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Short Communication

Potential margin reduction in prostate cancer proton therapy with prompt gamma imaging for online treatment verification

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ABSTRACT

The potential of proton therapy is currently limited due to large safety margins. We estimated the potential reduction of clinical margins when using prompt gamma imaging (PGI) for online treatment verification of prostate cancer. For two adaptive scenarios a potential reduction relative to clinical practice was evaluated. The use of a trolley-mounted PGI system for online treatment verification to trigger an adaptation reduced the current range margins from 7 mm to 3 mm. In a case example, the dose reduction due to reduced range margins was substantially larger compared to reduced setup margins when using pre-treatment volumetric imaging.

1. Introduction

The finite penetration depth of protons as well as their Bragg-peak shaped depth-dose curve are the main characteristics employed by proton therapy (PT), which allow to reduce the integral dose to healthy tissue compared to photon therapy [1]. However, calculating proton stopping-power-ratios (SPR) from CT introduces uncertainties in range prediction, for which generous safety margins around the target are needed [2]. Moreover, potentially occurring anatomical changes between planning and treatment have to be considered. Due to its online capabilities, treatment verification with prompt gamma imaging (PGI) bears the potential to reduce these safety margins [3]. A first PGI prototype system has been tested under clinical treatment conditions [4,5] while a second-generation trolley-mounted PGI system [6] is currently used in an ongoing observational clinical study. Online treatment verification with PGI offers not only a "safety net" quality assurance functionality and can act as trigger for interventions, but also offers the potential of substantially reduced margins.

The aim of this study was to assess the potential margin reduction when using PGI for online treatment verification and intervention in prostate cancer PT and its associated dose sparing.

2. Methods and materials

Data from ten PGI-monitored prostate-cancer patients treated at the University Proton Therapy Dresden (UPTD) were considered (PRIMA: DRKS00009224 / ethics approval: EK181042015). All patients received 20 fractions, each delivering 3 Gy to the primary and 2.4 Gy to the elective target volume by two opposing lateral fields (considering a relative biological effectiveness of 1.1). In total, PGI information from 74 fractions (148 field deliveries) was available.

First, we assessed for the so-called reference scenario the current clinical margin components considered during treatment planning for this cohort, namely a setup uncertainty of 3 mm and the DECT-based [7] range uncertainty of 7 mm (Supplementary Material). Second, the potential margin reduction was estimated when using PGI-based treatment verification (PGI-TV) to trigger a treatment adaptation; referred to as scenario A in the following. Third, we set the potential margin reduction when using PGI-TV in relation to other possibilities for reducing margins. In scenario B, not only PGI-TV but also volumetric imaging at isocenter for optimal patient setup was assumed. Finally, the impact of the reduced margins on dose parameters was investigated for an exemplary patient case.

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2.1. Scenario A: Margin reduction with PGI for online treatment verification

In scenario A, the potential margin reduction compared to the clinical reference scenario was estimated when using our current PGI system for treatment verification. Hereby, a setup protocol with daily orthogonal 2D imaging (no pre-treatment volumetric imaging) and online PGI-TV triggering re-imaging in case of deviations followed by treatment adaptation was assumed.

As the target structures (prostate and seminal vesicles) are surrounded by soft tissue which has a comparable stopping power, changes in the CTV position might not be detected with PGI in certain situations. We therefore kept the clinical iCTV margin unchanged. Setup errors might have an influence on the proton range and some, especially patient shifts in beam direction, would be detectable with PGI. However, as this is a rough estimation for a workflow without daily volumetric imaging or pre-treatment adaptation, we also kept the setup uncertainty unchanged.

PGI is able to detect range errors, which allows reducing margins for range uncertainties as deviations between expected and measured PGI signals could trigger control CT imaging followed by plan adaptation, if needed. The margins for range uncertainties should not be reduced further than the intrinsic uncertainty of the PGI system. We determined the accuracy of the current 2nd generation trolley-mounted PGI system (IBA, Louvain-La-Neuve, Belgium) [4] by calculating the uncertainty of the measured mean range shifts for 148 fields. For all 74 fractions, an in-room control CT in treatment position was acquired before irradiation, which served as ground-truth information for the calculation of expected PGI signals. In this way, resulting range shifts between expected and measured PGI signals are caused by errors in the CT-based range prediction (systematic errors) or by uncertainties of the PGI range determination (mainly due to statistical uncertainties [6]), but not by (inter-fractional) anatomical changes. For each monitored field, the mean weighted shift of all spots was calculated. Each spot shift was weighted with the number of protons delivered at the respective spot, as PGI signals from high-weighted spots are more reliable due to enhanced counting statistics [8]. While the average of the 148 weighted means represents the range prediction uncertainty (cf. [6]), here we were interested in an estimate for the statistical uncertainty of the PGI system per field. Therefore, we calculated the 2σ variation of the 148 weighted mean shifts.

2.2. Scenario B: Additional margin reduction using pre-treatment volumetric imaging along with PGI

In another scenario, we assumed the patient to undergo volumetric imaging before treatment start, after which the current PGI system is used for online treatment verification. Using volumetric imaging before treatment, margins for setup uncertainty can be reduced, as patients will be directly treated in imaging position and positioning uncertainties are expected to be marginal. Following other studies, the current setup uncertainty margins were reduced to 1 mm (-66%) [9,10].

2.3. Influence of reduced margins on dose parameters – a case study

The benefit of the potentially reduced margins in scenario A and B was investigated in terms of dose parameter changes and compared for an exemplary patient case. The clinical treatment plan was robustly re-optimized with the estimated reduced margins for both scenarios. All plans were generated in RayStation (v.8.99, RaySearch Laboratories AB, Stockholm, Sweden) using the initial clinical objectives and constraints, while maintaining the mean dose in the iCTVp. Dose parameters were extracted for the following regions of interest: iCTVp, a ring structure of 2 cm around iCTVp, bladder and rectum. Furthermore, the total monitor units (MU) were analyzed as surrogate of the integral dose.

3. Results

3.1. Reduced range margins with PGI for online treatment verification

The 2σ variation of the 148 weighted mean shifts per field, serving as surrogate for the intrinsic uncertainty of the current PGI system, was 3 mm. Hence, in scenario A and B, the range uncertainty margins were reduced from 7 mm to 3 mm (-57%) due to PGI-TV, while in scenario B also the setup uncertainty margins were reduced to 1 mm (-66%) due to volumetric imaging (cf. Table 1).

3.2. Influence of reduced margins on dose parameters

For an exemplary patient, the mean dose (33.5 Gy) inside a 2 cm ring structure around the iCTV was reduced by 1.8 Gy in scenario A and by 2.3 Gy in scenario B, also slightly affecting the organs-at-risk (rectum and bladder) dose volume histograms, cf. Fig. 1. The volume parameters V_{40Gy} and V_{50Gy} of the bladder and rectum were marginally reduced in the order of one percentage point. However, compared to the reference scenario, the total number of MUs was reduced by 2.8% for the plan in scenario A and by 4.1% for scenario B.

4. Discussion

Based on the so far largest data base worldwide for PGI data, we have investigated the margin reduction potential with PGI-based online treatment verification for prostate cancer patients. Current range margins were reduced from 7 mm to 3 mm (-57%) resulting in beneficial dose parameters as shown exemplarily. In fact, the positive impact on dose parameters of PGI-enabled tighter range margins was substantially larger than the effect of reduced setup margins. The reduction of range margins is even more auspicious as an already small range uncertainty margin is used in our reference scenario due to the application of the DECT-enabled DirectSPR approach in our institution. Most PT centers use larger range uncertainty margins between 3% and 3.5% plus 1–2 mm [11] which were recently justified in an inter-center comparison study on range prediction accuracy [12]. Hence for those centers, the margin reduction potential is even higher when implementing improved CT-based range prediction methods together with PGI-TV.

Using the current PGI system for online treatment verification does not have a big influence on the clinical workflow besides a small prolongation (1 min/field) for positioning the trolley underneath the patient table. An immanent prerequisite for the reduction of the range uncertainty margin by PGI-TV is the capability to react when PGI detects a relevant deviation. This means to adapt the treatment in case a triggered control CT confirms a relevant treatment deviation. In this study,

Table 1
Margin components for prostate cancer treatments for the current clinical situation (Ref) as well as when using PGI-TV (A) and when using PGI-TV with additional volumetric imaging for patient setup (B).

		CTV to iCTV margin	Patient setup uncertainty	Range uncertainty
(Ref)	Current margins	4 mm	3 mm	7 mm*
(A)	Reduced margins: PGI-TV	4 mm	3 mm	3 mm (-57%)
(B)	Reduced margins: PGI-TV and volumetric imaging for setup	4 mm	1 mm (-66%)	3 mm (-57%)

*Average range uncertainty of 10 prostate cancer patients (2%+2mm).

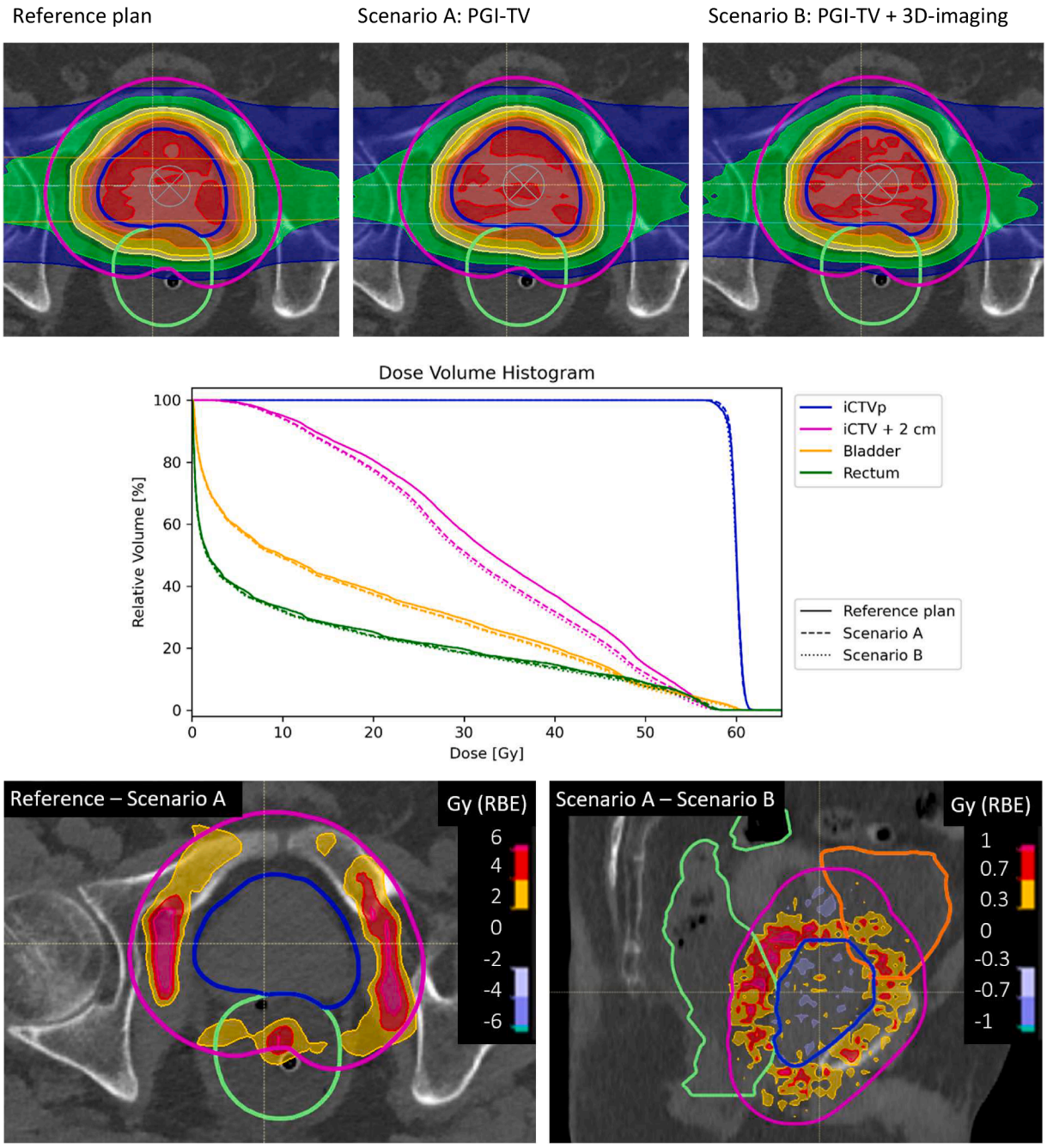

Fig. 1. *Top:* Reference plan with clinical margins for an arbitrarily selected patient with opposing lateral beams and re-optimized plans with reduced margins in scenario A and B. *Middle:* Dose volume histograms showing the differences for iCTVp, bladder, rectum and the 2 cm ring structure around the iCTVp. *Bottom left:* Dose difference between the reference scenario and scenario A in transversal view indicating a dose reduction mainly at the distal field edges due to the reduced range uncertainty margin. *Bottom right:* The dose difference between scenario A and B in sagittal view showing an additional minor dose reduction uniformly around the target due to the reduced patient setup margin.

the speed of the adaptation was not specified. The adapted plan can either be applied in the next fraction (in case of a systematic anatomical change) or – assuming an online-adaptive workflow – even for the same fraction where the deviation was detected if the treatment was interrupted before the fraction was completely delivered. The concrete intervention depends on the type of deviation detected on the control CT. While an adaptation for the next fraction would be reasonable for systematic anatomical changes, for intra-fractional changes an (online) adaptation would be more challenging. A temporal increase of margins would be another option.

Due to limited resources in current clinical practice, a treatment is only adapted when dose-volume-histogram parameters are violated. For the investigated cohort, large clinical margins were used so that no adaptation was performed during the course of treatment. However, when using reduced uncertainty margins, small treatment deviations could already have severe effects on the delivered dose and treatment verification becomes inevitable.

We further envision an improved intrinsic PGI accuracy such as having a gantry built-in PGI system in the future. We assume the positioning uncertainty of such a PGI system to be similar to other gantry-mounted systems, e.g. the orthogonal X-ray imaging, used in the current clinical workflow. The positioning precision of the current trolley-

based PGI camera is 0.5 mm (1σ) [6] while the uncertainty of the X-ray system is about 0.2 mm (2σ) according to regular machine quality assurance measurements. This additional reduction of range uncertainty margins could become even larger when future improvements, such as improved detectors or multi-feature treatment verification, are exploited [13].

Scenario A showed a reduction in mean dose of around 2 Gy in the 2 cm ring structure around the target, while the reduction in dose to the organs-at-risk was rather small. However, for other treatment sites, like head-and-neck patients, where the critical organs-at-risk are closer to the target, a mean dose reduction of about 2 Gy just by reducing the margins for range and setup uncertainty could make a substantial difference. Interestingly, in scenario B, where also the setup uncertainty margin was reduced from 3 to 1 mm (-66%), little additional benefit in terms of dose parameters was observed in our exemplary patient.

Imaging in treatment position enables reduced setup uncertainty margins, however, to reduce range uncertainty margins, online treatment verification, such as PGI-TV, is required. We exemplarily showed that the latter one has a substantially larger effect on the reduction of the mean dose in surrounding healthy tissue. Thus, we highly recommend the combination of pre-treatment volumetric imaging with online *in vivo* treatment verification to detect relevant deviations before and during treatment, e.g. enabled by PGI [14]. Artificial intelligence approaches can be beneficial for detecting relevant deviations from complex input data [15]. When considering re-planning on cone-beam CT based data, larger range uncertainty margins would be needed [16] which subsequently increases the need for online treatment verification.

In conclusion, for the patients analyzed in this study, our existing PGI system, which has been proven to be operational in real-world clinical treatments, would allow to reduce the current margins substantially when used as an online treatment verification and intervention tool. The positive impact on dose parameters due to the reduced margins has been exemplarily demonstrated. Especially, treatment sites with organs-at-risk close to the target would benefit. Further margin reduction and clinical benefit is expected when next-generation PG-based treatment verification systems become available.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: OncoRay has an institutional research agreement with Ion Beam Applications S.A. (IBA). G. Janssens and J. Smeets are employees of IBA. For the present study, the authors received no financial support involved in the study design or materials used, nor in the collection, analysis and interpretation of data nor in the writing of the publication. The other authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2023.100447.

References

[1] Paganetti H, Niemierko A, Ancukiewicz M, Gerweck LE, Goitein M, Loeffler JS, et al. Relative biological effectiveness (RBE) values for proton beam therapy. Int J Radiat Oncol Biol Phys 2002;53:407–21. https://doi.org/10.1016/S0360-3016(02)02754-2.

[2] Paganetti H. Range uncertainties in proton therapy and the role of Monte Carlo simulations. Phys Med Biol 2012;57:R99. https://doi.org/10.1088/0031-9155/57/11/R99.

[3] Hueso-González F, Fiedler F, Golnik C, Kormoll T, Pausch G, Petzoldt J, et al. Compton camera and prompt gamma ray timing: two methods for in vivo range assessment in proton therapy. Front Oncol 2016;6:80. https://doi.org/10.3389/fonc.2016.00080.

[4] 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. https://doi.org/10.1088/0031-9155/57/11/3371.

[5] 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. https://doi.org/10.1016/j.radonc.2016.01.004.

[6] Berthold J, Khamfongkhruea C, Petzoldt J, Thiele J, Hölscher T, Wohlfahrt P, et al. First-in-human validation of CT-based proton range prediction using prompt gamma imaging in prostate cancer treatments. Int J Radiat Oncol Biol Phys 2021;111:1033–43. https://doi.org/10.1016/j.ijrobp.2021.06.036.

[7] Peters N, Wohlfahrt P, Hofmann C, Möhler C, Menkel S, Tschiche M, et al. Reduction of clinical safety margins in proton therapy enabled by the clinical implementation of dual-energy CT for direct stopping-power prediction. Radiother Oncol 2022;166:71–8. https://doi.org/10.1016/j.radonc.2021.11.002.

[8] 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. https://doi.org/10.1088/0031-9155/59/19/5849.

[9] Nenoff L, Matter M, Lindmar JH, Weber DC, Lomax AJ, Albertini F. Daily adaptive proton therapy – the key to innovative planning approaches for paranasal cancer treatments. Acta Oncol 2019;58:1423–8. https://doi.org/10.1080/0284186X.2019.1641217.

[10] Nenoff L, Matter M, Charmillot M, Krier S, Uher K, Weber DC, et al. Experimental validation of daily adaptive proton therapy. Phys Med Biol 2021;66:205010. https://doi.org/10.1088/1361-6560/ac2b84.

[11] Taasti VT, Bäumer C, Dahlgren C v, Deisher AJ, Ellerbrock M, Free J, et al. Inter-centre variability of CT-based stopping-power prediction in particle therapy: survey-based evaluation. Phys Imaging Radiat Oncol 2018;6:25–30. doi: 10.1016/j.phro.2018.04.006.

[12] Peters N, Wohlfahrt P, Dahlgren Cv, de Marzi L, Ellerbrock M, Fracchiolla F, et al. Experimental assessment of inter-centre variation in stopping-power and range prediction in particle therapy. Radiother Oncol 2021;163:7–13. https://doi.org/10.1016/J.RADONC.2021.07.019.

[13] Pausch G, Berthold J, Enghardt W, Römer K, Straessner A, Wagner A, et al. Detection systems for range monitoring in proton therapy: Needs and challenges. Nucl Instrum Methods Phys Res A 2020;954:161227. https://doi.org/10.1016/J.NIMA.2018.09.062.

[14] Berthold J, Pietsch J, Piplack N, Khamfongkhruea C, Thiele J, Hölscher T, et al. Detectability of anatomical changes with prompt-gamma imaging: First systematic evaluation of clinical application during prostate-cancer proton therapy. Int J Radiat Oncol Biol Phys 2023. https://doi.org/10.1016/j.ijrobp.2023.05.002 (accepted).

[15] Pietsch J, Khamfongkhruea C, Berthold J, Janssens G, Stützer K, Löck S, et al. Automatic detection and classification of treatment deviations in proton therapy from realistically simulated prompt gamma imaging data. Med Phys 2022;50(1):506–17. https://doi.org/10.1002/mp.15975.

[16] Li H, Hrinivich W, Chen H, Sheikh K, Ho M, Ger R, et al. Evaluating proton dose and associated range uncertainty using daily cone-beam CT. Front Oncol 2022;12:830981. https://doi.org/10.3389/fonc.2022.830981.