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Imaging and IGRT in Liver Cancer

Kristy K. Brock, DABR, PhD [Associate professor]
Radiation Medicine Program, Princess Margaret Hospital, University Health Network, Department of Radiation Oncology, University of Toronto

Abstract

Imaging for radiation therapy treatment planning and delivery is a critical component of the radiation planning process for liver cancer. Due to the lack of inherent contrast between liver tumors and the surrounding liver, intravenous contrast is required for accurate target delineation on the planning CT. The appropriate phase of contrast is tumor specific, with arterial phase imaging usually used to define hepatocellular carcinoma, and venous phase imaging for vascular thrombosis related to hepatocellular carcinoma and most types of liver metastases. Breathing motion and changes in the liver position day-to-day may be substantial and need to be considered at the time of radiation planning and treatment. Many types of integrated imaging-radiation treatment systems and image guidance strategies are available to produce volumetric and/or planar imaging at the time of treatment delivery to reduce the negative impact of geometric changes that may occur. Image guided radiation therapy (IGRT) can improve the precision of radiation therapy, so that the prescribed doses are more likely to represent those actually delivered.

Introduction

Liver cancer, both primary and metastatic, presents challenges for imaging at simulation and at treatment delivery due to the lack of inherent contrast between the tumor and the normal liver and motion that occurs primarily as a result of respiration. The sensitivity of the normal liver to radiation therapy as well as the presence of many critical normal tissues that surround the liver demand that accurate delineation of the tumor and accurate and precise image guidance be used to ensure that liver tumors are targeted appropriately and that normal tissue can be spared from high doses of radiation.

Advances in imaging at the time of treatment planning, including precisely timed IV contrast and multi-modality imaging, have enabled improved identification of the primary liver cancer and liver metastases gross tumor boundaries. Technological advances associated with treatment delivery, including abdominal compression, breath hold liver immobilization, tumor tracking and[JT1][JT2] respiratory gating, have facilitated the use of reduced planning target volume (PTV) margins to account for breathing uncertainties. Integration of imaging in the treatment room has allowed visualization of sufficient anatomy immediately prior to or during radiation delivery, to ensure that the planned position of the liver is reproduced as closely as possible during radiation delivery. Together, these advances in imaging have enabled safe dose escalation, hypofractionation, and stereotactic body radiotherapy (SBRT) to be safely administered to primary and metastatic tumors of the liver.

Imaging for Treatment Planning

Imaging for radiation treatment planning requires that 1) diagnostic quality CT imaging is acquired at breath hold, to remove any artifacts due to respiration to facilitate target and normal tissue delineation, and that 2) additional imaging may be required depending on the type of breathing motion management planned for treatment delivery (e.g. breath hold, gating, or free breathing).

Simulation Imaging

In order to enable accurate dose calculations, a high quality CT image must be obtained of the patient in the treatment position. The immobilization device that will be used at treatment delivery should also be used during imaging to position the patient as closely as possible to the treatment position. For example, if the patient is to be treated with abdominal compression, all imaging should be acquired with the same degree of abdominal compression at the time of planning. In addition, it is critical for the tumor to be immobilized during imaging for appropriate target and normal tissue definition, i.e. a breath hold image acquisition is required for optimal target delineation. This will reduce systematic errors between simulation and treatment delivery, and will ensure accurate calculation of the tumor volume and normal tissue volumes. The image resolution must be optimized for the required coverage of the anatomy (e.g. the whole liver), while maintaining an acceptable dose to the patient, e.g. a recommended image resolution is 1 mm x 1 mm in plane with a 2 mm slice thickness.

Optimizing Imaging Contrast for Target Delineation

Visualization of the tumor and the tumor boundaries within normal tissues is critical for high precision treatment planning. Intravenous (IV) contrast has been shown to be critical for the identification of most tumors in the liver images using CT. The optimal phase of the contrast depends on the type of liver cancer. For hepatocellular carcinoma, multi-phase imaging is required. The primary hepatocellular carcinoma enhances more than the surrounding liver during the arterial phase (obtained after a 20 to 30 second delay), and enhances less than the surrounding liver (termed ‘washout’) during the venous (50 – 60 seconds) or late delayed phase (> 180 seconds) phases of imaging. Such a pattern of enhancement is highly specific for hepatocellular carcinoma, and can be used to diagnosis hepatocellular carcinoma, in the absence of a biopsy, as recommended by the American Association for the Study of Liver Diseases (AASLD).[1] The utility of multiphase imaging for target delineation during radiation planning of a hepatocellular carcinoma with portal vein thrombosis is shown in Figure 1. For most liver metastases, venous phase imaging is best for target delineation. The specific time for image acquisition can be optimized on a patient specific basis by injecting a small bolus of contrast and identifying the patient specific transit times. Oral contrast is usually also recommended to improve visualization and delineation of the adjacent gastrointestinal normal tissues (e.g. stomach). To reduce the impact of contrast in dose calculations, vasculature or oral contrast can be made tissue equivalent for radiation dose calculations.

Multi-Modality Imaging for Tumor Identification

The incorporation of multi-modality imaging (e.g. Magnetic Resonance Imaging (MR) or Positron Emission Tomography (PET)) can improve the identification of tumor boundaries and identify additional foci of cancer.[2,3] For patients with allergies or contraindications to IV CT contrast, contrast MR can be especially useful for identification of the liver tumor volume. Care must be taken to manage motion when acquiring the MR image as standard acquisition techniques often span a duration longer than that of a single breath hold. The imaging sequence must tradeoff the necessary coverage with signal to noise and slice

thickness (ideally less 5 mm or less) in order to obtain the image in a single breath hold. The use of parallel imaging can improve acquisition speed.[4] Similar to CT, arterial enhancement and venous phase washout is typical for hepatocellular carcinoma, and venous phase enhancement is typical for most liver metastases.

FDG PET may also be used to assist in staging and target definition for metastatic colorectal cancer, however it generally does not add additional information for most primary liver cancers.[5,6] As PET images are acquired over many breathing cycles, if respiration sorting is not performed care must be taken when using this image for tumor definition. The asymmetric breathing patterns that most patients exhibit may cause a systematic error in target definition,[7,8] so such images should be used to guide the observer to where the tumor is located on breath hold CT or MR, rather than guide the exact tumor boundary definition. Respiration correlated PET can substantially reduce respiratory blurring and is now clinically available, and should be used if PET is planned to be used to aid in target definition.[9]

Integrating MR or PET with the planning CT scan requires image registration. The complexity of the image registration required can be reduced by taking measures to reproduce the patient geometry between each imaging session. Using the same immobilization device and attempting to reproduce the same breath hold position can reduce the burden on the image registration, and these strategies are highly recommended if possible. Rigid registration can be optimized for integrating multi-modality imaging for liver tumor delineation during radiation treatment planning by focusing the registration on the liver only. In the presence of liver deformation between the different image sets, deformable registration should be considered. If deformable registration is not available, rigid image registration can be focused on the region of the liver where the tumor is to improve the registration results. If substantial deformation is observed between imaging modalities and rigid registration is used, additional margins may be necessary to account for residual uncertainties, especially if the secondary image dataset is the only image used for tumor definition.

Defining Treatment Volumes

Once the appropriate imaging is obtained, the treatment volumes and critical normal tissues must be delineated for treatment planning. As described in the International Commission on Radiation Units (ICRU) 62, the gross tumor volume (GTV), clinical target volume (CTV), and PTV should be defined.

The GTV is typically defined using the appropriate phase of the contrast enhanced CT scan (described above), possibly combined with MR and/or PET if available. The GTV is then expanded to account for microscopic disease, generating a CTV. The expansion varies depending on the tumor type, between treatment centers, protocols and type of radiation therapy used, typically ranging from 0 to 10 mm. Preliminary radiology-pathologic correlative studies suggest that CTV margins for hepatocellular carcinoma and for colorectal cancer metastases need not be larger than 5 mm.[10] Specifically in a study of 149 resected hepatocellular carcinoma patients, low platelet counts, larger tumor volume, presence of portal vein thrombosis and elevated alfa-feto protein level correlated with increased risk of microscopic extension of HCC beyond the tumor capsule.[11] Forty-seven percent of patients had no microscopic extension of tumor beyond the tumor capsule, and an additional 44% had microscopic tumor extension that was less than 2 mm. The maximal CTV extension was 4 mm, seen in tumors larger than 5 cm in maximal diameter. In contrast, a minimum of a 10 mm CTV expansion is recommended for biliary cancers, which are likely to have microscopic disease extension within the adjacent biliary ducts. Ongoing work that accounts for specimen shrinkage and deformation in radiologic correlative studies promises to

provide additional insight to what the most appropriate CTV expansion for each liver tumors may be.

PTV expansions are necessary to ensure that the tumor receives the intended dose in the presence of breathing motion and set-up uncertainties. Due to the wide range in breathing motion, patient specific measurements for the component of the PTV due to breathing motion are recommended for patients who are planned to be treated while breathing freely or with abdominal compression that may be used to reduce the amplitude of breathing motion. Methods to measure breathing motion are described below. For patients treated at breath hold or with gating or tracking techniques, the reproducibility and accuracy of the technique must be included in the PTV margin. In addition to the breathing motion, the set-up error, the relative changes between the liver and the adjacent tissues between each treatment fraction, and the accuracy of the image guidance approach need to be considered in the calculation of the PTV. At our center, even with breath hold and soft tissue image guidance prior to each radiation fraction, a minimal PTV margin of 5 mm is used.

Acquiring the CT simulation planning CT in a known breathing state (e.g. end exhale) allows the breathing component of the PTV margin to be applied asymmetrically; i.e. if the GTV is defined at the exhale position, the breathing motion can be accounted for by applying a PTV that is larger in the inferior and anterior directions, representing the magnitude of the measured breathing motion from inhale to exhale.[12] This known breathing state (e.g. exhale) can then be reproduced during imaging at treatment delivery for verification of the liver position to facilitate image guidance. The use of a mid-ventilation or mean position scan has been shown to be promising for target delineation and for image guidance for peripheral lung cancers. This is an attractive strategy since it allows smaller PTV margins to account for breathing motion to be used;[13,14] however due to the unique challenges in the liver where the tumor is not easily visible on non-contrast images (e.g. respiratory correlated planning CT scans or cone beam CT scans), more research is needed to determine the optimal strategies to use this approach for liver cancers.

Imaging for Motion Assessment

Measuring tumor motion is an important step in planning the radiation treatment for liver cancers. The American Association of Physicist in Medicine Task Group on the management of respiratory motion in radiation oncology (TG-76) recommends that motion management strategies be considered in patients whose breathing motion exceeds 5 mm.[15] Several imaging techniques are available to measure the motion of the tumor, or surrogates such as the liver or implanted fiducials, including 2D, 3D, and 4D techniques.

Two-dimensional imaging techniques include fluoroscopy and planar cine MR imaging. Fluoroscopy may be used to provide real time imaging of the liver (i.e. imaging of the liver during radiation therapy delivery); however the tumor is not typically visible using fluoroscopy so the diaphragm and lung interface must be used as a surrogate for tumor motion in the absence of any other radio opaque marker that may be present closer to the tumor.[12] Superior-inferior (SI) motion is easily discernable using fluoroscopy, however left-right (LR) motion is more difficult to measure. Lateral fluoroscopy may be used to quantify anterior-posterior (AP) motion, although this is not commonly used. Tumors farther from the diaphragm may move more or less that the diaphragm itself. Implanting radio-opaque fiducial markers near the tumor can improve the accuracy of measuring the true tumor motion and can also facilitate measuring the LR and AP motion.[16] Cine MR imaging enables visibility of the tumor at the expense of reduced temporal sampling (frequency typically ranges from 1 - 3 images per second).[17,18] Tumor visibility on MR, even without the use of contrast, enables direct measurement of the tumor motion in each plane. A limitation of this strategy is that out of plane motion can lead to inaccuracies of the

measured motion in 2D, compared to the true 3D motion of the tumor. 3D volumetric cine MR is a promising tool that is under investigation.

Repeat 3D imaging can enable measurement of tumor motion between 2 extreme states of the breathing cycle (e.g. normal inhale and exhale). Repeat CT images at each breathing phase can allow measurement of the breathing motion, however, due to the fast washout of the IV contrast, the tumor is often difficult to discern on a second image. Therefore, the liver (or implanted or naturally occurring fiducial markers) can be used to measure tumor motion using such an approach in all three directions. Care must be taken to coach the patient to hold their breath at normal inhale and exhale, to avoid over-estimating the breathing motion, and this voluntary effort introduces some inaccuracies in this method of estimating amplitude of breathing motion. Repeat breath hold MR images provide visualization of the 3D tumor, enabling direct quantification of the tumor motion. As with breath hold CT, it is important to ensure that the patient is not at deep inspiration or deep exhalation breath hold during imaging.

4D techniques provide the ability to measure breathing motion as well as hysteresis (i.e. the difference in trajectory of the tumor from inhale to exhale, compared to exhale to inhale during breathing).[19] Similar to repeat CT images, 4D CT acquisition is longer than the timing for tumor enhancement, so the tumor may not be visible, making direct tumor motion measurements challenging. Surrogates, such as the liver boundary, can be used to estimate liver tumor motion. The feasibility of using IV contrast 4D CT for measuring hepatocellular carcinoma breathing motion has been demonstrated. In this approach, imaging is suggested to occur during the late delayed phase that demonstrates tumor washout for a longer period than the tumor enhancement that occurs during the arterial phase of imaging.[20] When imaging during a specific phase of contrast uptake, imaging only a limited region of interest near the tumor may be required to reduce the imaging time. The use of IV contrast during 4D CT enables direct tumor motion detection on the 4D CT, but possibly at the expensive of accurate identification of the tumor boundary, as identified on an optimized breath hold, appropriate phase CT. One solution to these challenges is to obtain an IV contrast breath hold CT, then register it to a 4D CT obtained immediately after the breath hold imaging. 4D, or volumetric cine, MR images can also be acquired, although not widely available, which enables direct measurement of the tumor motion without IV contrast.[21]

Motion Management Strategies

For patients with breathing motion greater than 5 mm, several treatment planning and delivery options are available to ensure the tumor receives the intended dose while reducing the dose to the surrounding normal tissue. Applying a patient specific, asymmetric PTV margin, as described above, is the simplest strategy. Other strategies include reducing or eliminating breathing motion (e.g. abdominal compression or breath hold), gating the treatment delivery to a specific phase of the breathing cycle, or tracking the tumor motion with the treatment beam that may move with a robotic arm.

Reducing Motion: Abdominal Compression

Reducing the breathing motion of the patient can enable a reduction in the PTV margin, thereby sparing some of the surrounding normal tissue. Voluntary shallow breathing can be employed to reduce the breathing motion, however this is dependent on the patient being compliant and understanding the importance of maintaining the modified breathing throughout the treatment. It may be advised to do periodic monitoring over the course of treatment to ensure compliance. Abdominal compression has been successfully shown to reduce the motion of the liver due to breathing, with a median reduction of 7 mm reported.[22] Additional studies have shown the reproducibility of the position of the liver with the

compression plate between different fractions. As with voluntary shallow breathing, validation at treatment planning of a reduction in breathing motion amplitude, as well as periodic monitoring over the course of radiation treatment is recommended.

Eliminating Motion: Breath Hold Techniques

For patients with large breathing excursions, especially those close to critical normal tissues, eliminating the motion can be beneficial. Assisted or manual breath hold can allow dramatic reduction in the PTV in these cases. The reproducibility of the breath hold position, both in the intra-fraction and inter-fraction time scales, must be accounted for in the PTV margins. For voluntary breath hold, again it is critical that the patient understands the importance of maintaining the breath hold and good communication must be maintained between the radiation therapist and the patient. Studies have shown that the voluntary breath hold at the exhale position is more reproducible, with an intra-fraction reproducibility (standard deviation) of 2.2 mm ± 2.0 mm, compared to end inhale with a reproducibility of 4.0 mm ± 3.5 mm. Assisted breath hold reduces the variability, with reported intra-fraction reproducibility of 1.5 - 2.5 mm in the superior-inferior (SI) direction. The inter-fraction variability was larger (3.4 - 4.4 mm) in patients screened appropriate for breath hold immobilization, indicating the need for image guidance to ensure positioning of the liver at the time of each fraction to enable a reduction in the PTV margins.[23,24]

Incorporating Motion: Gating and Tracking

The previous two methods describe techniques that are applied to the patient to enable reduction of the PTV by reducing the motion. This can be difficult for the patient and requires patient compliance. An alternative method is to modify the treatment beam to account for the motion, either by only turning on the radiation when the tumor is at a given location or by tracking the tumor with the radiation beam. Both of these techniques switch the burden from the patient to the radiation device and associated technology.

Gating the treatment beam, i.e. turning the beam on when the tumor (or a surrogate for the tumor) is in a predefined location, and tracking, i.e. moving the radiation beam to correspond to the motion of the tumor, both require a technology link between detection of the tumor or surrogate and the linear accelerator.[25] The potential for baseline shifts of the liver, relative to adjacent tissues and vertebral bodies, requires evaluation of the link between the surrogate (if used) and the tumor position prior to the start of treatment and possibly periodically throughout the treatment, especially if the duration of the treatment is long.

Gated treatment and tracking both enable reduction of the PTV, as breathing motion can be excluded, however setup uncertainty and uncertainty in the relationship between the surrogate, e.g. implanted fiducial or external marker, and the tumor must be accounted for.[26,27]

Imaging for Treatment Delivery

Image guidance has the potential to substantially decrease the PTV margins necessary during the treatment of tumors within the liver due to the daily changes in the relative position of the liver to bones, breathing motion, and variation in shape and position of neighboring organs (e.g. bowel and stomach), which may change the position and shape of the liver and tumor. The use of 2D or 3D image guidance techniques, described below, can enable increased precision, compared to in-room laser beams and skin marks, therefore reducing margins and sparing additional normal tissue dose.

The use of image guidance for liver cancer radiotherapy has improved as technology has become available. Megavoltage (MV) treatment beams were initially used to align the spine and high contrast anatomy, such as the diaphragm, or implanted fiducial markers. The integration of kilovoltage (kV) imaging, ultrasound, and volumetric imaging (both kV and MV) has improved the visualization of the liver and surrounding anatomy and the ability to use these structures for accurate image guidance. In all of these imaging techniques, the tumor is often difficult, if not impossible, to visualize, leading image guidance techniques to rely on surrogates for positioning the liver tumor, including fiducial markers, calcifications, surgical clips, large vessels, and the entire liver or individual lobes. These image guidance technologies and strategies are described below.

IGRT Technologies

2D kV and MV Image Guidance—2D images can be used in a variety of ways to perform image guidance. The MV beam can be used to guide RT as well as to verify the shape of each treatment beam when used in conjunction with an electronic portal imaging device (EPID). For image guidance using orthogonal MV imaging, the vertebral bodies can be identified and used to guide the medial-lateral and anterior-posterior position of the patient. Due to the larger inter-fraction changes in position of the liver relative to the bones, the vertebral bodies cannot be used to guide the inferior-superior position of the liver. Surrogates, such as radio-opaque fiducial markers inserted near the tumor or the diaphragm may be used to position the liver. The use of MV imaging for SI positioning of the liver and left-right (LR) and anterior-posterior (AP) positioning of the vertebral bodies when combined with breath hold technology has been investigated. Following positioning using this simple strategy, based on a 3 mm threshold action level, the residual liver position, based on subsequent kV cone beam CT imaging, was less than 5 mm in each direction for the majority of patients. The random setup errors for the population was 2.7 mm (SI), 2.3 mm (LR), and 3.0 mm (AP). The systematic errors were less than 2 mm.[28]

A benefit of performing imaging with the MV beam and a corresponding EPID is the acquisition of cine images during treatment delivery. If the treatment beam contains a fiducial marker or high contrast anatomy (e.g. the diaphragm) than one can analyze the cine images obtained from the treatment beam to evaluate the positioning of the patient during treatment or retrospectively. For patients treated at breath hold, these images can be used to verify the maintenance of the breath hold during the beam delivery.

The inherent low contrast and 4-10 cGy of dose required per image using MV radiographs, helped to drive the development and use of kV radiographs for image guidance. The use of kV radiographs is very similar to that described above for MV, e.g. use of the diaphragm for SI positioning or fiducial markers, and the vertebral bodies for the LR and AP alignment. An example of the measurements performed to align the liver using kV imaging is shown in Figure 2. The positions are compared to a digitally reconstructed radiograph (DRR) generated from the CT scan performed for treatment planning. Alignment can be performed by measuring the distance to a single point on the highest portion of the diaphragm or by performing alignment of a line contour of the top of the diaphragm.

Either the kV or MV radiograph can be used for image guidance in the free-breathing, breath hold, or gated treatment delivery. In free-breathing, the anterior image should be acquired at a voluntary breath hold consistent with the planning CT image (e.g. normal exhale), this will enable consistent alignment of the liver position in the SI direction. For breath hold treatment, the anterior image should be acquired in the breath hold position. For gated treatment, the image should be acquired in the position where the beam will be turned on (e.g. the exhale position), this will enable positioning of the patient and correspondence of the surrogate (e.g. external surrogate for gating) with the internal anatomy.

Fluoroscopic kV imaging can also be used to confirm breathing motion (for confirmation of PTV margins calculated at treatment planning), breath hold stability (for use with breath hold treatment), and for real time tumor tracking (for gated treatment). For gated treatment an external surrogate can be combined with kV fluoroscopy, enabling acquisition of the kV fluoroscopy only when the tumor is expected to be in the designated treatment position, based on the position of the external surrogate. The fluoroscopic imaging can be acquired prior to treatment, to confirm correspondence between the external and internal (e.g. fiducial marker or diaphragm) surrogates and periodically throughout treatment to ensure the correspondence is maintained. The integration of kV x-ray tubes with the linear accelerator design has streamlined this endeavor.

Ultrasound Image Guidance—2D ultrasound imaging is a non-ionizing alternative for image guidance in the liver. Fuss et al first used this technique to localize and position tumors in the upper abdomen. In a study of 62 liver cancer patients, 96% of the 1337 alignments were usable.[29] Post-positioning CT images showed that the residual liver position was improved in 14 out of 15 alignments compared to the liver position prior to ultrasound guidance. 49% of the daily alignments were corrected by more than 10 mm, 25% by more than 15 mm. Compared to a population model for the PTV, ultrasound image guidance enabled a PTV reduction of 41%.

kV and MV Volumetric Image Guidance—Volumetric image guidance at the time of treatment is now commonly available due to technological advances to linear accelerators. With the acquisition of 3D imaging, the liver, adjacent structures, or implanted fiducial markers can be used for image guidance, improving the accuracy over positioning based on a combination of soft tissue and bony anatomy. The complex motion of the liver and the surrounding tissues can be visualized in 3D imaging, enabling the alignment to focus on the lobe of the liver with the tumor burden or to ensure avoidance of a critical normal tissue. Figure 3 illustrates the detection of a baseline shift between the liver and the vertebral bodies through the comparison of the planning CT image with a kV CBCT acquired at the time of treatment.

Volumetric in-room imaging modalities include a CT scanner within the treatment room[30] (e.g. Primatrom, Siemens Medical, Concord, CA, USA; ExaCT, Varian Medical Systems, Palo Alto, CA, USA), helical MVCT[31] (e.g. TomoTherapy, Madison, WI), kV cone-beam CT[32] (CBCT) (e.g. Synergy; Elekta Oncology, Crawley, UK and On Board Imager (OBI); Varian Medical Systems, Palo Alto, CA, USA; Artiste, Siemens, Concord, CA, USA), and MV CBCT[33]. In each of these systems a volumetric image of the patient can be acquired just prior to (or during or after) treatment.

As the image acquisition is longer than the 2D imaging described above, breathing motion and gastric motion can introduce artifacts into the volumetric image. Typically, for patients breathing less than 5 mm, a volumetric image acquired during free breathing can be used for image guidance using liver to liver registration in 3D. For patients with larger breathing motion, breath hold or respiration sorting techniques must be used to ensure accurate image guidance. Acquiring a CBCT image in multiple breath holds (e.g. three repeat 20 second breath holds can be used to obtain sufficient projections for volumetric reconstruction) or performing retrospective respiration sorting on the projection images after acquisition, as shown in Figure 4.[28,34] In addition, the administration of oral contrast can be used to improve the visibility of luminal normal tissues adjacent to the liver, as illustrated in Figure 5. The administration of IV contrast has been shown to enable direct visualization of the tumor on CBCT, however this can be challenging to perform at each treatment fraction. In the absence of IV contrast, and hence direct visualization of the tumor, surrogates may be

used for alignment, including the entire liver, the tumor-bearing lobe of the liver, or fiducial markers.

As with 2D imaging, volumetric imaging can be used in each of the motion management strategies. For free-breathing treatments, ideally a respiration sorted volumetric image is obtained. The breathing state that corresponds to the planning breathing state (e.g. end exhale) can then be used for patient alignment. The remaining images corresponding to the breathing cycle can be used to measure the patient breathing motion for comparison with the measured breathing motion at treatment planning (and therefore integrated into the PTV margin). In the absence of respiration sorting of the volumetric images, the 'blurred' image, or the image acquired while the patient is breathing, can be used to estimate the end exhale position and the breathing motion, as described by Guckenberger and colleagues. For patients treated in breath hold, ideally the volumetric image is acquired in a series of breath holds to enable 3D alignment of the anatomy in the breath hold position with the planning CT image.

Fluoroscopic images can also be obtained from any gantry angle using the kV CBCT system. The use of these images concurrent or intermittent with the MV radiotherapy treatment can enable real time monitoring and tracking. A limited number of projections over a shorter angular arc can also be acquired with the CBCT system and reconstructed to form tomosynthesis, which enables acquisition in a shorter amount of time with less dose while maintaining high spatial resolution in plane at the expense of limited depth of field.

IGRT Strategies—Two main IGRT strategies exist, online and offline. In the online strategy, the images are acquired, evaluated, and used to position the patient prior to treatment. For hypofractionated and stereotactic treatments, this approach is recommended. In the offline strategy, the images are acquired prior to treatment, however the analysis is performed offline, resulting in the correction of a systematic error and the quantification of a random error, for subsequent treatment fractions. Often 3-5 images are obtained and used to determine a systematic and random error.[35] The systematic error can then be corrected for and the random error must be accounted for in the PTV. Alternatively, offline strategies may involve replanning to account for new information gained from the patient imaging (e.g. changes in the average position or breathing motion).

It is important when describing image guidance strategies, which tend to focus on alignment of the tumor, to highlight the importance of evaluating the position of the surrounding critical normal tissue during image guidance. As the liver baseline position of the liver has been shown to vary, the relative position of the critical normal tissues to the high dose region may also vary. It is prudent when evaluating the patient position, to be mindful of the dosimetric consequences to these tissues if large deviations from the planned position, of all organs, exist. In the advent of these large discrepancies that may negatively impact the dose to critical structures, it may be necessary to replan the treatment.

Future Research

Many exciting research endeavors are ongoing in the area of imaging and image guidance for liver cancer patients. Further research of correlative pathology-radiology studies, that relate pathologic changes to in vivo imaging to validate the boundaries of the gross and microscopic disease, promises to improve the uncertainty in defining the target.[36] MR guided linear accelerators are being developed to improve the ability to visualize the soft tissue, including liver tumors, immediately prior to each radiation treatment. These advanced treatment units also have the potential to perform continuous imaging while delivering radiation therapy.[37,38] In addition, the use of deformable registration to improve the integration of multi-modality images at planning, improve IGRT for all imaging

modalities, and to calculate a more realistic measurement of the delivered dose in the presence of breathing motion and other uncertainties is being investigated.[39] These advancing technologies promise to improve the ability to define, plan, treat, and assess liver cancer patients treated with radiotherapy.

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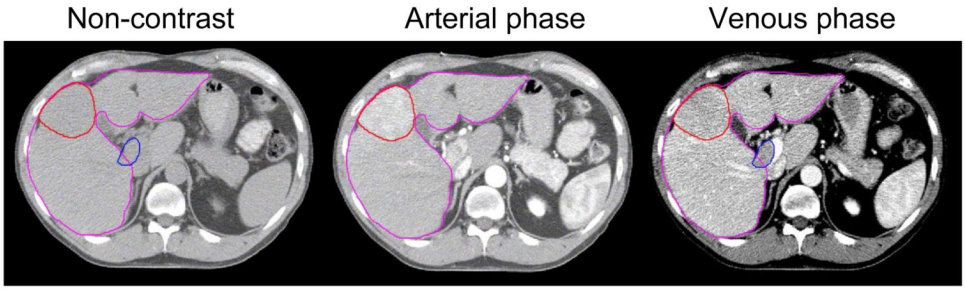

Figure 1.
CT planning images for an HCC patient. The liver (pink), the GTV (red) and the portal vein thrombosis (blue) are shown on a noncontrast CT (left), and on arterial phase (middle) and venous phase (right) images.

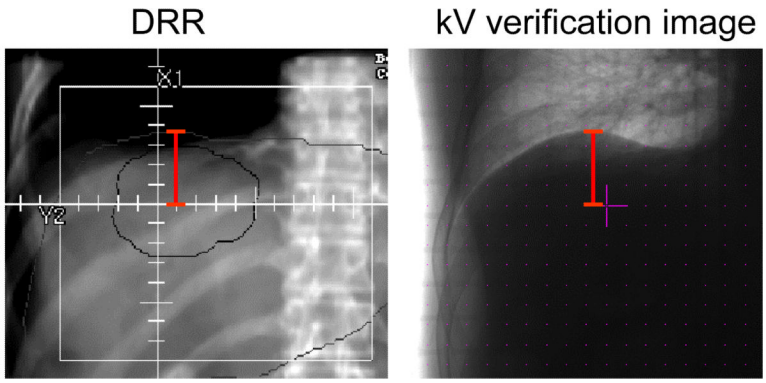

Figure 2.
Use of an AP kV image to assess superior-inferior positioning of a patient treated using breath hold for liver immobilization. Left=DRR from planning CT (exhale helical under ABC), Right: kV image at breath hold

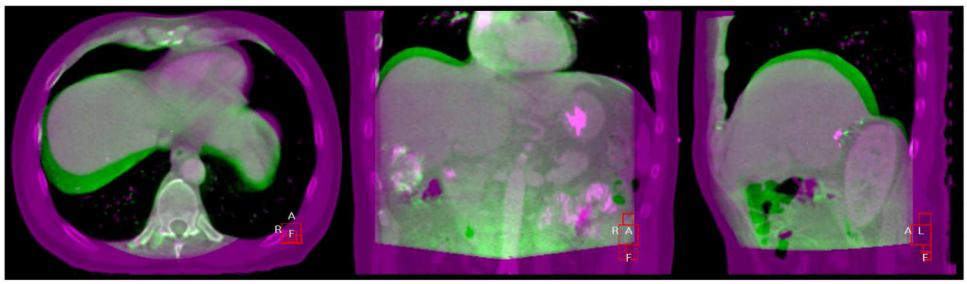

Figure 3.
An example of a kV CBCT (obtained with 3 repeat breath holds) registered to the planning CT using the vertebral bodies. The baseline shift of the liver, relative to the bones, is evident by the purple (planning CT)/green (CBCT) color display.

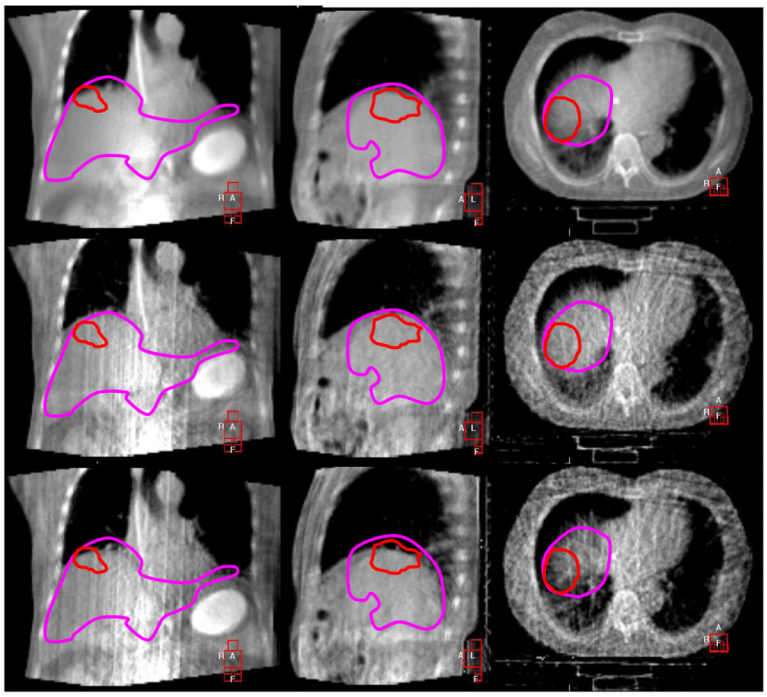

Figure 4.
An example of a kV 4D CBCT reconstruction acquired while the patient was breathing. Top=all projections combined (the image appears blurry due to the breathing motion), middle=exhale sorted images, bottom=inhale sorted images. The planning contours are overlaid for reference: Purple=planning exhale CT liver, red=GTV

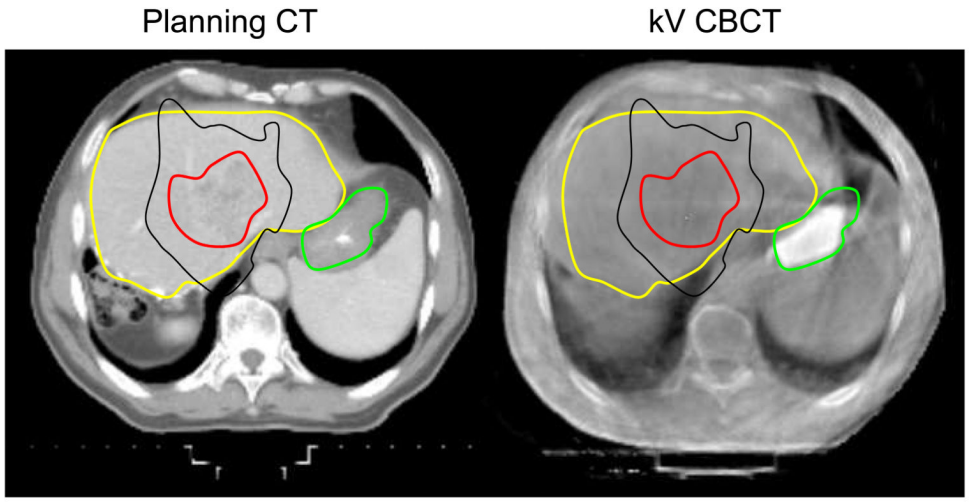

Figure 5.
Planning CT (left) and kV CBCT (right) with the administration of oral contrast to aid in IGRT and avoidance of the stomach. The planning contours are overlaid for visualization: yellow=liver, red=GTV, black=isodose representing 31Gy in 6 fractions, green=stomach