Physics Contribution

Active Breathing Control in Combination With Ultrasound Imaging: A Feasibility Study of Image Guidance in Stereotactic Body Radiation Therapy of Liver Lesions

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Summary

For image guidance, 3-dimensional ultrasound imaging in the stereotactic body radiation therapy of liver lesions is feasible. The use of surrogates in the close vicinity of lesions may be needed. The accuracy of 3-dimensional ultrasound image guidance is improved by using active breathing control; in free breathing the accuracy is 4 mm, and when it is combined with active breathing control the accuracy is 2 mm.

Purpose: Accurate tumor positioning in stereotactic body radiation therapy (SBRT) of liver lesions is often hampered by motion and setup errors. We combined 3-dimensional ultrasound imaging (3DUS) and active breathing control (ABC) as an image guidance tool.

Methods and Materials: We tested 3DUS image guidance in the SBRT treatment of liver lesions for 11 patients with 88 treatment fractions. In 5 patients, 3DUS imaging was combined with ABC. The uncertainties of US scanning and US image segmentation in liver lesions were determined with and without ABC.

Results: In free breathing, the intraobserver variations were 1.4 mm in left-right (L-R), 1.6 mm in superior-inferior (S-I), and 1.3 mm anterior-posterior (A-P), and the interobserver variations were 1.6 mm (L-R), 2.8 mm (S-I), and 1.2 mm (A-P). The combined uncertainty of US scanning and matching (inter- and intraobserver) was 4 mm (1 SD). The combined uncertainty when ABC was used was reduced by 1.7 mm in the S-I direction. For the L-R and A-P directions, no significant difference was observed.

Conclusion: 3DUS imaging for IGRT of liver lesions is feasible, although using anatomic surrogates in the close vicinity of the lesion may be needed. ABC-based breath-hold in midventilation during 3DUS imaging can reduce the uncertainty of US-based 3D table shift correction.

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Introduction

Stereotactic body radiation therapy (SBRT) of liver lesions requires tight margins for safe treatment with high radiation doses while limiting the normal liver dose. Accurate daily localization of the treatment target is highly important. Organ motion and patient setup are potential error sources. Currently, image guided radiation therapy (IGRT) is mostly based on x-ray imaging (eg, electronic portal imaging [EPI] and cone beam [CB] computed tomography [CT]). For liver lesions, however, these techniques provide inadequate imaging contrast. EPI images of bony anatomy cannot deal with the liver motion related to breathing and stomach and bowel filling. Case et al (1) assessed the interfraction and intrafracton variability of the liver position, treated with kV CBCT-guided SBRT. They demonstrated that interfractional liver position relative to the vertebral bodies is a source of geometric uncertainty. To alleviate the poor x-ray imaging contrast in soft tissue, fiducial markers have been proposed as a surrogate. Marker-guided setup accuracy decreases with increasing distance between the fiducial markers and the tumor (2). Furthermore, implanting fiducial markers is invasive and can result in tumor spread, liver inflammation, and embolization (3). Although kV CBCT may allow visualization of liver boundaries, the lesion or nearby blood vessels are not clearly visible. Furthermore, CBCT image quality is limited because of breathing artifacts leading to motion aliasing. The time to acquire a CBCT image makes breathing control problematic. The recently reported respiratory correlated CBCT (4D-CBCT) (1, 4) may solve the motion-related artifacts but will not solve the poor soft-tissue contrast.

A clear need is identified for an alternative imaging technique to guide radiation therapy. A reduction of geometric uncertainties may lead to reduced normal tissue irradiation, safer dose escalation, and improved local control for patients with hepatic malignancies. Ultrasound (US) imaging may offer a solution. In radiation therapy this is a fairly new technique, although it has been used extensively for many years as 2-dimensional (2D) US imaging in diagnostic radiology because of the high soft tissue contrast of US imaging. The feasibility of US imaging was demonstrated (5) for liver guidance, using the BAT device (Nomos, Cranberry Township, PA). This allows for superposition of anatomic contours derived from treatment planning CT onto real-time US images, for liver image guidance. The use of 2 different image modalities in an intermodality system, however, introduces additional uncertainty.

We investigated the use of an intramodality 3-dimensional (3D) US system as a novel IGRT application in liver treatment. The intramodality approach entails comparing US images acquired in the treatment room with a reference US image acquired at the time of CT simulation. The goal is to establish the accuracy of 3DUS imaging with and without active breathing control (ABC) for IGRT of liver lesions.

Methods and Materials

Eleven patients (Table 1) were included in this study (1 patient was not included in the study because of bad sonographic visibility). All patients gave written informed consent before entering this study, which was approved by the internal review board.

3DUS system

The Clarity intramodality US imaging system (Elekta, Stockholm, Sweden) was used for this study in a total of 88 treatment fractions. The system comprises 2 interlinked US stations, based in the CT room (US-Sim) and in the treatment room (US-Guide). Each US station is equipped with a 2DUS probe (3.3 MHz) designed for abdominal scanning and a ceiling-mounted infrared stereovision camera. Four reflective markers are attached to the probe and are tracked in real time by the infrared camera to determine the position and orientation of each ultrasound frame. The 2DUS frames are then reconstructed in space to form a 3DUS voxel dataset. These 3DUS images are calibrated to the room coordinate system of the corresponding CT and treatment room to allow a direct comparison of the reference 3DUS images at simulation with those acquired in the treatment room (referred to as image segmentation). From this, the difference in daily position of the lesion is derived, resulting in an absolute shift to reposition the patient for treatment.

Our first experiences in liver scanning demonstrated that, with the current transabdominal probe design, it is difficult to maintain a direct line of visibility between the reflective markers and the optical tracking system during scanning. This is due to the position of the markers on the probe, the wide range of angles of the probe during scanning, and the range of positions of the probe on the skin under various orientations. To obtain optimal scanning and probe tracking conditions for IGRT in liver lesions, we redesigned, in collaboration with the manufacturer, the reflective marker array fitted onto the curved abdominal probe (Fig. 1a). To ensure the accuracy of the prototype probe in relation to the room coordinates, a daily calibration check was performed before each treatment session. The uncertainty for each US station was within 1 mm, resulting in a combined uncertainty of 2 mm for the whole quality assurance procedure.

ABC system

For breathing control we used the Spiro SDX system (DynR, France), designed for radiation therapy. The system relies on maintaining a certain breath-hold (BH) volume to fix the position of the lesion absolutely in space. The spirometer is connected to the patient by use of a mouthpiece with a nose clip to prevent nasal air leakage (Fig. 1b). The spirometry sensor measures the patient’s breath flow (L/sec). A predefined BH level can be set, and video goggles guide the patient to this predefined level. We used 50% of the tidal volume for BH (midventilation, 50% expiration), referring to the breathing phase used for treatment planning (50% expiration based on respiratory-correlated CT imaging [RCCt]).

We verified that both spirometers used (in CT and treatment rooms) did not deviate by more than 0.01 L from a precisely known volume of 3 L, well within the manufacturer’s specified 2% uncertainty.

US procedure

We combined ABC with breathing feedback to the patient, in combination with 3DUS imaging. Before the first session, the patient was trained to become comfortable with the spirometer and video goggles and to determine the individual tidal volume
and midventilation BH level. The midventilation level, including a small tolerance ($\pm 0.05$ L) was displayed as a bar on the video goggles, guiding patients to the correct BH position (Fig. 1c). The patient was then requested to repeat a BH at the same pulmonary volume level during CT and radiation therapy sessions.

The standard procedure for CT simulation was followed for treatment planning. Patients were positioned supine with the arms above the head. A 4D helical RCCT scan was made with the patient in the treatment position (SOMATOM Sensation Open, Syngo CT 2006A, Siemens, Germany, 3 mm slice thickness). Small markers (BBs) were placed on the laser crossings on the patient’s skin to indicate the isocenter of the CT. CT contrast medium was injected by an intravenous line directly before scanning. During CT scanning, the patient’s respiration signal was recorded by use of a thorax band with a pressure sensor (Anzai, Germany) to allow respiration phase sorting of the images. The 50% expiration phase was used for treatment planning. Directly after the RCCT scan, a reference transabdominal US scan in midventilation BH was made. For scanning, the probe was placed between 2 ribs or directly under the lowest rib, depending on the position of the liver lesion. The probe was swept over the whole area of interest (lesion and surrounding structures), acquiring up to 250 image frames. This 2D image dataset was reconstructed into an axial 3D voxel dataset. After scanning, the location of the probe was marked on the patient’s skin to enable capturing approximately the same US volume in subsequent sessions.

The US image was automatically registered to the CT image, inasmuch as the 3D voxel dataset is calibrated to the room coordinate system of the CT scanner. The CT/US registration was verified by a trained radiation technologist by comparing the position of the lesion(s), liver veins and the liver surface on the CT and US images. CT contours were used as an additional tool to evaluate the fusion. In case of a mismatch between the 2 scans (caused, for example, by patient motion between acquisitions), the US scan was manually shifted to the coordinates of the CT scan to obtain an optimal overall match. Next, the reference positioning volume (RPV), the reference structure for imaging and segmentation in the treatment room, was contoured on the US scan. Additional structures of interest (surrogates) were also contoured, such as the hepatic and internal portal veins, the vena cava inferior, and the surfaces of the liver, kidney, and gall bladder, depending on their visibility. The RPV and surrogates used in our patient group are described in Table 1. We were not always able to use the automatic contouring tools available in the Clarity software because of the lack of specific tools for liver (the automatic contouring software is currently optimized for imaging of the prostate, breast, bladder, gynecologic organs). Manual contouring was performed when automatic contouring was not possible. To complete the preparation process, the isocenter and beams were imported from the treatment planning system into Clarity. A physician approved the RPV for image guidance.

For treatment, our standard online EPI correction procedure was followed. Directly after the treatment, additional EPIs were performed, and the residual shift as a result of patient movement during treatment was determined. This was followed by US liver scan acquisition, using the same probe position and scanning technique as was used during treatment preparation. Four sequential US scans were acquired during each treatment session: 2 US scans in free breathing (FB) and 2 scans in BH. US scans with and without ABC were performed to investigate the accuracy of 3DUS IGRT of liver lesions in FB and BH, respectively, to establish the optimal IGRT workflow. Repeated scanning was performed to investigate the total uncertainty as a result of repeated scanning in combination with image segmentation (referred to as repeated scan and match uncertainty). To minimize the time between the 4 US scans, image segmentation was performed retrospectively on the workstation. The review software, designed as a tool to evaluate daily imaging and US segmentation, was also used for training purposes. It is possible to simulate the whole image segmentation procedure in a manner similar to the procedure used on the US guide. The advantage of using this tool
is that image segmentation can be performed several times by different observers. Each observer is blinded to the results of the previous observer. These shifts were documented for future analysis. We were not able to use the automatic Adapt function, which adjusts the reference contour to the grey-level boundaries of the current contour because it was not designed for liver grey-scale values and is thus not included for liver lesion segmentation. Furthermore, no corrective rotations were calculated by the software for this analysis.

Accuracy of 3DUS image guidance in liver lesions

The accuracy of 3DUS image guidance in liver lesions was determined for both the FB and BH scans and was based on the mean directional difference within or between observers. The directional difference was defined between the RPV and the actual target position and was determined by manually aligning the RPV to the underlying anatomy of the actual US image. The resulting 3D table shift was independently assessed by 3 observers. In case of (image) deformation, it was impossible to correctly align both RPV and surrogates accurately to the predefined structures. In these cases, predefined surrogates at larger distances from the lesion were given less weight in determining the correct alignment compared with the RPV and surrogates close to the lesion.

The interobserver variation was defined as the mean standard deviation (SD) of the directional difference between 3 observers. It was determined for BH and FB. The intra observer variation was calculated as the mean SD of the mean directional difference within observers and was determined by selecting randomly for each patient 4 US scans (2 BH and 2 FB scans). The directional shift was determined 5 times in a random order by 3 observers. The variation was defined as the mean SD of the directional shift of the 5 repeated segmentations, averaged over the 3 observers.

The repeated scan variation combined the uncertainty resulting from both repeated scanning and repeated image segmentation. This was determined for BH and FB and was defined as the mean SD of the directional difference between 2 sequential US scans acquired within a treatment fraction by the same scanner and

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Target</th>
<th>Dose (Gy)</th>
<th>US fractions (out of)</th>
<th>No. of lesions</th>
<th>Lesion visible on US</th>
<th>RPV</th>
<th>Additional structures</th>
</tr>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>61</td>
<td>M</td>
<td>Meta (colon)</td>
<td>60</td>
<td>8 (8)</td>
<td>1</td>
<td>Y</td>
<td>Lesion</td>
<td>Gall bladder surface, kidney surface</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>F</td>
<td>Meta (rectum)</td>
<td>50</td>
<td>10 (10)</td>
<td>1</td>
<td>Y</td>
<td>Lesion</td>
<td>Liver surface, vena cava inferior</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>M</td>
<td>Meta (rectum)</td>
<td>60</td>
<td>10 (10)</td>
<td>1</td>
<td>Y</td>
<td>Lesion</td>
<td>Internal portal vein, vena cava</td>
</tr>
<tr>
<td>4</td>
<td>77</td>
<td>F</td>
<td>Meta (Colon)</td>
<td>60</td>
<td>3 (3)</td>
<td>1</td>
<td>N</td>
<td>Hilum (liver vein bifurcation)</td>
<td>Liver surface, vena cava inferior, gall bladder surface, aorta</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>M</td>
<td>Meta (colon)</td>
<td>60</td>
<td>3 (3)</td>
<td>1</td>
<td>Y</td>
<td>Lesion</td>
<td>Internal portal vein, liver surface, resection volume</td>
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<td>75</td>
<td>M</td>
<td>Primary T2N0M0</td>
<td>60</td>
<td>8 (8)</td>
<td>1</td>
<td>Y</td>
<td>Hilum (liver vein bifurcation)</td>
<td>-</td>
</tr>
</tbody>
</table>

| With spirometer |
| 1       | 71  | M   | Primary T2N0M0 | 50        | 10 (10)               | 1            | N                   | Liver vein | Liver (part), fat zone |
| 2       | 67  | M   | Primary T3N0M0 | 58        | 16 (29)               | 2            | Y                   | Liver vein | Gall bladder surface, kidney surface, liver inhomogeneity, liver (part), vena cava inferior |
| 3       | 62  | F   | Meta (breast)  | 50        | 8 (10)                | 1            | Y                   | Hilum (Liver vein bifurcation) | Kidney, liver (part), vena cava inferior |
| 4       | 53  | M   | Meta (rectum)  | 50        | 5(10)                 | 1            | Y                   | Lesion | Internal portal vein, aorta, liver inhomogeneity, stent |
| 5       | 69  | M   | Meta (stomach) | 60        | 7 (8)                 | 1            | Y                   | Lesion | Liver surface, kidney surface |

Abbreviations: RPV = reference positioning volume; US = ultrasound.
segmented by 3 observers. The results were averaged over all treatment fractions and over the 3 observers. In all, 184 US scans were used (5 patients, 46 treatment fractions).

**Results**

In 6 of 11 patients, a manual fusion was deemed necessary because of an offset between the CT and US structures. The median offset was 6.4 mm. Eleven patients with 88 treatment fractions were included in the study. In 6 of them, the lesion was used as a RPV. In the other 5 patients, the lesion could not be used for image segmentation because it was not completely displayed on the US image, owing to its size or shadowing of the ribs, or the structure itself did not have sufficient contrast for accurate delineation. In 6 of the 11 patients, for a total of 42 treatment fractions, we determined the accuracy of 3DUS for image segmentation without the use of ABC. In 5 patients, for a total of 46 treatment fractions, we determined the accuracy of 3DUS with ABC.

The mean tidal volume of the 5 patients was 0.32 ± 0.19 L. The average tolerance around the midventilation level was 0.05 ± 0.02 L. All patients were able to hold their breath for at least 10 to 15 seconds, which was sufficient for US scanning. An overview of the patient population is given in Table 1.

**Accuracy of 3DUS image guidance in liver lesions**

The mean intraobserver variation of the 3 observers is illustrated in Figure 2a. The FB intraobserver variations were 1.4 mm in L-R (0.7-1.7 mm), 1.6 mm in S-I (1.0-2.2 mm), and 1.3 mm in A-P (0.9-1.6 mm) directions. The intraobserver variations for BH were 1.2 mm in L-R (0.6-1.8 mm), 1.4 mm in S-I (0.8-1.8 mm), and 1.3 mm in A-P (0.8-1.5 mm) directions. No significant difference in intraobserver variation was observed between FB and BH.

The interobserver variation is illustrated in Figure 2b. For FB, the variations were 1.6 mm in L-R (0.3-2.7 mm), 2.8 mm in S-I (0.8-3.8 mm), and 1.2 mm in A-P (0.6-2.1 mm) directions. For BH, the variations were 0.7 mm in L-R (0.1-1.6 mm), 1.6 mm in S-I (0.6-2.5 mm), and 0.8 mm in A-P (0.2-1.9 mm) directions. When the FB and BH results were compared, the uncertainty reduced by 1.2 mm in the S-I direction using BH scans. In the A-P direction, no significant difference was observed, and in the L-R direction, a reduction of 0.9 mm was found.

The combined uncertainty of repeated scan uncertainty and inter- and intraobserver variation is illustrated in Figure 2c. For FB, the variations were 1.3 mm in L-R (0.5-4.1 mm), 3.7 mm in S-I (1.5-7.1 mm), and 1.8 mm in A-P (1.0-2.9 mm) directions. For BH, the uncertainties were 1.1 mm in L-R (0.3-2.8 mm), 2.0 mm in S-I (1.2-2.9 mm), and 1.4 mm in A-P (0.6-1.9 mm) directions. When FB and BH were compared, the mean uncertainty reduced by 1.7 mm in the S-I direction. For the L-R and A-P directions, no difference was observed.

**Discussion**

This study demonstrates that 3DUS imaging for image guidance in SBRT of liver lesions is feasible. The importance of US IGRT (BAT device) for upper abdominal lesions has previously been shown. Boda-Heggeman et al (5) demonstrated, using US image guidance after EPI image segmentation, a significant difference between the intended and actual positions of the liver lesion. Fuss et al (6) validated their residual shifts measured with a BAT system in 15 patients with abdominal malignancies, by repeated CT scanning. The CT analysis demonstrated that 14 of the suggested BAT shifts reduced the initial setup error by 15-95% compared with room laser alignment.

The accuracy of 3DUS imaging for image guidance in SBRT of liver lesions is often hampered by breathing motion. ABC-based US imaging leads to reduced blurring and reduced artifacts in the 3D generated US data. As a result, reduced intra- and interobserver variability in 3DUS-based IGRT was observed. Using BH during imaging reduced especially the uncertainty in the S-I direction. The effect of breathing on image quality depends on the patient’s breathing pattern (frequency and amplitude). In addition, breathing causes the liver to deform (7), and this changes the relationship between the lesion and surrogates in the liver (Fig. 3). Using an absolute BH volume during the sequential sessions optimizes image quality and results in a similar position of the lesion during image guidance compared with the treatment planning situation.

The midventilation level was 0.32 ± 0.07 L, meaning that the average tolerance window for BH was ~45% of the total tidal volume. Our patients (mean age, 71 years) were not able to hold...
their breath within the bar when its size was reduced. This may influence the repeated scan and match uncertainty. For 2 sequential US scans, the patients had 2 sequential BHs. The effect of the breathing uncertainty is expected to be small.

Our US scanning technique of superficial lesions between the ribs resulted in a small field of view. For deeper seated lesions, we preferably scanned abdominally under the lowest rib. Using additional guidance structures in the vicinity of the liver lesion was indispensable for accurate IGRT in liver lesions. In 2 of 11 patients, the lesion was not visible on the US image. In 3 patients, the lesion was visible; however, it was too large to fit within the US field of view because of its location directly under the ribs, or it was not sufficiently echogenic for accurate image segmentation. In these cases, liver veins close to the lesion, preferably with a clearly visible bifurcation (eg, hilum), were used as primary reference structure. This approach has been previously described (6). In case of deformations, surrogates farther away from the lesion were given less weight than were surrogates close to the lesion when alignments were performed. Structures and regions with motion artifacts were excluded from consideration. As with the currently available Clarity US prostate solution, proper training will avoid the need for a diagnostic radiologist to be present for liver scanning.

Clarity uses an intramodality workflow comparing US reference with current US images. Uncertainties as a result of speed of sound aberrations (8, 9) are thus limited. One should, however, be aware during US and CT fusion that uncertainties as a result of speed of sound errors play a role for deep-seated structures and that the fusion at this depth will have reduced accuracy. In our patient group, the difference between US and CT for deep-seated structures was on average 3.5 mm. When manual CT US fusion has to be performed, one should be aware of this effect. Manual fusion should be based on superficial structures, accepting differences at depth.

Replacing image guidance based on bony landmarks by direct visualization of liver lesions may allow reducing setup margins and consequently reducing the dose to healthy tissues. This needs to be evaluated in dosimetric evolution studies of 3DUS IGRT, possibly in comparisons with other marker-based or nonmarker-based 3D guidance systems.

This, however, will be limited by a lack of breathing control during treatment. The long-term aim of this work is to implement breath-holding control during treatment (gated irradiation) and to reduce treatment margins as a result of eliminating the tumor motion effect on the PTV margins. This may then enable dose escalation and hypofractionation studies.

**Conclusion**

3DUS imaging for image guidance in SBRT of liver lesions is feasible, although surrogates in the close vicinity of the lesion may need to be used. ABC-based breath-hold in midventilation during 3DUS imaging leads to reduced intra- and inter-observer variability in 3DUS-based 3D table shift correction.

**References**


