The prediction of radiation-induced liver dysfunction using a local dose and regional venous perfusion model

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We have shown that high dose conformal radiation combined with chemotherapy appears to prolong the survival of patients with unresectable intrahepatic cancers. The ability to safely deliver higher doses is primarily limited by the development of radiation-induced liver disease, characterized by venous occlusion. In this study, we investigated whether portal venous perfusion measured prior to the end of radiation therapy (RT) together with dose could predict liver venous perfusion dysfunction after treatment. Ten patients with unresectable intrahepatic cancer participated in an IRB-approved computer tomography (CT) perfusion study. Hepatic arterial and portal vein perfusion distributions were estimated by using dynamic contrast enhanced CT and the single compartmental model. Scans were obtained at four time points: prior to treatment, after 15 and 30 fractions of 1.5 Gy treatments, and one month following the completion of RT. Multivariant linear regression was used to determine covariances among the first three time point measurements plus dose for prediction of the post RT measurement. The reduction in the regional venous perfusion one month following RT was predicted by the local accumulated dose and the change in the regional venous perfusion after ~30 fractions ($F=90.6, p<0.000\,01$). Each Gy produced an approximately 1.2% of reduction in the venous perfusion. This local dose and venous perfusion model has the potential to predict individual sensitivity to radiation. This is the first step toward developing a method to deliver higher and potentially more curative radiation doses to the patients who can safely receive these higher doses. © *2007 American Association of Physicists in Medicine*.
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Key words: radiation-induced liver disease, liver neoplasms, liver perfusion, dynamic contrast enhanced imaging, radiation injury

INTRODUCTION

Approximately two thirds of patients with intrahepatic cancer present with unresectable disease. Our recent study shows that high dose conformal radiation combined with chemotherapy appears to prolong the survival of patients with unresectable intrahepatic cancers.[1] However, attempts to increase radiation dose still further have been limited by the development of radiation-induced liver disease (RILD).[2] Symptoms generally occur 2 weeks to 2 months following completion of radiation therapy (RT) and include tender hepatomegaly and weight gain secondary to ascites. Laboratory findings include elevations of alkaline phosphatase, transaminases, and bilirubin. The clinical outcome ranges from mild, reversible damage to death.[3–5] The pathology of RILD is veno-occlusive disease, which is characterized by thrombosis within the central veins of the liver producing "post" hepatic congestion.[6] The pathological changes may be present in the entire liver (rarely), a lobe, or a fraction of it.

Efforts to develop models to estimate the likelihood of developing RILD have been based primarily on the planned radiation dose distribution for the normal liver, expressed as a dose volume histogram. The ability to predict RILD is improved by including clinical factors.[4,7–12] These analyses have demonstrated that increasing mean liver dose correlates with the likelihood of developing RILD, and that the liver is reasonably well modeled as a parallel organ. This means that significant damage to a portion of the liver may not lead to RILD as long as a sufficient volume of liver remains undamaged and thus can carry out normal liver function. While these models have permitted the safe delivery of far higher doses of radiation than have previously been possible, they also suggest that there is a broad range of individual patient sensitivity that is not reflected by predictions made solely based on the physical dose distribution or general clinical features. If individual patient sensitivity could be better estimated before or during a course of treatment, it might permit higher doses of radiation to be delivered safely to the tumors of patients whose liver is relatively radiation resistant, thus

TABLE I. Patients information.

	Sex/age		DCE CT scan 1	DCE CT scan 2	DCE CT scan 3	DCE CT scan 4
1	M/51	Cholangio	Prior to RT	22.5 Gy	49.5 Gy	1 month after 78 Gy
2	M/80	mets	Prior to RT	22.5 Gy	43.5 Gy	1 month after 49.5 Gy
3	F/58	Cholangio	Prior to RT	21 Gy	43.5 Gy	1 month after 60 Gy
4	M/35	Hepato	Prior to RT	[a]	42 Gy	1 month after 48 Gy
5	F/73	Cholangio	Prior to RT	24 Gy	46.5 Gy	1 month after 76.5 Gy
6	M/72	Mets	Prior to RT	[a]	49.5 Gy	1 month after 67.5 Gy
7	F/55	Mets	Prior to RT	21 Gy	45 Gy	1 month after 72 Gy
8	M/57	Mets	Prior to RT	18 Gy	45 Gy	1 month after 67.5 Gy
9	M/74	Mets	Prior to RT	[a]	43.5 Gy	1 month after 75 Gy
10	M/74	Cholangio	Prior to RT	22.5 Gy	46.5 Gy	1 month after 54 Gy

[a]DCE CT scans were failed. The radiation doses listed in Table I correspond to what dose had been given when CT scans were performed.

improving cure rates without increasing complications. The challenge to developing such an approach is that the determination of risk would need to be made before the end of the course of treatment, while the patient is still asymptomatic.

As the basic pathophysiology of RILD is venous occlusion, we developed the hypothesis that early monitoring of venous perfusion would have the potential to select patients with preclinical signs of perfusion changes prior to the onset of symptomatic radiation-induced injury. As a first step in testing this hypothesis, we prospectively evaluated such changes in regional perfusion as a function of the dose delivered in patients treated with high dose focal radiotherapy. We hypothesized that regional perfusion dysfunction one month after the completion of RT could be predicted by the radiation dose and perfusion measured prior to the end of treatment.

MATERIALS AND METHODS

Patients

Ten patients with unresectable intrahepatic cancer (one with hepatocellular carcinoma, four with cholangiocarcinoma, and five with colorectal carcinoma metastatic to the liver) participated in an IRB-approved liver computer tomography (CT) perfusion study (Table I). All patients had signed written consent prior to enrollment. All patients were treated using three-dimensional conformal RT techniques. All patients were treated on our institution review board-approved prospective treatment protocol, which has been described in detail previously.[1] Briefly, radiation was delivered twice daily in 10–11 fractions/week, 1.5 Gy/fraction, with a minimal daily interfraction interval of 4–6 h. The median dose of radiation delivered was 67.5 Gy (range 48–78 Gy). Concurrent continuous infusion hepatic artery floxuridine was used as a radiation sensitizer for the first 4 weeks of RT.

Image acquisition

Patients were imaged, in their treatment positions, on a high-speed multidetector computed tomography (CT) system (Lightspeed, General Electric, Milwaukee, WI). To reduce breathing-related motion artifacts during scan acquisition, an active breathing control (ABC) device (Vmax, Sensormedics, Yorba Linda CA) was used to assist in briefly suspending breathing at normal expiration.[13] Axial planes within the liver were selected to encompass the entrance of the portal vein into the liver, the hepatic artery, and, if possible, a portion of the tumor within the scanning window of the CT detector array. Imaging was performed on each patient at four time points: prior to RT, after receiving approximately 15 and 30 fractions of 1.5 Gy treatment, and one month following the completion of RT. The intermediate scan times correspond to ~1.5 weeks and 3 weeks (excluding the two-week break) of treatment, at which times the tumors received cumulative doses of ~22 Gy and ~45 Gy, respectively.

Using the multidetector scanner, dynamic contrast enhanced (DCE) CT data were acquired. Briefly, after establishing a precontrast baseline scan, an extended cine series of images was obtained that lasted 120 seconds after contrast injection, using multiple breath hold intervals under the aid of an ABC system.[13] During the first 90 seconds, image volumes were acquired every second, followed by three sets of three one-second images that were 9 seconds apart (left panel of Fig. 1). This produced a series of 99 volume image data sets, each covering the entire liver in the axial plane and extending over a 2 cm slab in the cranial-caudal direction covering the regions of interest described above. As the liver position is not perfectly reproduced between breath holds, we aligned the images using an intensity-based limited degree of freedom automated alignment, which finds the optimal fit (by maximizing mutual information) within a limited range of rigid body transformations (right panel of Fig. 1).

Perfusion computation

Hepatic perfusion was estimated using a single compartmental model with dual input functions from the artery and portal vein,[14] similar to those used previously to analyze liver perfusion with dynamic positron emission tomography, CT, and MRI data.[15–18] In this model, the liver tissue, including the cells, space of Disse (extravascular space), and sinusoids, is considered to be a single compartment. The blood flows in from two sources (the hepatic artery and portal vein), travels through the sinusoids and space of Disse, and flows out to the central vein. Using pharmacokinetics, a change in the contrast concentration of liver parenchyma is given by the differential equation as

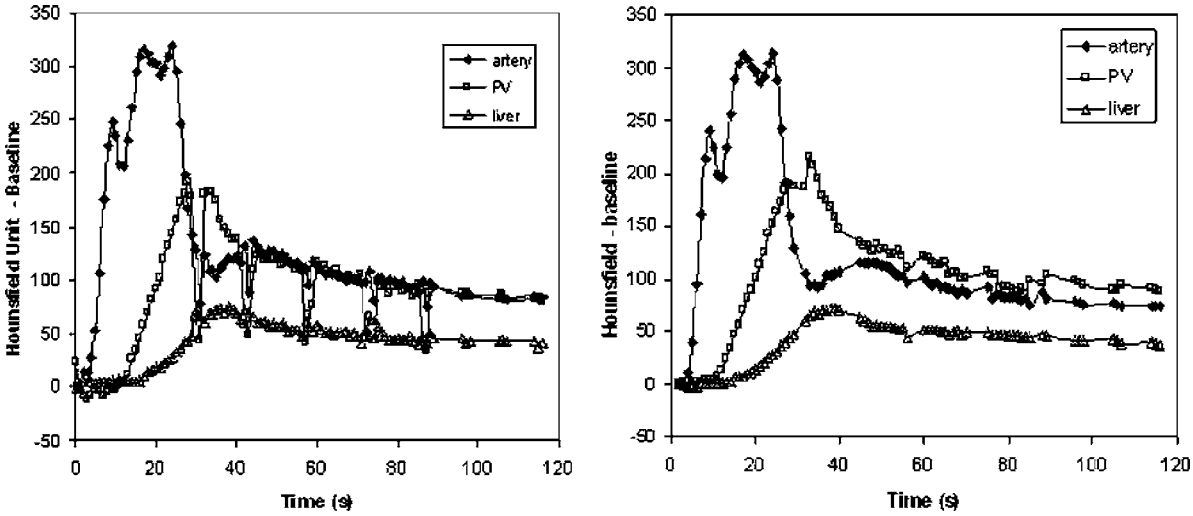

FIG. 1. Contrast concentration-time curves from artery (diamond), portal vein (square), and liver parenchyma (triangle) before (left) and after image registration (right). Time courses of signals after image registration (right) were used for fitting liver perfusion voxel-by-voxel.

$$\frac{dC_l(t)}{dt} = \frac{1}{(1-\mathrm{Hct})}[k_a C_a(t-\tau_a) + k_p C_p(t-\tau_p)] - K_2 C_l(t), \tag{1}$$

where C_l, C_a, and C_p are concentrations of the contrast agent in the respective liver parenchyma, artery, and portal vein, k_a and k_p are the transfer constants of the contrast agent from respective arterial and portal venous plasma to liver parenchyma, K_2 is the rate of the contrast agent that leaves the liver parenchyma back to the central vein, τ_a and τ_p are respective delay times of the arrival of artery bolus and portal vein bolus to the liver parenchyma, and Hct is the small vessel hematocrit. Total hepatic perfusion (F) is a sum of hepatic arterial perfusion (F_a) and portal vein perfusion (F_p) as

$$F = F_a + F_p = (k_a + k_p)/E, \tag{2}$$

where E is the extraction rate that is approximately equal to 1. In Eq. (1), hepatic arterial perfusion and portal vein perfusion are allowed to vary independently. K_2 has also been expressed as 1/MTT, where MTT is the mean transit time for the blood or the contrast agent to travel through the sinusoid and space of Disse and eventually to drain to the central vein.

Perfusion parameters (k_a, k_p, and K_2) can be obtained from mathematical fitting of the contrast concentration-time curves associated with the aorta, portal vein, and liver parenchyma. We developed a numerical approach for estimation of voxel-by-voxel liver perfusion, described in detail elsewhere,[14] which was used to estimate hepatic artery perfusion, portal vein perfusion, and the rate of blood outflow. In brief, Eq. (1) is converted to

$$(1-\mathrm{Hct})C_l(t) = k_a \int_0^t C_a(\tau-\tau_a)d\tau + k_p \int_0^t C_p(\tau-\tau_p)d\tau - (1-\mathrm{Hct})K_2 \int_0^t C_l(\tau)d\tau \tag{3}$$

by taking an integral of Eq. (1). Note that the contrast concentration of liver parenchyma is linearly related to unknown parameters of k_a, k_p, and K_2. Therefore, a linear least squared fit was used to estimate k_a, k_p, and K_2 from Eq. (3). The evaluation of this methodology is described in detail elsewhere.[14]

Changes in the portal vein perfusion (F_p) and the outflow rate (K_2) during and after RT were assessed in volumes of interest (VOIs) of normal liver parenchyma, which extended over the axial section to cover a large range of local radiation dose levels for these conformal treatments. Each of the VOIs was drawn in normal liver parenchyma that received similar doses. Also, we excluded the clinical tumor volume, large vessels, and the regions with motion artifacts from VOIs (Fig. 2). Within each of the VOIs, averaged portal vein perfusion (F_p) was calculated for each of the four perfusion imaging sessions.

Statistical analysis

A multivariate linear regression analysis was performed to determine covariances for prediction of percentage changes in the regional portal vein perfusion one month after the completion of RT vs prior to RT using SPSS (SPSS Software Products, INC, Chicago, IL). The tested variables included the local dose accumulated at the end of RT and the percentage changes in portal vein perfusion after ~1.5 weeks and ~3 weeks of treatment. The correlation between the percentage change in portal vein perfusion after ~1.5 weeks and ~3

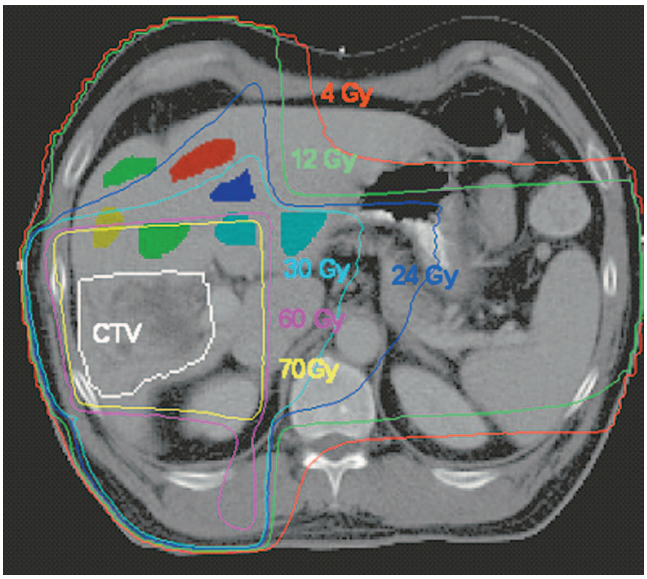

FIG. 2. Isodose curves and the clinical tumor volume (CTV) overlaid on a CT liver slice. Volumes of interest (in colors) were drawn in the regions beyond CTV and distributed over high to low doses.

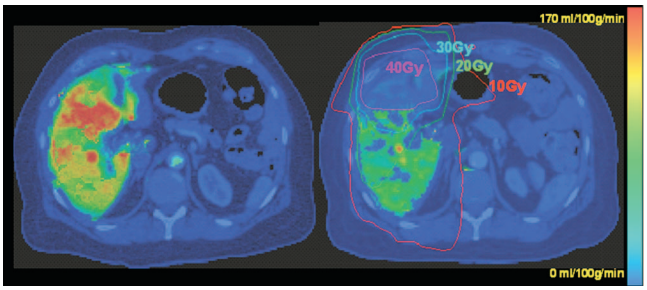

FIG. 3. Portal vein perfusion maps prior to RT (left) and after the tumor received 46.5 Gy (right) color-coded and overlaid on the liver axial CT. The reduction in venous perfusion after 30 fractions of radiation can be visualized in the color-coded venous perfusion images (right). The greater decrease in venous perfusion was associated with the higher dose received. Both images were windowed identically.

weeks of treatment with the local dose accumulated at the time of assessments was also tested. Similar analysis was applied to the blood outflow rate.

RESULTS

Perfusion prior to, during, and after radiation therapy

We begin with evaluation of portal vein perfusion changes over the course of RT and one month after the completion of treatment. Doses received within normal liver VOIs at the completion of RT varied from 11 to 78 Gy, with a median of 41 Gy, representing a wide range for evaluation of dependency of perfusion changes on the regional total dose. A total of 69 VOIs was obtained in the ten patients. The median volume of VOIs was 1.0 cc, and ranged from 0.2 cc to 6.5 cc. The number of VOIs per patient varied from five to nine, depending upon available normal liver parenchyma and the dose extension in the scanned axial planes. The mean portal vein perfusion of all VOIs had an initial value of 123.1±46.2 (mean±SD) ml/100 g/min prior to RT, and changed little after ~1.5 weeks of treatment (116.5±53.7 ml/100 g/min). However, after ~3 weeks of treatment (~45 Gy delivered to the tumor), the average portal vein perfusion decreased to 85.7±43.5 ml/100 g/min, and decreased still further to 60.3±55.8 ml/100 g/min one month after the completion of RT. These decreases in the average portal vein perfusion values after receiving ~3 weeks of treatment, and one month after the completion of RT were statistically significant ($p<0.001$ and $p<0.0005$, respectively). Figure 3 shows an example of a reduction in portal vein perfusion after the tumor received 46.5 Gy compared to prior to RT. Figure 4 shows that the relationship between portal vein perfusion and dose at the time of scanning. After ~1.5 weeks of treatment, regional portal vein perfusion was not correlated with the local dose accumulated at the time of scanning ($p>0.2$). After ~3 weeks of treatment, correlation was significant ($p<0.0001$), with an estimated slope of −1.6 ml/100 g/min per Gy. One month after the completion of RT, the slope of the linear correlation between portal vein perfusion and the accumulated dose at the end of RT became steeper at an estimated −2.5 ml/100 g/min per Gy.

Prediction of perfusion changes after radiation therapy

Our goal was to determine if regional portal vein perfusion changes one month after the completion of RT could be predicted by the dose and by perfusion measured prior to RT or during RT. First, we determined if the percentage change in the regional portal vein perfusion one month after RT compared to before treatment was predicted by the total dose accumulated locally in a region of the liver at the end of RT. We found that the percentage change in regional portal vein perfusion one month after RT was linearly related to the local accumulated liver dose at the end of RT with a coefficient of −1.4% per Gy and the intercept restricted to be zero ($R^2=0.39, p<0.0005$). Next, we wished to determine whether the change in perfusion measured after receiving approximately 3 weeks of radiation treatment (approximately thirty 1.5 Gy treatment fractions or 45 Gy to the tumor) was an independent predictor of the portal vein perfusion one month after the completion of RT. In fact, we found that both the local liver dose at the end of RT and the percentage change in regional portal vein perfusion after 45 Gy tumor dose were significant and independent predictors for the percentage change in the regional portal vein perfusion one month after completion of RT ($F=90.6$, $p<0.00001$, Table II and Fig. 5). In a linear model fit with the two independent variables, the first predictor suggests that every Gy of local total accumulated dose to the liver produced approximately a 1.2% reduction in the portal vein perfusion one month after RT; and the second predictor suggests that individual patient sensitivity that affects perfusion one month after treatment can be assessed during the course of therapy (Fig. 6). If there was no individual dependency of perfusion changes after RT upon measures during RT, the percentage changes in portal

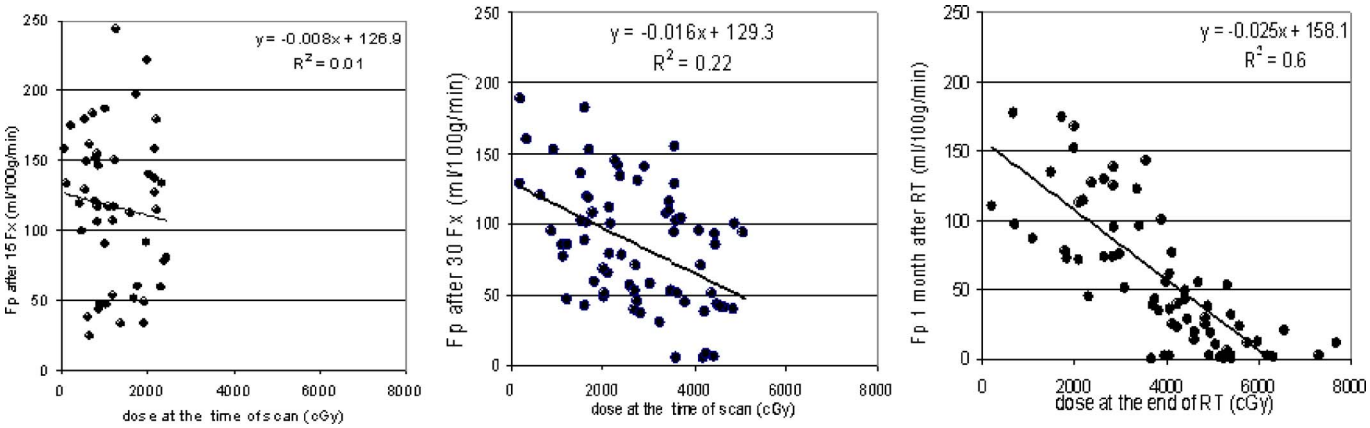

FIG. 4. Scattering plots of portal vein perfusion vs dose accumulated at the time of scanning after 15 fractions (left) and 30 fractions (middle) of 1.5 Gy treatment, and one month after the completion of RT (right). The correlation between regional portal vein perfusion and local dose accumulated at the time of scanning became significant after 30 fractions of treatment. The slope of the linear correlation was increased one month after the completion of RT, compared to after receiving 30 fractions of treatment, indicating there is a time effect.

vein perfusion one month after the completion of RT subtracted by a product of a coefficient of −0.012 and dose at the end of RT (the dose contribution) should be randomly scattered around zero. However, Fig. 6 shows that the difference was linearly correlated with the percentage change in portal vein perfusion after receiving 30 fractions of 1.5 Gy treatment, indicating the extent of the perfusion changes during RT influenced on the final extent of perfusion reduction one month after the completion of RT. Finally, we tested whether perfusion measured during the early course (~1.5 weeks) of radiation treatment could replace perfusion observed during the late course (~3 weeks) of RT for prediction of the portal vein perfusion one month following the completion of RT. We found that perfusion observed after receiving 1.5 weeks of radiation was also a predictor ($p<0.02$) (data not shown).

Prediction of perfusion change during radiation therapy

We further tested whether regional portal vein perfusion changes during RT could be predicted by accumulated dose to regions within the liver at the time of assessment. We found that regional changes in portal vein perfusion measured after delivery of approximately 15 1.5 Gy fractions (22 Gy) were not correlated with local accumulated liver doses at the time of measurement ($r=0.06$ and $p>0.5$); while after 30 fractions, the correlation between the regional changes in portal vein perfusion and local accumulated doses up to the time of measurement was significant ($r=0.24$ and $p<0.05$). The percentage changes in portal vein perfusion are positive in approximately 50% of data points after 15 fractions of radiation, and in approximately 30% of data

TABLE II. Model for prediction of reduction in portal vein perfusion (F_p) or blood out flow rate (K_2) one month after the completion of radiation therapy. $\Delta F_p\%$: the percentage change in the portal vein perfusion during or after RT compared to the perfusion before RT; 1 mon: one month after RT; 3 wk: after received 3 weeks of radiation treatment during which 30 fractions of 1.5 Gy were received; $\Delta K_2\%$: the percentage change in the blood outflow rate ($K_2=1/\mathrm{MTT}$) during or after RT compared to the perfusion before RT; MTT: mean transit time; B: coefficient; SE: standard error; *t*: *t* value.

	$\Delta F_p\%(1\text{ mon})=\mathrm{B1}*\text{dose(end of RT)}+\mathrm{B2}*\Delta F_p\%(3\text{ wk})$			
	$F=90.6$, $p<0.000\,01$			
	Coefficients			
Model	B	SE	*t*	*p*
dose (end of RT)	−0.012	0.0012	−10.10	<0.0001
$\Delta F_p\%$(3 wk)	0.26	0.0997	2.60	0.01
Model	$\Delta K_2\%(1\text{ mon})=\mathrm{B1}*\text{dose(end of RT)}+\mathrm{B2}*\Delta K_2\%(3\text{ wk})$			
	$F=89.9$, $p<0.000\,01$			
	Coefficients			
	B	SE	*t*	*p*
dose (end of RT)	−0.012	0.0011	−10.46	<0.0001
$\Delta K_2\%$(3 wk)	0.35	0.0978	3.58	0.0006

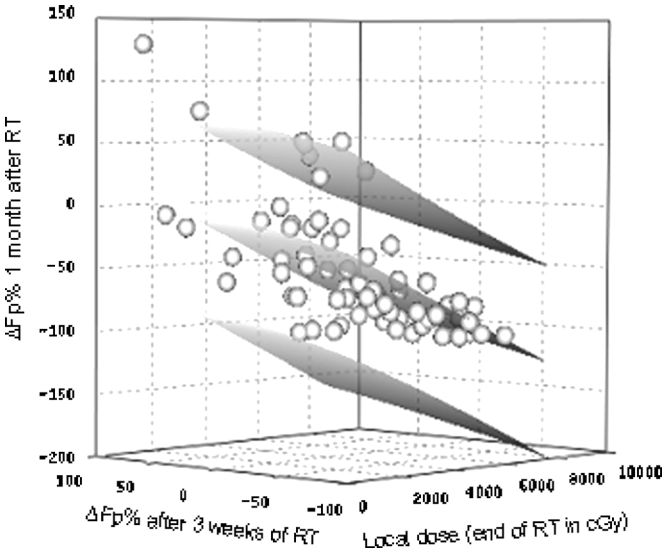

FIG. 5. A three-dimensional plot of the percentage change in the regional portal vein perfusion one month after the completion of radiation therapy vs the local accumulated liver dose at the end of radiation therapy and the percentage change in portal vein perfusion after received 3 weeks of radiation treatment (~30 fractions of 1.5 Gy treatment). The central plane represents the multivariant linear regression fit, and the two outer planes depict the 95% confidence interval.

points after 30 fractions. When inspecting individual patients' perfusion data, it was found that in 4 of 7 patients in whom perfusion after 15 1.5 Gy fractions was available, portal vein perfusion increased. These early increases in portal vein perfusion transitioned to decreases after 30 fractions, suggesting that it takes a certain amount of time for radiation injury to occur in hepatic vasculature.

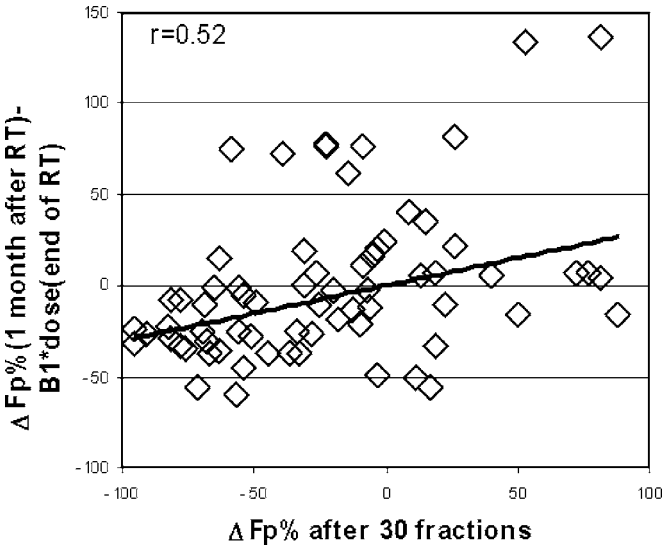

FIG. 6. A scattering plot of the percentage changes in portal vein perfusion one month after the completion of radiation therapy subtracted by a product of B1 (–0.012) and dose at the end of RT vs the percentage change in portal vein perfusion after received 30 fractions of 1.5 Gy treatment. If there was no individual variation in the radiation-induced venous perfusion reduction, the data points should be scattered around the origin.

Individual variations in perfusion changes after radiation therapy

The extent of the portal vein perfusion changes in response to radiation could depend upon individuals as indicated by the observation that both regional liver doses at the end of RT and changes in portal vein perfusion after receiving 3 weeks of radiation predicted the regional perfusion changes one month after the completion of treatment. Two examples (two extreme cases) are shown in Fig. 7. In one patient (left panel of Fig. 7) the percentage reduction in portal vein perfusion one month after RT was found to be approximately 1.6% per Gy with a near zero intercept of the fitted line, suggesting a relationship between dose and decrease in venous perfusion. In another case (right panel of Fig. 7), the percentage decrease in the venous perfusion was approximately 3.4% per Gy while the intercept of the fitted line with the axis representing the regional dose was ~35 Gy, suggesting there were other factors that influenced the venous perfusion response to radiation, possibly including a floor effect of dose and time delay effect. In two of the nine patients, a large positive intercept of the best fit line was observed.

Prediction of MTT changes after radiation therapy

In parallel to the tests performed for the portal vein perfusion, we determined whether changes in the MTT one month after radiation could be predicted by the total accumulated dose in a region of the liver and by the MTT observed before or during RT. In particular, we tested the percentage change in 1/MTT (the rate of blood outflow or drain to central vein) one month after RT vs before treatment. Similar to the findings in portal vein perfusion, the percentage changes in the regional 1/MTT one month after RT was linearly predicted by the regional dose accumulated at the end of RT and the percentage changes in the 1/MTT after ~3 weeks of radiation treatment (~45 Gy to the tumor) ($F=89.9, p<0.00001$, Table II).

Prediction of MTT changes during radiation therapy

We further tested whether regional changes in 1/MTT during RT could be predicted by accumulated dose alone at the time of assessment. We found that regional percentage changes in 1/MTT measured after the tumor received 22 Gy were not correlated with locally accumulated liver doses received at the time of measurement ($r=0.05, p>0.5$), but the correlation was significant after 45 Gy ($r=0.32$ and $p<0.01$).

DISCUSSION

In this study, we found that the extent of the regional reduction in the hepatic venous perfusion one month after RT depended upon both the local accumulated dose at the end of RT and the relative decrease in perfusion measured after delivery of approximately 30 fractions of 1.5 Gy radiation at which point the tumors had received 45 Gy. As an average over ten patients, every Gy of total dose delivered to liver

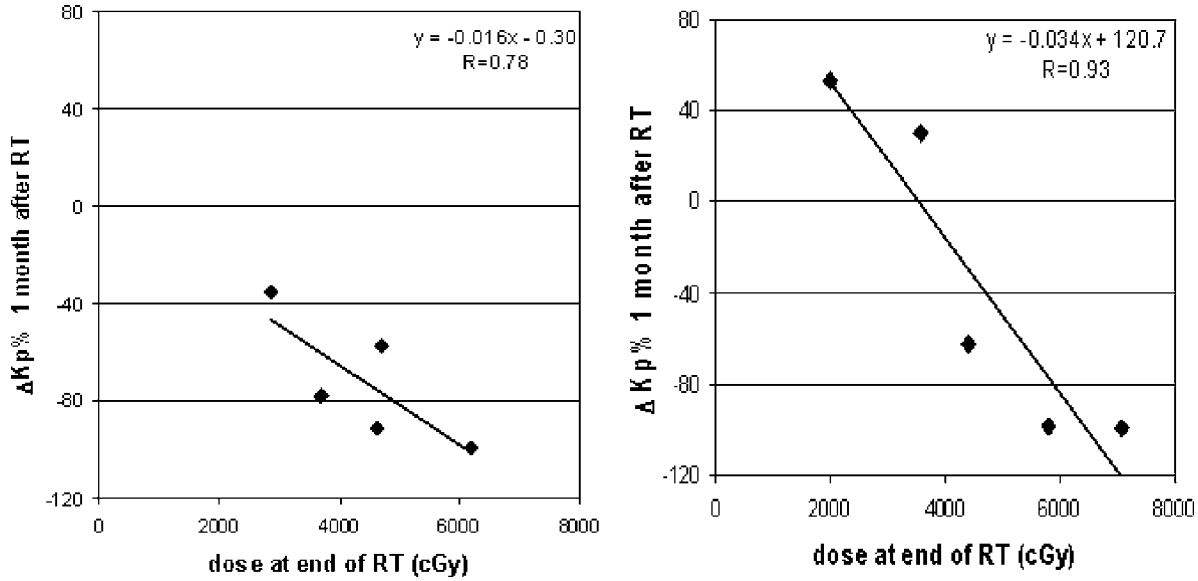

FIG. 7. Scattering plots of the percentage changes in the regional portal vein perfusion one month after radiation therapy vs the local dose accumulated for the corresponding volumes of interest at the end of RT in two individual patients.

parenchyma over the whole course of treatment causes approximately a 1% reduction in the venous perfusion one month after completion of treatment. Furthermore, prediction of the venous perfusion reduction for the group of the patients is improved by including the second predictor of the venous perfusion measured after delivery of ~45 Gy to the tumor. The second predictor indicates that the extent of the reduction in venous perfusion after RT varies from one percent per Gy in individuals as shown in Figs. 5 and 6. The venous perfusion measured after delivery of ~22 Gy to tumor might also be a predictor for the changes in venous perfusion after RT. Furthermore, our analysis of the mean transit time, which is derived independently from the DCE data using a single compartmental model, supports the findings regarding portal vein perfusion. This ability to predict decreased perfusion one month after treatment by perfusion measurements made during treatment is an important step toward the ability to predict, and therefore avoid, RILD that occurs after the completion of treatment.

Although liver changes following irradiation in cases with or without RILD have been assessed previously by CT and MRI,[19–25] we believe this is the first quantitative report studying the relationship between local radiation dose and regional reduction in venous perfusion. Our preliminary data suggest that a planned local liver dose and regional midtreatment course hepatic venous perfusion model could be able to determine individual liver tolerance to radiation during treatment, thereby permitting individualization of the therapy strategy. Our preliminary data enable a possible new paradigm for studying and avoiding radiation toxicity in the liver. We note that previous studies in other institutes have reported dose effects on regional lung perfusion and ventilation after irradiation.[26–34] Some of the later studies attempted to predict the degree of radiation-induced decline in pulmonary function after irradiation by using dose-response curves and dose-volume histograms.[34] The general concepts described by these studies could be applied to other parallel organs such as liver. Here we expended the methodology for indication of whether liver function after irradiation might be better predicted by assessments of function prior to the end of radiation therapy.

In the past, efforts to develop models to estimate the likelihood of developing RILD have been based primarily on the planned radiation dose distribution for the normal liver, expressed as a dose volume histogram.[4,7–12] These models currently provide guidance for dose prescription and safe delivery of doses to the liver. However, individual patient sensitivity to radiation is not reflected by predictions made solely based on the physical dose distribution and the patient population data. Many studies have attempted to identify clinical and patient-specific factors, and biological and genetic markers for prediction of individual sensitivity to radiation. One of our own analyses of incidences of RILD using a normal tissue complication probability (NTCP) model reveals that the susceptibility to RILD is different between patients who have metastases and primary liver tumors.[9] This finding has been used to further customize in-house models for dose prescription based on a predicted 10–15% NTCP. In another study, a multivariate analysis identified infection with hepatitis B virus, as well as presence of Child-Pugh B cirrhosis as factors that increased the incidence of RILD in patients treated with three-dimensional conformal radiotherapy for hepatocellular carcinoma.[35,36] These clinical factors provide information on preexisting conditions that influence tolerance of subgroups of patients to radiation. However, individual tolerance to radiation may be influenced beyond these factors that have been identified, and is likely to be both genetic and environmental. Although the identification of the genetic basis of RILD is of fundamental interest, this approach faces substantial challenges due to the fact

that the radiation response depends on the expression of multiple genes. Therefore, we have attempted to develop an approach that utilizes anatomically resolved perfusion before and during RT, and combines it with the radiation treatment plan to predict the radiation toxicity in the liver.

This study has some limitations. Most importantly, we estimated hepatic perfusion in a single slab (2 cm) of liver using DCE CT. This limited spatial coverage of the liver restricts us in relating what we found in the single slab to the whole liver. Thus, additional work will be required to establish the relationship between decreases in hepatic perfusion as measured in this study and both overall liver function and RILD. In order to carry out such analyses, we will need to develop a model of applying the changes in perfusion measured in the 2 cm slab to the remainder of the liver, presumably by using the full liver three-dimensional dose distribution. This limitation can be overcome by using volumetric DCE MRI with the parallel imaging technology that can improve the imaging speed by several factors. In addition, given that we could sample only a limited number of time points, it is difficult to fully analyze potentially important factors such as the role of fraction size and the time after received the dose. We did attempt to apply an α/β ratio of 2.5 to correct the fraction size effect,[37] which did not lead to an improvement in the correlation between the local dose and the regional venous perfusion change measured during treatment (data not shown). When inspecting individual patients' perfusion data we observed that, in 4 of 7 patients data in whom perfusion after approximately 1.5 weeks of radiation treatment were available, the venous perfusion increased. Thereafter, the venous perfusion started decreasing but the rate and the extent of the decreases varied greatly with individuals. Finally, one month after the completion of RT the direction and the extent of the venous perfusion changes became more predictable than during treatment. These observations suggest that in addition to individual sensitivity to dose there are great individual variations in the time to respond to radiation. Additional patients will need to be accrued to better quantify these relationships.

CONCLUSION

In this study, we demonstrated a possible new strategy to investigate radiation toxicity in the liver. Our preliminary data show that the reduction in regional hepatic venous perfusion after RT is predictable by the local accumulated liver dose and venous perfusion measured prior to end of RT. This local hepatic-perfusion injury model has the potential to predict symptomatic radiation damage to the liver.

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