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Technological Basis for Clinical Trials in FLASH Radiation Therapy: A Review

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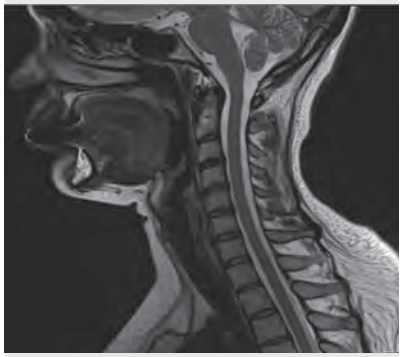

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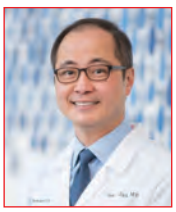

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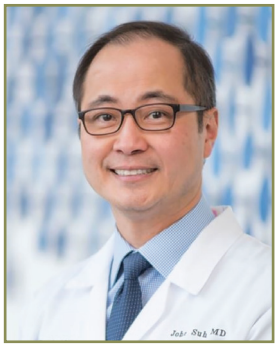
EDITORIAL

FLASH Into View: Clinical Implications of Ultrahigh Dose Rate RT



John Suh, MD, FASTRO, FACR
Editor-in-Chief

Welcome to the June issue of *ARO* focusing on the exciting prospect of FLASH radiation therapy (FLASH-RT). With much unknown about this burgeoning field, we are pleased to present two comprehensive review articles on current and emerging technologies for delivering ultrahigh dose rate (UHDR) RT and its potential to widen the therapeutic ratio in radiation oncology. Both reviews offer free SA-CME credit (with more topics available online).

In the first review, *Technological Basis for Clinical Trials in FLASH-RT*, the authors provide a terrific summary of the modalities, machinery and treatment parameters for UHDR RT, and describe associated limitations and potential indications of the technologies enabling these trials. The second review article, *FLASH RT: Review of the Literature and Considerations for Future Research and Proton Therapy FLASH Trials,* is a thorough, well-written examination of the rationale for and preclinical/clinical outcomes of proton FLASH-RT.

We also present the Technology Trends article *FLASH Stance – Updates in Ultrahigh Dose Rate RT*, in which industry leaders and clinical experts further describe important trials, linac modifications, areas of caution, and more.

In addition to the issue's FLASH focus, we are excited to present the timely research article, *The Role of Patient Reported Outcomes (PROs) in Esophageal Cancer Patients Receiving ChemoRT*. Among findings, the authors show how PROs and their associations with disease characteristics can predict potential toxicities in this complex patient population and help improve treatment planning and supportive care during treatment. A second research article, *Measured Distribution of Total Red Bone Marrow in Young Children*, is an exploratory pilot study with interesting implications for future research in MRI-guided radiation planning for TBI or marrow-sparing RT in patients undergoing radiation for other solid malignancies.

A case report is featured as well: *Craniospinal Irradiation for Leptomeningeal Disease (LMD) in Recurrent Breast Cancer* is a noteworthy report highlighting the need for a comprehensive workup if LMD is suspected.

Lastly, the editorial, *Medical School Curricula: Giving Radiation Oncology a Seat at the Table*, addresses the steep drop in medical student interest in our specialty, which underscores the critical need for initiatives to reverse this decline. As the authors stress, not understanding the basic principles of RT will undermine the ability of future providers to properly triage cancer patients and deliver quality care.

Beyond these pages, we are happy to introduce *ARO Insights*, a new blog featured on our website by our medical student liaison Nadia Saeed, an MD candidate at Yale. Please enjoy her excellent inaugural blog, *Applications of Virtual Learning to Diversify the Radiation Oncology Workforce*. In addition, more live ARO webinars will be featured online. We hope you enjoy these free offerings!

In closing, we wish you a safe and restorative summer as COVID-19 vaccinations climb and much-needed reconnections resume – at least in many areas. In parts of the world where cases continue to surge given the coronavirus variants, our shared knowledge, resources, and compassion will be important as we continue to tackle COVID-19 globally.

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.*

RESIDENT VOICE

Medical School Curricula: Giving Radiation Oncology a Seat at the Table

Sarah A. Dooley, MD; Avinash Chaurasia, MD; Jeremy G. Price, MD, PhD; Elizabeth B. Jeans, MEd, MD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Medical student interest in radiation oncology (RO) has declined more significantly than any other specialty in the past 5 to 6 years.[1] Suggested reasons for this decline include lack of RO exposure at the medical school level. Sixty-one percent of medical students have reported no exposure to RO.[2] We often reflect on our own stories of discovering radiation oncology whether it be through a special mentor or coincidental encounter. However, finding the right career path should not be serendipitous. Consensus amongst RO educators is that a stronger effort must be made to implement RO into the national medical school curricula. Despite this notion, no known formal national movements to do this have been knowingly reported.

The benefit of implementing RO into the national medical school curricula is multifold. Understanding the basic principles of radiation therapy (RT) is not only important for future oncologic subspecialists, but for all providers. Most physicians take care of former or active cancer patients during their career, and many providers are involved in cancer screening, treatment, symptom management, and survivorship.[3] Currently, cancer care is de-emphasized in preclinical and clinical curricula compared with other disciplines.[3] Nonsurgical cancer curricula, such as RO, are even further under-represented.[3] Given the need for all providers to understand cancer management, a lack of understanding of RT negatively impacts future providers' abilities to properly triage cancer patients and provide quality care.

An initiative to integrate RO into the curriculum should focus on cancer-specific pre-clinical and clinical blocks. In terms of pre-clinical years, basic radiobiology principles should be taught alongside cancer biology. Understanding concepts such as the synergism of RT and chemotherapy as well as the rudimentary mechanism of RT helps medical students better understand RO's role in the cancer treatment paradigm. During clinical years, medical students should be required to spend time on cancer care teams and be exposed to multidisciplinary tumor boards, in which medical oncologists, radiation oncologists, and surgical oncologists come together to discuss appropriate indications and sequencing of therapies. While an RT-specific rotation should not be required, a clinical rotation specific to cancer care that includes a short time rotating in the RO department would benefit those interested in oncologic subspecialties.

Lastly, increased involvement of RO providers in education at the pre-clinical and clinical levels is essential. Medical and surgical oncologists reportedly lead the majority of oncologic teaching during medical school training.[3] The RO field should promote and support RO providers' involvement in medical education as it will naturally increase medical students' exposure to radiation oncology and create potential mentorship opportunities.

We are facing a critical moment to claim a seat at the medical school table. Robustly optimizing RO presence in the pre-clinical and clinical years is not only necessary to improve knowledge of our patients' future providers (irrespective of field), but also to recruit talented students to our field.

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SA–CME Information

Technological Basis for Clinical Trials in FLASH Radiation Therapy: A Review

Description

With a steady increase in FLASH-RT human clinical trials underway, this review discusses the technological basis for FLASH-RT clinical trials and explores the modalities, treatment parameters, technical limitations, and potential indications of current ultrahigh dose RT (UHDR-RT) technologies.

Learning Objectives

1. Understand the modalities, machinery, and clinically significant parameters for UHDR-RT delivery.
2. Understand the current open trials in FLASH radiation therapy and the technologies enabling these clinical trials.
3. Understand the currently available and future planned technologies that can help inform guidance on future clinical trials in FLASH radiation therapy.

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Technological Basis for Clinical Trials in FLASH Radiation Therapy: A Review

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FLASH radiation therapy (RT) has shown potential to increase the therapeutic index for cancer treatment. In vivo animal studies have shown a differential response between normal tissues and tumor[1-3] with improved normal tissue sparing but comparable tumor control relative to conventional RT. This phenomenon, or the "FLASH effect," is exhibited at ultrahigh dose rates (UHDRs) of approximately 40 Gy/s or higher.[1,3,4] In this review, "FLASH" is used to describe biological FLASH effects and is distinct from "ultrahigh dose rate," pertaining simply to physical dose rate expressed in Gy/s. Although used interchangeably in the literature, this distinction is made since many complex physical parameters of radiation, beyond simply mean dose rate, may contribute to the biological effects, and is a topic under investigation.[5]

Studies of what we now recognize as the FLASH effect date to the 1960s,[6-8] although recently interest has been rekindled. Although technological advancements in RT delivery have improved toxicities associated with radiation, this remains an ongoing hurdle in optimizing treatment efficacy. Contemporary preclinical studies continue to show a stark reduction in normal tissue toxicity with FLASH-RT compared with conventional dose-rate RT, demonstrated across multiple organ systems, including the brain,[4,9-11] skin,[12-13] lungs,[1] and gastrointestinal tracts[2] in multiple species, including mice, zebrafish, cats, and pigs.[1,2,4,9-13] The clinical implications of the FLASH effect could provide major improvements in the oncologic care of patients and give rise to a new, highly impactful modality of treatment, providing the impetus for clinical translation of FLASH-RT.[5]

Pre-clinical FLASH-RT in animal studies has been made possible through dedicated experimental systems or modification of pre-existing RT systems, including specialized electron linear accelerators (linacs),[14] proton beamlines,[15] synchrotron light sources producing kilovoltage x-rays,[16] and conversion of clinical linacs.[17,18] Recently, the first human treatment with FLASH-RT was conducted for the treatment of a CD30+ T-cell cutaneous lymphoma lesion at Lausanne University Hospital in Switzerland.[19] The institution employed an Oriatron eRT6 5.6 MeV linac (PMB ALCEN), specifically engineered for accelerating

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Table 1. FLASH Technologies Currently in Use for Active Clinical Trials

Facility	Machine	Modality	Energy	Therapeutic depth	Nominal trial dose rate	Dose per pulse	Maximum field size	Trial indications	Trial start date	# of patients
CHUV[23]	IntraOp Mobetron	Electron	6 and 9 MeV	2 and 2.5 cm	300 Gy/s	3.0 and 3.3 Gy/s	6 cm diameter	Melanoma skin metastases	June 2021	7-21
Cincinnati Children's/ UC Health Proton Therapy Center[20]	Varian ProBeam PBS	Proton	250 MeV	~26 cm	60 Gy/s	N/A	7.5 x 20 cm	Painful extremity bone metastases	Nov 3, 2020	10

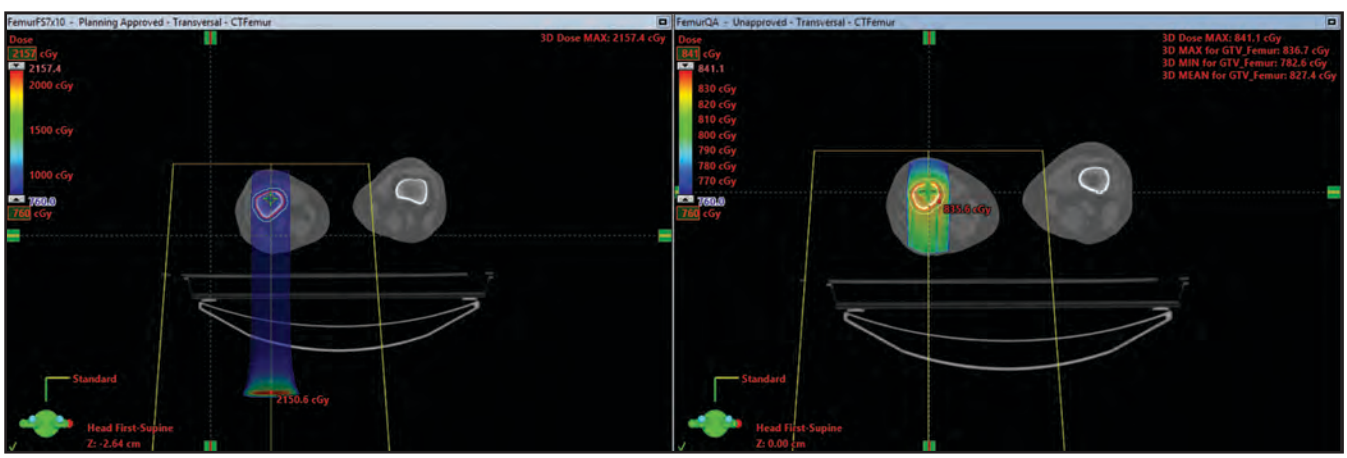

FIGURE 1. *FAST-01 clinical trial treatment plan for a right femoral metastasis. The blue dose cloud represents the plateau region of the proton beam, delivering ~8 Gy to the target. Contrary to conventional proton treatment planning, transmission fields traverse through the entire thickness of the right leg, with the Bragg peak deposited outside of the body at the distal end of the beam.*

electrons for UHDR-RT. The treatment intent was to achieve equivalent tumor control while reducing skin toxicity for a patient who received 110 prior spot radiation treatments to multiple lymphoma skin lesions. Given the numerous treatments that the patient has received in the past, FLASH-RT was considered for potential toxicity reduction. Ultimately, treatment was deemed feasible and safe, with favorable outcomes for both tumor control and skin toxicity, opening the door for further clinical evaluation of FLASH-RT.

Since then, enrollment and treatment in the world's first FLASH-RT clinical trial, FAST-01, has started at the University of Cincinnati, assessing feasibility of single fraction proton FLASH-RT for painful bone metastases.[20] With additional burgeoning FLASH-RT human clinical trials underway, this review aims to cover the technological basis for FLASH-RT clinical trials and explores the modalities, treatment parameters, technical limitations, and potential indications of current UHDR-RT technologies.

Technological Basis for Active Clinical Trials in FLASH-RT

Two clinical trials are active at the time of writing of this review article. They each employ different radiation modalities and delivery methods, which are summarized in **Table 1**. The technologically feasible treatment parameters are discussed below.

Cincinnati Children's/University of Cincinnati Health Proton Therapy Center (FAST-01)

Cincinnati Children's/University of Cincinnati Health Proton Therapy Center is actively enrolling in a single-arm, prospective, feasibility trial named FAST-01 sponsored by Varian Medical Systems to treat painful extremity bone metastases. The trial started in November 2020 with the plan to enroll 10 patients with up to 3 painful extremity bone metastases without prior radiation

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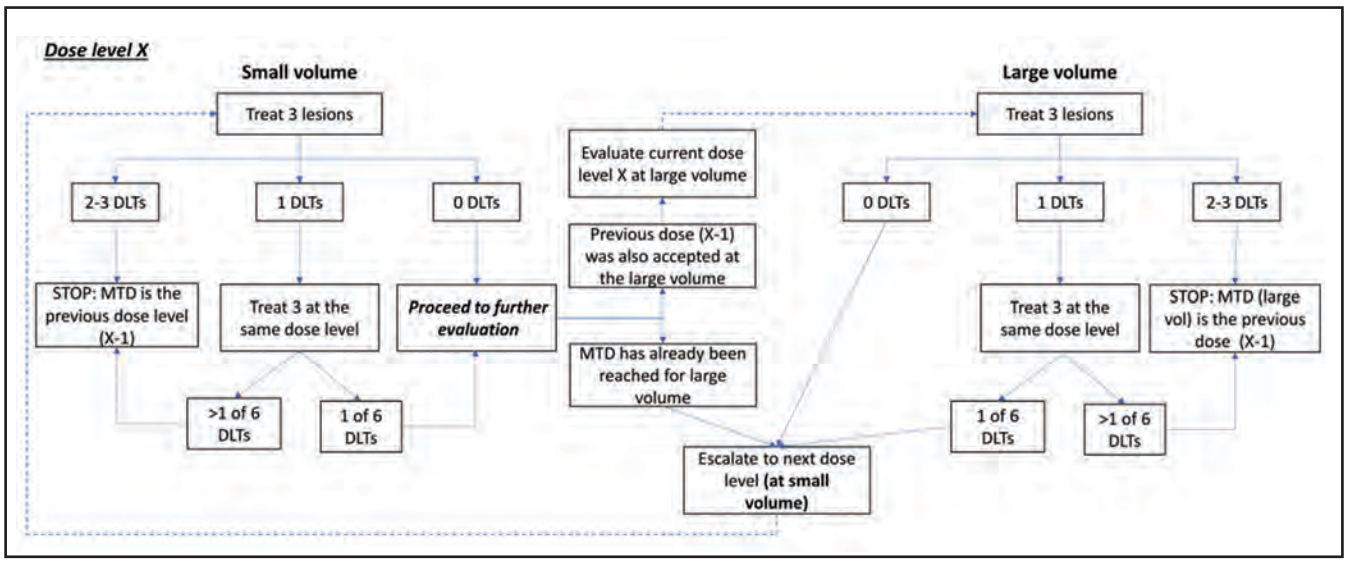

FIGURE 2. *Schematic representation of dose assignments in the 3+3 algorithm for two parallel groups (small/large volume skin metastases) of the CHUV FLASH-RT clinical trial for metastatic melanoma lesions. DLT = Dose limiting toxicity. MTD = Maximum tolerated dose.*

therapy or other local therapy to the treatment sites.[20] The goal of the trial is to assess the technical feasibility and safety of 8 Gy in 1 fraction of proton UHDR-RT for human treatment, and to evaluate the pain response and toxicity associated with this treatment.

This trial utilizes a Varian ProBeam pencil-beam scanning gantry with no significant modification of the beam line or accelerator. The primary modifications are a primary dose monitor, rated for UHDR, and a change to the treatment planning workflow. The proton therapy system delivers a monoenergetic 250 MeV single-layer transmission radiation field at no less than 40 Gy/s and a nominal isocenter dose rate of 60 Gy/s. Transmission fields enter and exit through the patient's body, thereby delivering therapeutic dose using the entrance plateau region of a Bragg peak, as opposed to using the Bragg peak region itself as in conventional proton therapy treatments (**Figure 1**). In some regards, the FAST-01 treatment plans are comparable to opposed-beam photon plans rather than intensity-modulated proton therapy or compensator-based passive scattering proton therapy.

Field sizes range from 7.5 x 7.5 cm^2 to 7.5 x 20.0 cm^2, which are suitable for treatment of a wide range of extremity tumors. The length of the plateau region of the beam is relatively homogenous up until the point where the Bragg peak begins to form, which is at a water-equivalent depth of 26 cm, and this point is defined as the maximum depth of treatment. However, a limitation of transmission fields is the lack of normal tissue sparing that would typically be achieved by elimination of exit dose from conventional Bragg peak fields.

Additional details regarding this system are published in Cunningham et al's recent study on soft tissue and skin toxicity in mice.[21] They describe delivering 35 Gy and 15 Gy to a 25 x 23 mm^2 field at isocenter via single-layer spot patterns made up of 30 separate spots with a uniformity specification of ± 2.5%. The frequency of beam directly from the cyclotron is quasi-continuous, at approximately 72 MHz, and the spot patterns contain spots of equal weight and are scanned continuously. For this study, a maximum mean dose rate of 115.1 Gy/s was achievable at isocenter.

This configuration with its relatively wide range of field sizes and depths will allow for a plethora of clinical indications. The FAST-01 trial is an important clinical and technological starting point for proton pencil-beam scanning UHDR-RT and will pave the way for additional trials and technological developments in the future. The design of the FAST-02 trial for another palliative indication is already under way.[22]

Centre Hospitalier Universitaire Vaudois (CHUV) / Lausanne University Hospital

Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne University Hospital, performed the first human treatment using FLASH-RT.[19] The team is now opening a FLASH-RT clinical trial that is enrolling as of June 2021. The approved phase I trial will determine the FLASH-RT dose that is able to provide durable tumor control for melanoma skin metastases without causing significant toxicity, with a goal to enroll 7 to 21 patients (**Figure 2**).

This trial utilizes an IntraOp Mobetron mobile linac optimized for UHDR delivery,[23] conventionally used intraoperatively or for dermatologic treatments. To accomplish UHDR, the control system was modified to enable prescribing

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Table 2. UHDR-RT Technologies with Published Parameters that Should be Suitable for Clinical Trials in Selected Indications

Facility	Machine	Modality	Energy	Therapeutic depth	Dose rate (at SSDs outside of treatment head)	Dose per pulse	Size of flat field	Potential clinical indications
Lund University[26]	ELEKTA Precise	Electron	8 MeV	1.0-2.0 cm	Up to 120 Gy/s at cross-hair foil	Up to 1.9 Gy, but 0.18 Gy at cross-hair foil	10 x 10 cm	Cutaneous malignancies
Dartmouth University[18]	Varian Clinac 2100 C/D	Electron	10 MeV	5.0 cm	Up to 271 Gy/s with applicator	0.75 Gy with applicator	1-1.5 x 1-1.5 cm	Small cutaneous malignancies
Stanford University[25]	Varian Clinac 21EX	Electron	16-18 MeV	5.5 cm	50-80 Gy/s	0.28-0.44 Gy	10 x 10 cm (potentially up to 20 x 20 cm)	Cutaneous malignancies, extremity soft-tissue tumors, partial breast irradiation
CHUV[14]	Oriatron eRT6	Electron	5 and 6 MeV	1.8-2.3 cm	1000 Gy/s	Maximum 10 Gy	20 cm diameter	Cutaneous malignancies
CHUV[42]	PMB FLASH KNiFE	Electron	10 MeV	~3 cm	350 Gy/s	1.2 Gy	10 cm diameter	Intraoperative RT
University of Pennsylvania[29]	IBA Proteus Plus	Proton	230 MeV	0-15 g/cm^2	60-100 Gy/s	N/A	1 x 2 cm	Small cutaneous malignancies or extremity tumors

the number of pulses for delivery, setting the number of pulses for both the electron gun and solid-state modulator.[23] The pulse width and pulse frequency are programmable and can be set from 0.5-4 µs and 5-90 Hz, respectively.

The Mobetron unit was commissioned for 6 and 9 MeV nominal energies using conventional protocols for commissioning of a medical linac as per the guidelines of AAPM TG-72.[24] As per Moeckli et al, commissioning was performed at the linac exit window, corresponding to a source-to-surface distance (SSD) of 17.3 cm, representing the maximal mean dose rate that can be achieved, as well as 20 cm further at 37.3 cm SSD, to be used for treatment under clinical protocol. This SSD corresponded to mean dose rates of ~300 Gy/s, similar to their preclinical experiments as well as for the first patient treated with FLASH-RT.[19]

At the protocol-specified treatment SSD of 37.3 cm, maximum dose-per-pulses of 3 Gy and 3.3 Gy is achieved for 6 and 9 MeV energies, respectively, with treatment depths – defined as the depth beyond the depth dose maximum at which 90% of the maximum dose is seen (R90) – of 2 to 2.5 cm, well-suited for cutaneous treatments. Treatment field sizes, defined by the 90% isodose line, are at a 6 cm maximum at treatment SSD.

Available UHDR-RT Technologies Enabling Future Clinical Trials

Current technologies for UHDR-RT delivery that have potential for future clinical trial use are summarized in **Table 2**.

Dedicated Electron UHDR Treatment Machines

Several dedicated electron UHDR-RT systems have been developed. The Oriatron eRT6 has been used for the first human treatment, as discussed previously.[19] This system was custom built by PMB ALCEN and commissioned by CHUV to deliver electrons with 5-6 MeV energy with a maximum dose-per-pulse of 10 Gy with a pulse repetition frequency of 5-200 Hz. The maximum average dose rate is 1000 Gy/s. The eRT6 is capable of delivering UHDR at a conventional treatment SSD of 100 cm with field sizes from 1.6 to 20 cm with an R80 of 1.8 to 2.3 cm.[14]

The IntraOp Mobetron intraoperative RT system is another dedicated electron UHDR machine that is discussed in the CHUV section above. In addition

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FIGURE 3. *Novel configuration for electron ultrahigh dose rate radiation therapy (UHDR-RT) by No and Wu et al at Stanford University. A coneless electron applicator system is used for field shaping and to allow for closer surface-to-surface differences to achieve UHDRs, using a reversible configuration of a Varian Trilogy. An anatomical phantom is pictured on the treatment couch as a patient surrogate.*

to CHUV, this UHDR system exists at Ohio State University Comprehensive Cancer Center, The University of Texas MD Anderson Cancer Center, University of California Irvine, and the Centre Hospitalier de l'Université de Montreal. In 2021, a commissioning paper was published with details of the system.[23]

Given the R80 value of the eRT6 (1.8 to 2.3 cm) and the R90 values of the Mobetron system (2 to 2.5 cm), these systems are most suitable for clinical trials involving cutaneous lesions, as well as intraoperative RT.

Clinical Linac-Based Electron UHDR-RT Delivery

To increase accessibility to FLASH-RT utilization and research, multiple groups have developed configurations using clinical linacs to output electron UHDR-RT. Without the need for a dedicated specialized UHDR machine, there is potential for a wider range of radiation teams and centers to be able to conduct future clinical trials.

Schüler et al at Stanford University configured a Varian Clinac 21EX for small animal irradiation.[17] They tuned the beam using a custom 20 MeV program printed circuit board to customize the control parameters, with the gun current and radiofrequency driver manually adjusted to achieve the maximum dose rate. The measured output showed a percentage depth dose (PDD) curve similar to that of 16-18 MeV conventional electron output; 220 Gy/s was attainable at the level of the mirror, which was used for animal experiments, with a field diameter encompassed by the 90% isodose level of 4.1 cm. Additional work is being conducted by No and Wu et al using a novel configuration on a Varian Trilogy that uses a flat electron-arc applicator in place of a standard electron cone, with the scattering foil retained in the beam's path (**Figure 3**).[25] This has shown UHDRs of 50 to 80 Gy/s at SSDs of 90 and 70 cm, respectively. The output is a flat, symmetrical beam with an 80% dose diameter of at least 10 cm (potentially up to 20 cm), with an R90 of 5.5 cm. This configuration is limited by the dose rate decreasing due to the presence of the scattering foil, which limits the SSDs that can be used to maintain UHDRs. However, the relatively large range of treatment field sizes will allow for potential future clinical trials on superficial tumors, such as cutaneous malignancies, sarcomas, or partial breast irradiation.

Lempart et al at Skåne University Hospital and Lund University in Sweden have modified an Elekta Precise clinical linac to deliver electron UHDR-RT.[26] The team manually adjusted the gun current, modulator charge rate, and beam steering values, as well as disabled the interlocks to operate the machine in electron mode without the electron applicator. With the scattering foils in the beam's path, dose rates of 30 and 300 Gy/s were achieved at the cross-hair foil (53 cm SSD) and at the wedge position (19 cm SSD), respectively, with the beams resembling 8 MeV electrons. Beam flatness of < 5% was found for a 20 x 20 cm^2 area and for a 2 cm diameter circular area, respectively, at those positions. When the scattering foils were removed, the dose rates increased to 120 to 1000 Gy/s, respectively, and the areas of beam flatness < 5% were reduced to 10 x 10 cm^2 and a 1.5 cm diameter circle, respectively. As such, at the clinically practical SSD position (ie, outside of the gantry head) published in this study of 53 cm SSD, the scattering foils had to be removed to achieve UHDRs, which limited the flat beam width to 10 cm. Furthermore, they observed that the total dose delivered seemed to become unstable (standard deviation increased to 7% to 11%) when >10 minutes passed after the machine warm-up procedure, although this improved with fine-tuning of the resonance frequency

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of the accelerator. As part of unpublished work, the team has been able to configure this system to produce a beam at a dose rate of 200 Gy/s at 100 cm SSD with a flat field size of 12 × 12 cm^2 (personal communication).

Rahman and Ashraf et al at Dartmouth University have developed a configuration on a Varian Clinac 2100 C/D whereby the team removed the x-ray target, flattening filter, and scattering foil from the path of the beam and selected a 10 MV photon beam energy.[18] With this set-up, a dose rate of 310 Gy/s at 100 cm SSD and depth of 4 cm with the jaws wide open (40 × 40 cm^2 field size) were achievable. Using an electron applicator, they found dose rates of 271 Gy/s with a 2 cm circular cutout and 235 Gy/s with a 1 cm circular cutout. The practical range of depth was approximately 5 cm. However, the team found that the dose per pulse required a "ramp-up" and did not become stable until delivery of ~10 pulses. Also, the beam profile was Gaussian in the absence of the flattening filter and scattering foil, which made for a relatively narrow flat beam width. Experiments on animal tumor models and clinical veterinary treatments are underway using this configuration. There is potential to treat patients in the future, with a possible upcoming feasibility trial on treating patients with advanced skin lesions that are surgically unresectable.[27]

Proton UHDR-RT

Currently, the technology for proton UHDR-RT has shown dose rates ≥ 40 Gy/s with proton pencil beams, but challenges exist with attaining mean dose rates in the UHDR range in a larger volume with a spread-out Bragg peak.[28] As such, many proton UHDR systems utilize a transmission radiation field, which directs the plateau region of the beam through the entire thickness of the body such that the proton beam enters, exits, and then stops outside the body.[21,28] The "FLASHForward Consortium" sponsored by Varian is an aggregate of 20 institutions (and growing) in the US, Europe, and Asia, representing radiation therapy centers with research programs in FLASH-RT with the goal of advancing research and clinical applicability of proton UHDR-RT.[22]

The Varian ProBeam system has been used for proton UHDR-RT and has been discussed above in the section on the FAST-01 clinical trial.

The IBA Proteus Plus system, another clinical proton machine, can deliver proton UHDR-RT with energies up to 230 MeV. Diffenderfer et al at the University of Pennsylvania created a configuration of this system whereby a double-scattered proton beam was delivered quasi-continuously at 106 MHz with a beam current up to 300 nA.[29] They were able to achieve mean dose rates of 60 to 100 Gy/s at isocenter. Homogenous dosimetry was observed within a range of 0 to 15 g/cm^2. This configuration has been used for mice experiments with a collimated beam size of 1 x 2 cm^2. This same group conducted a simulation experiment where they theorized that a beam current of > 500 nA would provide an effective field dose rate of ≥ 40 Gy/s for a field size of 4 x 4 cm^2. However, this did not account for scanning magnet slew time and energy switching time, which the authors discussed were limiting factors in achieving larger field sizes. The IBA Proteus Plus system was also used by Beyreuther et al for experiments on zebrafish embryos, where 100 Gy/s was delivered to a 6.5 mm diameter area.[30]

There are potential solutions to increase the field size of proton UHDR-RT while still reaping the benefits of the Bragg peak. For instance, passive scattering and the use of ridge filters can produce larger fields, but this leads to particle loss and decreased dose rate, as well as requiring significantly higher incident beam currents. Pencil-beam scanning is another possible option that can produce UHDRs at individual spots, but maintaining the dose rates across the entire treatment volume can be limited by the speed of the scanning magnets and the penumbra between scanning layers. Indeed, further experiments are required to assess the feasibility of these and other configurations for proton UHDR-RT, as well as their consequent biological effects.[29,31]

Upcoming FLASH-RT Technologies

Pluridirectional High-energy Agile Scanning Electronic Radiotherapy (PHASER)

Current state-of-the-art clinical RT machines based on x-rays can deliver highly conformal doses with image guidance to general large-volume deep-seated cancer targets, but are orders of magnitude too slow to deliver UHDR-RT owing in large part to the inefficiency of bremsstrahlung x-ray production and inherently slow mechanical systems for gantry rotation and intensity modulation. Major technical hurdles must therefore be overcome to deliver conformal photon FLASH-RT. Researchers at Stanford and the SLAC National Accelerator Laboratory discovered novel particle accelerator principles, originally conceived to overcome breakdown in ultrahigh gradient (>100 MeV/m) accelerator structures, which also greatly increase the radiofrequency (RF) power efficiency. This, combined with novel strategies to eliminate slow mechanical components, forms the basis of pluridirectional high-energy agile scanning electronic radiotherapy (PHASER).[32]

In the distributed RF-coupling architecture with genetically optimized cell design (DRAGON) for electron accelerators, the shape of the accelerating cells is optimized to minimize the peak surface magnetic fields, a key contributor to RF power loss to generating waste heat in the accelerator structure. More efficient transfer of RF power to the electron beam and the ability of the accelerator to operate with a higher

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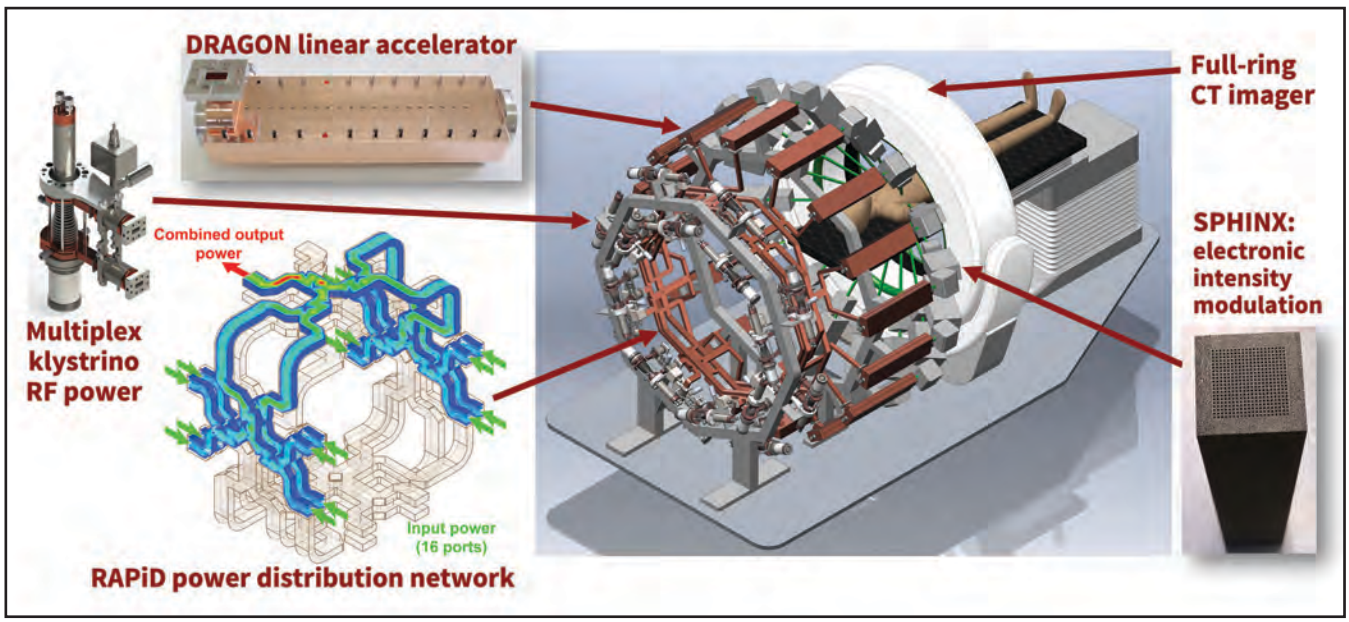

FIGURE 4. *Rendering of the integrated pluridirectional high-energy agile scanning electronic radiotherapy (PHASER) system, adapted from Maxim et al.[32] Multiplex klystrino RF power: Rendering of assembled klystrino, a compact, lower voltage RF power source. An array of klystrinos is arranged around the patient to provide irradiation from multiple angles in rapid succession for conformal RT. RAPiD power distribution network: RF phased-array power distribution (RAPiD) network of waveguides includes 16 input ports (green arrows) for 16 klystrinos, so their combined power can be directed to any of the 16 output ports (red arrow) connected to 16 treatment beamlines. DRAGON linear accelerator: Twenty-cell prototype of the distributed RF-coupling architecture with genetically optimized cell design (DRAGON) linear accelerator structure. RF is fed into each cell whose shape is optimized to minimize the peak surface magnetic fields for maximum power efficiency and resistance to RF breakdown. SPHINX electronic intensity modulation: A 20 × 20 channel prototype of the scanning pencil-beam high-speed intensity-modulated x-ray source (SPHINX) collimator array. This allows for intensity-modulation to be achieved electronically by scanning the electron beam in conjunction with an extended bremsstrahlung conversion target and this multichannel collimator array to produce scanning x-ray beamlets. Altogether, 16 klystrinos provide power through the RAPiD network, which is directed to 16 stationary DRAGON linear accelerators that each produce a beamline. The beamlines are arranged in a conical geometry that share an isocenter with a full-ring CT imager. Each beamline includes a SPHINX system to allow for intensity modulation.*

duty factor without exceeding temperature limits combine to enable 30-fold higher beam current compared with conventional clinical linacs operating at 10 MV energy.[33] A phased-array RF power network allows combining the output power of multiple small, lower voltage RF power sources (klystrinos) and rapidly switching the summed power to any one of an array of linac beamlines (eg, 16) arranged around the patient to provide irradiation from multiple angles in rapid succession for conformal RT, eliminating the need for a mechanical rotating gantry and providing a compact overall form factor. Intensity-modulation from each direction can also be achieved electronically by scanning the electron beam in conjunction with an extended bremsstrahlung conversion target and multichannel collimator array to produce scanning x-ray beamlets. **Figure 4** illustrates the core components that make up PHASER.

Very High-energy Electrons (VHEE)

As electron energy increases from conventional 4-20 MeV to very high-energy (eg, > 100 MeV), the depth-dose characteristics of the beam change from only superficially penetrating to deep penetration with lower entrance and exit dose for a given dose at depth compared to MV energy x-rays.[34-36] As a possible short-term path to clinical FLASH applications, the Stanford group simulated the impact of applying higher peak RF power (through pulse compression of output from a commercial klystron) to the 10 MeV DRAGON linac designed for the PHASER platform, finding that 40 MeV acceleration would be achievable at a beam current sufficient for UHDR when treating directly with electrons.[37] Opposing beams at this energy could produce a homogeneous dose distribution similar to a photon plan for anatomic sites with modest thickness, such as a pediatric brain, at dose rates up to > 400 Gy/s. The same principles are being used to design compact high-gradient accelerators with 100+ MeV beam energy for very high-energy electron (VHEE)-based conformal FLASH therapy.[32]

Another technology capable of delivering FLASH dose rates with VHEE is being investigated by researchers at CHUV and CERN.[38] The full details of this technology are not yet available

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at the time of this writing but report a conceptual design of a unique apparatus based on a compact linear collider (CLIC) accelerator technology enabled to accelerate electrons to treat tumors up to 15 to 20 cm in depth. We anticipate the proposed technology, noted to be capable of treating large and deep-seated tumors, would likely offer high clinical relevance.

Conclusion/Discussion

FLASH-RT holds exciting promise as technological advancements occur at a rapid pace. Preclinical studies show great potential for FLASH-RT to widen the therapeutic ratio in radiation treatments. Novel upcoming clinical trials, enabled by the development of new technologies in RT, are helping to test those preclinical findings for human translation.

As future trials in FLASH-RT develop, several considerations arise from limitations of current technologies. Electron therapy has limited tissue penetration, and is suitable mainly for superficial tumors and intraoperative RT.[39] However, this limitation could potentially be remedied with the use of VHEE, which has the penetration required for deep-seated tumors. Current linacs for conventional photon delivery cannot reach UHDRs. Solutions for this require novel innovations in linac development, such as those in the PHASER system.[32] While proton beam therapy is highly suited for targeting deep-seated tumors with normal tissue-sparing dosimetry, currently UHDR is achieved using transmission fields from a single-beam direction, which forfeits the conformity advantage of protons. FLASH treatments taking advantage of the Bragg peak are under development for more conformal treatment. Electron and proton-based FLASH platforms have already entered clinical trials for select indications, and Bragg peak proton FLASH delivery will likely be implemented clinically in the next 1-2 years. Meanwhile, x-ray and VHEE FLASH are actively under development and may reach the clinic within 3-5 years. Within this timeframe, however, much more research is needed for the clinical implementation of FLASH. Currently, the pulse structure, repetition rates, and other beam characteristics that are required to obtain an optimal FLASH effect are yet unknown, as well as whether these requirements are both strictly necessary and sufficient. Given the short beam on time, new technologies for accurate dose monitoring will need to be developed, including QA and calibrations procedures. While some of these technologies are costly for adoption by most clinics, current superficial electron FLASH and developing x-ray FLASH technology have the potential to be economical compared to conventional medical linacs and compatible with existing clinical vaults.

It is also important to mention that there are challenges in comparing FLASH study results between different modalities, as they vary significantly in physical parameters such as pulse structure, time structure, and definition of dose rate. Additionally, while many studies focus on the mean dose rate as the primary driver of the FLASH effect, more complex factors are likely at play, inclusive of dose per pulse, the total number of pulses, and the dose-rate within the pulse.[5] Also, as the biological mechanisms underlying the FLASH effect are still in question, the impact of different modalities on inducing this effect is an important topic of investigation.

As highlighted in this review, there is currently wide variability in UHDR-RT delivery spanning multiple modalities and delivery methods. Future standardization is essential in the development of larger UHDR-RT clinical trials that span different research teams and institutions. Initial steps to address this have begun,[40] with exploration of methods to precisely measure the delivered UHDR radiation, which can then lead to reference standards and dosimetry methods. This would allow for both stringent quality assurance and comparison across different RT modalities, configurations, and experimental settings.[41]

As preclinical data on FLASH-RT expands, and radiation therapy technology continues to advance, the converging of the two have heralded the beginning of FLASH human clinical trials. Many complex questions remain, including optimal indications, whether the FLASH effect translates from animal models to patients, the selection of treatment modality, and the implementation of dosimetry / quality assurance. By being vigilant in this next step into clinical translation of this new technology, we can carefully unlock the vast potential impact that FLASH-RT may have on radiation treatment and oncologic care at large.

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SA–CME Information

FLASH Radiation Therapy: Review of the Literature and Considerations for Future Research and Proton Therapy FLASH Trials

Description

In this manuscript, the authors review the proposed mechanisms of action for FLASH radiation therapy (FLASH RT), summarize early preclinical results, discuss the first-in-human treatments with a focus on proton FLASH, and highlight challenges and future considerations of FLASH RT.

Learning Objectives

1. Understand the potential mechanisms of normal tissue sparing when delivering FLASH RT.
2. Understand the potential benefits of FLASH RT across different patient populations being considered for future early in-human clinical trials.

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FLASH Radiation Therapy: Review of the Literature and Considerations for Future Research and Proton Therapy FLASH Trials

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Radiation therapy (RT) is routinely used in cancer care but may cause acute- and long-term toxicities as a consequence of ionizing radiation deposition in normal tissues surrounding cancer cells. These potentials for toxicities can often limit the dose of RT that can be delivered safely in the curative setting. Additionally, the risks of toxicities are often amplified with the delivery of concurrent chemotherapy or when RT is delivered as part of multimodality treatment.[1]

One method being increasingly employed to reduce acute- and long-term side effects commonly encountered with traditional photon therapy is the use of proton therapy. Mechanistically, protons are heavier, charged particles exhibiting unique physical properties compared with photons or electrons more traditionally used for RT.[2] Protons can be delivered with precise energies to a desired depth, preferentially depositing energy at a specific depth known as the Bragg Peak, and have no exit dose. Photons, on the other hand, experience an exponential attenuation with increasing depth beyond the first few centimeters of entrance and peak dose, and they continue to deposit their energy in normal tissues beyond the tumor, thus exposing and potentially damaging normal tissue distal to the target volume.[3] These spatial advantages of proton therapy dose distribution have demonstrated improved clinical outcomes and reduced toxicities for subsets of patients with head and neck cancers,[4] esophageal cancers,[5] lung cancers,[6] liver cancers,[7] pediatric malignancies,[8] and others, as well as to better preserve performance status[9] and quality of life[10] across multiple disease sites. Additionally, proton therapy in select cases may be a safer way to deliver dose escalation and/or hypofractionation[11,12] and reirradiation.[13]

The intrinsic spatial advantages of charged particle RT have been explored in depth, yet the effects of dose rate on the therapeutic index have only recently received increased attention. Indeed, the use of ultrahigh dose rate "FLASH" proton RT holds the potential to further reduce toxicities and to be a transformative advancement in the field of radiation oncology. Initial preclinical in vitro and in vivo studies have shown that when RT is delivered at dose rates that far exceed those currently used in routine clinical practice, fewer toxic effects of RT are exhibited. This normal tissue protection at ultrahigh dose rates is termed the FLASH effect.[14] FLASH effects are thought to require dose rates delivered in excess of 40 Gy per second, whereas linear accelerators

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and proton accelerators used in clinical practice conventionally deliver dose at 0.06 to 0.40 Gy/s and 1.67 Gy/s, respectively. Furthermore, recent preclinical studies have suggested that such ultrahigh dose rates maintain treatment efficacy while decreasing the likelihood of toxicities.[15,16]

Research on FLASH RT is still in its infancy; future studies will be critical to verify whether FLASH RT will be a paradigm-changing innovation in the RT field or one of no true clinical benefit. In this manuscript, we review the proposed mechanisms of action for FLASH RT, summarize early preclinical results, discuss the first-in-human treatments with a focus on proton FLASH, and highlight challenges and future considerations of FLASH RT.

Mechanism of Action

The mechanism of action for FLASH RT's reduced toxicity is postulated to be multifactorial. FLASH RT can produce oxygen depletion that mimics hypoxia in normal tissue. A lack of oxygen in normal tissue prevents free radicals from reacting with oxygen to form damaging peroxyl radicals. This effect results in the subsequent increase in normal tissue radioresistance,[15,16] but the mechanisms by which RT-induced hypoxia might lead to differential effects between normal tissue and tumor tissue radiosensitivity remain controversial.[17] In addition to, or possibly in concert with, differential reactive oxygen species production, FLASH RT may alter the DNA damage response. Indeed, conventional RT induces G2 arrest and, therefore, radiation-induced apoptosis.[18] In one investigation, G2 cell cycle arrest was found to be significantly less pronounced 10 hours after irradiation with FLASH RT compared with conventional RT, which may allow for less normal tissue damage.[19] Other investigators have found that the yield of DNA double strand breaks as measured by γ-H2AX foci formation is less with FLASH than conventional RT,[17,20] possibly leading to a differential inflammatory response.

In this regard, FLASH RT may also induce differential expression of transforming growth factor beta (TGF-β), which is a pro-inflammatory cytokine. In one investigation, when measured 24 hours post-RT, FLASH RT only led to a 1.8 times increase in TGF-β levels, whereas conventional RT resulted in a 6.5-fold increase.[20] As a result, the amount of radiation-induced chronic inflammation and fibrosis may be less with FLASH RT relative to conventional-dose rate RT.[21-23]

Finally, FLASH RT has been associated with greater preservation of stem cells in normal tissue relative to conventional RT. In studies of acute intestinal damage following 15 Gy whole abdominal RT, mice treated with FLASH RT showed a significantly higher number of proliferating crypt stem cells compared with mice receiving conventional-dose rate RT.[23] In another study, while both conventional-dose rate RT and FLASH RT were found to be toxic for normal human hematopoiesis cells as reported by Chabi et al, only FLASH RT led to the preservation of stem cells.[24] Notably, hematopoietic stem cells exist in a lower oxygen environment than the circulating blood cells,[25] which could theoretically enhance the ability of FLASH-mediated depletion of molecular oxygen to achieve radiobiologically protective levels of hypoxia.

Preclinical Studies

In laboratory studies, electron FLASH RT led to fewer toxicities compared with conventional-dose rate RT. Favaudon et al irradiated C57BL/6J mice with conventional (0.03 Gy/s) or FLASH RT (≥40 Gy/s), observing significant fibrosis in the former and no apparent damage in the latter, akin to normal tissue without any irradiation.[22] In tissue samples of 6 cats with locally advanced T2/T3N0M0 squamous cell carcinoma of the nasal planum treated in a single-dose escalation trial with FLASH RT (25-41 Gy), FLASH RT led to observations of no erythema, no moist desquamation, no fibronecrosis, no hyperkeratosis, no inflammatory infiltrates and no dermal remodeling.[26] At 3 and 6 months, all cats experienced a complete response. One cat experienced clinical recurrence at 8 months and was euthanized shortly thereafter; the remaining 5 cats all had complete responses at 16 months. Across multiple studies, FLASH RT generally has been reported to provide better normal tissue protection with a dose modifying factor of 1.4 to 1.8.[22-23,26-28]

While FLASH RT has been shown to spare normal tissues, reported preclinical studies to date do not suggest that it protects tumors. Tumor kill has consistently been similar with – and in some reports, potentially even improved following – FLASH RT relative to conventional-dose rate RT. The observed dose rate-response relationship, in which higher dose rates may be associated with better tumor killing than standard dose rates, has been observed in conventional RT. Lohse et al[29] compared high dose per pulse flattening filter-free beam with standard flattened beam. They reported the most efficient tumor killing at the higher dose of 0.4 Gy/s, compared to 0.066 Gy/s or 0.003 Gy/s.

First-in-Human Case Study

The first patient reported to be treated with FLASH RT was a 75-year-old man in Switzerland, diagnosed with CD30+ T-cell lymphoma and classified as T3N0M0B0.[30] No prior treatments (corticoids, PUVA-therapy, Neotigason, Caryolisin, Methotrexate, Targretin, histone deacetylase inhibitor, Caelyx, brentuximab, resminostat) were successful at controlling this patient's disease. He had been treated with RT at 110 tumor sites, most frequently

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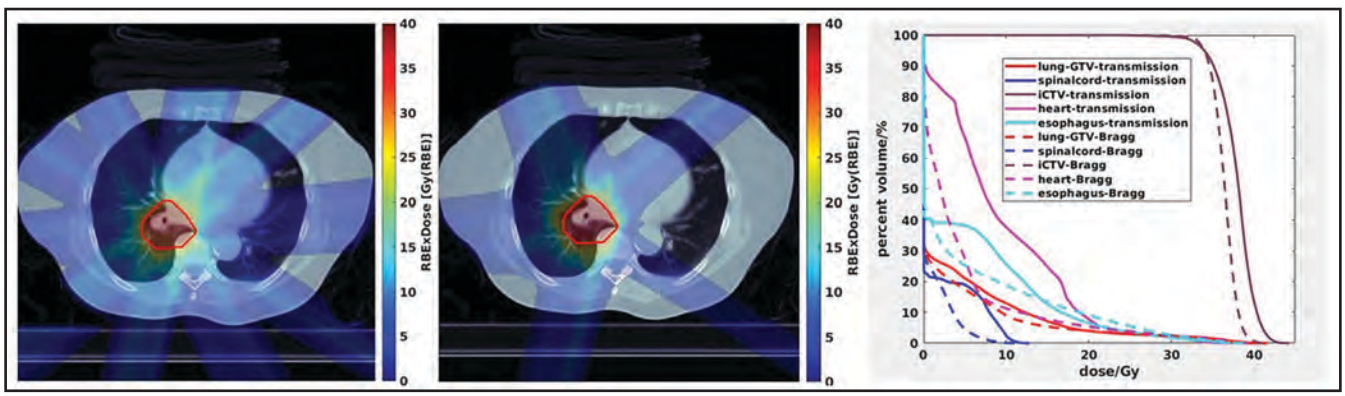

FIGURE 1. *Dose comparisons between transmission and Bragg peak proton FLASH plans. Plan comparisons for a representative patient with lung cancer using the same 5-field beam arrangement with 72 degrees equal angle intervals to deliver a uniform dose distribution to the target volume (red contour). Left is the single-energy intensity-modulated proton therapy (IMPT) transmission plan. Middle is the single-energy Bragg peak IMPT plan. Right is the dose-volume histogram comparison between transmission (solid lines) and Bragg peak (dashed lines) FLASH plans delivering 34 Gy in a single fraction.*

administered to 20 Gy in 10 fractions or 21 Gy in 6 fractions, but the patient continued to experience various ulcerative and/or painful cutaneous lesions. FLASH-RT was administered to him with the hypothesis that it could provide equivalent tumor control while also incurring fewer skin toxicities in this heavily pretreated patient.

A 3.5-cm diameter skin tumor was treated with 15 Gy delivered over 90 milliseconds, equivalent to 167 Gy/s. Tumor shrinkage began 10 days after irradiation, and a complete response was noted at 36 days; tumor response was durable for the next 5 months of follow-up at the time of publication. At 3 weeks after irradiation, often the peak of treatment reactions, only grade 1 epithelitis and transient grade 1 edema in soft tissues surrounding the tumor was observed. There was no decrease in thickness of the epidermis and no disruption at the basal membrane, with only limited increase in vascularization. Bourhis et al concluded that the first FLASH RT treatment in humans was both effective and safe.[30]

Rationale for FLASH Delivered with Protons

In its purest form, FLASH RT is merely the use of radiation delivered at a dose rate several orders of magnitude higher than conventional RT. While electron linear accelerators have been used in the aforementioned studies,[22,26,30] treatment using electrons has its limitations. Electron FLASH, in its current form and in keeping with conventional-dose rate electron therapy, has low tissue penetration and a general inability to treat deep-seeded tumor volumes, less conformal dose distributions, and limited field size, thereby effectively only allowing the treatment of superficial cancers such as skin cancers and cutaneous lymphomas.[31] In contrast, FLASH delivered with proton therapy can overcome this penetration limitation and treat any body depth based on its current delivery approach of transmission FLASH. When delivering transmission FLASH, which is currently the easiest way to deliver FLASH dose rates using proton therapy and which also eliminates uncertainties associated with the positioning of the Bragg Peak that might be magnified with ultrafast delivery of therapy and might result in underdosing of tumor and marginal misses in target, the Bragg peak is intentionally placed outside (behind) the patient such that the proton FLASH target volume is treated with the part of the beam before the Bragg peak.[8,32]

Beyond the currently sizable advantage in depth of penetration, there are additional advantages of using protons to deliver FLASH. Early studies have been conducted investigating how to optimize FLASH delivered with proton therapy,33 including the delivery of Bragg peak plans with the Bragg peak placed in the patient that allows for the elimination of exit dose and a reduction of irradiation beyond the tumor volume as opposed to transmission beams to the tumor (**Figure 1**). Proton FLASH could have both biological and physical advantages in achieving the FLASH effect with a high linear energy transfer while also administering the majority of its beam energy into a narrow range of the Bragg peak and sparing normal tissues beyond the target volume, respectively.[21] The physical advantages of proton FLASH using Bragg peak planning relative to electron FLASH or proton FLASH using transmission planning might be magnified when needing to treat to higher doses for tumor control. Furthermore, proton accelerators are currently much better suited to deliver FLASH RT over photon and electron linear accelerators that would require significant machine manipulation to attain the ultra-high dose rates needed to achieve the FLASH effect and that also suffer from field size restrictions. In acknowledgment, the first-in-human clinical trial investigates the feasibility of FLASH RT delivered with protons.

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First-in-Human Clinical Trial

As of this writing (April 2021), the first-ever FLASH RT human clinical trial underway is the only one initiated to date (ClinicalTrials.gov Identifier: NCT04592887, first posted 10/19/20). The trial, Feasibility Study of FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases (FAST-01), is being conducted at the Cincinnati Children's Proton Therapy Center. The target sample size for this open label, single-arm prospective feasibility study is 10 patients at least 18 years old with up to 3 painful bone metastases in the extremities who are estimated to have a life expectancy of at least 2 months. As of April 15, 2021, 4 patients have been accrued who received palliative FLASH RT. The primary endpoints are workflow feasibility and radiation-related toxicities; secondary endpoints are pain relief, pain flare, and use of pain medication. No interim results are available at this time.

In this first-in-human trial, patients are being treated in a single fraction with FLASH proton therapy to 8 Gy using a single transmission beam and predefined treatment field size. The target is the gross tumor volume, and a margin of 0.5 cm or more is used. The duration of the fraction is less than a second, and the dose rate is 40 Gy/s or greater.

Proton FLASH Trial Considerations

While several studies provide insights into the mechanism of action for FLASH RT, great uncertainty still exists. Further preclinical research is needed to investigate the mechanism of action, and this work and other preclinical work are needed to help inform and refine future clinical trials.[34,35] Moreover, ongoing studies of FLASH RT in veterinary cancer patients can complement and extend the mechanistic insights gained from these preclinical studies.

Aside from the ongoing trial in Cincinnati, additional human studies are needed and are being developed. These trials should be conducted in sites with strong preclinical evidence supporting the FLASH effect with tissue sparing and without tumor protection. Furthermore, as FLASH has the potential to be a transformative treatment modality, its benefit may be most significantly seen in disease sites with high toxicities, particularly those with poor local control. As such, endpoints of future studies should be selected in which a clear difference between FLASH and non-FLASH regimens can be identified should a difference exist, such as the reduction of high-grade toxicities.

Locally advanced non-small cell lung cancer (NSCLC) may be a suitable target – it has one of the highest normal tissue toxicity burdens across all cancers, and its 5-year survival rate is approximately only 30% to 40%.[36-39] Furthermore, dose escalation may improve local control and, thereby, overall survival when delivered safely.[40] However, this disease site has unique challenges of tumor motion with respiration. Intrafractional motion is a clinical concern with conventional fractionation and can result in an interplay effect with conventional-dose rate RT treatment delivery.[41] While less of an issue with transmission planning, this same interplay effect futher challenges the delivery of FLASH when using Bragg peak planning, although these concerns may be less significant since FLASH RT is anticipated to be delivered in a fraction of a second per beam and in a single or just a few fractions. Breath-hold strategies, therefore, may be particularly important when planning such FLASH trials for thoracic and upper gastrointestinal malignancies.

Early stage NSCLC, especially for central or ultracentral tumors that have considerably higher rates of toxicities from stereotactic body radiation therapy (SBRT) than peripheral tumors, may also be a suitable target. Aside from similar concerns of delivering FLASH to a moving target and in a curative population for an early clinical trial, study accrual may be relatively easier due to the large and increasing number of patients diagnosed with early stage NSCLC. FLASH may be an optimal approach for these central tumors given that there is currently no definitive standard-of-care treatment with traditional dose rate RT, especially for ultracentral lesions, and given the high toxicity and even mortality rates with current RT approaches.[42-45]

Thoracic metastases may also be appealing due to relatively high toxicity rates seen when delivering RT to the chest in patients who are on or have received several lines of systemic therapy, as well as the large volume of patients with intrathoracic metastases and corresponding ease of accrual. Furthermore, surgery or alternative ablative therapies can be salvage options if FLASH RT does not lead to adequate local control or symptomatic response. However, heterogeneous histologies and heterogeneous systemic therapies, including the potential for concurrent chemotherapy or immunotherapy, along with tumor motion, may complicate such trials.

Other notable sites include glioblastoma multiforme, hepatocellular carcinoma, and locally advanced pancreatic cancer, each of which is a common malignancy with high toxicity rates and guarded overall prognoses. Glioblastoma multiforme has failure patterns that are predominantly local, although prior attempts at dose escalation did not improve tumor control or survival.[46,47] Hepatocellular carcinoma similarly has failure patterns that are predominantly local before distant, but dose escalation can improve local control.[48,49] Furthermore, conventional RT treatments for liver tumors are currently limited by the inherent radiosensitivity of hepatocytes and the risks of radiation-induced liver toxicities. As such, FLASH holds the potential to improve the therapeutic ratio for these challenging tumors. However, no preclinical FLASH RT studies

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have been performed in liver tumors to date. Patients may be on heterogeneous systemic therapies, and tumor motion is also a factor. Direct visualization of the tumor prior to treatment may be more challenging as well. Likewise, there are no preclinical FLASH RT studies for locally advanced pancreatic cancer, and the potential for duodenal toxicity may prove challenging for early clinical trials in FLASH, in addition to concerns of systemic therapies, tumor motion, and pretreatment visualization. Lastly, consideration should be given to clinical trials in patients receiving preoperative FLASH therapy, such as for sarcoma, to gain insights into the biological effects of FLASH in resected tissue specimens.

Additional Trial Considerations

Several other considerations are critical when considering future human administration of FLASH RT. It is important to ensure that all or most regions of the treatment field receive dose rates above what is considered the threshold for the FLASH effect, as critical normal tissue treated at very high dose rates, but at rates insufficient to achieve the FLASH effect, could actually worsen the therapeutic ratio. Furthermore, it is unclear whether there is a differential effect with higher FLASH RT dose rates; further investigation, both in preclinical and clinical settings, are needed to determine whether 40 Gy/s is adequate, or if dose rates of 80 to 120 Gy/s or more are preferable. Additionally, preclinical data are needed assessing FLASH effects with fractionation, akin to conventional-dose rate SBRT, as current FLASH data have focused on single fraction delivery.

There also needs to be careful deliberation over the total irradiation per voxel, the number of times a voxel gets irradiated, and the overlapping of beams. Processes must likewise be developed and enacted for the scenario in which a treatment interruption might occur in the middle of a beam, as well as methods to ensure dose rate can be reliably measured at the ultrahigh dose rates used for FLASH RT. Additionally, development of Bragg peak delivey of FLASH is indicated to further optimize dose comformality and to allow for the FLASH treatment size to not be limited by the maximum beam energy, thus expanding the areas deliverable with FLASH to deep tumors such as gastrointestinal target volumes that might be challenging to treat with transimission FLASH plans. Of final note, successful delivery of FLASH RT is also contingent on technological advancement, including improved ease of delivering FLASH with current linear accelerators that at present require significant machine manipulation.

Conclusion

FLASH RT is a promising treatment option, but much research utilizing this technology is still in its infancy, and limited animal and human data exist. If it proves to have the normal tissue-sparing effects as demonstrated in multiple early preclinical reports, FLASH is poised to result in a significant evolution in the field of oncology.

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The Role of Patient Reported Outcomes in Esophageal Cancer Patients Receiving Chemoradiation Therapy

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Abstract

Background and Objectives: To determine if primary esophageal cancer (EsoCa) characteristics were related to unique Edmonton Symptom Assessment Scale (ESAS) symptom reports.

Methods: Records of patients with EsoCa receiving chemoradiation therapy (CRT) were retrospectively screened against a single institutional ESAS database. The majority of patients received concurrent folinic acid, fluorouracil, and oxaliplatin (FOLFOX) and 5.5 weeks of radiation therapy (RT) to 50.4-56.0 Gy. During treatment, patients completed a weekly ESAS survey. Relationships between clinical variables and ESAS scores were analyzed using the Mann-Whitney U test and variables were correlated using Kendall's tau-b tests.

Results: A total of 87 patients with EsoCa receiving CRT completed ESAS between February 2017 and July 2019 with 41 completing ≥ 3 ESAS surveys (median = 5, mean = 5.6, range = 3-12). In this cohort, 75.3% were men (n = 31) and 95.1% were White/Caucasian (n = 39). Seven patients had cervical lesions (17.1%), four (9.8%) middle, and 30 (73.2%) distal. A total of 72.5% of patients had adenocarcinoma (n = 29). Tiredness had the highest median ESAS score (4.00, median total score 22.4). Patients with middle lesions were more likely to experience pain (4.25 vs 0.5, $P = 0.038$) and drowsiness (2.5 vs 0, $P = 0.022$). Distal and cervical lesions did not demonstrate statistically significant relationships.

Conclusion: In this analysis of patient reported outcomes (PRO) in EsoCa, patients with middle esophageal lesions were more likely to experience pain and drowsiness.

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Meaningful patient-centered care requires the measurement of patient concerns and implementation of tailored clinical solutions. To personalize therapy informed by the patient perspective, objective clinical data is ideally combined with collection and assessment of patient-reported outcomes (PROs). In addition to providing actionable symptom burden data for intervention, PROs have been shown to correlate with diagnosis,[1,2] radiographic response to treatment,[3] and early identification of disease progression.[4]

Our center has been collecting PRO data using the Edmonton Symptom

Table 1. Clinical Parameters of the Subject Population

Patient Characteristics			
	Characteristics	**Number**	**Percentage (%)**
Gender	Male	31	75.6
	Female	10	25.4
Ethnicity	Caucasian	39	95.1
	Black	1	2.4
	Hispanic/Latino	1	2.4
Location	Cervical	7	17.1
	Middle	4	9.8
	Distal	30	73.2
Type	Adenocarcinoma	29	70.1
	Squamous Cell Carcinoma	12	29.3
		Median	**Range**
ESAS	Shortness of Breath	0	0-6
	Pain	1	0-9
	Tiredness	4.5	0-8
	Anxiety	0	0-9
	Nausea	0	0-7
	Depression	0	0-8.5
	Insomnia	2	0-9
	Drowsiness	0	0-7
	Appetite	2	0-9.5
	Constipation	0	0-9
	Overall Well-being	1	0-7
	Spiritual Distress	0	0-8
	Total	20	1-66.5

Assessment Scale (ESAS) for several years in our radiation oncology and supportive care clinics. We have previously discussed the role of ESAS data in unselected RT patients[5] and in specific cohorts with retroperitoneal sarcoma[6] and multiple myeloma.[7] Recently we have assessed the role of PRO in clinical scenarios such as anemia.[8]

The value of PROs to assess treatment-related toxicity and the effects of palliative chemotherapy and/or radiation therapy (RT) on the quality of life for patients with esophageal cancer has been confirmed.[9] However, PROs are also more likely than clinical outcome measures to provide information pertinent to the functioning of patients with esophageal cancer.[10] Patterns in the PROs of esophageal cancer populations may provide a basis to anticipate symptoms and provide proactive targeted treatment and increased support.[11] We were interested in investigating the role of PROs, specifically ESAS, in EsoCa because of the disparate clinical behavior of lesions by location within the organ. For instance, neck masses, odynophagia, hoarseness or referred otalgia[12] may be noted by patients with cervical lesions. Retrosternal pain may be due to mediastinal invasion of middle esophageal lesions. Advanced lesions of the distal esophagus often present solely with dysphagia and weight loss.[13] Very few studies exist describing the relationship between clinical characteristics and ESAS scores in patients being treated with chemoradiation therapy (CRT) for esophageal cancer.

We analyzed our institutional ESAS data to better characterize associations of patient-reported symptoms with esophageal cancer location, since earlier identification and control of esophageal symptoms may reduce patient burden and help avoid unplanned hospitalizations or need for IV fluid interventions.

Materials and Methods

After institutional review board approval, we performed a single-institution retrospective analysis of records of patients with EsoCa receiving RT with concurrent chemotherapy. These were compared with the institutional ESAS database and pertinent data collated. Patients coded as having gastroesophageal junction lesions were excluded to reflect pure esophageal treatment since, typically, less of the esophageal mucosa is involved in the 50.4 Gy field during treatment of these lesions. Patients were assessed for gender, marital status, vital status, histology, and tumor location, which were then analyzed to determine relationships between these variables and ESAS scores. Remaining patient characteristics are available in **Table 1**.

The majority of patients received concurrent FOLFOX (folinic acid/fluroruracil/oxaliplatin) with 5.5 weeks of intensity-modulated radiation therapy (IMRT) to 50.4-56.0 Gy in 1.8-2.0 Gy/fraction.[14-16] Patients on treatment were evaluated weekly by the staff radiation oncologist; on this visit they routinely completed an ESAS survey.

Relationships between clinical variables and ESAS scores were analyzed using the Mann Whitney U test, and correlations between variables were calculated by Kendall's tau-b tests performed using SPSS (Statistical Package for the Social Sciences) software.

Results

A total of 87 patients with EsoCa were identified who completed ESAS between February 2017 and July 2019. Of these patients, 41 completed ≥ 3 ESAS surveys (median = 5, mean 5.6, range 3-12) while on treatment and form the cohort further analyzed.

As outlined in **Table I**, most patients were men (75.6%, n = 31) and White/Caucasian (n = 95.1%, n = 39). Seven (17.1%) patients had cervical esophageal lesions, four (9.8%) had middle lesions and 30 (73.2%) had distal lesions. Most patients had adenocarcinoma (70.1%, n = 29). The ESAS item with the highest median score was tiredness (4.00) with a median total score of 22.4. Patients in this study were noted to lose 3.5% of their body weight after treatment.

Patients with middle esophageal lesions were more likely to experience pain (4.25 v. 0.5, $P = 0.038$) and drowsiness (2.5 v. 0, $P = 0.022$), but no statistically significant relationships were seen for those with distal or cervical lesions. Women (4.75 vs. 0.50, $P = 0.02$) and unmarried individuals (4.5 v. 0.5, $P = 0.021$) were more likely to have a worse appetite while those who died were more likely to experience constipation (2.5 v. 0, $P = 0.005$). Male gender, married status, histology, and remaining alive after treatment did not demonstrate any associations that were statistically significant.

The strongest correlation between symptoms were found between depression and spiritual pain (tb 0.645, $P < 0.001$). Shortness of breath was correlated with the most symptoms, including pain (0.373, $P = 0.005$), tiredness (0.283, $P = 0.027$), anxiety (0.314, $P = 0.022$), depression (0.462, $P = 0.001$), drowsiness (0.424, $P = 0.002$), appetite (0.298, $P = 0.023$), overall well-being (0.299, $P = 0.023$), and spiritual pain (0.342, $P = 0.018$).

Discussion

There is a paucity of studies discussing clinical characteristics and their relationship with ESAS scores. One study discussed the likelihood of severe symptom burden based on clinical characteristics and elapsed time after diagnosis while establishing the prevalence of various symptoms assessed using ESAS as a whole, but did not correlate symptoms with one another or with clinical characteristics,[11] while others have been solely focused on patients undergoing palliative care.[17,18] Additional studies have targeted the use of different PRO surveys and their association with T-stage,[19] to compare patient-reported quality of life between patients receiving CRT and surgery vs surgery alone,[20] to compare quality of life between patients receiving palliative brachytherapy and external beam radiotherapy,[21] to determine impact of treatment on quality of life,[22-24] and prognosis and/or survival[25-28] in patients with esophageal cancer. None of these studies have discussed the association of distinct clinical characteristics with ESAS scores and, therefore, symptoms in those patients receiving CRT for esophageal cancer.

Studies such as this one may inform a patient's potential for a variety of symptoms and provide proactive, personalized treatment tailored to the individual. We note that self-reporting of ESAS pain and drowsiness was only significant in patients with middle esophageal cancer, indicating that patients with esophageal cancer in different disease locations may demonstrate variability in self-reported symptoms as a function of the site of lesions. This variability may also point to differing risk for impairments in quality of life and care needs. For instance, some patients undergoing treatment may need pain medications due to treatment side effects or from the cancer itself. These medications tend to cause drowsiness and a host of other adverse effects, so those taking pain medications regularly are likely to experience more tiredness in their everyday life during treatment.

Additionally, some patients may encounter nutritional deficiencies due to treatment effects such as nausea or dysphagia. Patients who experience nausea, especially if it is refractory to antiemetic medication, may not be able to eat as much in terms of volume and variety of foods. In such cases, they may not have enough intake of calories or nutrients to sustain the energy levels they are used to.[29,30] Patients in this study experienced a median weight loss of 3.5% from their pre-treatment weight during treatment, demonstrating possible difficulty maintaining the proper level of nutrition. Additionally, if a tumor is obstructing a portion of the esophagus, they may have difficulty eating foods of a specific type or texture, which can lead to similar sequalae.

Other factors contributing to a patient's experience during treatment include various lifestyle changes. Smoking and alcohol use are two major risk factors for esophageal cancer. Unfortunately, while some patients may stop these activities during and even after treatment, others continue these behaviors throughout treatment.[31] This can lead to a worsening of side effects during treatment, including increasing odynophagia, which can also lead to nutritional problems since this would likely be exacerbated while eating. These variables were not studied in our patient cohort so we cannot comment on their relevancy to our findings.

Another factor to consider is the level of support a patient may have. A patient with a robust support system may be able to better adjust to the changes observed when undergoing treatment.[32] Friends or family who prepare meals for them, perform

household work, help them make lifestyle changes, and provide emotional support may drastically lift some of the burden on these patients so that they can focus their energy on healing rather than continuing to expend energy on other tasks. Including such additional factors was beyond the scope of this project but future work is planned to incorporate variables relating to the degree of support.

As the reliability and predictability of PROs linked to specific diagnoses such as EsoCa are confirmed, PROs may become important tools for clinicians to help plan treatments and supportive care. While intriguing, this retrospective analysis should be interpreted cautiously. Nevertheless, further analysis with other large PRO libraries is indicated to validate these findings.

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Recurrent Prostate Cancer

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CASE SUMMARY

A 58-year-old man with a Gleason score of 4+5=9 prostate cancer underwent radical prostatectomy in January 2016. At the time of surgery, the cancer had progressed through the capsule and into the seminal vesicles. However, no nodes were involved. His post-operative prostate specific antigen (PSA) was 0.27 ng/ml. Patient was deemed at high risk for recurrence and was referred for salvage pelvic and prostatic bed radiotherapy in October 2016. A ^{68}Ga PSMA-11 PET/CT was performed with no abnormal activity detected.

After radiotherapy, the patient's PSA decreased from 0.58 ng/ml to nadir of 0.46 ng/ml and then spiked to 0.63 ng/ml in July 2017. Repeat ^{68}Ga PSMA-11 PET/CT demonstrated no abnormal activity, and the patient entered an active surveillance program with repeat PSA tests every 3-6 months. At this time, the patient was not placed on hormone therapy or androgen deprivation therapy (ADT).

In March 2018, the patient's PSA levels rose significantly to 2.9 ng/ml, necessitating a third ^{68}Ga PSMA-11 PET/CT, which demonstrated PSMA-positive pathology**.** Patient received stereotactic radiotherapy to lymph nodes in the left internal iliac and right internal iliac stations. Active surveillance was again employed with no concomitant ADT.

IMAGING FINDINGS

Pursuant to the patient's rising PSA, a third ^{68}Ga PSMA-11 PET/CT exam in March 2018 (**Figures 1-2**) revealed a moderately PSMA avid lymph node in the left internal iliac station at the presacral region and a small, mildly PSMA avid lymph node in right internal iliac station. Activity was also detected in the bladder.

Due to continued rising PSA levels, the patient received a fourth ^{68}Ga PSMA-11 PET/CT exam in July 2020 (**Figures 3-4**), which detected a new PSMA avid right internal iliac node and a new PSMA avid right para-aortic node. Ureteric activity was also apparent. Sequential Ga-68 PSMA-11 PET/CT exams demonstrated an increase in physiologic activity. However, the previously treated nodal disease was improved.

DIAGNOSIS

Recurrent prostate cancer with possible metastasis to right paraaortic and pelvic lymph nodes

FOLLOW-UP

Patient reinitiated stereotactic radiotherapy without ADT.

DISCUSSION

Contrary to declining death rates for many common cancers, prostate cancer deaths are rising, with an increase of 5 percent from 2019 to 2020.[1] Although most primary prostate cancer cases can be managed with radiotherapy or radical prostatectomy, 40 percent of men treated for this cancer will have disease relapse,[2] with castration-resistant prostate cancer accounting for most deaths.[3] ^{68}Ga PSMA-11 PET/CT suggests better sensitivity to low levels

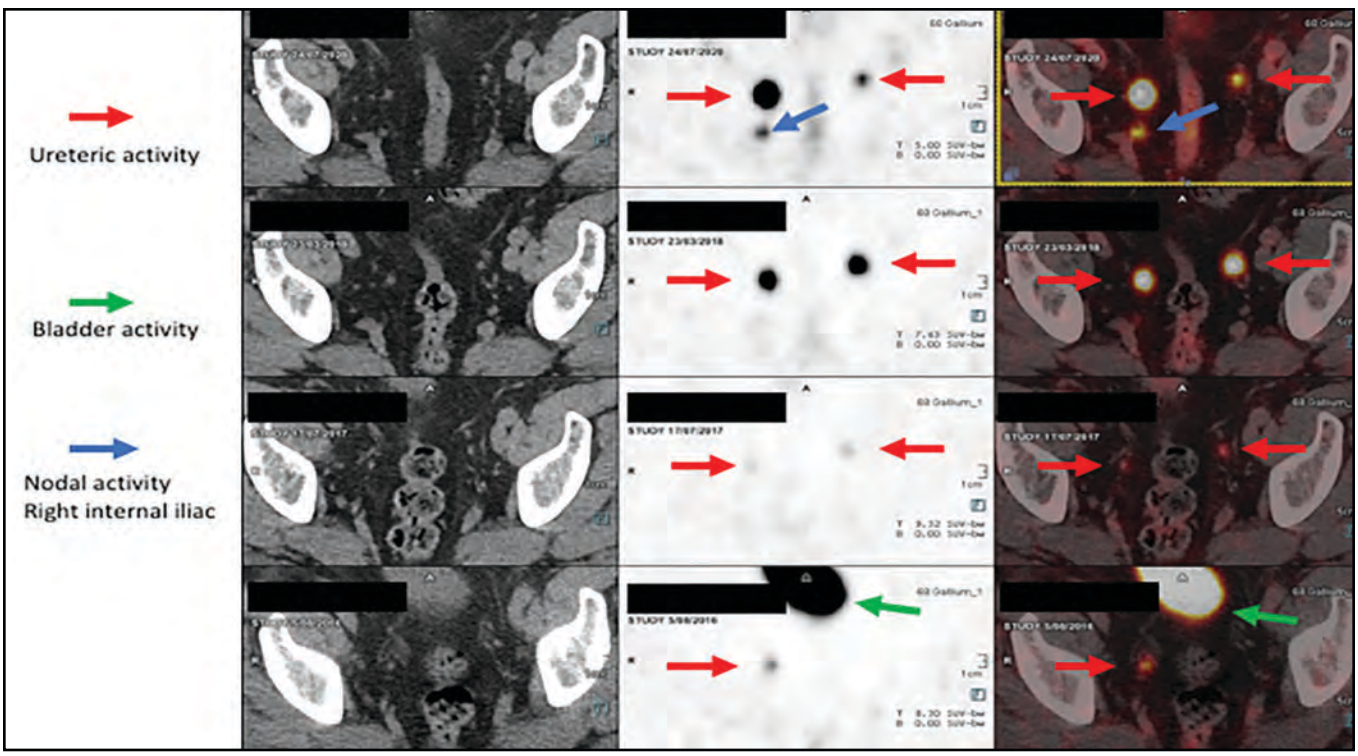

FIGURE 1. *Physiological ureteral uptake (red arrows). PSMA avid right internal iliac lymph node (blue arrow). Increased bladder activity (green arrow).*

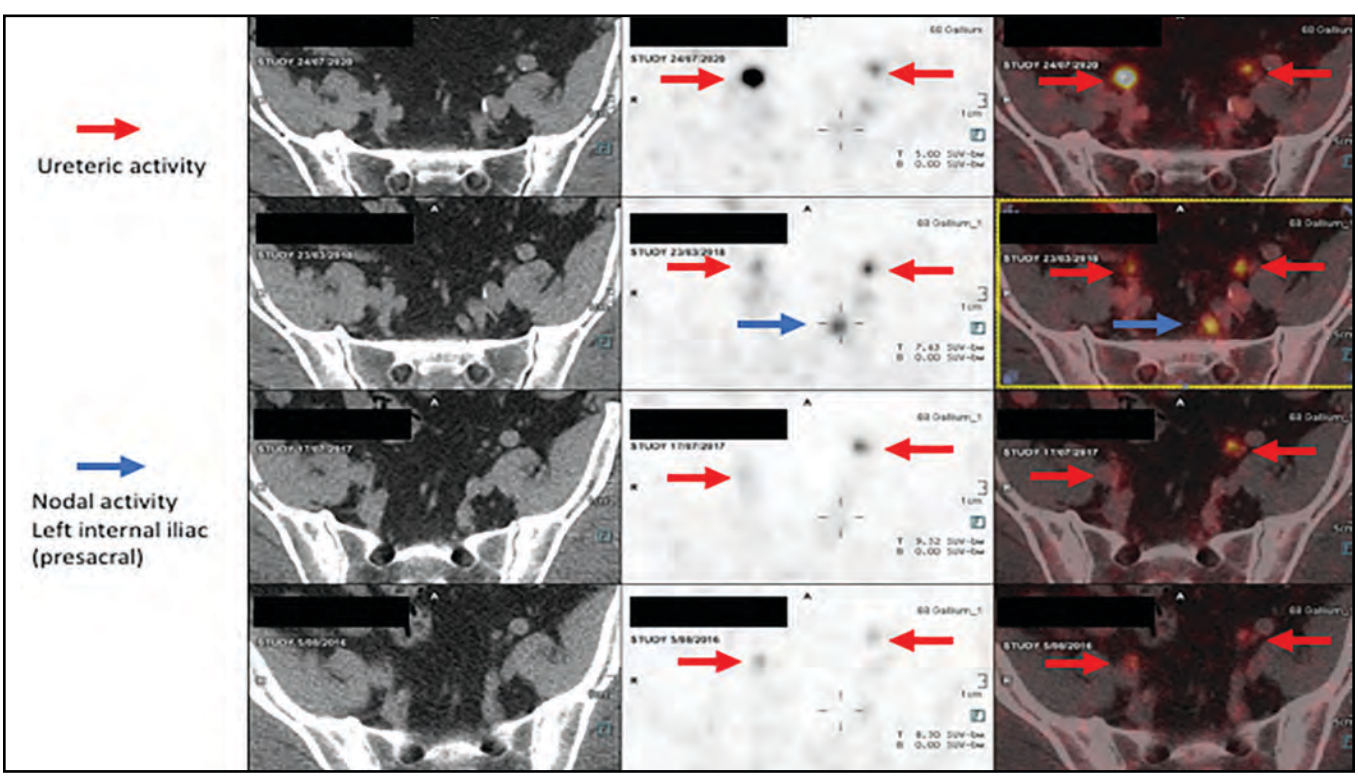

FIGURE 2 .*Physiological ureteral uptake (red arrows). PSMA avid left internal iliac lymph node (blue arrow).*

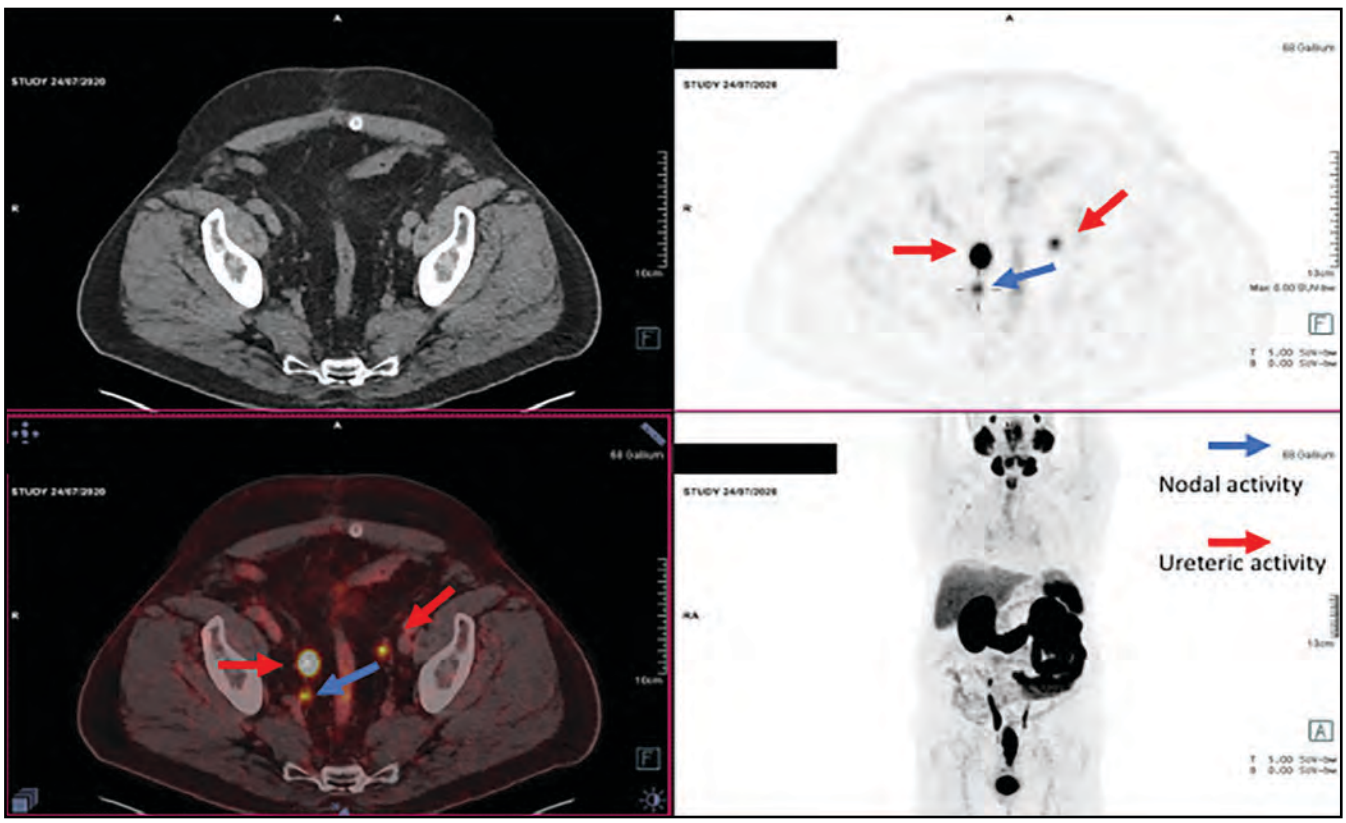

FIGURE 3. *Physiological ureteral uptake (red arrows). PSMA avid right internal iliac lymph node (blue arrow).*

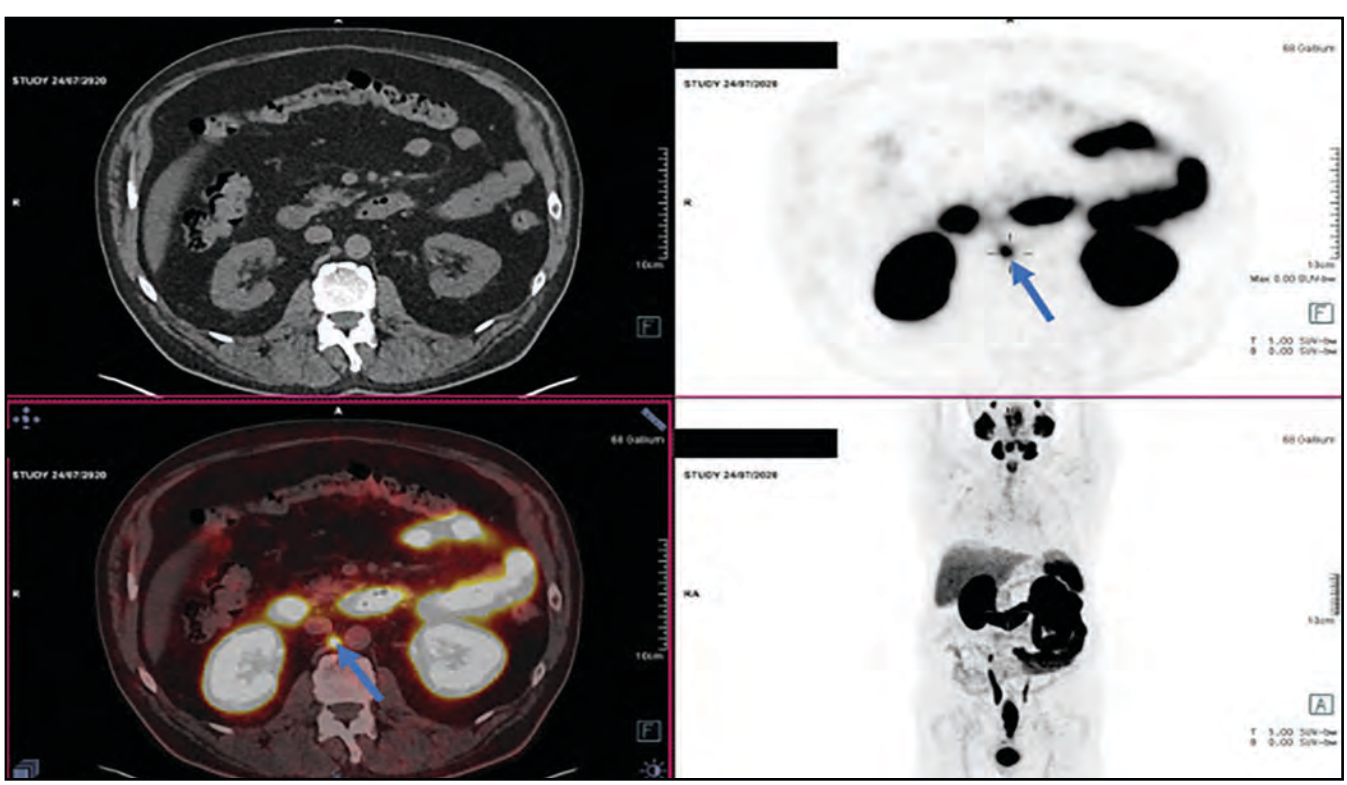

FIGURE 4. *PSMA avid right paraaortic lymph node (blue arrow).*

of PSA,[4] and the ability to identify the location of disease recurrence after radical prostatectomy in half of the patients with a PSA level between 0.5 and 1 ng/ml,[5,6] as demonstrated in this case study.

Additionally, ^{68}Ga PSMA-11 PET/CT is substantially more likely to detect metastases from prostate cancer than conventional imaging using CT and bone scan and using ^{68}Ga PSMA-11 PET/CT is more likely to change the course of treatment than conventional imaging.[7,8]

CONCLUSION

This case report confirms the value of ^{68}Ga PSMA-11 PET/CT in following patients with castration-resistant prostate cancer post-surgery and determining the most appropriate course of treatment when metastatic disease is detected.

Ureteric activity may be prominent. Physiologic increased activity may be seen in the kidneys, salivary glands and small bowel. The sensitivity of ^{68}Ga PSMA-11 PET increases with rising PSA levels, with a lower yield at PSA < 0.5 ng/ml and a higher yield at PSA > 2.0 ng/ml. Stereotactic radiotherapy may delay introduction of ADT, however, there is a survival advantage in treating oligometastatic disease.[9]

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Measured Distribution of Total Red Bone Marrow in Young Children

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Abstract

Background and Purpose: Pediatric radiation therapy survivors incur risk for radiation-induced hematological malignancies related to red bone marrow (RBM) dose. No measurement-based analysis has been performed to characterize RBM in children. As an exploratory pilot study, we aimed to measure RBM content in children's subvolumes through total-body MRI.

Materials and Methods: Ten pediatric total-body MRI sets were collected retrospectively, and anatomical subvolumes of RBM were delineated. The volumes of RBM in each subvolume and percentages of them in each bone region (%RBMs) were calculated as figures of merit. The %RBMs were compared to matched-age %RBM from a widely accepted mathematical model.

Results: Compared to our measured data, the model underestimated the %RBM in the cranium and mandible, as well as sternum and clavicles, and overestimated the %RBM in the upper extremities, ribs, and pelvis and vertebrae. Trends and rates of change in %RBM were consistent between our measurements and the model for these sites. We observed a gradual shift of %RBM toward the central skeleton with age.

Conclusions: The %RBM values measured in our study differed from those of the most accepted model for young children. This finding suggests that further study is warranted with a larger sample set that is more uniformly distributed in age and sex to assess the impact on clinical or research studies of the risk of subsequent hematological malignancies for survivors of childhood radiation therapy.

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Excess-radiation-induced hematological malignancies (eg, acute myeloid leukemia) have been observed in survivors of pediatric radiation therapy.[1-5] The risks of developing these malignancies are related to the absorbed dose deposited in the active red bone marrow (RBM).[6,7] The associated projected lifetime risks of children who receive radiation therapy may be roughly estimated based on dose-effect models and the RBM dose.[8] Because treatment-related radiation exposures are usually highly nonuniform throughout the body, it is important to know the accurate distribution of RBM within children's bodies to estimate RBM doses. In the pediatric population, physiologic conversion with age of RBM into yellow bone marrow (YBM) throughout the skeleton and along

Table 1. Characteristics of Selected Patients With Indexing by Age

Subject index	Age (months)	Sex
1	4	male
2	7	male
3	10	male
4	10	male
5	10	male
6	13	male
7	19	male
8	24	male
9	60	female
10	60	female

individual bones alters the RBM distribution and, consequently, the amount of RBM exposed to radiation.[9,10] Accurate estimation of the percentage RBM (%RBM) irradiated depends on how well the patients' actual RBM is delineated, such as by using manual or semi-automatic tissue contouring derived from computed tomography (CT) images and then extracting the mean absorbed dose in those volumes.[8]

Because of its enhanced contrast in soft tissues, MRI is a sensitive imaging modality for distinguishing RBM from YBM.[11] In general, RBM is composed of approximately 40% fat, 40% water and 20% protein, and YBM is composed of approximately 80% fat, 15% water and 5% protein. T1-weighted MRI image contrast is mostly influenced by the fat composition of the tissue.[12] For these reasons, unlike CT imaging that poorly differentiates soft tissues, T1-weighted MRI is a useful technique for detecting differences in bone marrow changes. In T1-weighted MRI, RBM appears as much less intense than YBM.[11]

Previous studies have implemented different techniques to estimate the whole-body distributions of RBM and YBM for humans of various ages. Quantitative distribution of marrow space in adults was reported by Mechanik et al.[13] In this report from 1926, the authors studied the weight of bone hematopoietic tissue plus fat in 13 carefully handled and dissected cadavers. Later, in 1961, Ellis[14] applied the correction factor of Custer and Ahlfeldt[15] to these data, which considered cellularity factor, and reported for each bone region the %RBM in adults. Also, in the 1960s, Atkinson[16] established an assumption-based model to estimate the bone marrow distribution in children. These findings, however, did not correlate to those of Hudson[17] who reported anatomical data for late-fetus and newborn infants. In what has become the gold standard for bone marrow distribution in humans, in the 1980s Cristy[18] developed a mathematical model that incorporated many of the previously mentioned anatomical and mathematical studies. Specifically, Cristy applied a mathematical interpolation of data from previous studies to estimate %RBM in different body regions among all age categories, including the pediatric age group. However, to our knowledge, only mathematical models have been used to estimate whole-body distributions of RBM for young children and adolescents, and no measurement-based study has been performed to date.

MRI-based studies[9,19] reported the changes in bone marrow volumes in portions of the body with respect to age. Ricci et al reported the pattern of change of bone marrow along the axial skeleton based on 420 site-specific examinations of the skull, cervical spine, thoracic spine, lumbar spine, pelvis and proximal femora of different patients of different age groups (6 months to 70 years). Patterns of changes in cellularity and bone marrow density with age at each site were reported, independent of sex.[9] A separate study by Simonson and Kao reported developmental patterns of bone marrow in the skull alone, using 324 examinations, with main findings showing the correlation between age and marrow intensity and patterns of marrow conversion in the skull and facial bones. They found no difference between sexes.[19] Neither study reported %RBM of each site with respect to the total-body RBM, as they lacked total-body imaging. On this basis, the literature lacked a measurement-based study that accurately characterized the distribution of RBM throughout the entire bodies of young children and adolescents.

The purpose of this study was to measure the distribution of RBM in bones of the pediatric age group based on T1-weighted total-body MRI (TB-MRI). Specifically, for an exploratory pilot set of 10 patients who had undergone TB-MRI in our institution, we delineated their entire skeletal RBM and calculated the %RBM in various regions of their bodies. We compared these measurement-based %RBM results for various-aged children with those of Cristy's model. The motivation for this study to improve our understanding of RBM distributions for children of various ages was greater certainty in absorbed dose in the RBM during childhood radiation therapy or other radiation exposures.

Methods and Materials

This study was performed under an approved protocol by our center's institutional review board. We set out to retrospectively collect all TB-MRI sets in our clinical database with the following selection criteria:

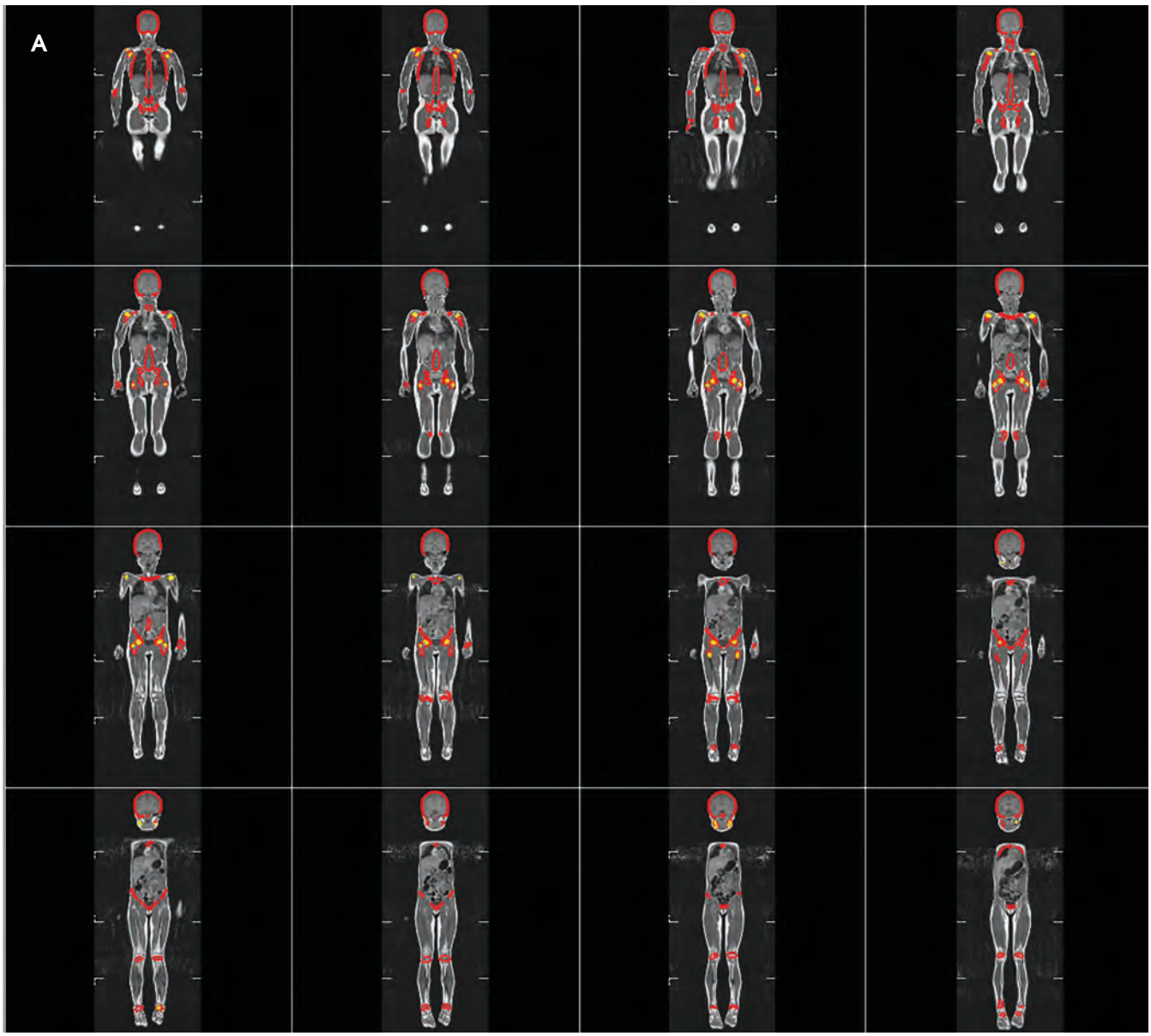
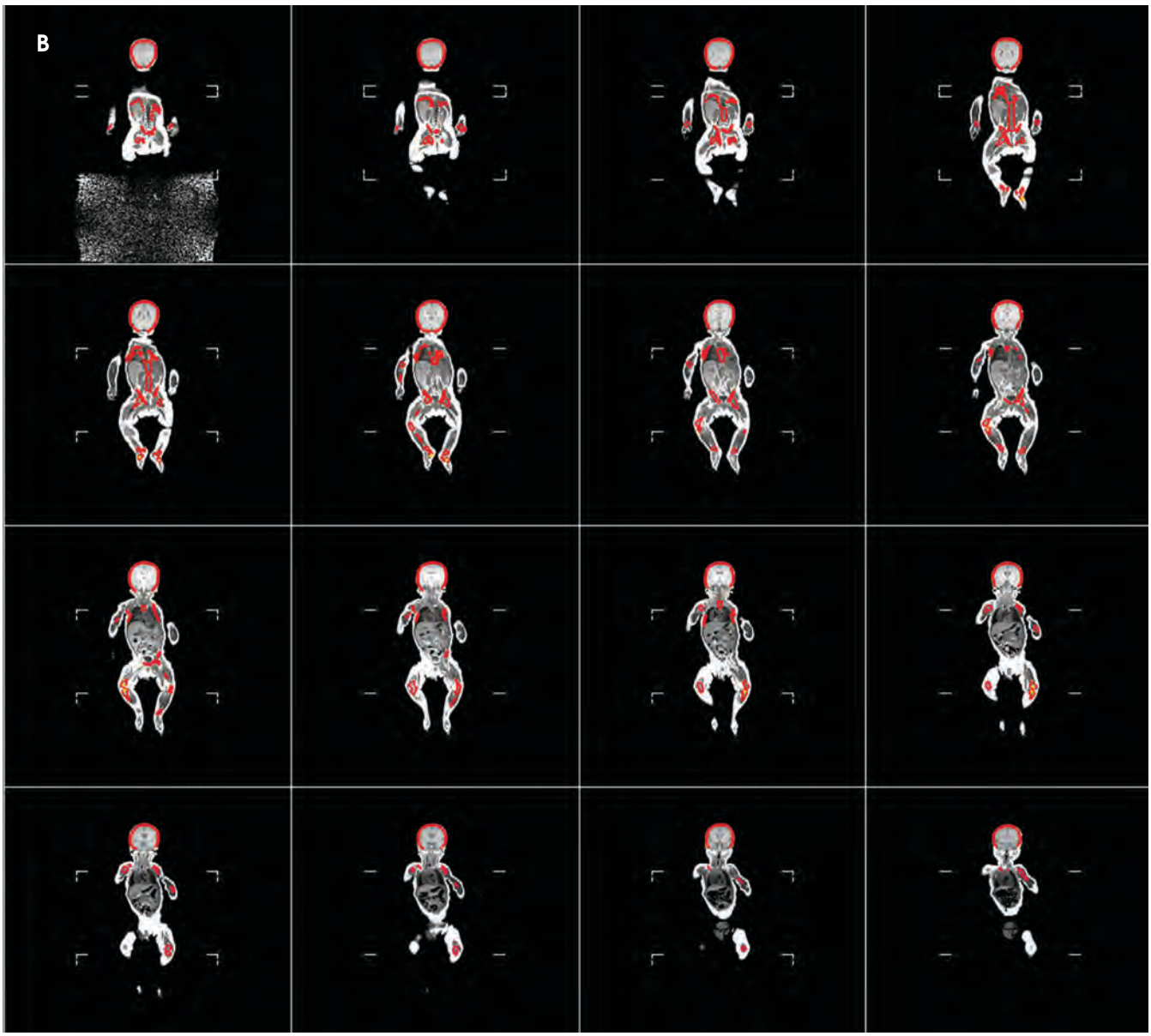


FIGURE 1. *Coronal views of the main portions of the T1-weighted total-body MRI (TB-MRI) sets showing red bone marrow (RBM) (red contours) and yellow bone marrow (YBM) (yellow contours) of a 5-year-old girl (A) and a 4-month-old boy (B).*

- Nine males and nine females of ages uniformly distributed from 1 month to 18 years at the time of MRI
- MRI dated January 1, 2005, to July 14, 2015
- Uniform distribution of ages of male or female
- Availability of high-resolution TB-MRI sets.

These initial targeted sample size and characteristics were chosen to obtain a set of subjects that spanned the full ranges of age and sex of young children and adolescents. Patients diagnosed with a disease affecting marrow content—including hematological malignancies, anemia, chronic infectious diseases, hemoglobinopathy, red marrow hyperplasia, obesity-related respiratory disorders, diabetes, or benign tumors with bone or marrow involvement—were excluded from the study. In addition, subjects were excluded if they were known to have received any form of bone-marrow-affecting treatment (such as chemotherapy, immunotherapy, steroids, hematopoietic growth factors, or radiation therapy) within 6 months prior to TB-MRI. Patients with multiple, repetitive follow-up MRI were considered as separate subjects if they satisfied the inclusion and exclusion criteria. The result of data collection was 10 patients, listed in **Table 1** (see section 3). A senior pediatric hematologist and oncologist reviewed all the



patients' charts and verified those who met the inclusion and exclusion criteria. Finally, a senior board-certified pediatric radiologist reviewed the quality of the subjects' TB-MRI sets, and those of poor quality or lacking a full-body reconstructed imaging sequence were removed from the study.

We considered the coronal T1-weighted sequence as the most consistently obtained in our pediatric population. Subsequently, all coronal T1-weighted sequences of the study population were extracted from our clinical picture archiving and communication system (Impax, version 6.5 AGFA HealthCare) and saved as image objects in the Digital Imaging and Communications in Medicine (DICOM) format. The image sets were de-identified and electronically transferred to our clinically commissioned treatment planning system (TPS) (Panther, version 5.10, Prowess, Inc.) as primary images of new patients.

The RBM and YBM contouring was performed in the following manner for each patient: First, all RBM was identified and contours were drawn manually on each slice of the reconstructed MRI set. Second, the YBM found within these RBM contours was identified by fat-tissue-like high-signal intensity and then contoured on each slice. Third, to define the pure RBM volumes, a Boolean subtraction was performed automatically between the RBM and partial YBM volumes (**Figure 1**). Areas of intermediate-intensity bone marrow, which are functionally a mixture of RBM and YBM, were considered RBM because they produce

Table 2. Volume of RBM in cm^3 in Each Anatomic Location of All Subjects

Subject index	Lower extremities	Pelvis	Vertebrae	Ribs	Clavicle	Sternum	Scapula	Upper extremities	Head & neck	Whole body
1	74.2	25.5	31.6	30.0	1.9	4.8	7.6	23.2	126.7	325.5
2	47.3	23.5	36.2	19.0	1.7	1.9	5.3	15.9	97.7	248.5
3	47.0	15.3	28.5	17.7	0.8	2.8	8.9	13.3	65.1	199.4
4	129.7	72.9	94.5	43.8	2.7	2.9	5.5	47.0	242.3	641.3
5	169.2	75.6	109.7	131.2	6.0	10.0	11.5	71.7	249.2	834.1
6	43.9	20.0	27.0	9.5	0.9	1.3	3.8	10.2	73.9	190.5
7	135.4	43.0	83.8	33.5	4.0	7.0	13.7	41.8	149.2	511.4
8	119.4	40.2	65.4	34.2	2.9	11.4	7.0	45.7	127.3	453.5
9	70.8	87.3	89.5	38.8	4.4	13.8	23.9	20.8	153.3	502.6
10	180.3	127.4	172.5	52.8	6.2	18.7	27.7	50.8	195.1	831.5
Average	101.7	53.1	73.9	41.1	3.2	7.5	11.5	34.0	148.0	473.8
Standard deviation	51.6	36.5	46.3	34.2	2.0	5.8	8.1	20.2	64.3	239.6

Key: RBM = red bone marrow

Table 3. Percentage Volumes of RBM in Each Anatomic Location of Every Subject Based on High-Resolution T1-Weighted TB-MRI and Compared With Those for Interpolated Ages of Cristy's Mathematical Model[18]

	Cranium & mandible		Lower extremities		Upper extremities		Sternum & clavicle		Scapula		Ribs & vertebrae		Pelvis	
Subject index	Cristy	TB-MRI	Cristy	TB-MRI	Cristy	TB-MRI	Cristy	TB-MRI	Cristy	TB-MRI	Cristy	TB-MRI	Cristy	TB-MRI
1	28.8	39.0	22.9	22.8	10.2	7.1	1.1	2.1	2.7	2.3	9.1	9.2	25.3	17.6
2	28.3	39.5	22.4	19.1	9.8	6.4	1.3	1.5	2.7	2.1	9.0	7.7	26.7	24.2
3	27.8	32.6	21.8	23.6	9.4	6.7	1.5	1.8	2.7	4.5	9.0	8.9	28.1	22.0
4	27.8	38.1	21.8	20.4	9.4	7.4	1.5	0.9	2.7	0.9	9.0	6.9	28.1	26.3
5	27.8	29.9	21.8	20.3	9.4	8.6	1.5	1.9	2.7	1.4	9.0	15.7	28.1	22.2
6	27.3	38.8	21.5	23.0	9.1	5.4	1.6	1.2	2.7	2.0	8.9	5.0	29.2	24.7
7	26.0	29.2	21.9	26.5	8.9	8.2	1.7	2.2	2.7	2.7	8.9	6.6	30.1	24.8
8	25.0	28.1	22.2	26.3	8.7	10.1	1.9	3.2	2.7	1.5	8.9	7.5	30.9	23.3
9	17.5	30.5	24.6	14.1	7.5	4.1	2.6	3.6	2.7	4.8	8.8	7.7	36.5	35.2
10	17.5	23.5	24.6	21.7	7.5	6.1	2.6	3.0	2.7	3.3	8.8	6.4	36.5	36.1
Average	25.4	32.9	22.5	21.8	9.0	7.0	1.7	2.1	2.7	2.6	8.9	8.2	29.9	25.6
Standard deviation	4.3	5.6	1.2	3.6	0.9	1.7	0.5	0.9	0.0	1.3	0.1	2.9	3.8	5.8

Averages and standard deviations across all subjects were also calculated and listed.
Key: RBM = red bone marrow, TB-MRI = total-body MRI

blood cell products. Fourth, anatomical landmarks were used to segment between different body regions and create regional subvolumes of RBM. For the volumetric data, we categorized the regions as the lower extremities, pelvis, vertebrae, ribs, clavicle, sternum, scapula, upper extremities, and head and neck. For comparison with the previous mathematical model, these regions were re-categorized into head and neck, lower extremities, upper extremities, sternum and clavicle, scapula, ribs, and pelvis and vertebrae. These contours and final regional RBM were verified by the senior board-certified pediatric radiologist. Finally, volumes of regional RBM were calculated by the TPS, and

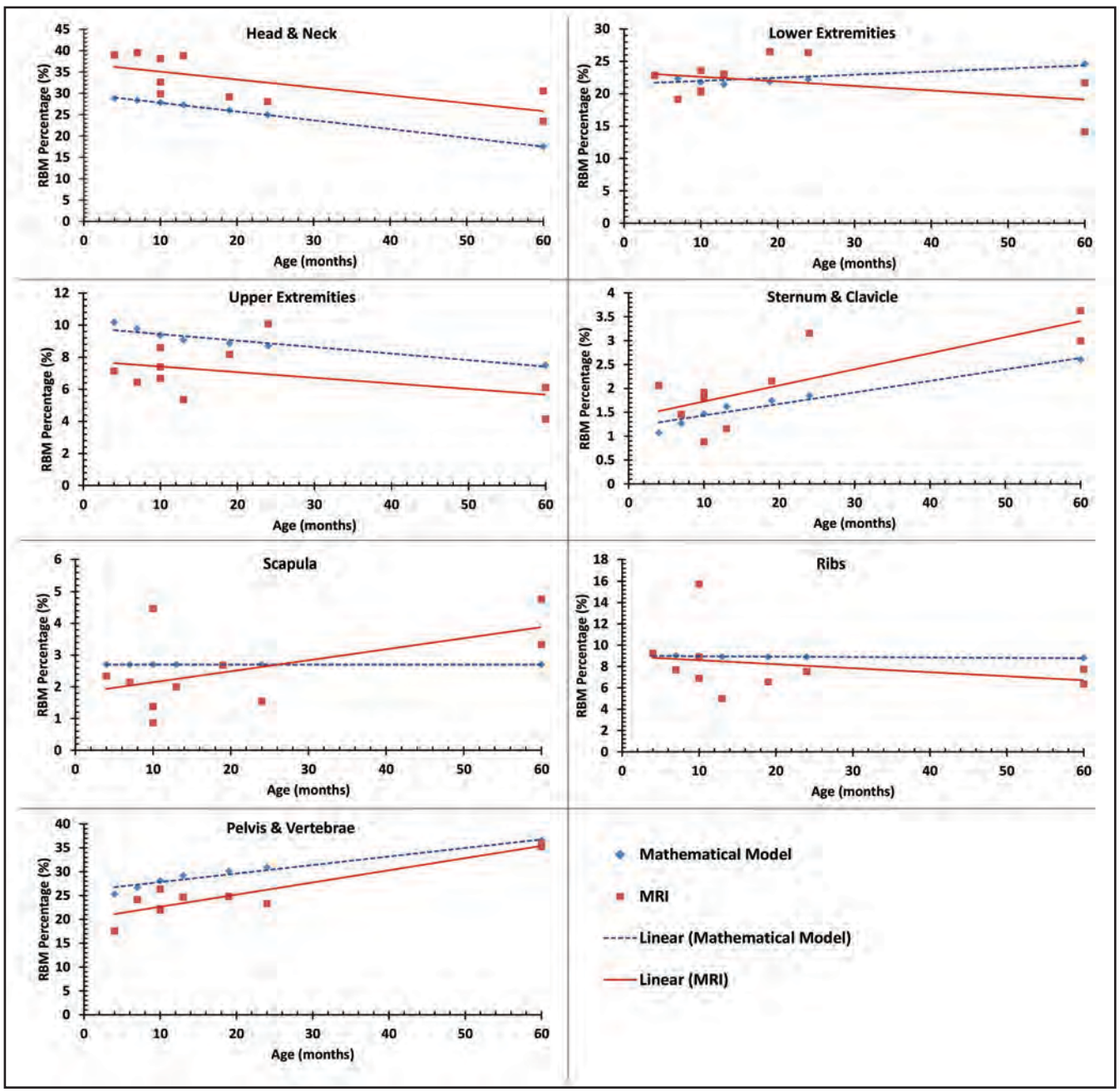


FIGURE 2. *MRI-based %RBM of our study (red squares) compared with mathematical-model-based %RBM of Cristy[18] (blue diamonds) for various anatomical regions. Linear trend lines are shown for the MRI-based data (red solid line) and the mathematical-model-based data (blue dashed line).*

%RBM in each body region was determined by dividing its volume by the volume of RBM in the whole body of each subject.

Results

After accounting for all inclusion and exclusion criteria, we identified 10 high-resolution TB-MRI sets in which bone marrow could be delineated throughout each subject's entire body. Upon review of all cases in our clinical database, we found it lacked the inventory necessary to produce a full cohort of pediatric patients consisting of equal numbers of both sexes and uniformly distributed from 1 to 18 years of age. The set of 10 subjects was nonuniformly distributed in age from 4 months to 60 months and in sex, with eight boys and two girls having high-resolution TB-MRI (**Table 1**). Therefore, this final cohort was re-categorized as a young pediatric age group, not as both children

and adolescents, and this became a pilot study for further exploration.

Volumes in anatomical regions for each subject are listed in **Table 2**. The head and neck RBM accounted for the largest amount of RBM among the designated regions. The RBM in the lower extremities roughly tripled that of the upper extremities. More RBM was found in the vertebrae than in the pelvis for every subject. We observed that active marrow gradually shifted from the periphery toward the central skeleton with increasing age in this young pediatric set of patients.

For an age-matched comparison, we interpolated linearly the mathematical-model-based %RBM values from Cristy's study[18] (**Table 3**) for the ages of the subjects in our MRI-based study. The mean values of %RBM average across ages of these young children were within approximately one standard deviation between the two studies, suggesting that the values of Cristy's model were roughly on track with measured data. Both the MRI- and mathematical-model-based data are plotted in **Figure 2** for each body region. Similar to the Cristy model, our measured %RBM rose with increasing age in the sternum and clavicle as well as pelvis and vertebrae regions, and fell with increasing age in the head and neck, and upper extremities regions. Our data contradicted the upward trend in the lower extremities and the flat %RBM in the scapulae vs age in the Cristy model. Our measurements were consistent with Cristy's flat model vs age for the ribs.

Discussion

In this pilot study of 10 subjects, we used T1-weighted MRI to estimate the volumes and %RBM in various regions of the bodies of young children. We observed a gradual shift and redistribution with age of RBM from appendicular to central skeleton. This natural trend was expected and coincides with the previously reported mathematical and imaging models. We found some differences in trends between the measured MRI-based data and the mathematical-model-based data in estimating the distribution of %RBM in different body parts in young children. Finally, our limited sample set agreed with others' previous findings that no differences exist in red bone marrow distribution between sexes.

Compared with previously published results of %RBM based on mathematical modeling, our measured data confirmed these estimations for some body regions but disagreed in other regions. In the lower extremities, ribs and scapulae, the modeled data agreed well with our measured data. However, compared with the children in our study, the mathematical model underestimated the %RBM in the head and neck, and sternum and clavicle regions and overestimated the %RBM in the upper extremities, and pelvis and vertebrae regions.

We also compared qualitatively the measured and modeled results in the relationship between %RBM and age. The %RBM values in lower extremities tended to be lower for children older than 5 years in the mathematical model, but our data suggest they may lower at a younger age. Moreover, the %RBM in the scapulae did show a trend toward increase at a later age (greater than 5 years) in the mathematical model, yet again we noted that trend in an earlier age group (less than 5 years). Therefore, our data suggest that changes in the percentages of RBM at the lower extremities and scapulae occur earlier than what has been previously estimated. Finally, our findings confirmed the %RBM at the pelvis and vertebrae in that age group compared with Cristy's model.

This was the first study, to our knowledge, to estimate the %RBM in various body regions of children using TB-MRI. With the availability of high-resolution MRI, we were able to delineate active RBM from inactive YBM. The ability to identify bone marrow and distinguish between RBM and YBM is especially important for pediatric cancer patients, many of whom undergo MRI for evaluation of their primary tumor, radiation therapy treatment planning, or follow-up assessments of treatment response. Moreover, in the current trend toward developing MRI-based radiation therapy treatment plans, RBM quantification and delineation by TB-MRI may become more readily available in clinical settings. This could improve targeting of treatment volumes and avoidance of organs and tissues at risk for acute and late radiation therapy side effects. High-resolution TB-MRI may aid understanding of radiation-induced secondary hematological malignancies[3,8] and improve training of dose-effect models of hematological toxicities and malignancies after childhood exposures.[7] Finally, using TB-MRI to delineate bone marrow structures and substructures could increase precision for targeted radiation therapy—for example, in stem cell sterilization—when fused with CT simulation images. This application introduces the possibility of less severe morbidities and reduced late mortalities than total-body irradiation while maintaining disease control. These potential advanced applications of MRI-based RBM and YBM delineation are particularly relevant considering the substantial improvements in MRI speed and progress of MRI-guided radiation therapy in mainstream cancer care.[21]

Because of the highly specific inclusion and exclusion criteria for patient selection and the limited data in our institution, our post-IRB-approval data collection resulted in a small sample size. The small and nonuniform distribution of our sample set with age and sex was an unpredictable limitation a priori. This retrospective study demonstrated the feasibility of performing forward research protocols with larger sample sets of pediatric patients using high-resolution MRI to further characterize the %RBM in various region of the body in young children and adolescents, for example by institutions with

large throughputs of pediatric patients and high-speed MRI. The findings and implications of our study warrant a larger, more representative sample set across both sexes and a broader range of ages. A second limitation and opportunity for improvement in future studies was that not all TB-MRI sets were collected under the same protocol. This resulted in inconsistent TB-MRI image quality between subjects. For this reason, we standardized our contouring on coronal views and T1 weighting, choosing consistency in protocol between patients over segregation of fine details of RBM in small bones, such as facial, ribs and small extremities. This tradeoff led to deficiencies in measuring %RBM in these bones. Finally, another study limitation was that the detailed pathology of the included list of patients was not reported, which could lead to an information bias potentially affecting the RBM distribution among this cohort. However, our initial exclusion criteria were strict in excluding all patients known to have pathologies that could affect RBM distribution.

In conclusion, our average %RBM values in young children measured using TB-MRI were consistent with those of a widely accepted mathematical model, but trends and rates of change vs age were not. We demonstrated the feasibility of high-resolution TB-MRI for measuring RBM distributions in children. Further studies are needed with larger and more uniformly distributed sample sets to establish more definitive results.

Acknowledgements

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FLASH Stance — Updates in Ultrahigh Dose Rate Radiation Therapy

Mary Beth Massat

FLASH radiation therapy (FLASH-RT), a technique that delivers an ultrahigh dose of radiation in 1 second or less, is being heralded as a promising treatment option that could potentially transform cancer care.

In the 1960s, early experiments found reduced damage and greater variability in noncancerous mammalian cells irradiated at very high dose rates compared with conventional dose rates.[1] Piquing more recent interest was the key factor that cancerous tissue does not observe the saturation effect with FLASH-RT.

"It was pretty evident from very early that this needed to be much more than just a technology foray," says Agam Sharda, vice president of FLASH Solutions at Varian, which is examining FLASH-RT as holistic therapy. "It could affect tissue in a different way than radiation typically does."

FLASH-RT produces a phenomenon called the FLASH effect, which provides tumor control and minimal toxicity to normal surrounding tissues. While underlying mechanisms behind the FLASH effect are not fully known, two primary hypotheses have emerged. One is that an immune response contributes to the FLASH effect.

"There are indications that delivering the dose so quickly has an effect on the immune system," says Kristoffer Petersson, PhD, medical research council investigator and group leader – FLASH Radiation, Department of Oncology, Medical Sciences Division, University of Oxford. "There has to be something else also contributing, since we still see a FLASH sparing effect in immunocompromised animals."

The second hypothesis centers on oxygen depletion in the cells, in which the ultrahigh doses produce a period of hypoxia that does not seem to change tumor radioresistance. However, in normal tissue it leads to large, rapid increases in tissue radioresistance, thereby protecting the normal tissue.[2]

"We've seen in vitro and in vivo that when you modify the oxygen content you get a modified effect," says Dr. Petersson, who is investigating the biology and underlying mechanisms behind the FLASH effect. "But we also have very recent studies now showing that we have an effect at low doses in normal conditions where you wouldn't expect oxygen depletion to play a role."

A recent study demonstrated in vitro that after a certain dose level, cells exposed to FLASH irradiation begin to behave in a hypoxic manner. In this study, there was a clear FLASH effect that relied on oxygen concentration.[3]

David Gladstone, ScD, DABMP, FAAPM, chief of clinical physics at Dartmouth-Hitchcock's Norris Cotton Cancer Center, is leading a group that has also studied oxygen depletion in mice under FLASH conditions.[4] "So far, we have not measured a change in oxygen sufficient to explain the clinical effects that are seen in terms of reduction of damage to the normal tissues," he says. "That's not to say that oxygen isn't involved, but it's not the entire story."

The Dartmouth group is also conducting a genetic analysis of irradiated tissues, comparing FLASH to conventional doses, looking for molecular markers that could shed light on what part of the process is changing.

Another area under exploration is how FLASH may work in tandem with other treatment modalities, such as immunotherapy and chemotherapy. According to Swati Girdhani, director of Research Collaborations at IBA, FLASH would enable faster and shorter treatments, reducing the volume of blood irradiated,

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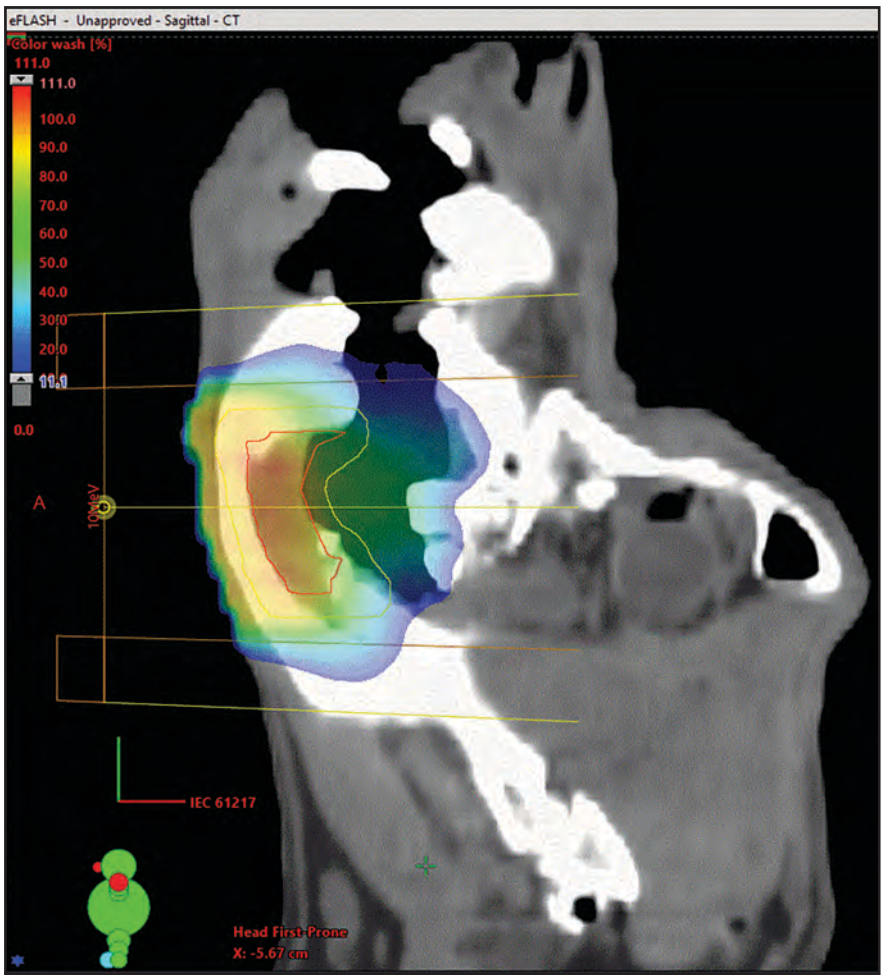

FIGURE 1. *Example of a canine treatment plan using FLASH-RT.*

and lower subsequent reduced killing of circulating immune cells, including lymphocytes, the main mediator of immune response to cancers.[5]

FLASH-RT may also expand the reach and indications for RT treatment, says Girdhani. "With FLASH therapy, if we can reduce normal tissue toxicity, it opens the potential to perform dose escalation on radioresistant tumors like glioblastomas and radiation treatment of tumors surrounded by radiosensitive tissue like ovarian cancers."

There is also a radical-radical interaction that has an effect, says Dr. Petersson. "When you irradiate, you generate radicals that can damage DNA. With FLASH, you put in so much dose at one time that the concentration of the radicals formed is greater, with a much higher probability of these to interact with each other before they damage DNA. So that could be one explanation: that these radicals that are created when the radiation interacts in and around the cell result in a concentration that is so high that the effect on DNA may be lower than when using lower dose rates."

Dr. Petersson found that current radiation dose detectors for beam monitoring decrease in efficiency down to just a few percent.

"When you go to an ultrahigh dose rate that lasts a few microseconds, it is much more challenging to get a good measurement of the dose that you are delivering and also to control the delivery," Dr. Petersson explains. "In my opinion, FLASH will be introduced in the clinic as a hypofractionated treatment, possibly at even larger volumes than we normally do now."

First Human Clinical Trial and Treatment

In November 2020, the Cincinnati Children's/UC Health Proton Therapy Center began the first clinical trial and human treatment using FLASH-RT. The Feasibility Study of FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases (FAST-01) is sponsored by Varian and will include up to 10 patients ages 18 years or older who have up to three painful bone metastases in the extremities.

The Proton Therapy Center houses a $24 million research facility with a 300-ton gantry that mirrors the dosimetry and operation of the clinical gantry. Having combined clinical and research centers under one roof allows for simulated treatments in the animal models to translate right to patients, says John Perentesis, MD, director of the Division of Oncology and Cancer Programs at Cincinnati Children's.

"With FLASH, we were able to do in vitro studies on what happens in the test tube on cancer cells and then, even more importantly, take it to the next dimension in terms of side effects in animals and then in animals with cancer," he says. "That pre-clinical data supported the hypothesis that FLASH radiation of the extremities … was less toxic."

Study participants will only include patients with arm or leg bone metastases so if adverse side effects arise, critical organs or structures will not be affected. "We are looking at whether or not we can use FLASH to deliver radiation and have fewer side effects in patients," says John C. Breneman, MD, medical director of the Proton Therapy Center on the Liberty Campus of Cincinnati Children's. "With FLASH therapy, the preclinical data in the animal studies show that you can have efficacy

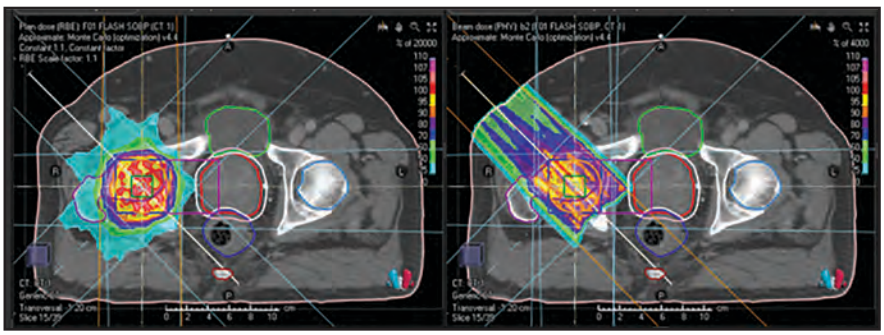

FIGURE 2. *Example of conformal FLASH, which uses FLASH dose rates as well as the Bragg peak. Image courtesy IBA*

in treating tumors but with fewer side effects."

Future investigations at the Proton Therapy Center include pre-clinical studies comparing FLASH-RT with proton therapy in thorax and lung cancer in terms of induction of pulmonary fibrosis and in efficacy of tumor death, Dr. Perentesis says. There is also interest in chest/thoracic and brain cancers, particularly comparing efficacy with tissue toxicity.

Modifying the Accelerator

Clinical linear accelerators can be modified to deliver FLASH-RT, and throughout much of his career, Dr. Gladstone has conducted experiments on modified linear accelerators. Examples include adding one of the first electronic portal imaging devices on a linac prior to commercial development[6] and gating an accelerator to the cardiac cycle, demonstrating a mechanism to spare the heart from radiation damage.[7]

To create a high-intensity beam from a clinical linear accelerator, Dr. Gladstone worked with a team of medical physicists and biomedical engineers at Dartmouth College and Dartmouth-Hitchcock Medical Center. They programmed an older accelerator that had limited clinical use to deliver a pristine electron beam by pulling the x-ray target out of the beam's path to achieve the desired dose rate. To perform these experiments, the team developed a new optical technique to measure the dose rate and dose distribution that would enable acquisition of a three-dimensional dosimetry using a single pulse of radiation from the linac.[8]

Dr. Gladstone and his colleagues then tackled beam control, achieving approximately 1 Gy of dose per pulse. "We have control over the machine by counting pulses," he explains. "We want to integrate the dose per pulse as they come through — like any normal accelerator using an ionization chamber — to increase the precision of dose delivery to fractional pulse levels."

Using a FLASH beam, three animals from the community have been treated at Dartmouth-Hitchcock on the modified linac under an NCI-funded spontaneous animal tumor grant.

"We have been able to safely use uncharacteristically high RT doses in our spontaneous canine cancer FLASH patients," Dr. Gladstone says. "Although the total dose has been spread temporally over a longer period than typically used in clinical medicine, the dose is approximately 30% higher than what we would generally believe acceptable."

While two of the canine tumors treated with FLASH were oral melanoma and soft-tissue sarcoma, which are historically incurable with conventional surgery and radiation, both dogs remain in full health remission 9 and 12 months post RT, he adds. While superficial skin and mucosa damage was noted, healing is progressing well without additional support. In the oral melanoma case, the dog has thrived. (**Figure 1** shows a canine treatment plan using FLASH-RT.)

"It's really going to be fascinating work in the years ahead to try to bring this to humans to increase the therapeutic ratio and get better outcomes both in terms of tumor control and reducing normal tissue toxicities," he adds.

The Technology Behind FLASH-RT

Three proton therapy manufacturers are developing FLASH-RT. At Mevion Medical Systems, the FLASH delivery capability is being pursued with the company's pencil-beam scanning system. The architecture with a downstream range shifter keeps high dose rates at all energies for different delivery depths, explains Townsend Zwart, vice president of Advanced Development at Mevion. The company's proton multileaf collimator with an adaptive aperture can sculpt sharp edges that may be useful for constructing large volumes.

The expectation is that components will be added to existing proton therapy systems to enable FLASH-RT — from dosimetry to accurately measure the short, intense pulses of radiation, to patient positioning equipment. Zwart believes positioning and the errors allowed in treatment planning will need to improve across the field to allow for clinical use of FLASH-RT.

FLASH delivery will also make motion management much more attractable, says Zwart. "People don't move much inside a quarter of a second," he says. "It will make setup and image guidance before delivery that much more critical."

Plus, with the expectation that FLASH may lead to more hypofractionated treatments, Zwart sees an opportunity to increase the utilization of proton therapy systems to treat more patients and provide greater access to proton therapy.

Regarding standard dose rate for FLASH-RT, while 40 Gy per second seems common in current studies, Zwart says Mevion is preparing to hit higher dose rate levels if research shows higher is better.

At Varian, the company is looking at FLASH holistically, focusing on the role of technology throughout the entire patient experience.

"FLASH is a very promising therapy that, if it comes to pass, will benefit a lot of patients," says Agam Sharda, vice president of FLASH Solutions at Varian. "But these current machines were not really validated to do this. So Varian is being extra cautious to make sure we develop the tools, mechanisms and technologies that will maximize safety for all involved."

Although Varian provides various radiation therapy technologies potentially adaptable for FLASH—proton, photon, electron and brachytherapy—Sharda believes protons offer the greatest initial potential.

"We are convinced that the fastest, most effective and efficient way of giving FLASH to deep-seated tumors is via proton therapy," says Sharda. "Electrons are better suited for superficial targets, so there is fantastic complementarity between electron FLASH and proton FLASH."

To enable FLASH proton RT required an almost complete redesign of the control system of the beam delivery mechanism to count the rapid rate of protons, he says.

However, Sharda sees photon FLASH requiring greater engineering investments and innovation, positioning it behind proton and electron FLASH development.

Varian is also looking at electron FLASH in the same way it has pursued proton FLASH over the last four years. In the near future, Varian will provide electron FLASH research capabilities to interested linac customers.

In treatment planning, the key parameter is the dose rate being delivered. As such, in addition to looking at the spatial distribution of the dose rate, treatment planning for FLASH-RT must also consider the temporal distribution of dose. "We have to start thinking about a patient's treatment plan as a dose-rate-volume histogram in addition to dose-volume histogram," Sharda says.

At IBA, the company is pursuing conformal FLASH, which uses FLASH dose rates as well as the Bragg peak, says Nicolas Denef, emerging therapies director at IBA. By combining a single layer of pencil-beam scanning irradiation with a field-specific filter, the technology may enable FLASH irradiations that also stay conformal to the target, thereby combining FLASH and the superior dose conformality of proton beams. (See example in **Figure 2**.)

However, more work remains before initiating clinical trials that use the Bragg peak of protons in FLASH-RT. In terms of existing IBA accelerators, any future FLASH capability will likely be provided as an upgrade. While the primary focus is on proton therapy, IBA's subsidiary Normandy Hadrontherapy is building a carbon therapy system that may have the capability to provide FLASH.

Proceeding With Caution

As progress continues, avoiding haste and unnecessary risks is essential. With FLASH, clinicians are not afforded the same time they have with conventional RT to react and adjust to issues that arise during treatment.

"We want to make sure that with FLASH we have the same level of quality assurance that we have with 30 treatments as with one treatment that will take a fraction of a second," says Denef. "We also need to have high precision electronics that ensure FLASH is safely delivered."

While RT has focused on improving the physics of beam delivery for years, FLASH is part of a trend of better understanding and optimizing the biology of ionized particles, Denef says.

"The biology studies currently being carried out may help us understand the molecular pathways generated by FLASH radiation, and potentially lead to new treatments in the future," he says.

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RADIATION ONCOLOGY CASE

Craniospinal Irradiation for Leptomeningeal Disease in Recurrent Breast Cancer

Jaime K. Kwok, MD; Megan Yaraskavitch, MD, MSc; Jan-Willem Henning, MBChB; Darren Graham, MRT(T), CMD; Natalie Logie, MD

CASE SUMMARY

We present a case of leptomeningeal disease (LMD) as the first recurrence of breast cancer in a 40-year-old woman with BRCA2 germline mutation. Initially diagnosed in 2017 with left-sided cT2N1 ER-positive, PR-negative, HER-2-negative invasive mammary carcinoma, she received neoadjuvant FEC-D chemotherapy and bilateral mastectomy with immediate reconstruction with near complete pathologic response (ypT1bN0). She then received adjuvant chest wall and regional nodal irradiation, followed by tamoxifen.

She remained in remission for 22 months before developing progressive headaches, neck cramps, bilateral extremity paresthesias, myalgias, arthralgias and memory impairment. In the absence of focal neurologic deficit, tamoxifen was discontinued in October 2019. Re-staging computed tomography (CT) scans and a bone scan showed no evidence of recurrent disease.

She presented a month later with severe headache, nausea, vomiting, pulsatile tinnitus and visual blurring. Neurological examination identified bilateral sensory loss in the C8 distribution and marked papilledema. Enhanced MRI of the brain and cervical spine showed no evidence of LMD. Lumbar puncture revealed elevated opening pressure, high cerebrospinal fluid (CSF) protein and mild pleocytosis. High-volume (10 cc) CSF cytologic analysis confirmed metastatic breast cancer. Dexamethasone 8 mg twice daily was initiated with symptomatic improvement but with side effects including increased appetite, insomnia and agitation.

Her case was reviewed at multidisciplinary tumor board rounds and craniospinal irradiation (CSI) was recommended. Karnofsky performance status (KPS) was 80%. CSI using 3600 cGy in 20 fractions was delivered by volumetric-modulated arc therapy (VMAT) technique, completed in January 2020 and tolerated well (**Figure 1**). Three 360-degree arcs with separate isocenters and x coordinates aligning to the lateral midpoint of the full spinal column were planned using 6 MV photons. Linearly ramping junctions were designed as developed according to previously published institutional protocols.[1] As per institutional image-guided radiation

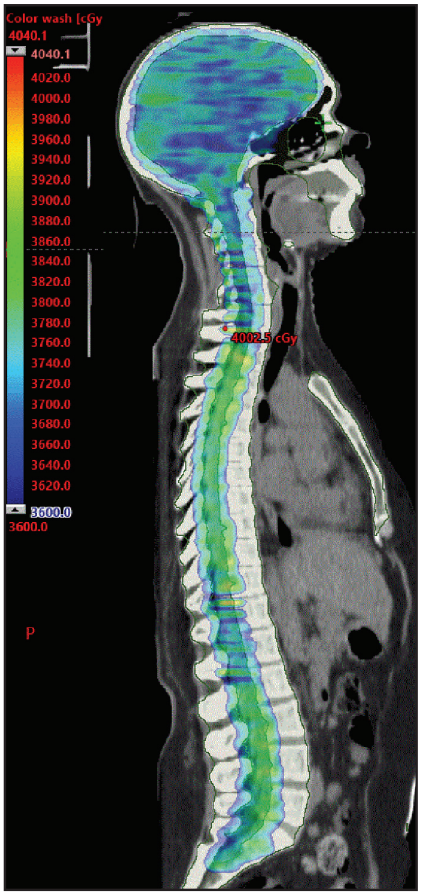

FIGURE 1. *Craniospinal irradiation using the volumetric-modulated arc therapy (VMAT) technique.*

Dr. Kwok is a radiation oncology chief resident, Dr. Henning is a medical oncologist, Mr. Graham is a senior dosimetrist and radiation therapist, and Dr. Logie is a radiation oncologist, all at the Tom Baker Cancer Centre, Alberta Health Services, Cancer Care Alberta, Canada. Dr. Yaraskavitch is a general neurologist, Clinical Neurosciences, University of Calgary, Alberta, Canada. Dr. Yaraskavitch, Dr. Henning and Dr. Logie are also clinical assistant professors at the Cumming School of Medicine, University of Calgary. *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.*

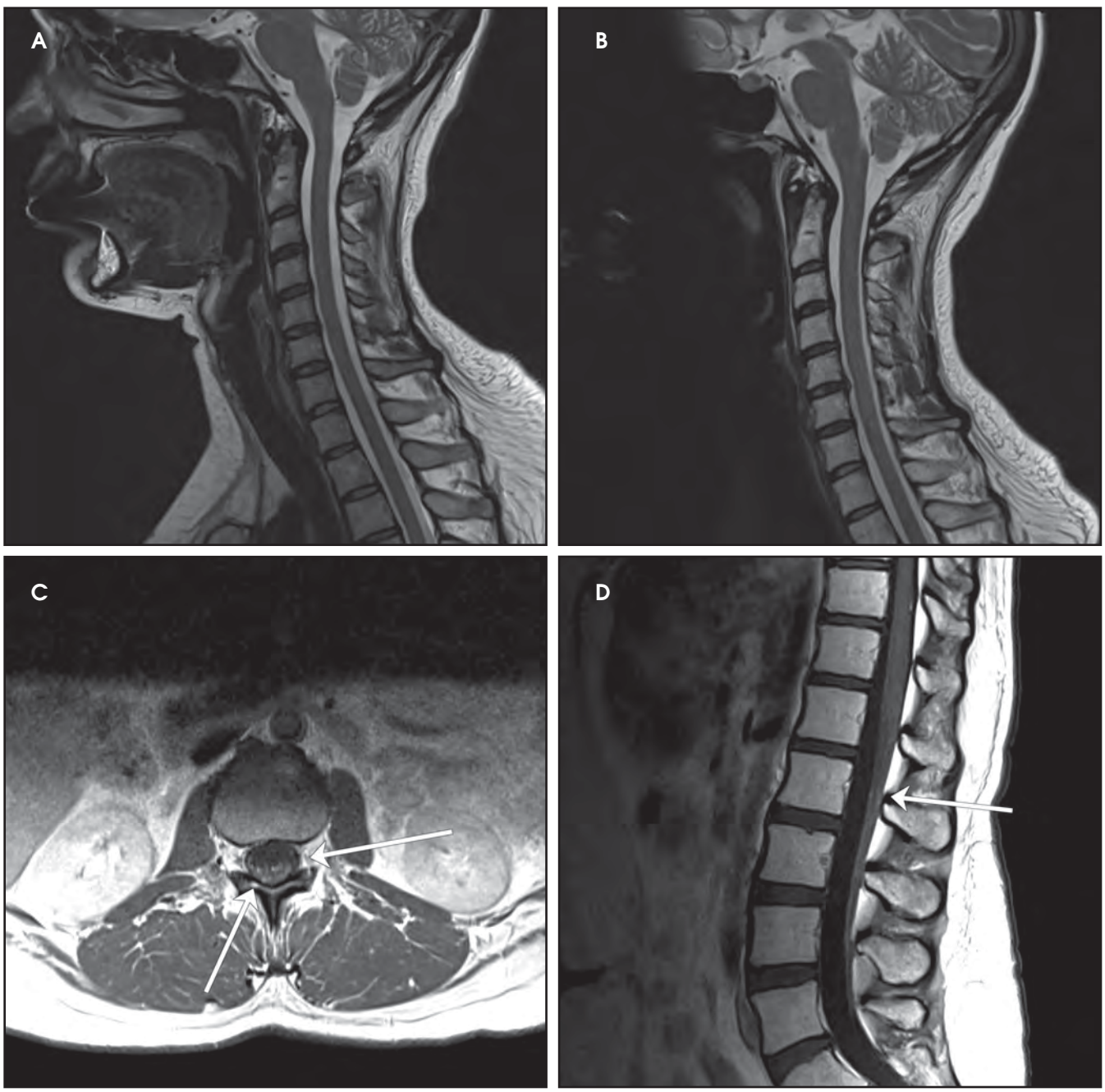

FIGURE 2. *Sagittal views of T2-weighted MRI of cervical spine pre- (A) and post-radiation therapy (B). Axial (C) and sagittal (D) views of T1-weighted post-gadolinium MRI of lumbar spine post-radiation therapy.*

therapy guidelines, we used kV imaging for patient straightening and cone-beam CT imaging for each isocenter matched to anatomical setup prior to treatment. A 6-degrees-of-freedom couch was used. Re-imaging tolerances were 2 mm for translation and 1.5 degrees for rotation.[2] The dose variance for set-up errors was expected to be less as shifts were always applied. The match was adjusted preferentially to optimize the overlap region, followed by ensuring complete planning target volume coverage of the entire brain and spine. The effects of allowable dose variance are not modelled prior to treatment on patient-specific plans at our institution. Her course was interrupted after fraction nine by a hospital admission for a right-hand burn and she was subsequently diagnosed with mania requiring

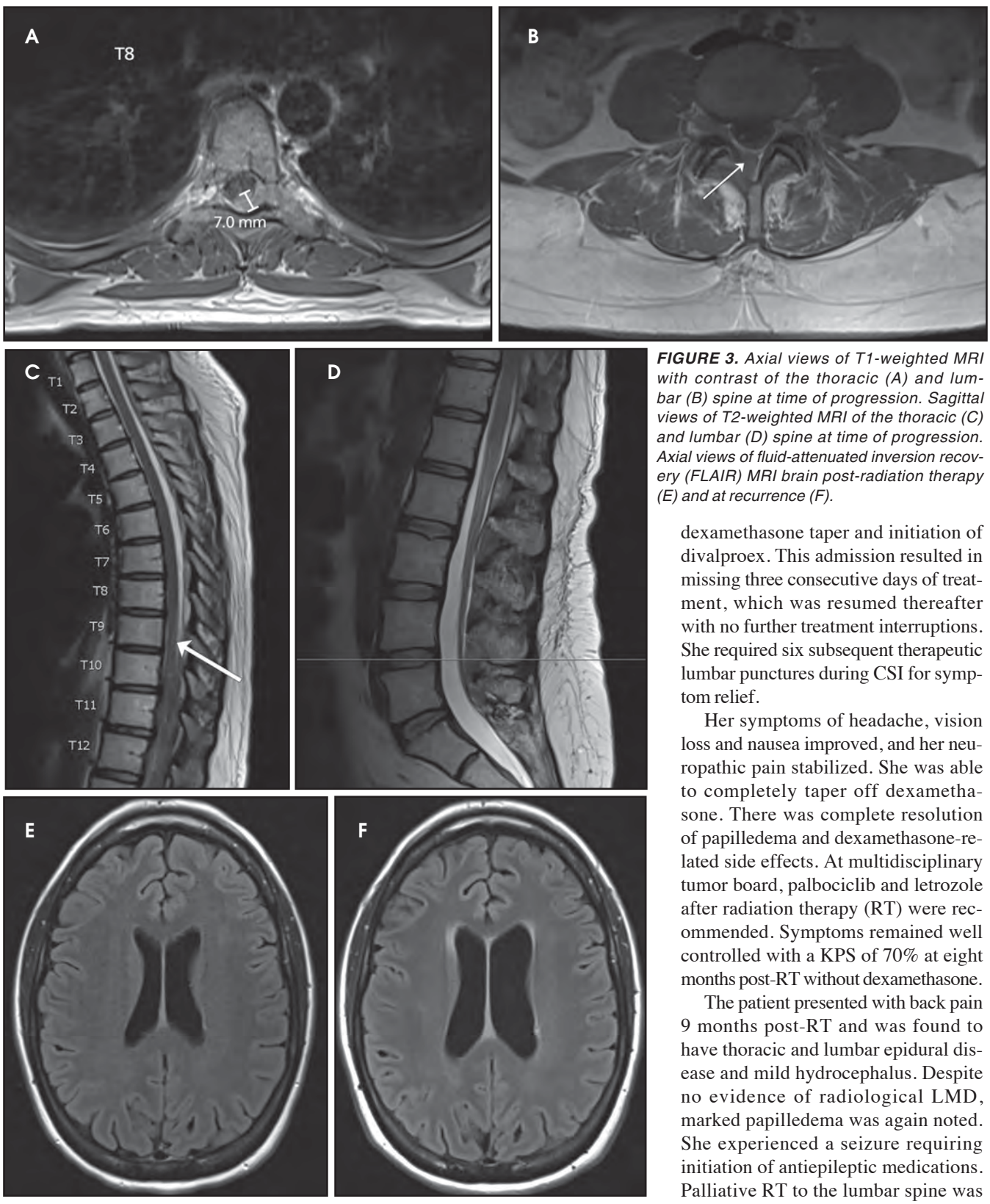

FIGURE 3. *Axial views of T1-weighted MRI with contrast of the thoracic (A) and lumbar (B) spine at time of progression. Sagittal views of T2-weighted MRI of the thoracic (C) and lumbar (D) spine at time of progression. Axial views of fluid-attenuated inversion recovery (FLAIR) MRI brain post-radiation therapy (E) and at recurrence (F).*

dexamethasone taper and initiation of divalproex. This admission resulted in missing three consecutive days of treatment, which was resumed thereafter with no further treatment interruptions. She required six subsequent therapeutic lumbar punctures during CSI for symptom relief.

Her symptoms of headache, vision loss and nausea improved, and her neuropathic pain stabilized. She was able to completely taper off dexamethasone. There was complete resolution of papilledema and dexamethasone-related side effects. At multidisciplinary tumor board, palbociclib and letrozole after radiation therapy (RT) were recommended. Symptoms remained well controlled with a KPS of 70% at eight months post-RT without dexamethasone.

The patient presented with back pain 9 months post-RT and was found to have thoracic and lumbar epidural disease and mild hydrocephalus. Despite no evidence of radiological LMD, marked papilledema was again noted. She experienced a seizure requiring initiation of antiepileptic medications. Palliative RT to the lumbar spine was

delivered with 2000 cGy in 8 fractions. Unfortunately, she continued to progress and a lumbar drain trial was unsuccessful for managing symptoms of increased intracranial pressure (ICP). Malignant cells were confirmed in CSF. She died 10 months post-RT, approximately one year after diagnosis of LMD.

IMAGING FINDINGS

Pre-RT MRI of the brain and cervical spine showed no evidence of LMD or intracranial abnormality (**Figure 2**). A CT head venogram failed to demonstrate evidence of venous thrombosis. A re-staging bone scan and CT scans of the head, chest, abdomen and pelvis showed no evidence of recurrent or metastatic disease. Post-RT MRI spine images showed suspicious mild nodular enhancement of the cauda equina at the level of L2 and L3 suggestive for LMD (**Figure 2**). There was no evidence of intracranial LMD or disease elsewhere in the spine. At the time of disease progression, MRI spine showed diffuse thoracic and lumbar epidural enhancement with extension into the neural foramina and mild spinal canal stenosis from T6 to T10 (**Figure 3**). Mild progressive ventriculomegaly was also noted. There was no evidence of leptomeningeal enhancement.

DIAGNOSIS

LMD secondary to recurrent breast cancer

DISCUSSION

LMD occurs in up to 5% of breast cancer cases and portends a poor prognosis.[3] Higher incidence rates and median survival in recent years may reflect improved detection on imaging and advances in systemic treatment options. LMD is defined as tumor cell infiltration of the pia mater, arachnoid, and subarachnoid space, which line the spine and brain. Common symptoms include headache, nausea, emesis, gait instability, cranial nerve deficits, seizures, motor and sensory impairment, and altered mental status. These symptoms result from increased ICP due to impaired CSF resorption or disease infiltration of local structures. MRI usage has now led to asymptomatic diagnoses of LMD.

LMD diagnosis often requires a combination of CSF cytologic analysis, imaging and neurological assessment. T1-weighted MRI with gadolinium is superior to CT for detecting LMD, although the sensitivity is only approximately 70%.[4,5] MRI should be done prior to lumbar puncture and ventricular shunt placement where possible to prevent false positives from procedure-related meningeal contrast enhancement. Cytologic analysis is the gold standard for LMD diagnosis and is highly specific but poorly sensitive. High-volume CSF samples (>10 cc), immediate processing with avoidance of refrigeration, and CSF collection from a site known to have LMD can reduce false negative results. Repeat sampling of three high-volume CSF samples can increase cytology sensitivity up to 90%.[4,5] Other abnormal CSF findings may include elevated opening pressure, elevated leukocyte count, elevated protein, and decreased glucose.[4] Diagnostic algorithms recommend obtaining both cerebrospinal MRI and lumbar puncture.[4,6]

This case highlights the diagnostic challenges of LMD. Despite presenting with signs and symptoms of increased ICP and irritation of the C8 nerve roots, no metastatic disease was visualized on gadolinium-enhanced MRI of the brain and cervical spine. We note that a full spine MRI was not included as part of the initial workup and it is unknown whether the lumbar spine disease seen on baseline pre-chemotherapy imaging was present prior to CSI. We recommend obtaining an MRI of the entire neuroaxis if LMD is suspected. In cases where no disease is visualized on MRI despite signs and symptoms suggestive of LMD, a high-volume lumbar puncture for cytologic analysis is also recommended. If there is a high degree of clinical suspicion for LMD, a total of three high-volume lumbar punctures may be pursued.[4,5]

Management options for LMD consist of a combination of systemic therapy, intrathecal chemotherapy, radiation therapy and best supportive care. Radiation therapy is indicated for symptomatic obstructive or bulky disease and may enhance intrathecal therapy delivery.[7] Localized radiation approaches include whole-brain radiation therapy, involved-field radiation therapy and stereotactic radiation therapy. Several guidelines caution against CSI due to toxicity, namely myelosuppression.[3,6] We would expect major toxicities to be limited by modern CSI delivery techniques including the use of VMAT, helical tomotherapy and proton therapy due to better dose conformity. For our VMAT CSI radiation therapy plan, mean bone marrow dose delivered was 1530 cGy and bone marrow V20 was 36%.

Historically, CSI has been a technically challenging approach and modern CSI delivery techniques attempt to address several of these technical considerations. Multiple field junctions pose dosimetric challenges for which shifts were conventionally used. Setup inaccuracies could result in either increased toxicity or reduced tumor control. In VMAT CSI, auto-feathering of field junctions aims to optimize multiple isocenter placement to lengthen the dose gradient, thereby improving dose homogeneity to the planned target volume and robustness to field setup error.[8] Helical tomotherapy has the advantage of delivering a homogeneous dose over an extended vertical field without requiring field junctions, thus avoiding the associated challenges. Proton CSI results in less toxicity owing to more favorable dosimetry with dramatic dose sparing of anterior structures, and has been demonstrated to reduce gastrointestinal and hematologic toxicities.[9] Vertebral

Table 1. Case Series of Craniospinal Irradiation for Leptomeningeal Disease in Breast Cancer

Study	Breast cancer primary	LMD diagnostic method	Radiation therapy technique	Median total dose	Breast cancer median OS from LMD diagnosis (months)	Symptom control
El Shafie, et al[13] (n = 25)	n = 15	MRI + CSF (n = 20) MRI only (n = 5)	Helical tomotherapy	3520 cGy (range: 1440-3600 cGy)	4.4	40% stabilized and 28% improved neurological symptoms
Hermann, et al[14] (n = 16)	n = 9	MRI + CSF (n = 9) MRI only (n = 1) CSF only (n = 6)	2D	3600 cGy	4.0	69% improved, 19% progressed and 12% stable neurological symptoms
Schiopu, et al[15] (n = 15)	n = 6	CSF + MRI (n = 13) MRI only (n = 2)	Helical tomotherapy	3240 cGy (range: 1800-3960 cGy)	6.0	53% resolved or improved neurological symptoms Breast cancer-specific: 67% resolved or improved neurological symptoms
Devecka, et al[16] (n = 19)	n = 5	MRI (n = 18) CSF only (n = 1)	2D before 2007 (n = 3); helical tomotherapy thereafter (n = 16)	3060 cGy (range: 300-3600 cGy)	4.7	58% clinical, radiological or CSF response

Key: 2D = two-dimensional, CSF = craniospinal fluid, LMD = leptomeningeal disease, n = number of patients, OS = overall survival, RT = radiation therapy

body-sparing proton CSI is of particular interest in the pediatric population to preserve adult height potential and to reduce the risk of second malignancy.[10] While preliminary study of a hypofractionated proton CSI regimen suggests safe delivery, it requires further investigation.[11] A prospective clinical trial investigating vertebral body-sparing proton therapy in the pediatric population is underway and results are eagerly awaited.[12]

A summary of studies in breast cancer CSI for LMD indicate a role for palliation of symptoms (**Table 1**).[13-17] Median overall survival from LMD diagnosis treated with CSI ranged from four to six months, with the majority of patients in each study reporting improvement or stability of response. Our patient responded remarkably well with several months of durable response before passing away 12 months after LMD diagnosis. In contrast to our patient treated with the VMAT technique, the majority of these studies used the helical tomotherapy technique, with evidence suggesting comparable effectiveness with the technical advantages previously discussed.[18] The challenge of LMD diagnosis as seen in our case was also illustrated by a subset of patients who only demonstrated evidence of LMD on CSF cytology. However, it was unclear whether all patients received both imaging and CSF studies. We suspect that the number of patients with radiologically occult LMD is higher given that CSF cytology requires an additional invasive procedure that may not be pursued without a high degree of clinical suspicion.

With careful patient selection, evidence suggests that multimodality treatment with CSI has the potential for durable response.[19] Criteria for consideration of palliative CSI, which have been associated with favorable responses, include KPS of 70 or greater, absence of extra-CNS disease, neurologic response, and age less than or equal to 55 years at LMD diagnosis.[13,16]

In our case of symptomatic LMD requiring multiple therapeutic lumbar punctures, treatment with CSI attained a good response facilitating dexamethasone tapering and no further therapeutic lumbar punctures.

CONCLUSION

LMD is an uncommon complication of breast cancer associated with a poor prognosis. We highlight the challenges of diagnosis and the importance of obtaining an MRI of the entire neuroaxis, cytologic analysis, and correlation with neurological assessment. In a carefully selected population, palliative CSI can provide a significant symptomatic benefit with minimal toxicity and should be considered in addition to systemic therapy and best supportive care.

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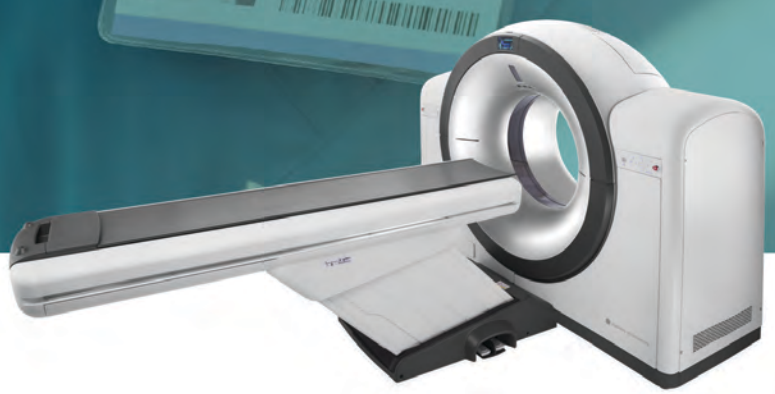

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