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Treatment of Primary Hepatocellular Carcinoma (HCC) with Active Pencil Beam Scanning Protons in Singapore

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Abstract

To show how to proceed the treatment of HCC with proton beams, we report our experience which was the first time of HCC treatment with proton therapy in Singapore. The prescription was 66 Gy in 10 fractions. Treatment plans and proton beam delivery was performed using an active pencil beam scanning mode using the Probeam system (Varian Medical, Palo Alto, CA). Two treatment plans, one is deep inspiration breath holding (DIBH) and the other is free breathing (FB) plan, were prepared following observation of liver motion during 4DCT image acquisition. For the actual treatment, the free breathing mode plan was selected since the DIBH mode was not advisable following evaluation of patient setup image prior to the first treatment.

Keywords:
hepatocellular carcinoma, proton

Introduction

The superiority of liver cancer treatment using proton beams has been demonstrated in many studies.[1–5] Therefore, many proton centres currently use either Stereotactic Body Radiation Therapy (SBRT) (50 Gy in 5 fractions) and also hypofractionation schemes (60-66 Gy in 10 fractions) using proton therapy for the treatment of liver cancer.[6–10]

In addition, each institution has adopted a different treatment strategy depending on the amplitude of liver motion. In order to perform SBRT or hypofractionated proton therapy for liver cancer, it is necessary to consider the range of movement of the organ due to respiration, localization through images, and the interplay effect [8,10], which will be explained subsequent section.

For accurate treatment of moving organs, the range of movement of the target is first identified based on 4DCT, and then the various options for accurate delivery will be determined such as gating [9], breath holding [8], and free breathing [8,10]. In particular, for a treatment with free breathing (FB), additional steps should be applied to reduce the interplay effect. [11,12]. These include using a large spot size [13] and repainting [14,15]

In this paper, we present our recent experience with hypofrationated proton therapy for liver cancer. Through this report, we introduce our clinical protocol, quality assurance procedure and criteria for treatment technique to present detail process of radiation treatment of HCC with proton pencil beam scanning mode.

Methods

Simulation and Planning Criteria

A 71-year-old male patient was diagnosed with Hepatocellular Carcinoma (HCC) involving segment VI/VII and was selected for proton therapy. Prescription dose was 66 Gy in 10 fractions. During the simulation stage, 3DCT images of deep inspiration breath holding (DIBH) and 4DCT images with free breathing (FB) were acquired. The 4DCT images were used to check the range of the movement of liver.

When the organ where the tumour is located is moving with respiration, the DIBH technique using SDX system (DYN'R Medical System) is used in our institution. In particular, the range of the movement of the tumour is first identified, and if the total movement exceeds 1 cm (amplitude of 5 mm), it is recommended to use DIBH. Conversely, if the movement of the organ is less than 1 cm (amplitude of 5 mm), free breathing (FB) treatment is recommended. However, if the patient has difficulty holding breath for more than 30 seconds, or if the shape of the organ is different during the treatment setup which is verified by on-board imaging, treatment should be performed with free breathing (FB) even if the movement of the organ exceeds 1 cm (5 mm of amplitude).

In our patient, the maximum movement of the liver (superior region) was up to 1.3 cm, but in the case

Table 1. Prescription and constraints for Organs at Risk (OARs).

Items		Criteria	Plan results	
Prescription for Target		66Gy in 10fx	DIBH Plan	FB Plan
Robust planning goal (CTV)		V95 > 95% D95 > 62.7Gy	V95=100% D95=65.6Gy	V95=100% D95=65.0Gy
Worst plan criteria		V95 > 90%	V95=90%	V95=97.5%
OAR constraint	**Total Liver**	V27Gy < 60%	24.5%	30.2%
	Liver-GTV	V27Gy < 50%	22.2%	27.7%
	Esophagus	V37Gy < 2cc	0cc	0cc
	Stomach	V37Gy < 2cc	0cc	0cc
	Small Bowel	V35Gy < 2cc	0cc	0cc
	Large Bowel	V35Gy < 2cc	0cc	0cc
	Right Kidney	V20Gy < 30%	2.1%	3.6%
	Left Kidney	V20Gy < 30%	0%	0%
	Spinal cord	Max < 27Gy	6.5Gy	0.9Gy

of the tumour region (inferior region), the movement was about 1.0 cm, so it was determined that both DIBH and FB technique were acceptable.

Treatment Planning

Treatment planning was performed using the Eclipse treatment planning system (Version 15.6; Varian Medical Systems). Contouring for DIBH plan and FB plan was performed on DIBH 3D scanned images and 4D scanned average CT images, respectively. In particular, in the case of FB, maximum intensity image (MIP) and minimum intensity image (MinIP) were used to confirm whether all tumour regions of all phases were included in the target contouring of average CT.

Proton beams with gantry angles of G315, G280 and G250 were selected, so that the beams did not pass through the edge part of the couch, and the Single Field Optimization (SFO) method was used to improve the robustness of the plan. For robust optimization, 5 mm setup uncertainty and 3.5 % CT curve uncertainty were used, and for the free breathing plan, a 2 cm range

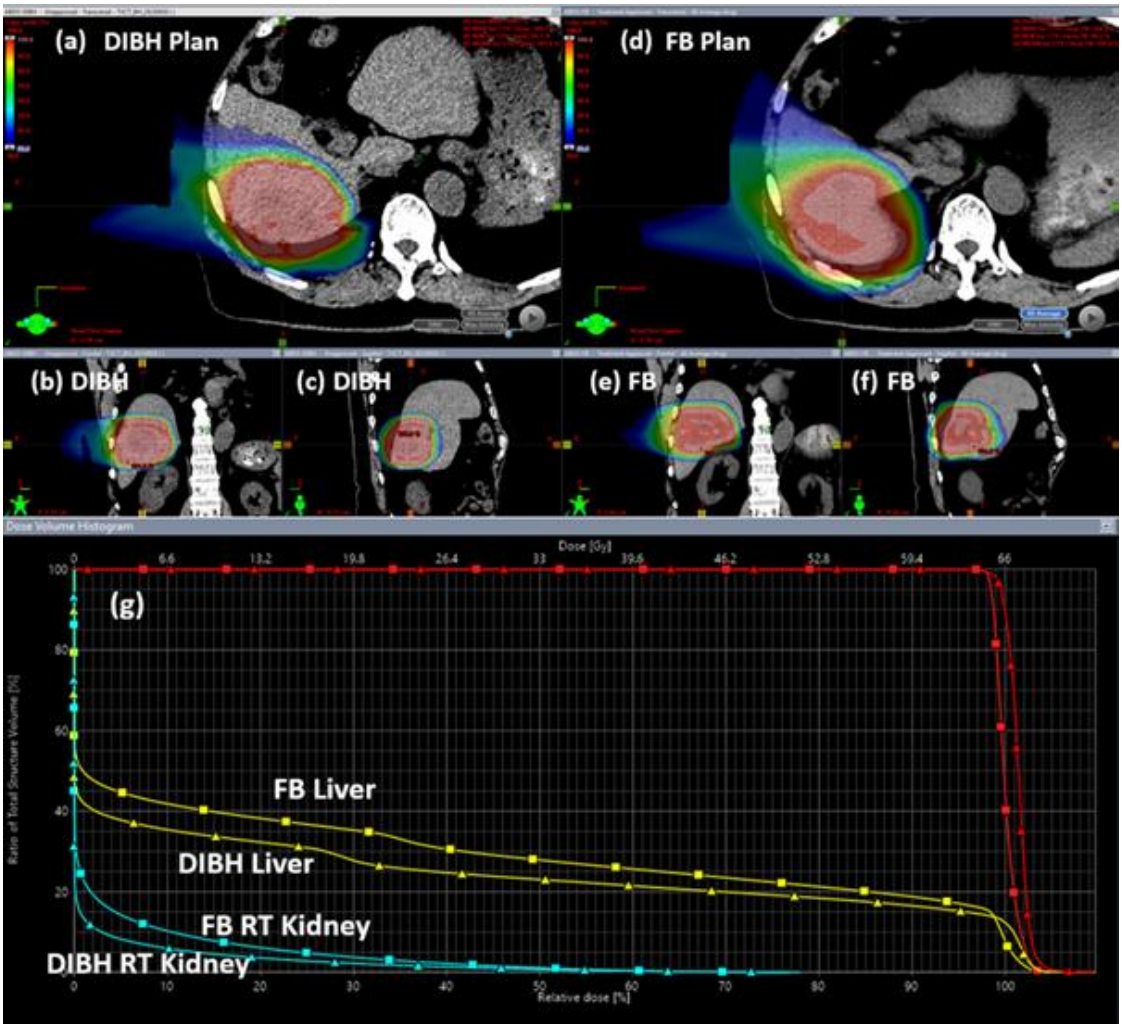

Figure 1. Planning results of DIBH and FB plans. Dose distribution from 30% to 100% of the prescription dose in (a)(d) axial, (b)(e) coronal and (c)(f) sagittal view. DVHs are shown here with rectangular (FB) and triangular (DIBH) marks in (g).

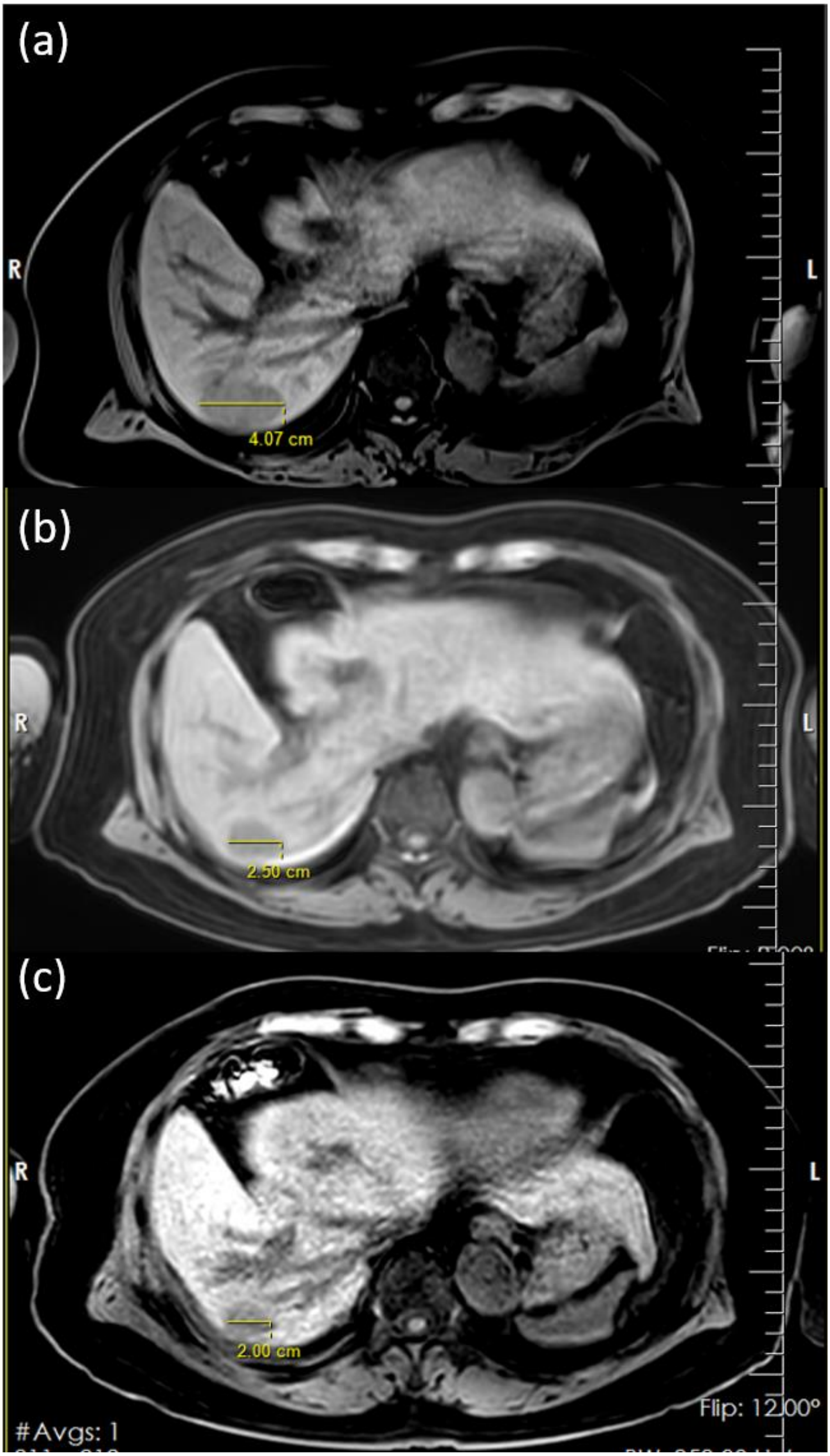

Figure 2. Treatment response. The MR image showed the tumour size was reduced. Image (a) showed a 4 cm mass taken before radiation therapy was carried out (July 2023), then radiation was given from 11 September 2023 to 22 September 2023. Image (b) showed the mass size became 2.5 cm after 2 months post-irradiation (November 2023). Image (c) shows a 6-month follow-up post-radiation, and the mass size had become 2 cm.

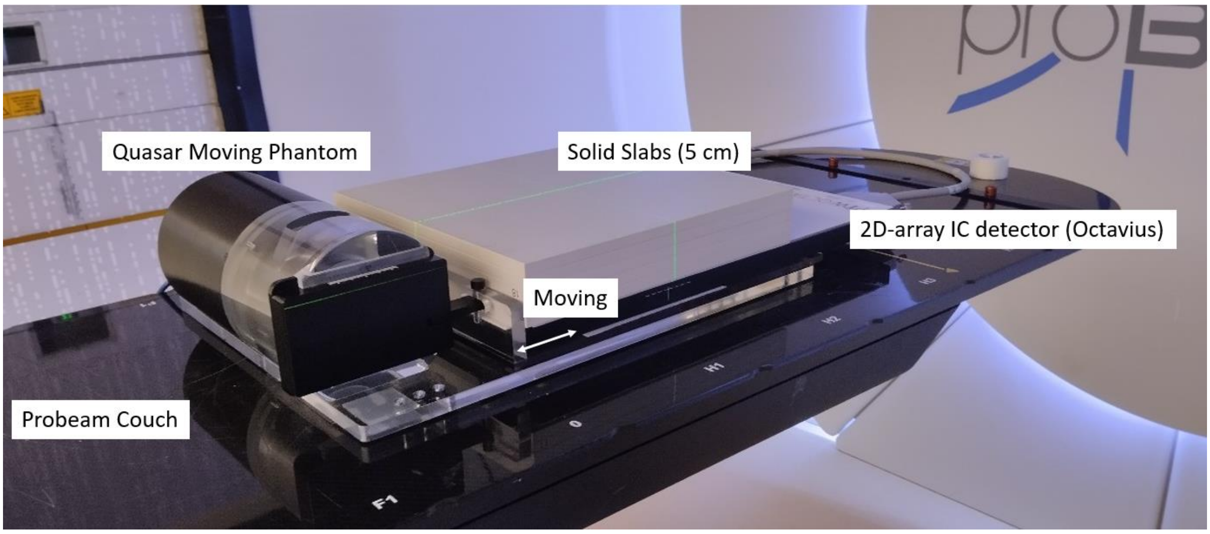

Figure 3. Setup for measurement of gamma analysis with moving phantom. White arrow shows the moving direction to superior and inferior directions.

shifter was used to reduce the interplay effect, which will be discussed in detail in the following section. Prescription and OAR constraints are described in Table 1.

Figure 1 displays the treatment planning results for DIBH and FB plan. Dose distributions are presented in axial Fig. 1(a)(d), coronal (b)(e) and sagittal (c)(f) planes with relative dose ranging from 30% to 100% of the prescription dose (Figure 1(a)(b)(c) and (d)(e)(f) represent the dose distribution from DIBH and FB plan respectively). Figure 1(g) shows dose-volume histograms (DVHs) of liver and right kidneys for FB (rectangular mark) and DIBH (triangular mark) plan respectively.

Results

In this paper, we reported the steps and the parameters that require rigorous attention for both DIBH and FB in the treatment of liver cancer (HCC) using proton beams. The target was contoured on the 4D average CT images to account for the target movement, ensuring inclusion of the target in all phases and enhancing dosimetric coverage through robust planning with sufficient margins. In addition, a 2 cm range shifter was used to mitigate the interplay effect. It was observed that this approach was effective without the need for repainting in the context of a hypofractionation scheme (10 fractions). FB approach was selected, and the patient's respiratory signal pattern was continuously monitored throughout the entire treatment course. It was verified that the patient's breathing remained stable and consistent, with the patterns observed during the simulation. Also, we checked tumour size was reduced significantly via follow up MR images after irradiation. Figure 3 showed the MR images before and after treatment. Tumour size was reduced from 4 cm (before treatment) to 2 cm (6 months after irradiation).

Discussion

Investigation for interplay effect (PSQA)

The patient-specific quality assurance (PSQA) process was successfully conducted in accordance with our protocols. This included 2D-array ion chamber detector measurement with gamma analysis (90% passing rate with criteria of 3%/3mm), point dose measurement using ion chamber (IBA Dosimetry CC04) and water tank. Gamma analysis is the analysis that compares the delivered dose distribution (measured by 2D-array detector in this case) to that of the planned by the treatment planning system (TPS) based on a dose difference (%) criteria and a distance to agreement (mm) criteria.

In pencil beam scanning mode of proton therapy, interplay effect is observed when the target moves, which can result in dose degradation.[11,12] The mechanism of the interplay is caused by the motion of the target and the scanning motion of the pencil beam. Thus, in the case of FB treatment, it is crucial to consider the interplay effect which can results in hot and cold regions within the tumour to reduce the interplay effect. Other institutions use layered or volumetric repainting method.[13,14] Layer repainting is the redistribution of proton beam over one motion cycle

Table 2. Gamma analysis results of amplitude effect on the moving phantom (P and F means Passed and Failed, with 90 % passing rate)

Items/Amplitude	6mm	7mm		8.5mm	10mm
Number of irradiation (fractions)	1	1	5	10	10
G315	90.2%(P)	89.1%(F)	98.6%(P)	92.6%(P)	87.6%(F)
G280	96.3%(P)	90.5%(P)	93.7%(P)	97.7%(P)	85.4%(F)
G250	90.3%(P)	90.1%(P)	100.0%(P)	97.8%(P)	90.2%(P)

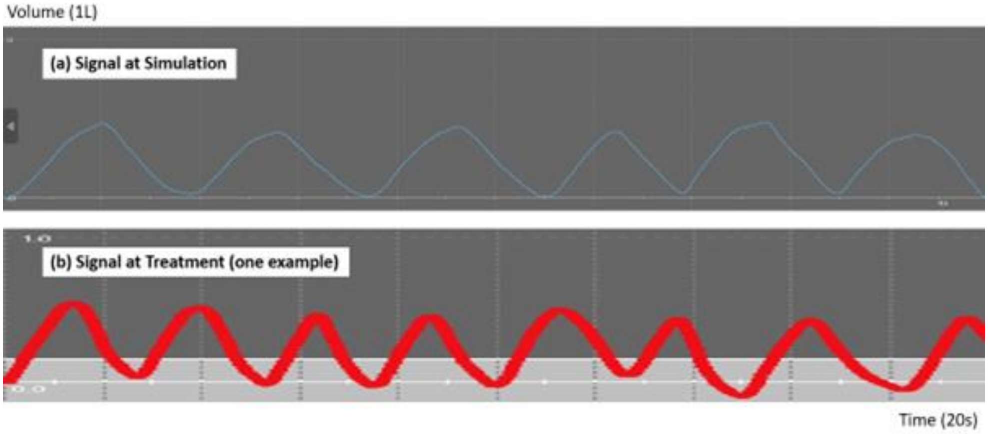

Figure 4. Patient's respiration signal from SDX at the (a) simulation and (b) treatment respectively.

before the next energy layer switching.[13] Volumetric repainting is the redistribution of proton beam from the distal to the proximal energy layers, back-and-forth over different phases of motion cycle.[14] In our institution, we opted for another approach, utilizing the range shifter to increase the spot size, thereby reducing interplay effect on dose distribution.[15] To determine the tolerable extent of target motion in the FB plan, we conducted a gamma evaluation analysis based on the amplitude of target motion, using a moving phantom (Quasar System) equipped with an 2D-array ion chamber detector (Octavius, PTW). In our preliminary investigation, we observed that even with a 2 cm range shifter, the mitigation effect on the interplay effect was reduced when compared with the plan without range shifter. It was found that a passing rate of 98.1 % could be achieved with the 2 cm range shifter related with 5mm amplitude of motion, which yielded results similar to those obtained with the 3 cm range shifter (97.5 %). These results were significantly improved from the result without range shifter case (70.2 %).

Following this, the impact of varying target motion amplitudes—ranging from 6 mm to 1 cm was investigated using a 2 cm range shifter during the PSQA process. To control the target motion amplitude, the actual respiration signal from the patient was extracted from the SDX system after CT simulation. This signal was then integrated into the respiratory moving phantom device (Quasar System) with different amplitudes to control the motion range. A verification plan consists of the CT image of the 2D-array ion chamber detector was created for gamma evaluation. The gamma analysis was performed using Verisoft (PTW), applying criteria of 3 % dose difference and 3 mm distance to agreement, with a 90 % passing rate. Figure 3 shows the setup of respiratory motion phantom with 2D-array ion chamber (IC) detector on the Probeam (Varian Medical System) couch.

Table 2 shows the results of gamma analysis. As shown in Table 2, for the 6 mm amplitude, corresponding to the liver motion of the current patient, the gamma passing rate is more than 90% in a single irradiation and meeting the passing criteria (over 90%). However, when the amplitude increases to 7 mm, the G315 field does not meet the criteria after the initial irradiation. After more than 5 irradiations (5 fractions), it is observed that the passing rate sufficiently satisfies our criteria again. With an 8.5 mm amplitude, the passing rate is met after 10 irradiations. In the extreme scenario of a 10 mm amplitude, the criteria are still not met even after 10 irradiations (refer to G315 and G280). Therefore, it is crucial to ensure that the patient's free breathing pattern is maintained below 8.5 mm as much as possible throughout the treatment.

If the range of the motion is less than the tolerable range related with interplay effect, then FB is better for patient to feel more comfortable, but still patient need to keep shallow free breathing. The most important advantage of DIBH is to reduce the margin. The detailed characteristics of the DIBH was reviewed in the Ref.[16]

Treatment for FB approach

In our first clinical experience at patient's first treatment setup, after the first cone beam CT (CBCT) images were taken, the heterogeneity of the shape of the liver part was observed. Image matching between simulation and plan was not suitable for DIBH plan, so we decided to go ahead with FB plan. The patient's setup was assessed with CBCT to make sure the bone and soft tissue region are matched with planned image. Following this, an orthogonal kV image was taken before each treatment beam, allowing us to re-evaluate the setup based on the bony structure before the irradiation. Throughout the whole treatment process, the FB signal pattern was continuously monitored using the SDX system to ensure consistency with the simulation data.

Figure 4 illustrates the patient's FB pattern during simulation (a) and treatment (an example) (b). During simulation, the patient's FB pattern did not exceed 0.5 L, and this pattern was generally maintained during most of the actual treatments. The respiratory cycle was 0.3 breaths per second (BPS) during simulation and 0.3 to 0.4 BPS during therapy sessions. This slight difference in BPS did significantly impact the interplay effect. In practice, the patient's respiratory amplitude was monitored to ensure it remained below 0.5 L, consistent with the simulation data.

In this case, compression belt was not used, because patient feel uncomfortable. However, the respiration pattern showed very stable with shallow depth, which make the motion of target region within the tolerable range for FB technique. We need to investigate more cases to get robust criteria for clinical practice.

Conclusion

Through this paper, we showed the proton active pencil beam mode can be effective way of the radiation therapy for HCC patient to reduce normal organ dose compared to photon radiation therapy. But, to get those advantages, many points should be considered and monitored during the whole clinical process. For free breathing technique with liver motion, suitable range shifter need to be used to reduce interplay effect and tolerable motion range has to be evaluated via quality assurance process before treatment. Also, real time patient's respiration pattern should be monitored for every fraction to assure the signal is matched well with that of simulation process.

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