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Proton FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases
The FAST-01 Nonrandomized Trial

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Supplemental content

IMPORTANCE To our knowledge, there have been no clinical trials of ultra-high-dose-rate radiotherapy delivered at more than 40 Gy/sec, known as FLASH therapy, nor first-in-human use of proton FLASH.

OBJECTIVES To assess the clinical workflow feasibility and treatment-related toxic effects of FLASH and pain relief at the treatment sites.

DESIGN, SETTING, AND PARTICIPANTS In the FAST-01 nonrandomized trial, participants treated at Cincinnati Children's/UC Health Proton Therapy Center underwent palliative FLASH radiotherapy to extremity bone metastases. Patients 18 years and older with 1 to 3 painful extremity bone metastases and life expectancies of 2 months or more were eligible. Patients were excluded if they had foot, hand, and wrist metastases; metastases locally treated in the 2 weeks prior; metal implants in the treatment field; known enhanced tissue radiosensitivity; and implanted devices at risk of malfunction with radiotherapy. One of 11 patients who consented was excluded based on eligibility. The end points were evaluated at 3 months posttreatment, and patients were followed up through death or loss to follow-up for toxic effects and pain assessments. Of the 10 included patients, 2 died after the 2-month follow-up but before the 3-month follow-up; 8 participants completed the 3-month evaluation. Data were collected from November 3, 2020, to January 28, 2022, and analyzed from January 28, 2022, to September 1, 2022.

INTERVENTIONS Bone metastases were treated on a FLASH-enabled (≥40 Gy/sec) proton radiotherapy system using a single-transmission proton beam. This is consistent with standard of care using the same prescription (8 Gy in a single fraction) but on a conventional-dose-rate (approximately 0.03 Gy/sec) photon radiotherapy system.

MAIN OUTCOME AND MEASURES Main outcomes included patient time on the treatment couch, device-related treatment delays, adverse events related to FLASH, patient-reported pain scores, and analgesic use.

RESULTS A total of 10 patients (age range, 27-81 years [median age, 63 years]; 5 [50%] male) underwent FLASH radiotherapy at 12 metastatic sites. There were no FLASH-related technical issues or delays. The average (range) time on the treatment couch was 18.9 (11-33) minutes per patient and 15.8 (11-22) minutes per treatment site. Median (range) follow-up was 4.8 (2.3-13.0) months. Adverse events were mild and consistent with conventional radiotherapy. Transient pain flares occurred in 4 of the 12 treated sites (33%). In 8 of the 12 sites (67%) patients reported pain relief, and in 6 of the 12 sites (50%) patients reported a complete response (no pain).

CONCLUSIONS AND RELEVANCE In this nonrandomized trial, clinical workflow metrics, treatment efficacy, and safety data demonstrated that ultra-high-dose-rate proton FLASH radiotherapy was clinically feasible. The treatment efficacy and the profile of adverse events were comparable with those of standard-of-care radiotherapy. These findings support the further exploration of FLASH radiotherapy in patients with cancer.

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The unique biologic effects of ultra-high-dose-rate radiotherapy delivered at more than 40 Gy/sec, now known as FLASH therapy, were first reported more than 50 years ago.[1] Interest in this modality began re-emerging recently, concurrent with the advent of commercial radiotherapy equipment capable of delivering these ultra-high dose rates in a clinical setting.

Multiple animal experiments have demonstrated that FLASH can increase the therapeutic ratio of radiotherapy by decreasing normal tissue injury while maintaining the tumoricidal effects of conventional-dose-rate radiotherapy (conventional radiotherapy) or by allowing for dose escalation and improved tumor control probability without increasing normal tissue injury.[2-7] The mechanisms by which FLASH spares normal tissues are not fully understood, but there are data that suggest FLASH produces lower levels of toxic oxygen reactive species in normal tissues compared with conventional radiotherapy.[8]

In the seminal study for the contemporary use of FLASH, Favaudon et al[2] irradiated mouse lungs in vivo with both FLASH therapy and conventional-dose-rate radiotherapy.[2] Using a single dose of 17 Gy, 100% of mice receiving conventional radiotherapy developed pneumonitis and fibrosis, whereas none of the mice given FLASH therapy developed these toxic effects. FLASH therapy doses were escalated to 30 Gy delivered in a single dose before the mice exhibited evidence of radiation pneumonitis and fibrosis. The same investigators treated orthotopic lung tumors in mice with single-dose FLASH therapy and conventional radiotherapy. A dose of 15 Gy using conventional radiotherapy controlled tumors in only 20% of mice, most of which developed considerable radiation pneumonitis. In contrast, 27 Gy FLASH therapy controlled tumors in 70% of mice, none of which developed radiation pneumonitis.

The normal tissue-sparing effects of FLASH have also been observed in several other tissues and animal models, including mouse brain and neurocognition,[3] mouse intestine,[4] mouse skin,[5] mouse extremities,[6] and cat and pig skin.[7] In preclinical studies of proton FLASH, we irradiated mouse extremities with 35 Gy using either FLASH or conventional proton radiotherapy.[6] Subsequent leg contracture, skin toxic effects, and serum transforming growth factor β 1 levels were significantly decreased in the FLASH group. In this same study, tumor control of mouse head and neck cancer cell lines was equivalent between FLASH and conventional radiotherapy. A separate mouse extremity proton irradiation study by Velalopoulou et al[8] demonstrated similar results with diminished normal mesenchymal tissue toxic effects and inflammatory response with FLASH compared with conventional proton therapy and preservation of sarcoma tumor control.

To date, and to our knowledge, there has been 1 published case report of the use of FLASH therapy in a human—a single patient with cutaneous T-cell lymphoma and extensive prior radiotherapy to the skin who was safely and effectively treated with electron FLASH therapy for a recurrent cutaneous lymphoma lesion.[9] A single dose of FLASH therapy delivered with electron radiotherapy to 15 Gy was delivered. This resulted in a complete response of the lesion with minimal toxic effects of the heavily pretreated surrounding skin.

Electron radiotherapy is limited to superficial targets such as skin lesions. In contrast, proton radiotherapy can deliver FLASH at depth, for example, to bone, lymph node metastases, or visceral organ tumors.[10-15] In addition, proton FLASH may provide superior uniformity of dose distribution compared with electrons.

We conducted a prospective nonrandomized clinical study to assess the workflow feasibility and clinical outcomes of proton FLASH therapy based on the extensive preclinical data suggesting that use of FLASH could reduce normal tissue toxic effects while achieving equivalent efficacy of treatment. To mitigate potential risks for toxic effects in, to our knowledge, this first-in-human clinical trial of FLASH, the clinical study focused on treatment of painful bone metastasis sites in the extremities.

Key Points

Question Is proton FLASH radiotherapy, delivered at 1000 times the dose rate of conventional-dose-rate photon radiotherapy for its potential normal tissue-sparing effects, feasible for the palliation of painful bone metastases in the extremities?

Findings This nonrandomized trial of 10 patients with bone metastases in the extremities found that proton FLASH was clinically feasible, and its safety was supported by the minimal severity of related adverse events. In this small sample size, the efficacy of FLASH treatment for pain relief appeared to be similar to that of conventional-dose-rate photon radiotherapy.

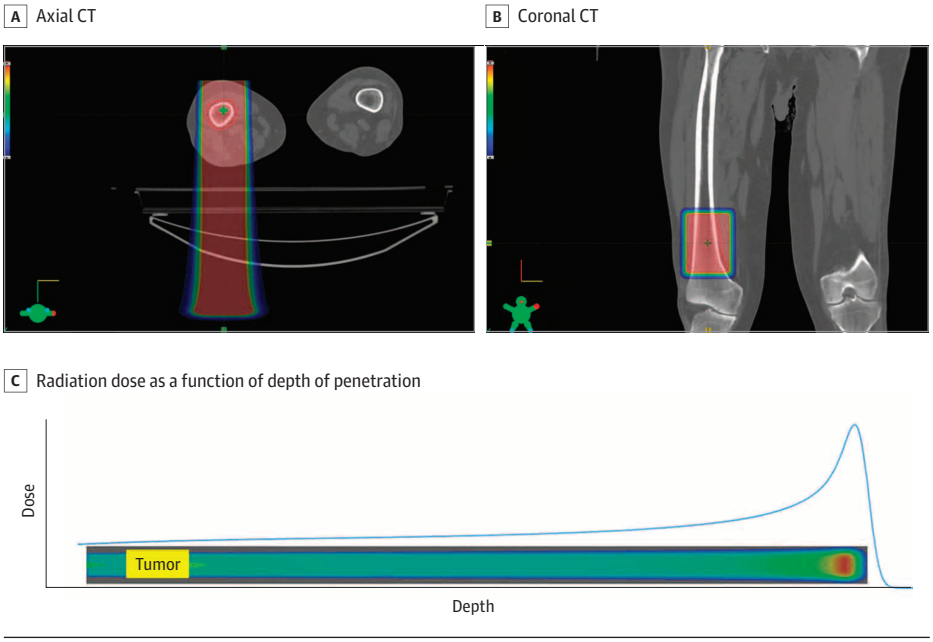
Meaning The results of this study confirm the workflow feasibility of delivering ultra-high-dose-rate proton FLASH radiation treatment in a routine clinical setting and support the further exploration of proton FLASH radiotherapy.

Methods

Enrollment and treatment of 10 patients was approved by the US Food and Drug Administration as an investigational device exemption for a FLASH-enabled proton therapy system (ProBeam [Varian Medical Systems]) and by the Cincinnati Children's Hospital institutional review board (Supplement 1). Study conduct and progress were monitored by an external Data Safety Monitoring Committee. Patients provided informed consent before undergoing treatment. Where applicable to the study design, Transparent Reporting of Evaluations With Nonrandomized Designs (TREND) reporting guidelines were followed.

Patients with up to 3 painful metastases in the extremities (excluding hands, wrists, and feet) were evaluated for enrollment. Eligibility criteria also included age of 18 years or older, no prior radiotherapy to the intended target lesion(s), and a life expectancy of more than 2 months. Patients were excluded if there was tumor lysis of more than 50% of the circumferential bone cortex, there were fracture and/or metal implants in the treatment field, they had undergone cytotoxic

Figure 1. Sample FLASH Treatment Plan and Bragg Curve Showing Radiation Dose in Color Wash



A, Axial computed tomography (CT) through a lesion treated in the right distal femur. B, Coronal CT through the same lesion. C, The radiation dose, drawn as a blue line, as a function of depth of penetration into the body for FLASH delivery with a 250-MeV transmission beam. The radiation dose is represented on the vertical axis, with depth of penetration into the body on the horizontal axis. The yellow box on the aqua-colored bar represents the position of the tumor in the radiation field, and the brighter red spot is the location of the increased dose at the Bragg peak, occurring outside of the patient's body. In all panels, darker red color indicates higher dose.

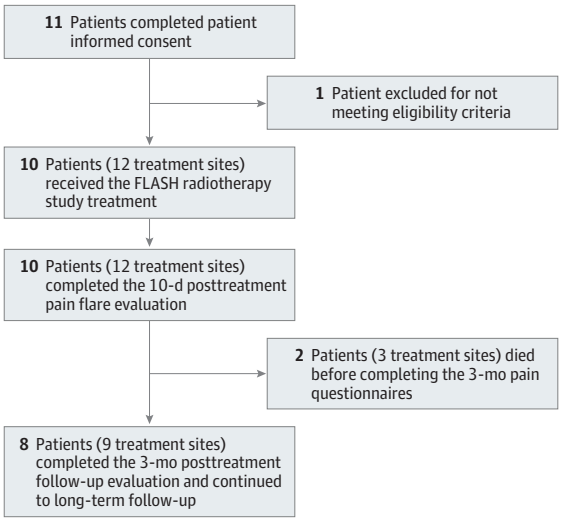
chemotherapy within 1 week prior to or following FLASH therapy, they had local therapy to the treated sites within 2 weeks prior to FLASH therapy, they were pregnant or breastfeeding, they had an implanted pacemaker, or they had known risk of enhanced normal tissue sensitivity to radiotherapy. In addition, it was required that the target lesion(s) could be treated with 1 of a library of 7 precalculated rectangular radiotherapy fields. Following signing of informed consent, patients underwent computed tomography simulation of the affected site(s). A treatment plan was generated using 1 of these predefined, transmission, high-energy, pencil-beam scanning proton therapy FLASH fields (eAppendix in Supplement 2). A transmission proton therapy field enters and exits the patient, treating the target lesion with the entrance region of a Bragg peak, whereas conventional proton therapy treats the target lesion with Bragg peaks. A dose of 8 Gy in a single fraction was planned with a nominal dose rate of 60 Gy/sec. An example treatment plan is shown in **Figure 1**, and the proton spot list and dose distribution for this same field are illustrated in eFigure 2 in Supplement 2.

Day-of-treatment study activities included taking photographs of the treatment site(s), performance status evaluation, and a physical examination. Additionally, multiple pain questionnaires were administered, including Brief Pain Inventory (BPI), treated site pain, and pain flare questionnaires. Pain medication use was recorded. Patients were positioned on the treatment couch and, using radiographic image guidance, the target lesions were localized. Treatment was delivered using a modified Varian ProBeam proton system with a dose monitoring chamber specifically developed to accurately measure delivered radiation dose given at FLASH dose rates (IDE No. G200155). In addition to quality assurance guidance from the American Association of Physicists in Medicine task group 224,[16] dose-rate quality assurance was performed before and after treatment as per the methodology in Folkerts et al.[17] Total time for patient alignment and treatment was recorded. Telephone follow-up to assess for pain flares and changes in pain medications was carried out daily for 10 days following treatment.

Posttreatment, patients were evaluated at day 1 (day of treatment), day 15, month 1, month 2, month 3, and every 2 months thereafter until patients died or were lost to follow-up. Follow-up visits were conducted in person when possible (according to the patient's medical condition and COVID-19 restrictions in effect at the time) and alternatively by telemedicine visit. The BPI and treated site pain questionnaires were administered, and pain medications were recorded at each follow-up. A spaghetti plot and corresponding table of the average pain score obtained from the treated sites pain questionnaire (which is a subset of the BPI form and particularly relevant for assessing pain relief at the treated site) is included in eFigure 1 in Supplement 2. The methodology of Hartsell et al in the Radiation Therapy Oncology Group (RTOG) 9714 trial,[18] which assessed pain response at the 3-month time point following treatment, was used to determine pain response rates. Photographs of the treated site(s) were taken at in-person visits; photographs were also taken by a caregiver when the follow-up visit was conducted by telemedicine, whenever possible.

All adverse events (AEs) were graded using the Common Terminology Criteria of Adverse Events, version 5.0, and recorded independent of their relationship to the treated metastasis. A serious AE was defined per International Organization for Standardization 14155 criteria. All AEs were scored by 1 of the investigators as being definitely related, probably related, possibly related, probably not related, or definitely not related to the FLASH treatment. Stopping rules would have been triggered if 3 patients experienced a serious AE related

Figure 2. CONSORT Participant Flow Diagram



to treatment, if 3 patients had a delay of more than 7 business days from simulation or required more than 1 hour of time on the treatment couch, or if a major malfunction of the dose-monitoring device occurred.

Results

Patient Population

Eleven patients were included in the study; however, 1 patient did not meet eligibility criteria, and subsequently 10 were enrolled (**Figure 2**). No patients were lost to follow-up. Median (range) follow-up was 4.8 (2.3-13.0) months. Patient ages ranged from 27 to 81 years (median, 63 years). An equal number of men and women were enrolled. All patients reported their ethnicity as not Hispanic/Latino and their race as White. There was a spectrum of histologic diagnoses, the most frequent being non-small cell lung cancer, breast cancer, and multiple myeloma. The clinical characteristics of the study population are summarized in **Table 1**.

There was a total of 12 treatment sites for the 10 enrolled patients. Eight patients received treatment to 1 anatomic site, and 2 patients received treatment to 2 distinct anatomical sites. All metastases fit within the predefined treatment field sizes and met the required dosimetric constraints specified in the study protocol. All treatments were delivered at a FLASH dose rate (range, 51-61 Gy/sec) normalized at 5-cm depth (eFigure 3 in Supplement 2).

FLASH Treatment Workflow Feasibility

The elapsed time the patient spent on the treatment couch (including the time for patient setup and positioning, imaging, and FLASH treatment delivery) was an average (range) of 15.8 (11-22) minutes per treatment site and 18.9 (11-33) minutes per patient. The 2 patients who received treatment to 2 anatomical treatment sites were on the treatment couch for 32 and 33 minutes, respectively. There were no delays in treatment, and FLASH treatment was delivered without any device-related problems.

Table 1. Baseline Demographics and Clinical Characteristics

Demographics and characteristics	No. (%)
Patient demographics	
Total No.	10
Sex	
Male	5 (50)
Female	5 (50)
Race and ethnicity	
White, non-Hispanic/Latino	10 (100)
Clinical characteristics	
Histologic diagnosis, No.	10
Breast	
Adenocarcinoma	1 (10)
Unspecified malignant neoplasm	1 (10)
Epithelioid hemangioendothelioma	1 (10)
Lung	
Adenocarcinoma	1 (10)
Neuroendocrine carcinoma	1 (10)
Unspecified malignant neoplasm	1 (10)
Multiple myeloma	2 (20)
Prostate adenocarcinoma	1 (10)
Thyroid squamous cell carcinoma	1 (10)
FLASH treatment sites, No.	12
Femur, lower proximal	5 (42)
Humerus	
Upper distal	2 (17)
Upper proximal	3 (25)
Tibia	
Lower anterior	1 (8)
Lower distal	1 (8)

Table 2. Adverse Events (Possibly, Probably, or Definitely) Attributed to FLASH Treatment (N = 10)

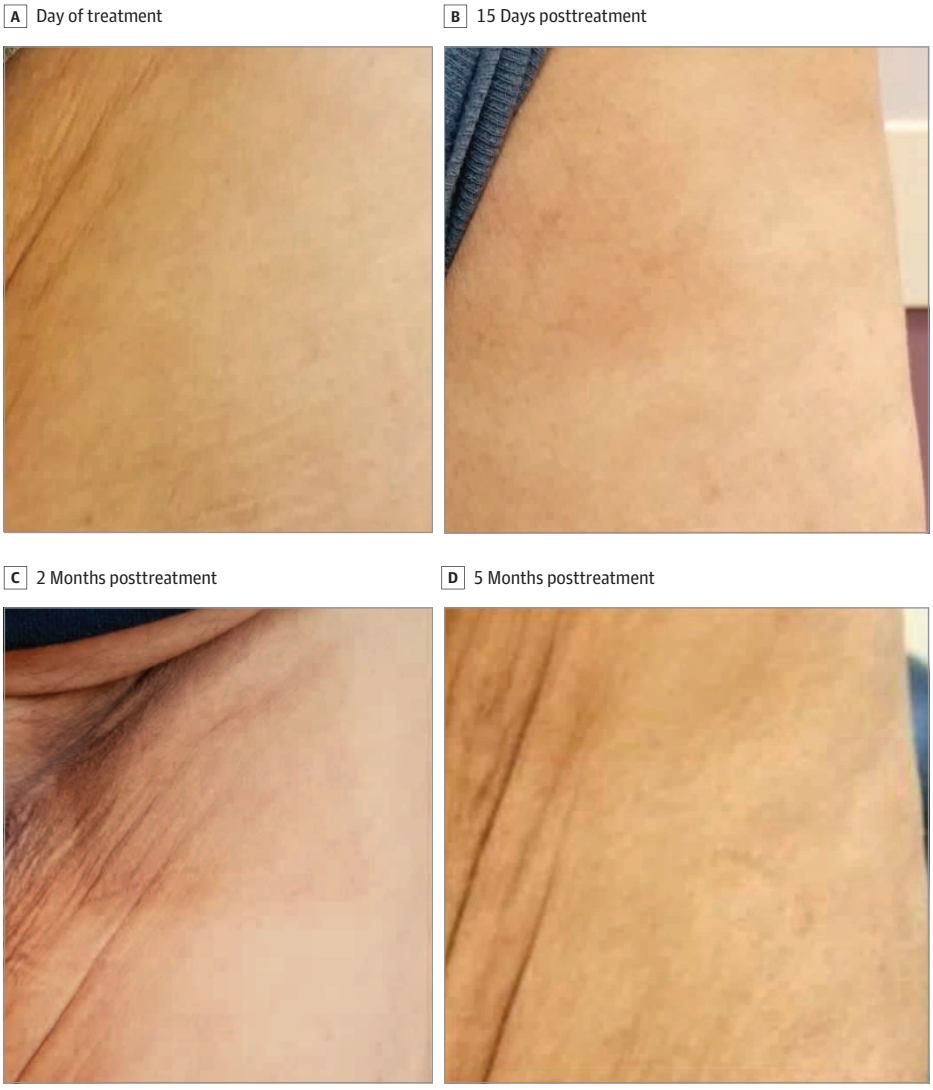
Adverse events[a]	Patient, No. (%)
Acute (≤3 mo posttreatment)	
Edema, limb (grade 1)	1 (10)
Erythema (grade 1)	1 (10)
Extremity pain (grade 2)	1 (10)
Fatigue (grade 1)	1 (10)
Pruritus (grade 1)	2 (20)
Skin hyperpigmentation (grade 1)	4 (40)
Long term (>3 mo posttreatment)	
Skin discoloration (grade 1)	1 (10)

[a] Adverse events were graded using the Common Terminology Criteria of Adverse Events, version 5.0.

Adverse Events

There were 12 AEs attributed as being possibly/probably/definitely related to FLASH treatment noted in 6 patients, with no serious AEs (**Table 2**). Most AEs (8 of 12) were related to skin changes, with 5 consisting of mild hyperpigmentation.

Figure 3. Posttreatment Hyperpigmentation



Photographs of a transient, mild hyperpigmentation adverse event in the area of FLASH treatment in a single patient. The photographs may have been taken under different lighting conditions and/or with different cameras. To facilitate comparison across images, the brightness was uniformly decreased and the warmth uniformly increased in panel C, and the brightness was uniformly increased in panel D.

Representative photographs of skin changes in 1 patient are shown in **Figure 3**.

Eleven of these 12 AEs were grade 1, and 1 of these AEs was grade 2 pain in the extremity. This patient received FLASH treatment to the distal tibia; they experienced grade 1 edema at 3 months posttreatment, grade 1 trace-mild hyperpigmentation at 2 months posttreatment, and grade 2 pain in the extremity at 1 month posttreatment. At the time of publication, the pain in the extremity was ongoing and being managed with medications.

Bone fractures in or near a treated site occurred in 2 patients. Approximately 4 weeks after treatment, 1 patient with approximately 40% cortical destruction pretreatment experienced a humeral fracture in the setting of mild trauma to the FLASH treatment site. This lesion was classified as Mirels score 8 prior to treatment, indicating a moderate risk for impending pathologic fracture. Due to the short time interval after FLASH and the associated trauma, the principal investigator (J.C.B.) assessed the event as probably unrelated to the patient's treatment. A second patient who received FLASH therapy for a tibial metastasis experienced a fracture of the ipsilateral ankle after a fall. The fracture was located outside of the FLASH treatment field and was attributed as probably unrelated to the study treatment.

There were 352 AEs that were attributed as being probably not related or definitely not related to study treatment (eTable 1 in Supplement 2). Of these, 23 AEs were serious (22 were definitely not and 1 probably not related to FLASH treatment) in 7 patients. Each of these AEs was attributed to systemic cancer treatments or due to disease activity and/or progression.

Pain Flare Following Treatment

Applying the criteria of Chow et al,[19] a pain flare following treatment was recorded by patients in 4 of 12 (33%) treated lesions. The pain flares occurred from 2 to 9 days following FLASH treatment. Additionally, 1 patient's pain management regimen was changed on day 11 from a modest dose of

acetaminophen to low-dose hydrocodone at the recommendation of the patient's pharmacist, but this medication change was not attributed to a flare in pain symptoms.

Pain Relief

Patient-reported pain scores were collected for the 12 treated metastatic sites. Three-month pain scores were available for 9 of the 12 treated metastatic sites in 8 of the 10 patients. One patient, treated at 2 metastatic sites, died shortly after the 2-month posttreatment evaluation. This patient had a complete response of pain at 1 treated site and a partial response at the other site at the 1-month follow-up visit. A second patient died 3 months following FLASH treatment. This patient had a pain complete response at the 2-month follow-up visit.

In 6 of the 12 treated sites, patients reported a complete relief of pain, for a complete response rate of 50%. In 2 of the 12 treated sites patients reported a partial relief of pain for a partial response rate of 16.7%. Two of 12 sites were referred for retreatment with conventional photon radiation to the FLASH irradiated site due to recurrence/progression of pain. Including all 10 patients, a complete or partial pain response following FLASH therapy was seen in 8 of 12 treated sites (7 of 10 patients) for an overall response rate of 66.7%. The temporal response of patient-reported average pain rating at treated sites is shown in eFigure 1 in Supplement 2, and pain response scoring for each patient is shown in eTable 2 in Supplement 2.

Discussion

Herein we describe, to our knowledge, the first-in-human study of FLASH proton radiotherapy. Patients with bone metastases in the extremities were selected with the expectation that these patients were likely to receive benefit equivalent to the same treatment with conventional-dose-rate radiotherapy. Additionally, extremity treatment sites have minimal risk of unexpected toxic effects due to their distance from organs with the greatest sensitivity to radiation. The choice of workflow feasibility as a primary end point was selected in recognition of the need to validate this technically complex new modality in a routine clinical setting. Many components of FLASH implementation are more demanding than radiation delivered at conventional dose rates. A FLASH treatment occurs in milliseconds rather than minutes, which requires more rigorous validation of beam delivery, advanced dosimetry (incorporating dose-rate information into treatment planning), quality assurance, patient positioning, and safety interlocks. Confirming that all of these elements can be seamlessly integrated to deliver FLASH within a conventional timeslot for patient treatment seemed an appropriate end point for this first-in-human study. This prospective study confirmed that FLASH is clinically feasible and appears to be safe in this patient group.

Treatment-related AEs were mild, and most were transient hyperpigmentation and pruritus in the treatment field. It should be noted that, unlike megavoltage photon radiotherapy, transmission FLASH proton radiotherapy as used in this study has no skin-sparing effects so that the skin received the full 8 Gy of prescribed radiotherapy. No patient experienced fibrosis or visible vascular changes in the treatment field. There have been no serious AEs attributable to the study treatment, and administration of FLASH therapy did not result in delays in treatment planning or delivery. Long-term toxic effects may be underrepresented in this investigation owing to the advanced cancer stages and related mortality in this study population. However, in light of the modest radiation dose used in the FAST-01 study, one would anticipate predominantly short-term toxic effects.

Although the study was not powered to evaluate pain relief as a primary objective, most patients experienced pain relief in the range expected for this 8-Gy single-fraction regimen of palliative proton FLASH radiotherapy (8 of 12 treatments sites for an overall response rate of 67%). This rate is comparable with the outcomes of 8-Gy single-fraction conventional-dose-rate radiotherapy administered for painful bone metastases, such as the 65% overall response rate achieved in the RTOG 9714 trial.[18] It should be noted that the present study enrolled 2 patients with multiple myeloma, which is generally more radiosensitive compared with carcinomas, and this diagnosis was not included in the RTOG 9714 study. With regard to pain flare, the incidence in this study was 33%, again comparable with other reports using similar, non-FLASH photon techniques.[20]

Strengths and Limitations

Strengths of this study include its prospective design, meticulous tracking of AEs, and thorough workflow analysis. In addition, because concurrent systemic therapies were not permitted, there is confidence that the results are directly attributable to FLASH radiotherapy. Study limitations include the small study population size and that treatment sites were limited to extremity bone metastases. Consequently, assessment of normal tissue effects was limited to skin, bone, muscle, and lymphatic/vascular and connective tissues. Prior to granting approval for the study, these limitations to the study population were developed and agreed on in consultation with the regulatory agencies to minimize risk for study participants in this, to our knowledge, first-in-human clinical trial. Additionally, owing to the underlying diseases of the patient population, long-term follow-up data are limited. These limitations can be addressed in future clinical trials by including other patient groups.

Considerable further study and technology development will be required to elucidate what place FLASH may eventually have in the radiotherapy armamentarium. Much additional work remains to be done to find optimal dose regimens for the FLASH effect, technologies to deliver conformal FLASH, and to better elicit the biologic mechanisms at work.[21]

Conclusions

In this nonrandomized trial, we provide, to our knowledge, a first experience in humans showing minimal toxic effects and the desired therapeutic benefit for most patients. Based on

clinical workflow metrics, treatment efficacy and safety data, we conclude that ultra-high-dose-rate proton FLASH therapy is feasible in a clinical setting. Future clinical trials of proton FLASH should extend these findings to other parts of the body (eg, thorax, pelvis, head and neck) to demonstrate the applicability of this technology to multiple cancers.

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Correction: This article was corrected on March 2, 2023, to change the license to CC-BY-NC-ND open access.

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Concept and design: Mascia, Xiao, Sertorio, Woo, McCann, Russell, Levine, Sharma, Khuntia, Bradley, Simone, Perentesis, Breneman.
Acquisition, analysis, or interpretation of data: Mascia, Daugherty, Zhang, Lee, Woo, Backus, McDonald, McCann, Russell, Levine, Sharma, Bradley, Perentesis, Breneman.
Drafting of the manuscript: Daugherty, Woo, Backus, McDonald, Russell, Levine, Sharma, Perentesis, Breneman.
Critical revision of the manuscript for important intellectual content: Mascia, Daugherty, Zhang, Lee, Xiao, Sertorio, Woo, McCann, Russell, Levine, Sharma, Khuntia, Bradley, Simone, Perentesis, Breneman.
Statistical analysis: Lee, Woo.
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Administrative, technical, or material support: Mascia, Daugherty, Zhang, Lee, Xiao, Sertorio, Woo, Backus, McDonald, McCann, Sharma, Bradley, Perentesis, Breneman.
Supervision: Mascia, Daugherty, McCann, Russell, Levine, Khuntia, Simone, Perentesis, Breneman.

Conflict of Interest Disclosures: Dr Mascia reported grants and personal fees from Varian Medical Systems during the conduct of the study. Dr Daugherty reported personal fees from Varian Medical Systems during the conduct of the study. Dr Sertorio reported grants from Varian Medical Systems during the conduct of the study. Ms Woo reported employment at Varian Medical Systems, the commercial sponsor of the study. Dr McCann reported employment at Varian Medical Systems, the commercial sponsor of the study. Dr Russell reported employment at Varian Medical Systems, the commercial sponsor of the study. Dr Levine reported employment at Varian Medical Systems, the commercial sponsor of the study. Dr Sharma reported employment at Varian Medical Systems, the commercial sponsor of the study. Dr Khuntia reported employment at Varian Medical Systems, the commercial sponsor of the study, as well as multiple FLASH patents issued. Dr Bradley reported grants and personal fees from Varian Medical Systems outside the submitted work. Dr Simone reported personal fees from Varian Medical Systems during the conduct of the study. Dr Perentesis reported grants from Varian Medical Systems, Bristol Myers Squibb, Jazz Pharmaceuticals, and Incyte outside the submitted work. Dr Breneman reported funds from Varian Medical Systems to institute during the conduct of the study and personal fees from Varian Medical Systems. No other disclosures were reported.

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Invited Commentary

The First FLASH Clinical Trial—The Journey of a Thousand Miles Begins With 1 Step

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It took the field of radiation oncology 40 years (1969) to appreciate and reinvestigate the phenomenon we now call the FLASH effect,[1] which is normal tissue sparing from ultra-high-dose-rate (UHDR) delivery. Less than a decade ago (2014), the normal tissue sparing by UHDR delivery was confirmed in animal studies.[2] Now, in this issue of *JAMA Oncology*, Mascia et al[3] report their phase 1 trial of proton FLASH radiotherapy in humans. As a first-in-human trial, the primary objectives were simply feasibility and safety of UHDR treatment. The trial was small—10 patients—and the dose delivered was modest—8 Gy. The authors achieved their stated objectives by demonstrating feasibility with acceptable time to deliver the treatment, and toxic effects were mild, mostly consisting of grade 1 skin reactions.

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While the translation of UHDR into the clinic for the first time is a meaningful accomplishment, we should also reflect on the state of the technology for UHDR planning and delivery, dose monitoring, and the basic understanding of the factors that are critical for achieving any radiobiological FLASH effect. The FLASH effect has become defined as tissue sparing from radiation delivery at average dose rates of greater than 40 Gy/sec, and here the dose rate was achieved clinically using a proton therapy system.[3] However, the actual definitions of what is required in UHDR delivery to achieve the FLASH effect are still evolving and likely may involve technical factors such as the instantaneous per-pulse dose rate, the total dose delivered, and key features of the pulse structure.[4] So at present, it is not yet possible to fully know if this trial achieved a FLASH effect with the given UHDR parameters used.

It is important to note that the proton technology used in this study[3] does not take advantage of the Bragg peak, which is essential for minimizing integral dose and eliminating exit dose that is beneficial in conventional proton therapy. As such, and without skin sparing by protons, the treatment plans used in this study are less conformal and give higher surface doses than can be achieved using standard-of-care modalities. In the current iteration, this proton UHDR delivery technique is unlikely to be translatable to definitive treatment doses at sites near critical structures, unless the benefits of the FLASH effects (currently estimated between 10% and 40% of additional sparing in preclinical models for limited tumor and tissue types with nonconventional and frequently aggressive hypofractionation schemes) outweigh the trade-offs inherent to this treatment technique.[5] To realize clinical benefit, UHDR radiation treatment plans will likely require equivalent conformality as those used in standard-of-care conventional radiation, but with the added biological response advantage achieved by the FLASH effect.

Another major unknown factor in the FLASH effect is the minimum dose required to see the benefits of the UHDR treatment, and while estimates of this range near 8 Gy,[5] this question towers over the use of FLASH because determining appropriate fractionation schemes is a key factor in the pathway toward successful clinical implementation. The state of FLASH trials today is in a safety phase, as this one was,[3] but determination of safety in a responsible fractionation scheme will be critical to future studies that will be designed with therapeutic end points.

While early-phase safety trials proceed, it is important to support basic studies to understand the mechanism for various tumor and tissue types, the dependency on parameters such as fractionation, dose threshold, mean dose rate, instantaneous dose rate, and linear energy transfer, which are modulated by hypervariables such as the modality, delivery technology, modulations of energy, range and intensity, spot map, beam geometry, and patient anatomy. For the future, the FLASH effect should be quantitatively modeled in the planning phase for trade-offs to be made against state-of-the-art conventional radiotherapy.[6] New planning and delivery technologies are needed to optimize and safely deliver the FLASH effect without compromising what is already achievable in conventional radiotherapy. The justifications of using the FLASH effect with trade-offs to achieve a net improved efficacy should be analyzed rigorously and thoroughly.

Mascia et al[3] should be commended for taking a careful approach to the first clinical trial of UHDR radiotherapy in patients, and even more importantly, the patients enrolled in this study should be thanked for their contributions to translation of this treatment technology into the clinic for the first time. It is now imperative that the basic understanding of the FLASH effect and the approaches to ensure optimal delivery and quality assurance of UHDR delivery are in place for future trials that will ultimately use higher delivered doses to treatment sites that have the potential for increased toxic effects. This trial is the first step of a long journey to bring UHDR radiation therapy to clinical use with the hope of seeing value from the FLASH effect.