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Cone-Beam CT Images as an Indicator of QACT During Adaptive Proton Therapy of Extremity Sarcomas

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ABSTRACT

Purpose: Periodic quality assurance CTs (QACTs) are routine in proton beam therapy. In this study, we tested whether the necessity for a QACT could be determined by evaluating the change in beam path length (BPL) on daily cone-beam CT (CBCT).

Patients and Methods: In this Institutional Review Board–approved study, we retrospectively analyzed 959 CBCT images from 78 patients with sarcomas treated with proton pencil-beam scanning. Plans on 17 QACTs out of a total of 243 were clinically determined to be replanned for various reasons. Daily CBCTs were retrospectively analyzed by automatic ray-tracing of each beam from the isocenter to the skin surface along the central axis. A script was developed for this purpose. Patterns of change in BPL on CBCT images were compared to those from adaptive planning using weekly QACTs.

Results: Sixteen of the 17 adaptive replans showed BPL changes ≥ 4 mm for at least 1 of the beams on 3 consecutive CBCT sessions. Similarly, 43 of 63 nonadaptively planned patients had BPL changes < 4 mm for all of the beams. A new QACT criterium of a BPL change of any beam ≥ 4 mm on 3 consecutive CBCT sessions resulted in a sensitivity of 94.1% and a specificity of 68.3%. Had the BPL change been used as the QACT predictor, a total of 37 QACTs would have been performed rather than 243 QACTs in clinical practice.

Conclusion: The use of BPL changes on CBCT images represented a significant reduction (85%) in total QACT burden while maintaining treatment quality and accuracy. QACT can be performed only when it is needed, but not in a periodic manner. The benefits of reducing QACT frequency include reducing imaging dose and optimizing patient time and staff resources.

Introduction

Proton therapy, in particular, intensity-modulated proton therapy (IMPT) with pencil-beam scanning, has been the focus of significant recent interest because of its ability to treat tumors with high conformity to tumor targets and better sparing of normal tissues. Proton therapy is widely accepted as the preferred radiation modality in treating sarcomas because of its capability to save proximal and distal normal tissues, for example, strips of soft tissue, skin, joints, bones, etc.[1–3] Proton therapy of extremity soft tissue sarcomas is expected to improve target conformality and reduce integral dose, dose to the bone while sparing lymphatic channels, and limiting dose to the circumferential limb.[4] However, proton therapy is more sensitive to changes in setup uncertainties and/or patient anatomy, which can result in incomplete target coverage and inadequate normal tissue sparing.[5] Frequent verification and adaptive planning are recommended during the course of proton therapy to ensure that targets are well covered and organs at risk (OARs) are spared in a manner consistent with the initial plan.[6–8]

Patients treated with IMPT undergo routine quality assurance CTs (QACTs) to monitor any inter-fractional changes (eg, weight variation, anatomy change, tumor growth or shrinkage, and swelling) that might require altering treatment plans and warrant adaptive planning on QACTs.[6,9,10] Identifying a method to predict when a QACT is needed and when an adaptive plan is needed could provide benefits in reducing imaging dose and optimizing the use of patient time and staff resources, providing such a method maintains the same quality of care. Periodic QACT has been regarded as routine in the clinic.[10–14] Several methods

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have been published for predicting the time to replan based on the above-mentioned change variables. In-room CT and cone-beam CT (CBCT) range-based registrations, deformable image registrations, range-corrected dose distributions, intensity correction, gamma index, and water-equivalent thickness change on CBCT have been reported for adaptive proton therapy.[7,8,15–19] However, data are limited on adaptive proton therapy for patients treated with sarcomas. In this Institutional Review Board (IRB)–approved study, we retrospectively analyzed 959 CBCT images acquired in 78 patients with extremity tumors treated with PBT at our institution. We tested whether changes in beam path length (BPL) can serve as an indicator of the need for QACT in these patients.

Materials and methods

A Patients

In this IRB-approved study, 78 extremity (15 upper and 63 lower) sarcoma patients treated with image-guided IMPT between 2017 and 2023 at an academic proton center, were retrospectively analyzed.

B Treatment planning

Simulation scans were performed on a Siemens Somatom Definition Edge CT scanner (Siemens Healthineers; Erlangen, Germany) in the head-first or feet-first supine position with customized immobilization devices. Axial images were obtained every 3.0 mm and tentative isocenter (or coordinate reference) positions were marked with radiopaque markers. Target volumes and surrounding OARs were contoured in the RayStation 8A (RaySearch Laboratories; Stockholm, Sweden) treatment planning system (TPS). Preoperative clinical target volumes (CTVs) were created from the gross tumor volumes with a 1.5 cm radial and 3.0 cm superior/inferior margins for intermediate and high-grade tumors and 1.0 cm radial and 2.0 cm superior/inferior margins for low-grade tumors. CTVs did not include adjacent bone or cross-fascial planes. Any suspicious edema was added to the CTV. CTVs were pulled out from the skin surface by 2 to 5 mm unless the disease included the skin. Postoperative CTVs were created with the tumor bed plus areas of postoperative change and scar with 1.5 cm radial expansion and 3.5 to 4.0 cm superior/inferior expansion. Typically, 2 beams with a hinge angle $>$ 30 degrees were utilized for treatment planning for cases in which the CTV did not wrap around the bone. If the target wrapped around the bone, then 3 beams were utilized for treatment planning. The beam angles were chosen to spread out the end-of-range effect for OARs to spread the impact of the distal relative biological effectiveness. The energy layer and spot spacing were between 0.7 and 1.3 σ. A range shifter of 2 to 5 cm water equivalent thickness was used based on whether the skin was included in the target or cropped by 3 to 5 mm. Treatment plans were optimized on a single-filed optimization approach for 2-beam plans and on a multi-field optimization if CTV was wrapped around the bone. The robustness setting was 3.5% range and 5-mm setup uncertainties, with 12 worst-case scenarios, with a goal of 95% CTV covered by 95% of prescription dose. Typically for sarcomas of the extremity, maximum dose, maximum dose-volume histogram, and maximum equivalent uniform dose objectives were used to achieve a uniform dose to target while sparing the dose off of the skin strip or adjacent bone. The Monte Carlo–based dose calculation engine was used to generate treatment plans. OARs utilized for robust optimization were the longitudinal strip of soft tissue, skin, bones, and joints.

C Radiation treatment

Plans were delivered with daily kV and daily or weekly CBCT image guidance. During the course of treatment, QACTs were performed either weekly or once every 2 weeks to evaluate whether the initial plan was still valid for the treatment.

D Data collection and analysis

Daily/weekly CBCT images were ray-traced from the skin to the isocenter along the beam central axis, using a homemade automatic tool in the ARIA 15.1 Oncology Information System (Varian Medical Systems; Palo Alto, CA). The pCT and CBCT processing pipelines are presented in Figures 1A and 1B respectively. First, the program gets the isocenter and the gantry/couch angles of each beam and the virtual source position in the patient-based coordinate system. Then it gets a line profile between the isocenter and the virtual source position. The line profile is composed of 3-D coordinates of a series of points and the corresponding HU values. The beam depths of all the beams of pCT are calculated through the intersection between the line profile of each beam and the patient contour. Each acquired CBCT image is rigidly registered to the pCT through the therapists' daily patient setup recorded in ARIA. A similar line profile is obtained through the isocenter and the source position. The isocenter and the source position in pCT are transformed to the CBCT images. By parsing the HU values on the line profile on each CBCT image, the intersection between the line profile and the patient surface on each CBCT image can be computed. Then the beam depths on the CBCT images are calculated. The time taken in processing one beam takes $\sim$ 5 seconds. Hence for the whole plan with 2-3 beams, it is around a quarter of 1 minute. The process of patient registration and CBCT image retrieval are verified as shown in Figure 1 C. The CBCT images were analyzed from the start of the treatment to the end of course of the treatments or until an adaptive plan was triggered on a QACT, if applicable. As a result, 83 CBCT images were analyzed for adaptive patients and 876 CBCT images were analyzed for nonadaptive patients. Of the total 78 patients, 15 were replanned on QACTs (total of 17 adaptive replans) for various reasons (Table 1). The BPL of the planning CT (pCT) was considered as a reference. The BPL change (ΔBPL) was defined as:

$$\Delta\text{BPL} = BPL_{pCT} - BPL_{CBCT}. \quad (1)$$

Changes in BPL between the pCT and CBCT were analyzed to identify any correlation with the need for QACTs (probably adaptive plans). True-positives (TPs) were outcomes in which the BPL change correctly predicted the need for QACTs, and true-negatives (TNs) were outcomes in which the BPL change correctly predicted that no QACTs would be required. Similarly, false-negatives (FNs) failed to predict the QACT requirement, and false-positives (FPs) incorrectly predicted such QACTs. Sensitivity was the ability to predict true adaptive planning based on BPL change, and specificity was the ability to correctly indicate that adaptive planning was not required (nonadaptive), expressed as:

$$Sensitivity = \frac{TP}{TP + FN} \times 100\ ,\ Specificity = \frac{TN}{TN + FP} \times 100. \quad (2)$$

In this study, we conducted statistical analysis using MATLAB (version 2023b, MathWorks, Natick, Massachusetts) to assess the significance of differences between the 2 groups. We focused on the variable ΔBPL, over 3 consecutive CBCT images and measured in millimeters.

To determine the statistical significance of group differences, we employed Welch's t test, which is suitable when sample variances are unequal. In this case, the assumption of unequal variances was reasonable due to the distinct sample sizes in the 2 groups. We utilized MATLAB's 'ttest2' function, specifying 'Vartype' as 'unequal' to account for unequal variances. This function calculated the t-statistic and associated P-value.

E Automatic data collection

We implemented an automatic data processing pipeline for this study without human intervention. This pipeline can be used for both retrospective and prospective studies. Figure 1 C shows the data

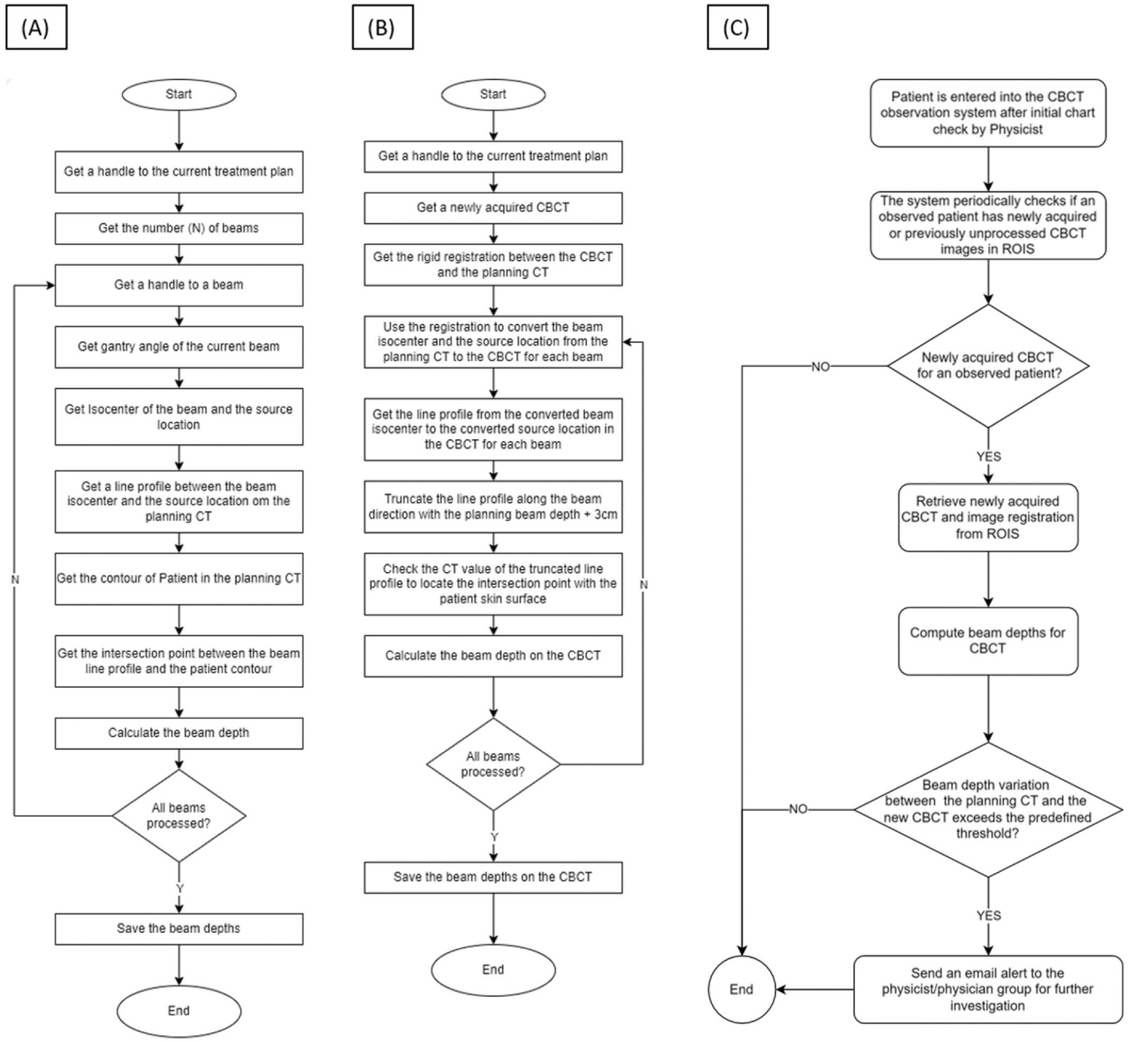

Figure 1. (A) Data processing pipeline of beam depth calculation for pCT, (B) data processing pipeline of beam depth calculation for CBCT, (C) the clinical procedure of beam depth-based adaptive planning.

processing pipeline, with a complete workflow of the automatic ray tracing along the beam path to identify any changes greater than the threshold, as well as an automatic alert system to the clinical care team. Figure 1 C shows that a patient under observation is registered into the data processing pipeline and CBCT images are retrieved from the ROIS. On average, it takes about 3～4 minutes to retrieve the needed data from ARIA for each patient.

Results

A total of 243 QACTs were performed during patient treatments, of which 17 (7%) were used for adaptive planning on QACTs. Of the 78 patients, 15 (12 with lower extremity and 3 with upper extremity tumors) were adaptively planned, and 2 were replanned twice, for a total of 17 adaptive replans. Out of these, 10 were due to anatomic changes, 2 to tumor swelling, 3 to tumor growth, 1 to tumor shrinkage, and 1 due to a hotspot in a critical organ. In 2 of the 17 adaptive replans and 30 of the 63 nonadaptives the BPL changes were negative. Thus, in most of the cases, BPL changes were positive, indicating swelling and weight gain. Such changes for 2 representative patients are presented in Figure 2. Overlaid pCT and CBCT images of sagittal and axial planes in a patient replanned at fraction 20 due to changes in anatomy are presented in Figure 2(A) and (B) respectively. Similarly, the sagittal and axial planes in a patient replanned at fraction 13 due to swelling are presented in Figure 2(B) and (D) respectively. The red contour is the gross tumor volume, and the green contour is the patient body. In both cases, the BPL changes were positive. The maximum BPL changes over each session were recorded, and, if the change was beyond the threshold for 3 consecutive sessions, then the plan was predicted for adaptive planning. By raising the BPL change threshold from 3 to 5 mm, sensitivity remained constant and specificity increased from 60% to 79.4%. Table 2 presents a 2 × 2 contingency table at a 4-mm threshold. Clinical replans indicate what actually has happened with each patient and predicted replans are those indicated by the BPL change.

Table 1
Replanned treatment sites, replan reasons, maximum BPL change, and predictions. Abbreviations: FN, false-negative; TP, true-positive.

Adaptive plan no.	Treatment site	Replan reasons	Prediction from CBCT images	Maximum BPL change (mm)
1	Rt. Face	Hotspot on eye, eye redness	TP	4.9
2	Lt. Thigh	Anatomical change	TP	10.0
3	Lt. Thigh	Anatomical change	TP	17.0
4	Rt Thigh	Anatomical change	TP	13.9
5	Rt Thigh	Anatomical change	TP	16.5
6	Rt Leg	Anatomical change and tumor swelling	TP	9.6
7	Lt Arm	Anatomical changes	TP	16.8
8	Lt Leg	Tumor growth	TP	7.6
9	Rt Leg	Tumor shrinkage	FN	3.9
10	Lt Arm	To reduce overlap hotspots between arm and axilla target	TP	18.5
11	Rt Leg	Swelling and anatomical changes	TP	8.7
12	Lt Leg	Anatomical change	TP	14.4
13	Lt Leg	Anatomical change	TP	16.8
14	Lt Thigh	Anatomical change	TP	15.5
15	Rt Thigh	Anatomical change	TP	16.8
16	Rt Thigh	Tumor growth	TP	12.5
17	Rt Leg	Tumor changes	TP	17.7

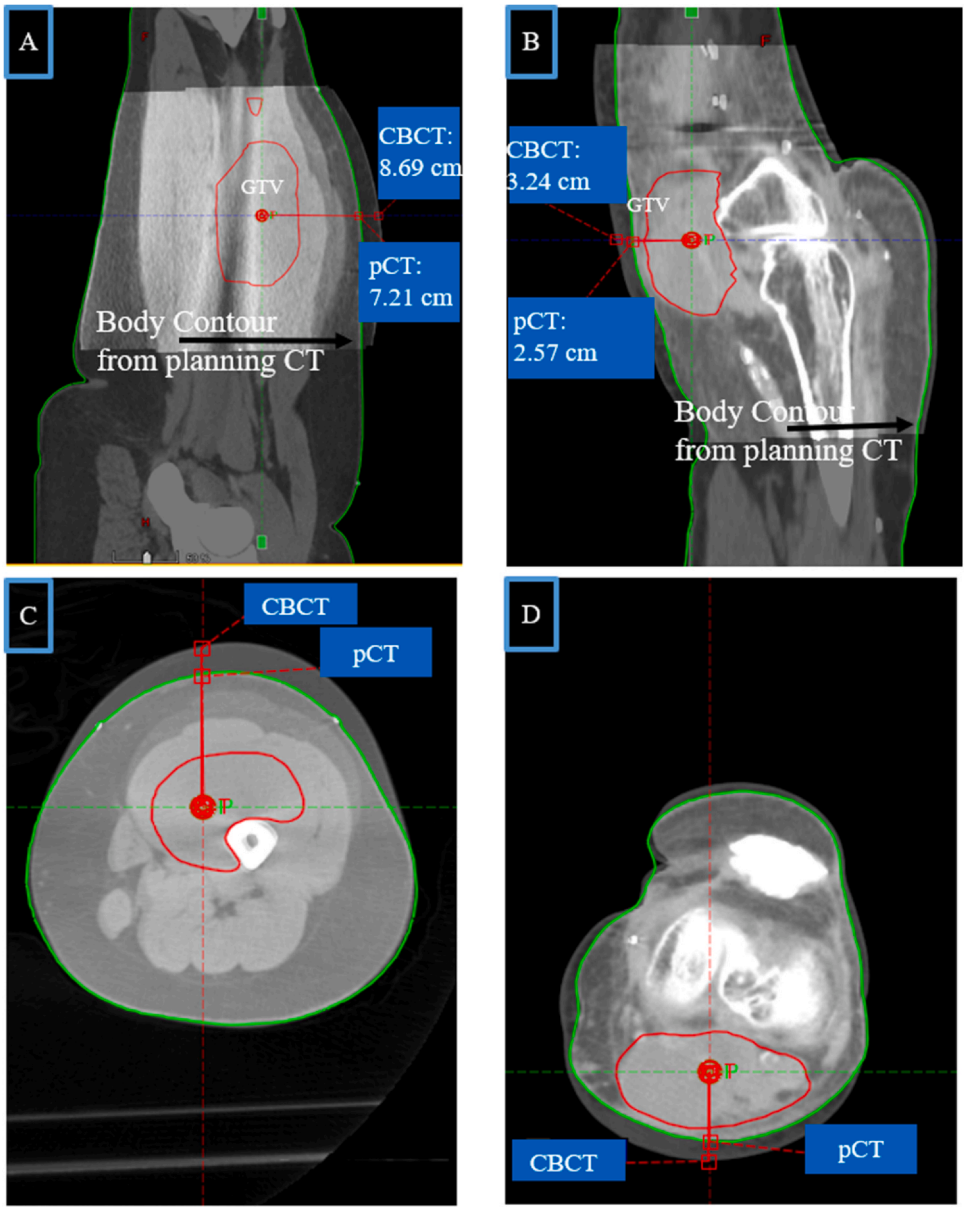

Figure 2. Overlaid planning CT (pCT) and cone-beam CT (CBCT) images of sagittal (A) and axial (C) planes in a patient replanned at fraction 20 due to changes in anatomy; and sagittal (B) and axial (D) planes in a patient replanned at fraction 13 due to swelling. The red contour is the gross tumor volume (GTV), and the green contour is the patient body. These images are solely for demonstration purpose. The BPL change is acquired automatically using the home-grown software.

Table 2
2 × 2 contingency table at 4-mm threshold.

	Clinical replan	Clinical no-replan
Predicted replan	16	20
Predicted no-replan	1	43
	Sensitivity: 94.1%	Specificity: 68.3%

Clinical replans are what actually has happened and predicted replans that are predicted from the BPL change.
Abbreviation: BPL, beam path length.

Figure 3 displays the differences between the adaptive and non-adaptive groups. Each box chart in Figure 3(A) displays the median, lower and upper quartiles, any outliers (computed using the interquartile range), and the minimum and maximum values that are not outliers. A clear difference is shown between the adaptive and nonadaptive groups, with a P value of 1.6×10^{-18}. A receiver operating characteristic (ROC) curve, is a graphical plot that illustrates the diagnostic ability of a binary classifier system as its discrimination threshold is varied. The area under the curve, which measures the entire 2-dimensional area underneath the entire ROC curve was 0.93 (Figure 3(B)), using the current classifier (0.00, 0.22). Hence there is a clear distinction between the adaptive and nonadaptive groups. The absolute values of BPL changes for both groups are presented in Figure 3(C), where each point is the minimum value of BPL change over 3 consecutive session's maximum values along all the beams. There's only 1 outlier in the adaptive group and multiple outliers in the non-adaptive group.

In this study, 16 of the 17 adaptive replans showed BPL changes ≥ 4 mm on 3 consecutive days, resulting in a sensitivity of 94.1% for BPL change as an indicator of the need for adaptive planning. The patient whose BPL changes were false-negative was replanned due to tumor shrinkage. This was a 67-year-old woman with right leg sarcoma. The treatment plan was done with 2 beams (Gantry angles at 205° and 335°). The tumor shrinkage was at the posterior side of the target, which was at the distal end of the beams, and hence it was missed by the BPL change, which accounts for change from the skin to the isocenter along the beam path. However, the tumor shrinkage was visible on the CBCT, so it would have been detected by therapists during the setup daily imaging. The maximum BPL change was 3.9 mm for the duration of the treatment with the initial plan. Similarly, 43 of the 63 nonadaptively planned patients had BPL changes < 4 mm, resulting in a specificity of 68.3%. Clinical and predictive replan and no-replan values are presented in Table 2.

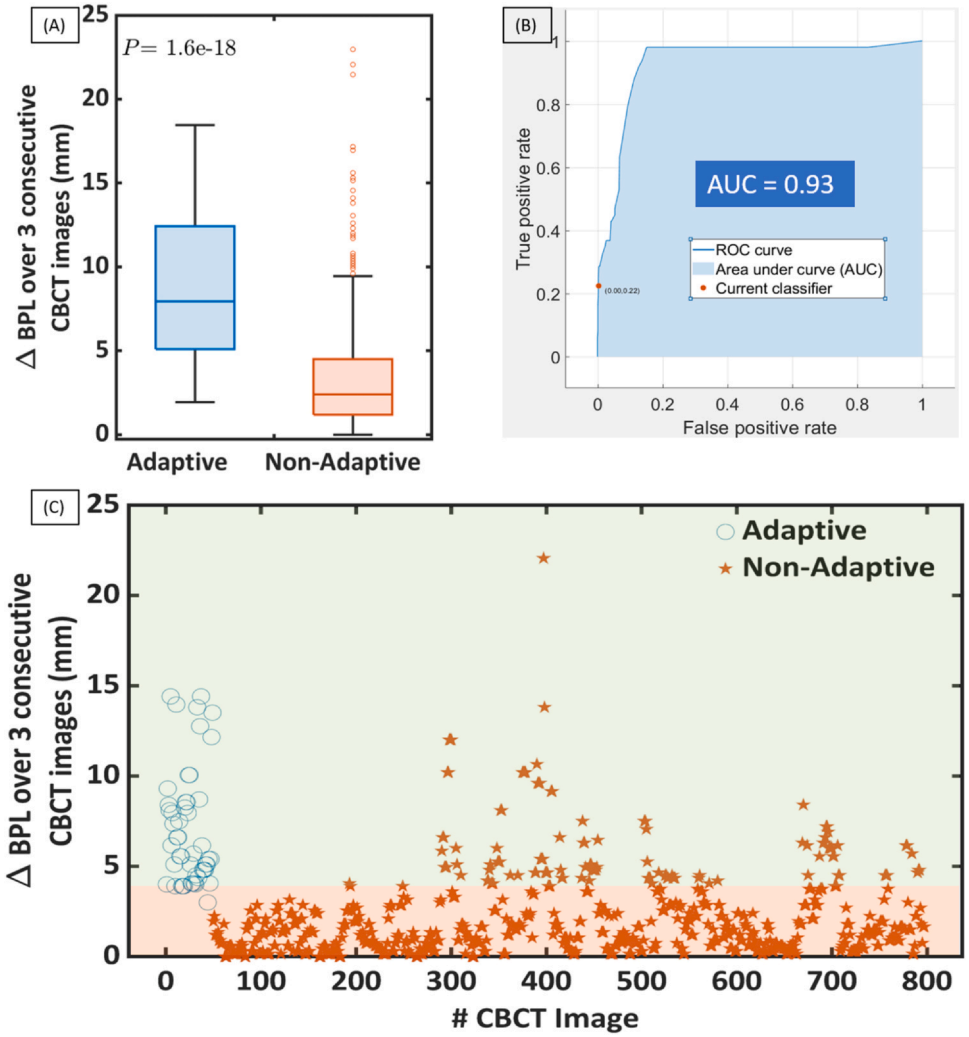

Figure 3. Maximum absolute BPL change of beams on CBCT sessions with and without replans. (A) Δ*BPL* differences between adaptive and nonadaptive groups. Each box chart displays the median, lower and upper quartiles, any outliers (computed using the interquartile range), and the minimum and maximum values that are not outliers. (B) The area under the curve (AUC), which measures the entire 2-dimensional area under the entire ROC curve is 0.93 (Figure 3(B)), using the current classifier (0.00, 0.22). (C) The absolute values of BPL change for both groups, where each point is the minimum value of BPL change over 3 consecutive session's maximum values along all the beams.

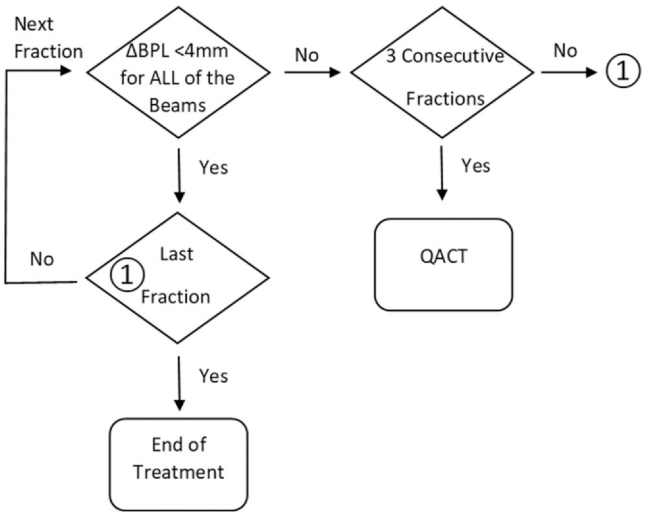

Figure 4. QACT Workflow. QACT is needed when ΔBPL is > 4 mm for any of the beams for 3 consecutive fractions.

Discussion

In our institution, adaptive replanning is determined by dosimetric analysis of routine QACT, for example, weekly QACT. Our method analyzes the variation in setup CBCTs to determine whether there is a need for a QACT, as an alternative to routine QACT for dosimetric analysis for adaptive replanning. There have been a great number of research interests in post-processing CBCT images for adaptive replanning in head-and-neck (HN), lung and prostate cancers.[7,8,15,19–22] Yao et. al. reported that range-based registration can efficiently mitigate range deviation due to patient positioning and anatomical changes in prostate cancer patients.[15] Deformation of pCT to CBCT and generation of synthetic CT (sCT) from CBCT have been heavily explored as options for automated adaptive proton therapy for HN cancers.[7,20–22] However, it involves complex methods and may mislead in contour propagation from pCT to sCT. In another study, Yao et. al. has presented WET changes on setup CBCT images and initial plan robustness as indicators of QACT requirements in HN proton treatments.[19] However, all the methods involve several complex steps and sometimes it may face challenges in clinical translation, and none of the studies presented for extremity sarcomas. Contrary to other published methods for predicting re-planning, our approach of using change in BPL is a simple reliable, and easily adaptable technique. The decision to perform adaptive replanning depends on many factors. Our data analysis shows that the range change in CBCT is a reliable surrogate to predict the requirement for adaptive plans for sarcomas patients. Furthermore, the frequency of QACTs can be significantly reduced based on the present study. This method can be implemented as either an offline or online monitor system. For offline monitor system implementation, data processing can be scheduled to run periodically. For an online monitor system implantation, an event can trigger the data processing to be run. For example, the therapists can trigger the data processing and alert the care team during patient setup. A total of 243 QACTs were performed for 78 patients; however, by using the BPL change as a predictor for QACTs, only 37 (17 adaptive plans due to 94.1% sensitivity and 20 QACTs due to 68.3% specificity) QACTs would have been performed and the remaining 206 QACTs could have been eliminated (an 84.8% reduction). The benefits of reducing QACT frequency include reduced imaging dose and optimized use of patient time and staff resources.

Figure 4 shows the suggested workflow for QACT. This workflow suggests acquiring QACT images when indicated from the daily/weekly CBCTs.

Each data process step can be scheduled for automatic launch and execution. Once the initial chart check is done for a patient, the patient can be automatically registered to the monitoring or observation system through a script. For retrospective studies, multiple patients can be registered to the system simultaneously. Once a patient is in the system, the system will periodically check for a newly acquired CBCT or a previously unprocessed CBCT image and retrieve the image. The data processing pipeline will periodically check for newly retrieved CBCT images and import these into TPS for BPL calculation. Once the BPL variation exceeds the predefined threshold, the system will send out an alert to the clinical stakeholders, such as physicists and physicians. The system will also send out a daily result summary.

Conclusion

Our study demonstrates a strong correlation ($P = 1.6 \times 10^{-18}$) between changes in BPL along the beam central axis on CBCT and clinical adaptive replanning, suggesting BPL change as an excellent indicator of the need for adaptive therapy during proton treatment of extremity tumors. BPL change can accurately predict when a QACT is required with a sensitivity of 94.1% and specificity of 68.3%. This suggests that a routine periodic QACT is not necessary if the BPL of CBCT is used. The use of BPL changes on CBCT images can represent a significant reduction (84.7%) in total QACT burden while simultaneously and reliably maintaining treatment quality and accuracy.

Author Contributions

NCB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing - original draft, Review and editing. **BZ**: Data collection, Scripting, Software, Formal analysis, Review and editing. **EN**: Project administration, Resources, Supervision, visualization. **MEW**: Project administration, Resources, Supervision, review and editing. **WFR**: Project administration, Resources, Supervision, review and editing. **BY**: Formal analysis, Project administration, investigation, methodology, Resources, Supervision, review and editing. Each author in this manuscript has contributed to one or more assignments; for example, conceptualization, data curation, idea development, data collection, scripting and software development, data analysis, result discussions, manuscript writing, review and editing.

Declaration of Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

IRB Statement

All patient data have been collected under internal review board (IRB)-approved protocol.

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References

1. Frisch S, Timmermann B. The evolving role of proton beam therapy for sarcomas. *Clin Oncol.* 2017;29(8):500–506.
2. ASTRO MODEL Policies, Proton Beam Therapy. 2017.
3. Keole S, Ashman JB, Daniels TB. Proton therapy for sarcomas. *Cancer J.* 2014;20:409e414.
4. Laughlin BS, Golafshar MA, Ahmed S, et al. Early experience using proton beam therapy for extremity soft tissue sarcoma: a multicenter study. *Int J Part Ther.* 2022;9(1):1–11.
5. Jagt TZ, Breedveld S, van Haveren R, Heijmen BJM, Hoogeman MS. Online-adaptive versus robust IMPT for prostate cancer: How much can we gain? *Radiother Oncol.* 2020;151:228–233.

6. Janopaul-Naylor J, Stanforth A, McDonald MW, et al. Prediction of need for proton adaptive plan in head and neck cancers using clinical and radiographic features. *Int J Radiat Oncol Biol Phys.* 2020;108(3):e282–e283.
7. Kurz C, Nijhuis R, Reiner M, et al. Feasibility of automated proton therapy plan adaptation for head and neck tumors using cone beam CT images. *Radiat Oncol.* 2016;11:64–72.
8. Veiga C, Janssens G, Teng CL, et al. First clinical investigation of cone beam computed tomography and deformable registration for adaptive proton therapy for lung cancer. *Int J Radiat Oncol Biol Phys.* 2016;95(1):549–559.
9. Nichols EM, Regine WF, Simone CB, Langen KM. Single-institutional experience assessing the role of quality assurance (QA) CT scans and their impact on adaptive planning with pencil-beam scanning proton therapy in the setting of cone beam CT (CBCT). *Int J Radiat Oncol Biol Phys.* 2018;102(3):e539.
10. Evans JD, Harper RH, Petersen M, et al. The importance of verification of CT-QA scans in patients treated with IMPT for head and neck cancers. *Int J Part Ther.* 2020;7(1):41–53.
11. Hedrick SG, Fagundes M, Case S, et al. Validation of rectal sparing throughout the course of proton therapy treatment in prostate cancer patients treated with SpaceOAR. *J Appl Clin Med Phys.* 2017;18:82–89.
12. Ding X, Younkin JE, Shen J, Bues M, Liu W. A critical review of the practices of proton daily quality assurance programs. *Ther Radiol Oncol.* 2021;5(1-17):22–38.
13. Zhang Y, Alshaikhi J, Amos RA, et al. Improving workflow for adaptive proton therapy with predictive anatomical modeling: a proof of concept. *Radiother Oncol.* 2022;173:93–101.
14. Ger RB, Sheikh K, Gogineni E, et al. Planning and treatment recommendations for breast proton therapy from a single center's experience. *Adv Rad Oncol.* 2023;8(1-9):101069.
15. Yao W, Krasin MJ, Farr JB, Merchant TE. Feasibility study of range-based registration using daily cone beam CT for intensity-modulated proton therapy. *Med Phys.* 2018;45(3):1191–1203.
16. Schaly B, Kempe J, Venkatesan V, Mitchell S, Battista JJ. Using gamma index to flag changes in anatomy during image-guided radiation therapy of head and neck cancer. *J Appl Clin Med Phys.* 2017;18(6):79–87.
17. Schaly B, Kempe J, Venkatesan V, Mitchell S, Chen J. Alert system for monitoring changes in patient anatomy during radiation therapy of head and neck cancer. *J Appl Clin Med Phys.* 2021;22(8):168–174.
18. Nenoff L, Matter M, Amaya EJ, et al. Dosimetric influence of deformable image registration uncertainties on propagated structures for online daily adaptive proton therapy of lung cancer patients. *Radiother Oncol.* 2021;159:136–143.
19. Yao W, Zhang B, Han D, et al. Use of CBCT plus plan robustness for reducing QACT frequency in intensity-modulated proton therapy: Head-and-neck cases. *Med Phys.* 2022;49:6794–6801.
20. Stanforth A, Lin L, Beitler JJ, et al. Onboard cone-beam CT-based replan evaluation for head and neck proton therapy. *J Appl Clin Med Phys.* 2022;23(5):1–11.
21. Reiners K, Dagan R, Holtzman A, et al. CBCT-based dose monitoring and adaptive planning triggers in head and neck PBS proton therapy. *Cancers.* 2023;15:3881–3895.
22. Xu Y, Jin W, Butkus M, et al. Cone beam CT-based adaptive intensity modulated proton therapy assessment using automated planning for head-and-neck cancer. *Rad Oncol.* 2024;19:1–15.