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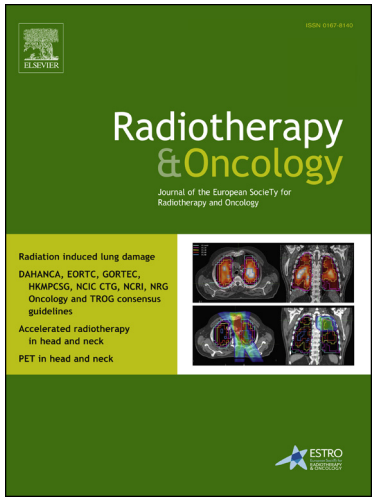

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First clinical application of a prompt gamma based *in vivo* proton range verification system

Christian Richter[a-e], Guntram Pausch[a-c], Steffen Barczyk[a,b], Marlen Priegnitz[c], Isabell Keitz[a], Julia Thiele[b], Julien Smeets[f], Francois Vander Stappen[f], Luca Bombelli[g], Carlo Fiorini[h], Lucian Hotoiu[f], Irene Perali[h], Damien Prieels[f], Wolfgang Enghardt[a-e], Michael Baumann[a-e]

Institutions:

[a] OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden - Rossendorf, Dresden, Germany

[b] Department of Radiation Oncology, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

[c] Helmholtz-Zentrum Dresden – Rossendorf, Dresden, Germany

[d] German Cancer Research Center (DKFZ), Heidelberg, Germany

[e] German Cancer Consortium (DKTK), Dresden, Germany

[f] Ion Beam Applications SA, Louvain-la-Neuve, Belgium

[g] XGLab S.R.L., Milano, Italy

[h] Politecnico di Milano, Dipartimento di Elettronica, Informazione e Bioingegneria, Milano, Italy

Running title: First clinical PGI based range verification

Corresponding author: Christian Richter, OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany, Tel. +49 351 458 6536, E-mail: christian.richter@oncoray.de

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Abstract

Background and Purpose: To improve precision of particle therapy, *in vivo* range verification is highly desirable. Methods based on prompt gamma rays emitted during treatment seem promising but have not yet been applied clinically. Here we report on the worldwide first clinical application of prompt gamma imaging (PGI) based range verification.

Material and Methods: A prototype of a knife-edge shaped slit camera was used to measure the prompt gamma ray depth distribution during a proton treatment of a head and neck tumor for seven consecutive fractions. Inter-fractional variations of the prompt gamma profile were evaluated. For three fractions in-room control CTs were acquired and evaluated for dose relevant changes.

Results: The measurement of PGI profiles during proton treatment was successful. Based on the PGI information, inter-fractional global range variations were in the range of ±2 mm for all evaluated fractions. This is in agreement with the control CT evaluation showing negligible range variations of about 1.5 mm.

Conclusions: For the first time, range verification based on prompt gamma imaging was applied for a clinical proton treatment. With the translation from basic physics experiments into clinical operation, the potential to improve the precision of particle therapy with this technique has increased considerably.

Introduction

Range uncertainties can compromise the physical advantage of proton therapy [1–4]. Currently, large range uncertainties lead to substantial safety margins and the irradiation of normal tissue. Furthermore, they influence the choice of beam angles as in the presence of range uncertainties the beam should not stop directly in front of an organ at risk. Hence, it is widely accepted in the particle therapy community that a reduction of range uncertainties is crucial for the success of particle therapy in the long term and will relevantly influence the ongoing controversial of the benefit of particle therapy [5–10].

The measurement of the proton range in the patient, so-called *in vivo* range verification, has been pursued as an important means to reduce range uncertainties. Several methods for range verification using either nuclear interactions of the particle beam (particle therapy positron emission tomography [11,12] and prompt gamma ray based methods [13–16]) or induced biological changes visualized with tomographic imaging [17,18]. In contrast to other methods of range verification in proton therapy, prompt gamma based techniques promise range assessment in real time during dose delivery [19]. Range information could be extracted from spectral [14], temporal [15], or spatial patterns [20] of the prompt gamma rays produced in interactions of protons with atomic nuclei of the tissue crossed. The latter approach, called prompt gamma imaging (PGI), has been pursued by research groups throughout the world following different imaging concepts.

So far, however, none of the prompt gamma based range verification techniques was applied in patient treatments but only in phantom and basic physics experiments. Currently the knife-edge slit camera [13,21] is the only system with a proven potential of providing range information not only in dedicated laboratory experiments but in real patient treatments. In autumn 2014, OncoRay and IBA have started a project dedicated to the translation of this PGI system into clinical application. Several challenges concerning this goal have been tackled in many translational oriented experiments, like a robust energy calibration procedure [22]. Furthermore, workflow and tools have been developed for this task.

Here we report on the worldwide first clinical application of prompt gamma imaging (PGI) based range verification, namely the knife-edge slit camera, for evaluation of inter-fractional range variations. Although developed for application in active scanning proton therapy, it was applied for a passive scattered proton treatment as active scanning was not available yet at the proton center in Dresden when this study was conducted. The application for passive scattered proton therapy (PSPT) increases the challenge but also limits the spatial information from the prompt gamma measurement.

Material and Methods

The application of the PGI slit camera was performed at the Universitäts Protonen Therapie Dresden (UPTD) at OncoRay in Dresden, Germany within a clinical study (PRIMA, DRKS00009224) that was approved by the local ethics committee (EK181042015). The patient gave written consent for participating in the study and the use of his data.

The knife-edge shaped slit camera

The PGI knife-edge shaped slit camera, mounted on a trolley for flexible positioning and alignment, is a non-commercial prototype developed by IBA [13,21]. This camera basically consists of a knife-edge shaped slit collimator projecting the prompt gamma-ray emission profile produced by the particle beam in the patient onto an array of 40 individual scintillation detectors, arranged in two rows and optimized for detecting gamma rays of 3-6 MeV energy, resulting in a spatially resolved gamma profile. Details of the camera construction and operation are presented in [13,21]. Before clinical application, the camera prototype was intensively characterized, calibrated, optimized and its application in passive scattered proton therapy (PSPT), so-called double scattering, was tested in phantom experiments. This work will be published elsewhere [22]. Originally, the camera was designed for pencil beam scanning (PBS) application only. However, at time of clinical application at UPTD only PSPT was available for clinical use. PSPT holds the challenge of an increased neutron induced gamma background. Nevertheless, we were able to show that valuable prompt gamma

profiles can be acquired by subtraction of a separately measured background with the slit collimator closed [22]. Furthermore, no spot-by-spot information is available since the whole target volume is irradiated at once. Still, it is possible to resolve different iso-energy layers corresponding to different steps of the modulator wheel - in addition to the sum profiles including prompt gamma signal from the whole irradiation. The procedure of application, including the alignment of the camera trolley, was tested before in a dedicated workflow training together with the RTTs.

The patient and radiotherapy treatment

The 60 year old patient, was referred for primary radiotherapy of an adenoid cystic carcinoma of the left salivary gland. A mixed modality treatment with photon IMRT of 50 Gy to the tumor and lymphatic drain and a proton boost of 24 Gy-RBE to the tumor region and the involved lymph nodes was prescribed, both with 2 Gy-RBE per fraction. The proton boost was delivered before the photon treatment to minimize the anatomical changes during the course of proton treatment. Proton treatment was delivered at the UPTD that is based on an IBA C230 cyclotron and a universal nozzle (IBA). Clinical proton treatment planning was done with XIO® (Elekta AB, Stockholm, Sweden) using PSPT. For the last 7 consecutive fractions (Fx) of the proton boost, the PGI slit camera was applied during the delivery of one of three treatment fields. The double scattering field is characterized by a range of 13.5 cm, a spread out Bragg peak (SOBP) modulation of 10.7 cm and a gantry angle of 45°. Nominal dose rate was set to 2 Gy (RBE) / min. For this field 99.5 monitor units were delivered each fraction. Patient positioning was performed using orthogonal x-Ray information by optimizing bony anatomy match to the planning CT in the target region.

Control CTs and dose reconstruction

At three of the seven fractions, a control CT was acquired with a diagnostic in-room CT on rails (Siemens Definition AS, Siemens Healthcare GmbH, Erlangen, Germany) in Dual Energy mode. Pseudo-monoenergetic CT scans (E=77 keV) were reconstructed from the two dual energy scans (80 kVp, 140 kVp). To monitor potential changes in dose distribution due

to anatomical changes, the nominal treatment plan was recalculated on all available CT data sets, after manual rigid registration with the planning CT by the responsible RTT, using Raystation 4.7 (Raysearch Laboratories AB, Stockholm, Sweden). For analyzing the presence of dose-relevant anatomical inter-fractional changes, dose volume histograms (DVH) and line dose profiles were retrospectively evaluated.

Background subtraction and further PGI data processing

For one of the seven fractions the background signal was measured by using a closed slit hindering most of the prompt gamma photons to reach the detector. Additionally, the background measurement was performed on a daily basis after the end of patient treatments in a homogenous water phantom to take into account potential inter-fractional changes in the relative detector sensitivity. This was possible for 5 of the 7 days. After ensuring that the shape of the background signal (counts over detector number) is similar for both types of background measurements (for water vs. patient irradiation), the respective water-measured background profiles were used for background subtraction. Before subtraction, the background profiles needed to be scaled as the prompt gamma integral count rate depends on the target. A normalization method assuming a constant ratio of the integral count rate between measurement with open slit and closed slit was applied. For the two days when no water background measurement was performed (Fx 1 and Fx 7), the background measurement from the adjacent treatment day (Fx 2 and Fx 6, respectively) were applied. In Table 1 an overview over available PGI and control CT data is presented.

Moreover, for PGI based evaluation of the inter-fractional changes the shift of the PGI net sum profiles against each other was determined using an automated shift detection algorithm published earlier [23]. To ensure that random noise does not influence the shift detection, standardly a Gaussian filter (σ = 8.5 mm) was applied [23]. Furthermore, iso-energy resolved net profiles were calculated performing a time-resolved analysis of the PGI signal incorporating the information of the modulator step length, first proposed and shown in [24,25].

Results

We report on the first clinical application of the PGI slit camera from IBA that is by the knowledge of the authors the first clinical application of a PGI based range verification system.

The patient was selected because of the relatively large lateral field size (large aperture opening), resulting in a high ratio of prompt gamma induced signal to neutron-induced background. Furthermore, it was ensured that the angle of the selected field and the patient positioning allows the application of the slit camera.

The camera was applied during 7 consecutive fractions. The position of the camera trolley during proton treatment is shown in Figure 1. The slit opening was oriented perpendicular to the beam direction (45°). The slit-to-isocenter distance and detector-to-slit distance were 25 cm and 20 cm, respectively, resulting in a nominal field of view of 10 cm (valid for the central beam axis). The room lasers were used for positioning of the camera relative to the isocenter. The inter-fractional stability of the relevant lasers was controlled daily, using check marks in the room. The positioning accuracy of the patient relative to the room isocenter (careful positioning with orthogonal X-rays) in the direction of the beam was estimated to be well below 1 mm.

The prompt gamma net sum profiles, after application of the background subtraction, are presented in Figure 2. Already from the visual impression the similarity of the prompt gamma ray profiles is evident. However, the profile acquired in fraction 1 possesses a higher grade of non-uniformity, especially in the region of the count rate maximum. This can be explained with small changes in the relative detector response (gains) between the patient measurement and the background measurement that were not at the same day for this fraction. For this reason it was excluded from further analysis.

The results of the iso-energy layer resolved prompt gamma profile analysis is shown in Figure 3. Basically, it is in consistence with the sum net profile analysis. The fragmentation of the PGI information for the different iso-energy layers provides additional spatial range information, compared to the sum net profiles.

The automated shift detection of the PGI net profiles after application of the Gaussian filter resulted in inter-fractional range deviations between -2.0 and +1.3 mm from the mean range. This is within the uncertainty of the PGI measurement, as already the position accuracy of the PGI slit camera was previously determined with 1.1 mm (2σ) [22]. Together with the positioning accuracy of the patient relative to the isocenter, the total uncertainty of the slit camera position is in the range of 2 mm. Automated shift detection with the unsmoothed PGI net profiles resulted in comparable results.

Independently, also the evaluation of the control CT based dose reconstruction, available for three fractions, showed only negligible deviations in the dose distribution, cf. Figure 4. Line dose evaluation revealed typical inter-fractional range deviations of 0-1.5 mm. No influence of target volume DVH was found. Also for organs at risk, no substantial DVH variations were seen. Therefore, PGI based and control CT based evaluations of inter-fractional variations are in agreement to each other.

Discussion

Twelve years after the original presentation of the idea of using prompt gamma-rays for range verification [26] and 9 years after the first evidence in a basic physic phantom experiment [20], we report on the first in man application of a prompt gamma based range verification. The applied knife-edge slit camera, dedicated for clinical application, has been continuously developed over the last 5 years. In Dresden, we have developed robust workflows for energy calibration, quality assurance and positioning [22].

With the work presented here, we could demonstrate that the slit camera can be applied under clinical conditions and derive spatial information of the prompt gamma production and therefore information of the proton range. For reasons of treatment mode availability, the camera was applied in PSPT, which is not optimal for prompt gamma measurements due to the high neutron-induced background and loss of the spot-by-spot information. The increased neutron background could be tackled by background measurement and its subtraction. The reduced spatial information of the prompt gamma signal due to the averaging over a large treatment area, instead of spot wise information, is intrinsic to the beam delivery in PSPT. This can lead to the non-detectability of local range shifts for two conditions: (a) The change of the PGI signal caused by a local range shift appearing in a small area is too small, compared to the unchanged PGI signal, so that the change is not detectable in the sum PGI signal. (b) If two different local range shifts occur in the treatment area with one resulting in a higher range and the other in a smaller range, these shifts could compensate each other resulting in an unchanged sum signal. As the importance and probability of both effects is directly related to the size/volume of the treatment field that is averaged for the prompt gamma sum signal measurement, we judge the separation in the different iso-energy layers and thereby increasing the spatial information, as applied in the work, as an important procedure to reduce the influence of these effects. Even if we know, that not every range shift can be detected with the application of the slit camera in PSPT mode, there is still a strong value in having this additional information for range verification and the detection of local shifts in a bigger volume or even global range shifts. Further improvements can be expected from not only evaluating shifts of the profile but also changes in the profile gradient, that is a measure for the different ranges that are mixed in the average signal.

For application of the slit camera in PBS mode due to be performed in the near future, better spatial and statistical information is anticipated and no background subtraction will prove

necessary. For PSPT application currently no simulation of the expected prompt gamma profile is available. Hence, the presented work was focusing on relative inter-fractional variations rather than on absolute range determination.

Furthermore, it should be noted that with the current trolley setup that application of the slit camera is limited to specific target sites and beam directions due to geometrical limitation. For example, the camera cannot be positioned below or above the patient as it would be needed for monitoring horizontal beams as used for example in prostate treatments. However, this is no general limitation of the method as the camera could in future be mounted to the gantry. This would also minimize the influence of camera positioning relative to the isocenter.

The inter-fractional analysis of the PGI measurements revealed minimal variation in the prompt gamma profiles of ±2 mm in the sum profiles, in consistence with the control CT based evaluation of dosimetric variations. This is an important finding for the first clinical application. The inter-fractional variation needs to be set into relation to the absolute range uncertainty that is assumed in our clinic, being 6.7 mm in the case of this field (3.5% of the nominal range + 2 mm). Even if having in mind that a substantial part of this uncertainty can be interpreted as systematic, e.g. the uncertainties in the CT to water equivalent path length transformation, the inter-fractional range variation analysis confirms that for the random contribution of the range uncertainty the treatment was well within the allowed range variation window. However, it would be too early to draw general quantitative conclusions on the sensitivity of the method from this single case. From phantom experiments we know that range shifts of about 2 mm can be detected. However as discussed above, for PSPT application the sensitivity depends on the lateral size of the region where the range shift occurs as the measured profile is an average over the whole SOBP region (sum profiles) or at least over the respective iso-energy layer. With more clinical data, acquired in the near future by the continuation of our clinical study, a systematic correlation between measured prompt gamma profiles and anatomical changes visible in control CT will be possible.

Translational relevance and outlook

This work demonstrates for the first time that prompt gamma ray based range verification can be applied for clinical treatment of patients. With the translation from basic physics experiments into clinical operation, the potential to improve the precision of particle therapy with this technique has increased considerably, and substantial technical and practical challenges have been solved. Further plans include the continuation of the clinical study to perform systematic evaluations based on an appropriate patient number. Moreover, the application of the slit camera in PBS proton treatments is planned to make use of the spot-by-spot range information and the comparison with available analytical simulation allowing not only relative (inter-fractional) but also absolute range evaluations. Also further technical improvements of the slit camera as well as the translation of another prompt gamma based verification method, prompt gamma ray timing (PGT) [15], are planned. If these further steps confirm that prompt gamma ray based technology is capable for range verification it might be used in the near future for online quality assurance as well as in midterm for potential margin reduction with clinical benefit.

Acknowledgements

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Conflict of Interest Statement

The authors report no conflict of interest. This work was performed within a research cooperation between IBA, OncoRay and HZDR. The authors alone are responsible for the content and writing of the paper.

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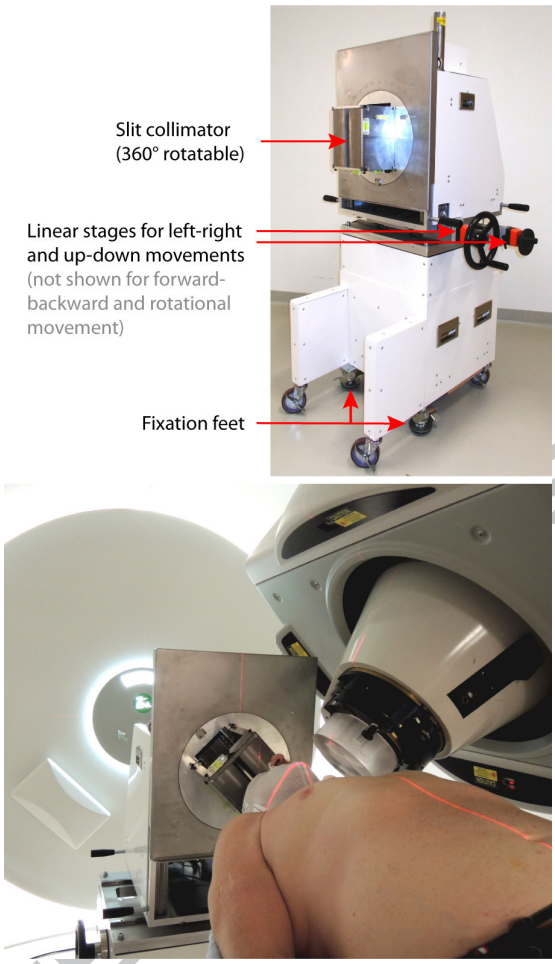

Figure 1: PGI slit camera trolley (upper row) and its application during patient treatment (lower row).

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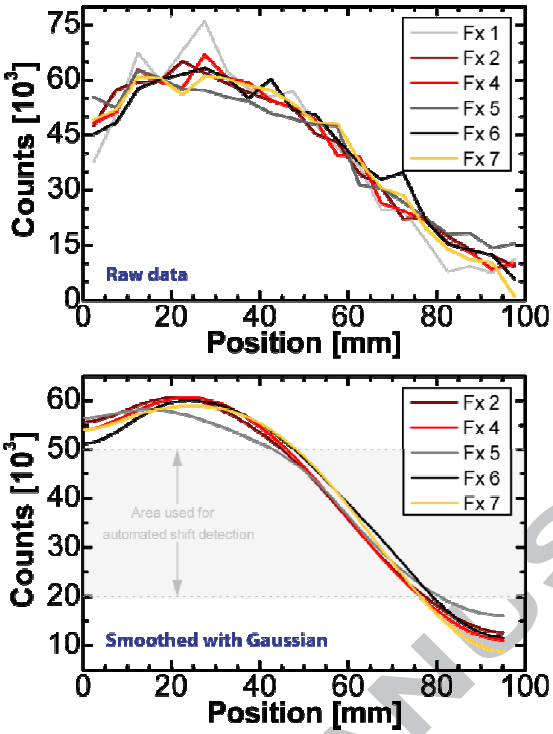

Figure 2: PGI net sum profiles before (upper row) and after (lower row) application of a Gaussian filter (20 mm). The area that was used for automated shift detection is shown in grey. Detected inter-fractional range shifts relative to the mean range were below 2 mm. Please note that fraction 1 had to be excluded from automated shift detection as the non-uniformity of the profile resulted in an evident distortion of the smoothed profile.

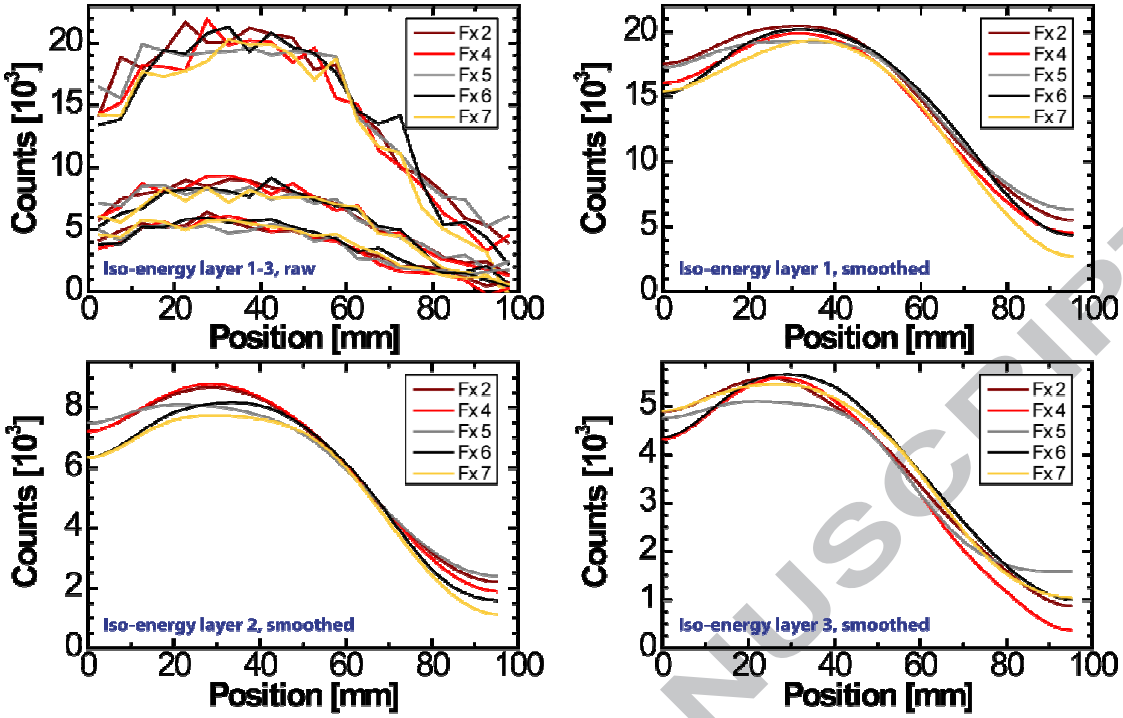

Figure 3: PGI net profiles for the first three iso-energy layers corresponding to the first three modulator wheel steps. The upper left figure shows the raw net profiles; in the other figures the Gaussian smoothed data for the first three iso-energy layers is shown. Due to different dose deposited by the corresponding Bragg peaks the prompt gamma net profiles possess different signal heights. Note the different scale on the y-axis.

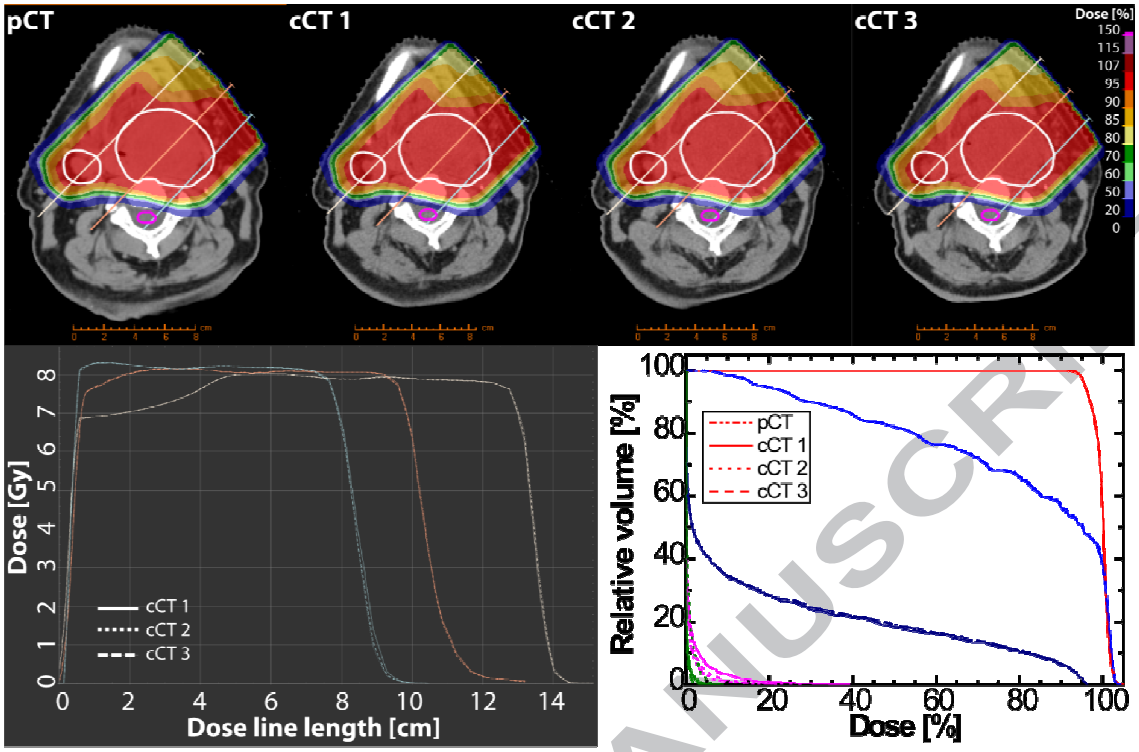

Figure 4: Control CT evaluation. Upper row: Dose distribution of the beam monitored with the slit camera on the planning CT and recalculated on three control CTs. Lower row: Representative line dose profiles (see upper row for location of lines) for the three control CTs. Range variations were below 1.5 mm. DVH for the nominal treatment plan and the three recalculated dose distributions (red: CTV, blue: left parotic gland, dark blue: right parotic gland, purple: spinal cord, green: brain stem). Note, that for cCT3 no DVH for CTV and spinal cord are shown because the CT field of view was too short in caudal direction.

Table 1: Overview of available measurements and schedule.

	Fx 1	Fx 2	Fx 3	Fx 4	Fx 5	Fx 6	Fx 7
Slit open measurement during patient treatment							
Background measurement during patient treatment (slit closed)							
Background measurement in water phantom (slit closed)							
Control CT + Dose reconstruction		cCT1		cCT2			cCT3

Figure legends

Figure 1: PGI slit camera trolley (upper row) and its application during patient treatment (lower row).

Figure 2: PGI net sum profiles before (upper row) and after (lower row) application of a Gaussian filter (20 mm). The area that was used for automated shift detection is shown in grey. Detected inter-fractional range shifts relative to the mean range were below 2 mm. Please note that fraction 1 had to be excluded from automated shift detection as the non-uniformity of the profile resulted in an evident distortion of the smoothed profile.

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