; and past president of the McGaw Medical Center Housestaff Association. In her role with *ARO*, Dr. Bajaj will assist with a variety of editorial responsibilities, including coordinating the Resident Voice editorial featured in every issue. Dr. Bajaj succeeds Justin Anderson, MD, PGY5 resident physician at Mayo Clinic Arizona, whom we thank for his wonderfully conscientious and dedicated service from 2020 to 2022.

We also thank the peer reviewers who critiqued submissions throughout 2022. An integral component to scholarly publishing, the peer review process is a time-consuming volunteer effort, and we are deeply indebted to those who made room in their demanding schedules to assess, filter and ultimately improve review articles, research papers, and case reports for the journal. Please see p. 24 for our acknowledgement of these committed clinicians who deserve high praise and recognition.

Finally, a word of gratitude to our readers for your many contributions to our growth over the last 11 years. Your support remains a key pillar to our advancement and success. We wish you a joyful holiday season and peaceful New Year!

Breaking Barriers: The Past, Present and Future of Focused Ultrasound and Diffuse Intrinsic Pontine Glioma

Description

The blood-brain barrier (BBB) remains a significant blockade for effective drug delivery in treating diffuse intrinsic pontine glioma (DIPG). Low-frequency focused ultrasound (FUS) therapy in conjunction with intravenous microbubbles can transiently disrupt the BBB in a localized manner to facilitate drug delivery. This review examines recent preclinical studies evaluating the safety and feasibility of FUS-mediated BBB opening in the brainstem. The authors also discuss the published phase 0-2 clinical trials of low-frequency FUS therapy in the adult glioma population, and phase 1 clinical trials in DIPG that are underway.

Learning Objectives

Upon completing this activity:

Practitioners will be better educated regarding the history of DIPG therapies, their limitations, and the current standard of care.

Clinicians will become aware of the various clinical trials are underway for the BBB opening in DIPG.

Authors

Zachary K. Englander, MD, MS;[1]
Christopher Troy, MD;[2]
Masih Tazhibi, BA;[3]
Nina Yoh, MD;[1]
Hong-Jian Wei, PhD;[3]
Neil Feldstein, MD;[1]
Elisa Konofagou, PhD;[4]
Luca Szalontay, MD;[5]
Cheng-Chia Wu, MD, PhD[3,6]

Affiliations: [1]Department of Neurological Surgery, Columbia University Irving Medical Center, New York, New York. [2]Department of Neurosurgery, University of Tennessee Health Science Center, Memphis, Tennessee. [3]Department of Radiation Oncology, Columbia University Irving Medical Center, New York, New York. [4]Department of Biomedical Engineering, Columbia University, New York, New York. [5]Department of Pediatrics, Columbia University Irving Medical Center, New York, New York. [6]Herbert Irving Comprehensive Cancer Center, New York, New York.

Target Audience

- Radiation Oncologists
- Related Oncology Professionals

Commerical Support

None

Accreditation/ Designation Statement

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Institute for Advanced Medical Education (IAME) and Anderson Publishing. IAME is accredited by the ACCME to provide continuing medical education for physicians. IAME designates this activity for a maximum of 1 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Instructions

To successfully earn credit, participants must complete the activity during the valid credit period.

1. Review this article in its entirety.
2. Visit appliedradiology.org/SAM.
3. Login or create an account.
4. Complete the post test and review the discussion and references.
5. Complete the evaluation.
6. Print your certificate.

Estimated time for completion:
1 hour

Date of release and review:
December 1, 2022

Expiration date:
November 30, 2024

Disclosures

All authors disclose no relationships with ineligible companies.

IAME has assessed conflicts of interest with its faculty, authors, editors, and any individuals who were in a position to control the content of this CME activity. Any relevant financial relationships were mitigated with an independent peer review of this activity, and no conflicts or commercial bias were detected. IAME's planners, content reviewers, and editorial staff disclose no relationships with ineligible entities.

Breaking Barriers: The Past, Present and Future of Focused Ultrasound and Diffuse Intrinsic Pontine Glioma

Zachary K. Englander, MD, MS;[1] Christopher Troy, MD;[2] Masih Tazhibi, BA;[3] Nina Yoh, MD;[1] Hong-Jian Wei, PhD;[3] Neil Feldstein, MD;[1] Elisa Konofagou, PhD;[4] Luca Szalontay, MD;[5] Cheng-Chia Wu, MD, PhD[3,6*]

Abstract

Diffuse intrinsic pontine glioma (DIPG) is a malignant childhood tumor of the brainstem with a dismal prognosis. While recent progress has been made in understanding the molecular underpinnings of the disease, the blood-brain barrier (BBB) remains a significant blockade for effective drug delivery. Low-frequency focused ultrasound (FUS) therapy in conjunction with intravenous microbubbles can transiently disrupt the BBB in a localized manner to facilitate drug delivery. This is achieved through stable cavitation, the process by which oscillations in bubble volume induce minor mechanical stress at the cellular level, disrupting endothelial tight junctions and leading to increased BBB permeability. Here we review preclinical studies performed over the last decade that have evaluated the safety and feasibility of FUS-mediated BBB opening in the brainstem. Furthermore, we cover the published phase 0-II clinical trials of low-frequency FUS therapy in the adult glioma population, as well as the phase I clinical trials in DIPG that are underway.

Keywords: DIPG; diffuse intrinsic pontine glioma; brainstem glioma; convection-enhanced delivery; focused ultrasound

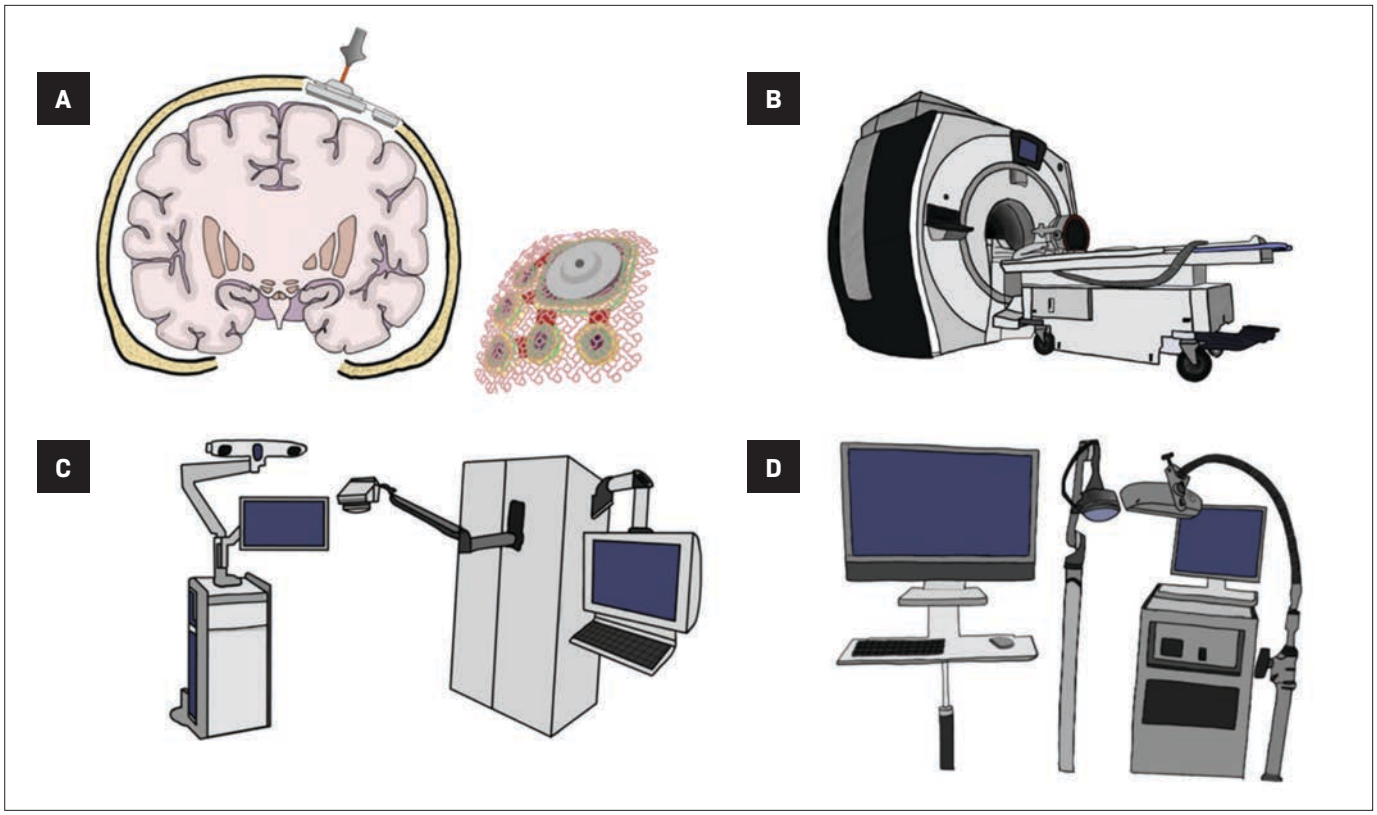
Introduction to Focused Ultrasound and DIPG

Focused Ultrasound

Since it was first described by brothers Pierre and Jacques Curie in the late 1800s, the piezoelectric effect — the generation of electricity by crystals under mechanical stress — has been leveraged for remarkable technological achievements. The first application was seen in World War I with the development of sonar devices by the French government to detect submarines.[1] In 1935, Johannes Gruetzmacher fit a curved lens on the end of a piezoelectric generator and found that ultrasound waves could be focused.[2,3] In the late 1940s, the first attempt at clinical ultrasonography in the diagnosis of brain tumors ultimately failed due to the high density of the skull. However, 1 year later George Ludwig made great progress by imaging gallstones across the abdomen and advancing research into the interactions between ultrasound waves and soft tissues. While this work was occurring, other researchers attempted to utilize ultrasound technology for therapeutic effects by focusing the acoustic energy to heat and lesion tissue. This was first reported in animals by Lynn and Miller at Columbia University in 1942 and advanced by

Affiliations: [1]Department of Neurological Surgery, Columbia University Irving Medical Center, New York, New York. [2]Department of Neurosurgery, University of Tennessee Health Science Center, Memphis, Tennessee. [3]Department of Radiation Oncology, Columbia University Irving Medical Center, New York, New York. [4]Department of Biomedical Engineering, Columbia University, New York, New York. [5]Department of Pediatrics, Columbia University Irving Medical Center, New York, New York. [6]Herbert Irving Comprehensive Cancer Center, New York, New York.
Corresponding Author: *Cheng-Chia Wu, MD, PhD, Department of Radiation Oncology, Columbia University Irving Medical Center, 622 W 168th Street, New York, NY 10032 (cw2666@cumc.columbia.edu).
Disclosure: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.

Figure 1. Focused ultrasound (FUS) devices: Carthera SonoCloud (A), Insightec Exablate (B), NaviFUS (C), TheraWave (D)



others such as Ballantine at Massachusetts General Hospital and the Fry brothers in Indianapolis.[4] Therapeutic ultrasound now encompasses a wide variety of categories including thermal ablation, histotripsy, nerve stimulation, and the opening of the blood-brain barrier (BBB).

The desired bioeffect of ultrasound depends both on the acoustic parameters of the waves as well as the characteristics of the target tissue. Generally, there are thermal and nonthermal effects, but all involve some degree of mechanical alteration induced by the waves' energy.[5] Thermal effects secondary to high-frequency FUS are achieved by simple absorption of ultrasonic energy by the tissue. The sustained exposure to higher intensities produces heat and leads to irreversible tissue injury. This mechanism is well established and can be employed for tumor ablation, clot lysis, and intracranial lesioning for pathologies such as essential tremor,[6] Parkinson's disease, chronic intractable neuropathic pain and obsessive-compulsive disorder.[7,8] Lower-frequency FUS exhibits its effects through nonablative, nonthermal mechanisms. With a lower frequency and thus a smaller amount of acoustic energy directed at the targeted area, the threshold to produce ablative lesions is not met. Instead, a mechanical effect of low-intensity FUS can be achieved through interactions with intravenously delivered gases, which can ultimately lead to disruption of the BBB.

BBB

The BBB is a highly discriminatory barrier between the central nervous system (CNS) and its vasculature. The structure of the BBB includes astrocyte foot processes and specialized endothelial cells. Unique to the cerebrovasculature, these endothelial cells form a continuous barrier, anchored to each other by tight junctions, which prevents the intercellular passage of material into the CNS. Additionally, there are fewer fenestrations and a variety of efflux pumps, which help protect the CNS from potentially harmful substances in the blood stream, but also prevent the passage of therapeutics into the brain.[9] Although the BBB is protective, transiently and focally increasing the permeability of the BBB has been a target for investigation. BBB disruption could allow for the delivery of drugs like chemotherapy, immunotherapy, stem cells, and gene therapy to CNS targets.[10] To improve penetration, investigators have explored changes in drug molecular size and lipophilicity, as well as carriers that can cross the BBB.[11,12] Current attempts to disrupt the BBB have shown moderate success but with potentially significant adverse effects: direct injection of

drugs through convection-enhanced delivery is invasive and carries risks of damage to neural tissue; and the use of hypertonic solutions, such as mannitol, to osmotically induce BBB opening, leads to a nonselective, global increase in BBB permeability that can cause unwanted drug-induced CNS toxicity.[13-15] Violating the BBB in a safe, targeted, and transient manner using noninvasive sound delivery is a unique application of FUS and has the potential to change the medical management of infiltrative brain tumors.

FUS and BBB

Investigations of the nonthermal effects of FUS have been underway for decades.[16] The success of FUS in BBB disruption is largely achieved through the process of cavitation and the resultant mechanical stress on the endothelium. With the application of ultrasonic waves, injectable gaseous microbubbles within the cerebrovasculature absorb the energy and begin to oscillate.[17] This oscillation is known as acoustic cavitation and can be inertial or stable. Inertial cavitation is a violent implosion or explosion of the microbubbles that leads to tissue destruction. Stable cavitation on the other hand is the process by which these oscillations in volume induce minor mechanical stress at the cellular level, disrupting endothelial tight junctions and leading to increased BBB permeability.[18] The continuous expansion and compression of the microbubbles is transmitted to the vessel wall as mechanical stress, separating the endothelial lining. The oscillation also induces jet streaming, or acoustic streaming, which adds further stress to the vessel wall.[19] Passage through the temporarily disrupted BBB is thought to be through 4 mechanisms: widening of interendothelial spaces due to opening of tight junctions, upregulation of transcytosis as evidenced by increased cytoplasmic vesicles, channel and fenestration formation, and free movement across the injured endothelium.[20]

DIPG

DIPG is a malignant tumor that arises from the brainstem primarily in children ages 5 to 9. It is a difficult disease carrying a mean life expectancy of less than a year, with less than 10% of patients surviving more than 2 years.[21] Given that these tumors grow diffusely through the pons, one of the most highly eloquent regions of the brain, surgical resection is not feasible.[22] The mainstay of treatment for this disease is fractionated radiation therapy, which is the only treatment modality that has been shown to prolong survival in these patients.[23] Many trials have been conducted to evaluate different combinations of chemotherapy without success. Over the last decade, significant advancements have been made in understanding the molecular characteristics of these tumors. Nevertheless, there remains little success with these targeted therapies in clinical trials. The BBB, as described above, is thought to be a major factor in limiting the penetrance of drugs to these infiltrative brain tumors. Furthermore, there is very minimal tumor-induced BBB disruption in these patients as evidence by the absence of contrast enhancement on MRI in the majority of cases. Thus, FUS appears to be a promising option for the treatment of this highly malignant cancer.

FUS — Current Devices

Three classes of FUS devices are under investigation for use in humans: fixed-frame MRI-guided devices (MRgFUS), implantable ultrasound devices, and frameless neuronavigation-guided devices[24] (**Figure 1**).

Exablate

One of the first FDA-approved devices was the Exablate system by Insightec, an MRgFUS machine initially developed to treat uterine fibroids by thermal ablation.[7] The technology was adapted, and the newer Exablate Neuro system has been FDA-approved for thalamotomy and is in use in more than 10 clinical trials investigating its ability to disrupt the BBB. The device consists of a helmet transducer that includes more than 1000 elements coordinated to transmit ultrasound to a precise target. The treatment planning and monitoring is performed using real-time MRI guidance. Treatment with the device requires placement of a stereotactic head frame with fixed skull pins. The extended duration of the procedures coupled with the discomfort of lying in a fixed frame within an MRI machine can be a limiting factor.

SonoCloud

The SonoCloud-9, developed by the French company Carthera, is an implantable, unfocused, ultrasound system that features 9 transducers. The device is placed within the skull bone following a craniotomy, which can occur either during a scheduled brain tumor resection, or as a standalone ambulatory procedure. While the noninvasive systems require mathematical calculations to overcome the complexities of achieving effective sonication through bone, the SonoCloud bypasses the skull and sits directly above the dura. As the investigators on the original clinical trial note, the absence of bone-induced attenuation of the US waves eliminates the need for intraprocedure MRI monitoring.[25] The SonoCloud-9 recently received an FDA breakthrough device designation and is under investigation in multiple clinical trials.

NaviFUS and TheraWave

The most recently developed devices rely on neuronavigation tracking, a technology commonly used for many neurosurgical procedures. Using infrared cameras, the precise location

of FUS transducer placement can be achieved by registering the coordinate system developed from the preprocedural MRI or CT with the coordinates of the patient's skull. There are 2 such devices in varying stages of development: the NaviFUS System, developed by a group in Taiwan, and a similar device developed by our group at Columbia University.[26,27] Like the SonoCloud, these neuronavigation-based devices have largely been explored with low-frequency ultrasound and BBB disruption.[28] The NaviFUS device has been used in multiple clinical trials investigating its efficacy in the treatment of both glioblastoma (GBM) and drug-resistant epilepsy.[29] The Columbia device (TheraWave) has demonstrated targeted and reproducible BBB disruption in several nonhuman primate studies. It is currently classified under an FDA investigational device exemption and has been registered in a clinical trial for Alzheimer's disease and another for DIPG (discussed below). The advantages to these systems are the avoidance of invasive procedures and the absence of prolonged time in the MRI scanner. These are lightweight, portable devices that can be used in an outpatient setting, allowing for potentially wider access and application.

Preclinical Work

The past decade has seen a significant increase in preclinical FUS-mediated BBB-opening studies, with several groups narrowing their focus on drug delivery to the brainstem. In 2018, Alli and colleagues from the Hynynen lab at the University of Toronto demonstrated the safety of doxorubicin delivery to the murine brainstem following ultrasound treatment.[30] Using an animal MRgFUS device, BBB opening was achieved and confirmed both with contrast-enhanced MRI and Evans blue staining. Using liquid chromatography/mass spectrometry (LCMS), significantly higher doses of doxorubicin were found in the brainstem of mice that underwent sonication. This group also found that treatment was not associated with any cardiopulmonary or motor deficits.

During the same year, the Chen lab from Washington University in St. Louis published 2 papers on the delivery of nanoparticles to the pons. The first study evaluated the use of FUS in the presence of intravenous, radiolabeled gold nanoclusters.[31] In contrast to the previous study, which used contrast-enhancement as a marker of BBB disruption, this project allowed for a more precise, real-time tracking of drug delivery via in vivo microPET/CT imaging of ^{64}Cu-integrated gold nanoclusters. Additionally, the spatiotemporal distribution of these nanoclusters was then quantified by imaging at different time points post-sonication. In their follow-up study, Ye and colleagues attempted to curtail the systemic drug exposure by utilizing intranasal delivery.[32] They successfully demonstrated less systemic uptake but equivocal pontine distribution with radiolabeled gold nanoclusters following inhaled intranasal delivery in mice. In their most recent preclinical study, using a RCAS/tv mouse DIPG model, Zhang et al demonstrated a twofold increased uptake of ^{64}Cu-Cu nanoclusters in the murine tumors that were exposed to FUS compared with the nontreated tumors. In a follow-up study, Ye et al evaluated the ability of FUS to enhance the delivery of immune checkpoint inhibitor therapy in a murine brainstem glioma model.[33] Using an intranasally delivered programmed cell death-ligand 1 antibody (aPD-L1) tagged with a fluorescent dye, they demonstrated an approximately fourfold increase in drug concentration following FUS therapy compared with intranasal delivery alone.

Building on these studies, our group set out to investigate the safety of FUS-mediated chemotherapy delivery in a preclinical pontine glioma model.[34] We implanted high-grade glioma cells into the pons of immunocompetent mice. Once tumor formation was identified on MRI, we treated mice with FUS and found no significant cardiopulmonary or motor deficits associated with treatment. Histological analysis did not show any harmful effects. Furthermore, using LCMS, a fivefold increase in the concentration of etoposide in mice that underwent FUS was noted compared with mice treated with etoposide alone. Our study also found that multiple FUS treatments were not associated with any negative effects.

Ishida et al published similar experiments using doxorubicin but in immunocompromised mice with patient-derived xenografts.[35] While the tumor model was more accurate, the absence of immune response in this model was a limitation. The justification behind using doxorubicin was rooted in several in vitro studies demonstrating its efficacy in treating multiple DIPG cell lines, plus its known limited ability to cross the BBB. These authors similarly found a fourfold increase in drug concentration within the mouse tumors that underwent FUS compared with the control group. Additionally, they found decreased tumor growth rate on MRI and decreased ki67 – a marker of tumor proliferation – on immunohistochemical staining in the treated mice. Nevertheless, there was no survival benefit in the study, which the authors attributed to the limited single treatment plan as well as the systemic toxicity of doxorubicin. Future animal studies will need to optimize drug formulations to avoid systemic toxicity, while incorporating a more robust FUS regimen that can increase tumor exposure to higher drug concentrations over a prolonged period.

Clinical Trials

BBB Opening Trials in Adult Glioma

Multiple published clinical trials have investigated the utility of FUS-me-

Table 1. BBB-Opening Clinical Trials With Published Results

TRIAL	DEVICE/THERAPEUTIC	RADIOGRAPHIC CONFIRMATION	LARGEST BBB OPENING	BBB NORMALIZATION TIME
Idbaih et al[36] NCT02253212	SonoCloud-1 / Carboplatin	Gd enhancement	N/A	N/A
Mainprize et al[37] NCT02343991	Exablate/ None	Gd enhancement	2.43 cm^3	24 hours
Anastasiadis et al[38] NCT03322813	Exablate/ None	Gd enhancement	10.08 cm^3	N/A
Chen et al[27] NCT03626896	NaviFUS/ None	Gd enhancement	N/A	24 hours
Meng et al[39] NCT03714243	Exablate/ Trastuzumab	Gd enhancement/ Radioisotope	N/A	24 hours

diated BBB opening in the adult supratentorial glioma population (**Tables 1 and 2** summarize the clinical trials and serious adverse events, respectively). The first published trial came from the Carpentier group at the Pitie Salpetriere University Hospital using the SonoCloud CarThera device.[25,36] In a single-arm, phase 1/2a study, 19 patients were implanted and treated with the CarThera device alongside the delivery of carboplatin. A total of 65 treatments were delivered, more than 50 of which demonstrated evidence of BBB disruption on MRI. This radiographic effect was quantified based on the degree of contrast enhancement and correlated with amount of acoustic pressure. They found an increased delivery of energy associated with a more robust BBB opening. No significant adverse events (SAEs) were observed. One patient experienced a transient facial nerve palsy, which resolved within 2 hours followed by the administration of steroids. Several patients also experienced transient brain edema that resolved with steroids. Although the study was underpowered, patients who underwent radiographic BBB breakdown lived longer than those who did not (OS 12.94 months vs 8.64 months).

In 2019, Mainprize et al published the first clinical trial evaluating the safety of noninvasive FUS and drug delivery in brain tumor patients.[37]

Table 2. Adverse Events in BBB-Opening Clinical Trials

TRIAL	PATIENTS (N)	TREATMENT-RELATED ADVERSE EVENTS
Idbaih et al[36] NCT02253212	21	Transient cerebral edema (n = 2, 11%) Transient facial palsy (n = 1, 5%)
Mainprize et al[37] NCT02343991	5	Back pain (n = 1, 20%) Headache (n = 2, 40%)
Anastasiadis et al[38] NCT03322813	4	None
Chen et al[27] NCT03626896	6	None
Meng et al[39] NCT03714243	4	Pin site tenderness (n = 1, 5%) Headaches (n = 1, 5%) Back pain (n = 1, 20%)

In this phase 1, single-arm study, 5 patients with GBM underwent MRgFUS treatment with concurrent chemotherapy (temozolamide or doxorubicin) 1 day prior to surgical resection. No adverse clinical or radiographic events were observed. To quantify radiographic BBB opening, they measured the percentage of sonicated tissue that exhibited contrast enhancement (increased signal intensity compared with the nontreated adjacent brain tissue), the highest of which was 50%. Four of the 5 patients had evidence of contrast enhancement following treatment. In 2 of the patients, chemotherapy levels were quantified with LCMS. The authors found a trend toward increased drug concentration in the treated tissue compared with the nontreated tissue. A phase 0 study published in *Proceedings of the National Academy of Sciences of the United States of America (PNAS)* 2021 similarly evaluated the safety of MRgFUS in 4 adult patients with lobar diffuse glioma.[38] They did not observe any SAEs with treatment, although no therapeutic was delivered. Furthermore, histological analysis of treated tissue did not demonstrate any necrosis or microhemorrhage. Each treatment volume was measured, the largest of which was 10.08 cm^3. Using intravenously administered fluorescein, they found a 2.2-fold increase in drug accumulation in the brain tissue that underwent FUS-mediated BBB opening, compared with nontreated tissue.

In Taiwan, Chen et al reported their findings in a 6-patient, phase 1 pilot study. They performed a dose escalation design with the NaviFUS Neuronavigation-guided focused ultrasound system device, without drug delivery, to determine a safe energy

level for BBB disruption.[27] No SAEs were observed. Similar to the Carpentier study, they found a correlation between degree of signal change on MRI and the amount of acoustic energy delivered. All radiographic changes were transient and returned to near baseline at 24 hours. Interestingly, they found a lack of significant immunological response on histological analysis 1 week following treatment.

Meng et al published their phase 1, FUS-mediated drug-delivery study in brain tumor patients, specifically in those with Her2-positive breast cancer and brain metastases.[39] Four patients were treated with MRgFUS and radiolabeled trastuzumab, a monoclonal antibody for the Her2 receptor. No treatment-related serious adverse events were observed. Unlike prior studies that relied on contrast-enhanced, T1-weighted MRI, single-photon emission computerized tomography (SPECT) imaging was used to track radiotracer uptake. Following MRgFUS and intravenous injection of 111In-BzDTPA-NLS-trastuzumab, increased SPECT signal intensity was observed only in regions in which FUS was targeted, but not in other metastatic lesions that weren't sonicated. This was the first study to demonstrate real-time tracking of drug delivery to brain tumors following BBB opening.

Current and Future Trials in DIPGs

There are 3 current trials in the DIPG patient population. Our group began the first phase 1 clinical trial (NCT04804709) in children with recurrent diffuse midline glioma. Study participants underwent treatment with FUS combined with oral panobinostat. The purpose of the study was to evaluate the feasibility of opening the BBB safely in 1, 2, or 3 tumor sites. The trial followed a 3+3 Number of Tumor Sites (NOTS) escalation scheme, which refers to the number of openings in the BBB. Subjects started the first cycle of the treatment arm with 1 tumor site and moved on to incrementing NOTS levels if no dose-limiting toxicities (DLTs) were observed.

Another trial (NCT05123534) has recently opened at Children's National Hospital, University of California San Francisco (UCSF), and the Ivy Brain Tumor Center using sonodynamic therapy, a technology that utilizes ultrasound-generated light, or sonoluminescence. This light can then trigger the byproduct of an injectable therapy, SONOALA-001, to activate cell death exclusively within glioma cells. This is a phase 1/2 study in newly diagnosed DIPG following radiation therapy using a dose escalation model with both drug dose and energy delivered. Patients are administered SONOALA-001 and sonicated using the Exablate Neuro system several hours later. This treatment modality is also being studied in adult GBM patients in a clinical trial in Arizona, and early reports have noted its safety. Most recently, a single-arm, nonrandomized, prospective feasibility study was opened at Children's National Hospital to treat DIPG patients with FUS and doxorubicin using the Exablate Neuro system (NCT05630209). This study is recruiting as of press time.

Other Applications – Liquid Biopsy

The first liquid biopsy study following FUS was performed by the Chen lab. Using an enhanced green fluorescent protein (eGFP)-transduced GBM cell line, Zhu et al observed a significant increase in plasma eGFP mRNA in multiple preclinical mouse models using a variety of acoustic pressures.[40] Meng et al published the first study in humans to evaluate the feasibility of liquid biopsy following treatment with ultrasound.[41] In 9 patients undergoing clinical trial for GBM with Exablate, blood samples were collected before and after sonication. Non-brain-tumor patients undergoing FUS alone were used as controls. They found an increase in cell-free DNA (cfDNA) as well as neuron-derived vesicles and brain derived proteins associated with the treatment. They also found methylation signatures within the cfDNA samples following BBB opening that were distinct from the cfDNA collected pre-BBB opening. Interestingly, for the 1 patient in the trial with an IDH1 mutant glioma, they observed a two- to threefold increase in IDH1 mutant cfDNA following BBB opening. These findings altogether are very early but demonstrate the feasibility of using FUS-mediated BBB opening as a tool for both drug delivery and noninvasive diagnostics.

Conclusion

Despite recent advancements in the molecular understanding of DIPG, the BBB remains a significant challenge for advancing care in this disease. The advent of FUS-mediated BBB opening has led to an exciting new era in the field of neuro-oncology. Preclinical studies have demonstrated the efficacy of increasing drug distribution within the brainstem and brainstem tumors using FUS. Multiple successful phase 1 clinical trials have been reported in the adult glioma population, and several are underway for those with DIPG. Although it is still early, our hope is that FUS will provide a platform for delivering cutting-edge therapies to improve outcomes for this population.

References

1) Man K, Sabourin VM, Gandhi CD, Carmel PW, Prestigiacomo CJ. Pierre Curie: the anonymous neurosurgical contributor. *Neurosurg Focus.* 2015;39(1):E7. doi:10.3171/2015.4.FOCUS15102

2) Gruetzmacher J. Piezoelectric crystal with ultrasonic convergence. *Z Phys.* 1935;96(5-6):342-349. doi:Doi 10.1007/Bf01343865

3) Harary M, Segar DJ, Huang KT, Tafel IJ, Valdes PA, Cosgrove GR. Focused ultrasound in neurosurgery: a historical perspective. *Neurosurg Focus.* 2018;44(2):E2. doi:10.3171/2017.11.FOCUS17586

4) Ballantine HT, Hueter TF, Nauta WJH, Sosa DM. Focal destruction of nervous tissue by focused ultrasound - biophysical factors influencing its application. *J Exp Med.* 1956;104(3):337-360. doi:DOI 10.1084/jem.104.3.337

5) Miller DL, Smith NB, Bailey MR, et al. Overview of therapeutic ultrasound applications and safety considerations. *J Ultras Med*. 2012;31(4):623-634. doi:DOI 10.7863/jum.2012.31.4.623

6) Elias WJ, Lipsman N, Ondo WG, et al. A randomized trial of focused ultrasound thalamotomy for essential tremor. *New Engl J Med*. 2016;375(8):730-739. doi:10.1056/NEJMoa1600159

7) Abe K, Taira T. Focused ultrasound treatment, present and future. *Neurol Med Chir (Tokyo)*. 2017;57(8):386-391. doi:10.2176/nmc.ra.2017-0024

8) Lee EJ, Fomenko A, Lozano AM. Magnetic resonance-guided focused ultrasound: current status and future perspectives in thermal ablation and blood-brain barrier opening. *J Korean Neurosurg Soc*. 2019;62(1):10-26. doi:10.3340/jkns.2018.0180

9) Burgess A, Shah K, Hough O, Hynynen K. Focused ultrasound-mediated drug delivery through the blood-brain barrier. *Expert Rev Neurother*. 2015;15(5):477-491. doi:10.1586/14737175.2015.1028369

10) Beccaria K, Sabbagh A, de Groot J, Canney M, Carpentier A, Heimberger AB. Blood-brain barrier opening with low intensity pulsed ultrasound for immune modulation and immune therapeutic delivery to CNS tumors. *J Neurooncol*. 2021;151(1):65-73. doi:10.1007/s11060-020-03425-8

11) Johnsen KB, Gudbergsson JM, Skov MN, Pilgaard L, Moos T, Duroux M. A comprehensive overview of exosomes as drug delivery vehicles - endogenous nanocarriers for targeted cancer therapy. *Biochim Biophys Acta*. 2014;1846(1):75-87. doi:10.1016/j.bbcan.2014.04.005

12) Pardridge WM. Blood-brain barrier and delivery of protein and gene therapeutics to brain. *Front Aging Neurosci*. 2019;11:373. doi:10.3389/fnagi.2019.00373

13) Doolittle ND, Miner ME, Hall WA, et al. Safety and efficacy of a multicenter study using intraarterial chemotherapy in conjunction with osmotic opening of the blood-brain barrier for the treatment of patients with malignant brain tumors. *Cancer*. 2000;88(3):637-647. doi:10.1002/(sici)1097-0142(20000201)88:3<637::aid-cncr22>3.0.co;2-y

14) Kroll RA, Neuwelt EA. Outwitting the blood-brain barrier for therapeutic purposes: osmotic opening and other means. *Neurosurgery*. 1998;42(5):1083-99; discussion 1099-1100. doi:10.1097/00006123-199805000-00082

15) Mitrasinovic S, Appelboom G, Detappe A, Sander Connolly E, Jr. Focused ultrasound to transiently disrupt the blood brain barrier. *J Clin Neurosci*. 2016;28:187-189. doi:10.1016/j.jocn.2015.12.011

16) Bakay L, Ballantine HT, Jr., Hueter TF, Sosa D. Ultrasonically produced changes in the blood-brain barrier. *AMA Arch Neurol Psychiatry*. 1956;76(5):457-467. doi:10.1001/archneurpsyc.1956.02330290001001

17) Burgess MT, Apostolakis I, Konofagou EE. Power cavitation-guided blood-brain barrier opening with focused ultrasound and microbubbles. *Phys Med Biol*. 15 2018;63(6):065009. doi:10.1088/1361-6560/aab05c

18) Shang X, Wang P, Liu Y, Zhang Z, Xue Y. Mechanism of low-frequency ultrasound in opening blood-tumor barrier by tight junction. *J Mol Neurosci*. 2011;43(3):364-369. doi:10.1007/s12031-010-9451-9

19) Caskey CF, Stieger SM, Qin S, Dayton PA, Ferrara KW. Direct observations of ultrasound microbubble contrast agent interaction with the microvessel wall. *J Acoust Soc Am*. 2007;122(2):1191-200. doi:10.1121/1.2747204

20) Sheikov N, McDannold N, Vykhodtseva N, Jolesz F, Hynynen K. Cellular mechanisms of the blood-brain barrier opening induced by ultrasound in presence of microbubbles. *Ultrasound Med Biol*. 2004;30(7):979-89. doi:10.1016/j.ultrasmedbio.2004.04.010

21) Rashed WM, Maher E, Adel M, Saber O, Zaghloul MS. Pediatric diffuse intrinsic pontine glioma: where do we stand? *Cancer Metastasis Rev*. Dec 2019;38(4):759-770. doi:10.1007/s10555-019-09824-2

22) Warren KE. Diffuse intrinsic pontine glioma: poised for progress. *Front Oncol*. 2012;2:205. doi:10.3389/fonc.2012.00205

23) Haas-Kogan DA, Banerjee A, Poussaint TY, et al. Phase II trial of tipifarnib and radiation in children with newly diagnosed diffuse intrinsic pontine gliomas. *Neuro Oncol*. 2011;13(3):298-306. doi:10.1093/neuonc/noq202

24) Chen KT, Wei KC, Liu HL. Theranostic strategy of focused ultrasound induced blood-brain barrier opening for CNS disease treatment. *Front Pharmacol*. 2019;10:86. doi:10.3389/fphar.2019.00086

25) Carpentier A, Canney M, Vignot A, et al. Clinical trial of blood-brain barrier disruption by pulsed ultrasound. *Sci Transl Med*. 2016;8(343):343re2. doi:10.1126/scitranslmed.aaf6086

26) Pouliopoulos AN, Wu SY, Burgess MT, Karakatsani ME, Kamimura HAS, Konofagou EE. A clinical system for non-invasive blood-brain barrier opening using a neuronavigation-guided single-element focused ultrasound transducer. *Ultrasound Med Biol*. 2020;46(1):73-89. doi:10.1016/j.ultrasmedbio.2019.09.010

27) Chen KT, Chai WY, Lin YJ, et al. Neuronavigation-guided focused ultrasound for transcranial blood-brain barrier opening and immunostimulation in brain tumors. *Sci Adv*. 2021;7(6)doi:10.1126/sciadv.abd0772

28) Wu SY, Aurup C, Sanchez CS, et al. Efficient blood-brain barrier opening in primates with neuronavigation-guided ultrasound and real-time acoustic mapping. *Sci Rep*. 2018;8(1):7978. doi:10.1038/s41598-018-25904-9

29) Lee CC, Chou CC, Hsiao FJ, et al. Pilot study of focused ultrasound for drug-resistant epilepsy. *Epilepsia*. 2022;63(1):162-175. doi:10.1111/epi.17105

30) Alli S, Figueiredo CA, Golbourn B, et al. Brainstem blood brain barrier disruption using focused ultrasound: a demonstration of feasibility and enhanced doxorubicin delivery. *J Control Release*. 2018;281:29-41. doi:10.1016/j.jconrel.2018.05.005

31) Ye D, Sultan D, Zhang X, et al. Focused ultrasound-enabled delivery of radiolabeled nanoclusters to the pons. *J Control Release*. 2018;283:143-150. doi:10.1016/j.jconrel.2018.05.039

32) Ye D, Zhang X, Yue Y, et al. Focused ultrasound combined with microbubble-mediated intranasal delivery of gold nanoclusters to the brain. *J Control Release*. 2018;286:145-153. doi:10.1016/j.jconrel.2018.07.020

33) Ye D, Yuan J, Yue Y, Rubin JB, Chen H. Focused ultrasound-enhanced delivery of intranasally administered anti-programmed cell death-ligand 1 antibody to an intracranial murine glioma model. *Pharmaceutics*. 2021;13(2) doi:10.3390/pharmaceutics13020190

34) Englander ZK, Wei HJ, Pouliopoulos AN, et al. Focused ultrasound mediated blood-brain barrier opening is safe and feasible in a murine pontine glioma model. *Sci Rep*. 2021;11(1):6521. doi:10.1038/s41598-021-85180-y

35) Ishida J, Alli S, Bondoc A, et al. MRI-guided focused ultrasound enhances drug delivery in experimental diffuse intrinsic pontine glioma. *J Control Release*. 2021;330:1034-1045. doi:10.1016/j.jconrel.2020.11.010

36) Idbaih A, Canney M, Belin L, et al. Safety and feasibility of repeated and transient blood-brain barrier disruption by pulsed ultrasound in patients with recurrent glioblastoma. *Clin Cancer Res*. 2019;25(13):3793-3801. doi:10.1158/1078-0432.CCR-18-3643

37) Mainprize T, Lipsman N, Huang Y, et al. Blood-brain barrier opening in primary brain tumors with non-invasive MR-guided focused ultrasound: a clinical safety and feasibility study. *Sci Rep*. 2019;9(1):321. doi:10.1038/s41598-018-36340-0

38) Anastasiadis P, Gandhi D, Guo Y, et al. Localized blood-brain barrier opening in infiltrating gliomas with MRI-guided acoustic emissions-controlled focused ultrasound. *Proc Natl Acad Sci U S A*. 2021;118(37). doi:10.1073/pnas.2103280118

39) Meng Y, Reilly RM, Pezo RC, et al. MR-guided focused ultrasound enhances delivery of trastuzumab to Her2-positive brain metastases. *Sci Transl Med*. 2021;13(615):eabj4011. doi:10.1126/scitranslmed.abj4011

40) Zhu L, Cheng G, Ye D, et al. Focused ultrasound-enabled brain tumor liquid biopsy. *Sci Rep*. 2018;8(1):6553. doi:10.1038/s41598-018-24516-7

41) Meng Y, Pople CB, Suppiah S, et al. MR-guided focused ultrasound liquid biopsy enriches circulating biomarkers in patients with brain tumors. *Neuro Oncol*. 2021;23(10):1789-1797. doi:10.1093/neuonc/noab057

Focused Ultrasound for Ablation in Neurosurgery — Present Use and Future Directions

Nina Yoh, MD, MS;[1] Masih Tazhibi, BA;[1] Zachary Englander, MD, MS;[1] Cheng-Chia Wu, MD, PhD;[2] Gordon Baltuch, MD, PhD[1]*

Abstract

Focused ultrasound (FUS) as a therapeutic modality for the treatment of neurological conditions has seen a rapid expansion over the past decade due to its ability to produce controlled and precise effects noninvasively. FUS has multiple mechanisms of action, but at higher frequencies, thermal ablation is predominant and is capable of precise and controlled lesioning of brain tissue. In particular, transcranial MR-guided focused ultrasound (MRgFUS) surgery has become a well-established tool in functional neurosurgery for movement disorders such as essential tremor and Parkinson's disease. Since its first US Food and Drug Administration (FDA) approval in 2016, MRgFUS has gained popularity amongst researchers, clinicians, and patients. Ongoing studies to evaluate additional indications are underway. Multiple clinical trials are open for the treatment of psychiatric illness, chronic pain, and epilepsy. Given an aging population as well as the increasing prevalence of diseases treated, the risk-benefit ratio of MRgFUS as a noninvasive ablative therapy should solidify its role as a treatment option for an increasing number of patients.

Keywords: focused ultrasound, high-frequency focused ultrasound, ultrasonic therapy, minimally invasive surgery, clinical device, ablation, brain, essential tremor, Parkinson's disease, depression

Focused ultrasound (FUS) as a therapeutic modality for the treatment of neurological conditions has seen a rapid expansion over the past decade due to its ability to produce controlled and precise effects noninvasively. In contrast to stereotactic radiosurgery, FUS is capable of nonionizing tissue destruction. This narrative review will focus on its use in thermoablation of brain tissue, though notably FUS is being avidly investigated for applications within neuromodulation as well as transient blood-brain barrier opening.

Although ultrasound was discovered in the late 1800s, the invention of FUS is attributed to Johannes Gruetzmacher who placed curved quartz on a piezoelectric generator to concentrate waves. Initial trials in humans targeted deep structures for movement disorders, but lesions were imprecise prior to the advent of modern imaging. Furthermore, large portions of skull were removed to mitigate wave distortion and surface heating. In 1998, the use of MRI and a helmet equipped with 2 arrays and 64 elements was shown to transmit pulsed sonication through a piece of a human skull to induce tissue destruction in an in vivo rabbit brain, which catapulted FUS as a noninvasive modality.

Since that time, myriad developments such as live MRI guidance have improved the safety and efficacy of FUS ablation **(Figure 1)**. As of this writing, 3 neurological

Affiliations: [1]Department of Neurological Surgery, Columbia University Irving Medical Center, New York, New York. [2]Department of Radiation Oncology, Columbia University Irving Medical Center, and Herbert Irving Comprehensive Cancer Center, New York, New York.
Corresponding Author: *Gordon Baltuch, MD, PhD, Department of Neurological Surgery, Columbia University Irving Medical Center, 622 W 168th Street, New York, NY 10032. (gb2774@cumc.columbia.edu)
Disclosure: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.

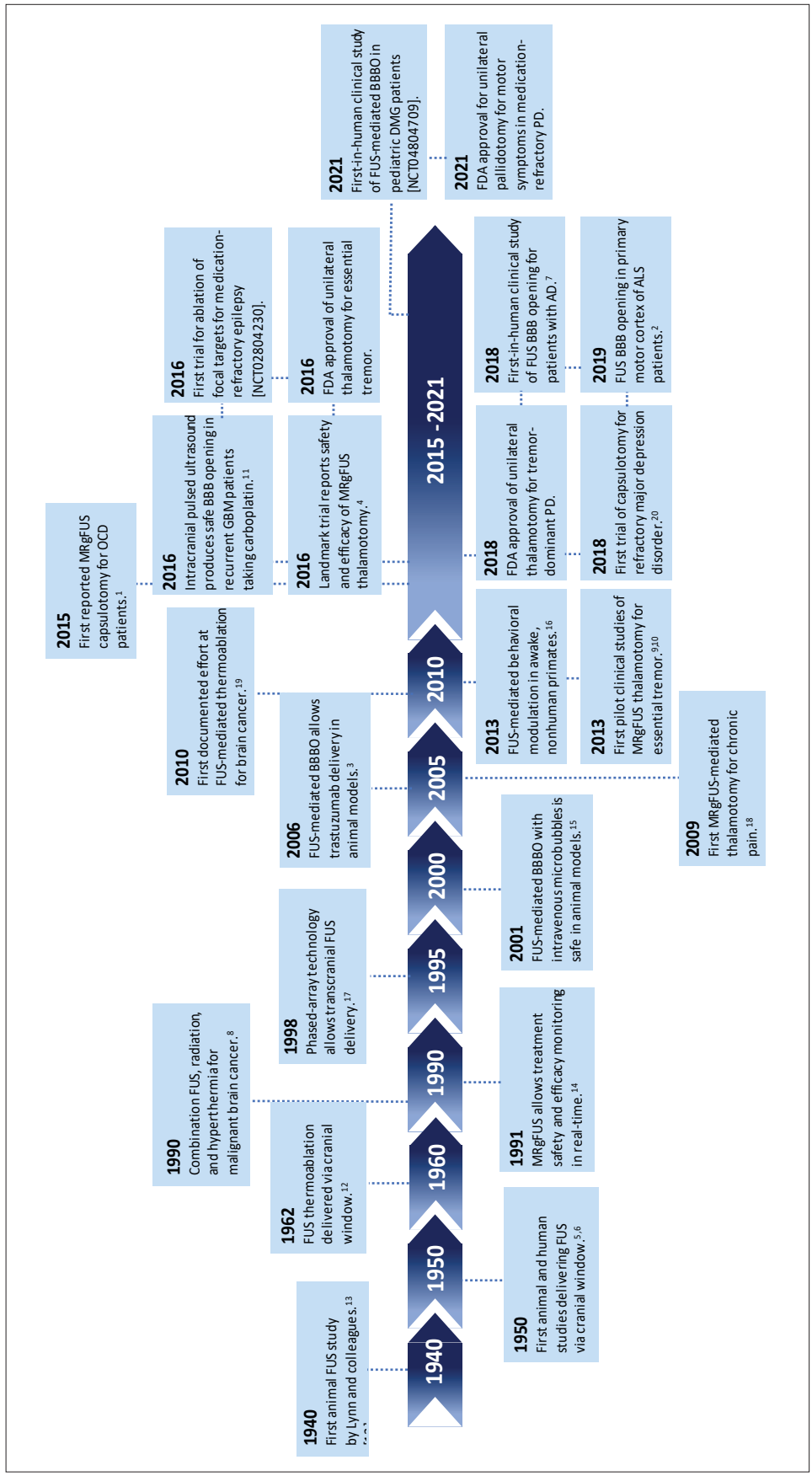


Figure 1. Timeline of the focused ultrasound (FUS) development and use from 1940 until 2021. Figure 1 references are in a separate section at the end of the article. Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BBB, blood-brain barrier; BBBO, blood-brain barrier opening; DMG, diffuse midline glioma; FDA, US Food and Drug Administration; GBM, glioblastoma; MRgFUS, MR-guided focused ultrasound; OCD, obsessive-compulsive disorder.

indications have been FDA approved for MRI-guided FUS (MRgFUS): thalamotomy for essential tremor (ET), thalamotomy for tremor-dominant Parkinson's disease (TDPD), and pallidotomy for the motor symptoms of Parkinson's disease. Multiple additional indications are being investigated in clinical trials as of this writing **(Table 1)**.

Mechanism of Action for Ablation

The ablative action of FUS depends on frequency, which leads to either thermal or mechanical tissue destruction. At higher frequencies of 650 kHz, thermal ablation is predominant. The FDA-approved hemispherical transducer (Exablate 4000; Insightec) can achieve peak temperatures of 51°C to 60°C under continuous visual MR guidance and MR thermometry with an accuracy of < 2 mm. Within 48 hours of treatment, 3 concentric zones appear on T2-weighted sequences: 2 inner zones representing necrosis and a zone of perilesional, vasogenic edema, which subsides within 10 days. Several pitfalls should be considered **(Figure 2)**. Higher frequencies and higher incident angles can lead to overheating of the skull due to its high acoustic absorption. High incident angles (> 20°) prohibit targets more proximal to the skull from successful treatment; thermal ablation can only be applied to central brain regions (approximately 3 cm radius around the midcommissural point, the halfway point on a line joining the anterior and posterior commissures). Thick and poorly homogenous skulls limit the penetration of ultrasound. Preoperative computerized tomography is obtained to assess patient-specific metrics such as skull thickness and skull homogeneity as quantified by skull density ratio (SDR). An SDR below 0.4 is considered inconducive to optimal thermal lesioning and FDA labeling includes only patients with an SDR of 0.4 or higher. At a single-center study in Taiwan, 246 patients were evaluated and 50% had a skull score under 0.4

Table 1. Clinical Trials of Focused Ultrasound for Intracranial Ablation

TRIAL NAME	LOCATION	ENROLLMENT STATUS	TRIAL NUMBER
Essential Tremor (ET)			
Bilateral Treatment of Medication Refractory ET	The Ohio State Medical Center, Ohio, United States	Active, not recruiting	NCT04112381
A Second Magnetic Resonance Guided Focused Ultrasound Thalamotomy for ET	Sunnybrook Health Sciences Centre, Ontario, Canada	Recruiting	NCT04720469
Bilateral ET Treatment With FUS	Toronto Western Hospital, University Health Network, Ontario, Canada	Recruiting	NCT04501484
Transcranial Ultrasound Therapy of ET	Pitié-Salpêtrière Hospital, Paris, France	Recruiting	NCT04074031
Exablate Transcranial MRgFUS for the Management of Treatment-Refractory Movement Disorders	Sunnybrook Health Sciences Centre, Ontario, Canada Toronto Western Hospital, Ontario, Canada	Active, not recruiting	NCT02252380
Parkinson's Disease (PD)			
Exablate Pallidotomy for Medically-Refractory Dyskinesia Symptoms or Motor Fluctuations of Advanced PD	Multicenter: United States, Canada, Israel, Italy, Korea, Spain, Taiwan, UK	Active, not recruiting	NCT03319485
Exablate Transcranial MRgFUS of the Subthalamic Nucleus for Treatment of PD	University of Virginia, Virginia, United States	Active, not recruiting	NCT02246374
MRgFUS Pallidothalamic Tractotomy for Therapy-Resistant PD	Chinese PLA General Hospital, Beijing, China	Not yet recruiting	NCT04996992
A Clinical Trial for the Safety and Effect of MRGuided FUS Subthalamotomy for Medication Refractory PD	Osaka University Hospital, Osaka, Japan	Recruiting	NCT04744493
Obsessive-Compulsive Disorder (OCD)			
The Use of Transcranial Ultrasound Treatment of OCD	Neurological Associates of West LA, California, United States	Enrolling by invitation	NCT04775875
Trial of MR-guided Focused Ultrasound (MRgFUS) Bilateral Capsulotomy for the Treatment of Refractory OCD	Foothill Medical Centre, Alberta, Canada Sunnybrook Health Sciences Centre, Ontario, Canada	Recruiting	NCT03156335

suggesting that the portion of patients who are ineligible for MRgFUS due to skull characteristics is significant. Air trapped in hair will severely attenuate transmission of ultrasound, thus necessitating a thorough and full shave of the head, a cause of distress in some patients.

Lower frequencies around 220 kHz produce therapeutic mechanical energy by interacting to rapidly expand and contract entrapped gas in a process called cavitation. Cavitation to the point of tissue destruction can be accomplished through a process called histotripsy in which short-duration pulses produce sufficient mechanical action to fragment extracellular matrices and to disintegrate cells into their subcellular constituents. This process is focal and leaves the surrounding tissue intact. Lower frequencies are less susceptible to acoustic absorption and higher incident angles, expanding the potential reach of MRgFUS beyond a 3-cm radius to encompass the entire intracranial space. This remains an area of research but its use intracranially is limited by concerns of an increased risk of hemorrhage in comparison to thermoablation. However, evidence in large animal models suggests there is minimal effect 200 µm from target boundaries and that major hemorrhage and other complications do not occur.

Current FDA-Approved Indications

MRgFUS ablation has become a well-established tool in functional neurosurgery for movement disorders such as ET and Parkinson's disease. Given the small size of tissue targets, central location within the skull, and an aged patient population with higher operative risk,

Table 1 continued. Clinical Trials of Focused Ultrasound for Intracranial Ablation

TRIAL NAME	LOCATION	ENROLLMENT STATUS	TRIAL NUMBER
Depression / Anxiety			
The Use of Transcranial Focused Ultrasound for the Treatment of Depression and Anxiety	Neurological Associates of West LA, California, United States	Enrolling by invitation	NCT04250441
The Impact of Focused Ultrasound Thalamotomy of the Anterior Nucleus for Focal-Onset Epilepsy on Anxiety	The Ohio State University, Ohio, United States	Not yet recruiting	NCT05032105
Trial of MR-guided Focused Ultrasound for Treatment of Refractory Major Depression	Sunnybrook Health Sciences Centre, Ontario, Canada	Recruiting	NCT03421574
Pain			
Feasibility Study of Exablate Thalamotomy for Treatment of Chronic Trigeminal Neuropathic Pain	University of Virginia, Virginia, United States	Active, not recruiting	NCT03309813
MR Guided Focused Ultrasound (FUS) for the Treatment of Trigeminal Neuralgia	University of Maryland Medical Center, Maryland, United States	Recruiting	NCT04579692
Feasibility Study of Exablate Thalamotomy for Treatment of Chronic Trigeminal Neuropathic Pain	Univ. of Maryland School of Medicine, Maryland, United States Univ. of Maryland Medical Systems, Maryland, United States	Active, not recruiting	NCT03111277
Multimodal MRI for MRgFUS Central Lateral Thalamotomy in Neuropathic Pain	Chinese PLA General Hospital, Beijing, China	Recruiting	NCT05122403
Focused Ultrasound (FUS) Mesencephalotomy for Head & Neck Cancer Pain	University of Virginia UVA Health, University Hospital, Virginia, United States	Recruiting	NCT03894553
Epilepsy			
A Pilot Study: Focused Ultrasound Thalamotomy for the Prevention of Secondary Generalization in Focal Onset Epilepsy	The Ohio State University, Columbus, Ohio, United States	Recruiting	NCT03417297
MR-Guided Focused Ultrasound in the Treatment of Focal Epilepsy	Stanford University Medical Center, California, United States University of Kansas Medical Center, Kansas, United States Mayo Clinic, Minnesota, United States University of Virginia, Virginia, United States	Recruiting	NCT02804230

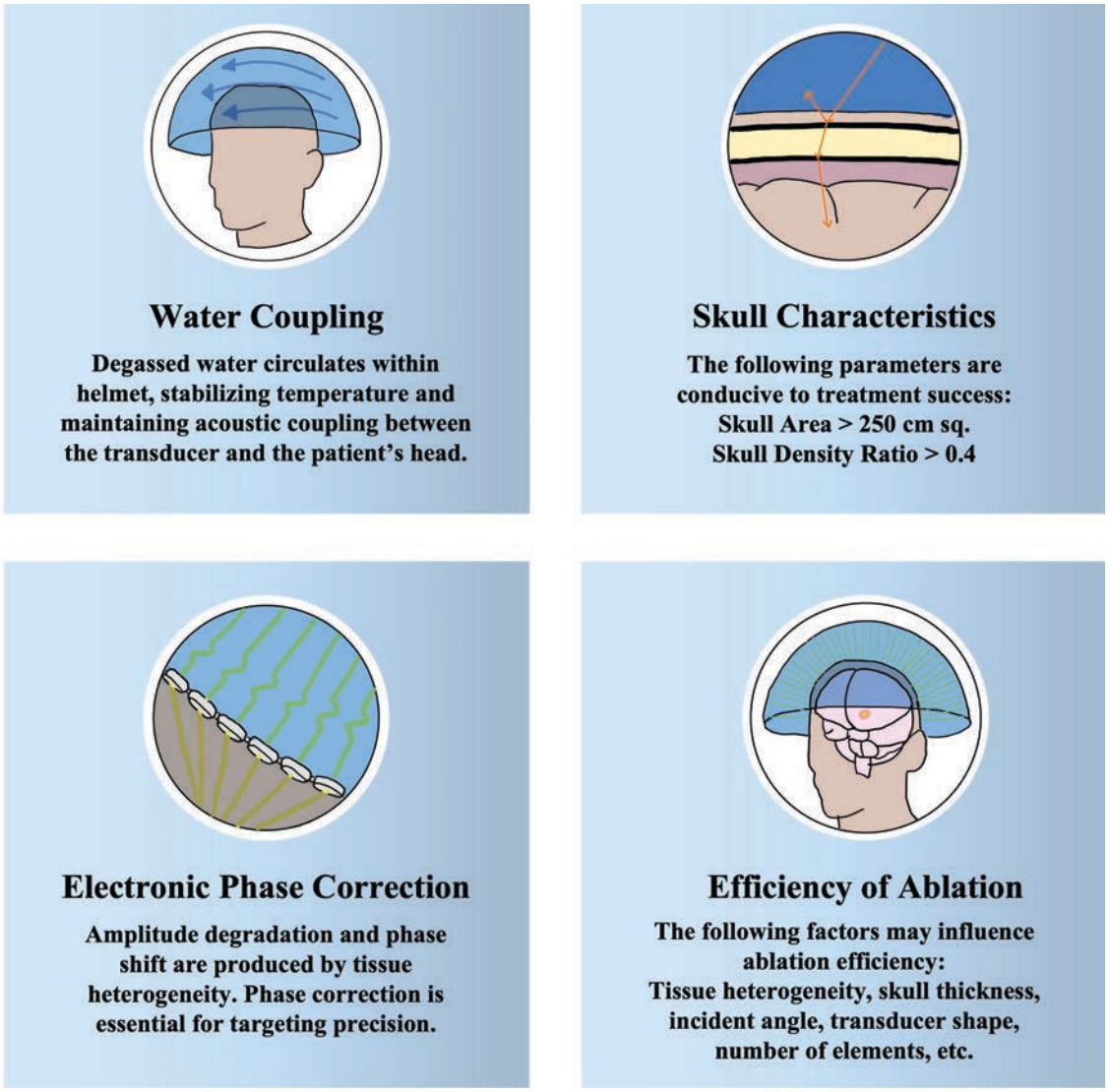


Figure 2. Factors to consider during MR-guided focused ultrasound surgery include water coupling to regulate surface temperature, patient skull characteristics such as skull thickness or density, and electronic phase correction to mitigate amplitude degradation caused by skull heterogeneity. The efficiency of ablation is also affected by the transducer shape, number of elements used, and ultrasound incident angles.

movement disorders approximate ideal indications for noninvasive thermal ablation.

Essential Tremor

In July 2016, thalamotomy (intentional destruction of thalamic tissue) for refractory ET became the first FDA-approved intracranial use of MRgFUS. ET was once referred to as "benign essential tremor;" however, "benign" was dropped out of consideration for a disease that is often debilitating, involving the hands and arms, and is worse when reaching the target during common daily activities such as holding a glass, eating with utensils, and writing. ET is the most common cause of action tremor in adults and remains a progressive process with no disease-modifying agents. The overall prevalence of ET in 2021 in ages over 65 was 5.67%. In the oldest age groups, median prevalence is 9.3%, with several studies reporting values over 20% without a predilection for gender. Current first-line treatment for ET consists of monotherapy with either propranolol or primidone; however, 30% and 32% of patients see no therapeutic benefit, respectively. Second-line treatments include combination drug therapy of these 2 first-line agents as well as the addition of gabapentin or topiramate. Success rates are generally lower and side effects can be dose limiting. Patients failing adequate trials of at least propranolol and primidone may be offered surgical options, which include treating the ventral intermediate nucleus (VIM) of the thalamus with deep brain stimulation (DBS) or thalamotomy (conventional thalamotomy, Gamma Knife [Elekta], or MRgFUS). A clinical trial randomizing 76 patients with ET to MRgFUS or a sham procedure showed a 47% tremor

reduction at 3 months after MRgFUS, which largely persisted after 1 year. Adverse events included gait disturbance in 36% of patients and paresthesias or numbness in 38%, which persisted at 1 year in 9% and 14% of patients, respectively.[10] Treatment is largely unilateral due to concerns for increased complications with bilateral thalamotomy, but recent evidence suggests a bilateral staged plan can be safe and effective. A prospective, single-arm, single-blinded phase 2 trial of second-side MRgFUS thalamotomy in 10 patients with ET showed clinically significant improvement in quality of life at 3 months (mean Quality of Life in Essential Tremor score difference, 19.7; 95% CI, 8.0-31.4; $P = 0.004$). Patients reported they would elect a second-side procedure despite mild adverse effects including 2 with transient gait impairment and a fall, 1 with dysarthria and dysphagia, and 1 with mild dysphagia persisting at 3 months. Currently, ET remains the subject of numerous active clinical trials to expand and optimize its treatment.

Parkinson's Disease (PD)

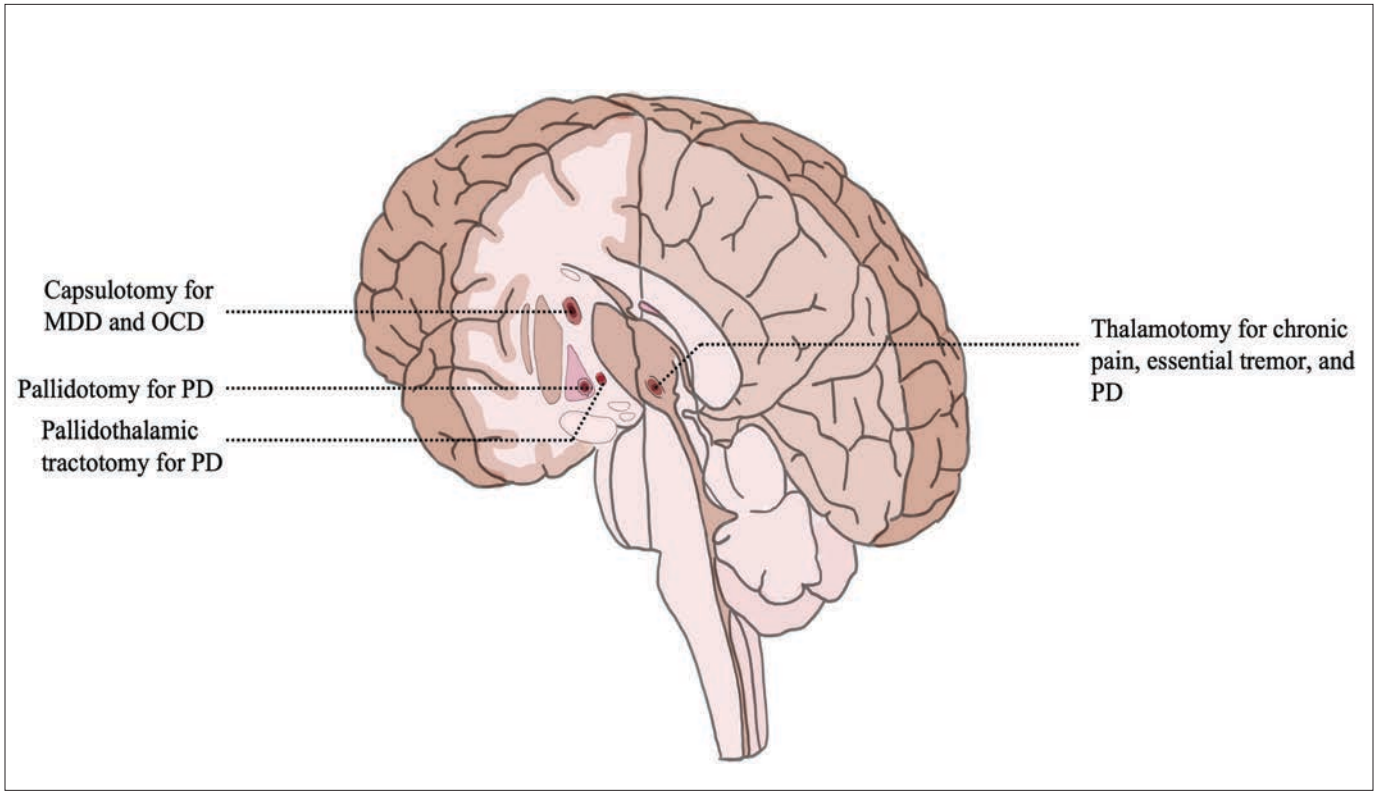
PD is the second most common neurodegenerative disease with a steadily increasing global prevalence. More than 6 million individuals are currently affected, which corresponds to a 2.5-fold increase in prevalence over the past generation. This number is projected to double again to over 12 million by 2040 or even as high as 17 million given increasing longevity, declining smoking rates, and increasing industrialization. Tremor due to PD is a rest tremor and typically begins unilaterally, which distinguishes it from ET. Of historical note, 50 patients with PD were amongst the first humans to be treated with FUS in 1960, a procedure that required creation of a skull window and took 14 hours to complete, with temporary improvement at best. As the drug L-dopa was developed, this procedure was understandably abandoned in favor of medical management. It was not until 2018 that thalamotomy for tremor-dominant PD received FDA regulatory approval in the US, becoming the only additional intracranial indication for FUS other than ET. For patients with treatment-resistant PD, DBS has largely replaced conventional lesioning, and targets include the ventral intermediate nucleus, subthalamic nucleus, and internal globus pallidus, depending on specific patient symptomatology. A randomized, sham-controlled trial of VIM MRgFUS involving 27 tremor-predominant PD patients showed that medication median tremor scores improved 62% in FUS-treated patients compared with 22% after sham procedures; the between-group difference was significant (Wilcoxon $P = .04$). All adverse events were mild and resolved within 3 months. Initially, transcranial MRgFUS targeting of the subthalamic nucleus was well-tolerated in an open-label pilot study with improvements in motor function; however, a subsequent randomized, sham-controlled trial revealed significant adverse effects including persistent new dyskinesias, motor weakness, and gait and speech disturbances. As a result, efforts to pursue this target have stalled. The internal globus pallidus is commonly targeted in DBS, but its lateral location can be challenging for thermoablation. Nevertheless, MRgFUS pallidotomy in a nonblinded study improved Unified PD Rating Scale part III scores by 39.1% and the Unified Dyskinesia Rating Scale by 42.7% at 12 months, and FDA approval for this location has been granted. The scales measure nonmotor and motor experiences of daily living, patient perceptions, time factors, anatomical distribution, objective impairment, severity, and disability. A promising area of study is lesioning of the pallidothalamic tract for chronic therapy-resistant PD. A recent study of 47 patients resulted in a mean reduction of 84% for tremor, 70% for rigidity, and 73% for distal hypobradykinesia. At present, multiple clinical trials to study thermoablation targets for PD, including international trials, are underway.

Frontier Indications

Psychiatric Diseases

MRgFUS capsulotomy is being studied as a potential treatment for obsessive-compulsive disorder (OCD), depression, and anxiety with small studies published to date. OCD is related to an imbalance of excitatory and inhibitory pathways in the corticostriatal-thalamocortical circuit. Patients are noted to have hyperactive caudates, orbitofrontal cortices, or anterior cingulates. As such, DBS targets have included the ventral striatum, the subthalamic nucleus, the anterior limb of the internal capsule, and the anterior cingulate cortex. MRgFUS treatment has focused on the anterior limb of the internal capsule. Two human trials studied MRgFUS anterior capsulotomy for medically refractory OCD with a mean reduction in the Yale-Brown Obsessive Compulsive Scale of 33% to 37.8% at 2 years in some patients. No serious adverse events were reported. A case report of refractory OCD in the form of constant, debilitating musical obsession achieved durable improvement after MRgFUS capsulotomy. These small studies suggest that the overall response to MRgFUS capsulotomy with respect to symptom response rate and magnitude is comparable to stereotactic radiosurgery capsulotomy, which uses high-dose ionizing radiation. Additional clinical trials to further evaluate OCD and MRgFUS are underway. Major

Figure 3. Intracranial targets for MR-guided focused ultrasound ablation include thalamotomy, pallidotomy and pallidothalamic tractotomy for Parkinson's disease (PD); anterior capsulotomy for major depressive disorder (MDD) and obsessive-compulsive disorder (OCD); and thalamotomy for chronic pain and essential tremor.



depressive disorder (MDD) is highly prevalent and treatment-refractory in a third of patients and is often comorbid with anxiety and other psychiatric illness. It is a heterogeneous disorder implicating numerous structural and functional brain circuits with historical surgical treatments including the internal capsule, bilateral anterior cingulotomy, subcaudate tractotomy, and limbic leucotomy. In a phase 1 trial of anterior capsulotomy for MDD with MRgFUS, 2 of 6 previously treatment-resistant patients met criteria for response at 6 months (50% reduction in Hamilton Depression Rating Scale) with 4 out of 6 showing no significant change. Clinical trials to further evaluate the efficacy of MRgFUS for MDD and anxiety are underway.

Chronic Pain

The prevalence of pain lasting more than 3 months is as high as 6.9% to 10% in the general population. Extracranial application of FUS was FDA approved in the treatment of pain for bone metastasis in 2012, and clinical trials to investigate intracranial applications of MRgFUS for pain are ongoing. Anterior cingulate, brainstem, spinal cord, and pituitary gland targets have all been discussed in the literature, but the thalamus remains a principal target for ablative therapy given its role in the relay of ascending nociceptive input from neurons of the spinal thalamic tract to key cortical areas. Bilateral central lateral thalamic nuclei thermoablation in 9 patients with chronic neuropathic pain produced pain relief in > 50% at 1 year. A particular area of study is neuropathic pain associated with trigeminal neuralgia, which is being treated with MRgFUS bilateral medial thalamotomy in clinical trial.

Chronic pain is a heterogeneous disease with multifactorial effectors and MRgFUS will not be a cure-all, but will likely join the broad armamentarium of medical and surgical treatment for suffering patients.

Epilepsy

Few case reports have detailed MRgFUS as a treatment in epilepsy patients. One 26-year-old man with gelastic epilepsy and hypothalamic hamartoma received MRgFUS ablation to the boundary area of the lesion to disconnect the hamartoma cells from the base of the hypothalamus. He was able to achieve seizure freedom by decreasing his antiepileptic dosage. One female patient with left temporal lobe epilepsy was treated with 12 sonication sessions to the hippocampus, but failed to achieve the target temperature of (> 54 °C). Nevertheless, at 12 months, seizure frequency had decreased from 3 or 4 seizures per month to near seizure freedom, suggesting either a partial physiological

or neuromodulatory effect. Tierney et al performed MRgFUS on 5 patients with benign brain tumors, 3 of whom presented with primary concern for seizure secondary to hypothalamic hamartomas, and for whom thermoablation resulted in 90%, 95% and 100% seizure freedom at 1 year follow-up. Two phase I clinical trials of MRgFUS and epilepsy are ongoing to investigate ablation of the anterior nucleus of the thalamus to prevent secondary generalization in focal onset epilepsy and in patients with comorbid moderate-severe anxiety, respectively. MRgFUS for epilepsy remains a nascent field for continued study.

Conclusion

Since its first FDA approval in 2016, FUS has gained popularity amongst researchers, clinicians and patients as judged by an increase in the number of presentations at international meetings, the volume of publications, and the increase in the number of patients treated. As of 2020, 375,000 patients had received some form of FUS treatment, of which 1% was intracranial. Its utility for noninvasive tissue destruction is particularly relevant in neurological disease where small, deep lesions provide a large effect in a multitude of pathological conditions (**Figure 3**). FUS is an acoustic, non-ionizing therapy and there may be a future role for radiation oncologists in utilizing this treatment. MRgFUS thalamotomy for ET and thalamotomy or pallidotomy for Parkinson's disease are increasingly utilized by patients and surgeons since regulatory approval in 2016 and 2018, respectively. Initial studies of safety and efficacy for additional indications from depression to trigeminal neuralgia are reassuring and may soon warrant additional regulatory approvals. Use of FUS in neuro-oncology is a nascent and promising frontier. Given an aging population as well as increasing prevalence of diseases considered for treatment, the risk-benefit ratio of MRgFUS as a noninvasive ablative therapy should solidify its role as a treatment option for an increasing number of patients.

References

1) Harary M, Segar DJ, Huang KT, et al (2018). Focused ultrasound in neurosurgery: a historical perspective. *Neurosurg Focus.* 2018;44(2)E2.

2) Hynynen K, Jolesz FA. Demonstration of potential noninvasive ultrasound brain therapy through an intact skull. *Ultrasound Med Biol.* 1998;24:275-283.

3) US Food and Drug Administration. 2022. Exablate Model 4000 Type 1.0 and 1.1 System ("Exablate Neuro"). Accessed September 7, 2022. https://www.fda.gov/medical-devices/recently-approved-devices/exablate-model-4000-type-10-and-11-system-exablate-neuro-p150038s014

4) Martin E, Jeanmonod D, Morel A, Zadicario E, Werner B. High-intensity focused ultrasound for noninvasive functional neurosurgery. *Ann Neurol.* 2009;66(6):858-861. doi:10.1002/ana.21801

5) Elias WJ, Khaled M, Hilliard JD, et al. A magnetic resonance imaging, histological, and dose modeling comparison of focused ultrasound, radiofrequency, and Gamma Knife radiosurgery lesions in swine thalamus. *J Neurosurg.* 2013;119(2):307-317. doi:10.3171/2013.5.JNS122327

6) Chang KW, Rachmilevitch I, Chang WS, et al. Safety and efficacy of magnetic resonance-guided focused ultrasound surgery with autofocusing echo imaging. *Front Neurosci.* 2021;14:592763. doi:10.3389/fnins.2020.592763

7) Tsai KW, Chen JC, Lai HC, et al. The distribution of skull score and skull density ratio in tremor patients for MR-guided focused ultrasound thalamotomy. *Front Neurosci.* 2021;15:612940. doi:10.3389/fnins.2021.612940

8) Raymond SB, Hynynen K. Acoustic transmission losses and field alterations due to human scalp hair. *IEEE Trans Ultrason Ferroelectr Freq Control.* 2005;52(8):1415-1419. doi:10.1109/tuffc.2005.1509801

9) Bader KB, Vlaisavljevich E, Maxwell AD. For whom the bubble grows: physical principles of bubble nucleation and dynamics in histotripsy ultrasound therapy. *Ultrasound Med Biol.* 2019;45(5):1056-1080. doi:10.1016/j.ultrasmedbio.2018.10.035

10) Arvanitis CD, Vykhodtseva N, Jolesz F, Livingstone M, McDannold N. Cavitation-enhanced nonthermal ablation in deep brain targets: feasibility in a large animal model. *J Neurosurg.* 2016;124(5):1450-1459. doi:10.3171/2015.4.JNS142862

11) Louis ED, McCreary M. How common is essential tremor? Update on the worldwide prevalence of essential tremor. *Tremor Other Hyperkinet Mov.* 2021;11:28. doi: 10.5334/tohm.632.

12) Koller WC, Vetere-Overfield B. Acute and chronic effects of propranolol and primidone in essential tremor. *Neurology.* 1989;39(12):1587-1588. doi:10.1212/wnl.39.12.1587

13) Elias WJ, Lipsman N, Ondo WG, et al. A randomized trial of focused ultrasound thalamotomy for essential tremor. *N Engl J Med.* 2016;375(8):730-739. doi:10.1056/NEJMoa1600159

14) Iorio-Morin C, Yamamoto K, Sarica C, et al. Bilateral Focused Ultrasound Thalamotomy for Essential Tremor (BEST-FUS Phase 2 Trial). *Mov Disord.* 2021 Nov;36(11):2653-2662. doi: 10.1002/mds.28716

15) GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019 May;18(5):459-480. doi: 10.1016/S1474-4422(18)30499-X

16) Dorsey ER, Sherer T, Okun MS, Bloem BR. The emerging evidence of the Parkinson pandemic. *J Parkinsons Dis.* 2018;8(s1):S3-S8. doi: 10.3233/JPD-181474

17) Fry WJ, Fry FJ. Fundamental neurological research and human neurosurgery using intense ultrasound. *IRE Trans Med Electron.* 1960;ME-7:166-181. doi:10.1109/iret-me.1960.5008041

18) Sinai A, Nassar M, Sprecher E, Constantinescu M, Zaaroor M, Schlesinger I. Focused ultrasound thalamotomy in tremor dominant Parkinson's disease: long-term results. *J Parkinsons Dis.* 2022;12(1):199-206. doi: 10.3233/JPD-212810

19) Kleiner-Fisman G, Herzog J, Fisman DN, et al. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Mov Disord.* 2006 Jun;21 Suppl 14:S290-304. doi: 10.1002/mds.20962

20) Martínez-Fernández R, Rodríguez-Rojas R, Del Álamo M, et al. Focused ultrasound subthalamotomy in patients with asymmetric Parkinson's disease: a pilot study. *Lancet Neurol.* 2018;17(1):54-63. doi:10.1016/S1474-4422(17)30403-9

21) Martínez-Fernández R, Rodríguez-Rojas R, Del Álamo M, et al. Focused ultrasound subthalamotomy in patients with asymmetric Parkinson's disease: a pilot study. *Lancet Neurol.* 2018;17(1):54-63. doi:10.1016/S1474-4422(17)30403-9

22) Martínez-Fernández R, Máñez-Miró JU, Rodríguez-Rojas R, et al. Randomized trial of focused ultrasound subthalamotomy for Parkinson's disease. *N Engl J Med.* 2020;383(26):2501-2513. doi:10.1056/NEJMoa2016311

23) Jung NY, Park CK, Kim M, Lee PH, Sohn YH, Chang JW. The efficacy and limits of magnetic resonance-guided focused ultrasound pallidotomy for Parkinson's disease: a phase I clinical trial (published online ahead of print, August 1, 2018). *J Neurosurg.* 2018;1-9. doi:10.3171/2018.2.JNS172514

24) Health C for D and R. Exablate Model 4000 Type 1.0 and 1.1 System ("Exablate Neuro") – P150038/S014. FDA. Published online January 3, 2022. https://www.fda.gov/medical-devices/recently-approved-devices/exablate-model-4000-type-10-and-11-system-exablate-neuro-p150038s014

25) Gallay MN, Moser D, Rossi F, et al. MRg-FUS pallidothalamic tractotomy for chronic therapy-resistant Parkinson's disease in 51 consecutive patients: single center experience. *Front Surg.* 2020;6:76. Published January 14, 2020. doi:10.3389/fsurg.2019.00076

26) Kim SJ, Roh D, Jung HH, Chang WS, Kim CH, Chang JW. A study of novel bilateral thermal capsulotomy with focused ultrasound for treatment-refractory obsessive-compulsive disorder: 2-year follow-up. *J Psychiatry Neurosci.* 2018;43(5):327-337. doi:10.1503/jpn.170188

27) Davidson B, Hamani C, Rabin JS, et al. Magnetic resonance-guided focused ultrasound capsulotomy for musical obsessions. *Biol Psychiatry.* 2021;90(10):e49-e50. doi:10.1016/j.biopsych.2020.07.005

28) Mustroph ML, Cosgrove GR, Williams ZM. The evolution of modern ablative surgery for the treatment of obsessive-compulsive and major depression disorders. *Front Integr Neurosci.* 2022;16:797533. Published April 6, 2022. doi:10.3389/fnint.2022.797533

29) Volpini M, Giacobbe P, Cosgrove GR, Levitt A, Lozano AM, Lipsman N. The history and future of ablative neurosurgery for major depressive disorder. *Stereotact Funct Neurosurg.* 2017;95(4):216-228. doi:10.1159/000478025

30) Davidson B, Hamani C, Rabin JS, et al. Magnetic resonance-guided focused ultrasound capsulotomy for refractory obsessive compulsive disorder and major depressive disorder: clinical and imaging results from two phase I trials. *Mol Psychiatry.* 2020;25(9):1946-1957. doi:10.1038/s41380-020-0737-1

31) di Biase L, Falato E, Caminiti ML, Pecoraro PM, Narducci F, Di Lazzaro V. Focused ultrasound (FUS) for chronic pain management: approved and potential applications. *Neurol Res Int.* 2021;2021:8438498. Published 2021 Jun 29. doi:10.1155/2021/8438498

32) Martin E, Jeanmonod D, Morel A, Zadicario E, Werner B. High-intensity focused ultrasound for noninvasive functional neurosurgery. *Ann Neurol.* 2009;66(6):858-861. doi:10.1002/ana.21801

33) InSightec. A feasibility study of focused ultrasound to perform bilateral medial thalamotomy for the treatment of chronic trigeminal neuropathic pain. clinicaltrials.gov. Published August 10, 2021. Accessed August 19, 2022. https://www.clinicaltrials.gov/ct2/show/NCT03309813

34) Lescrauwaet E, Vonck K, Sprengers M, et al. Recent advances in the use of focused ultrasound as a treatment for epilepsy. *Front Neurosci.* 2022;16:886584. Published 2022 Jun 20. doi:10.3389/fnins.2022.886584

35) Yamaguchi T, Hori T, Hori H, et al. Magnetic resonance-guided focused ultrasound ablation of hypothalamic hamartoma as a disconnection surgery: a case report. *Acta Neurochir (Wien).* 2020;162(10):2513-2517. doi:10.1007/s00701-020-04468-6

36) Abe K, Yamaguchi T, Hori H, et al. Magnetic resonance-guided focused ultrasound for mesial temporal lobe epilepsy: a case report. *BMC Neurol.* 2020 Apr 29;20(1):160. doi:10.1186/s12883-020-01744-x

37) Tierney TS, Alavian KN, Altman N, et al. Initial experience with magnetic resonance-guided focused ultrasound stereotactic surgery for central brain lesions in young adults (published online ahead of print, January 14, 2022). *Neurosurg.* 2022;1-8. doi:10.3171/2021.10.JNS21416

38) State of the Technology. Focused Ultrasound Foundation. Published May 4, 2022. Accessed August 18, 2022. https://www.fusfoundation.org/the-technology/state-of-the-technology/

Figure 1 References

1) Jung HH, Kim SJ, Roh D, et al. Bilateral thermal capsulotomy with MR-guided focused ultrasound for patients with treatment-refractory obsessive-compulsive disorder: a proof-of-concept study. *Mol Psychiatry.* 2015;20(10):1205-1211.

2) Abrahao A, Meng Y, Llinas M, et al. First-in-human trial of blood-brain barrier opening in amyotrophic lateral sclerosis using MR-guided focused ultrasound. *Nat Commun.* 2019;10(1):4373.

3) Kinoshita M, McDannold N, Jolesz FA, Hynynen K. Noninvasive localized delivery of Herceptin to the mouse brain by MRI-guided focused ultrasound-induced blood-brain barrier disruption. *Proc Natl Acad Sci USA.* 2006;103(31):11719-11723.

4) Elias WJ, Lipsman N, Ondo WG, et al. A randomized trial of focused ultrasound thalamotomy for essential tremor. *N Engl J Med.* 2016;375(8):730-739. doi:10.1056/NEJMoa1600159

5) Meyers R, Fry WJ, Fry FJ, Dreyer LL, Schultz DF, Noyes RF. Early experiences with ultrasonic irradiation of the pallidofugal and nigral complexes in hyperkinetic and hypertonic disorders. *J Neurosurg.* 1959;16(1):32-54.

6) Nelson E, Lindstrom PA, Haymaker W. Pathological effects of ultrasound on the human brain. A study of 25 cases in which ultrasonic irradiation was used as a lobotomy procedure. *J Neuropathol Exp Neurol.* 1959;18:489-508.

7) Lipsman N, Meng Y, Bethune AJ, et al. Blood-brain barrier opening in Alzheimer's disease using MR-guided focused ultrasound. *Nat Commun.* 2018;9(1):2336.

8) Guthkelch AN, Carter LP, Cassady JR, et al. Treatment of malignant brain tumors with focused ultrasound hyperthermia and radiation: results of a phase I trial. *J Neurooncol.* 1991;10(3):271-284.

9) Lipsman N, Schwartz M, Huang Y, et al. MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study. *Lancet Neurol.* 2013;12(5):462-468.

10) Elias WJ, Huss D, Voss T, et al. A pilot study of focused ultrasound thalamotomy for essential tremor. *N Engl J Med.* 2013;369(7):640-648.

11) Carpentier A, Canney M, Vignot A, et al. Clinical trial of blood-brain barrier disruption by pulsed ultrasound. *Sci Transl Med.* 2016;8(343):343re2.

12) Fry WJ, Meyers R. Ultrasonic method of modifying brain structures. *Confin Neurol.* 1962;22:315-327.

13) Lynn JG, Zwemer RL, Chick AJ, Miller AE. A new method for the generation and use of focused ultrasound in experimental biology. *J Gen Physiol.* 1942;26(2):179-193.

14) Hynynen K, Darkazanli A, Unger E, Schenck JF. MRI-guided noninvasive ultrasound surgery. *Med Phys.* 1993;20(1):107-115.

15) Hynynen K, McDannold N, Vykhodsteva N, Jolesz FA, et al. Noninvasive MR imaging-guided focal opening of the blood-brain barrier in rabbits. *Radiology.* 2001;220(3):640-646.

16) Deffieux T, Younan Y, Wattiez N, Tanter M, Pouget P, Aubry JF. Low-intensity focused ultrasound modulates monkey visuomotor behavior. *Curr Biol.* 2013;23(23):2430-2433.

17) Hynynen K, McDannold, Clement G, et al. Pre-clinical testing of a phased array ultrasound system for MRI-guided noninvasive surgery of the brain – a primate study. *Eur J Radiol.* 2006;59(2):149-156.

18) Martin E, Jeanmonod D, Morel A, Zadicario E, Werner B. High-intensity focused ultrasound for noninvasive functional neurosurgery. *Ann Neurol.* 2009;66(6):858-861. doi:10.1002/ana.21801

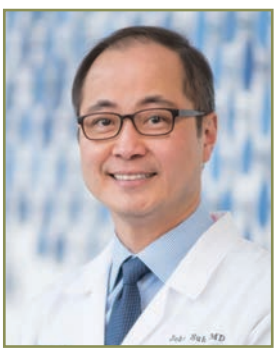
19) McDannold N, Clement GT, Black P, Jolesz F, Hynynen K. Transcranial magnetic resonance imaging-guided focused ultrasound surgery of brain tumors: initial findings in 3 patients. *Neurosurgery.* 2010;66(2):323-332; discussion 332.

20) Kim M, Kim C-H, Jung HH, Kim SJ, Chang JW. Treatment of major depressive disorder via magnetic resonance-guided focused ultrasound surgery. *Biol Psychiatry.* 2018; 83(1):e17-e18

CALL FOR PAPERS

Applied Radiation Oncology

A key resource for practical clinical information and SA-CME credits



John Suh, MD, FASTRO, FACR

Dear Colleagues:

We are pleased to let you know that our journal and community of registered radiation oncologists have continued to expand over the last several years. We appreciate your support and, as part of our mission to foster a community where peers share practical solutions in the clinical setting, *Applied Radiation Oncology* is issuing a call for clinical cases, review articles and research articles.

We are looking for authors to write and submit on topics that include (but are not limited to): imaging, contouring, target delineation, treatment planning, patient immobilization, organ tracking, safety and quality, and other timely topics essential to the discipline. Important to note is that review articles accepted for publication may be accredited for Continuing Medical Education (CME). Submissions will undergo a double-blind peer review process through our external peer review panel.

If you or your colleagues have an interesting case, review article or research paper for publication consideration in *Applied Radiation Oncology*, please read our Submission Guidelines. As a reference for the types of articles published in *Applied Radiation Oncology*, visit appliedradiationoncology.com and browse our archives.

This is a wonderful opportunity to impart your knowledge to your peers and we look forward to your submissions.

Sincerely,

John Suh, MD, FASTRO, FACR
Editor-in-Chief, Applied Radiation Oncology

Dr. Suh is the editor-in-chief of *Applied Radiation Oncology,* and professor and chairman, Department of Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.

2022 Peer Reviewer Recognition

Applied Radiation Oncology extends its sincere appreciation to the radiation oncologists and related experts who peer reviewed manuscripts for the journal in 2022, graciously volunteering their time and expertise. We are grateful for these invaluable efforts, which are critical to effective scholarly publishing through the assessment of importance, validity and quality of work.

Thank you to the following peer reviewers
for their insight, commitment and contributions in 2022!

- May Abdel-Wahab, MD, PhD, FASTRO, FACR, Atomic Energy Agency
- Mohamed Latif Abouegylah, MD, PhD, Alexandria University
- Fiori Alite, MD, Geisinger Lewisburg Cancer Center
- Vilija N. Avizonis, MD, Intermountain Healthcare*
- Steve Braunstein, MD, PhD, University of California, San Francisco
- Jeffrey V. Brower, MD, PhD, Seacoast Cancer Center
- Levi Burns, MSc, MMgt, BSc, McMaster University
- Leslie Chang, MD, Johns Hopkins Medicine
- Sheen Cherian, MD, Cleveland Clinic
- Jay Ciezki, MD, Cleveland Clinic
- Lee Daesung, MD, Cleveland Clinic*
- John Dombrowski, MD, PhD, Saint Louis University, Saint Louis University Hospital*
- Mohamed Elshaikh, MD, Henry Ford Health System
- Jessica M. Frakes, MD, Moffitt Cancer Center
- Gary M. Freedman, MD, Penn Medicine
- Shefali Gajjar, MD, Penn Medicine
- Ahmed Ghanem, MD, PhD, Henry Ford Health System
- Caitlin Gomez, MD, City of Hope†
- G. Daniel Grass MD, PhD, Moffitt Cancer Center
- Myrsini Ioakeim Ioannidou, MD, Massachusetts General Hospital and Harvard Medical School
- Mohammad K. Khan, MD, PhD, MS, FACRO, FACR, DABR, Emory University School of Medicine
- Amar U. Kishan, MD, University of California, Los Angeles

- Anna Lee, MD, MPH, MD Anderson Cancer Center*
- Daesung Lee, MD, Cleveland Clinic*
- Hefei Liu, BS, Medical College of Wisconsin
- Jason Liu, MD, City of Hope*
- Natalie Logie, MD, FRCP(C), Alberta Health Services†
- Raymond B. Mailhot, MD, MPH, University of Florida*
- Townes Alston Mickel, BS, Medical University of South Carolina
- Homan Mohammadi, MD, Dana-Farber, Brigham & Women's Cancer Center*
- Shalini Moningi, MD, Dana-Farber Cancer Institute
- Elizabeth M. Nichols, MD, University of Maryland Medical Center*
- Russell F. Palm, MD, Moffitt Cancer Center
- Neil R. Parikh, MD, MBA, San Antonio Cancer Center
- Ravi Patel, MD, PhD, University of Pittsburgh Medical Center*
- Lauren Powlovich, MD, University of Virginia University Hospital
- Robert A. Price Jr, PhD, DABR, FAAPM, FASTRO, Fox Chase Cancer Center
- Mack Roach III, MD, FACR, FASTRO, UCSF Helen Diller Family Comprehensive Cancer Center
- Catarina Martins Silva, MD, Hospital de Braga, Portugal
- Jacob Shabason, MD, MTR, Perelman School of Medicine, University of Pennsylvania
- Jeevin Shahi, MD, FRCPC, DABR, Saint Louis University School of Medicine*
- Tarek Shouman, MD, PhD, National Cancer Institute, Cairo University
- Kevin Shrake, BS, Medical University of South Carolina
- Farzan Siddiqui MD, PhD, CPE, Henry Ford Cancer Institute
- Austin J. Sim, MD, JD, Moffitt Cancer Center
- Leila Teodora Tchelebi, MD, Northwell Health
- Sewit Teckie, MD, MBA, NYC Health and Hospitals
- Martin C. Tom, MD, MD Anderson Cancer Center
- Anna Torgeson, MD, City of Hope Radiation Oncology*
- Mark Trombetta MD, FACR, Allegheny Health Network Cancer Institute
- Peter Zaki, MD, UW Medicine*

**Completed two reviews.* *†Completed three or more reviews.*

Teaching Case: Radiation Myonecrosis Following Stereotactic Body Radiation Therapy in Metastatic Renal Cell Carcinoma

Yvonne Su, BA;[1] Sana Dastgheyb, MD, PhD;[2*] Naomi Balzer-Haas, MD;[3] Jae W. Song, MD, MS;[4] Joshua Jones, MD[2]

Abstract

Cases of radiation-induced myonecrosis are exceedingly uncommon in radiation literature. We present a rare case of radiation myonecrosis in a 39-year-old woman with metastatic renal cell carcinoma (RCC) on concurrent immunotherapy, following 40 Gy in 5 fractions of radiation to a paravertebral muscle metastasis in the neck. We describe a 1-year timeline wherein the patient receives radiation therapy, develops clinical signs of radiation myonecrosis, and then shows radiographic resolution of the lesion followed by radiographic evidence of radiation myonecrosis at the treatment site. The patient improved clinically within 1 month following radiographic diagnosis. We add this to the collection of published radiation-induced myonecrosis cases to caution radiation experts about potential side effects of radiation therapy.

Keywords: radiation myonecrosis, toxicity, renal cell carcinoma, RCC, immunotherapy, stereotactic body radiation therapy, SBRT

Introduction

Renal cell carcinoma (RCC) is the 7th most diagnosed cancer in the developed world and one of the fastest-growing cancer diagnoses in the US.[1] It comprises many histopathologic variants, the most common being the clear cell variant, with the rhabdoid variant associated with higher mortality rate and poorer prognosis.[2] Although no clear explanation exists, laboratory experiments have shown that RCC is also relatively radioresistant and evidence suggests that hypofractionated radiation therapy with higher doses and fewer fractions are necessary to overcome these tumor cells.[3,4] Thus, stereotactic body radiation therapy (SBRT) is now preferred over conventional radiation therapy.[4,5]

We present a rare case of radiation myonecrosis in a patient with metastatic RCC, treated with concurrent immunotherapy and SBRT. This is the first case of radiation myonecrosis following radiation therapy for RCC, and only the second case of radiation myonecrosis following SBRT.

Case Summary

Our patient is a 39-year-old woman diagnosed with metastatic RCC after resection of a left-forearm mass in July 2018. Initial x-rays followed by MRI revealed a soft-tissue mass and ulnar lytic lesion concerning for malignancy, and positron emission tomography / computed tomography (PET/CT) revealed a left renal mass presumed to be her primary site of disease. Her disease course/time-

Affiliations: [1]Perelman School of Medicine, University of Pennsylvania, Philadelphia; [2]Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia; [3]Department of Hematology and Oncology, Hospital of the University of Pennsylvania, Philadelphia; [4]Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia.
Corresponding Author: *Sana Dastgheyb MD, PhD, Department of Radiation Oncology, Hospital of the University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA 19104 (Sana.dastgheyb@pennmedicine.upenn.edu).
Disclosure/Informed Consent: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere. The patient has provided informed consent for the publication of this case report.

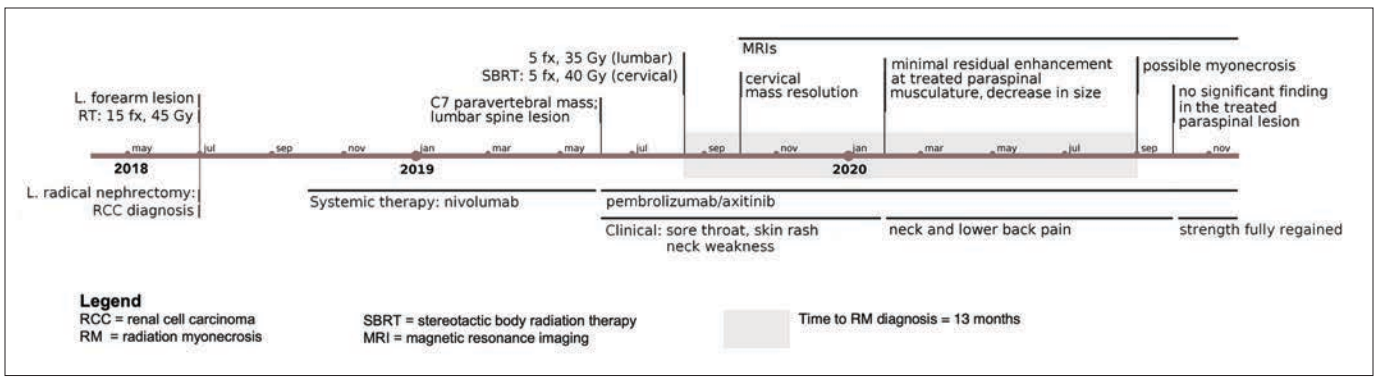


Figure 1. Patient timeline. Renal cell carcinoma (RCC) was diagnosed in July 2018. Cervical stereotactic body radiation therapy (SBRT) was performed in August 2019, with concurrent systemic therapy on pembrolizumab and axitinib. Radiation myonecrosis (RM) was not diagnosed by MRI until September 2020. Clinical recovery was shown 4 weeks in October 2020 after the diagnosis of radiation myonecrosis.

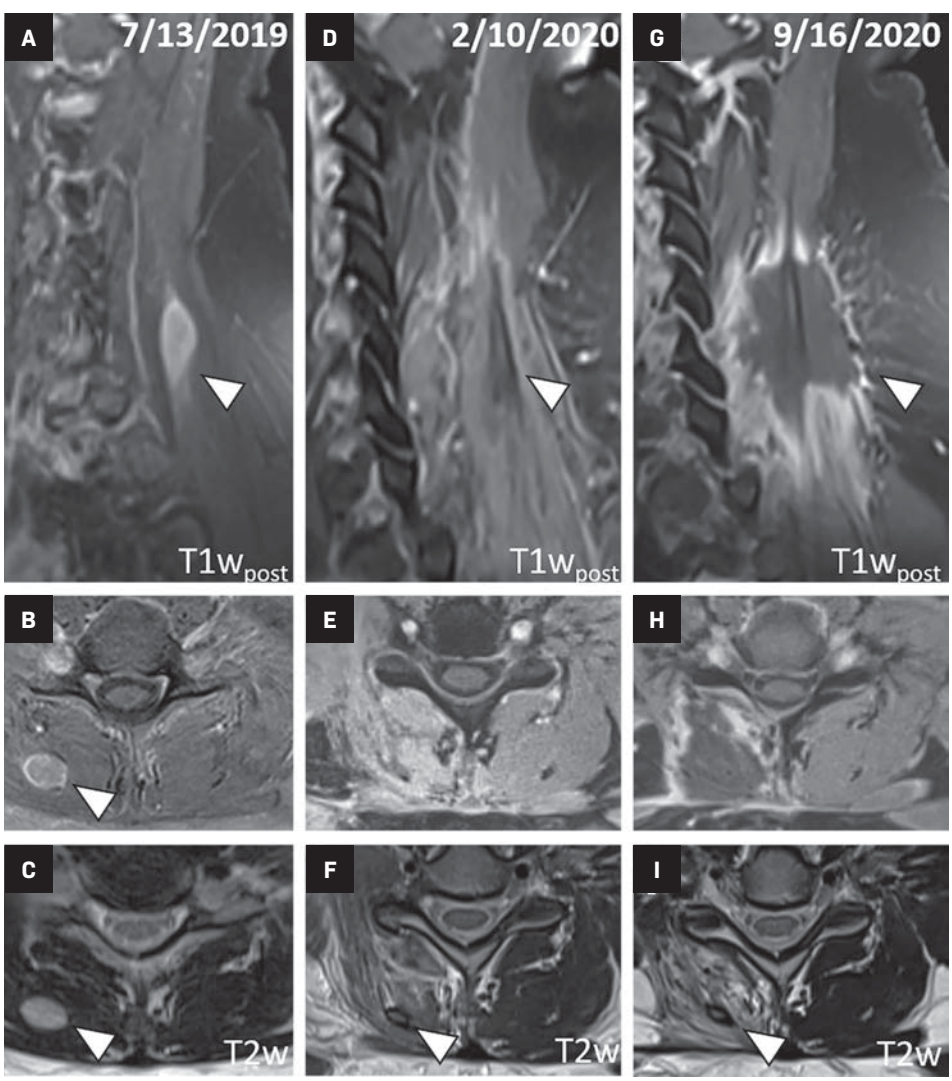


Figure 2. Pretreatment sagittal and axial T1-weighted postcontrast MR images show a homogeneously enhancing (A, B), T2 hyperintense (C) ovoid metastatic deposit (arrowheads, A-C) in the right splenius capitis muscle. Post-treatment MRI on February 10, 2020, shows no residual enhancing mass on the sagittal (D, arrowhead) or axial (E) T1-weighted postcontrast images consistent with treatment response. There is mild patchy enhancement (E) and T2 hyperintensity of the right paravertebral muscles consistent with post-treatment changes at the radiation treatment field. (F) A subcentimeter nonenhancing treated lesion with T2 hypointense rim (arrowhead, F) is noted. MRI on September 16, 2020, revealed findings consistent with radiation myonecrosis manifesting with central hypoenhancing tissue at the site of the treated metastatic deposit surrounded by radiating (star-like) peripheral enhancement at the margins of the treatment field (G, arrowhead). The right posterior paravertebral muscles show T2 hyperintense atrophic changes of the muscle around the T2 hypointense treated lesion (I, arrowhead). (Affected muscle: multifidus, semispinalis cervicis, semispinalis capitis, splenius capitus and trapezius)

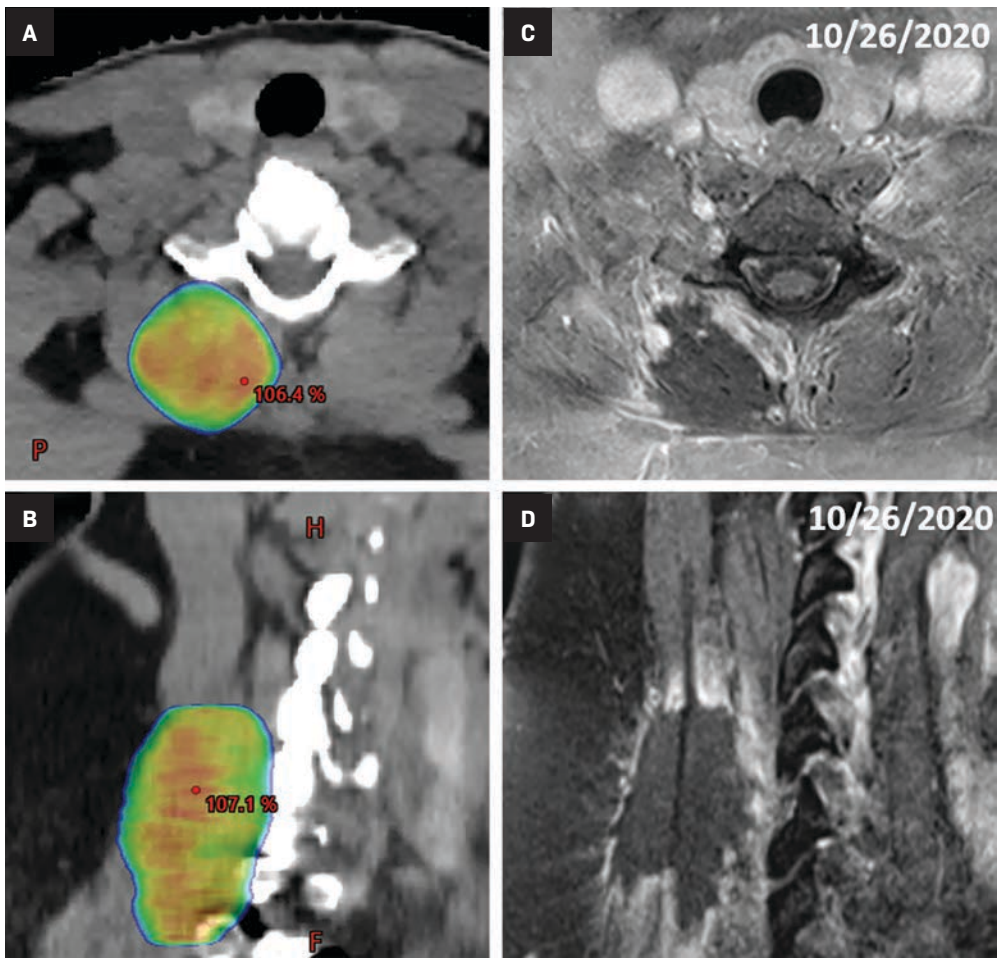


Figure 3. Axial (A) and sagittal (B) views of radiation plan overlap with myonecrosis sites shown on MR images taken on October 26, 2020 (C, D). This stereotactic body radiation therapy (SBRT) plan was constructed using a 1-cm expansion to the planning target volume (PTV) directly from the gross tumor volume (GTV) (institutional practice). The radiation plan display is set to the 90% isodose line of the 40 Gy plan. Hot spots are labeled in each view at midline of the gross tumor.

line is depicted in **Figure 1**. Ultrasound-guided biopsy followed by left radical nephrectomy confirmed clear cell RCC. Her forearm received postoperative RT to 45 Gy in 15 fractions.

Following nephrectomy, systemic therapy was initiated with nivolumab. Within 8 months, she developed a C7 paravertebral 2.4 x 0.8-cm soft-tissue homogeneously enhancing deposit suspicious for metastasis (**Figure 2A-C**). Given disease progression, the patient was switched to combination pembrolizumab (200 mg infusion, 3 times weekly) and axitinib (5 mg, twice daily) 6 weeks after SBRT. The C7 lesion received SBRT to 40 Gy in 5 fractions, every other day. Radiation dose distributions are shown in **Figure 3**. She simultaneously had a lumbar spine lesion, which received 35 Gy in 5 fractions to comply with dose constraints in the pelvis and abdomen. Within several weeks of therapy, she reported neck stiffness. MRI of the cervical spine 8 weeks later showed no residual enhancement, indicating desirable treatment response. Twelve weeks later, she reported ongoing weakness in her neck, and difficulty holding up her head.

Five months following radiation, she reported intermittent neck pain. MRI of the cervical spine showed no nodular enhancement to suggest recurrence (**Figure 2D and 2E**). There was only mild, ill-defined right paraspinal muscle enhancement correlating with the radiation treatment field centered around a subcentimeter nonenhancing treated lesion with a T2 hypointense rim (**Figure 2F**). These findings suggested inflammation/myositis and were favored to be post-treatment changes.[6,7]

Fourteen months following RT, the neck pain/weakness worsened, and imaging revealed central hypoenhancement surrounded by a peripheral rim of irregular, patchy and "star-like" enhancement corresponding to the radiation field (**Figure 2G and 2H**). An axial T2-weighted image showed T2 hyperintensity of the right paravertebral muscles around an unchanged nonenhancing treated lesion (**Figure 2I**). This suggested myonecrosis within the treatment area.[8-10] Four-week follow-up MRI showed the lesion was unchanged, signifying myonecrosis (**Figure 3A-D**).

After symptoms largely resolved, follow-up revealed a left C3 metastatic lesion that extended to the left deltoid muscle. After discussing treatment options, the patient opted for radiation therapy and received SBRT (40 Gy, 5 fractions) concurrent with

Table 1. Previously Reported Cases of Radiation Myonecrosis in Literature

CASE REPORT	SUMMARY	RT PRESCRIPTION	CHEMOTHERAPY	TIME TO RM SYMPTOM ONSET/DIAGNOSIS	OUTCOME
Redvanly et al,[13] 1992	65 yo, male, SCC of the right pyriform sinus, developed RM in left SCM muscle	EBRT, 39.6 Gy in 22 fx, 20 Gy boost in 10 fx; 186 cGy/fx Max dose: 7590 cGy hot spot in the left SCM	N/A	7 mo.	Surgically removed
Welsh et al,[14] 1999	60 yo, Caucasian, male, TCC of the bladder, developed RM in b/l superior gluteal regions	EBRT, 2-field, 45 Gy in 18 fx; 250 cGy/fx; no max dose reported	Gemcitabine, cisplatin; administered 4 weeks after RT	5 mo.	Muscle atrophy with loss of subcutaneous fat observed 10 months after RT
Velcheti et al,[11] 2007	60 yo, African American, male, SCC of LUL lung, developed RM in left trapezius muscle	EBRT, 70 Gy in 35 fx, 200 cGy/fx RM site: 5000 cGy isodose line	Paclitaxel, carboplatin; concurrent with RT	6 mo.	Spontaneous resolution 10 months after RT
Florczynski et al,[15] 2016	65 yo, male, rectal adenocarcinoma of distal rectal wall, developed RM in b/l iliopsoas muscles	EBRT, 6-field, 50 Gy in 25 fx, 200 cGy/fx Max dose in iliopsoas: 4950 cGy (R), 4705 cGy (L)	Capecitabine (neoadjuvant) concurrent with RT; FOLFOX (adjuvant)	5 mo.	Muscle strength regained and pain reduced after steroid treatment
Facer et al,[16] 2020	43 yo, female, leiomyosarcoma metastasized to right hip, developed RM in right iliopsoas muscles	SBRT, 3 field, 21 Gy in 3 fx, 700 cGy/fx	Doxorubicin, ifosfamide, docetaxel, gemcitabine; administered 10 months before RT	5 mo.	Spontaneous near-resolution 7 months after RT

Abbreviations: RM, radiation-induced myonecrosis; yo, year old; SCC, squamous cell carcinoma; SCM, sternocleidomastoid; EBRT, external beam radiation therapy; fx, fractions; TCC, transitional cell carcinoma; b/l, bilateral; RT, radiation therapy; LUL, left upper lobe, SBRT, stereotactic body radiation therapy

systemic therapy to the lesion in February 2021. She now has radiographically stable radiation myonecrosis in the site at C7 and has only minimal pain with excessive movement, but has no further development of any other site of radiation myonecrosis.

Discussion

Little is known about radiation-induced myonecrosis. It is believed to be caused by vascular insufficiency from proliferation of collagen resulting in ischemia.[11] Use of concurrent chemotherapy along with radiation increases the risk of acute and delayed radiation-related side effects.[12] Just 5 other case reports are published regarding myonecrosis, none of which are associated with RCC. **Table 1** summarizes the previous cases reported in the literature.

In 1992, Redvanly et al reported myonecrosis in the left sternocleidomastoid muscle following radiation for a squamous cell carcinoma of the pyriform sinus. The maximum dose point dose to the sternocleidomastoid was 7590 cGy. Necrotic muscle was surgically removed, and histology revealed myonecrosis. We concluded that this is a case of radiation-induced myonecrosis.[13]

In 1999, Welsh et al described radiation myonecrosis in a patient who received 45 Gy in 18 fractions to the inferior pelvis for a parasacral mass from bladder cancer. He received adjuvant gemcitabine and cisplatin. Five months following RT, he developed gluteal pain bilaterally and MRI revealed a band-like pattern of edema on T2-weighted images. He was managed on NSAIDs and a short course of prednisone. Ten months following RT, he had atrophy and loss of the overlying subcutaneous fat.[14]

In 2007, Velcheti et al reported radiation myonecrosis of the left trapezius in a patient receiving 70 Gy in 35 fractions to his left upper lobe; he was on concurrent paclitaxel/carboplatin. Six months following radiation, the patient developed pain in his upper back, corresponding to the area that received at least 50 Gy. Biopsy revealed skeletal muscle with necrosis. Four months later, an MRI was obtained and findings were consistent with radiation myonecrosis.[11]

In 2016, Florczynski et al published a case of severe myositis of the hip flexors in a patient on concurrent capecitabine for rectal cancer receiving adjuvant FOLFOX. Five months following radiation, he developed bilateral weakness of the iliopsoas muscles. Authors concluded from clinical and radiographic findings that this was radiation myonecrosis induced through radiation recall after starting FOLFOX following the completion of radiation.[15]

In 2020, Facer et al described a case of radiation myonecrosis in the iliopsoas muscle following SBRT for leiomyosarcoma in the right

iliac bone. This patient completed treatment with docetaxel and gemcitabine and then developed pain in the right hip associated with a lesion that was treated with SBRT to the iliac bone (21 Gy in 3 fractions). Five months later, the patient was diagnosed with radiation-induced myonecrosis by MRI. Similar to other cases, the MRI showed band-like abnormal signal intensity in the area overlapping radiation. Follow-up MRI at 7 months showed persistent radiographic changes.[16]

Our report is the first radiation myonecrosis case resulting from radiation therapy for RCC. Clinically, the patient experienced general stiffness and weakness in the cervical lesion and was in moderate but tolerable pain. She was instructed to use heat, ice, and over-the-counter medicine as home treatments to relieve symptoms. As shown in **Figure 3**, the radiation treatment area directly overlaps with the site of myonecrosis. Our case demonstrates that radiation myonecrosis occurred with a dose fractionation of 40 Gy in 5 fractions (the bioequivalent dose would be ~131 Gy, assuming α/β ~3.5 for muscle).[17] This dose is well above the reported threshold of 55 Gy, which is known to cause late muscle morbidity after radiation therapy, particularly in sarcomas.[18]

Our patient was not treated with conventional radiation. Instead, similar to the myonecrosis case presented by Facer et al in 2020, our patient received SBRT, which has a much higher dose per fraction (800 cGy). Previous reports have associated spinal SBRT with an increased risk of radiation-induced myositis, which could further cause myonecrosis.[16,19] These recorded associations between SBRT and radiation-induced myopathies suggest that our use of SBRT may have contributed to our patient's myonecrosis.

Interestingly, our patient received no chemotherapies that were reported in the previous 5 historical radiation myonecrosis cases. Rather, she underwent systemic therapy using pembrolizumab/axitinib, a combination anti-PD-1/L1 immunotherapy with a VEGF/VEGFR inhibitor (a preferred regimen).[20] While there are no reports of radiation-induced myonecrosis in patients on concurrent pembrolizumab/axitinib, it is possible that these agents and high-dose radiation contributed to the development of her radiation myonecrosis. It is also worth noting that in the previously reported radiation myonecrosis cases, all patients received systemic therapies, which suggests that general caution should be taken in treating with concurrent SBRT and systemic therapies. Case reports in the past have suggested that one of our patient's immunotherapies, pembrolizumab, could induce necrotizing myositis in patients.[21-23] It is therefore possible that pembrolizumab secondarily influenced the formation of radiation myonecrosis. Furthermore, the VEGF inhibition effect of axitinib might exacerbate toxicity by decreasing angiogenesis in the lesion. Little is reported on concurrent axitinib-radiation therapy, but ongoing clinical trials on the combination therapy do not report any related adverse effects either.[24]

Our case features an atypical course of radiation myonecrosis. In the 5 reported cases, imaging diagnosis could be made approximately 5 to 7 months after radiation therapy, but our case was diagnosed radiographically at 14 months. This suggests variability in the course of disease for radiation myonecrosis and should be considered for future diagnoses. Interestingly, our patient developed myonecrosis overlapping the 40 Gy in 5 fractions in her cervical spine but did not develop this phenomenon in her lower spine where she was simultaneously treated to 35 Gy in 5 fractions. She did not have other adverse side effects after either of the other 2 treatments.

From the radiographic findings and clinical presentations in this case, we assumed a true radiographic diagnosis of radiation-induced myonecrosis. The differential diagnosis included tumor recurrence, infection, and radiation recall myositis. Stability of radiographic presentation over follow-up MRIs rules out tumor progression and infection was ruled out from clinical and laboratory findings. This case differentiates itself from radiation recall myositis in several ways. Radiation recall myositis is most likely triggered by gemcitabine and sometimes triggered by other chemotherapeutics.[25] The mechanisms of action of these agents are either related to DNA damage and synthesis or microtubule function, which differ from our patient's therapy of pembrolizumab and axitinib. Pembrolizumab is associated with cutaneous and pulmonary radiation recall reactions,[26,27] but not with radiation recall myositis. Axitinib has no reports of radiation recall reactions. Therefore, it is unlikely that the patient's symptoms were caused by radiation recall myositis.

Conclusion

To our knowledge, only 5 other reported cases describe this postradiation phenomenon. Our case shows both similarities and differences to the previously reported cases in terms of symptom presentation, disease timeline and treatments received. In this modern era, it is important to consider the possible effects of immunotherapy and systemic therapies in general with radiation therapy. We add this to the published collection of radiation-induced myonecrosis cases and caution experts on this rare but serious potential side effect of radiation therapy.

References

1) Padala SA, Barsouk A, Thandra KC, et al. Epidemiology of renal cell carcinoma. *World J Oncol*. 2020;11(3):79-87. doi:10.14740/wjon1279

2) Mohamed AH, Mohamud HA. Renal cell carcinoma with rhabdoid features: a rare aggressive and fatal variant. *Urol Case Rep*. 2020;32:101244. doi:10.1016/j.eucr.2020.101244

3) Deschavanne PJ, Fertil B. A review of human cell radiosensitivity in vitro. *Int J Radiat Oncol Biol Phys*. 1996;34(1):251-266. doi:10.1016/0360-3016(95)02029-2

4) Blanco AI, Teh BS, Amato RJ. Role of radiation therapy in the management of renal cell cancer. *Cancers (Basel)*. 2011;3(4):4010-4023. doi:10.3390/cancers3044010

5) Rühle A, Andratschke N, Siva S, Guckenberger M. Is there a role for stereotactic radiotherapy in the treatment of renal cell carcinoma? *Clin Transl Radiat Oncol*. 2019;18:104-112. doi:10.1016/j.ctro.2019.04.012

6) Schulze M, Kötter I, Ernemann U, et al. MRI findings in inflammatory muscle diseases and their noninflammatory mimics. *Am J Roentgenol*. 2009;192(6):1708-1716. doi:10.2214/AJR.08.1764

7) Garner HW, Kransdorf MJ, Bancroft LW, Peterson JJ, Berquist TH, Murphey MD. Benign and malignant soft-tissue tumors: posttreatment MR imaging. *RadioGraphics*. 2009;29(1):119-134. doi:10.1148/rg.291085131

8) Becker M, Schroth G, Zbären P, et al. Long-term changes induced by high-dose irradiation of the head and neck region: imaging findings. *RadioGraphics*. 1997;17(1):5-26. doi:10.1148/radiographics.17.1.9017796

9) Smitaman E, Flores DV, Mejía Gómez C, Pathria MN. MR imaging of atraumatic muscle disorders. *RadioGraphics*. 2018;38(2):500-522. doi:10.1148/rg.2017170112

10) Theodorou DJ, Theodorou SJ, Kakitsubata Y. Skeletal muscle disease: patterns of MRI appearances. *Br J Radiol*. 2012;85(1020):e1298-e1308. doi:10.1259/bjr/14063641

11) Velcheti V, Gilstrap E, Bradley J, Govindan R. Radiation-induced myonecrosis presenting as a subcutaneous mass after combined modality therapy for non-small cell lung cancer. *J Thorac Oncol*. 2007;2(9):875-876. doi:10.1097/JTO.0b013e31811f3a91

12) Byhardt RW, Scott C, Sause WT, et al. Response, toxicity, failure patterns, and survival in five Radiation Therapy Oncology Group (RTOG) trials of sequential and/or concurrent chemotherapy and radiotherapy for locally advanced non-small-cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys*. 1998;42(3):469-478. doi:10.1016/s0360-3016(98)00251-x

13) Redvanly RD, Hudgins PA, Gussack GS, Lewis M, Crocker IR. CT of muscle necrosis following radiation therapy in a patient with head and neck malignancy. *Am J Neuroradiol*. 1992;13(1):220-222.

14) Welsh JS, Torre TG, DeWeese TL, O'Reilly S. Radiation myositis. *Ann Oncol*. 1999;10(9):1105-1108. doi:10.1023/a:1008365221440

15) Florczynski MM, Sanatani MS, Mai L, et al. Severe myositis of the hip flexors after pre-operative chemoradiation therapy for locally advanced rectal cancer: case report. *BMC Cancer*. 2016;16:243. doi:10.1186/s12885-016-2269-2

16) Facer BD, Dutta SW, Showalter TN. Stereotactic body radiation therapy induced myonecrosis in a patient with prior gemcitabine administered for leiomyosarcoma. *J Radiosurg SBRT*. 2020;7(1):77-80.

17) Kotha VS, Rewari A, Lakhiani C, et al. Radiation oncology applications in plastic and reconstructive surgery: a nonsystematic review of concepts and principles. *Plast Reconstr Surg*. 2021;147(2):314e-324e. doi:10.1097/PRS.0000000000007582

18) Karasek K, Constine LS, Rosier R. Sarcoma therapy: functional outcome and relationship to treatment parameters. *Int J Radiat Oncol Biol Phys*. 1992;24(4):651-656. doi:10.1016/0360-3016(92)90710-y

19) Lockney DT, Jia AY, Lis E, et al. Myositis following spine radiosurgery for metastatic disease: a case series. *J Neurosurg Spine*. 2018;28(4):416-421. doi:10.3171/2017.8.SPINE17162

20) Rini BI, Plimack ER, Stus V, et al. Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma (ccRCC): results from 42-month follow-up of KEYNOTE-426. *JCO*. 2021;39(15_suppl):4500-4500. doi:10.1200/JCO.2021.39.15_suppl.4500

21) Claus J, Van Den Bergh A, Verbeek S, Wauters E, Nackaerts K. Pembrolizumab-induced necrotizing myositis in a patient with metastatic non-small-cell lung cancer: a case report. *Lung Cancer Manag*. 2019;8(2):LMT10. doi:10.2217/lmt-2018-0017

22) Haddox CL, Shenoy N, Shah KK, et al. Pembrolizumab induced bulbar myopathy and respiratory failure with necrotizing myositis of the diaphragm. *Ann Oncol*. 2017;28(3):673-675. doi:10.1093/annonc/mdw655

23) Vallet H, Gaillet A, Weiss N, et al. Pembrolizumab-induced necrotic myositis in a patient with metastatic melanoma. *Ann Oncol*. 2016;27(7):1352-1353. doi:10.1093/annonc/mdw126

24) Yang KL, Chi MS, Ko HL, et al. Axitinib in combination with radiotherapy for advanced hepatocellular carcinoma: a phase I clinical trial. *Radiat Oncol*. 2021;16(1):18. doi:10.1186/s13014-020-01742-w

25) Maeng CH, Park JS, Lee SA, et al. Radiation recall phenomenon presenting as myositis triggered by carboplatin plus paclitaxel and related literature review. *J Cancer Res Ther*. 2014;10(4):1093-1097. doi:10.4103/0973-1482.146090

26) Wang YY, Tian XC, Zhu L, Bai XH, Zhao R. Concomitant radiation recall dermatitis and radiation recall pneumonitis induced by pembrolizumab. *J Thorac Oncol*. 2020;15(10):e160-e162. doi:10.1016/j.jtho.2020.05.014

27) Itamura H, Ohguri T, Yahara K, et al. Pembrolizumab-induced radiation recall pneumonitis after the resolution of typical asymptomatic radiation pneumonitis. *J UOEH*. 2020;42(3):261-266. doi:10.7888/juoeh.42.261

Resident-Led Education Committee: Fostering Leaders and Impactful Change in Radiation Oncology Education

Christina Phuong, MD; Lisa Ni, MD; Horatio R. Thomas, MD, MSc; Benjamin Li, MD, MBA; Jie Jane Chen, MD; Katie E. Lichter, MD; Steve E. Braunstein, MD, PhD; Sumi Sinha, MD*

Dr. Phuong is a PGY4 and chief resident physician, Department of Radiation Oncology, University of California San Francisco.

Dr. Ni is a PGY4 and chief resident physician, Department of Radiation Oncology, University of California San Francisco.

Dr. Thomas is a PGY5 resident physician, Department of Radiation Oncology, University of California San Francisco.

Radiation oncology training follows an apprenticeship model. However, radiation oncologists must eventually lead multidisciplinary teams. Residency programs have focused on incorporating leadership training into their curricula to meet this need, and residents are often involved in peer-to-peer or near-peer teaching.[1,2] Still, many have expressed interest in more teaching opportunities.[3] At our institution, the desire to take a more active role to impact radiation oncology education resonated with a number of our residents.

With the support of departmental leadership, in 2020 we formed a resident-led Education Committee to increase engagement in medical education, scholarship, and leadership. Over the last 2 years of growth and development, we have established dedicated monthly meetings, created a leadership board, and established 4 core goals of the committee:

1. Identify and address gaps in residency education.
2. Implement sustainable educational initiatives across various interprofessional groups.
3. Share ongoing projects within medical education to identify resources and invite collaboration.
4. Cultivate future leaders in medical education.

To meet these goals, we have undertaken a host of interprofessional projects. The committee collaborated with departmental and institutional leadership to implement initiatives that address gaps identified in radiation oncology resident education and to refine existing curricula. For 2 years, the committee has co-hosted medical student summer interns in partnership with the American Society of Clinical Oncology (ASCO) and mentored a medical-student-led tumor board seminar series.[4-6] The Education Committee also leads a monthly medical

Disclosure: The authors declare the following financial interests/personal relationships. Dr. Braunstein reports grants from Blue Earth Diagnostics and Elekta; consulting for icotec and Novocure; honoraria from icotec and the *International Journal of Radiation Oncology, Biology, Physics*; editor fees for RadOncQuestions; and board membership of the Radiation Oncology Education Collaborative Study Group (ROECSG). Dr. Li reports grants from Elekta, the American Medical Association, and Silicon Valley Community Foundation; support for attending meetings and/or travel from the American Association of Medical Dosimetrists and American Society of Radiation Oncology; and an unpaid leadership role as president of Rayos Contra Cancer. Dr. Sinha reports editing honoraria for RadOncQuestions. Dr. Chen reports grants from UCSF Helen Diller Family Comprehensive Cancer Center – Diversity, Equity, Inclusion and Accessibility Award and Harvard Medical School Dean's Innovation Award in Diversity and Inclusion. The remaining authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.
Corresponding Author: *Sumi Sinha, MD, 1600 Divisadero St, Suite H1031, San Francisco, CA, 94115 (Sumi.sinha@ucsf.edu).

Taking part in this committee has empowered us to be pioneers of education — to refine, implement, and sustain initiatives across various facets of medical education.

assistant radiation oncology curriculum in our department, which is undergoing multi-institutional expansion.[7] Finally, committee meetings serve as a platform for structured discussion of the growing body of medical education literature during journal clubs and an opportunity to share and collaborate on ongoing education-related projects. The result has been a thriving education community with ever-growing interest in medical education.

The Education Committee has been instrumental in supporting both medical and physics residents with any degree of background in medical education and in turning ideas into structured projects. It has inspired confidence in residents to take on leadership roles, become involved in medical education opportunities outside of our institution, and present our work at conferences to influence the field of radiation oncology globally.

With the growing recognition that teaching and leadership training during residency are integral components of professional development for residents, this Education Committee has provided a unique opportunity to develop these skills.[2] Taking part in this committee has empowered us to be pioneers of education — to refine, implement, and sustain initiatives across various facets of medical education, as well as to participate in education-related scholarship. The resulting wave of new educators continues to ripple through our program. We believe members will be empowered and equipped with the skills necessary to engage future generations and lead our field.

References

1) Blumenthal DM, Bernard K, Bohnen J, Bohmer R. Addressing the leadership gap in medicine: residents' need for systematic leadership development training. *Acad Med*. 2012;87(4):513-522. doi:10.1097/ACM.0B013E31824A0C47

2) Berriochoa C, Amarnath S, Berry D, Koyfman SA, Suh JH, Tendulkar RD. Physician leadership development: a pilot program for radiation oncology residents. *Int J Radiat Oncol Biol Phys*. 2018;102(2):254-256. doi:10.1016/J.IJROBP.2018.05.073

3) Ni L, Thomas HR, Raleigh DR, Boreta LC, Park CC, Braunstein SE. Residents-as-teachers curriculum for radiation oncology: a targeted needs assessment. *Int J Radiat Oncol Biol Phys*. 2021;111(3):638-642. doi:10.1016/j.ijrobp.2021.06.024

4) Arbab M, Holmes JA, Olivier KR, et al. Integrating radiation oncology into undergraduate medical education. *Adv Radiat Oncol*. 2021;6(6). doi:10.1016/J.ADRO.2021.100765

5) Chen JJ, Lichter KE, Sinha S, et al. Pilot implementation of a multidisciplinary tumor board seminar series to foster increased understanding of and interest in oncologic care among medical students. *Int J Radiat Oncol Biol Phys*. 2022;114(1):e15-e16. doi:10.1016/j.ijrobp.2022.06.031

6) Reyes K, Wong P, Phuong C, et al. A targeted interest survey of preclinical medical students for implementation of exposure opportunities in multidisciplinary oncology education. *Int J Radiat Oncol Biol Phys*. 2022;114(1):e23. doi:10.1016/j.ijrobp.2022.06.050

7) Sinha S, Xu MJ, Yee E, Buckmeier T, Park C, Braunstein SE. Interprofessional education curriculum for medical assistants in radiation oncology: a single institution pilot program. *Adv Radiat Oncol*. 2021;6(6). doi:10.1016/J.ADRO.2021.100800

Dr. Li is a PGY5 resident physician, Department of Radiation Oncology, University of California San Francisco.

Dr. Chen is a PGY3 resident physician, Department of Radiation Oncology, University of California San Francisco.

Dr. Lichter is a PGY3 resident physician, Department of Radiation Oncology, University of California San Francisco.

Dr. Braunstein is faculty, Department of Radiation Oncology, University of California San Francisco.

Dr. Sinha is faculty, Department of Radiation Oncology, University of California San Francisco.

High-Dose-Rate Brachytherapy (HDRBT) Followed by Concurrent Chemoradiotherapy for Esophageal Adenocarcinoma

Gokula Kumar Appalanaido, MD, FRANZCR;[1] Syadwa Abdul Shukor, MD, MCO, FRCR;[2*] Hasmah Hussin, MD, MMed;[1] Leow Voon Meng, MD, MMed;[1] Nazri Mustaffa, MBBS, MMed, PhD;[3] Mohd Zahri Abdul Aziz, MSc, PhD[1]

Abstract

This is a case report of a patient with unresectable locally advanced esophageal adenocarcinoma treated with high-dose-rate brachytherapy (HDRBT) followed by chemoradiotherapy (CRT) with intensity-modulated radiation therapy (IMRT). The treatment regimen consisted of 3 fractions of weekly 7 Gy HDRBT followed by CRT to 50.4 Gy in 28 fractions. The patient achieved complete clinical response shown by radiological imaging and endoscopic examination after 3 months of treatment completion, and the response was sustained at 18 months based on radiological imaging. Her dysphagia markedly improved from tolerating fluids only at presentation to managing a semisolid diet after the second fraction of brachytherapy and a solid diet while on CRT. While the patient refused further investigation and did not come for follow-up after the 18-month assessment, she reported no symptoms of disease recurrence up to 40 months in our regular verbal communication/follow-up via telephone.

Keywords: Esophageal brachytherapy, dysphagia, esophageal adenocarcinoma

Case Summary

A 62-year-old woman was referred to our center for a moderately differentiated fungating esophageal adenocarcinoma at 25 cm from the incisors. A computed tomography (CT) scan (**Figure 1**) showed a mid to lower esophageal tumor with radial extension into to the pericardium and distally into the cardioesophageal junction (COJ) but no regional nodes or distant metastasis (TNM7 cT4 N0 M0). The patient was assessed by an upper gastrointestinal surgeon, who deemed the disease was inoperable. Treatment options were discussed, including upfront high-dose-rate brachytherapy (HDRBT) followed by definitive radiation therapy (dRT) or concurrent chemoradiotherapy (CRT). The patient understood and consented to the proposed treatment regimen consisting of 3 fractions of HDRBT followed by CRT to a dose of 50.4 Gy in 28 fractions.

HDRBT Procedure

Brachytherapy Applicator Insertion

The insertion was completed under sedation in the operation theater with endoscopic and fluoroscopic guidance. During the first insertion, there was a circumferential tumor at 24 cm from the incisor with near complete obstruction of the lumen, needing balloon dilatation (**Figure 2**). Using endoscopy with fluoroscopic guidance, a radio-opaque marker was placed on the chest wall corresponding to the superior and inferior extension of the tumor. Following marker placement, a 6-mm diameter Nucletron intraluminal brachytherapy applicator was inserted with the distal part into stomach, also under fluoroscopic guidance. The brachytherapy applicator was

Affiliations: [1]Advanced Medical and Dental Institute, University of Science, Malaysia, Bertam. [2]Department of Radiation Oncology, National University Cancer Institute, Singapore. [3]Department of Medicine, School of Medicine Sciences, University of Science, Malaysia.
Corresponding Author: *Syadwa Abdul Shukor, MD, MCO, FRCR; Department of Radiation Oncology, National University Cancer Institute, NUH Medical Centre, Levels 8 to 10, 5 Lower Kent Ridge Road, Singapore 119074. (syadwa_shukor@nuhs.edu.sg)
Disclosure/informed consent: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere. The patient has provided informed consent for the publication of this case report.

Figure 1. Coronal and axial computed tomography showed circumferential thickening of the esophageal wall extending into the stomach.

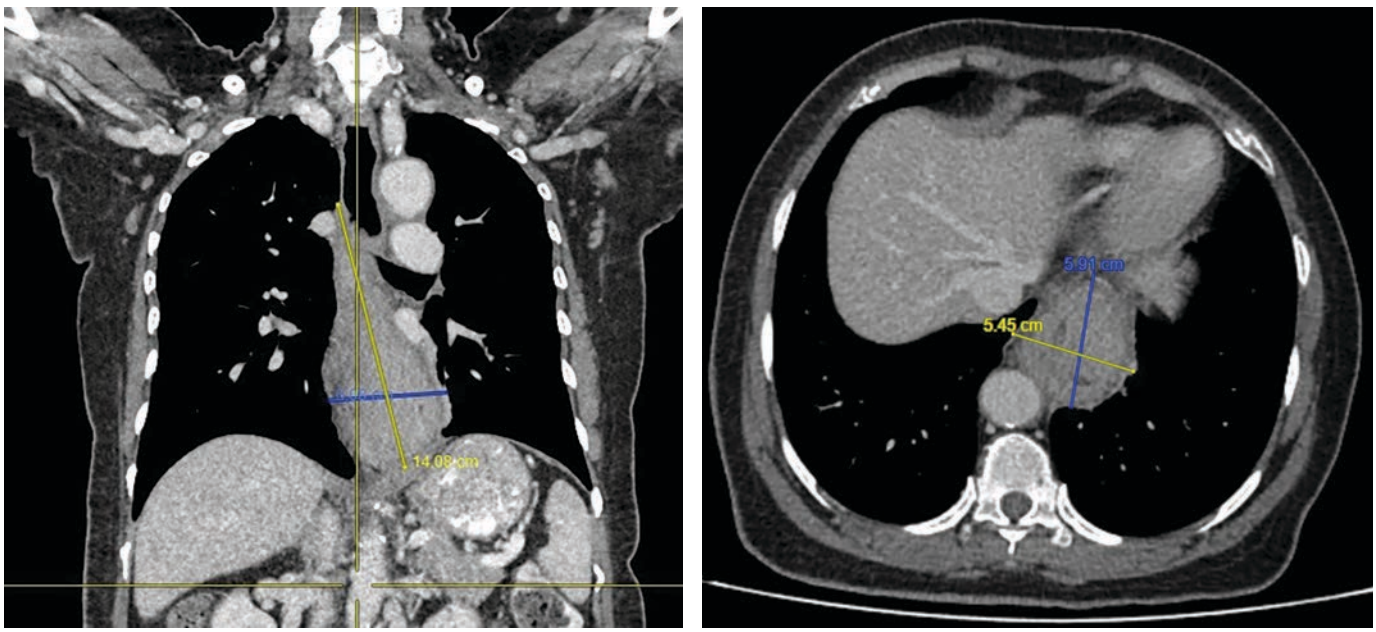
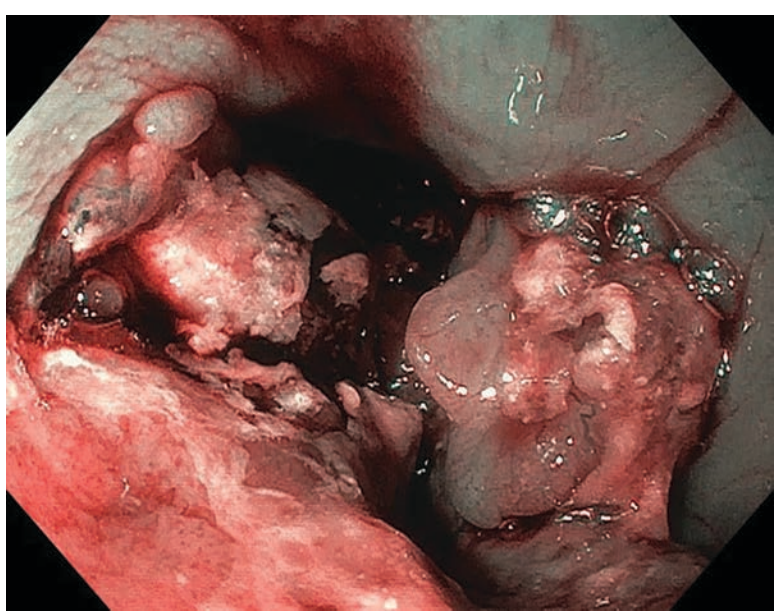


Figure 2. Esophagogastroduodenoscopy before brachytherapy showed a bleeding fungating tumor affecting full circumference of the esophageal wall.



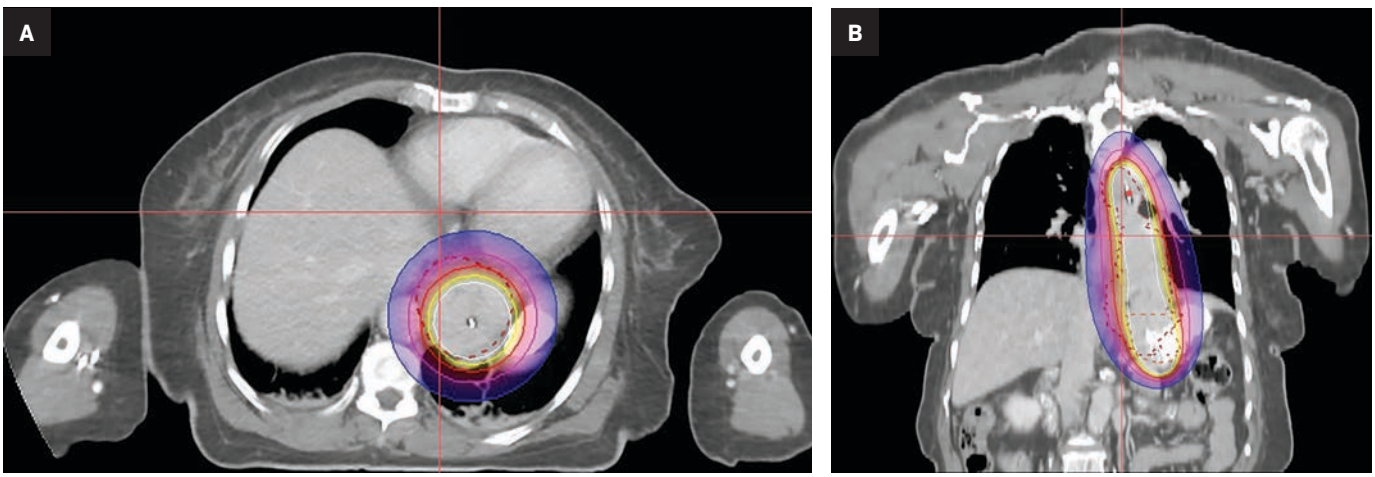
anchored at the mouth with a bite block. For the second and third sessions, no balloon dilatation was needed due to good tumor response.

Treatment Planning

In the 2-mm-slice CT-simulation images, the contrast-enhancing tumor was marked as the gross tumor volume (GTV) with the superior and inferior extension corresponding to the ball bearing that was placed on the chest wall. A dose of 7 Gy was prescribed to cover the GTV plus a 1-cm safety margin superiorly and inferiorly using the Oncentra Masterplan V5.0 brachytherapy treatment planning system. Thereafter, the isodoses were normalized and adjusted graphically to have the 7 Gy isodose line covering the GTV, and heart dose constrained to the 6 Gy isodose line. The radial distance of the 7 Gy isodose is limited to 7 mm from the center of the applicator at the safety margin region superiorly and inferiorly, while allowing a more generous coverage at thicker tumor depth (**Figures 3A-C**). Maximum esophageal surface dose is 25 Gy to 52.88 Gy.

Treatment

The patient was treated with the Nucletron HDRBT afterloader system using an iridium-192 brachytherapy source with an initial source strength



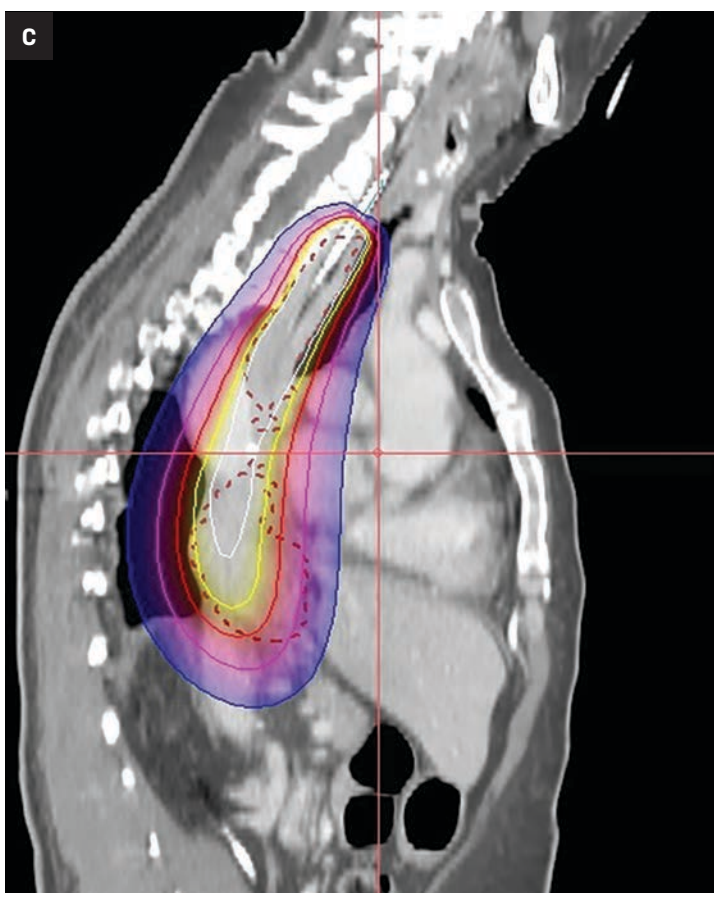


Figure 3. High-dose-rate brachytherapy dose distribution in axial (A), coronal (B) and sagittal (C) computed tomography slices.

of 10 mCi. She was treated with 3 fractions of weekly 7 Gy HDRBT using the same plan. The intraluminal applicator was removed immediately after each session.

Following the second fraction of HDRBT, the patient had marked improvement in the dysphagia score. She was tolerating a semisolid diet and her weight was progressively increasing. During the third HDRBT applicator insertion, esophagogastroduodenoscopy showed gross resolution of the intraluminal esophageal tumor (**Figure 4**).

After completing HDRBT treatment, the patient was subjected to external-beam radiation therapy (EBRT) using IMRT to a total dose of 50.4 Gy in 28 fractions over 5 weeks with concurrent oral capecitabine 1g twice a day on radiation therapy days only. The treatment volume encompassed a 4-cm superior and 4-cm inferior margin, which extend into the fundus of the stomach; a 1-cm radial margin around the GTV to generate the clinical target volume (CTV); and a 1-cm margin was added for the planning target volume (PTV)

Figure 4. Esophagogastroduodenoscopy on third brachytherapy showed disappearance of esophageal tumors.

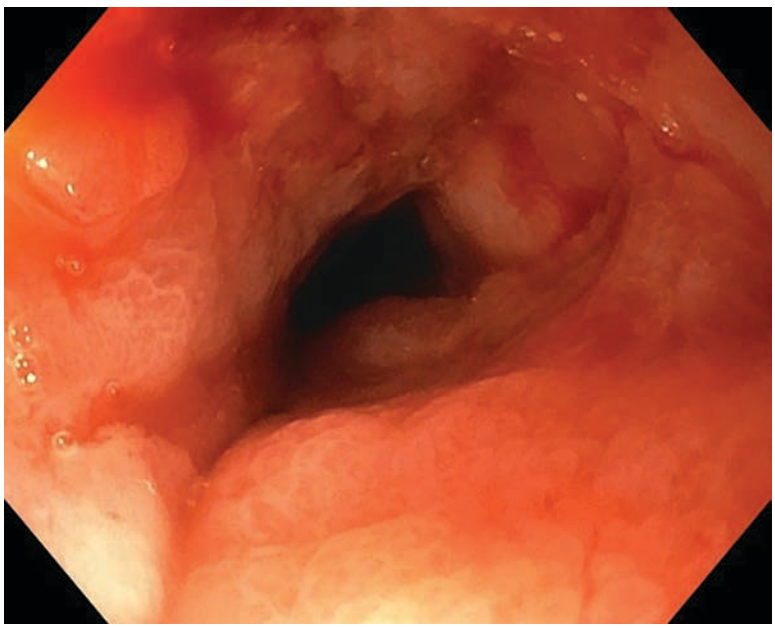
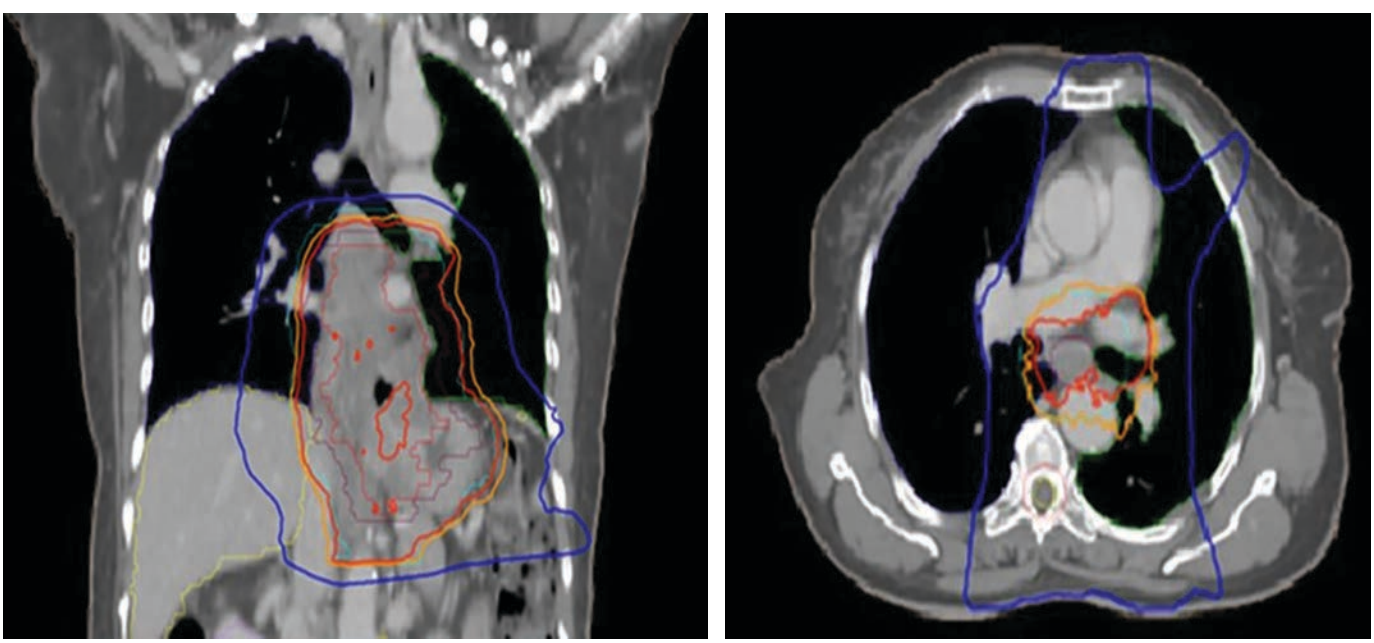


Figure 5. External-beam radiation therapy plan.



(**Figure 5**) as per standard contouring guidelines. No elective nodes were included. All organs at risk such as bilateral lung, heart, spinal cord, bilateral kidney, and liver were defined in each CT slice and met the normal tolerance as per QUANTEC. Daily electronic portal imaging and weekly cone-beam CT were used for treatment verification. Oral capecitabine was used as the patient refused intravenous chemotherapy. On completion of CRT, the patient had grade 1 esophagitis but was still tolerating well orally. She was prescribed a proton pump inhibitor for 6 months.

Follow-up

Endoscopic examination after 3 months showed complete clinical response with fibrosis and mild stricture at the gastroesophageal junction, which was easily dilated with a balloon (**Figure 6A**). CT-TAP (CT of the thorax, abdomen and pelvis) at 3 (**Figures 6A-B**) and 18 months (**Figure 7**) showed focal wall thickening along the irradiated esophagus with no evidence of recurrence.

The patient's last physical follow-up with us was 12 months after completing treatment, at which time she refused endoscopy or imaging investigations. She was tolerating an oral diet with mild grade 1 dysphagia and had gained weight. Thereafter, we

Figure 6. Clinical (A) and radiological information (B) showed good response with no evidence of disease after 3/12 of treatment.

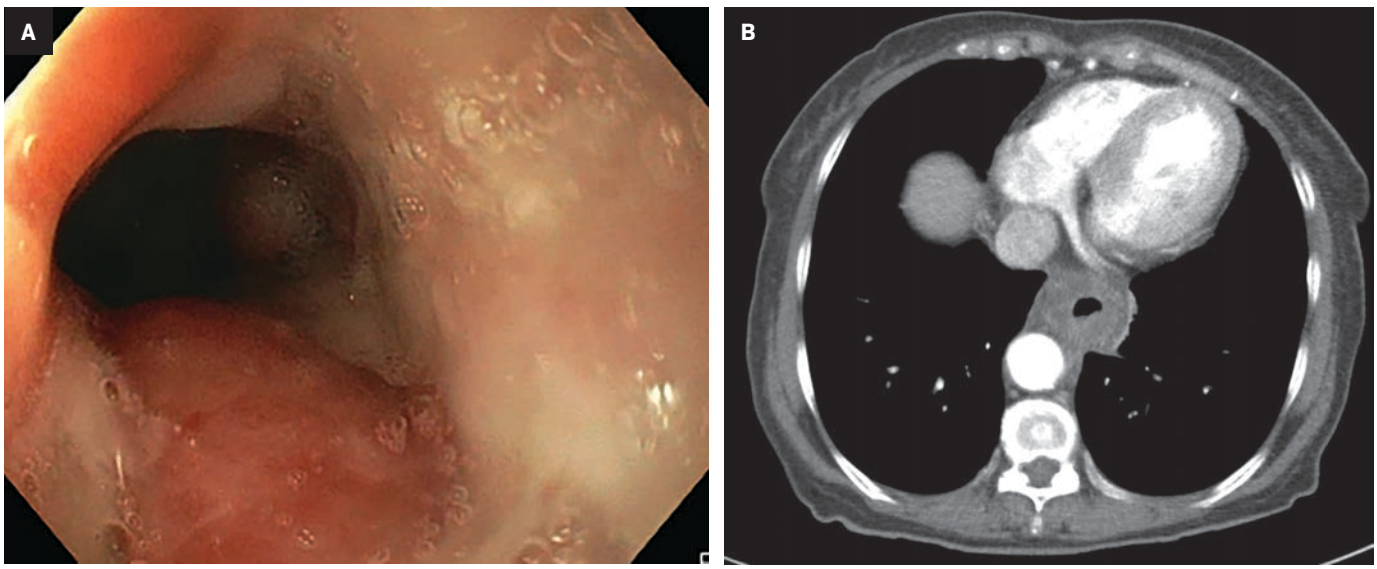
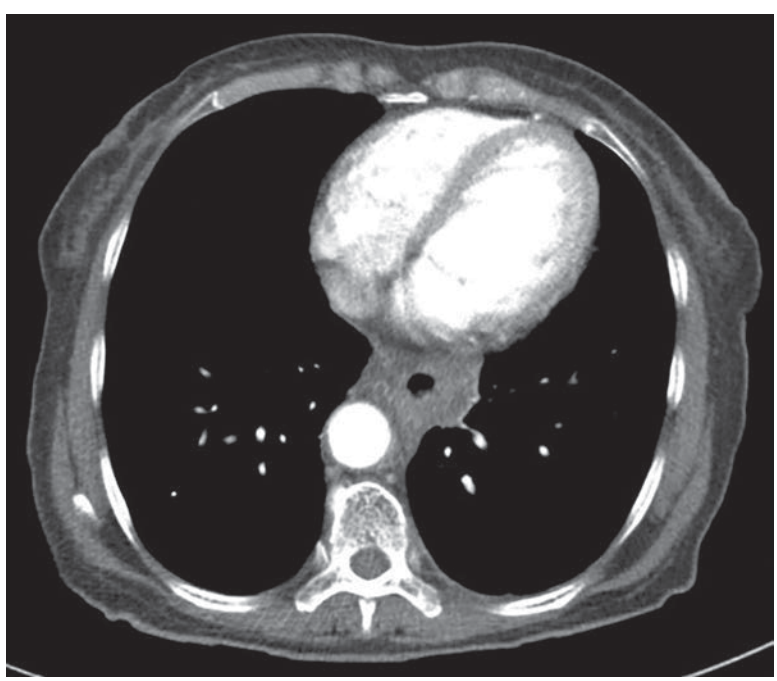


Figure 7. Axial computed tomography scan 18 months after treatment showed no evidence of residual disease.



followed up with her via 2 monthly phone calls as she declined any assessment and reported a good quality of life. During phone assessments at 29, 34 and 40 months, she reported grade 1 dysphagia and was otherwise well. Unfortunately, at 48 months following treatment, we were informed by a family member that the patient had died 1 week earlier, with a likely diagnosis of a cerebrovascular accident.

Discussion

Based on the RTOG 85-01 intergroup trial and RTOG 94-05, radiation dose to 50 Gy with concurrent chemotherapy is the preferred treatment for patients with unresectable esophageal cancer.[1,2] While CRT improves locoregional control, locoregional recurrence (LRR) still affects about 50% of patients, half of whom have an isolated recurrence without distant metastases.[3] Furthermore, the majority of LRRs occur at the primary site vs being nodal, suggesting a benefit from dose escalation to the primary tumor.[3] Radiation therapy dose escalation has been reported to improve the outcomes in a few studies involving unresectable esophageal cancer patients.[2,4] The ARTDECO dose escalation trial in esophageal cancer patients showed a numerically superior 3-year, local

progression-free survival (LPFS) in the dose-escalated (61.6 Gy) arm at 73% vs 70% in the standard (50.4 Gy) arm, although it did not reach statistical significance. This study, which used advanced radiation therapy techniques, had better pretreatment staging investigations and a different choice of concurrent chemotherapy regimen compared with earlier studies that showed increased acute and late toxicity with dose escalation.[5]

Intraluminal HDRBT of the esophagus has the distinct advantage of delivering a high dose of radiation to the tumor while sparing the normal organs. However, use of HDRBT is riddled with significant toxicity, such as esophageal fistula and stricture.[6-9] American Brachytherapy Society recommendations for esophageal HDRBT include use of an external applicator whose diameter is 0.6 to 1.0 cm, EBRT delivered before HDRBT, and maximum tumor length under 10 cm.[10] The initial rationale for the larger applicator size was to reduce the mucosal dose in relation to dose at the prescription point. However, this is an old guideline and has since been removed from the ABS website. Newer studies have included tumors larger than 10 cm in length, and some have delivered HDRBT before commencing EBRT.[6,10]

We theorize that the addition of HDRBT to EBRT in esophageal cancer improves the local control rate and provides durable alleviation of dysphagia.[11,12] One randomized controlled trial even showed the superiority of HDRBT over EBRT boost.[13] In most literature, an HDRBT boost was added following EBRT, not prior to it. While an HDRBT boost is usually delivered after EBRT, in 1 single-arm phase 2 study, HDRBT before EBRT is shown to be safe and effective in inducing rapid and durable relief from dysphagia prior to commencing curative intent CRT.[13-16] Delivering HDRBT upfront also has the advantage of providing easy tumor identification and defining the target volumes as opposed to doing so after EBRT, which could significantly shrink the esophageal tumor. In addition, by starting with HDRBT, we could better recognize the tumor location compared with post-EBRT when usually no tumor is visible. Additional advantages are that with rapid significant tumor shrinkage, patients tend to have immediate improvement in their dysphagia score and nutrition status, and tend to be more receptive to subsequent proposed treatment with CRT.[16]

One study reported that applicator size may not correlate with the esophageal fistula rate.[4] However, the dose per fraction of HDRBT showed a strong correlation with the fistula rates.[17] In a study by Vuong et al, with the use of lower-dose fractionated HDRBT, there was only 1.2% fistula rates for all 70 patients. This study also shortened the overall treatment time by delivering HDRBT twice a week to a total dose of 20 Gy in 5 fractions and commencing EBRT the week immediately following HDRBT completion.[4] When overall treatment time is below 8 weeks, studies have shown fewer local recurrences.[18]

In this patient, HDRBT was delivered over 3 weekly fractions of 7 Gy each to a total dose of 21 Gy. This dose schedule was chosen as the patient refused a more fractionated schedule of 20 Gy in 5 fractions treating 2 fractions a week due to logistical reasons. In the treatment planning process, we applied a 3D planning method with dose manipulation similar to dose painting in the IMRT. Rather than apply the dose prescription to a point at a radial distance from the center of the applicator, which produces a uniform cylindrical target, we ensured that 90% of the GTV received the prescribed dose of 7 Gy. The 7 Gy isodose curve was manipulated in such a way that generous coverage was allowed to areas with thicker tumor depth, while the same isodose line was restricted at smaller tumor depth or the safety margin region. This method of dose painting was described by Lettmaier et al who suggested that the use of 3DCT-based treatment planning has the advantage of dose manipulation over an applicator-based approach, which ignores surrounding normal structures.[19]

Conclusion

Use of an upfront 3D HDRBT boost with dose manipulation followed by IMRT showed good tumor response and minimal toxicity in this patient. Upfront HDRBT has the advantage of rapid relieving dysphagia, making the patient more receptive to subsequent treatment with concurrent CRT. Dose escalation with the aim to improve local control rate is feasible with HDRBT. Treatment for postradiation stricture, a known toxicity of radiation therapy/HDRBT, can be addressed by endoscopic balloon dilatation.

References

1) Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA.* 1999;281:1623-1627.

2) Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol.* 2002;20(5):1167-1174.

3) Versteijne E, van Laarhoven HWM, van Hooft JE, et al. Definitive chemoradiation for patients with inoperable and/or unresectable esophageal cancer: locoregional recurrence pattern. *Dis Esophagus.* 2015;28:453-459.

4) Vuong T, Szego P, David M, et al. The safety and usefulness of high-dose-rate endoluminal brachytherapy as a boost in the treatment of patients with esophageal cancer with external beam radiation with or without chemotherapy. *Int J Radiat Oncol Biol Phys.* 2005;63(3):758-764.

5) Hulshof MCCM, Geijsen D, Rozema T, et al. A randomized controlled phase III multicenter study on dose escalation in definitive chemoradiation for patients with locally advanced esophageal cancer: ARTDECO study. *J Clin Oncol.* 2020 38:4_suppl, 281-281.

6) Taal BG, Aleman BM, Koning CC, Boot H. High dose rate brachytherapy before external beam irradiation in inoperable oesophageal cancer. *Br J Cancer.* 1996;74(9):1452-1457.

7) Gaspar LE, Winter K, Kocha WI, Coia LR, Herskovic A, Graham M. A phase I/II study of external beam radiation, brachytherapy, and concurrent chemotherapy for patients with localized carcinoma of the esophagus (Radiation Therapy Oncology Group Study 9207): final report. *Cancer.* 2000;88(5):988-995.

8) Schraube P, Fritz P, Wannenmacher MF. Combined endoluminal and external irradiation of inoperable oesophageal carcinoma. *Radiother Oncol.* 1997;44(1):45-51.

9) Sharma V, Agarwal J, Dinshaw K, et al. Late esophageal toxicity using a combination of external beam radiation, intraluminal brachytherapy and 5-fluorouracil infusion in carcinoma of the esophagus. *Dis Esophagus.* 2000;13(3):219-225.

10) Gaspar LE, Nag S, Herskovic A, Mantravadi R, Speiser B. American Brachytherapy Society (ABS) consensus guidelines for brachytherapy of esophageal cancer. Clinical Research Committee, American Brachytherapy Society, Philadelphia, PA. *Int J Radiat Oncol Biol Phys.* 1997;38(1):127-132.

11) Hujala K, Sipilä J, Minn H, et al. Combined external and intra luminal radiotherapy in the treatment of advanced oesophageal cancer. *Radiother Oncol.* 2002;64:41-45.

12) Rosenblatt E, Jones G, Sur RK, et al. Adding external beam to intra-luminal brachytherapy improves palliation in obstructive squamous cell oesophageal cancer: a prospective multi-centre randomized trial of the International Atomic Energy Agency. *Radiother Oncol.* 2010;97:488-494.

13) Sur RK, Singh DP, Sharma SC, et al. Radiation therapy of esophageal cancer: role of high dose rate brachytherapy. *Int J Radiat Oncol Biol Phys.* 1992;22:1043-1046.

14) Petrovich Z, Langholz B, Formenti S et al. Management of carcinoma of the esophagus: the role of radiotherapy. *Am J Clin Oncol.* 1991;14:80-86.

15) Hyden EC, Langholz B, Tilden T et al. External beam and intraluminal radiotherapy in the treatment of carcinoma of the esophagus. *J Thorac Cardiovasc Surg.* 1988;96:237-241.

16) Safaei AM, Ghalehtaki R, Khanjani N, et al. High-dose-rate intraluminal brachytherapy prior to external radiochemotherapy in locally advanced esophageal cancer: preliminary results. *J Contemp Brachy.* 2017;9(1):30-35.

17) Muijs CT, Beukema JC, Mul VE, Plukker JT, Sijtsema NM, Langendijk JA. External beam radiotherapy combined with intraluminal brachytherapy in esophageal carcinoma. *Radiother Oncol.* 2012;102(2):303-308.

18) Nishimura Y, Ono K, et al. Esophageal cancer treated with radiotherapy: impact of total treatment time and fractionation. *Int J Radiat Oncol Biol Phys.*1994;30(5):1099-1105.

19) Lettmaier S, Strnad V. Intraluminal brachytherapy in oesophageal cancer: defining its role and introducing the technique. *J Contemp Brachy.* 2014;6(2):236-241.

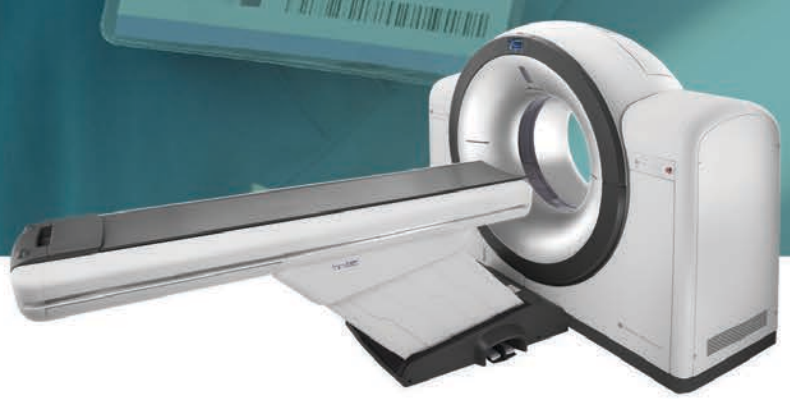
FUJIFILM
Value from Innovation

People-First Design.

For the Radiation Therapist, your patient's positive experience builds trust during treatment.

Persona CT delivers an intuitive design, 64 slice, 85cm big bore, for optimized speed, comfort and accuracy.

Be Visionary.



#VisionaryCT

Persona CT

thermoscientific

Got radiation?
See what you've been missing

Imaging in radiation environments just got easier

With superior capabilities for operating in radiation environments, the MegaRAD cameras provide excellent image quality well beyond dose limitations of conventional cameras, and are well suited for radiation hardened imaging applications

MegaRAD3 produce color or monochrome video up to 3 x 10^6 rads total dose

MegaRAD1 produce monochrome video up to 1 x 10^6 rads total dose

KiloRAD PTZ radiation resistant camera with Pan/Tilt/Zoom

In the United States:
For customer service, call 1-800-888-8761
To fax an order, use 1-315-451-9421
Email: sales.cidtec@thermofisher.com

International:
For customer service, call [01) 315-451-9410
To fax an order, use [01) 315-451-9410
Email: sales.cidtec@thermofisher.com

Find out more at **thermofisher.com/cidtec**

ThermoFisher SCIENTIFIC