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SPECT/CT differential avoidance

Differential hepatic avoidance radiation therapy: Proof of concept in hepatocellular carcinoma patients

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ABSTRACT

Purpose: To evaluate the feasibility of a novel planning concept that differentially redistributes RT dose away from functional liver regions as defined by ^{99m}Tc-sulphur colloid (SC) uptake on patient SPECT/CT images.

Materials and methods: Ten HCC patients with different Child–Turcotte–Pugh scores (A5-B9) underwent SC SPECT/CT scans in treatment position prior to RT that were registered to planning CT scans. Proton pencil beam scanning (PBS) therapy plans were optimized to deliver 37.5–60.0 Gy (RBE) over 5–15 fractions using single field uniform dose technique robust to range and setup uncertainty. Photon volumetrically modulated arc therapy (VMAT) plans were optimized to the same prescribed dose and minimum target coverage. For both treatment modalities, differential hepatic avoidance RT (DHART) plans were generated to decrease dose to functional liver volumes (FLV) defined by a range of thresholds relative to maximum SC uptake (43–90%) in the tumor-subtracted liver. Radiation dose was redistributed away from regions of increased SC uptake in each FLV by linearly scaling mean dose objectives during PBS or VMAT optimization. DHART planning feasibility was assessed by a significantly negative Spearman's rank correlation (R_S) between dose difference and SC uptake. Patient, tumor, and treatment planning characteristics were tested for association to DHART planning feasibility using non-parametric Kruskal–Wallis ANOVA.

Results: Compared to conventional plans, DHART plans achieved a 3% FLV dose reduction for every 10% SC uptake increase. DHART planning was feasible in the majority of patients with 60% of patients having $R_S < -0.5$ ($p < 0.01$, range -1.0 to 0.2) and was particularly effective in 30% of patients ($R_S < -0.9$). Mean dose to FLV was reduced by up to 20% in these patients. Only fractionation regimen was associated with DHART planning feasibility: 15 fraction courses were more feasible than 5–6 fraction courses ($R_S < -0.93$ vs. $R_S > -0.60$, $p < 0.02$).

Conclusion: Differential avoidance of functional liver regions defined on sulphur colloid SPECT/CT is achievable with either photon VMAT or proton PBS therapy. Further investigation with phantom studies and in a larger cohort of patients may validate the utility of DHART planning for HCC radiotherapy.

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Liver function is critically important in the radiation therapy (RT) management of patients with hepatocellular carcinoma (HCC) [1]. In addition to risk of local intrahepatic progression, cirrhosis from chronic liver disease (viral hepatitis, alcohol injury, and steatosis) places HCC patients at higher risk for radiation induced liver disease (RILD) [2–4]. Risk of RILD reported in the literature is variable, ranging from 5% to 63% [5–7]. Reasons for this variability are likely multifactorial, including heterogeneity in patient characteristics, RILD definitions, and RT regimens. Other sources of variability may stem from the assumption that liver function is spatially homogenous, which is reflected by current anatomic liver dose objectives that presume uniform dose–responses from population-based normal tissue complication models [8,9]. These dose objectives ignore potential differences in radiosensitivity between cirrhotic, necrotic, and viable liver tissue. In patients with a high degree of liver function heterogeneity, it is unclear whether anatomic liver dose–volume objectives can effectively spare radiation to functional liver regions.

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Incorporating functional liver imaging into RT planning may aid in addressing these issues. Several imaging modalities have been investigated for diagnostic imaging of liver function, including positron emission tomography (PET) with [^{18}F]fluorodeoxygalactose [10,11], dynamic contrast-enhanced magnetic resonance imaging [12] with gadoxetic acid [13] or gadoxetate disodium [14,15]. Single photon emission tomography (SPECT) radiotracers of liver function include [^{99m}Tc]hepatobiliary iminodiacetic acid [16], [^{99m}Tc]galactosyl-human serum albumin [17], as well as [^{99m}Tc]sulphur and [^{99m}Tc]phytate colloid [18]. Sulphur colloid is taken up by the Kupffer cells of the reticuloendothelial system, which are intimately related to hepatocyte function. Sulphur colloid (SC) uptake has been shown to correlate to the blood serum marker indocyanine green, a well-established quantitative measure of liver function [18]. Furthermore, quantitative imaging parameters from colloid uptake such as the perfused hepatic mass were associated with explanted liver functional mass [19] and predicted clinical outcome [20]. While other imaging surrogates such as [^{99m}Tc] hepatobiliary iminodiacetic acid SPECT provide direct imaging of hepatocytes, they rely on dynamic SPECT/CT image acquisition which presents challenges for accurate and reproducible quantification. Both galactosyl-human serum albumin and colloid tracers rely on simpler pharmacokinetics to perform static image acquisition of albumin and Kupffer cells, respectively, which may prove advantageous for defining functional liver regions on quantitative images during radiotherapy planning or therapeutic response assessment.

Quantitative molecular imaging as a surrogate for liver function may provide objective measures by which to characterize spatial variation in liver function. Spatial heterogeneity in molecular images can guide the spatial modulation of radiation dose, a radiotherapy formalism known as 'dose painting' [21,22]. Intense investigation on the utility of dose painting has focused on non-uniform tumor dose escalation, primarily based on [^{18}F]fluorodeoxyglucose PET as a surrogate for local failure risk [23,24], in a range of disease sites [25–28]. However, preliminary dose painting clinical trials in head-and-neck cancer [29,30] and non-small cell lung cancer [31] have not considered heterogeneity in normal tissue function. The concept of functional tissue avoidance is to spatially modify (i.e. paint) radiation doses such that normal tissue function is preserved while maintaining RT target dose coverage, which has been explored in avoidance planning of perfused lung [32,33]. Dose painting strategies in tumor versus strategies in normal tissue would ideally complement one another in a manner that substantially enhances the overall therapeutic ratio.

For primary HCC radiotherapy, dose painting based on functional liver heterogeneity has the potential to decrease complication rates of current treatment regimens and enable safer dose escalation strategies. The aim of this study was to develop a novel Differential Hepatic Avoidance Radiation Therapy (DHART) paradigm. As a proof of concept, we compared conventional RT and DHART plans in a cohort of HCC patients. The DHART planning paradigm using [^{99m}Tc] sulphur colloid SPECT/CT was implemented for both proton pencil beam scanning (PBS) therapy and photon volumetrically modulated arc therapy (VMAT). Preliminary results of feasibility are reported and implications for patients who may benefit from this treatment paradigm are discussed.

Materials and methods

Patient characteristics

After obtaining Institutional Review Board approval, ten patients (6 male, 4 female) with a median age of 65 years (range 41–83) were included in the study. All patients had a diagnosis of HCC and were ineligible for other liver-directed therapies. Each patient had a single HCC lesion, and gross tumor volumes (GTV) ranged from 1 cm^3 to 434 cm^3 (median 88 cm^3). Six lesions were located in the periphery of the liver, with four located centrally. Six patients had received prior liver-directed therapy for HCC and presented with treatment failure, local recurrence, or new HCC lesions. Prior treatments included radiofrequency ablation ($n = 3$), transarterial chemoembolization ($n = 5$) or radioembolization ($n = 1$), and bland embolization ($n = 1$). The median number of prior liver directed therapies per patient was 4.5 (range 1–9). All patients had underlying cirrhosis with either well-compensated or mildly decompensated liver function, including Child–Turcotte–Pugh (CTP) A ($n = 5$) and CTP B ($n = 5$) respectively (range A5–B9). Cirrhosis was related to either hepatitis C ($n = 6$), alcohol intake ($n = 3$), non-alcoholic fatty liver disease ($n = 2$), hepatitis B ($n = 1$) or a combination of these factors. Six patients received stereotactic body RT (SBRT) in 5–6 fractions, while four received longer hypofractionated radiation courses of 15 fractions, with total doses ranging from 37.5 Gy to 60.0 Gy (RBE) in accordance with the NRG-GI001 cooperative trial protocol.

SPECT/CT image acquisition, reconstruction and registration

Patients underwent [^{99m}Tc] sulphur colloid (SC) SPECT/CT scans prior to definitive radiotherapy and were reproducibly immobilized in treatment position. SPECT/CT images were acquired on a Precedence™ (Philips Healthcare, Andover, MA) scanner comprising a dual head gamma camera and 16 slice CT scanner. Following the injection of 7 mCi (259 MBq) [^{99m}Tc] sulphur colloid, SPECT scans were acquired 15 min post-injection over a fixed time-averaged frame (64 views, 20 s/view, 180 degree arc). Emission images were corrected for scatter, collimation, and attenuation using a tidal breathing end-exhale position CT image. Reconstructions were performed with the Astonish™ (Philips Healthcare, Andover, MA) ordered subset expectation–maximization (OSEM) iterative algorithm over 2 iterations and 16 subsets that included a 10 mm Hanning filter and isotropic 4.64 mm voxels. Liver counts were normalized to spleen counts to form a relative liver-to-spleen uptake ratio, which facilitated inter-patient comparison of images.

Liver anatomy from the end-exhale attenuation correction CT acquired with each SPECT scan was registered to the reference liver anatomy from the end-exhale respiratory phase of a radiotherapy planning CT acquired the same day, either under free-breathing or active breathing control (ABC™, Elekta Inc., Stockholm, Sweden) breath-hold conditions. Rigid registration between the planning CT and SPECT/CT was performed in MIM 6.2™ (MIM Software Inc., Cleveland, OH) using built-in mutual information methods. The resulting spatial transformations estimated from CT-to-CT registration were applied to the respective SPECT images, and the rigidly translated/rotated matrices were resampled using a cubic spline filter onto a common planning grid in MIM. Deformable registration techniques were initially evaluated but did not provide sufficiently improved liver registration accuracy, particularly in the context of end-exhale CT scans and low spatial resolution SPECT, to warrant their implementation for this study.

Functional liver avoidance paradigm

In the absence of direct clinical evidence on the relationship between SC SPECT uptake and functional liver radiosensitivity, a simple modeling approach was adopted as a proof of concept. Under the assumptions that increased SC uptake is a surrogate for viable liver tissue at risk of radiation-induced complication and that SC avid areas are of higher preservation importance, the planning paradigm was designed to preferentially reduce dose to