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Scientific Article

Dosimetric Evaluation and Reproducibility of Breath-hold Plans in Intensity Modulated Proton Therapy: An Initial Clinical Experience

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Purpose: Breath-hold (BH) technique can mitigate target motion, minimize target margins, reduce normal tissue doses, and lower the effect of interplay effects with intensity-modulated proton therapy (IMPT). This study presents dosimetric comparisons between BH and nonbreath-hold (non-BH) IMPT plans and investigates the reproducibility of BH plans using frequent quality assurance (QA) computed tomography scans (CT).

Methods and Materials: Data from 77 consecutive patients with liver (n = 32), mediastinal/lung (n = 21), nonliver upper abdomen (n = 20), and malignancies in the gastroesophageal junction (n = 4), that were treated with a BH spirometry system (SDX) were evaluated. All patients underwent both BH CT and 4-dimensional CT simulations. Clinically acceptable BH and non-BH plans were generated on each scan, and dose-volume histograms of the 2 plans were compared. Reproducibility of the BH plans for 30 consecutive patients was assessed using 1 to 3 QA CTs per patient and variations in dose-volume histograms for deformed target and organs at risk (OARs) volumes were compared with the initial CT plan.

Results: Use of BH scans reduced initial and boost target volumes to 72% ± 20% and 70% ± 17% of non-BH volumes, respectively. Additionally, mean dose to liver, stomach, kidney, esophagus, heart, and lung V20 were each reduced to 71% to 79% with the BH technique. Similarly, small and large bowels, heart, and spinal cord maximum doses were each lowered to 68% to 84%. Analysis of 62 QA CT scans demonstrated that mean target and OAR doses using BH scans were reproducible to within 5% of their nominal plan values.

Conclusions: The BH technique reduces the irradiated volume, leading to clinically significant reductions in OAR doses. By mitigating tumor motion, the BH technique leads to reproducible target coverage and OAR doses. Its use can reduce motion-related uncertainties that are normally associated with the treatment of thoracic and abdominal tumors and, therefore, optimize IMPT delivery.

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Introduction

Proton therapy provides many benefits for treating primary and recurrent tumors, including a lower entrance dose and a finite range of charged particles.[1-6] Pencil beam scanning (PBS) is a technique that allows for a more precise dose distribution around the target and nearby organs at risk (OARs), which can lead to improvements in plan quality and robustness.[7-9] However, scanned beams are more susceptible to perturbations caused by scanning and intrafield organ motion, which can result in distortions and degradations in the delivered dose.[10,11] The dose distribution in PBS is local in nature and highly dependent on the spots traversing or deposited at the region of interest. Therefore, the interplay between spot placement and organ motion can cause a loss of target conformity, geometric misses, and areas of local underdosage or overdosage.[12] For example, a study by Phillips et al[13] found that respiratory motion greater than or equal to 1 cm can compromise target coverage significantly, with up to 30% of the target receiving less than 95% of the prescribed dose, and minimum doses as low as ~65% of the prescribed dose. Similarly, Bert et al reported that just 8 mm of motion can lead to reductions in homogeneity to 90%, with further reductions for larger motion ranges, and the percentage of target volume receiving 95% of the prescription dose varied from 71% to 14% in a single fraction.[10] Although PBS can provide many advantages, the interplay between spot placement and organ motion must be mitigated in cases of target motion to avoid unintended effects on target coverage and dose homogeneity.

To improve the precision and effectiveness of radiation therapy, 2 main categories of mitigation techniques can be used: beam delivery techniques and motion-limiting techniques.[14-19] Beam delivery techniques involve adjusting the way the radiation beam is delivered to the target and include tracking, gating, and repainting. In such treatments, the beam is often gated when a measured surrogate enters a preassigned gating window. For example, Kanehira et al[17] reported that a 2 mm gating window fulfilled the clinical target volume (CTV) coverage criteria while allowing for an average reduction in the lung V20 of more than17%. Motion-limiting techniques, such as the use of a compression belt and coaching, aim to reduce movement of the target during treatment. One approach that takes advantage of both beam delivery and motion-limiting techniques is the breath-hold (BH) technique. There are several methods to achieve BH, including deep inspiration breath hold (DIBH), active breathing control, BH coaching, and audiovisual biofeedback, each with their own benefits and drawbacks and expected levels of reproducibility.[10,20-23,25,26] During simulation and treatment, it is recommended to verify tumor positional reproducibility using multiple computed tomography (CT) scans and quality assurance CTs to ensure effective treatment.[26]

Despite these recommendations, there are limited clinical data on the use of BH with PBS treatment for tumors affected by respiratory motions. Edvardsson et al evaluated the use of DIBH for mediastinal Hodgkin lymphoma patients,[27] and Gorgisyan et al evaluated BH PBS plans on patients with locally advanced non-small cell lung cancer previously treated with photons.[28] Fracchiolla et al[29] presented a clinical implementation of BH for patients undergoing liver treatment. In this study, we investigate the dosimetric benefits associated with the use of BH for tumors with respiratory motion in patients treated with proton PBS. To do this, we present a dosimetric comparison between BH and non-BH plans for a large collection of patients treated with PBS. Subsequently, we evaluated reproducibility using weekly quality assurance (QA) CT scans to investigate the underlying anatomy and delivered dose with the BH technique.

Methods and Materials

Patient data selection

Data from 77 consecutive patients treated with intensity modulated proton therapy (IMPT) were used in this institutional review board–approved study. Patients were categorized by treatment sites, which included 32 liver, 21 lung and mediastinum, 20 nonliver upper abdomen, and 4 gastroesophageal junction (GEJ) patients (Table 1). All patients were treated with the gated spirometry system (SDX-Dyn'R) at deep-inspiration voluntary BH. CT scans were acquired with a Siemens Somatom Definition Edge (Siemens Healthineers) scanner according to the institution's site-specific imaging protocols.

Scans were reconstructed at 1.5 to 3 mm slice thickness with voxel resolution of 0.9 to 1.1 mm^2. The CT simulation session included a BH CT acquired at 75% to 80% of deep inspiration, and a 4-dimensional CT (4DCT) with the average CT scan used for treatment planning of non-breath-hold (non-BH) treatment. Depending on the tumor location and motion, 4DCT scans were acquired with compression belt (52 patients) or without compression belt (25 patients).

Table 1 (top) shows the treatment sites and number of patients selected in dose comparison evaluation for 1) BH versus non-BH analysis, and 2) reproducibility analysis using QA CTs. Table 1 (bottom) shows the number of BH patients treated with conventional (≤200 cGy/fraction) and hypofractionated dose fractionation.

Breath-hold eligibility

Our institutional criteria for proceeding with BH scan and treatment require patients to be able to maintain a

Table 1 Number of patients in each treatment site and number of breath-hold patients treated with conventional (≤200 cGy/fraction) and hypofractionated (>200 cGy/fraction) dose fractionation

	Number of patients	
Treatment site	**BH vs. non-BH**	**QACT analysis**
Liver	32	14
Mediastinum/lung	21	10
Pancreas	10	3
Abdomen	9	2
Gastroesophageal junction	4	1
Spleen	1	0
Fractionation	**Dose range (cGy)**	**Number of patients**
Conventional	D ≤ 200 cGy	28
Hypofraction	D > 200 cGy	49
	200 cGy < D < 400 cGy	27
	400 cGy < D < 600 cGy	17
	600 cGy < D < 900 cGy	5

Abbreviations: BH = breath-hold; CT = computed tomography; QA = quality assurance.

BH for 30 to 35 seconds during the training session. This is important because the Cone Beam CT (CBCT; half rotation) lasts about 30 seconds. Generally, if patients can hold this duration before coaching and actual treatment, they can usually achieve BH for the duration of the CBCT. Although it is technically possible to stop and resume the CBCT, we prefer not to do so to avoid exacerbating artifacts.

Breath-hold training and simulation

The gated BH treatment workflow (shown in Fig. 1) starts with patient evaluation for BH suitability and training to establish the BH level (gating window). The patient is instructed to breathe through the spirometer to establish a stable breathing baseline, followed by multiple DIBH to determine the comfortable BH volume. Based on the DIBH level, 75% to 80% of the DIBH will be set as the BH level. After establishing the DIBH level, a 10% gating window is uniformly implemented for all subsequent BHs. Assuming a direct relationship between tidal flow and tumor motion, this gating window provides about 10% tolerance for target motion measured from the end of exhale to the DIBH. For instance, a tumor with a 1-cm motion range would have a 1-mm tolerance within the gating window. However, it should be noted that the gating window does not account for residual motion resulting from factors such as muscle fatigue or other influences beyond tidal flow.

Once the patient is trained and the BH level is established, the patient will undergo planning CT image acquisition using the BH technique using SDX system with real-time feedback provided via the video goggles. In all cases, normal 4DCT images are also acquired and used for a backup non-BH treatment. After simulation, the images are imported to a treatment planning system for tumor motion evaluation and treatment planning. Both plans are evaluated by the physician and the final decision for treatment choice is made based on comparison of OAR and target doses between the 2 plans. If the BH plan is chosen, both plans are still prepared for patient-specific QA to serve as back-up in the possible scenario that BH treatment cannot be delivered. Of 93 patients who were consulted for SDX treatment at the time of this study, 77 were able to perform an adequate BH and underwent SDX simulation, and 73 were treated with the BH plan. Three non-BH plans were chosen over the BH plan, and one patient could not tolerate BH treatment during the course of treatment and switched to the non-BH plan.

Treatment planning

The Monte Carlo dose calculation engine of RayStation treatment planning system (version 8A and 11A, RaySearch Laboratories) was used for plan optimization and dose calculation. Both BH and non-BH plans were generated based on the BH and phase-average CT scans. For nonBH plans, the target was delineated in each phase of the 4DCT to create an internal target volume (iGTV). On the other hand, a gross tumor volume (GTV) was contoured for BH plans. Additionally, a larger motion encompassing CTV was generated, which was bigger than the iGTV or GTV. The expansion of the CTV was

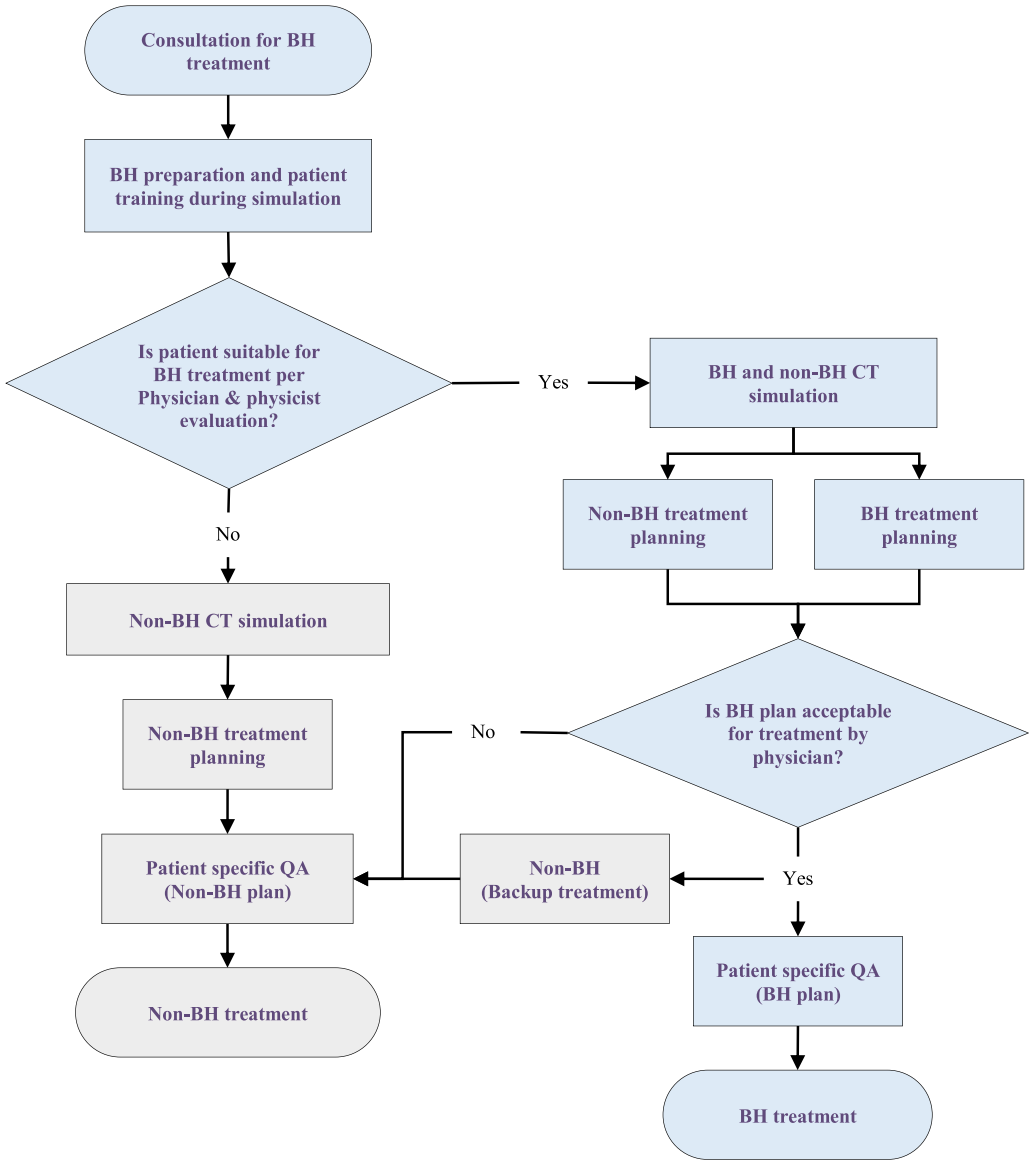

Figure 1 The workflow of breath-hold treatment. *Abbreviations*: BH = breath-hold; CT = computed tomography; QA = quality assurance.

determined based on the recommendations specific to the disease site. In both treatment techniques, a standard margin of 3 to 5 mm was typically added to the GTV or iGTV to generate the expansions. Furthermore, lymph nodes, prechemotherapy disease sites, and other high-risk areas were included in treatment plan based on the disease site. In this study initial and boost targets will be referred as CTV1 (or CTV for cases without a boost plan) and CTV2, respectively.

Optimization was performed robustly for both plans, taking into account a 5 mm setup uncertainty specific to each CTV. When at least one beam significantly transversed lung tissue, a 5% range uncertainty was applied. Otherwise, a 3.5% range uncertainty was used. Importantly, these uncertainties were incorporated during the robust optimization process by enlarging the dose cloud, rather than directly modifying the prescription target. It is worth noting that these uncertainty values are specific to the institution and were established through studies on setup reproducibility and range verification measurements.[22]

Treatment plan evaluation

A robustness evaluation criteria that 95% of the target receives 95% of the dose was assessed for both plans using above setup and range uncertainty criteria. Robustness for non-BH plans was also evaluated for the 4DCT end of inhale and exhale phases. Both plans were reviewed and approved by the treating radiation oncologist. Target size

and coverage metrics, as well as OAR mean and maximum dose limits (D1), were compared between BH and non-BH plans for each patient. Patient specific QA was performed at 2 depths using a detector ionization array with a 90% gamma acceptance (3%/3 mm criteria).

Reproducibility of breath-hold plans

A total of 62 QA CTs from 30 consecutive thoracic, liver, abdomen, and GEJ patients were used to examine the anatomic and dosimetric reproducibility of BH treatments. For each patient, rigid registration was used to fuse the available QA CTs (range, 1-3) with the planning CT. Subsequently, OAR and target contours were deformed using the automatically constraint deformation algorithm (ANACONDA).[23] Target and OAR contours were subsequently reviewed for accuracy by the physician and modified as clinically indicated.

Dosimetric analysis

Target size and coverage metrics, as well as OAR mean and maximum dose limits, were compared between BH and non-BH plans. Mean GTV motion was computed based on 3-dimensional centroid displacement for non-BH cases simulated with and without compression belt. Mean GTV motion with and without compression belt was also evaluated in non-BH cases. For each OAR metric, linear regression was used to evaluate the changes from BH, and the fit quality was reported by the coefficient of determination (R^2). Paired Student *t* test was used to evaluate the statistical significance in the data with .05 level of significance.

Dose was recomputed on the QA CT, and the reproducibility of the plans was assessed as the percentage difference with respect to the nominal plan and the standard deviation reporting the spread in the dosimetric parameters with respect to the delivered dose. Target coverage dosimetric changes in QA CTs were reported as percent differences with respect to the nominal plan on the initial CT. OAR dose differences were reported as absolute.

Results

Dosimetric evaluation

An example of BH and non-BH lung plans with 66 Gy prescribed to the target is shown in Figs. 2 A-B, respectively. Single-field optimization using one anterior and 2 posterior oblique fields was used for both plans. In comparison to non-BH, approximately a 20% reduction in the target volume (yellow contour) was noted with the use of BH technique (Fig. 2A-B). As such, the BH plan resulted in better conformity to the gross tumor volume (GTV conformity index: 2.37 vs 3.33) with significant reductions in the high dose lung

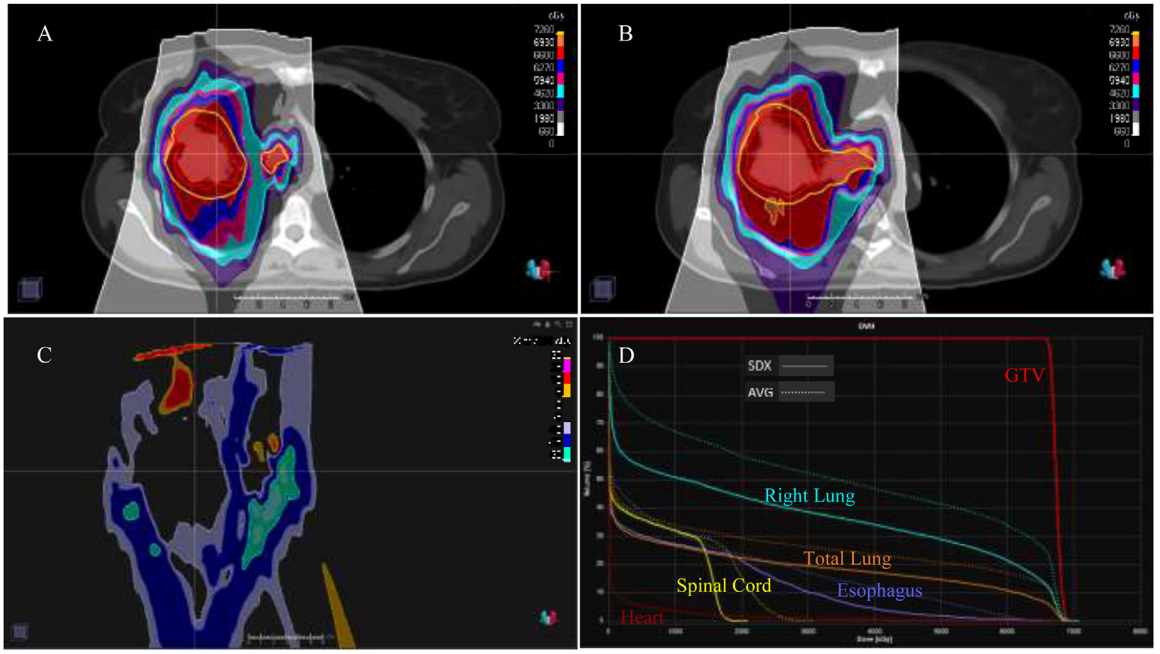

Figure 2 Dose distribution of (A) BH plan and (B) non-BH plan. Gross tumor volume (red) and clinical target volume (yellow) contours show a larger volume in the non-BH plan due to respiratory motion. (C) Dose differences between BH and non-BH plans. (D) Comparison of dose-volume histogram of multiple organs at risk and gross tumor volume target for BH (solid line) and non-BH (dotted line) plans. *Abbreviations*: BH = breath-hold; GTV = gross tumor volume.

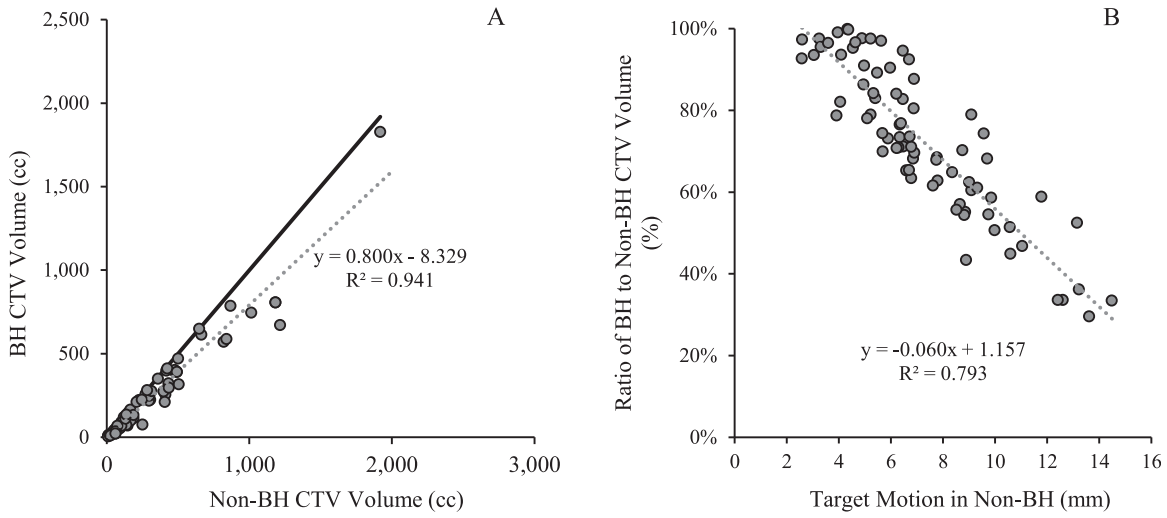

Figure 3 (A) Reductions in clinical target volume size associated with BH for all 77 patients. (B) Ratio of BH to non-BH clinical target volume volumes versus the target motion in free-breathing scan. *Abbreviations*: BH = breath-hold; CTV = clinical target volume.

volume (Fig. 2C). Total lung V20 was reduced from 30% (non-BH) to 23% (BH), and mean heart dose was reduced from 2.3 to 1.1 Gy. Spine maximum and esophagus mean doses were also reduced by 9.0 and 2.5 Gy, respectively. Comparison of DVH of multiple OARs and GTV target for BH and non-BH plans is shown in Fig. 2D.

Mean GTV motion range for all 77 patients was 7.41 ± 2.64 mm with submillimeter differences in the magnitude of motion observed between the compression belt (7.6 ± 2.73 mm; 52 patients) and noncompression belt (7.04 ± 2.46 mm; 25 patients) groups. Our interpretation is that the belt was not effective for the noncompression group, whereas the amplitude was reduced to this value for the compression group. Compression belt is generally most useful for only lower lobe target volumes.[30] Figure 3A shows that the use of BH resulted in a 20% reduction in the CTV size based on the analysis of 77 patients ($R^2 = 0.94$). The reduction in BH CTV volume, compared with the non-BH CTV volume, showed a linear relationship with the target motion range, resulting in an approximate 6% reduction per millimeter (Fig. 3B). For target motions of 1.4 cm, a substantial reduction of up to 70% in CTV size was observed. It is worth noting that no reduction was observed for targets with a motion range below 3 mm, which aligns with the resolution of the acquired CT scans. On average, the use of BH resulted in a 21% reduction in the CTV size for patients undergoing treatment for the liver ($R^2 = 0.96$), 18% reduction for the lung ($R^2 = 0.93$), and 30% reduction for the abdomen and pancreas ($R^2 = 0.99$). A lack of tumor motion due to respiration resulted in similar BH and non-BH CTV sizes which corresponds to the points positioned on the unity line (Fig. 4A, C, E). In such instances, even when motion without BH was limited, and thus the dosimetric benefits of BP were more limited, radiation oncologists favored BH techniques for its additional advantages, such as the improved image quality associated with BH images in comparison to 4DCT, as well as reduced treatment uncertainties.[31] Associated with the reduced CTV sizes were lower doses to the healthy OARs adjacent to the tumor (Fig. 4B, D, F). Reductions in mean healthy liver (liver-CTV) doses ranged from 2% to 42% with an average 14% reduction ($R^2 = 0.93$). Lung V20 doses were reduced by as much as 43%, with a 26% average reduction ($R^2 = 0.90$). For abdomen and pancreas patients, mean kidney dose was reduced by as much as 92%, with a 24% average reduction ($R^2 = 0.87$).

In all cases, the linear correlations between the BH and non-BH doses had relatively high coefficient of determinations indicating confidence in the linear fit. For all patients, larger reductions in CTV size were correlated with higher reductions in OAR doses ($P < .01$). Additionally, use of BH consistently reduced mean and maximum OAR doses ($P < .05$). On average, mean heart, stomach, esophagus, and kidney doses were reduced by 21% to 29% (Table 2). Significant reduction was observed for maximum doses (D0.03 cc) to the large (32%) and small (22%) bowels as well as spinal cord (18%).

Reproducibility of breath-hold plans

Initial and boost target volumes (CTV1 and CTV2) were reproducible within 1.3% and 7% (95th percentile) of the initial planning-CT volumes (Fig. 5A), respectively. In the BH initial plans, the median and average percent changes in absolute volume were determined to be −0.58% (−1.30 cc) and −0.64% (−1.69 cc), respectively.

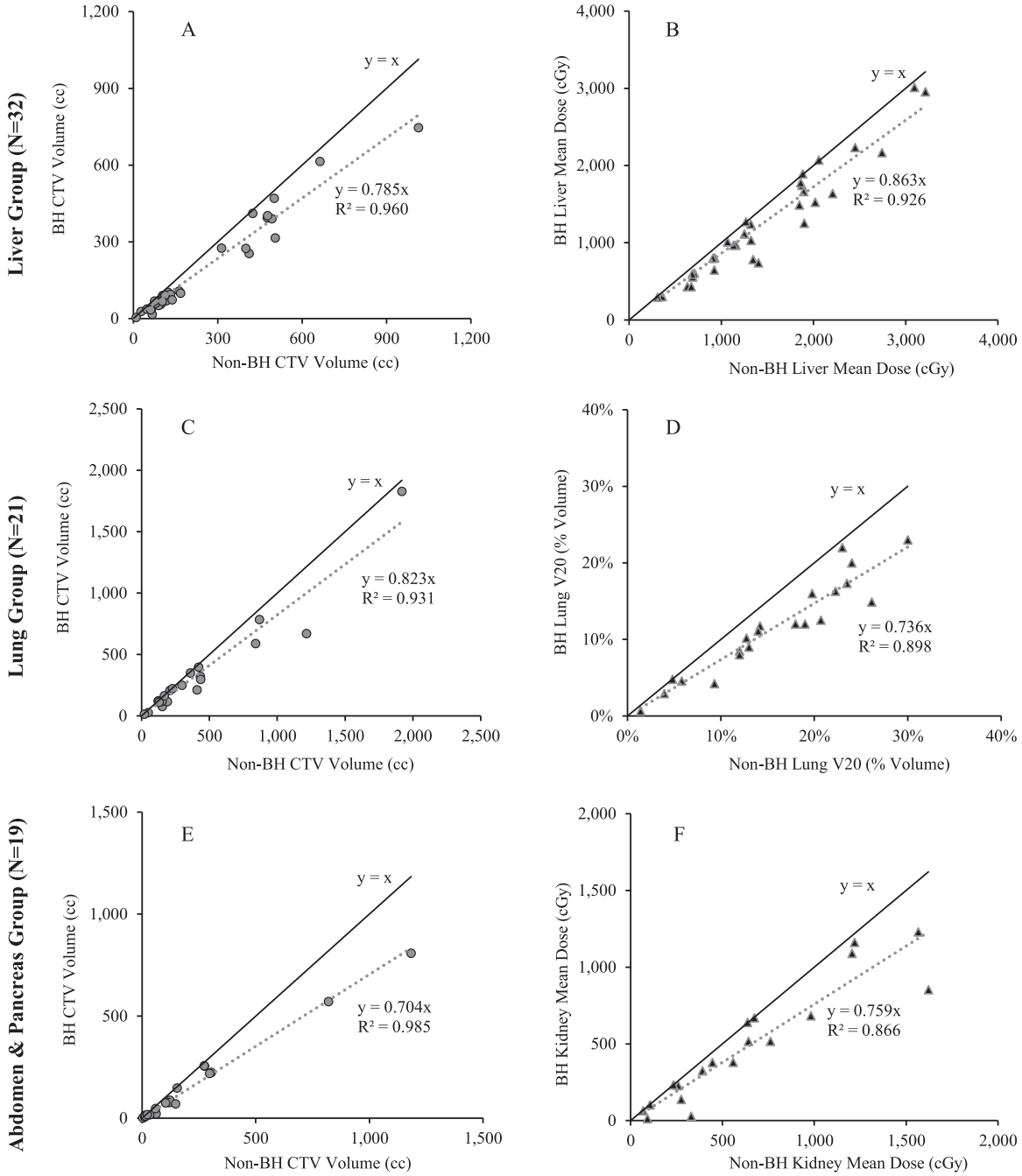

Figure 4 Improvements with breath-hold (BH) over non-breath-hold (non-BH). Reductions in (A) clinical target volume (CTV) size associated with BH for patients undergoing liver treatment. (B) Healthy liver (liver − CTV) mean dose (cGy) associated with BH. (C) CTV size associated with use of BH for lung patients. (D) Lung V20 associated with the use of BH. (E) CTV size associated with use of BH for abdomen and pancreas patients. (F) Kidney mean dose associated with the use of BH.

Regarding the BH boost plans, the median and average percent changes (absolute volume) were found to be −3.40% (−1.54 cc) and −4.80% (−1.83 cc), respectively. CTV1 V95%, D95% and mean doses were also within 3% of the nominal plan. Similarly, CTV1 max dose was within 5% of the nominal plan. The 95th percentile maximum variations for mean liver, stomach, and heart doses were within 0.6 Gy and for mean kidney dose were within 0.2 Gy (Fig. 5F). Larger variations for esophagus mean dose were observed with 95th percentile maximum variations lying within 1.7 Gy. Similarly, maximum variations were within 1 Gy for bowel maximum dose, 2.9 and

Table 2 Target volume and dosimetric parameters of BH and non-BH plans of 77 consecutive patients

Parameter	Target or OAR	BH plan	Non-BH plan	Ratio of BH normalized to non-BH (%)	*P* value	No. patients
Volume (cc)	Initial plan target volume (CTV1)	229.8 [1827.6, 3.8)	301.8 (1918.35, 10.4)	72.0% ± 19.6%	<.01	77
	Boost plan target volume (CTV2)	167.5 (685.66, 3.13)	226.7 (771.1, 4.6)	70.0% ± 17.4%	<.01	24
Mean dose (cGy)	Liver	769.1 (3011.0, 0.1)	924 (3743, 0.3)	76.7% ± 26.9%	<.01	56
	Stomach	507.9 (3779.8, 0.2)	766.4 (5044.3, 0.3)	78.1% ± 43.7%	<.01	44
	Kidney	324.6 (1315.0, 0.1)	486.3 (2621.3, 0.1)	78.5% ± 32.1%	.01	49
	Esophagus	729.4 (4582, 0.1)	852.4 (4594.0, 0.1)	77.8% ± 25.7%	<.01	53
	Heart	243.4 (1824.0, 0.0)	358.6 (2279.0, 0.1)	71.3% ± 29.8%	<.01	61
V20 (%)	Lung	8.8% (24.0%, 0.7%)	18.2% (35.0%, 0.8%)	75.0% ± 40.5%	<.01	43
Max dose (cGy)	Small bowel	1818.7 (5150.0, 0.3)	2260.5 (5160.0, 0.2)	78.1% ± 37.0%	.09	43
	Large bowel	1230.4 (4914.0, 0.2)	1926.9 (5187.2, 0.2)	67.6% ± 40.3%	<.01	43
	Heart	2407 (5647.0, 0.2)	2783.6 (5657.0, 0.2)	84.4% ± 31.9%	<.01	61
	Spinal cord	1170.5 (4296.0, 0.2)	1362.8 (4613.4, 0.2)	82.3% ± 39.8%	<.01	71

Abbreviations: BH = breath-hold; OAR = organs at risk; V20 = volume receiving 20 Gy, small field boost.
For non-BH plans, an internal target volume based on the 4-dimensional computed tomography phases was created accounting for accompanying motion. Patient selection: 32 liver, 21 mediastinum/lung, 10 pancreas, 9 abdomen, 4 gastroesophageal junctions, and 1 spleen. Last column shows the number of patients used for each parameter. Absolute values are shown as average (maximum, minimum), and relative values are shown as average ± standard deviation.

4.0 Gy for spinal cord and heart maximum dose, respectively. QA CT indicated replan for 4 patients due to loss of target coverage or increased dose to OARs stemming from underlying changes in the anatomy.

Treatment delivery and breath-hold analysis

Delivery time for a beam in proton therapy depends on several factors, including the size of the target being treated, the number of energy layers involved, and the beam delivery dose rate. Analysis of 77 patients, encompassing a total of 3585 BHs, revealed that the average BH time per patient was 49.98 ± 7.04 seconds. This finding indicates a relatively consistent duration of BH across the patient group. On average, each treatment field required 1.46 ± 0.59 BHs, providing insight into the typical number of BH performed during treatment. It is important to note that to capture the duration of BH relevant to the treatment process, the analysis excluded short BHs lasting less than 20 seconds, which were primarily used for delivering the residual beam after the initial BH.

Discussion

The BH technique aims to deliver radiation doses with enhanced precision by minimizing motion consistently. Higher motion amplitudes are identified as the primary factor causing interplay patterns and increased dose degradation.[10] Restricting motion range reduces expected dose degradation. In our study, QA CT scans assessed treatment effectiveness in maintaining target coverage and minimizing doses to OARs. Proton therapy offers advantages over photon therapy for mediastinal targets, reducing lung, heart, and breast doses.[24,25,27,32] It also benefits contralateral lung and heart doses compared with photon SBRT.[33-35] Our work, unlike single-diagnosis studies, includes various primary tumor diagnoses, resulting in a practical and heterogeneous approach. Table 2 reveals statistically significant benefits with BH across several OARs, although the clinical significance varies. Some reductions, such as a 1.4 Gy decrease in mean stomach dose and a 1.3 Gy decrease in mean kidney dose, may have limited clinical effect, particularly when patients typically receive doses well below organ tolerance. Nevertheless, these reductions hold value in cases of reirradiation or pediatrics, where minimizing radiation exposure (ALARA) is crucial. Conversely, BH offers more clinically significant reductions for OARs such as the heart and lung. For instance, lowering the mean heart dose could reduce the risk of major cardiac events by an estimated 7.4% for every 1 Gy reduction.[36] Similarly, reducing lung V20 has the potential to decrease the risk of radiation pneumonitis and pulmonary fibrosis. A study by Bradley et al[37] suggests that a 10% reduction in V20 can lead to

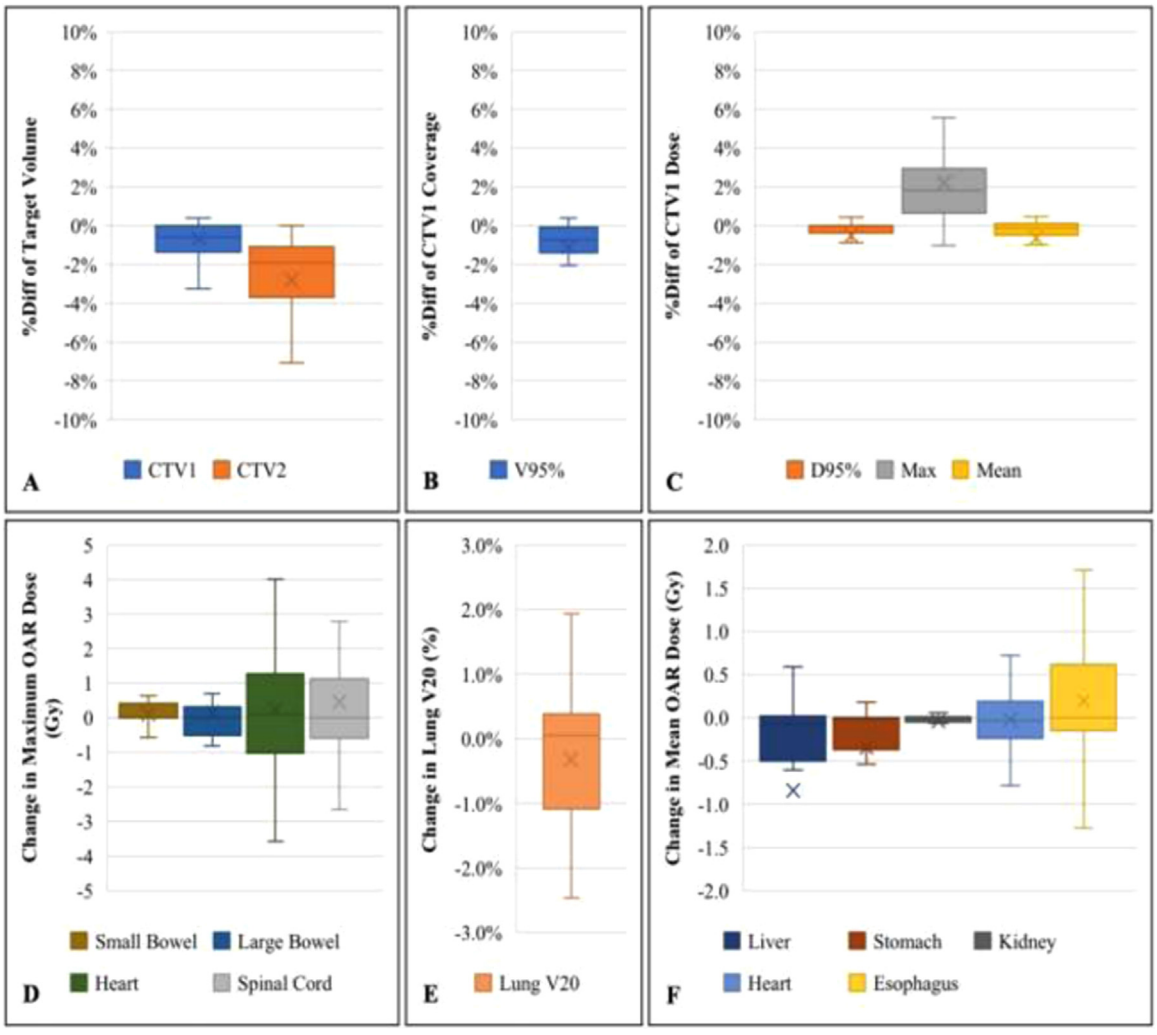

Figure 5 Box plots of relative change of quality assurance computed tomography plan parameters with respect to the initial plan. (A) Target volumes: CTV1 (initial: 30 patients) and CTV2 (small field boost: 9 patients). (B) Percent difference of CTV1 coverage V95%. (C) Percent difference of CTV1 dose (D95%, maximum, and mean dose). (D) Change in maximum dose to small bowel, large bowel, heart, and spinal cord. (E) Change in V20 of lung. (F) Change in mean dose to liver, stomach, kidney, heart, and esophagus. Patient selection: 14 mediastinum/lung, 10 liver, 3 pancreas, 2 abdomen, 1 gastroesophageal junction. The statistical variation is shown in "boxes" that span the 25% to 75% quartiles. The error bars are set to 1.5 times the interquartile range and " × " shows the median value. *Abbreviation*: OAR = organs at risk.

up to a 25% reduction in pneumonitis probability, especially for tumors located caudally. Further analysis of data using various normal tissue complication probability models could highlight additional benefits.

Ensuring reproducibility in BHs during treatment is crucial. Lens et al observed organ and diaphragm position variations in BHs without feedback.[38] Challenges in surface monitoring during breath-holding were noted by Parkes et al.[39] To address these concerns, we use an internal surrogate with audiovisual feedback and use daily pretreatment CBCTs and QA CT evaluations for target and diaphragm position verification. Although QA CTs are essential for assessing variations and verifying BH reproducibility, the limited number used assumes applicability to multiple BHs. Additional QA CTs can enhance confidence, but patient dose increase should be considered. BH stability and reproducibility are verified during planning CT and before treatment. At our institution, we instruct patients to perform multiple BHs before planning CT to assess reproducibility. BH reproducibility is evaluated with CBCT before each treatment session, with additionally midtreatment kV images used if necessary to verify diaphragm position.[37] It is worth noting that 4DCT-based treatment plans offer advantages in target reproducibility by capturing organ and tumor motion throughout the breathing cycle. This comprehensive characterization enhances the accuracy and reliability of the internal target volume (ITV), which can encompass tumor motion and

is less vulnerable to reproducibility challenges compared with BH techniques. Goossens et al[40] report tumor motion range reproducibility within 2 mm, highlighting the robustness of 4DCT-derived ITVs. Although motion range reproducibility is generally high, there have been documented systematic deviations, including baseline shifts, during free breathing (FB) treatments, especially with prolonged treatment times. Because 4DCT only represents an average of the breathing cycle, these deviations are not typically considered without additional monitoring techniques.[41,42]

BH reproducibility was ensured through pretreatment volumetric imaging, but real-time intrafraction monitoring was lacking to detect residual motion. Lens et al reported ~5 mm target motion during BH.[38] A spirometry-based study observed 4.2 mm and 2.7 mm tumor motion in the superior−inferior (SI) and anterior-posterior (AP) directions during BH.[43] Vogel et al[44] found 59% of DIBH cases had residual motion <2 mm, with 36% ranging from 2 to 5 mm. Their analysis indicates minimal effect on treatment integrity for low magnitudes (<5 mm) in 95% of patients. The clinical plans used in this work used range shifters to increase spot-sizes, with spot and energy layer spacing between 0.55 to 0.75 cm and 1 to 3 MeV (scaled with energy). The study by Dowdell et al[45] suggests ~5 mm motion has minimal effect on dosimetric parameters within this spot size range. Vogel et al[44] observed residual motions of 5 to 8 mm in 4% of the population and motions exceeding 8 mm in 1%. Such a residual motion can potentially degrade treatment, emphasizing the need for additional monitoring techniques and further investigation in future studies.

AAPM Task Group 290 reviews tumor motion, motion management techniques, and their limitations.[46] The recommendations stress the importance of respiratory motion management in particle therapy, including beam angle selection, motion encompassing techniques, and reproducibility. Our methodology closely aligns with these recommendations. For FB treatments, we use 4DCT with motion encompassing ITVs and select beam angles with minimal density variations. Spot placement considers beam-specific water-equivalent path length to incorporate respiratory motion. Abdominal compression is used to reduce motion range and enhance target reproducibility. Enlarged spot sizes and tighter spot spacing are used to reduce parameter sensitivities. We verify BH reproducibility using volumetric imaging (CBCT). Several international guidelines recommend consideration of ITV generation with multiple BH scans. Our clinical workflow includes multiple CBCT scans and QA CT scans to verify position and dose. In cases where fluctuations in the patient's respiratory signal are observed midtreatment, kV images before beam delivery are used to verify diaphragm position or a repeat CBCT is performed. In cases where daily volumetric IGRT is not available, we agree with the consideration for BH ITV generation as recommended by PTCOG Lymphoma Subcommittee consensus.[47] One inherent limitation of our noted institutional standards is the absence of preplanning reproducibility studies with repeat imaging during simulation. Inclusion of this assessment can highlight the need for extra margins, reducing the treatment delivery team's workload and improving patient comfort. Additionally, the availability of multiple BH images, when necessary, can enhance treatment plan robustness, which may only be partially captured in QA CT evaluations due to multiple confounding factors.

A planning study of 18 patients for HL found no significant reduction in mean heart dose from DIBH compared with free breathing with proton therapy.[27] However, our analysis of clinical proton PBS dosimetric data for mediastinal and abdomen cases demonstrates lower mean heart dose with the DIBH technique compared with non-BH technique (Table 2). This difference may be attributed to our use of robust optimization instead of PTV-based optimization methods with density overrides. Robust optimization ensures greater conformity index and plan robustness by minimizing the dose cloud and accounting for heterogeneities along the beam path.[48] The OAR doses presented in this study, using robust optimization for both non-BH and BH plans, represent lower limit estimates for treatment while maintaining plan robustness. Although the inclusion of additional CT datasets in robust optimization could enhance robustness, the computational intensity would increase significantly, making it currently impractical for our clinic.

One area of concern when using BH and PBS is setup or anatomic changes throughout treatment that may affect target coverage or OAR dose. To date, there are limited data on the setup and anatomic reproducibility throughout treatment. Gorgisyan et al[28] demonstrated on retrospective BH PBS planning of locally advanced non-small cell lung cancer that 3 of 15 (20%) of plans had degradation of >5%, raising concern for adequate longitudinal target coverage. The majority of other studies have evaluated BH PBS planning largely in the context of comparisons to photon plans or non-BH plans only. In our experience, 4 of 30 (13.3%) treatments required replanning. For the remaining cases, the CTV coverage was excellent with −2% difference for CTV1 and limited hot spots to <5% above the nominal plans. These data suggest that BH PBS treatments with robust planning, along with weekly QA evaluations, can provide adequate target coverage while limiting OAR doses in a reproducible fashion.

BH treatments in radiation therapy offer benefits for both large and small target volumes, particularly when there is noticeable target motion or when the target is in proximity to sensitive OARs. Implementing BH treatment is generally easier for smaller targets due to faster beam delivery, which improves patient comfort. Overall, the decision to use BH treatment should be evaluated on a case-by-case basis. However, it is particularly critical for

tumors near the diaphragm where motion is typically higher, and the effect of breathing motion on the beam path can result in significant variations in the water-equivalent path length. Additional, larger studies with longer follow-up are required to evaluate clinical benefits of BH in proton treatments.

Two voluntary BH techniques for clinical use are external surrogates and spirometric techniques for internal lung volume. Several studies note potential external-internal correlation changes, dependent on tumor location.[50-52] The assumption between surrogate motion and tumor requires verification during treatment fraction and across fractions.[49,50] In contrast, Emert et al[21] report reproducibility advantages for relative lung structure location with DIBH. Our QA CT analysis confirms this and demonstrates reproducibility of dosimetric metrics for target coverage and OAR dose, affected by respiratory motion. Despite high reproducibility, verify tumor and OAR positions using multiple QA CTs during treatment.[26] Fracchiolla et al[29] implemented DIBH with PBS for liver treatment, assessing BH reproducibility using the active breathing control system. They used end-of-expiration BH with shorter BH criterion (15 seconds), 3 BH per treatment field, and larger PTV margins (7 mm) due to limited imaging. Their planning approach involved PTV-based single uniform dose plans, with limited use of range shifters. Differences in technology included longer energy layer switch time (1.2 seconds) compared with our Varian ProBeam System (0.2 seconds), which most likely resulted in modifications in treatment planning approach to enhance treatment delivery efficiency. Despite variations, desired target coverage was achieved for most patients, indicating modest limitations of BH variability.

For beam gating, the gating window must be selected during the simulation. The requirements for adequate gating windows in scanned particle therapy are comparable to those in conventional radiation therapy: position as well as width of the gating window within a patient's typical respiratory cycle must be selected.[52] Based on the vendor recommendation and initial experience, a gating window of $\pm$ 0.1 liter was used in our study. When possible, depending on the location of the target and surrounding critical OARs as well as the patient's BH ability, this window was reduced to as low as $\pm$ 0.05 liter. The increased lung volume associated with DIBH, along with the associated reduction in lung and heart irradiation doses make DIBH an attractive tool for hypofractionated and stereotactic body proton therapy treatments such that a number of the patients included in this study were treated with hypo-fractionated regimens. In our study, we maintained a consistent clinical workflow and treatment process by treating thoracic and abdominal cases at the end of inspiration. Although the use of DIBH is often advantageous for thoracic cases due to the increased distance it provides between the treatment site and nearby OARs, it is worth mentioning that several studies have reported lower residual motions and higher confidence in reproducibility when using end-of-expiration treatments.[53,54]

In hindsight, valuable lessons from our proton treatment implementation include 1) incorporating additional beams or rescanning reduces delivery time and interruptions, enhancing treatment efficiency; 2) preparatory BH practice helps identify patients struggling with breath-holding, maximizing eligibility for BH treatment; 3) for tumors located in the upper lung lobes, assessing tumor motion and 4DCT image quality can streamline planning by excluding unnecessary BH treatment; 4) acquiring QA CT scans for both BH and FB techniques enables accurate reproducibility comparisons; and 5) implementing these suggestions enhances efficiency, patient eligibility, comparability, and clinical decision-making.

Conclusion

Breath-hold significantly reduces the irradiated volume and is associated with lower dose to critical OARs. The BH technique leads to reproducible target coverage and OAR doses and can mitigate several uncertainties associated with the treatment of thoraco-abdominal tumors. The elevated level of reproducibility permits the delivery of hypofractionated and stereotactic body PT.

Disclosures

Charles B. Simone II reports honorarium from Varian Medical Systems. Sina Mossahebi reports honorarium from Dyn'R USA.

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