INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
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BRIEF REPORT

First In Vivo Monitoring of Helium-Ion Radiation Therapy With Secondary Ions

Laurent Kelleter, PhD,[a,b,c] Semi Harrabi, MD,[a,b,d,e] Pamela Ochoa-Parra, PhD,[a,b,f] Marcus Winter, PhD,[e] Oliver Jäkel, PhD,[a,b,c,e] Jürgen Debus, MD, PhD,[a,b,d,e,g] and Maria Martisikova, PhD[a,b,c]

[a]National Center for Radiation Research in Oncology (NCRO), Heidelberg Institute for Radiation Oncology (HIRO), Heidelberg, Germany; [b]Division of Medical Physics in Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [c]National Center for Tumor Diseases (NCT), NCT Heidelberg, a Partnership Between DKFZ and University Medical Center, Heidelberg, Germany; [d]Department of Radiation Oncology, Heidelberg University Hospital, Heidelberg, Germany; [e]Department of Radiation Oncology, Heidelberg Ion-Beam Therapy Center (HIT), Heidelberg University Hospital, Heidelberg, Germany; [f]Department of Physics and Astronomy, Heidelberg University, Heidelberg, Germany; and [g]Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany

Received May 3, 2025; Revised Nov 29, 2025; Accepted for publication Dec 13, 2025

Purpose: Ion beam radiation therapy offers steep dose gradients and high biological effectiveness required for the treatment of complex cancer cases. While the vast majority of ion beam therapy centers currently use protons and carbon ions, there is renewed interest in helium ions due to their unique physical and radiobiological properties. All ion-beam treatments are subject to beam-range uncertainties, mainly due to potential changes in patient morphology. In vivo treatment monitoring of secondary ions could potentially provide feedback on treatment quality, enabling dose reduction in healthy tissue or escalation of the tumor dose.
Methods and Materials: This work presents the first in vivo monitoring of a patient undergoing helium-ion therapy for a solitary fibrous tumor. The method is based on tracking secondary ions emitted from the patient as a natural byproduct of ion beam radiation therapy.
Results: The comparison of 2 measured secondary-ion distributions confirmed high treatment reproducibility for the reported patient. However, significant differences between the 2 fractions were detected at the border of the skull base and the sinus sphenoidalis, which could originate from potential interfractional cavity filling.
Conclusions: We successfully performed the world's first in vivo monitoring of innovative helium-ion therapy. In the future, the observed signals will need to be validated in patients who receive regular control computed tomography scans. Moreover, Monte Carlo simulations and phantom measurements will help establish a robust link between changes in the secondary-ion distribution and clinically relevant changes in dose.

Introduction

Ion beam radiation therapy is used to tackle complex solid cancer cases that require steep dose gradients and, in the case of heavy ions, high biological effectiveness.[1] Today, the vast majority of ion beam therapy centers use protons or carbon ions.[2] However, helium ions are regaining interest due to their intermediate physical and radiobiological

Corresponding author: Maria Martisikova, PhD; E-mail: m.martisikova@dkfz-heidelberg.de

Author Responsible for Statistical Analysis: Laurent Kelleter.

Disclosures: The authors have no relevant conflict of interest to disclose. L.K. acknowledges funding by the NCT Heidelberg. P.O.-P. acknowledges funding by the international PhD program of DKFZ Heidelberg.

Data Sharing Statement: Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

https://doi.org/10.1016/j.ijrobp.2025.12.036

properties and their potential cost-effectiveness.[3] This makes them especially promising for the treatment of pediatric patients.[4]

Interfractional changes in the patient's internal anatomy or position may lead to clinically relevant changes in the dose distribution. However, control computed tomography (CT) scans are rarely performed daily due to the additional radiation dose to the patient and the available resources. Secondary radiation, such as prompt gammas, electron-positron annihilation photons, and charged nuclear fragments (secondary ions), is a natural byproduct of ion beam radiation therapy. In vivo monitoring with secondary radiation could provide direct feedback on treatment quality without the need for an additional dose.[5,6] Recently, secondary ions were used to detect morphologic changes in patients undergoing carbon-ion therapy at Centro Nazionale di Adroterapia Oncologica (Pavia, Italy).[7,8]

This contribution reports the world's first in vivo monitoring of helium-ion therapy using secondary ions, conducted at the Heidelberg ion beam therapy center.[9] This proof of concept was achieved with a custom-built monitoring system, which is currently being used in a phase 1 feasibility study in patients undergoing carbon-ion therapy.[10]

Methods and Materials

Monitoring system

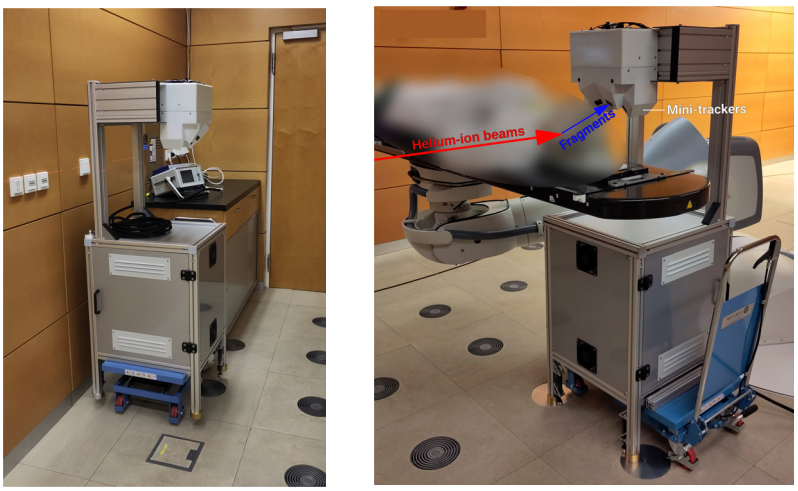
The monitoring system is a custom-developed system optimized for in vivo monitoring of patients with brain as well as head and neck cancer undergoing ion beam therapy.[10] It uses 7 mini-trackers to measure the paths of charged nuclear fragments (secondary ions) that escape the patient during irradiation. Each mini-tracker comprises 4 Timepix3 (ADVACAM s.r.o., Prague, Czech Republic) detectors organized into 2 tracker layers, with a spacing of 20.3 mm between them.[11,12] Each tracker layer spans 2.8 cm × 1.4 cm with a pixel pitch of 55 μm. The 7 mini-trackers are located behind the patient at distances of 16 cm to 24 cm to the isocenter and angles of 20° to 36° to the beam axis.[10] The monitoring system is fixed to the concrete floor with anchors for reproducible positioning. Moreover, the detector position is cross-checked against markers that intersect the in-room lasers. The fragment signal of the static ripple filter is used as an additional verification.

Monitoring workflow

Figure 1 shows photographs of the monitoring system in its measurement and parking positions. A monitoring workflow was developed in collaboration with medical physicists, radiation oncologists, and medical radiation technologists to ensure minimal interference with the clinical workflow. The additional time required is less than 3 minutes per monitored field and treatment fraction.

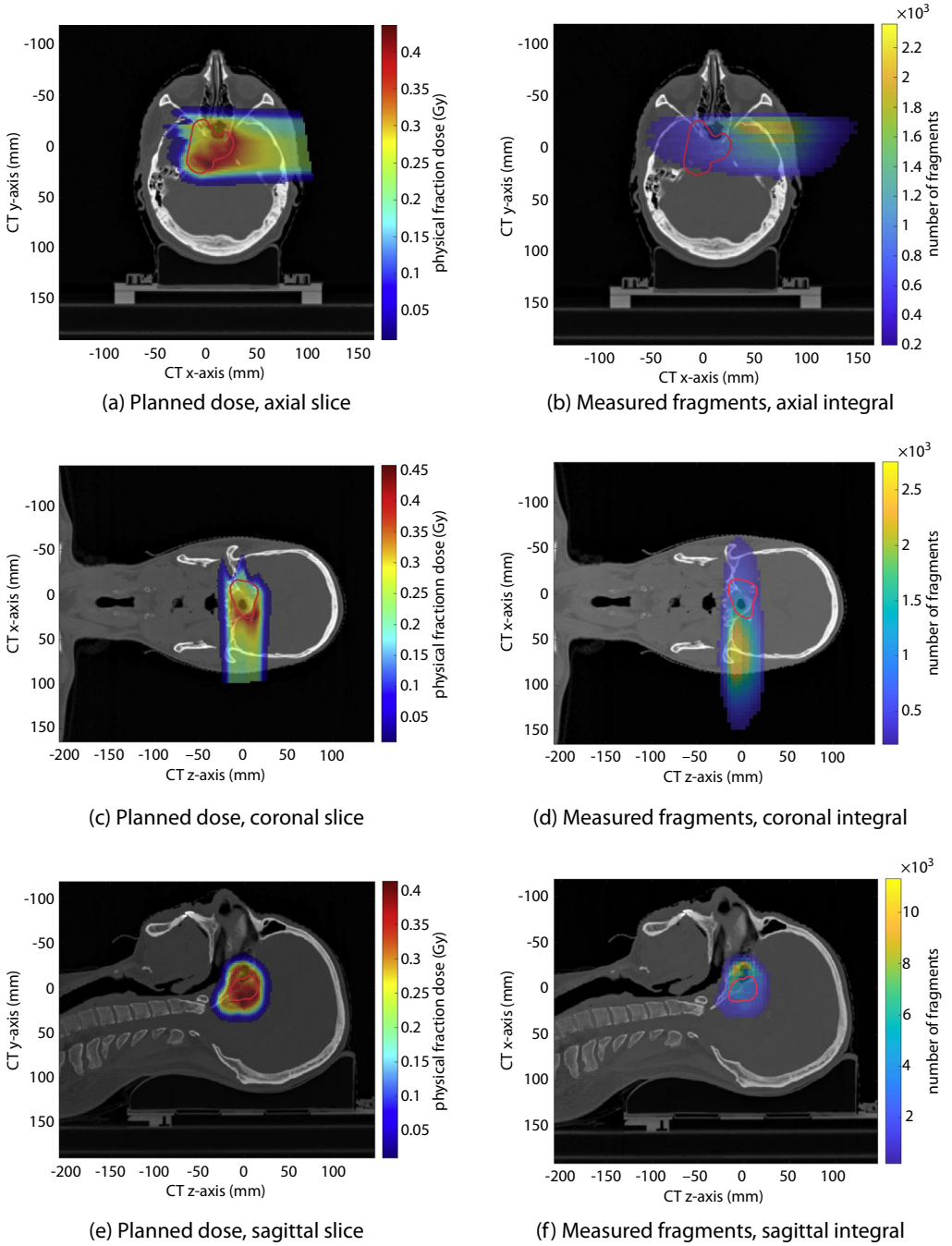
Monitored patient case

The monitored patient was referred for treatment of a progressive, histologically proven solitary fibrous tumor located at the base of the skull with infiltration of the cavernous sinus and the brain stem. The patient was prescribed helium-ion therapy with a total Relative Biological Effectiveness-weighted target dose of 60 Gy (RBE), administered in 30 fractions and split into 3 fields. Treatment planning was performed using RayStation 11B (RaySearch Laboratories AB).[13] The total number of primary helium ions in the monitored treatment field was 1.12×10^9. Three slices of the planned physical dose distribution of the monitored field are shown in the



(a) Parking position (b) Measurement position

Fig. 1. (a) Photograph of the monitoring system in the parking position in the corner of the treatment room before and after therapy. (b) Monitoring system in the measurement position with the anonymized patient on the patient table.



(a) Planned dose, axial slice (b) Measured fragments, axial integral

(c) Planned dose, coronal slice (d) Measured fragments, coronal integral

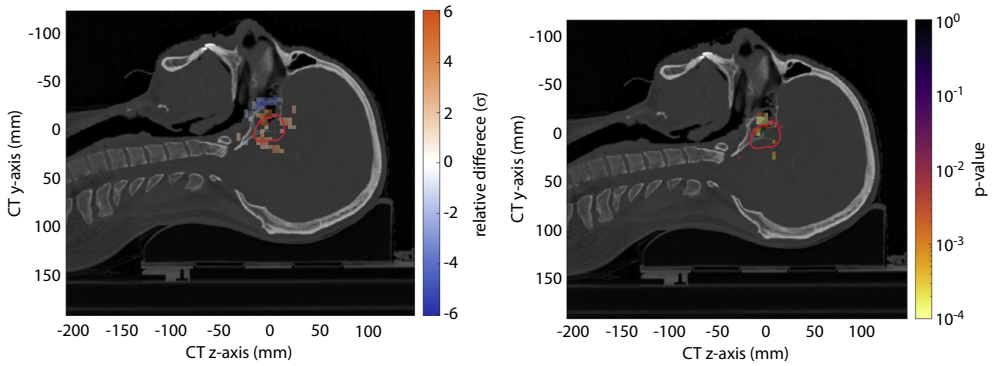
(e) Planned dose, sagittal slice (f) Measured fragments, sagittal integral

Fig. 2. (a, c, e) Slices of the planned physical dose distribution. (b, d, f) Integral fragment distributions measured with the monitoring system (treatment fraction 18). The red line delineates the planning target volume. *Abbreviation:* CT = computed tomography.

left column of Figure 2. Two treatment fractions (numbers 18 and 25), 10 days apart, were monitored.

Analysis

We evaluated the relative fragment count difference in SDs and the Kolmogorov-Smirnov (KS) test result along the beam axis as 2 complementary analysis techniques. On the one hand, the relative difference enables identification of regions that overperform or underperform in fragment emission. The difference is sensitive to absolute numbers and their positive/negative signs; however, it does integrate information along the beam axis. A relative difference exceeding 2 SDs was considered significant. On the other hand, the KS test quantifies the similarity of the 2 fragment



(a) Relative difference of measured fragments

(b) KS statistical test result

Fig. 3. Comparison of the measured fragment distributions in the sagittal plane. The red line delineates the planning target volume. (a) Relative difference of the measured fragment distributions. (b) Two-sample KS statistical test result of the measured fragment distributions. *Abbreviation:* CT = computed tomography; KS = Kolmogorov-Smirnov.

distributions along the beam axis. It is sensitive to variations in the shape of the longitudinal fragment distribution but insensitive to changes in the absolute fragment counts (due to normalization) or their positive/negative signs. We selected $p < .01$ as the significance threshold for the KS test. Both metrics were calculated using a lateral moving window with a 10 mm × 10 mm area and a step size of 4 mm in order to better visualize data trends and increase the sensitivity of the analysis.

Results

Measured fragment distributions

Figure 2a-e shows 3 slices of the single-fraction physical dose distribution of the monitored treatment field. In addition, Figure 2b, d, and f shows the measured fragment distribution of the first monitored treatment fraction. The total number of detected fragments was 2.2×10^6 (0.002 per helium ion).

Comparison of the monitored treatment fractions

In order to search for significant interfractional treatment deviations, the relative difference between the 2 monitored fragment distributions is shown in the sagittal plane in Figure 3a. Only pixels with an absolute relative difference greater than 2 SDs and a minimum of 1000 fragments within the moving window are displayed. A reduction in the fragment count was observed along the border of the base of the skull and the nasal cavities. Simultaneously, an increase in the fragment count was measured in the sinus sphenoidalis as well as at the posterior and superior edges of the planning target volume. The KS test result is shown in Figure 3b. Only pixels with a p value <.01 and at least 1000 fragments within the moving window are displayed. Here, a clustered signal was observed at the location of the sinus sphenoidalis.

Discussion

We successfully completed the first in vivo treatment-monitoring study of helium-ion therapy using a novel system to monitor secondary ions generated as byproducts of ion-beam radiation therapy. A comprehensive monitoring workflow was established to integrate the measurement into the existing clinical framework. Over 2 million fragments were measured for each treatment fraction, which is sufficient for robust statistical analysis of treatment quality. The measured fragment distributions are consistent with the literature on clinical helium-ion fragmentation.[14–16]

High treatment reproducibility was confirmed by the monitoring system, as evidenced by the overall small differences between the 2 fragment distributions measured 10 days apart. However, the data analysis revealed statistically significant differences near the base of the skull and the sinus sphenoidalis. This difference could be explained by mucus filling or emptying the sinus sphenoidalis. The only way to reliably confirm a morphologic change is to link the observed signal to a change in Hounsfield units in a control CT. Unfortunately, a control CT was unavailable because it was not part of this patient's planned treatment procedure. Another potential explanation for the observed signal could be a slight rotation of the head within the immobilization mask after x-ray positioning. Such movements are also clinically relevant and can be independently verified by our monitoring system.

It remains to be established, using validated Monte Carlo (MC) simulations and head phantom measurements, how sensitive the fragment distributions from helium-ion beams are to different types of morphologic changes. However, a major challenge on the path to reliable MC simulations is the insufficient accuracy of nuclear cross-section tables for helium-fragment production. More sophisticated analytical techniques will be required to determine whether the observed signals are associated with clinically relevant dose changes in order to make an informed decision on a potential treatment intervention. For example, neural networks

could be trained to generate synthetic CTs that show the expected anatomic changes or patient mispositioning, based on the planning CT and the 2 measured fragment distributions, the latter of which encode the evolution of the patient's anatomy over time. Moreover, the nanosecond time resolution, together with a runtime-optimized analysis, offers the possibility of real-time monitoring and motion tracking.[17] All of this will be part of future work, paving the way for online adaptive ion beam therapy. As an intermediate step, a large observed difference in fragment distributions could trigger a control CT to verify the patient's morphology before the next treatment fraction.

Conclusions

This work describes the first successful measurement of secondary ions from a patient undergoing helium-ion radiation therapy for in vivo treatment verification. A high fragment count, measured with high reproducibility, indicated a high overall treatment quality. Significant differences were found between the measured fragment distributions near the base of the skull and the sinus sphenoidalis, which could be explained by a change in the level of mucus fill or by head rotation. Without a control CT or a comparative MC simulation, it is not possible to draw a definitive conclusion, and more studies will be needed to transition from this first proof-of-concept to a clinically useful in vivo monitoring technique. In the future, machine learning-powered algorithms could allow for the reconstruction of the underlying anatomic change based on the observed signals in the fragment distributions.

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