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Critical Review

Deep Inspiration Breath Hold—Based Radiation Therapy: A Clinical Review

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Several recent developments in linear accelerator–based radiation therapy (RT) such as fast multileaf collimators, accelerated intensity modulation paradigms like volumeric modulated arc therapy and flattening filter-free (FFF) high-dose-rate therapy have dramatically shortened the duration of treatment fractions. Deliverable photon dose distributions have approached physical complexity limits as a consequence of precise dose calculation algorithms and online 3-dimensional image guided patient positioning (image guided RT). Simultaneously, beam quality and treatment speed have continuously been improved in particle beam therapy, especially for scanned particle beams. Applying complex treatment plans with steep dose gradients requires strategies to mitigate and compensate for motion effects in general, particularly breathing motion. Intrafractional breathing-related motion results in uncertainties in dose delivery and thus in target coverage. As a consequence, generous margins have been used, which, in turn, increases exposure to organs at risk. Particle therapy, particularly with scanned beams, poses additional problems such as interplay effects and range uncertainties. Among advanced strategies to compensate breathing motion such as beam gating and tracking, deep inspiration breath hold (DIBH) gating is particularly advantageous in several respects, not only for hypofractionated, high single-dose stereotactic body RT of lung, liver, and upper abdominal lesions but also for normofractionated treatment of thoracic tumors such as lung cancer, mediastinal lymphomas, and breast cancer. This review provides an in-depth discussion of the rationale and technical implementation of DIBH gating for hypofractionated and normofractionated RT of intrathoracic and upper abdominal tumors in photon and proton RT. © 2016 Elsevier Inc. All rights reserved.

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Introduction

Several recent developments in linear accelerator—based photon radiation therapy (RT), such as intensity modulated RT (IMRT) (1) and volumetric modulated arc therapy (VMAT) (2, 3), allow the application of highly complex treatment plans with steep dose gradients. Photon dose distributions in rigid treatment volumes have approached physically achievable complexity and accuracy limits as a consequence of the introduction of precise dose calculation algorithms (4), daily online soft tissue—based 3-dimensional (3D) image guided patient and target positioning for image guided RT (IGRT) (5, 6), and continuously improved delivery devices with fast collimators (7). Flattening filter-free (FFF) high-dose-rate applications (1, 8-13) have dramatically accelerated small-field delivery, particularly for the stereotactic body RT (SBRT) paradigm, while maintaining biological properties of the beam (14, 15). It has several further advantages such as less scatter from the treatment source, less leaf transmission, and less head leakage (1, 16).

The combination of all these technical possibilities has refined and accelerated (8) the therapy of both large stationary targets like head and neck cancer (17, 18) and smaller mobile targets, resulting in clinical benefits such as excellent local control rates in the treatment of early non-small cell lung cancer (NSCLC) or lung and liver metastases with SBRT (19-24), with very reasonable total treatment times now in the range of 15 minutes per treatment fraction.

Proton therapy is now applied with increasing frequency, with new treatment facilities being activated on a regular basis. It has made significant technological progress recently with more widespread use of scanned beams and the introduction of 3D image guidance. Nine times rescanning of a 1-L volume within 1 minute is now technically feasible, bringing into reach treatment deliveries during the time span of 1 breath hold (25). An innovative design for image guidance is the integration of a beams-eye view imager at Gantry 2 at the Paul Scherrer Institute in Switzerland, which is a fast parallel beam scanning proton therapy unit with small spot size and penumbra, allowing x-ray imaging in fluoroscopy mode during treatment delivery (25, 26). However, target motion implies a much bigger challenge for proton therapy than for photon therapy, especially for a scanned delivery, where interplay effects can significantly disturb the planned dose distribution (27). Furthermore, image guided approaches are much more advanced in photon RT, and online 3D motion monitoring has not been realized for particle therapy to date (28).

Despite constant efforts to mitigate motion effects (29-31) in both advanced photon therapy and proton therapy of body regions that are affected by breathing motion with motion amplitudes of up to 2 to 3 cm and potentially including hysteresis and deformations (32), methodical improvements are still needed. Resolving remaining issues may improve the treatment of several disease entities and clinical situations, among which are these:

1. RT of locally advanced NSCLC, where escalated doses in combination with chemotherapy may improve local control (33, 34) but are limited by normal lung tolerance and methodical imprecisions. Insufficient target coverage prompted by concerns about lung toxicity may have contributed to a lack of efficacy of dose escalation in the treatment of locally advanced lung cancer in the randomized Radiation Therapy Oncology Group (RTOG) trial 0617 (35, 36).

2. Exposed lung volume also plays a role in considerations regarding secondary malignancy after RT of all mediastinal tumors (37, 38). Exposed heart volume after mediastinal or breast RT is linked to long-term cardiac toxicity (39-44).

3. Treatment of nonstatic targets with passively scattered proton beams, which currently is not unlocking its full potential because of limitations on image guidance.

4. Treatment of nonstatic targets with scanned proton beams, which has been performed clinically only rarely to date because of concerns regarding interplay effects (45).

This review describes the different methods and characteristics of available motion management strategies in photon and proton RT and then outlines how deep inspiration breath hold (DIBH) can be efficiently performed and where it may resolve or mitigate the issues and unmet methodical needs just described. Table 1 provides a synopsis of the dosimetric and clinical characteristics of DIBH treatments and compares them with other currently available motion management strategies regarding their advantages and disadvantages.

Breathing Motion Management Strategies and Methods

Even for short beam-on times now achievable with FFF treatments, motion management strategies are necessary to compensate for intrafractional breathing motion. Different strategies aim at a reduction of margins between clinical target volume (CTV) and planning target volume (PTV) and/or improved geometrical precision of dose delivery.

1. Motion amplitude of free breathing (FB) can be reduced by mechanical abdominal compression (46). Recently, however, it has been shown to be beneficial only for lower lobe tumors and has no effect or a negative effect on middle and upper lobe tumors (47). Whereas the intrafractional amplitude of tumor motion can be

Table 1 Characteristics of DIBH treatments within the framework of advantages and disadvantages of currently available motion management strategies

Motion compensation method	DIBH	Spontaneous breathing gating	Real-time tracking	ITV/individualized margins
Available techniques	Free DIBH Computer-controlled DIBH (spirometry, surface tracking with markers or markerless)	Spirometry, surface tracking with markers or markerless	Couch tracking Steering of beam	Treatment planning with 4D CT, potentially with abdominal compression
Imaging	All imaging under DIBH: planning CT, CBCT, ultrasound surveillance in breath hold, simultaneous VMAT-CT during treatment	Dynamic planar or ultrasound imaging 4D CBCT immediately before treatment Simultaneous VMAT-CT during treatment	Dynamic planar or ultrasound imaging and VMAT-CT possible during treatment, depending on platform used	4D CT, 4D MRI for treatment planning 4D CBCT immediately before treatment Simultaneous VMAT-CT during treatment
PTV margins	Small (residual motion after breath hold)	Small (residual motion in gating window)	Small (tracking inaccuracy)	Large (end-expiratory-to-end-inspiratory position)
Characteristics of achievable dose distribution	Reduced lung dose resulting from lung expansion and smaller PTV Typically reduced cardiac dose and dose to most other OARs	Depends on gating phase (inspiration: favorable; expiration: unfavorable)	Typically high exposure of lung and other OARs because treatment is performed during all breathing phases. Dose ideally has to be accumulated on a dynamic model.	Typically high exposure of lung and other OARs caused by treatment in all breathing phases and large margins. Dose ideally has to be accumulated on a dynamic model
QA	Standard treatment and imaging QA	Standard treatment and imaging QA	QA of the dynamic treatment process in addition to standard QA	Standard treatment and imaging QA
Patient convenience	Optimal patient collaboration and compliance needed Sufficient pulmonary reserve needed	Patient collaboration and regular breathing pattern needed	Patient collaboration and a sufficiently slow breathing pattern needed	Abdominal compression frequently needed to reduce target motion
Treatment time	Longer treatment time	Longer treatment time	Short treatment time	Short treatment time
Scanned particle therapy	Minimal risk of interplay effects	Small risk of interplay effects	Small risk of interplay effects	Higher risk of interplay effects
Toxicity	For small lesions low for all techniques, for larger lesions no comparative data available, theoretical benefits for DIBH			

Abbreviations: 4D = 4-dimensional; CBCT = cone beam computed tomography; CT = computed tomography; DIBH = deep inspiration breath hold; ITV = internal target volume; OAR = organ at risk; PTV = planning treatment volume; QA = quality assurance; VMAT = volumetric modulated arc therapy.

reduced by abdominal compression, interfraction motion can even be increased (48). Mechanical abdominal compression has also been evaluated theoretically (49) and used clinically in particle therapy to reduce intrafractional motion (50).

2. One of the most widely used strategies is treatment planning with individual determination of CTV-PTV margins based on 4D CT in FB (31, 51). 4D planning requires appropriately chosen PTV margins (internal target volume [ITV] concept) considering the end-expiratory and end-inspiratory position of the tumor. Inclusion of all breathing phases during the actual treatment ensures optimal treatments for small tumors but results in increasing volumes of healthy lung tissue exposed to high doses with increasing CTVs if the CTV-PTV margins are kept constant (52). For particle therapy, in addition to geometrical considerations, changes in tissue densities resulting from motion that affect the particle range have to be considered in the design of margins (53). Several publications have recently reported uncertainties in the 4D CT approach regarding breathing pattern (54), motion uncertainties, dosimetry, and verification difficulties. Uncertainties have been shown regarding 4D CT—based motion measurements for lung SBRT. Confirmed by megavoltage imaging during beam-on, Zhang et al (55) have shown that 4D CT may underestimate the overall maximum tumor motion range during lung SBRT. For liver SBRT, a single 4D CT

image for planning did not always correctly represent the mean motion amplitude (measured by kV and MV marker-based imaging) during treatment (56). Large variations in intrafractional and interfractional motion patterns for various targets have been also observed (57), especially in the anterior-posterior direction and in a fraction duration−dependent manner (58, 59). Measurements of the motion of implanted fiducials with daily orthogonal fluoroscopy have shown that 4D CT overestimated daily 3D motion in 39% of fractions and underestimated it in 53% of fractions. Breathing patterns varied from breath to breath and from day to day, and the intrafractional variation of the amplitude was significantly larger than the interfractional variation (59). FB cone beam computed tomography (CBCT) potentially underestimates the ITV if the respiratory pattern is characterized by a disparate length of time spent in inspiration versus expiration, potentially leading to misalignments, depending also on tumor size and localization (60, 61). 4D CBCT is the logical continuation of the 4D concept through the whole treatment chain. It has become available recently and remedies several of the abovementioned issues but trades image quality for time resolution (62-64). In particle therapy, the value of 4D magnetic resonance imaging (MRI), which enables the capturing of motion variations and drift effects, has been explored (65).

3. Whereas 4D treatment planning results in an individualized choice of PTV margins that may result in an expansion of margins compared with the population mean, real-time target tracking or continuous patient position adjustment with robotic treatment couches with 6° of freedom can minimize the PTV margins for all individuals (66, 67). Several tracking technologies have been clinically established and can, for example, be found in the Cyberknife concept (68, 69) or the recently released (and already discontinued) Vero System (Vero SBRT, Brainlab, Feldkirchen, Germany) (70, 71) with steering of the beam application, or, in an experimental system, with steering of the patient couch (72). Tracking is typically based on an individual motion model created during treatment planning that is frequently verified by planar EPID (Electronic Portal Imaging Device) imaging of implanted fiducials or the tumor shadow (when detectable) and/or optical surface tracking (ExacTrac) (73, 74); (Cyberknife) (75). The clinical introduction of online 4D MRI during photon treatment (76, 77) may further advance the concept of instantaneous tumor tracking, but significant developments still have to be made. Tracking seems to be the ideal motion mitigation technique for a steerable particle beam (78). Because it relies on real- time 3D imaging information of the patient, which is not yet available for particle therapy, it has not yet been implemented clinically.

4. Respiratory gating as FB gating or with voluntary or computer-controlled breath hold minimizes PTV margins across a patient cohort, similar to what is achieved by tracking. FB gating strategies have typically been used during end-expiration, which occupies the majority of the breathing cycle. This approach therefore allows for the application of large doses during the gating phase. Plan comparison studies, however, have demonstrated that IMRT plans for the inspiration phase of the breathing cycle as DIBH resulted in better V10, V20, V40, and mean lung dose when compared with plans for end-expiration, also for normofractionated treatments of advanced lung tumors (52, 79-82). Gating is the most commonly used motion mitigation technique for particle therapy (83).

5. A motion mitigation technique that is unique for scanned particles is rescanning, which refers to repeated irradiations during 1 treatment fraction to statistically smooth out interplay effects (27). Rescanning is suggested to be combined with other motion mitigation techniques (84).

The characteristics of DIBH gating were summarized by a review in the framework of the Soutien aux techniques innovantes couteuses de 2003 (STIC 2003) (82), which confirmed the feasibility and good reproducibility of various respiratory gated RT (RGRT) systems. Improvement of dosimetric parameters predictive of reduced pulmonary, cardiac, and esophageal toxicity by RGRT has already been described in this article. Since then, additional data have been published that solidify the rationale for the use of DIBH gating in various clinical situations and are reviewed in this article.

Methods for Establishing DIBH

DIBH can be achieved by repeated voluntary breath hold or with computer-controlled commercially available devices, which can assist DIBH through airway blocking, feedback approaches, or both. Breath hold gating signals now automatically trigger treatments across all major treatment device manufacturers.

Free DIBH/voluntary breath hold

A fully free (non−computer-controlled) breath hold technique can be used during RT for breast cancer aiming at heart, lung, and liver dose reduction (85-87). Voluntary breath hold does not require any additional equipment. To monitor breath hold, the distance moved by the anterior and lateral skin marks away from room lasers and additional light field verification can be used; therefore, voluntary breath hold typically is not completely “uncontrolled” (86). Despite clear dosimetric benefits (heart and lung) for both 3D tangential and VMAT plans in right-sided and left sided breast cancer (85, 88, 89) and acceptable precision data even in a randomized setting (89), this method is not yet in widespread use (86), although interest is increasing. The UK HeartSpare study (89) has shown comparable electronic portal imaging and CBCT derived precision data (systematic and random error vector of 3 to 5 mm regarding chest wall position) of voluntary breath hold when compared with computer-controlled breath hold (Active Breathing Coordinator, Elekta AB, Sweden). Similar CBCT-based precision data were published by Betgen et al (90) with good intrafraction reproducibility of chest wall position and interfraction systematic and random error of 2-5 mm and 1.56°. However, in these publications, no position information is provided of OARs (heart and lung), and no intrafraction EPID verification was performed (89, 90). Patients and staff preferred voluntary breath hold to computer-controlled breath hold because of the easier workflow and reduced cost (89). The method seems therefore to be acceptable for breast tangential RT. Given that evaluated patient numbers are low, and information on heart and lung position with a 3D soft tissue imaging method (eg, breath hold CBCT) was lacking in these studies, this issue needs further evaluation, especially if the method is used in the context of RT and SBRT to the lung and liver.

Computer-controlled DIBH

Breathing volume—based methods

Computer-controlled breath hold systems aim at creating a static geometrical situation of the body and the GTV within the body during the planning CT. Breathing volume—based methods quantify the inspiration volume with a spirometer. Patient feedback can be established and provided with an open airway audiovisually (a “target zone” is projected on a screen or through video goggles, and the patient is instructed to inhale to reach a certain signal position on the screen) (91), as performed with the SDX System (SpiroDynr'X; France) (82, 92) or by actually closing the airway for a defined time, as performed with the ABC System (Elekta). Intrafractional and interfractional reproducibility for ABC are 1.7 mm and 3.7 mm, respectively (93-100). Brock et al (101) measured with repeat breath hold CTs consistent intrafraction tumor position but with interfraction variations of mean (range) values of 5.1 (0-25), 3.6 (0-9.7), and 3.5 (0-16.6) mm in the superior-inferior, right-left, and anterior-posterior directions. However, different breathing maneuvers (thoracic vs chest breathing) can lead to variations in chest wall position even if inspiration volume is the same, which can lead to uncertainities regarding tumor position (102). Recently, surface fiducial tracking methods have allowed the monitoring of breath hold during 1 fraction. Data derived from additional optical infrared tracking have shown a mean intrafraction variation vector among breath holds of less than 2.8 mm (102). Uncertainties were observed in the anterior-posterior direction (maximal 12 mm). This had no influence on target coverage but on OAR doses, and therefore optical tracking has been recommended for the surveillance of ABC-based breath hold (102).

Visual feedback/optical surface detection/tracking

Breath hold with visual feedback requires optimal patient compliance and has been shown to be accurate for lung lesions, with intrafraction reproducibility of <3 mm (103, 104). Both intra—breath hold and inter—breath hold measurements during feedback-guided voluntary breath hold with computer-controlled visual feedback (video goggle) resulted in a reproducibility of GTV centroid positions of 1.0 ± 0.5 mm, 1.3 ± 1.0 mm, and 0.6 ± 0.4 mm in the anterior-posterior, superior-inferior, and left-right directions, respectively, compared with more than 1 cm of tumor motion at FB (103).

An indirect approach for breath hold gating is optical surface tracking as it is established with reflectors within the RPM (Varian, Palo Alto, CA) (105), Exac-Trac (Brainlab, Feldkirchen, Germany), or Synchrony (Accuray, Morges, Switzerland) systems or with markerless systems such as alignRT (VisionRT, London, UK) or Catalyst (C-RAD, Uppsala, Sweden) (106).

The markerless systems project visible light on the patient and detect the surface and surface movements caused by respiration. This movement detection can be used to verify the tumor position during respiration and to gate the beam during treatment. Several studies with different systems (107-110) compared the agreement of an optical surface tracking system and CBCT regarding static targets and found good agreement between both techniques in most situations, indicating the general robustness of this approach. Alderliesten et al (111) evaluated the accuracy of a 3D surface imaging system compared with CBCT for the guidance of DIBH-RT of left-sided breast cancer and found a good correlation between setup errors detected by both methods. Daily real-time surface monitoring has been shown to ensure accurate interfraction and intrafraction repositioning (112, 113), reduced heart dose, and acceptable treatment time of left-sided breast cancer patients, especially those with unfavorable cardiac anatomy (114-117). Some data indicate that for RT for left-sided breast cancer, surface monitoring systems are superior to spirometer-based systems regarding repositioning of the external surface (118).

Characteristics and Advantages of DIBH

Possibility to image under DIBH

Serpa et al (119) have shown that markerless EPID tracking is principally suitable for treatment verification of gated SBRT, but marker-based EPID imaging is also being used. For Cyberknife SBRT, breath hold imaging was performed after implantation of 2 to 4 fiducials directly into the tumor, and a maximal tumor vector movement of 3.8 mm (detected by kV flat-panel detectors) was reported (120).

Linac-mounted CBCTs currently on the market provide the possibility to interrupt imaging and image acquisition with reconstruction after the intended imaging angle has been completed. Such a stop-and-go approach allows the acquisition of a complete volume dataset under breath hold (121). Although the acquisition time is longer than that of FB CBCT, image quality is significantly improved over imaging in FB only, FB interlaced with 3 to 4 breath holds (94, 122), or 4D CBCT at identical imaging doses. The approach provides superior image quality, particularly for middle-lobe and lower-lobe lung tumors (Fig. 1) (121), and it also improves soft tissue contrast in upper abdominal lesions (Fig. 2). First experiences report feasibility, speed, and better interobserver variability of DIBH CBCT for lung SBRT (123). Single breath hold CBCT has also been implemented (124) but is not yet broadly used.

A development that is currently undergoing final refinement before clinical testing is combined kV-MV imaging (125, 126) that makes use of both kV and MV imaging devices on a linac in combination with faster gantry movement and dedicated reconstruction algorithms (127, 128). It offers the possibility to acquire a full 3D dataset during 1 breath hold (<15 sec) with acceptable imaging doses and excellent positioning precision (129).

The position of target and surrogate structures in breath hold for liver and upper abdominal SBRT can be also controlled by stereotactic ultrasound systems (98, 130-132). Surveillance of breath hold with ultrasound-based tracking is also under development (133, 134). Breath hold imaging can be also completed with MRI-based IGRT systems by matching of intratreatment orthogonal cine MRI planes to pretreatment 3D MRI datasets (76, 135).

Clinical application and dosimetric features of DIBH

In 1987, the potential for improvement in RT treatments of mobile targets by reducing respiratory effects was first reported. An American team noticed that treatment in deep inspiration spared parts of the lungs, and they suggested a need to develop RT gated to respiration (136). In the following paragraphs we discuss the site-specific advantages of DIBH.

SBRT of liver lesions

Intra-breath hold liver motion and intrafraction and interfraction reproducibility of liver and diaphragm position relative to vertebral bodies during ABC-based liver SBRT was assessed by kV fluoroscopy and by MV EPIs and movies (94). The average maximal diaphragm motion measured by fluoroscopy during a single ABC breath-hold was 1.4 mm, also confirmed by the MV movies. Repeated CT scans in breath hold have shown a mean difference (intrafractional) in the liver surface position of −0.9 mm, −0.5 mm, and 0.2 mm in the cranial-caudal, anterior-posterior, and medial-lateral directions; the average absolute interfraction cranial-caudal offset in diaphragm position relative to vertebral bodies was 3.7 mm (94).

Whereas SBRT of lung and liver lesions was initiated with stereotactic body frames, including devices to limit liver excursion during treatment with the sole objective to improve dose delivery accuracy and thus reduce PTV margins, DIBH was introduced soon after the clinical introduction of SBRT to immobilize the diaphragm movement less invasively. Intrafraction precision was excellent when fiducial markers and EPID imaging (maximal craniocaudal offset 1.7 mm) were used (94). The clinical results were comparable with those reported for body frame fixation. Meanwhile, based on DIBH, a minimally invasive frameless workflow could be established together with ultrasound (98, 131) or CBCT. The results have also been

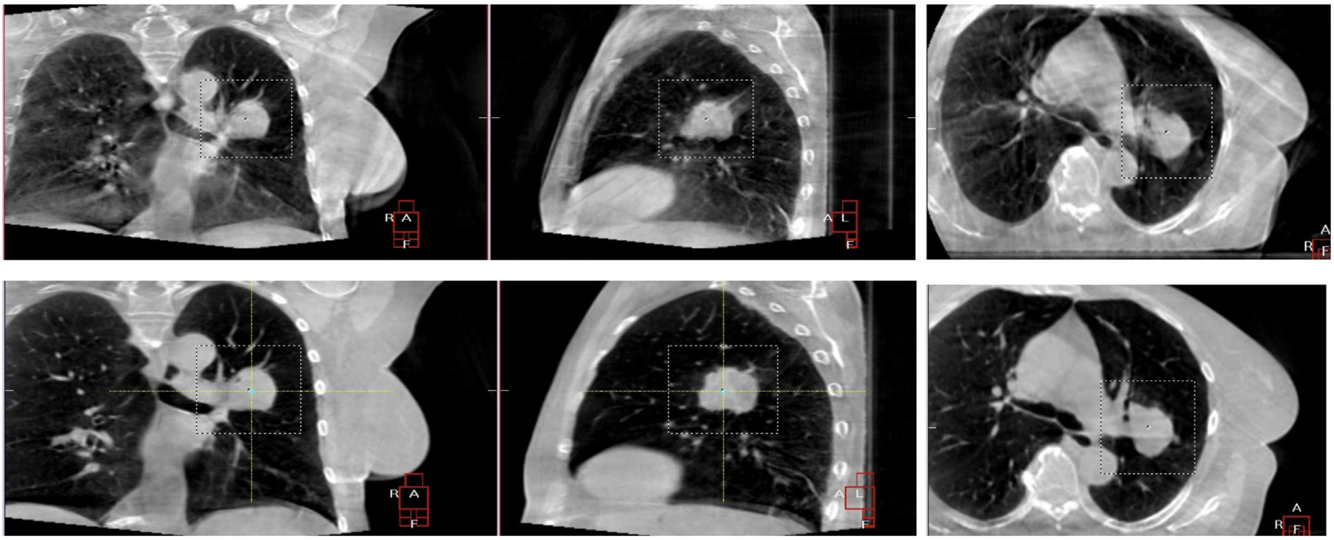

Fig. 1. Comparison of imaging paradigms for lung lesions. Upper row: Cone beam computed tomography (CBCT) under repeat breath hold, including free breathing phases into the reconstruction. Notice the blurring at the tumor surface and diaphragm. Lower row: CBCT stop-and-go (same number of frames in reconstruction but all frames acquired under breath hold conditions). Notice the improved image quality and reduction of blurring.

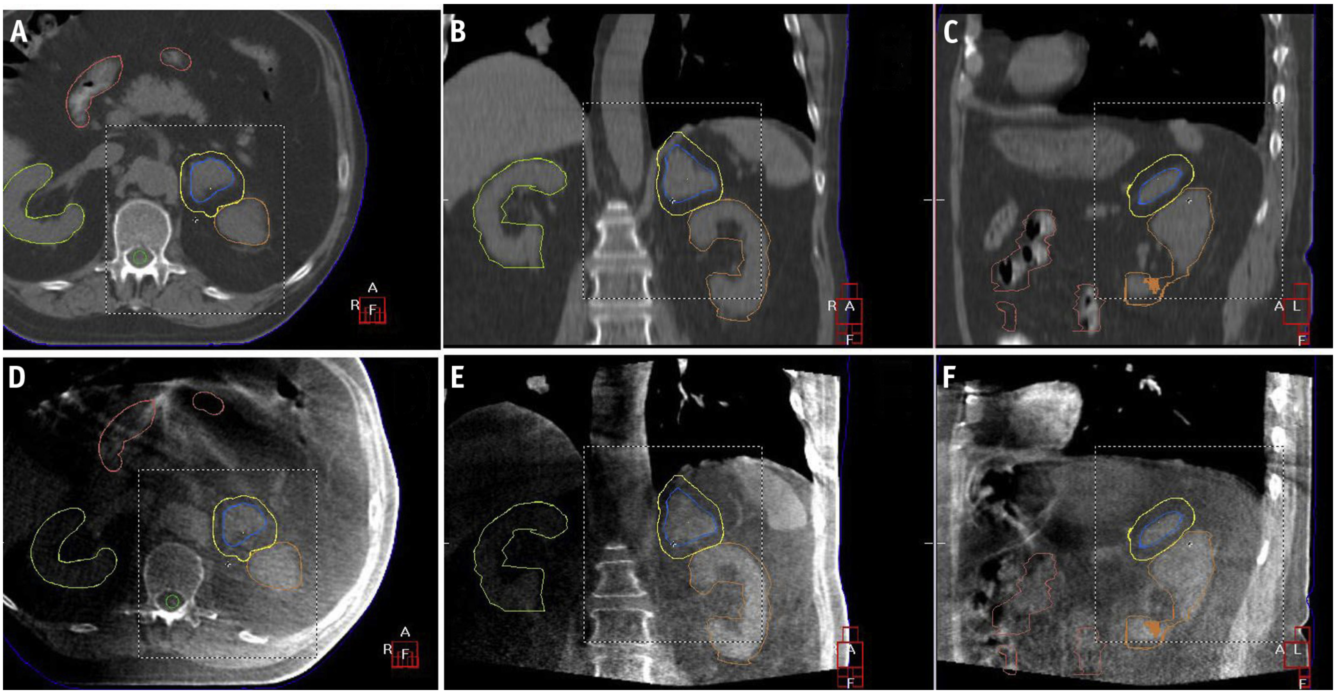

Fig. 2. (A-C) Helical treatment planning computed tomography (CT) for comparison. (D-F) Excellent cone beam CT image quality in upper abdomen with stop-and-go acquisition (all frames acquired under breath hold).

excellent for hepatocellular carcinoma (137, 138), where RT as a bridging treatment before transplantation or as definitive therapy has seen renewed interest (139).

Particle RT has seen an increasing role in the treatment of hepatocellular carcinoma because of the potential of increased normal liver sparing (140). Often hypofractionated regimens are applied (50, 141, 142). The combination of high motion sensitivity of particle treatments with the unforgiving character of hypofractionation (little statistical smoothing of interplay effects, sensitivity to drift effects resulting from increased fraction duration) makes the application of motion mitigation techniques essential. Clinically, abdominal pressure plates and gating are most commonly used to mitigate motion effects. Especially for scanned proton therapy, the combination of rescanning with other motion mitigation techniques like gating or breath hold have been suggested (26, 45).

SBRT of lung lesions

The theoretical advantages of RT for lung cancer in DIBH were published in 2005 by Underberg et al (143): a maximally expanded healthy lung tissue allows minimizing lung dose; complete immobilization of the PTV allows reduction of PTV margins, which again reduces lung dose (144, 145) (Fig. 3). This approach has since increasingly been used for simple and reliable tumor immobilization, reduction of lung exposure (146), and heart protection (49).

Scotti et al (147) investigated the impact of ABC-based DIBH on PTV margins and OAR sparing for 3D CRT and SBRT for lung cancer. In comparison with FB CT, the PTV margins could be reduced, and all dosimetric lung parameters (V20, MLD) were significantly improved with the use of DIBH gating.

Corresponding with the dosimetric data, the clinical results of DIBH-based SBRT are promising (and comparable with results of 4D CT based/mixed SBRT cohorts) (22) for both primary lung tumors and metastases. The actuarial 1-year local control rates are between 90% and 95% (3-year local control 82%-88%), with very low toxicity (19, 128, 148-150). The results seem to depend on applied dose and size of PTV (19), and the method seems to be suitable even in the reirradiation situation (151).

By creating a static situation during treatment, DIBH prevents interplay effects. Although these are likely of minor importance in modulated photon RT (with some exceptions) (152), they can significantly disturb particle treatment plans (153, 154). Especially for lung indications, nonrigid deformations that relocate high-density (ribs) and low-density (soft tissue) regions can result in severe overshoots or undershoots. Therefore, methods to restrict motion or to mitigate motion effects are highly desired.

Georg et al (49) evaluated passively scattered proton treatments and intensity modulated proton (IMPT) plans for shallow breathing with abdominal compression and DIBH (49). Irrespective of treatment modality, they found that dose-volume histograms were improved with the DIBH technique. However, the differences between shallow breathing and DIBH did not reach statistical significance. They stated that although respiration-controlled proton and ion beam therapy with gating and tracking approaches is technically feasible, shallow breathing with abdominal compression or DIBH is probably more practical for the

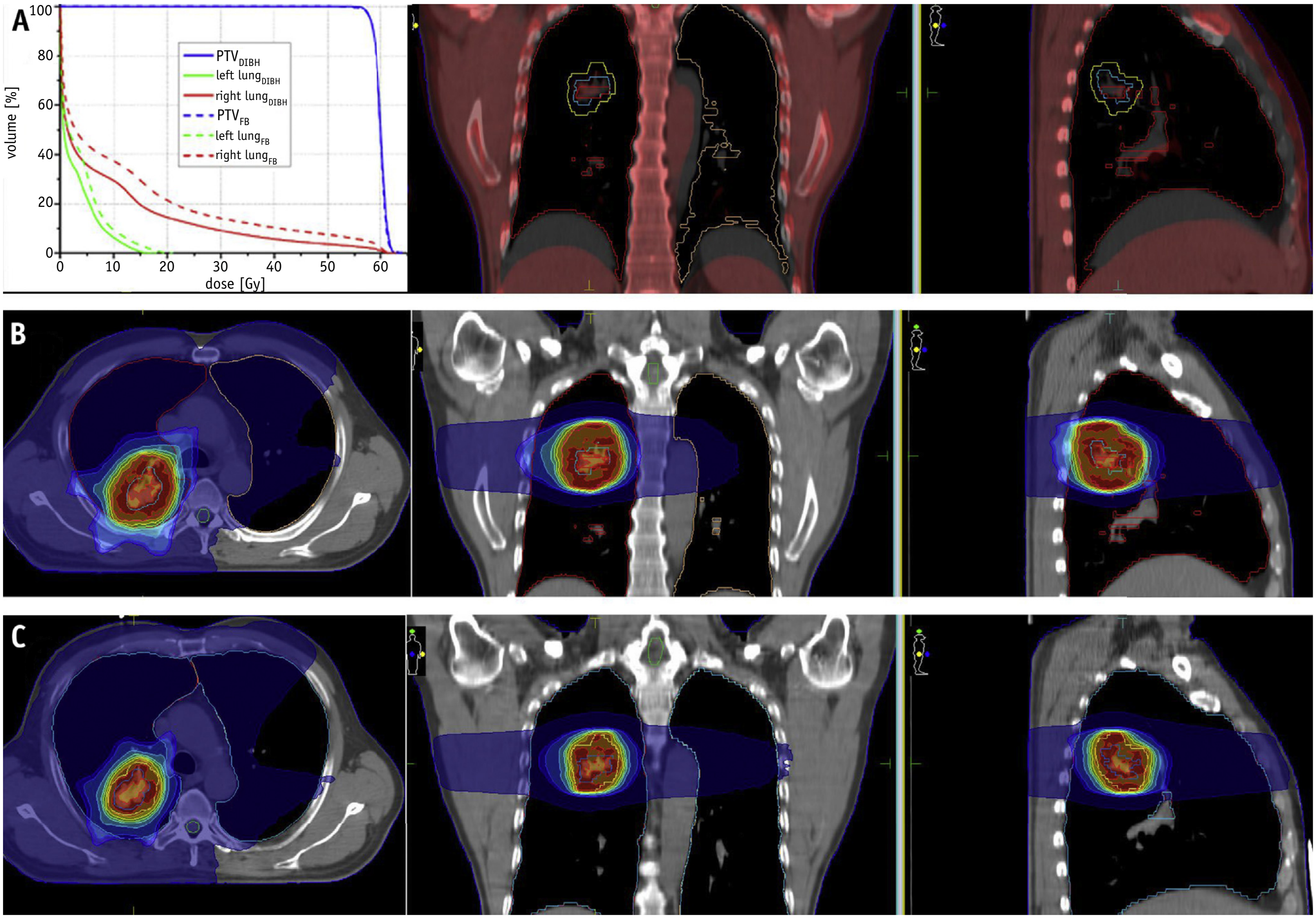

Fig. 3. Treatment planning for lung stereotactic body radiation therapy. (A) Comparison of planning treatment volume (PTV) and lung dose-volume histograms in free breathing (FB) versus deep inspiration breath hold (DIBH), coronal and sagittal matched planning computed tomographic images in DIBH and FB. (B) Treatment plan without breathing management (predominantly end-expiration). (C) Treatment plan in DIBH. Note expanded lung tissue and smaller PTV margins. *Abbreviations:* CBCT = cone beam CT; CT = computed tomography; FFF = flattening filter-free; IGRT = image guided radiation therapy; MLC = multileaf collimator.

delivery of high fractional doses. Stuschke et al (155) showed the robustness of single-field uniform dose proton plans and IMPT plans for lung patients in a breath hold scenario. As much as this was only a planning study, concerns about the feasibility to deliver the dose for 1 treatment field entirely during 1 breath hold were raised. Given that inter—breath hold positional variations during the same fraction tend to be larger than intra—breath hold variations, a scan across the whole target volume during 1 breath hold would be required to ensure robustness. Lin et al (156) estimated that energy switching times and average spot delivery times of 1 second/5 milliseconds are required to deliver treatment fields in about 74% of lung SBRT cases within 1 breath hold. Current commercial systems are mainly slower than that. A system that fulfils these requirements is the Gantry 2 at the Paul Scherrer Institute in Switzerland, which is a fast parallel beam scanning proton therapy unit with small spot size and penumbra, which was optimized for the treatment of moving targets (25, 157).

Normofractionated treatments of advanced lung tumors

As discussed earlier, PTV margin reduction is essential in RT of locally advanced NSCLC to maximally exploit normal tissue tolerance so tumor doses can be escalated. Given that methodical insufficiencies may have invalidated the results of RTOG 0617 (35, 36), breathing management, potentially in combination with adaptive strategies are now tested in RTOG 1106 (36). Potentially, particle therapy will be mandatory for any further attempts to improve survival based on better local control.

Hanley et al (158) and Rosenzweig et al (159) have published planning studies comparing dosimetric parameters of FB versus DIBH, reporting the advantages of DIBH as early as 15 years ago. Hanley et al (158) also provided proof of tolerability of breathing maneuvers by the patient.

Mah et al (160) expanded on this, reporting their initial experience of a feasibility study with DIBH for NSCLC.

Since then, dosimetric advantages with reduced lung and cardiac dose have been repeatedly demonstrated for DIBH RT in the setting of advanced lung cancer treatments (82, 145). In plan comparison studies, IMRT plans in inspiration were significantly favorable regarding V10, V20, V40, and mean lung dose if they were compared with expiration plans also for normofractionated treatments of advanced lung tumors (52, 79-82).

Clinical outcome regarding toxicity and economic aspects has also been analyzed by Giraud et al (82) in the framework of the STIC project between 2004 and 2008 in 20 French centers. The reported dosimetric benefits were correlated clinically with a significant reduction of pulmonary acute toxicity and with pulmonary, cardiac, and esophageal late toxicities (82).

DIBH to reduce cardiac and pulmonary toxicity after adjuvant radiation therapy of breast cancer

Cardiac damage has been the main concern in whole-breast RT. Whereas improved RT techniques seem to have measurably reduced cardiac toxicity (161), every measure should be taken to minimize cardiac exposure to doses in excess of 30 Gy (39). A very recent review summarizes the advantages of DIBH in breast cancer RT (162).

Data for DIBH RT of left-sided breast cancer confirmed good reproducibility (163) and dosimetric advantages such as reduced lung and cardiac dose (164-166) in comparison with FB planning. Sung et al (165) have shown significant reduction in irradiated heart volume and V25 using DIBH compared with plans in FB. Verhoeven et al (167) compared plans of supine FB, supine DIBH, and prone FB. Whereas target coverage was similar with all modalities, doses to the heart, left anterior descending coronary artery, and contralateral breast could be most effectively reduced by supine DIBH planning. A prospective trial has shown that ABC-based breath hold can reduce the mean heart dose by 20% and dose to the lung (168). Reduced cardiopulmonary dose by DIBH was reported by several other groups (44, 169-173), even for nodal irradiation (174). A possible drawback of the method is the potentially higher dose to the contralateral breast (175); however, the estimated risk of a second cancer was the same for the FB and DIBH plans (176).

Whereas the dosimetric benefits of DIBH treatments for breast cancer are striking, a recent report of functional imaging results after DIBH or conventional RT did not find a difference in cardiac muscle perfusion 6 months after treatment (177). Although the correlation between these imaging changes and the clinical late effects is by no means established (39), these results may be explained by too high sensitivity of the chosen imaging method or heart volumes exposed to high doses in this series that were still too large even with DIBH despite low mean heart doses. At this stage there is therefore no clinical proof of DIBH benefits.

A comparative study of whole breast irradiation between IMRT and IMPT by Mast et al (178) showed a significant dose reduction to the heart and region of the left anterior descending coronary artery for IMPT even without breath hold. The results showed that a breath hold technique had no added value when IMPT was used. However, using breath hold may improve the robustness of the IMPT technique because the tissue shift will be less.

Hodgkin disease

In addition to the potential reduction of functional damage to normal tissue, in patients with Hodgkin lymphoma, a supremely curable disease frequently encountered in younger patients, reduction of irradiated tissue may reduce the risk of a second cancer (179), adding a further motivation to perform breath hold treatments in these patients. Involved node RT in DIBH has been shown to be safe and effective (180). Dosimetric advantages with reduced lung and cardiac/coronary dose have been demonstrated for supradiaphragmic Hodgkin lymphoma (180), also in a prospective phase 2 study (181) and especially for tumors of the upper mediastinum (180) and in combination with IMRT (182). Long-term toxicity data with functional imaging are still missing.

Protons have been stated to theoretically provide both excellent high-dose conformality and reduced integral dose (179). In combination with breath hold they could enable superior treatments for involved field and involved node treatment of mediastinal Hodgkin lymphoma. Clinical evidence is, however, not yet available.

Other tumor entities

Dosimetric advantages with reduced lung and cardiac dose have been also demonstrated for thoracic esophageal cancer (183, 184). The noninvasive ablation of kidney tumors has become an intriguing concept, now that evidence regarding the abscopal effects of large radiation doses is mounting (185). It is already being explored within the framework of clinical studies (NCT02334709: phase 1-2, SBRT with tyrosine kinase inhibitors, Ghent). Both online image guidance with ultrasound (133, 134) and online MRI (76, 135) now provide the technical basis for these treatments that will benefit dramatically from breath hold strategies.

So far, only limited experience of particle therapy treatments in combination with breath hold can be found in the literature. Studies are restricted to the above-mentioned indications. The reason is that moving targets present a special challenge for particles and are not yet commonly clinically treated. A clinical trial for lung cancer, breast cancer, gastrointestinal indications, and lymphomatous malignancies has recently been completed at the Abramson Cancer Center of the University of Pennsylvania (186). The outcomes will give more evidence on the benefit of DIBH treatment in the context of proton radiation therapy.

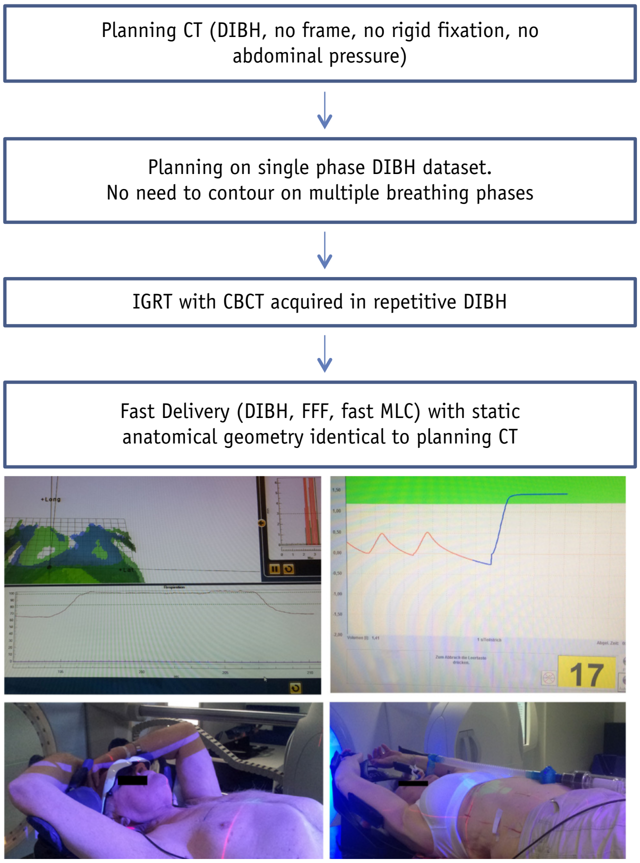

Fig. 4. Hallmarks of deep inspiration breath hold (DIBH) workflow. Left, breath curve and patient with Catalyst. Right, breathing curve and patient with Active Breathing Coordinator.

Recent Developments That Have Facilitated the Use of DIBH, and Outlook

Quality assurance and workflow for breath hold application is fast and easy (8, 82). Frequently voiced concerns regarding DIBH have concentrated on the necessity for optimal patient collaboration and compliance with the procedure, sufficient pulmonary reserve, and the longer treatment time in comparison with nongated or tracked treatments (187). With the advent of fast multileaf collimators, VMAT, and particularly the FFF technology, the prolongation of treatment time of a gated over a nongated treatment has been considerably reduced (8). Patient collaboration is excellent under these conditions if assisted breath hold is used and a minimum of training is provided. DIBH has been shown to be safe and effective (144) and to have positive effects in fractionated therapy of various thoracic and upper abdominal tumor entities (Table 1).

In the future, DIBH will likely facilitate the development of new treatment paradigms and the refinement of existing ones. Therapy with scanned particle beams will likely be more robust, and more mobile targets will therefore be accessible to this treatment paradigm. Online MRI-based IGRT will provide the possibility for instant replanning on a daily basis. DIBH in this context increases the similarity of target and body geometry from treatment day to treatment day and thus may facilitate instant replanning using previous knowledge.

It is concluded that DIBH gating is a precise, reliable technique that is applicable to most patients and, with the advent of fast delivery techniques, no longer results in excessive treatment times (Fig. 4). It facilitates the application of complex treatment plans with steep dose gradients to moving targets for both photon therapy and particle therapy by widening the therapeutic window and improving dosimetric accuracy.

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