Optimized dynamic contrast-enhanced cone-beam CT for target visualization during liver SBRT

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Abstract. The pharmacokinetic behavior of iodine contrast agents makes it difficult to achieve significant enhancement during contrast-enhanced cone-beam CT (CE-CBCT). This study modeled this dynamic behavior to optimize CE-CBCT and improve the localization of liver lesions for SBRT. We developed a model that allows for controlled study of changing iodine concentrations using static phantoms. A projection database consisting of multiple phantom images of differing iodine/scan conditions was built. To reconstruct images of dynamic hepatic concentrations, hepatic contrast enhancement data from conventional CT scans were used to re-assemble the projections to match the expected amount of contrast. In this way the effect of various parameters on image quality was isolated, and using our dynamic model we found parameters for iodine injection, CBCT scanning, and injection/scanning timing which optimize contrast enhancement. Increasing the iodine dose, iodine injection rate, and imaging dose led to significant increases in signal-to-noise ratio (SNR). Reducing the CBCT imaging time also increased SNR, as the image can be completed before the iodine exits the liver. Proper timing of image acquisition played a significant role, as a 30 second error in start time resulted in a 40% SNR decrease. The effect of IV contrast is severely degraded in CBCT, but there is promise that, with optimization of the injection and scan parameters to account for iodine pharmacokinetics, CE-CBCT which models venous-phase blood flow kinetics will be feasible for accurate localization of liver lesions.

Introduction
The efficacy of Stereotactic Body Radiation Therapy (SBRT) of the liver is hindered by the inability to accurately localize the lesion at the time of treatment. Liver metastases and the liver parenchyma are iso-attenuating, so these tumors cannot be seen directly with cone-beam CT (CBCT). The image quality of CBCT is also degraded by the large respiratory-induced motion of the abdomen, and it is difficult to visualize the surface of the liver. The lack of direct anatomical landmarks for localization necessitates larger safety margins, which in turn increases the mean dose to the liver and potentially increases the incidence of radiation-induced liver disease [1].

Despite these difficulties, the unique dual-supply architecture of the liver makes it possible to improve the quality of imaging with IV agents. This concept is exploited in Contrast-Enhanced CT (CECT), and can be used in diagnosis and/or treatment planning to visualize liver metastases [2]. If an image is acquired during venous perfusion of the liver, the parenchyma appears bright while the tumor is unchanged, and thus the lesion can be differentiated from the surrounding tissue.
In order to improve the accuracy of liver SBRT, we investigated the feasibility of Contrast-enhanced Cone-Beam CT (CE-CBCT) with the goal of using iodinated IV contrast to visualize liver metastases. CE-CBCT has been attempted at a handful of institutions, but has met with little success. Iodine washes in and out of the liver on a roughly one-minute timescale, while CBCT can take up to two minutes to acquire. Additionally, one of the difficulties in studying the effect of contrast-enhanced imaging is the pharmacokinetics of the contrast agent. IV agents exhibit dynamic behavior within a biological system, and the image quality can vary greatly between different injection/acquisition protocols. Moreover, it is difficult to manufacture a phantom that can duplicate this complex behavior [3]. In order to optimize the effect of iodine imaging, we have developed a model that allows for controlled study of CE-CBCT image quality using static phantoms. Using this model, we have identified several key properties of the iodine injection, the physics of the CBCT image, and the relative timing of the injection and image acquisition which optimize the image quality of CE-CBCT.

Methods and Materials
The most straightforward way to study image quality in CE-CBCT would be to mimic the conditions of patient imaging using a phantom. However, since the iodine concentration in vivo changes during the course of imaging, studying this scenario would require a phantom with variable iodine concentration. Instead of constructing such a phantom, we simulated CE-CBCT imaging by acquiring many CBCT images with different concentrations of iodine, and then re-assembled these projections in such a way as to mimic published patient data. The first step was to assemble a database of CBCT projections which encompass the full range of possible contrast parameters (such as iodine concentration) or CBCT conditions (such as kV/mA and geometry). This database was assembled by acquiring multiple static CBCT images of the phantom containing an iodine-loaded insert whose concentration varied between images. Next, Hepatic Enhancement vs. Time (HEVT) curves were retrieved from literature in order to model realistic dynamic behavior in CE-CBCT [4]. These HEVT curves are given for different injection parameters, such as iodine dose, injection rate, and timing. Finally, to generate the predicted CE-CBCT image, CBCT projections are chosen from the database such that the concentration of iodine in the phantom matches the expected HU value from the HEVT curve. These projections are assembled into a pseudo-scan and re-reconstructed to yield an image, the content of which is equivalent to the hypothetical expected image (were the phantom iodine concentration to vary as given by the patient-derived HEVT curve). In this way, our model translates a given HEVT curve into a CE-CBCT image that accounts for the dynamic behavior of IV contrast.

![Fig 1: Dynamic Phantom Model: Selecting from the projection database. A) A projection database is built by acquiring numerous images, each containing various concentrations of iodine. The database consists of thousands of projections, with each one containing differing concentrations of iodine and acquired at different gantry angles. B) To reconstruct a dynamic image, a HEVT curve is used to select projections from the database. In this example, projections are chosen from the database such that at each moment in time the iodine concentration matches that expected from the HEVT curve.](image)

A Gammex 467 Tissue Characterization Phantom was used to acquire static images with various concentrations of iodine. A series of 50 mL conical tubes were filled with a mixture of Isovue-370 (Iopamidol, 37% Iodine by weight) and water. The proportion of these mixtures was chosen such that
the tubes corresponded to 10-120 Hounsfield units (HU) when imaged, and these values were verified using a Phillips Big Bore CT Scanner. Next, a projection dataset was assembled on a TrueBeam Accelerator by acquiring numerous CBCT scans, each acquired with various concentrations of iodine and under different CBCT conditions. In order to study the effect of a certain injection parameter (for instance, iodine dose or injection rate), the HEVT curve for that factor was retrieved from the published literature [4]. Likewise, to analyze the effect of imaging physics (e.g. x-ray scatter or kV/mA), a separate set of static CBCTs were acquired under these parameters, and our model was applied. To study the effects of the relative injection/CBCT imaging timing, appropriate adjustments were made in our model when converting from time (on the HEVT curve) to gantry angle. Signal-to-noise ratio (SNR) was chosen as the primary metric of image quality, which is suitable in the current early stage of development as a crude indicator of conspicuity [5]. HEVT curves were normalized to represent a hypothetical adult male (30 years old; weight, 70 kg) under various injection conditions. Also note that, while the HU of CT and CBCT are generally different, HEVT curves were derived entirely from CT studies. The HU in CBCT images were used only to calculate SNR, which requires only relative (and not absolute) accuracy.

Results
Fig. 2 shows the effects of various parameters of the iodine injection, CBCT acquisition, and relative injection/imaging timing on the SNR of the resulting image. As expected, the SNR increases as the average amount of iodine present during CBCT acquisition increases. Fig. 2A demonstrates the relationship between SNR and injection rate. As the injection rate increases, the peak hepatic enhancement increases, but the width of the peak is shorter [3]. For the full-fan (180º) acquisition, which takes 30 s to acquire, there is not much enhancement in SNR as the injection rate is increased above 3 mL/s. In the half-fan (360º) acquisition, there was no different in SNR with respect to injection rate due to the length of the CBCT acquisition (60s) compared to the width of the enhancement peak (30-60s). Fig. 2B shows that SNR increases as the iodine dose is increased. There is a larger relative increase in the full-fan acquisition, which is again a result of the shorter scan time.

![Fig. 2: Optimization of Signal-to-Noise Ratio (SNR) in CE-CBCT. A) Varying injection rate of a 125 mL injection of contrast medium (350 mgI/mL). B) Varying dose of contrast medium (350 mgI/mL) injected at 2 mL/s. C) Varying the imaging dose used in the CBCT acquisition. Results are normalized such that the dose per unit mAs is equal. D) Varying the time over which the CBCT is acquired. E) Varying the delay between the initiation of the iodine injection and initiation of the CBCT image acquisition. Time is shown relative to the theoretical best time (t=0).](image)

Fig. 2C shows the relationship between SNR and CBCT imaging dose. As expected, SNR increases with higher dose, due to the reduction in noise in the reconstructed images. Results are shown for both the half- and full-fan acquisitions; one may note that since the half-fan acquisition is roughly twice as long, the number of projections acquired (and thus the image dose) is increased. This results
in a reduction in noise and a higher SNR for half-fan images. No significant different in SNR was seen when the tube voltage changed from 125 kV to 100 kV. Since the attenuation coefficient for iodine is greater at lower photon energies, there was a larger signal observed in the iodine-loaded samples. However, this increase is offset by a reduction in imaging dose due to the lower bremsstrahlung production efficiency within the photon source of 100 keV electrons (compared to 125 keV). This increased the noise in the images, and resulted in no net SNR change.

Fig. 2D demonstrates the effect of total CBCT acquisition time for a 125 mL injection at 3 mL/s. As the scan time increases, a greater portion of the image is taken at a time where either the iodine has not arrived at the liver, or the iodine has washed out of the liver. As a result, the mean iodine concentration in the image decreases and the SNR is reduced. Fig. 2E demonstrates the magnitude of the effects of sub-optimal timing between the initiation of the iodine injection and initiation of the CBCT acquisition. SNR is degraded as much as 40% if the CBCT acquisition is started at the incorrect time. The degradation is lessened for delays greater than the optimum time; this is due to the fact that iodine washes out of the liver slower than the initial bolus enters, or in other words, the slope of the HEVT curve is lower on the receding side.

Discussion and Conclusions

CE-CBCT takes advantage of the unique architecture of the liver to increase the visibility of hepatic malignancies. This, in turn, facilitates better treatment accuracy in intense therapies such as SBRT that rely on very large dose gradients to spare normal tissue. In order to improve the image quality of CE-CBCT, we have investigated factors which affect the amount of iodine present during imaging, and have developed a model to optimize these parameters. In general, SNR increases as the mean iodine concentration during imaging increases. Increasing the dose of iodine injected has a large effect (up to 100% SNR increase, Fig. 2B); increasing the rate of injection also plays a role.

Several challenges remain to be addressed before CE-CBCT can be successful clinically. One can optimize the CE-CBCT acquisition for a given HEVT curve, but these curves are known to vary based on patient-specific factors such as weight and cardiac output. Our results indicate that the resulting image quality can be very sensitive to errors in timing, and so it is crucial to know the time to peak enhancement for a given patient. Possible solutions are to use bolus-tracking during the simulation CECT, and record the relative timing during that acquisition, or to acquire liver perfusion images prior to treatment. A more comprehensive way may be to investigate an injection/acquisition protocol which is less sensitive to differences in the time to peak enhancement.

The ultimate goal of this work is to improve the accuracy of liver SBRT. In this preliminary study, we demonstrate techniques to increase the signal-to-noise ratio of CE-CBCT imaging; however, conspicuity of liver lesions can depend on many factors (tumor size, shape of the lesion, SNR, background characteristics, and other factors). The results of this study will be used to guide future clinical implementations of contrast-enhanced CBCT. A pilot study is underway in our department to assess the clinical impact of IV contrast on the visibility of liver lesions and the localization accuracy benefit of this imaging.

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