Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2013 January 1; 85(1): 258–263. doi:10.1016/j.ijrobp.2012.02.037.

Prediction of Liver Function by Using Magnetic Resonance-based Portal Venous Perfusion Imaging

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Abstract

Purpose—To evaluate whether liver function can be assessed globally and spatially by using volumetric dynamic contrast-enhanced magnetic resonance imaging MRI (DCE-MRI) to potentially aid in adaptive treatment planning.

Methods and Materials—Seventeen patients with intrahepatic cancer undergoing focal radiation therapy (RT) were enrolled in institution review board-approved prospective studies to obtain DCE-MRI (to measure regional perfusion) and indocyanine green (ICG) clearance rates (to measure overall liver function) prior to, during, and at 1 and 2 months after treatment. The volumetric distribution of portal venous perfusion in the whole liver was estimated for each scan. We assessed the correlation between mean portal venous perfusion in the nontumor volume of the liver and overall liver function measured by ICG before, during, and after RT. The dose response for regional portal venous perfusion to RT was determined using a linear mixed effects model.

Results—There was a significant correlation between the ICG clearance rate and mean portal venous perfusion in the functioning liver parenchyma, suggesting that portal venous perfusion could be used as a surrogate for function. Reduction in regional venous perfusion 1 month after RT was predicted by the locally accumulated biologically corrected dose at the end of RT ($P < .0007$). Regional portal venous perfusion measured during RT was a significant predictor for regional venous perfusion assessed 1 month after RT ($P < .00001$). Global hypovenous perfusion pre-RT was observed in 4 patients (3 patients with hepatocellular carcinoma and cirrhosis), 3 of whom had recovered from hypoperfusion, except in the highest dose regions, post-RT. In addition, 3 patients who had normal perfusion pre-RT had marked hypervenuous perfusion or reperfusion in low-dose regions post-RT.

Conclusions—This study suggests that MR-based volumetric hepatic perfusion imaging may be a biomarker for spatial distribution of liver function, which could aid in individualizing therapy, particularly for patients at risk for liver injury after RT.

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Abstract presented at the 53rd Annual Meeting of the American Society for Radiation Oncology (ASTRO), in Miami Beach, FL, on October 2–6, 2011.

Conflict of interest: none.

Introduction

High-dose conformal radiation therapy (RT) can be effective in controlling unresectable primary and metastatic intrahepatic tumors and may prolong survival of patients (1). However, delivery of high-dose RT to the liver has been limited by the risk of radiation-induced liver disease (RILD) (2–4), which can be fatal. Normal tissue complication probability (NTCP) models have been developed for predicting the risk of RILD based upon dose-volume parameters (5) and have provided guidance for treatment planning. These models, however, do not take into account an individual patient's liver function prior to therapy or the heterogeneity of sensitivity as the radiation treatment course progresses. The development of methods to determine regional and global liver functions (6–9) prior to and during the course of radiation could open up the possibility of individualizing therapy. This individualization could include altering the total dose delivered and rearranging dose to spare functioning liver while permitting increased radiation doses to liver that has already been damaged. The result could maximize tumor dose and simultaneously minimize the risk for liver injury.

Given the fact that RILD is the clinical manifestation of venoocclusive disease (3), computed tomography (CT)-based hepatic perfusion imaging has been investigated to relate regional venous perfusion after liver irradiation to local dose and overall liver function assessed by clearance of indocyanine green (ICG) (9, 10). It was found that the reduction of regional portal venous perfusion for individual patients after RT was predicted by the local dose and perfusion measured during RT. Also, regional perfusion dysfunction in the liver parenchyma depended upon both the delivered dose distribution and the individual's sensitivity to radiation (10). However, CT-based hepatic perfusion imaging has limited spatial coverage, so it seemed unlikely that this information could be consistently extrapolated to understand whole-liver perfusion and function.

To further develop hepatic perfusion imaging as an effective tool for risk management of liver RT, we hypothesized that early assessment of global and spatial liver functions by the use of ICG tests and magnetic resonance imaging (MRI)-based volumetric perfusion imaging would ultimately allow us to develop a response-driven individual and adaptive treatment strategy to maximize tumor doses and protect functional reserve. As a first step toward that goal, we conducted a study to assess the potential for MRI-based volumetric perfusion imaging to predict both global and regional liver functions by relating imaging findings to both ICG clearance and spatial dose deposition. We also aimed to assess whether early changes in perfusion during RT could predict later changes after completion of treatment in patients treated for a variety of pathologies with diverse treatment schedules.

Methods and Materials

Patients

Seventeen patients (2 women and 15 men; ages 43–80 years) with unresectable intrahepatic cancer participated in a prospective institutional review board-approved liver dynamic contrast-enhanced (DCE) MRI study (Table 1). Fifteen of these patients were also enrolled in a separate prospective IRB-approved ICG study for liver function assessment. Seven patients had hepatocellular carcinoma (HCC), 3 had cholangiocarcinoma, and 7 had metastasis to the liver. Six of 7 HCC patients had cirrhosis (except patient no. 6 [Table 1]). Patients were treated using 3-dimensional (3D) conformal RT (n = 12) or stereotactic body RT (SBRT) (n = 5) as clinically indicated. Generally, treatment was planned using UMPLAN, an in-house optimization system, on a contrast-enhanced CT obtained at end-exhalation using active breathing control for immobilization, as previously described (1). The prescribed dose for each patient was determined by our in-house NTCP model to have

10% or less of the risk for RILD (11). For 3D conformal RT, median dose was 62 Gy (48–82 Gy) in 2- to 3-Gy fractions. For SBRT, 3 patients received 50 Gy in 5 fractions, 2 patients received 30 Gy in 3 fractions, and 1 patient received 60 Gy in 3 fractions sequentially to 3 tumors. No patient developed RILD after RT. Each point of the dose distribution within the liver was corrected to 2-Gy equivalent values (12) by using the linear quadratic model with $\alpha/\beta = 2.5$ Gy for analysis of the dose response of perfusion changes.

Liver DCE MRI scans were acquired within 2 weeks prior to RT, after delivery of ~60% of the planned dose and 1 and 2 months after completion of RT. ICG testing was done within ± 2 days of each of the DCE MRI scans. The half-life of ICG clearance was estimated from serum samples, with a prolonged clearance time indicating worse liver function. The median half-life of ICG clearance prior to RT was 4.5 min (range, 3.75–14.5 min) (Table 1).

MRI-based liver perfusion

Volumetric DCE MRI of the patients was acquired on a 3T scanner (Philips, The Netherlands) using a 3D gradient echo pulse sequence (TR/TE/FA, 4.48 ms/2.15 ms/20°; matrix, $320 \times 320 \times 66$; field of view (FOV), $33 \times 33 \times 19.8$ cm; Sensitivity Encoding for Fast MRI (SENSE) factor, 2 in 2 different directions). The DCE image volumes covering the whole liver in a coronal or oblique-coronal orientation (to avoid the blood in-flow effect) were acquired approximately every 2.4 sec for a total of 2 min, during which a breathing control paradigm, developed in our previous DCE-CT liver perfusion study, was used (10). Voxel-by-voxel hepatic arterial and portal venous perfusion was quantified by fitting DCE data to a dual-input single-compartment model as previously described (10, 13, 14). After spatially registering volumetric MR perfusion images to treatment planning CTs using affine transformation, bio-dose distributions (ie, scaled to 2-Gy per fraction equivalent normalized total doses) were coregistered to perfusion images for analysis.

Dose-response of portal venous perfusion

To assess dose response of portal venous perfusion, liver volumes were divided into subvolumes based upon local bio-doses accumulated up to the end of RT, in 5-Gy increments. This dose region-based analysis has more tolerance to image misregistration than voxel-based analysis. Care was taken to exclude image artifacts, large vessels, and gross tumor volume from the liver volume. The dysfunctional liver parenchyma prior to RT, which was due to previous therapies and would not respond to dose, was excluded from analysis (by excluding the voxels with portal venous perfusion < 0.1 mL/100 g/min) prior to RT). Mean doses and mean venous perfusion values in each of the dose-defined subvolumes were calculated for each time point to determine the dose response of portal venous perfusion. A linear mixed effects model in which random effects (individual patients) can be accounted for was used to relate regional venous perfusion 1 month after RT to local bio-dose and regional perfusion measured prior to or during the mid-course of RT. The tested models are described in the Appendix.

Correlation of portal venous perfusion with liver function

To test whether spatially resolved venous perfusion could be used to estimate liver function, the volume-weighted mean of portal venous perfusion over the whole liver, excluding gross tumor volumes and large vessels, was correlated to overall liver function measured by the ICG clearance rate ($1/t_{1/2}$) by linear regression.

Results

Correlation between liver function and venous perfusion

We evaluated whether overall liver function measured by ICG clearance was correlated with the volume-weighted mean of portal venous perfusion over the whole liver volume. We found that the volume-weighted mean of portal venous perfusion in the liver volume was linearly correlated with the $1/t_{1/2}$ clearance rate of ICG ($r = 0.70$; $P < .0000001$) (Fig. 1), suggesting that spatially resolved portal venous perfusion may be a biomarker for liver function.

Perfusion change over time and dose response

The mean average $\pm$ SEM portal venous perfusion of the patients decreased from 104.0 ± 11.1 (mL/100 g/min) pre-RT to 73.2 ± 6.8 at 1 month after completion of RT ($P < .03$). The magnitude of the perfusion decrease depended upon local doses received in the regions and was linearly correlated to local bio-dose accumulated at the end of RT ($r = 0.95$, $P < .0001$), with each Gy producing an average 0.54 mL/100 g/min venous perfusion reduction 1 month after RT (Fig. 2). On average, the regional decrease in venous perfusion became significant after the locally accumulated bio-doses were equal to or greater than 17 Gy ($P < .05$) (Fig. 2), which is coincident with the dose threshold for hepatic tissue regeneration reported previously (15). However, in individual patients, the regional dose responses of portal venous perfusion after RT could show differences from the average response, for example, as shown in Figure 3 and discussed further below. Note that no significant changes in portal venous perfusion of the liver were observed during the course of radiation. For the 5 patients who had scans 2 months after RT, portal venous perfusion 2 months after RT recovered from the decreases 1 month after RT in the low-dose regions but not in the high-dose regions, and the changes were not significant (Fig. 2, right).

Early prediction of portal venous perfusion change

To determine whether regional portal venous perfusion changes after RT could be predicted by local bio-doses and regional baseline perfusion (prior to RT), we built a linear mixed effects model (Appendix). We found a significant dose effect on venous perfusion measured 1 month after completion of RT ($P = .0007$) but no baseline perfusion effect ($P > .19$) (Table 2). Next, we incorporated mid-course perfusion into the model. In model 2, we found significant fixed effects of both baseline and mid-course perfusion measurements on venous perfusion 1 month after completion of RT ($P = .03$ and $P < .00001$, respectively) but no fixed dose effect ($P > .1$) (Table 2), suggesting the effect of dose was accounted for in the individual response of perfusion to dose assessed during the mid-course of RT. Also, the coefficient of the second predictor (mid-course perfusion) was approximately 10 times greater than that of the first predictor (baseline perfusion), suggesting the sensitivity to dose assessed during the mid-course of treatment possibly determines the extent of reduction in perfusion post-RT.

Hypoperfusion prior to RT and reperfusion after RT

We evaluated individual patient responses to radiation as well as responses in separate liver regions, segments, or lobes of these patients treated with RT. Five of 6 patients with HCC and cirrhosis had global or regional hypovenous perfusion in the liver parenchyma pre-RT. Overall, there were 4 patients with global hypoperfusion pre-RT (3 patients with HCC and cirrhosis and 1 patient with metastases), in whom the volume-weighted means of venous perfusion were below 60 mL/100 g/min (range, 25–58 mL/100 g/min). Of the 4 patients, 3 patients (no. 5, no. 8, and no. 10) had an overall increase in venous perfusion of the liver parenchyma, except in the highest dose regions, from pre- to post-RT (Fig. 3), as the mean

venous perfusion increased to 33 to 78 mL/100 g/min). Also, the ICG clearance of patient no. 10 was improved by ~40% from pre- to post-RT (Table 1), indicating an improvement in liver function. Three patients (no. 12, no. 15, and no. 16), who had normal perfusion prior to RT, had marked hypervenuous perfusion or reperfusion observed in subvolumes that received low doses 1 month after completion of RT compared to prior to RT.

Patient no. 12 had hyperperfusion in the left lobe that received less than 20 Gy 1 month after RT (Fig. 3), and that patient's ICG scores stayed approximately the same before and after RT, suggesting compensatory left lobe function to offset the portion of the right lobe that received high doses. Similar compensatory hyperperfusion was observed in the posterior portion of the right lobe of patient no. 15 and in the lateral portion of the right lobe in patient no. 16.

Discussion

This study assessed individual and spatial changes in portal venous perfusion during and after completion of RT in patients with unresectable intrahepatic tumors using volumetric DCE MRI. We investigated the relationships between individual and spatial portal venous perfusion distribution, overall liver function assessed by ICG clearance, and locally accumulated dose. Analyses revealed that the volume-weighted mean of portal vein perfusion over the whole liver parenchyma correlated with the half-life clearance rate of ICG. Regional reductions in portal venous perfusion 1 month after RT depended upon spatial dose deposition. Indeed, regional portal venous perfusion measured during RT predicted for regional perfusion 1 month after RT, suggesting assessment of individual response to dose is critical for prediction of liver dysfunction after RT. Spatially resolved perfusion imaging could be a biomarker for regional liver function and has the potential to be an effective tool for radiation risk assessment and adaptation when used before and during radiation therapy.

A previous study showed the relationship between overall liver function assessed by ICG clearance and volume-weighted mean of CT-based portal venous perfusion over the liver parenchyma 1 month after completion of RT (9), in which the spatially distributed perfusion over the whole liver volume was estimated from 2-cm slab perfusion images by using an individual portal venous dose response function rather than direct measurement. This estimation could generate additional uncertainty in the spatial distribution of liver perfusion. Volumetric DCE MRI can overcome the challenge of limited spatial coverage by DCE CT. In this study, we verified the fact that the spatially distributed portal venous perfusion in the whole liver parenchyma derived from volumetric DCE MRI was related to overall liver function assessed by the ICG test. This relationship was robust in response to the tests performed prior to, during, and after RT for a wide range of liver functions ($t_{1/2}$ of ICG from 3.75–14.5 min), for patients with primary or metastatic cancers and for fractionated RT or SBRT. This study suggests that DCE MRI can complement the global liver function assessment provided by ICG with spatial information for rearranging the dose distribution in order to preserve functioning liver parenchyma.

In patients with poor liver function, DCE MRI can identify which lobe, segment, or portion of liver has poor perfusion or function. These regions of the liver can be marked as “expendable” if normally perfused portions can be spared by intelligent beam angle selection and/or optimization. Similarly, reperfusion and/or compensatory hyperperfusion after liver irradiation can be identified spatially by volumetric perfusion imaging. In the surgical literature, segmental portal vein embolization is described as a strategy to increase functional reserve prior to resection of another lobe (16). Sparing a lobe or segments from high-dose radiation during the first portion of planned treatment in patients who are at high

risk for liver injury could be a strategy to increase functional reserve before delivery of the last portion of treatment, and deserves further investigation.

Previous studies have identified primary tumor, cirrhosis, large tumor volume, and previous treatments as risk factors for radiation-induced liver injury. Some of these clinical factors have been considered in NTCP models in order to improve prediction of the models for clinical subgroups (11, 17). However, some risk factors (eg, previous treatments) are not easily quantitatively accounted for in NTCP models. Therefore, it is important to assess individual spatial distribution of liver function prior to radiation treatment planning and individual biological response to dose during the course of therapy, to adapt an individually tailored treatment strategy to best preserve liver function while delivering adequate tumor dose.

In this study, we investigated a group of patients who had heterogeneous pathologic diagnoses and radiation treatments. Despite the heterogeneity in the patient group, we demonstrated a strong correlation between overall liver function assessed by ICG clearance and the volume-weighted mean of MRI-derived venous perfusion in the nontumor liver volume, suggesting that this imaging technique can be applied to a broad intrahepatic cancer population with patients who are treated with different radiation techniques. MRI-based perfusion imaging can assess spatial perfusion distribution in patients who have cirrhosis and therefore have global liver dysfunction, as well as those who have previously undergone liver-directed therapies (eg, transcatheter arterial chemoembolization [TACE], radiofrequency ablation [RFA], and RT) that would compromise local liver function. The 6 patients who had previous treatments in this study had the five worst ICG scores and had complex, heterogeneous perfusion distributions pre-RT, which would require individualized treatment planning, dose prescription, and beam arrangement in order to manage their risk for liver injury. In this study, we adapted the linear quadratic model correction for local fraction size in the liver. Whether this model is adequate for large fraction size is still a subject of research. We are currently investigating the venous perfusion dose response function for a particular treatment regimen.

Conclusions

In conclusion, in this study we demonstrated that MRI-based liver perfusion imaging can be applied to patients who have a wide range of pathologies and treatment regimens. ICG tests and MRI-based perfusion imaging can provide complementary information on global and spatial liver function. Early assessment of changes in liver function could allow us to individualize radiation treatment strategies for patients at high risk for liver injury by guiding mid-course adaptation of not only total tumor dose but also distribution of dose within the rest of the liver parenchyma, with the goals of both maximizing tumor control and minimizing the risk of liver injury.

Acknowledgments

This work was supported in part by NIH/NCI grants RO1CA132834, R21CA126137, and 3 PO1CA59827.

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Appendix

A linear mixed effects model was used to determine whether regional venous perfusion 1 month after RT could be predicted by local bio-dose and regional perfusion measured prior to or during the mid-course of RT. A box-Cox power transformation analysis suggested a log transformation of the dependent variable of portal venous perfusion (F). The tested Model 1 is given by:

$$\log(F_{idj}) = \alpha + a_i + \gamma_0 F_{i0j} + \beta d_j + b_i d_j + e_{idj}$$

where F_{idj} is the perfusion 1 month after completion of RT for subject i , dose d_j , in region j . The α value is the fixed effect intercept, a_i is the random intercept, β is the fixed dose effect, b_i is the random dose effect, γ is fixed baseline (pre-RT) perfusion effect, and e_{idj} is the model error. The F_{i0j} term is the baseline perfusion in region j at (obviously) dose 0. Also,

we tested Model 2, in which portal venous perfusion measured during the mid-course of RT is added as a covariable.

Summary

Concerns about radiation-induced liver toxicity limit high-dose radiation therapy for intrahepatic cancers. Toxicity risk models based on dose-volume parameters do not account for individual patient radiosensitivity. Developing tools for assessing early response of the liver to radiation both globally and spatially may support patient-specific treatment adaptations such as identifying patients at high risk for radiation injury, as well as selecting “expendable” segments of the liver to direct higher doses to in order to spare other more functional segments.

Fig. 1.

The ICG clearance rate is significantly correlated with the volumetric mean of portal venous perfusion in the nontumor liver ($r = 0.7$, $P < .0000001$). The data included pre-, during, and post-RT.

Fig. 2.

Averaged portal venous perfusion dose response functions observed during RT and at 1 and 2 months post-RT. (Left) the whole group; (right) the 5 patients who had scans 2 months post-RT. Significant decreases in perfusion 1 month post-RT were observed in the regions where doses were greater than 17 Gy. Error bar = SEM.

Fig. 3.

Color-coded portal venous perfusion images overlaid on coregistered treatment planning CT pre-RT (left) and 1 month post-RT (middle) in patients 10 (top) and 12 (bottom). For each patient, the images pre- and post-RT are windowed identically, and color bars on the left side indicate perfusion in a unit per mL/100 g/min). Hypoperfusion pre-RT and reperfusion post-RT were observed in patient no.10, associated with improvement in overall liver function post-RT. Reperfusion in the left lobe post-RT was observed in patient no. 12. Perfusion dose response functions of the 2 patients are plotted in the panels at right. Isodose curves = 10, 20, 30, 40, 50, and 55 Gy for red, green, blue, cyan, pink, and yellow, respectively.

Table 1

Patient information

Patient	Sex/age	Pathology	Physical dose Gy/fx	T _{1/2} of ICG (min)	
				Pre-RT	1 m post-RT
1	M/55	HCC	62/31	5.5	9.25
2	M/77	Cholangio	48/24	4	5.25
3*	M/58	HCC	30/3	10.75	12.5
4	M/55	Cholangio	62/31	4.5	6.25
5*	M/54	HCC	50/5	14	14
6*	M/65	HCC	50/5	7	8
7	F/45	Colorectal mets	63/21	5.25	5.5
8	M/79	Colon mets	50/20	NA	NA
9	M/62	Anal mets	52.5/21	4	5.75
10*	M/43	HCC	64/32	10.25	6
11*	M/65	HCC	30/3	13.5	13.5
12*	M/72	Colon mets	75/25	6.5	6.75
13	F/76	Cholangio	70/35	14.5	11.5
14	M/80	Neuroendocrine mets	55/22	4.5	6.5
15	M/56	Gastric mets	60/3	NA	NA
16	M/72	HCC	50/20	5.25	7
17	M/58	Mets	82/41	3.75	NA

Abbreviations: cholangio = cholangiocarcinoma; fx = fraction; HCC = hepatocellular carcinoma; ICG = indocyanine green; mets = metastasis; NA = data not available; RT = radiation therapy.

* Patient had previous liver-directed therapy including TACE, RFA, SBRT, or resection.

Table 2

Linear mixed effects

	Coefficient	±SE	DF	t-value	P value
Model 1					
Intercept (α)	4.3241	0.1453	166	29.75	.0000**
F Pre-RT (γ_0)	0.0011	0.0009	166	1.31	.1934
Dose (β) (Gy)	-0.0093	0.0027	166	-3.46	.0007**
Model 2					
Intercept (α)	3.6583	0.0479	143	76.32	.0000**
F pre-RT (γ_0)	0.0005	0.0002	143	2.16	.03*
F mid-RT (γ_1)	0.0082	0.0003	143	31.29	.0000**
Dose (β) (Gy)	-0.0018	0.0012	143	-1.54	.13

Abbreviations: DF = degree of freedom; F = portal venous perfusion; mid-RT = during the mid-course of RT; SE = standard error; = The dependent variable is venous perfusion 1 month after completion of RT.

* $P = P < .05$.

** $P = P < .001$.