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FULL PAPER

Prompt gamma imaging for the identification of regional proton range deviations due to anatomic change in a heterogeneous region

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Objectives: Prompt gamma (PG) imaging has previously been demonstrated for use in proton range verification of a brain treatment with a homogeneous target region. In this study, the feasibility of PG imaging to detect anatomic change within a heterogeneous region is presented.

Methods: A prompt gamma camera recorded several fractions of a patient treatment to the base of skull. An evaluation CT revealed a decrease in sinus cavity filling during the treatment course. Comparison of PG profiles between measurement and simulation was performed to investigate range variations between planned and measured pencil beam spot positions.

Results: For one field, an average over range of 3 mm due to the anatomic change could be detected for a subset of spots traversing the sinus cavity region. The

two other fields appeared less impacted by the change but predicted range variations could not be detected. These results were partially consistent with the simulations of the evaluation CT.

Conclusion: We report the first clinical application of PG imaging that detected some of the expected small regional proton range deviations due to anatomic change in a heterogeneous region. However, several limitations exist with the technology that may limit its sensitivity to detect range deviations in heterogeneous regions.

Advances in knowledge: We report on the first detection of range variations due to anatomic change in a heterogeneous region using PGI. The results confirm the feasibility of using PG-based range verification in highly heterogeneous target regions to identify deviations from the treatment plan.

INTRODUCTION

Prompt gamma imaging (PGI) is a promising method for *in-vivo* proton range verification via detection of the instantaneous emission of high-energy photons during beam delivery. Over the past 15 years, this modality was proposed,¹ demonstrated experimentally,² and performed clinically in both passive scattering³ and pencil beam scanning⁴ modes with a knife-edge collimated camera^{5,6} that was further used in the present study. Alternative PGI concepts rely on Compton imaging,^{7,8} two-dimensional collimators,^{9,10} or other information encoding the proton range like the characteristic photon energies,¹¹ the proton transit time,^{12,13} and the integrated number of photons.¹⁴

The mean range shifts measured by the knife-edge slit camera for a homogeneous brain target volume were smaller than the applied safety margins.⁴ Here, we present the results of a patient treated to the base of skull. Range verification is more valuable but also more challenging for such highly heterogeneous regions, especially around air cavities, where patient position errors (movement or setup) result in strong variations of the tissue composition in the beam path, leading to range shifting and mixing.¹⁵ Furthermore, the present target region can be prone to anatomic change, such as changes in sinonasal cavity filling observed during the treatment course. We assessed the feasibility of PGI in detecting such anatomic change by evaluating the

Figure 1. Schematic setup of the knife-edge slit camera for monitoring the PG emission of the LIO field. Exemplary tracks for protons (blue lines) and photons (green lines) are depicted as well as the dose from all three treatment fields. LIO, left inferior field; PG, prompt gamma.

Figure 2. Axial view of the initial (a) and evaluation (b) CT scans highlighting the anatomic change (red contour) due to reduced nasal cavity filling that occurred during the treatment course. Coronal views of the planning CT and LIO only field dose for the selected CT slice (yellow lines in (a, b)) for the initial (c) and evaluation (d) CT scans. White arrow indicates beam direction, orange shaded contour the PTV and green contour 98% isodose line. Red circle denotes the region with shift in isodose line. Corresponding shifts in LSO1 and LSO2 only field isodose lines are shown in (e, f) and (g, h) respectively. Red and blue dotted lines indicate sampling region of dose profiles shown in Figure 3. LIO, left inferior field.

impact of the decreased sinus filling on the range retrieval of individual spots.

METHODS AND MATERIALS

The prototype knife-edge slit camera developed by Ion Beam Applications (IBA), Belgium, consists of lutetium–yttrium oxyorthosilicate (LYSO) scintillation crystals arranged in 2 rows of 20 slabs each for one-dimensional imaging along the beam axis.⁶ The sensitive volume amounts to 504 cm³ with 8 cm width along the beam direction, 20 cm in height, and 3.15 cm in depth. The distance between the center of the collimator and the detector plane was fixed to 16 cm, while the distance between the central beamline and the center of the collimator was set to 26 cm with a <2 cm daily variation for each field (cf. Figure 1). The distance between the central beamline and the center of the collimator mainly affects the magnification of the PG signal profile and was included as a parameter in the PG simulation in the proton range retrieval results. After the patient was set up for each treatment field, the collimator opening, *i.e.* the center of the field of view (FOV), was first aligned to the treatment isocenter using a collimator mounted laser system. A translational offset was then applied to optimize monitoring of the distal layers with the highest dose contribution. This field specific offset ranged from several millimeters to around 2.5 cm over the treatment course. With the X-ray imaging for patient setup, the beam isocenter to target isocenter, *i.e.* the patient positioning has an uncertainty of 1.5 mm. The camera to beam isocenter positioning has an uncertainty of about 1 mm (see Xie et al⁴ discussion for additional details).

The patient under study was treated for a malignant neoplasm of the brain located at the base of skull at the Roberts Proton Therapy Center of the University of Pennsylvania, PA, USA. The study was approved by the institutional review board and the subject gave informed consent to the PGI. A total relative biological effective (RBE = 1.1) dose of 54 Gy was prescribed in 30 fractions with 1.8 Gy (RBE) per fraction. The treatment was delivered in pencil beam scanning mode in a fixed beam treatment room. Three equally weighted oblique fields, namely one left inferior field (LIO) with couch rotation angle at 5°, and two left superior fields (LSO1 and LSO2) with couch angles at 345° and 305° respectively, were optimized with single-field uniform dose technique to cover the PTV (CTV plus 3 mm) on patient CT scan. The patient also had an evaluation CT scan on the day of fraction #21, which was acquired in the same position as the planning CT and treatment position using the same immobilizations but in a different room. Rigid image registration was performed between the planning CT (fixed image) and the evaluation CT (moving images), which revealed a reduction in the nasal cavity filling (cf. Figure 2). This anatomic change resulted in over ranging of a small number of spots in several layers and is manifested as broadened single field and plan dose profiles in Figure 3. Although the target coverage was not compromised, a new plan based on the evaluation CT was generated to improve conformality. In order to avoid a long break between fractions, the patient continued treatment with the initial plan until the revised plan was ready for the last four treatment fractions.

Figure 3. Dose profiles of the individual LIO (a), LSO1 (b) and LSO2 (c) fields along the directions indicated by Figure 2. Red profiles are for the initial CT and blue profiles for the evaluation CT. The range shifts are calculated at R50. Dose color wash of the total plan dose in the evaluation (d) and initial (e) CTs with horizontal dose profile shown in (f). LIO, left inferior orbit field.

PG profiles were acquired six times with the initial plan, and twice with the revised one. The interval between PG acquisition days was not evenly distributed between treatment fractions due to constraints on clinical treatment schedule. Of particular interest, the sixth set of profiles was recorded for fraction #22 (of the initial plan), the day after the evaluation scan. The PG profiles of the proton pencil beams traversing through the anatomic change were therefore expected to show an over range compared to initial plan. To investigate the impact, PG profiles were simulated using an analytical model¹⁶ on both initial and evaluation CT scans. A map of the range variation was extracted for each individual spot by determining the shift between the two simulated PG profiles.

Figure 4. Measured PGI range variations with spot aggregation for selected layers of the three fields near the anatomic change region for fraction # 22. The color scale indicates the magnitude and direction of the range shift which is defined as measured range minus expected range from initial CT where positive (negative) values indicate beam over ranging (under ranging). The PTV is shown as the outer contour while the region of anatomic change is indicated by the inner contour in the beam's eye view. For each layer, the weighted average range shift is given for ROI-I (upper value) and the residual spots (lower value). PGI, prompt gamma imaging; PTV, planning target volume; ROI, region of interest.

Following the same analysis procedure as in Xie et al,⁴ the measured PG profiles were compared to simulated PG profiles (initial treatment plan with planning CT, revised plan with evaluation CT, respectively) per spot for 11 most distal layers in order to identify spots with range variations. Spot aggregation for noise reduction in the measurements has been suggested in Xie et al⁴ to be less suitable for heterogeneous targets due to the reduced sensitivity from range mixing. However, in order to account for the limited counting statistics, Gaussian-weighted spot aggregation with a sigma of 7 mm was still applied in this study. As trade-off, a reduced lateral resolution was accepted to improve the overall accuracy of the measured data. Around 15% of the measured spots were identified as unreliable and excluded from the analysis if it fails to meet any one of the following criteria: 1) having the PG profile falling-edge within the inner half of the FOV (so that the falling edge of the profile is completely recorded) (2.4% of spots); 2) achieving one-sigma range retrieval precision below 4 mm (computed from 1000 randomly generated noisy profiles) (5.6% of spots); 3) exhibiting one-sigma range sensitivity of the patient position below 4 mm (7% of spots). Due to tissue heterogeneity along the beam path and lateral boundaries between bone, soft tissue and air, some calculated spot shifts were very sensitive to patient position since pencil beams were used in the analytical calculation of the PG profiles and the expected spot positions. If those spots were included in the range analysis, they could skew the range variation results. We performed multiple-simulations to investigate the patient position sensitivity on range retrieval by shifting the CT image within ± 3 mm with 1 mm interval in both directions perpendicular to the central beam path. The sigma of range difference compared to nominal case per spot was determined, and a threshold of 4 mm was used to filter out spots that were deemed too sensitive to beam path heterogeneity.

The average over the entire isoenergy layer⁴ was not used to determine the range shift as it washed out the regional tissue heterogeneities and localized anatomic change. Instead, a three-dimensional visualization approach was developed to examine the trends across layers by displaying the range shift for each spot along the beamlet path. This display helped to identify spot clusters by path differences (e.g. highly variable interfraction range shifts vs consistent range shifts over the treatment course). Range variations were determined for different types of region of interest (ROI): anatomic change region (ROI-I), other specific regions identified in the three-dimensional (3D) visualization (in Results), and the residual spots (ROI-Res).

RESULTS

Spot map analysis of measured range variations of fraction #22

Dose profile comparison between the initial and evaluation CTs seen in Figure 3 indicated that single field dose shifts of up to 6 mm (LIO field, Figure 3(a)) and 3 mm for the summed plan dose profiles (Figure 3(f)) could be expected. Figure 4 shows the spot maps of the differences between measured PG profiles versus simulated PG profiles of the initial CT with no spot filtering applied. The spot maps were noisy and did not show an obvious trend in range shifts at the regions where over ranging

Figure 5. Simulated PGI profile range variations due to the anatomic change for selected layers of the three fields using the initial and evaluation CTs. The color scale indicates the magnitude and direction of the range shift. The PTV is shown as the outer contour while the region of anatomic change is indicated by the inner contour in the beam's eye view. For each layer, the weighted average range shift is given for ROI-I (upper value) and the residual spots (lower value). PGI, prompt gamma imaging; PTV, planning target volume; ROI, region of interest.

was expected based on the previous dose profiles. This was believed to be caused by several factors: (1) tissue heterogeneity of the anatomic change region with admixtures of air, tissue and bone, (2) poor counting statistics, (3) sensitivity of simulated PG profiles to camera position (4) limitation of PG camera to resolve range shifts that are comparable to precision of camera (~ 2 mm with setup error included) in a heterogeneous region and (5) lack

Figure 6. (a) 3D PG measurement data from fraction #15 of the LIO field. The PTV (blue volume), the anatomic change (red volume) as well as the beam direction (black arrow) are depicted. Each colored line represents a spot location, where color and length are measures of the sign and magnitude of the range variation while the thickness is proportional to the spot weight. Two additional ROIs, ROI-II (magenta) and ROI-III (green), are highlighted. (b) Simulation of 3D shifts using initial and evaluation CTs for the LIO field. (c) 3D PG measurement data from fraction #22 of the LIO field. 3D, three-dimensional; LIO, left inferior field; PTV, planning target volume; ROI, region of interest.

of ground truth CT acquired on the same day as the PG measurement, *i.e.* the true anatomy is unknown but an assumption is made that the anatomy at fx#22 is identical to the evaluation CT acquired on fx#21. b) Simulation of expected range variations due to anatomic change.

Based on a comparison between simulated PG profiles with and without the anatomic change, the expected range variations are presented in Figure 5 for selected layers of the three fields of the initial plan. For the spots traversing the region of the anatomic change (ROI-I) and those outside, the expected weighted average range shift was calculated separately for each layer. The simulations showed range deviations of up to 6 mm for individual spots for the LIO field (layer 3) and up to 4 mm for the LSO1 field (layer 3), while the LSO2 field showed mixed results with spots exhibiting potential under ranges (*e.g.* layers 5 and 6). As expected, spots with high over ranges were located in or close to the anatomic change (primarily in layers 2–4). For these layers, the average shift for ROI-I varied from 2.7 to 3.8 mm. When averaged over all layers, *i.e.* averaging only over spots traversing through ROI-I, the expected range shifts were: 2.5 ± 1.0 mm for LIO, 2.0 ± 0.8 mm for LSO1, and 0.1 ± 0.5 mm for LSO2. Some under ranging was observed in LSO2 which could not be account for based on the 2 CTs. The under ranging seen in layers 5 and 6 have an aggregated shift of less than 1.5 mm in ROI-I while only a small number of individual spots were above 2 mm. These spots are located in a highly heterogeneous region and range mixing effects may account for these deviations. The residual spots, located within ROI-Res, showed less than 1 mm average variation, indicating no impact as expected, since these were spots not traversing the region of anatomic change. c) Three-dimensional visualization of PG measurements

A 3D visualization of the PG-based range measurements is depicted in Figure 6(a) showing exemplary results from fraction #15 of the LIO field. A line, the color and length of which are measures of the sign and magnitude of the range variation, represents each spot while the thickness is proportional to the spot weight. The line originates at the planned Bragg peak position and terminates at the location retrieved from the PG measurement. In case of no range shift, only a point is visible. For this measurement, most spots show absolute range variations below the average of 2 mm with a relatively random distribution. However, we identified two clusters of spots showing similar range variations throughout the recorded fractions in the LIO and LSO1 fields. Spots grouped in ROI-II show high interfraction volatility with range shift variations between 0 and 20 mm. As those spots of ROI-II are close to the maxillary sinus, simulations confirmed our hypothesis that this volatility is the result of patient position variation. Figure 6(b) shows the corresponding results of the expected shifts from the simulation comparing the initial and evaluation CTs where ROI-II indicates almost no shifts. The spot cluster in ROI-III shows a consistent over ranging of several millimeters in every recorded fraction. For LSO2, no further ROI was identified. Figure 6(c) shows the 3D plot for fraction #22, 1 day after the acquisition of the evaluation CT where the anatomical change was detected. Several spots with positive shifts within right portion of ROI-I seen in Figure 6(c)

Figure 7. Histograms of shifts for the filtered spots in the PG measurement for fraction #22 (day after verification CT) for the LIO field. Panels depict the expected (blue) and measured (red) shifts inside ROI-I for layers 1 through 10. LIO, left inferior field; PG, prompt gamma.

(measurement) were however not visible in Figure 6(b) (simulation). This could be attributed to measurement noise or the effect of heterogeneity on the PG profile detection but the exact cause is unknown.

Quantitative range analysis of different ROIs

For the LIO field in fx# 22, the histograms of the spot shifts between measured and expected values within ROI-I of the filtered spots are presented in Figure 7. While the histograms show the effect of noise and measurement uncertainty, layer 4 shows the largest positive shift as predicted in Figure 5. The shifts expected in layer 3 did not show up well in the measurement. For all three treatment fields, the quantitative average range shift analysis for spots traversing through ROI-I is presented in Figure 8. The recorded fractions (black crosses) prior to the anatomic change do not show any range variations beyond the uncertainties (two sigma statistical uncertainties and 1.2 mm

Figure 8. Results of the quantitative range shift analysis of ROI-I for the LIO (left), the LSO1 (middle), and the LSO2 field (right). The initial treatment plan was used for the first 26 fractions and the revised version for last four. On the day of fraction #21, an evaluation CT was performed. The measured range shift (black crosses) is presented for all recorded fractions, as well as the expected shift (red circle) in case of fraction #22 due to the anatomic change. Additionally, the last two recorded fractions were evaluated also with the initial CT (cyan markers) and the measured results for LIO imply the restoration of the cavity filling. Black dotted lines indicate the applied safety margins. The date of each fraction is given as well. LIO, left inferior field; ROI, region of interest.

Figure 9. Top: Range shift analysis for pencil beams traversing through ROI-II for LIO (left) and LSO1 (right) fields. A high variance is visible which could potentially be attributed to patient positioning variations. Bottom: Range shift analysis for ROI-III (LIO left, LSO1, right), showing a consistent over range for pencil beamlets clustered in this region. The average over range over the recorded fractions is indicated by the blue dashed line. The date of each fraction is given as well. LIO, left inferior field; ROI, region of interest.

positioning uncertainty⁴). However, in fraction #22, we identified an over range of (2.6 ± 1.4) mm for the LIO field (compare with Figure 2(a) for isodose line shift) but no shifts for the LSO1 and LSO2 fields which were within the measurement uncertainty (± 1.4 mm). The result for LIO is consistent with the expected range shift due to the dissolved cavity filling seen on the evaluation CT calculated with the initial plan (red points). In case of the LSO1 and LSO2 fields, no conclusive answer can be given since the expected shifts are at the edge of the measurement shift error bars. The fractions recorded for the revised plan (#28 and #29) are also in agreement with simulations for the two LSO fields, while an under range of (4 ± 1.3) mm was observed for the LIO field. A potential scenario of restored sinus filling was studied by simulating the revised treatment plan on the original CT (cyan markers), which resulted in better agreement with measurement. Note that the first recorded LSO1 was missing in Figure 8 because the camera was aligned such that no spots in ROI-I were inside the FOV.

For LIO and LSO1, the two additional regions (ROI-II for patient positioning variations, ROI-III for consistent over ranges) were analyzed for all recorded fractions (cf. Figure 9). In the LIO field, ROI-II showed no variations for most fractions, although, fraction #15, showed a 4 mm over range. For LSO1, most fractions showed consistent range offset in ROI-II, with a maximum shift of about 4 mm in fraction #22. Since ROI-II is distal to ROI-I for the LSO1 field, the larger shift seen in fraction #22 for the LSO1 field can be correlated to the over range seen in LIO for ROI-I for the same fraction. Since ROI-II is sensitive to patient setup, the observed consistent range offset in ROI-II might reduce the detectability of the expected over range for the LSO1 field. In ROI-III, the average range shifts were 2.4 mm for LIO and 1.3 mm for LSO1, which agrees with the hypothesis of a consistent range shift for spots in that volume.

DISCUSSIONS

Phantom studies have characterized the benefits and limitations of PGI in heterogeneous targets. Steep lateral gradients in tissue density can result in range mixing, impact the proton range and make the dose distribution sensitive to patient positioning variations. Steep density gradients along the beam axis close to the end of range can also complicate range retrieval analysis. A minimum of 7 mm proton penetration beyond an air cavity¹⁵ was essential to obtain sufficient PG signal. This study is the first investigating the detectability of anatomic change in a heterogeneous region within a patient. Sensitive spots were selected for analysis based on PG profile simulations with random sampling for range mixing and by shifting the CT image perpendicular to the beam for setup error sensitivity determination.

Due to the observed anatomic change in the sinus region, the expected range shifts were determined from comparison of the simulated PG profiles using the initial treatment plan on both CT images. Average range variations for ROI-I were found to be 2.5 mm (LIO), 2.0 mm (LSO1), and 0.1 mm (LSO2). Thus, LIO and LSO1 fields were more sensitive to the anatomic change compared to LSO2. Between LIO and LSO1, the LIO field was slightly more affected by this anatomic change and more spots showed higher individual over range (e.g. only two spots in LSO1 with $a \geq 4$ mm shift, compared to 10 spots in LIO). Based on the simulations, the detection of an over range would be possible for both fields and more likely and easily detected for the LIO field with larger range variations.¹⁷ Additionally, the spots with larger shift had increased probability to have the required 7 mm penetration depth beyond the air cavity.¹⁵ The range variation for fraction #22 (PG data acquired on day following evaluation CT) was detected for the LIO field with a shift of (2.6 ± 1.4) mm compared to the expected 2.5 mm. The LSO1 and LSO2 fields exhibited no over range beyond the measurement uncertainties which was dominated by the 1.2 mm (two sigma) camera positioning uncertainty. Even though the fractions treated prior to the anatomic change revealed no significant PG measured range deviations from the simulations, we cannot make a definitive conclusion that there was no anatomic change without ground truth CT data. In the last two recorded fractions, a range variation in ROI-I was also observed for the LIO field with the revised plan. An under ranging of around (4 ± 1.3) mm was detected. This under ranging could possibly be accounted for by a refilling of the sinus cavity for fractions #28 and #29. This agrees better with the expected shifts from the simulation of the revised plan on the initial CT (i.e. with refilled cavity). No additional evaluation CT was available to verify the hypothesis that the cavity filling recurred in the last four treatment fractions. In summary, all detected range shifts were within the 5 mm planning margin.

In this retrospective analysis, only averaged values for ROI-I were investigated. In such a workflow, ROIs can be predefined whenever a risk of change over the treatment course is suspected (e.g. due to cavity filling or swelling) and PG profiles could be evaluated daily for those volumes. Other scenarios would be at the gross tumor volume or within a critical organ at risk such as the brainstem where anatomic change could impact tumor control

probability or normal tissue toxicity. In this study, in-room CT or CBCT was not available prior to any treatment.

Periodic volumetric imaging such as in room CBCT or fan beam CT can be used in proton therapy to monitor anatomic change. While daily CBCT is now routine for patient setup for photon therapy, it is not available for this study in a fixed beam room. Future PGI studies should include volumetric imaging to benchmark the performance of the PG. Without setup volumetric imaging, the detection of a range deviation using PGI could potentially be used to trigger an evaluation CT scan or other imaging methods to confirm the change and revise the treatment plan if adaptation was deemed necessary. However, it is still an open question on what range error or volume threshold, frequency of detection are needed for the anatomic change to be considered a positive trigger for additional imaging and replanning.

The 3D spot maps were used to identify ROIs with highly variable range deviations or consistent deviations. The detected range shift results within these ROIs were potentially caused by patient positioning variability (ROI-II) or potentially uncertainty in the conversion of HU to proton stopping power (SPR) (ROI-III). Since the tissue composition along the beam path varies with position, spots that traverse more bone, which has higher SPR uncertainty,¹⁸ may experience larger shifts. Several other factors such as change in patient anatomy or tissue composition could also cause the range deviation seen in ROI-III but these cannot be confirmed without CTs acquired on the day of PG imaging.

There are several limitations to this work. The acquired patient data showed some inconsistencies as well as very marginal sensitivity in terms of detectability of the expected range deviation due to the small region of anatomical change, poor signal to noise which required spot aggregation in small ROIs in an inhomogeneous region, camera positioning variability, heterogeneity effects and lack of daily volumetric imaging. While increasing spot aggregation can improve the signal to noise, the effect of transverse heterogeneity and range mixing smears out the PG profiles and reduces the overall accuracy of the range shift detection algorithm. In addition, the definition of beam range becomes ill defined when a pencil beam traverses through or stops in a heterogeneous region. Despite these shortcomings, the presented data are the first patient PG measurement in a heterogeneous target region for *in vivo* verification of proton range. While the measured PG results demonstrated some consistency with simulation results of anatomic change, the detected range shifts are close to the detection limit of the PGI system. Some predicted large shifts from simulation (e.g. 6 mm in LIO field layer 3) could not be detected, demonstrating the limitation of PGI in a heterogeneous region.

CONCLUSIONS

We report on the first hints of detection of range variations due to anatomic change in a heterogeneous region using PGI. A decrease in nasal cavity filling was observed on an evaluation CT scan and could be retrospectively detected in a spot-by-spot analysis of PG profiles recorded with a prototype knife-edge slit

camera. Two of the three fields had sufficient sensitivity to the anatomic change according to simulations, but an over range could only be detected for one of the two. For this field, a (2.6 ± 1.4) mm average shift was detected, which was in agreement with the predictions. Furthermore, a 3D visualization was developed to aid in identifying regions with range variations. Based on the measurements, two additional clusters of spots were identified that were potentially attributable to patient positioning variations and Hounsfield unit to SPR conversion uncertainties, respectively. While, identification of range deviations in individual spots is challenging and complex, the results confirm the feasibility and demonstrated the limitations of using PG based range verification in highly heterogeneous target regions to identify deviations from the treatment plan.

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CONFLICT OF INTEREST

J.Smeets and D. Prieels have a patent on apparatus for particle therapy verification issued. D. Prieels has a patent Method and apparatus for particle beam range verification issued.

REFERENCES

1. Jongen Y, Stichelbaut F. Verification of the proton beam position in the patient by the detection of prompt gamma-rays emission. *39thPTCOG* 2003;.
2. Min C-H, Kim CH, Youn M-Y, Kim J-W, et al. Prompt gamma measurements for locating the dose falloff region in the proton therapy. *Appl Phys Lett* 2006; **89**: 3517. doi: <https://doi.org/10.1063/1.2378561>
3. Richter C, Pausch G, Barczyk S, Priegnitz M, Keitz I, Thiele J, et al. First clinical application of a prompt gamma based in vivo proton range verification system. *Radiother Oncol* 2016; **118**: 232–7. doi: <https://doi.org/10.1016/j.radonc.2016.01.004>
4. Xie Y, Bentefour EH, Janssens G, Smeets J, Vander Stappen F, Hotiou L, et al. Prompt Gamma Imaging for In Vivo Range Verification of Pencil Beam Scanning Proton Therapy. *Int J Radiat Oncol Biol Phys* 2017; **99**: 210–8. doi: <https://doi.org/10.1016/j.ijrobp.2017.04.027>
5. Smeets J, Roellinghoff F, Prieels D, Stichelbaut F, Benilov A, Busca P, et al. Prompt gamma imaging with a slit camera for real-time range control in proton therapy. *Phys Med Biol* 2012; **57**: 3371–405. doi: <https://doi.org/10.1088/0031-9155/57/11/3371>
6. Perali I, Celani A, Bombelli L, Fiorini C, Camera F, Clementel E, et al. Prompt gamma imaging of proton pencil beams at clinical dose rate. *Phys Med Biol* 2014; **59**: 5849–71. doi: <https://doi.org/10.1088/0031-9155/59/19/5849>
7. Muñoz E, Barrio J, Etxebestea A, Ortega PG, Lacasta C, Oliver JF, et al. Performance evaluation of MACACO: a multilayer Compton camera. *Phys Med Biol* 2017; **62**: 7321–41. doi: <https://doi.org/10.1088/1361-6560/aa8070>
8. Draeger E, Mackin D, Peterson S, Chen H, Avery S, Beddar S, et al. 3D prompt gamma imaging for proton beam range verification. *Phys Med Biol* 2018; **63**: 035019. doi: <https://doi.org/10.1088/1361-6560/aaa203>
9. Krimmer J, Chevallier M, Constanzo J, Dauvergne D, Rydt MD, Dedes G, et al. Collimated prompt gamma TOF measurements with multi-slit multi-detector configurations. *J. Inst.* 2015; **10**: P01011. doi: <https://doi.org/10.1088/1748-0221/10/01/P01011>
10. Ready Development of a multi-knife-edge slit collimator for prompt gamma imaging during proton beam therapy. *Medical Imaging Conference* 2015;.
11. Verburg JM, Seco J. Proton range verification through prompt gamma-ray spectroscopy. *Phys Med Biol* 2014; **59**: 7089–106. doi: <https://doi.org/10.1088/0031-9155/59/23/7089>
12. Golnik C, Hueso-González F, Müller A, Dendooven P, Enghardt W, Fiedler F, et al. Range assessment in particle therapy based on prompt γ -ray timing measurements. *Phys Med Biol* 2014; **59**: 5399–422. doi: <https://doi.org/10.1088/0031-9155/59/18/5399>
13. Hueso-González F, Enghardt W, Fiedler F, Golnik C, Janssens G, Petzoldt J, et al. First test of the prompt gamma ray timing method with heterogeneous targets at a clinical proton therapy facility. *Phys Med Biol* 2015; **60**: 6247–72. doi: <https://doi.org/10.1088/0031-9155/60/16/6247>
14. Krimmer J, Angellier G, Balleyguier L, Dauvergne D, Freud N, Hérault J, et al. A cost-effective monitoring technique in particle therapy via uncollimated prompt gamma peak integration. *Appl Phys Lett* 2017; **110**: 154102. doi: <https://doi.org/10.1063/1.4980103>
15. Priegnitz M, Helmbrecht S, Janssens G, Perali I, Smeets J, Vander Stappen F, et al. Measurement of prompt gamma profiles in inhomogeneous targets with a knife-edge slit camera during proton irradiation. *Phys Med Biol* 2015; **60**: 4849–71. doi: <https://doi.org/10.1088/0031-9155/60/12/4849>
16. Sterpin E, Janssens G, Smeets J, Vander Stappen F, Prieels D, Priegnitz M, et al. Analytical computation of prompt gamma ray emission and detection for proton range verification. *Phys Med Biol* 2015; **60**: 4915–46. doi: <https://doi.org/10.1088/0031-9155/60/12/4915>
17. Nenoff L, Priegnitz M, Janssens G, Petzoldt J, Wohlfahrt P, Trezza A, et al. Sensitivity of a prompt-gamma slit-camera to detect range shifts for proton treatment verification. *Radiother Oncol* 2017; **125**: 534–40. doi: <https://doi.org/10.1016/j.radonc.2017.10.013>
18. Paganetti H. Range uncertainties in proton therapy and the role of Monte Carlo simulations. *Phys Med Biol* 2012; **57**: R99–117. doi: <https://doi.org/10.1088/0031-9155/57/11/R99>