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Original Article

ESTRO-ACROP guideline: Recommendations on implementation of breath-hold techniques in radiotherapy

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ABSTRACT

The use of breath-hold techniques in radiotherapy, such as deep-inspiration breath hold, is increasing although guidelines for clinical implementation are lacking. In these recommendations, we aim to provide an overview of available technical solutions and guidance for best practice in the implementation phase. We will discuss specific challenges in different tumour sites including factors such as staff training and patient coaching, accuracy, and reproducibility. In addition, we aim to highlight the need for further research in specific patient groups. This report also reviews considerations for equipment, staff training and patient coaching, as well as image guidance for breath-hold treatments. Dedicated sections for specific indications, namely breast cancer, thoracic and abdominal tumours are also included.

Introduction

In radiotherapy (RT), respiratory gating by using a breath-hold (BH) technique has the potential to mitigate interfractional and intrafractional breathing-motion and/or to reduce the dose to organs-at-risk (OARs), depending on the primary disease site. This approach has been applied to different anatomical regions such as the thorax, breast and abdomen.

The most common approach is the deep-inspiration breath-hold (DIBH) technique: this technique requires the patients to inhale to a specified level and hold their breath during image acquisition and treatment delivery. Although less commonly applied than DIBH, expiration BH can be advantageous for upper abdominal tumours.

Available strategies differ significantly with regard to adopted devices, additional equipment required, intrafractional monitoring and patient feedback systems [1]. This consensus guideline aims to provide a broad overview of BH techniques with regard to available solutions and their implementation, utilization, patient compliance, benefits, and challenges, in order to facilitate the clinical implementation (or expansion) of this procedure in daily practice.

BH techniques have been used for at least twenty years in RT. However, the implementation has been slow, and the recent POP-ART survey has revealed large variations in usage amongst RT centres and highlights that BH is still considerably under-used [2]. As a result of this slow adoption, a considerable amount of pragmatic clinical knowledge is restricted to a few centres having treated many patients. In this guideline, we have strived to combine recommendations both from published reports and from common empirical experience ("consensus of experts") reflecting current clinical practice. Though we recognise there is no "one-size fits all" solution, we offer specific examples of the implementation of the selected technological solutions. We also discuss the selection and coaching of patients, as well as specific issues relating to different patient groups (e.g. breast, lung, abdomen) for BH. The nomenclature used in this document is defined in Table 1 and illustrated in Fig. 1.

Equipment

When implementing a BH technique in RT, a surrogate measure for the position of the target is needed. The most commonly used surrogate measures can be roughly divided into surface-based or spirometry-based equipment, often combined with visual feedback systems to the patient. The spectrum ranges from simple in-house

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Table 1
Glossary of types of breath-hold variations and their definition (BH = breath-hold). See also a visual representation in Fig. 1.

Nomenclature	Definition
Interfraction BH variation	Variation in breath-hold between different fractions (i.e. from one day to the next).Possible causes include variation in: - breathing pattern (chest vs abdominal breathing); - internal organ movement - patient position (filling the lungs versus arching the spine). - - drifts of organs due to relaxation/ gravity.
Intrafraction BH variation	Variation in breath-hold within a single fraction (i.e. from beam-on to beam-stop).Possible causes include: - drift due to relaxation or gravity - patient exhaustion - breathing pattern (chest vs abdominal breathing); - internal organ movement - patient position (filling the lungs versus arching the spine). Includes two main components: BH-to-BH variation and intra-BH variation. • Intra-BH variation: Variation within a single breath-hold, e.g. a "deep" inspiration becoming less "deep" within seconds. The breath-hold duration may be too long, or the patient may require direct feedback to maintain the breath-hold. • BH-to-BH variation: Variation from one breath-hold to the next within one treatment fraction. Can be caused by fatigue, shifts in patient position as the treatment fraction is being delivered, or drifts of organs due to relaxation/gravity.

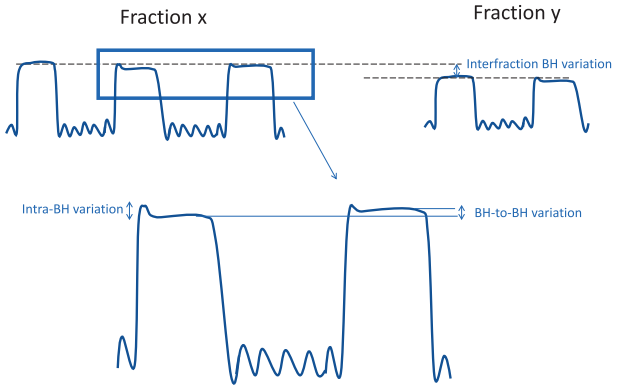

Fig. 1. Visual representation of types of breath-hold variations and their definition (BH = breath-hold). See also the glossary presented in Table 1.

designs to commercially available systems that can interlock with treatment delivery and allow automatic gating.

A detailed description of equipment examples is given in the supplementary section (see supplementary materials S1) and an overview of differences between the various techniques is shown in Table 1. Every system has advantages and disadvantages and is influenced by institution-specific factors, such as compatibility with pre-existing treatment-delivery systems, patient positioning equipment, acquisition costs or experience of neighbouring institutions. It is emphasised that most approaches, no matter how technologically advanced, use surrogates for the breathing/target motion: as a consequence, image guidance where the localization of the target can be directly verified is a necessary companion of those approaches.

Staff training and patient coaching

Staff training is an essential part of achieving the maximum benefit of a BH technique, regardless of the equipment. It is advisable to have 1–2 expert users [3] to develop internal protocols and cascade training, similar to the model used for IGRT implementation [4]. The number of expert users will depend on the size of the department. Well-trained and confident staff can help patients relax and comply [5]. Poor communication, on the other hand, may result in patients not tolerating the breath-hold technique [6,7].

Clear communication between staff and patient is a key component with written instructions and protocols. It may even be beneficial to document specifically which verbal cues to use to ensure consistent instructions are given from each staff member and avoid confusing the patient.

Information presented as flyers, videos or slide-presentations may be useful material that the patient can keep and use to practice BH at home if necessary [8,9]. It has been suggested that an effective coaching process can increase the dosimetric advantage of DIBH [10] and decrease the time required for the CT planning scanning appointment [9]. In addition, the radiation oncologist or other members of the treatment team can inform the patient about the BH procedure prior to the appointment for CT planning. It must be noted that there might be other reasons (non-performance related) why DIBH might not be the best choice for every patient, such as language barriers, psychological distress, or problems understanding and following the coaching instructions. The staff should reassure the patient that free-breathing (FB) is a safe option for treatment as well.

It is advisable to train patients in the BH procedure before computed tomography (CT), to familiarise them with the equipment and to inform them how the staff will communicate during the procedure. Patients can be trained directly before the planning CT, i.e. in the scanning room, or during a separate coaching session. The latter may be preferable for institutions beginning a BH programme and until the staff are familiar with the coaching procedure.

During the coaching, staff will clarify what kind of BH is expected, such as "moderately deep inspiration" vs expiration BH. The crucial element is that the patient feels comfortable with the procedure, in order to minimise variations in BH during imaging and treatment. It may be necessary to define a minimum threshold for the duration of the BH to enable Cone Beam CT (CBCT) acquisition or the delivery of particular beam segments: this is particularly essential if there is no interlock between the BH monitoring system and the linac (i.e. if the radiation therapist (RTT) needs to start and stop the beam manually). Finally, the coaching session can be useful to prevent the patient from performing BH patterns that are unsustainable (e.g. too deep, too long) or to identify abdominal vs chest breathing. For example, the BH is often restricted to 20–30 s, for fear that longer BH may strain the patient and introduce additional uncertainties. This doesn't reflect the maximum BH duration achievable by patients but is meant to be a pragmatic compromise (i.e. "long enough" for imaging and beam delivery) and is achievable by many patients [11–13]. Similarly, keeping BH as natural as possible for the patient ("moderately deep" rather than "as deep as possible") may avoid the need to re-scan during the course of treatment. For example, it

has been reported that when patients try to achieve or maintain a BH which is "too deep", they may arch their back to compensate for an insufficient BH level [14]. "Moderately deep" can be defined as roughly 70 to 85% of the maximum BH of each individual patient [12 15,16]. Note that in the published literature, the terms "deep" and "moderately deep" are often used interchangeably, but rarely reflect true differences in BH level. However, in the absence of quantitative measures, it can be useful to ask the patient to hold their breath without mentioning depth ("imagine you're going under water for 15 sec") to achieve a natural BH.

Most patients are able to hold their breath for 25–30 seconds: reports suggest that > 90% of breast cancer patients can achieve DIBH [17,18], as well as a large proportion of lung cancer patients [19] and liver cancer patients [20]. For liver and pancreatic tumours, a BH of 20 seconds appears to be more stable than longer BH. Lens et al. described that a longer BH of 30 seconds can lead to a less stable tumour position, therefore shorter BHs appear to be a better approach in radiation treatments of abdominal tumours [21]. Although adequate for some treatment sites, exhale BH appears to be more difficult for patients, and up to 39% of patients can be deemed unsuitable to perform an expiration BH for various reasons [22].

Image-guidance for breath-hold treatments

Pre-treatment image guidance

To maximise reproducibility and reduce the risk of introducing a systematic error, all relevant imaging for treatment planning should be performed in BH, and at the same BH level as used throughout the treatment course. Using the same BH equipment during pre-treatment imaging (dedicated CT scanners, positron emission tomography (PET)/CT scanners and magnetic resonance imaging (MRI) where available) and for on-treatment imaging minimizes the risk of systematic variations between planning and treatment. When introducing a BH technique, some institutions have historically acquired a FB CT followed by a BH scan during the same planning session. Although this approach can enable institutions to evaluate the dosimetric advantage of DIBH in their own environment during the initial implementation or "learning curve", this approach is not recommended for routine clinical practice beyond the implementation stage, given the additional radiation exposure. If intravenous contrast is required, it is advisable to use the contrast during the CT scan acquisition that is used for delineating the target volume. For patients requiring PET/CT planning, it is possible to acquire a single PET field of view in BH (e.g. over 6 BHs of 20 seconds each): the PET signal acquisition can be paused manually to allow patients to recover between BHs. In 2015 the first use of a modified Active Breathing Coordinator (ABC) in a standard MRI was described [23]. The device was modified to be MRI safe, and proof of principle of the feasibility of ABC-driven DIBH during MRI was confirmed.

Image guidance during treatment

Planning target volume (PTV) margins should account for: a) frequency of image guidance, b) residual tumour motion due to intra-BH and BH-to-BH intrafraction variation, c) differential motion (e.g., between involved nodes and peripheral primary tumours).

Delivery of hypofractionated treatments acquire the patient to perform multiple BH with an inherent risk of exhaustion. Therefore, flattening filter free (FFF) beams with high output should be preferred to shorten dose delivery time.

Interfraction BH variations may be relatively large [24], and are not always correlated to variations in the external surrogate breathing signal. Hence, regular target and organs at risk (OAR) position verification with x-ray based images is recommended [25].

If the target is well correlated to bony structures (e.g., the breast to the sternum), the position of the tumour and the BH level may be verified using 2D imaging (MV or kV), necessitating only a few seconds of BH per image. However, it must be noted that 2D imaging can underestimate set-up uncertainties since not all axes of deviations can be visualized [26]. A BH CBCT can be acquired over several short consecutive BHs while pausing the image acquisition manually to allow the patients to catch their breath, or in a single BH with a fast CBCT image acquisition. Some modern linacs also allow automatic gated CBCT in BH. In addition to position verification and BH level verification, BH CBCT can improve imaging quality for mobile targets considerably compared to FB CBCTs, and may help reducing interobserver registration uncertainties [1,27,28].

Intrafraction uncertainties such as intra- and BH-to-BH variations are difficult to correct and may need to be included in the treatment margin. Ideally, this would be done on a patient-specific basis: patients with small intrafractional DIBH variations benefit most from this approach, since standard margins would result in larger margins for these patients [29]. Visual coaching can decrease BH-to-BH variability in breast cancer patients. However, for thoracic and abdominal tumours, especially the intra-BH variation can be difficult to assess without extensive fluoroscopic imaging and in some cases implantation of radiopaque markers [30–33]. Repeated DIBH CT during planning can provide an estimate of the BH-to-BH variation to be incorporated into individualized margins [20,34] but the method probably underestimates the full extent of intrafraction motion, particularly in the abdomen (see section 7). Therefore, cautiousness is recommended regarding PTV margins shrinkage for thoracic and abdominal tumours. Continuous MV or kV imaging during DIBH treatment with open fields or with MRI on the recently clinically available MR-linacs may help us better estimate BH-to-BH and intra-BH variations [33,35], while appropriate patient coaching may help minimise those variations.

Breast cancer

The first large-scale application of BH techniques was in patients undergoing RT for breast cancer [36–38]. In this patient group, the purpose of performing DIBH is mainly to reduce the dose to the heart (by increasing the separation from the chest wall) [39], and possibly to the lungs (by increasing the total lung volume) [40], which can reduce the associated risks of heart disease [41,42] and lung cancer [43] respectively.

Patient selection and set-up

Several patient- and treatment-related factors may affect who is referred to or prioritised for DIBH, such as anatomical features or target volumes (e.g. regional nodal irradiation including internal mammary nodes) or laterality (left vs. right side). Patients are usually positioned supine on a flat or wedged positioning device, with one or both arms above the head. Reference skin marks or tattoos can be applied in FB to facilitate initial patient alignment and set-up, without the need of moving the patient whilst in DIBH. The planning CT should be performed in DIBH and additional DIBH skin marks (non-permanent) can be added as needed. An additional FB scan can be acquired, to create a back-up plan and/or assess the effective gain between DIBH and FB plan. However, the benefits of the acquisition of an additional FB CT scan are limited and add an increased imaging dose. The compliance in breast cancer

patients is excellent and the DIBH plan is usually not inferior to the FB plan [49].

Treatment planning and delivery: Techniques and considerations

DIBH is compatible with both 3D-conformal RT (3DCRT) and Intensity Modulated Radiation Therapy (IMRT)/Volumetric Arc Therapy (VMAT) techniques [44,45] and results in considerably lower doses to the heart and other cardiac substructures such as the Left Anterior Descending coronary artery (LAD). All target volumes and OARs should be contoured following guidelines (i.e. ESTRO [46]). The maximum available dose rate should be considered to optimise beam delivery time (e.g. each radiation field within a single BH).

For treatment delivery, image verification must encompass patient position (similar to treatments in FB) and verification of the BH level. As the ribs and sternum expand with the DIBH in relation to the spine, the structures used for co-registration have to be carefully chosen, with likely prioritisation of the upper part of the sternum and the ribs. As with FB treatments, fiducial markers or surgical clips can provide additional information. Cine MV imaging using the treatment beam can also be used to verify BH levels, based on commercial solutions or home-made software allowing automatic analysis [47]; or visual evaluation [37]. SGRT and IGRT are complementary technologies [48]and IGRT, specifically 3D position verification, should be performed to get information on the anatomical structures.

Published reports on uncertainties in DIBH for breast radiotherapy

Reproducibility of the DIBH should be within 2–5 mm, regardless of the used technique [24,49–51]. Systematic changes in BH levels may be detected during the first three treatment fractions, for example using a non-action level approach [52]. Reports of intrafraction and intra-BH reproducibility mention that an uncertainty of circa 2 mm or less is achievable [53,54]. However, there may still remain a relatively large variation in heart position during DIBH of up to 1 cm [55]. Variations in DIBH level may be most important in anterior-posterior (AP) direction [56,57], may occur more frequently between fractions rather than intrafraction [24], and may increase with an increasing number of DIBHs per fraction [56]. Additional verifications of BH level can include: a) the AP distance between the spine and sternum across the isocentre on 2D set-up images, b) EPID movie loops (Figure S2), and c) 2D fluoroscopic images, which are not limited to open tangential beams, but cause additional dose exposure [52]. Optical surface scanners can enable a continuous real-time motion management [58] of the patient surface during the whole fraction [48].

In conclusion, DIBH in breast RT does not necessarily increase treatment precision, as new sources of uncertainties are introduced. Nevertheless, the dosimetric benefits are considerable for the majority of patients, especially patients with left-sided breast cancer. DIBH treatment may require an additional treatment time of 2–5 minutes, depending on the equipment used [59]. In the HeartSpare study, Bartlett et al. [49] found that a voluntary BH technique (“equipment free”, see S1) was associated with shorter CT planning times and shorter treatment set-up times than a spirometry-based approach (ABC, see S1). These results were observed despite the personnel having more experience with the spirometry-based approach, and positioning reproducibility was higher with the voluntary BH approach.

Take Home message:

- Patient coaching is important to ensure compliance.
- Few studies compare several DIBH approaches.
- Voluntary approaches (using little or no equipment) have shown to be suitable for 3D-CRT breast treatments.

Thoracic tumours

The primary purpose of DIBH RT for lung cancer or lymphoma is to minimise dose to the heart and lungs. For lymphoma, this is achieved by increasing the total lung volume, as well as the separation between the heart and upper-mediastinal targets. Reduced dose to the heart can decrease the risk of late radiation-induced heart disease in younger patients with a long life expectancy (e.g., those with mediastinal Hodgkin Lymphoma) [60]. However, it is important to note that recent data suggest that heart dose also affects survival in patients with lung cancer [61,62]. More research is needed to understand which pathophysiological mechanisms are involved and which cardiac substructures should be spared in priority.

In lung cancer, an additional mode of action may be reducing the motion amplitude of very mobile targets (e.g. targets close to the diaphragm). However, since DIBH will introduce uncertainties both interfraction and intrafraction, it is crucial to assess the full range of these uncertainties when considering any reduction of internal target volume (ITV)/ irradiated volume [63].

Patient selection and set-up

Some lung cancer patients can hold their breath long enough (around 20 seconds) to facilitate treatment delivery [6,19,64] but there are reports of insufficient respiratory capacity and poor performance status in this patient population [12]. Dosimetric benefit of DIBH for intrathoracic tumours is harder to predict than for breast cancer patients, and, as a result, guidelines for patient selection are less straight-forward. Clinical studies have shown dosimetric benefits with DIBH for a majority of patients (e.g. with mediastinal lymphoma [60]) but, in selected patients, DIBH can have a detrimental effect. If the distance between multiple targets is increased in DIBH, the resulting dose delivered to the lung may be higher than in FB [65]. Additional advantage of DIBH is improved tumour visibility [28] compared to FB, especially for small mobile tumours that would otherwise hardly be visible on 3D imaging [66].

Due to the large anatomical variation in this patient group (range of tumour size and location), it is more challenging to recommend general selection criteria for DIBH. In particular, it is important to distinguish between “simple targets” (where the tumour volume consists of a single solid mass), and “complex targets” with multiple target volumes (e.g. a mediastinal mass and a peripheral lung or cardiophrenic mass).

With this in mind, patient selection could be based on the following criteria:

a) Patients with highly mobile thoracic tumours [67,68], where DIBH or other motion management approaches (abdominal compression, expiration BH or gating) may offer margin reduction benefits as long as DIBH-specific uncertainties are also accounted for.
b) Patients with mediastinal targets where DIBH may enable dose reduction to the heart and lungs. Note that for large mediastinal targets extending below the heart, the dosimetric benefit of DIBH may be reduced [69].

Other scenarios where DIBH may be considered are dose escalation strategies or difficulty in adhering to lung dose constraints even if the target motion is less than 5 mm (e.g. large tumours with little motion, where DIBH can increase the total lung volume and facilitate sparing of healthy lung tissue) [70,71].

Treatment planning and delivery

Since the dosimetric benefit of DIBH in thoracic tumours is more difficult to predict than in breast cancer, it is harder to make

general recommendations for patient selection. As a result, it is recommended to acquire both a FB (3D or 4D) CT scan and a DIBH CT scan for radiotherapy planning. Note that in some complex targets, DIBH may actually increase dose to the healthy lung [65]. The heart, and possibly cardiac sub-structures, should be contoured according to guidelines to estimate dosimetric benefit [72,73].

Online CBCT-based IGRT is necessary when using BH for thoracic tumours, since all surrogates, whether surface-based or volume-based, can be poorly correlated with the actual position of the tumour. Post-treatment or in-treatment imaging reflecting the position of the tumour is particularly desirable in this anatomic district in order to estimate intrafraction motion.

Published reports on uncertainties in DIBH for thoracic tumours

DIBH in patients with complex tumours (i.e. multiple target volumes) is particularly challenging: lack of interfraction reproducibility in BH level may affect the distance between target volumes and is difficult to correct in the absence of online adaptive solutions. BH for small lung tumours treated with stereotactic body RT (SBRT) is a simpler case with the main purpose of motion management and/or better target visualisation.

In a locally advanced NSCLC cohort, interfraction-BH tumour position variations > 1 cm in all directions were detected during the 6-week course of RT using a spirometry-based technique, despite little variation in lung volume and little BH-to-BH variation on CT in the planning session [74]: the authors conclude that breath-hold patterns can change during treatment, and highlight the role of 3D image guidance.

It is important to remember that surrogate signals can be poorly correlated with the true position of the internal targets. In this scenario, during-treatment and/or post-treatment imaging may be necessary to estimate intrafraction motion. Few studies have investigated BH-to-BH variations, and even fewer investigate intra-BH variations. This may be due to the complexity of acquiring reliable (e.g. 3D) images during treatment, concerns about patient fatigue (since post-treatment imaging requires additional BHs) or additional dose (especially in younger patient groups, such as Hodgkin Lymphoma (HL)).

A study analysed fluoroscopic movies acquired during DIBH and FB of nine patients with locally advanced NSCLC reported average (maximum) intra-BH variations of 1.4 (3.4), 1.2 (4.8), and 2.1 (5.1) mm in the AP, LR, and CC directions and a maximum BH-to-BH variation of 4.5 mm in the CC direction for visually guided DIBH [32]. For lung SBRT, two studies, both using surface guidance with visual feedback in patients with highly mobile tumours (>1 cm), have contradictory results. Peng et al. found that margin reduction was possible due to GTV position reproducibility within 1.5 mm (intra-BH and BH-to-BH) for voluntary inspiration BH with CBCT-guidance based on multiple planning BH-CTs of 13 patients [75]. In contrast, Ottosson et al. found that a margin expansion of 3.5 mm in the CC-direction was needed to encompass an increased intrafraction variation based on analysis of pre- and mid-fraction CBCTs of 42 patients [63].

Several studies report BH-to-BH variation at the time of CT planning, by acquiring multiple CTs in subsequent BHs, as a measure of overall BH-to-BH variation [11,74]. However, in a cohort of patients with complex targets from HL, sarcoma and lung cancer, the initial measured inter-DIBH variation underestimates the variation measured during the treatment course [11,75,76].

It should be noted that there is little information on intrafraction variation for thoracic tumours treated in FB, and it is hard to distinguish between variations due to (DI)BH and variations caused by other phenomena (e.g. changes in breathing patterns, patient position, anatomical changes) also occurring in FB treatments.

Take home messages:

- DIBH has shown promising results in thoracic tumours but further research is needed to clarify which patients get the most benefit.
- Margin reduction should be approached with caution, and with consideration of all uncertainties introduced by the DIBH procedure itself.
- However, DIBH may offer a dosimetric advantage in some patients even without margin reduction, due to the modification of the internal anatomy (lung inflation and increased separation between the heart and the target volume(s)) and reduced displacement of the tumour.
- Pragmatic intrafraction monitoring strategies where the target position BH-to-BH and intra-BH can be verified during the treatment (preferably without interrupting it) are sorely needed. In the meantime, those variations may be estimated using pre- and post-treatment images.

Abdominal tumours

The abdomen is arguably one of the most challenging anatomical site for motion management. Abdominal organs are affected by respiration, and motion of up to 40 mm has been reported, mostly in the superior-inferior direction [77,78]. In addition, interfraction motion and deformation are also present as a result of peristalsis and digestive processes. By reducing respiratory motion, BH has the potential to reduce the irradiated volume and improve the quality of 3D images.

For tumours of the liver and pancreas, hypofractionated regimens [79–81] are being investigated to improve local control [80] and motion management, such as BH, may help deliver these high doses while sparing the critical structures (bowel, stomach and duodenum). It is important to note, however, that anatomical variations in the abdomen are both larger and less predictable than in the thorax, and motion related to digestive processes and abdominal gas cannot be addressed by BH alone. The following sections will focus on tumours of the liver and pancreas, as the role of BH in adrenal gland and kidney SBRT is more uncertain and further research is needed [27].

Patient selection and set-up

For abdominal sites, BH is mostly used as motion management strategy. As a result, a deep inspiration is not the primary goal and some authors suggest that an expiration BH is more reproducible [7,34,82]. A possible disadvantage is the lower compliance in expiration BH: in hypo-fractionated liver treatment, a range of compliance rates have been reported (61% in expiration BH [22] compared to 95% [20] in inspiration BH), though it must be noted that comparing compliance between studies is challenging. In healthy volunteers asked to hold their breath for up to 60 s, it has been suggested that intra-BH motion of the pancreas was noticeably reduced in expiration BH [83]. Few recommendations have been published about patient selection. Huang at al. [84]suggest that patients with a larger body habitus have a higher inflation of lungs in DIBH (measured by spirometry) and higher positional errors in the SI directions. Abdominal SBRT is performed in supine position, and reference skin marks or tattoos can be applied in FB.

Patient selection is similar to that for thoracic tumours and mainly includes the following criteria: Patients with very mobile tumours (>5mm), in whom BH or other motion management approaches (abdominal compression, expiration BH or gating) may offer advantages in reducing irradiated volume compared to FB approaches.

Treatment planning and delivery

As mentioned above, anatomical variations in the abdomen are a combination of several physiological processes, including respiration and digestion. To address this complex situation, multiple BH CT scans can be made for target delineation, and the information used to calculate patient-specific margins [20,85]. Though these additional planning scans may provide information about residual intrafraction motion (BH-to-BH and intra-BH variation), the full extent of on-treatment motion may not be reflected [86]. BH fluoroscopy performed as part of the planning session can also help estimate intrafraction motion [82]. The use of population-based CTV-PTV margins of 5 mm was suggested [87] but an individualised margin approach may be more appropriate if all involved uncertainties can be quantified [20,27,85].

Online position verification is mandatory and registration using bony anatomy is not recommended due to the substantial internal anatomical changes and deformations in this region [88,89]. Surrogate structures can be delineated during treatment planning in order to help with image guidance, e.g., the diaphragm-liver interface, the liver volume, and natural, iatrogenic or implanted fiducials [79,88] for liver tumours. If fiducials are not present, the diaphragm dome is often the surrogate structure of choice for liver tumours, but is not considered an appropriate surrogate for pancreatic tumours [21].

During treatment delivery, 2D imaging can be complemented with fluoroscopy to assess intra-BH variations. For SBRT treatments a BH CBCT is recommended to assess liver deformation and monitor the position of critical OARs where sparing needs to be prioritised even at the expense of PTV coverage (e.g. duodenum, stomach and colon) [90,91].

Overlaying isodoses critical for OARs onto the CBCT [82] may be helpful. All actions prior to treatment should be as fast as possible to avoid patient motion (e.g a fast CBCT protocol [1]). If considerable changes in BH trace or a drift (larger than the expected BH-to-BH variation) are observed during treatment, imaging should be repeated, and repositioning should be considered. If there is a systematic variation for two consecutive fractions in a SBRT treatment, replanning should be considered depending on the clinical effects of this systematic variation [92], e.g. if it results in an acceptable dose to critical OARs. This needs to be decided on a patient-by-patient basis.

Published reports on uncertainties in BH for abdominal radiotherapy

Compared to other tumour sites, there is a large body of research on intrafractional uncertainties in abdominal tumours. Reported intrafractional uncertainties have included BH-to-BH displacements of the tumour of > 3 mm [29], intra-BH displacements of up to 1 cm [86]and "slow drifts" during BH [83]. Importantly, these variations are not always detected by pre- and post-treatment CBCT evaluation, nor by repeated BH CTs. In contrast, in a study where patients were pre-selected before liver SBRT, excellent intra-BH stability (<2mm in SI direction) was observed during expiration BH throughout the treatment course [7]. In this study, patients were screened before treatment using repeat fluoroscopies, and patients with a residual intra-BH motion of > 5 mm were deemed unsuitable for treatment in BH [7]. Ultrasound imaging [31] may offer an alternative and non-ionising method of monitoring intra-BH stability.

Motion management in the treatment of abdominal tumours, especially with SBRT, is an active field of research. Recent reports of MR-guided RT are offering a unique insight into geometric uncertainties in liver and pancreatic treatments. The online adaptive pathways available on MR-linacs can address interfraction uncertainties, while the on-board continuous imaging can assess residual BH-to-BH and intra-BH motion [93–95].

Take home messages:

- Anatomical variations in the abdomen occur frequently, and are arguably the most complex to characterise compared to other treatment sites.
- Repeat BH CTs at the time of planning do not capture the full extent of intra-BH and BH-to-BH variations but may give information about the BH-to-BH variation for the individual patient (to be included in the CTV-PTV margin [20].
- Additional imaging (e.g. repeat fluoroscopy [7]) or screening may be required to identify patients with stable anatomy under BH.

Discussion

This consensus guideline gives a broad overview of the available technical solutions (see suppl. Section) and reports of their clinical implementation to date.

In view of the available evidence, and the limited number of studies evaluating the impact of DIBH implementation and workflow, we recommend that the "ideal" implementation would include:

1) A lead professional or multi-disciplinary team to oversee the process and be responsible for the implementation process, specifically staff training and verification of the BH.
2) Adequate and appropriate time for staff training and patient coaching. The procedure can be streamlined later, but the implementation requires more time.
3) The chosen system to be available on all scanners used for RT planning (CT, PET-CT, MRI) to ensure consistency of all images used for treatment planning, as well as (at least) two treatment machines (linacs, ideally mirrored).
4) Daily imaging for the verification of the position of the target in BH as well as verification of the BH level (if necessary to ensure consistency in OAR sparing).
5) Target-related intra-fraction (intra-BH and BH-to-BH) monitoring (rarely available at the moment)
6) Ability to re-image and re-plan the patient if any change of breathing pattern is suspected
7) Time and resources for each institution to carry its own quality assurance programme to assess interfraction and (ideally) intrafraction uncertainties [96].

The last point should not be underestimated: BH is a valuable tool, but its success may vary according to implementation procedures and patient population. As a result, each system might lead to different results in different institutions. Since "ideal" situations are rarely realistic in the real world, we would encourage users to consider aligning the reproducibility and accuracy of the BH procedure with the complexity of their planning, delivery and image guidance approach. The reproducibility and accuracy required from a BH strategy will be different for a tangential breast treatment with open-beams (a treatment strategy more "forgiving" of uncertainties) than for a VMAT SBRT liver treatment.

In this guideline we focused on the main applications of BH and did not describe the use of a BH technique in children, as sparse data are published concerning this population. Two studies reported that the dose to the organs at risk could be diminished using a BH technique [49,53]. The "TEDDI" trial (NCT03315546) will investigate the dosimetric benefits as well as reproducibility and compliance/psychological impact of using breath-hold in paediatric patients [97].

Another limitation of this guideline is that we only considered widely available approaches. Recent reports have investigated the feasibility of longer breath-holds with ventilator-assisted solution [98]. Though the early results are promising, more results are needed about the tolerability and pragmatic implementation of these approaches. Newer technology, such as MR-guided linacs, may address some of the limitations listed in the guideline: MRI-guided BH or gating approaches with a direct visualisation of soft tissue are feasible and overcome the necessity of invasive fiducials implantation [99,100]. Finally, we tried to highlight where more research was needed (e.g. intrafraction monitoring) and where caution should be advised for a safe implementation of BH.

In conclusion a BH technique can contribute to a more targeted treatment delivery and/or allow better sparing of surrounding organs at risk. Every institution should find the most effective and appropriate BH strategy according to their available equipment. Readers are encouraged to be aware of the uncertainties and include them in their procedures. They should make the BH technique their own, assess its uncertainties in their practice, and re-evaluate the BH technique regularly and optimize it, if necessary.

Conflicts of Interest

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Declaration of Competing Interest

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

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Appendix A. Supplementary material

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