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Research Letter

Evaluation of Pretreatment Magnetic Resonance Elastography for the Prediction of Radiation-Induced Liver Disease

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Abstract

Purpose: Magnetic resonance (MR) elastography (E) is a noninvasive technique for quantifying liver stiffness (LS) for fibrosis. This study evaluates whether LS is associated with risk of developing radiation-induced liver disease (RILD) in patients receiving liver-directed radiation therapy (RT).

Methods and Materials: Based on prior studies, LS ≤3 kPa was considered normal and LS >3.0 kPa as representing fibrosis. RILD was defined as an increase in Child-Pugh (CP) score of ≥2 from baseline within 1 year of RT. Univariate and multivariate Cox models were used to assess correlation.

Results: One hundred two patients, 51 with primary liver tumors and 51 with liver metastases, were identified with sufficient follow-up. In univariate models, pre-RT LS >3.0 kPa (hazard ratio [HR] 4.9; 95% confidence interval [CI], 1.6-14; P = .004), body mass index (BMI), clinical cirrhosis, CP score, albumin-bilirubin (ALBI) grade 2, primary liver tumor, and mean liver dose were significantly associated with risk of post-RT RILD. In a multivariate analysis, LS >3.0 and mean liver dose both were significantly associated with RILD risk.

Conclusions: Elevated pre-RT LS is associated with an increased risk of RILD in patients receiving liver-directed RT.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Introduction

Before the development of advanced radiation delivery techniques, the risk of classic radiation-induced liver disease (RILD) limited the use of radiation therapy (RT) for the management of liver cancers.[1,2] Risk of developing classic RILD is 5% to 35% when the entire liver is irradiated to 30 to 35 Gy; however, ablative doses are often necessary to achieve local tumor control.[3,4] In the current era with image guided and ablative RT techniques, nonclassic RILD, which is more closely aligned with acute hepatic decompensation, remains a concern, has been typically evaluated by change in Child-Pugh (CP) score, and occurs in 3.6% to 31% of patients receiving either ablative or hypofractionated RT.[4-8] Predictive criteria for RILD are not well established.[9,10]

MRE is a noninvasive technique for staging liver fibrosis with excellent reproducibility.[11,12] In patients with chronic liver disease, elevated LS on MRE is associated with increased risk of hepatic decompensation, development of liver cancer, and death.[13] A recent pilot study of 17 patients treated with stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma (HCC) found pretreatment LS to be significantly higher in patients who developed RILD.[10] We sought to further evaluate the role of MRE in predicting the risk of RILD in a larger population of patients receiving SBRT and hypofractionated RT for primary liver cancer and liver metastasis.

Methods and Materials

Study population

With institutional review board approval, we retrospectively analyzed a population of patients who received liver-directed RT at our institution between January 2010 and June 2018. Inclusion criteria were age ≥18 years, receipt of RT (≥30 Gy), MRE examination within 6 months before RT, and post-RT laboratory studies.

CP score and albumin-bilirubin (ALBI) score were calculated.[14] The primary end point was cumulative incidence of RILD. RILD was defined as an increase in CP score ≥2 from baseline within 12 months of RT.[1] For patients with liver metastasis without clinical diagnosis of cirrhosis, a baseline CP score of A5 was assigned (n = 18). RT parameters including treatment modality (protons or photons), dose and fractionation, gross tumor volume (GTV), total liver volume (liver-GTV), and tumor-to-liver ratio were recorded. For all patients, normal liver dose constraints for either TG101[15], NRG-GI003 (NCT03186898), or NCT00976898[6] were met. For calculation of equivalent dose in 2 Gy fractions (EQD2), an α/β, 10 for tumor dose was used and an α/β, 3 for mean liver dose was used.

Liver MRE

The majority of liver MREs were completed on a departmental Discovery 750-Watt MR imaging device (GE Healthcare, Chicago, IL) as a treatment position MR imaging for radiation planning. The liver MRE technique has been well described.[16] Four axial slices were obtained through the largest cross-section of the liver. Mean liver parenchyma stiffness was calculated by averaging across manually drawn regions of interest, including only liver parenchyma, and measured by the reading radiologist. Based on previous studies, LS ≤3 kPa was considered normal and LS >3 kPa was consistent with the presence of fibrosis.[16] Pre-RT liver MRE results for 2 patients are shown in Figure 1.

Statistical analysis

Analyses were conducted using SAS® version 9.4 (SAS Institute, Cary, NC). The cumulative incidence of RILD was estimated considering death and liver transplantation as competing risks. The Cox model was used to assess association of baseline variables with risk of RILD.

Results

We identified 103 patients, and 102 patients had post-treatment follow-up—51 with primary liver tumors and

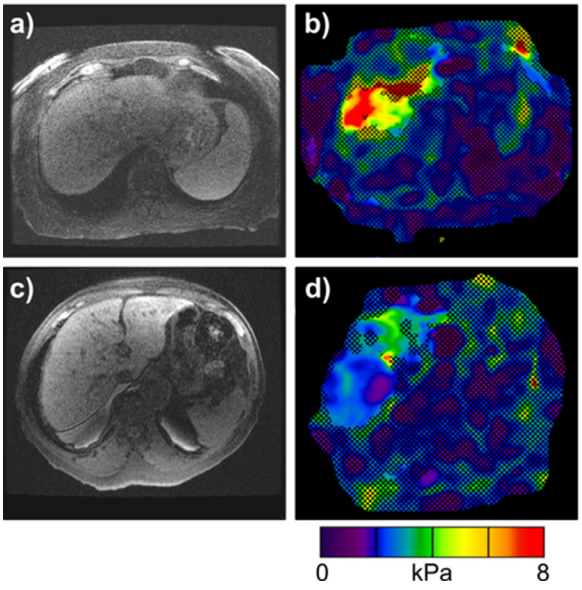

Figure 1 (A and B) Patient with hepatocellular carcinoma (HCC), Child-Pugh score A, and baseline LS 6.5 kPa who developed RILD. (C and D) Patient with HCC, Child-Pugh score A, and baseline LS 2.8 kPa who did not develop RILD. (A and C) MR liver imaging with volume acceleration (LAVA) from corresponding anatomical location of MRE stiffness images (B and D). *Abbreviations:* RILD = radiation-induced liver disease.

Table 1 Pre−radiation therapy characteristics

Variable	N or Mean (Range)
Age (years)	65 (30, 87)
Sex	
Male	62
Female	40
BMI (kg/m^2)	28.3 (15.3, 47.2)
Primary liver cancer	51
HCC	42
IHC	6
GBC	2
EHC	1
Metastatic lesion origin	51
Colorectal	16
Melanoma	11
Noncolorectal GI	9
Hematological	2
Genitourinary	4
Gynecologic	3
Breast	2
Other*	4
Cirrhosis etiology	
HCV	12
HBV	2
Alcohol	10
NASH	9
Other†	7
Child-Pugh Class‡	
A	28
B	11
C	1
Unknown	11
ALBI grade	
1	49
2	31
3	4
Unknown	18
RT parameters	
GTV (cm^3)	144.5 (0.7, 3035)
Liver-GTV (cm^3)	1574 (811, 3079)
Tumor-to-liver ratio (%)	5.75 (0.03, 71.6)
Total fractions <10/≥10	79/23
Photon/proton	76/26
Total dose (Gy)	55.8 (30, 70)
Total dose EGD2 (Gy)	92.4 (40, 150)
Mean liver dose (Gy)	11.5 (1.71, 25.1)
Mean liver EQD2 (Gy)	11.3 (1.10, 28.9)
Post-RT systemic therapy	20
Liver stiffness (kPa)	
≤3.0 kPa / > 3.0 kPa	43/59

Abbreviations: BMI = body mass index; EHC = extrahepatic cholangiocarcinoma; EQD2 = equivalent dose in 2 Gy fractions; GBC = gall bladder carcinoma; GTV = gross tumor volume; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IHC = intrahepatic cholangiocarcinoma; NASH = nonalcoholic steatohepatitis; RT = radiation therapy.

* Other metastatic lesions include adrenocortical carcinoma, thymoma, oropharynx cancer, and salivary duct cancer.

† Other etiologies include autoimmune hepatitis, alpha-1- antitrypsin, hemochromatosis, and cryptogenic cirrhosis.

‡ For patients with cirrhosis.

51 with liver metastasis. The most common primary liver tumor was HCC (n = 42/51, 82%), and the most common origin of metastasis was colorectal (16/51, 30%). Table 1 describes the pre-RT characteristics. Mean pre-RT LS was 3.9 kPa (range 1.8, 8.7). Variables associated with increased baseline LS >3.0 were primary versus metastatic tumors (4.9 kPa vs 3.0 kPa, $P < .0001$), CP score (A vs B/C, 3.9 kPa vs 5.2 kPa, $P = .002$), ALBI score (per 1 point, $P = .01$), and clinical cirrhosis (yes vs no, 5.2 kPa vs 3.1 kPa, $P < .0001$).

Twenty-three patients developed RILD (23/102, 23%) at a median of 4 months post-RT. Seven patients died within 1 year of treatment without RILD. Two patients underwent liver transplantation, 1 of whom had developed RILD before liver transplantation. Mean pre-RT LS was 4.9 kPa versus 3.6 kPa for those who did versus did not develop RILD ($P < .001$). For the entire cohort, the cumulative incidence of RILD at 6 months and 12 months post-RT was 26% (95% CI, 18-38) and 29% (95% CI, 21-42), respectively. The cumulative incidence of RILD at 6 and 12 months for pre-RT LS ≤3.0 kPa was 12% (95% CI, 4.9-31) and 12% (95% CI, 4.9-31) and for pre-RT LS >3.0 kPa was 36% (95% CI, 24-43) and 41% (95% CI, 29-59), respectively (Fig 2).

Univariate Cox models identified several pre-RT variables associated with development of RILD (Table 2). Pre-RT LS >3.0 kPa was associated with an increased risk of post-RT RILD (HR 4.9; 95% CI 1.6-14.3; $P = .004$) in overall analysis (Fig 2). Analysis was performed in patient subgroups of primary tumor versus metastasis and clinical diagnosis of cirrhosis (yes vs no) (Table 3). In these subgroups, the rate of RILD was higher for patients with LS >3 kPa (HR 2.4-2.9), although these associations were not statistically significant (all $P > 0.05$).

Because there were only 23 RILD events, an initial multivariable model included 3 clinically relevant variables that were significantly associated with RILD in the univariable model: CP score (A vs B/C), dichotomized

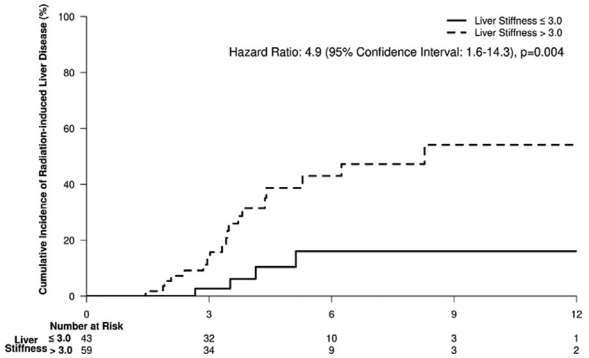

Figure 2 Cumulative incidence of radiation-induced liver disease in patients stratified by baseline liver stiffness. LS ≤ 3.0 kPa or LS > 3.0 kPa (hazard ratio 4.9; 95% confidence interval, 1.6-14.3; $P = .004$). *Abbreviations*: LS = liver stiffness.

Table 2 Univariate models for survival-free RILD after RT

Variable	No RILD (n = 79)	RILD (n = 23)	Hazard Ratio	95% CI	*P* value
Age (>65 years)	65.0 (30-87)	64.3 (42-87)	0.6	0.23-1.33	0.19
Sex Male/Female			0.9	0.37-1.93	0.69
Male	48	13			
Female	31	9			
BMI (kg/m^2)	27.6 (15.3-47.2)	30.5 (18.6-42.9)			
Per 1 point			1.1	1.001-1.54	0.047
BMI < 25			1.0 (ref)		0.11
25 ≤ BMI < 30			1.4	0.37-5.14	0.63
30 ≤ BMI < 35			3.4	1.07-10.9	0.04
BMI ≥ 35			3.1	0.79-12.6	0.11
Liver Function					
Normal	55	7	1.0 (ref)		
Clinical cirrhosis	24	16	5.0	2.03-12.2	<0.001
Child-Pugh Score*					
Per 1 point			1.5	1.06-2.04	0.02
Child-Pugh A	51	16	1.0 (ref)		
Child-Pugh B/C	10	7	2.0	0.81-4.76	0.14
ALBI grade					
Per 1 point			2.1	1.16-3.78	0.01
ALBI grade 1	44	2	1.0 (ref)		0.01
ALBI grade 2	16	14	4.6	1.66-13.0	0.003
ALBI grade 3	2	2	2.9	0.56-15.1	0.20
Liver tumor characteristics					
Metastasis	47	4	1.0 (ref)		
Primary	32	19	5.1	1.73-15.0	0.003
Gross tumor volume (cm^3) per 100 cm^3	152 (0.7-3034)	119 (4.4-928)	0.97	0.85-1.10	0.60
Liver-GTV (cm^3) per 100 cm^3	1555 (865-3079)	1640 (811-2747)	1.4	0.61-3.24	0.42
Tumor-to-liver ratio >0.02	0.06 (0.0003-0.72)	0.06 (0.003-0.33)	2.4	0.93-5.97	0.07
Parameters of RT					
Total number of fractions, ≤5	64	16	1.0 (ref)		
Total number of fractions, >10	15	7	1.5	0.61-3.67	0.37
Photon-based RT	59	17	1.0 (ref)		
Proton-based RT	20	6	0.9	0.36-2.30	0.83
Total dose (Gy), per 10 Gy	55.5 (45-67.5)	56.7 (30-70)	1.3	0.67-2.35	0.48
Mean liver dose (Gy), per 1 Gy	10.2 (1.7-23.4)	13.4 (3.4-22.8)	1.1	1.001-1.2	0.047
Mean liver dose (Gy) EQD2, per 1 Gy	10.4 (1.2-27.4)	13.7 (2.5-28.9)	1.9	0.999-3.61	0.05
Post-RT systemic therapy	18	2	2.4	0.57-10.4	0.23
Liver stiffness (kPa)	3.6 (1.8-8.7)	4.9 (2.1-8.6)			
Per 1 kPa			1.3	1.07-1.56	0.009
> 3.0 kPa			4.9	1.64-14.3	0.004

Results expressed as mean (range).

Abbreviations: ALBI = albumin-bilirubin; BMI = body mass index; CI = confidence interval; EQD2 = equivalent dose in 2 Gy fractions; RILD = radiation induced liver disease; RT = radiation therapy.

* For patients with metastasis and no signs of cirrhosis, a CP score of A5 was assigned.

pre-RT LS (≤3.0 vs >3.0), and continuous mean liver dose. This model included 84 patients (18 had missing CP scores); LS >3.0 (P = .041) and mean liver dose (P = .046) were associated with RILD, while CP score was not (P = .38). The final model included all 102 patients, and both variables were significantly associated with RILD risk, LS >3.0 (HR 5.0; CI, 1.7-14.8; P = .004) and mean liver dose (HR 1.08 per 1 Gy; CI, 1.01-1.2; P = .04) with concordance score 0.75.

Discussion

In this cohort of patients who received liver-directed RT, elevated pre-RT LS measured by MRE was associated with an increased risk of developing RILD. In the context of a known hepatic malignancy or metastasis, increased LS likely demonstrates a liver compromised by fibrosis with reduced hepatic reserve. Our results are

Table 3 Impact of elevated liver stiffness for RILD following liver RT in overall cohort and subgroups

Group	N (No RILD/RILD)	Hazard Ratio	95% CI	*P* value
Overall Cohort	102 (79/23)			
LS ≤ 3.0		1.0 (ref)		
LS > 3.0		4.9	1.64-14.3	0.004
Primary tumor	51 (32/19)			
LS ≤ 3.0		1.0 (ref)		
LS > 3.0		2.9	0.67-12.7	0.15
Liver metastasis	51 (47/4)			
LS ≤ 3.0		1.0 (ref)		
LS > 3.0		2.7	0.37-19.3	0.33
Clinical cirrhosis	40 (24/16)			
LS ≤ 3.0		1.0 (ref)		
LS > 3.0		2.4	0.3-18.0	0.41
No clinical cirrhosis	62 (55/7)			
LS ≤ 3.0		1.0 (ref)		
LS > 3.0		2.5	0.6-11.4	0.23

Abbreviations: CI = confidence interval; LS = liver stiffness; RILD = radiation induced liver disease.

consistent with those of Ichikawa et al, who found that elevated pre-RT LS was associated with a higher risk of RILD in a cohort of 17 patients with HCC undergoing SBRT.[10] Our study expands on this report with a larger cohort of patients with primary liver tumors, patients with liver metastasis, and those treated with hypofractionated RT techniques, and the inclusion of both photon-based and proton-based regimens.

Our evaluation supports multiple clinical and dosimetry factors that have previously been associated with an increased risk of developing RILD. These include pretreatment BMI, CP score, ALBI grade 2, primary liver tumor, and normal liver dose constraints.[9,10] Additionally, we found that RT prescription dose, fractionation schedule, and RT modality (proton vs photon) were not associated with the development of RILD. An exploratory analysis in subgroups of patients with primary liver tumor vs metastasis and clinical diagnosis of cirrhosis (yes vs no) suggested higher rates of RILD in patients with elevated LS in all subgroups. However, associations were not statistically significant, perhaps due to small numbers of events and patients.

MRE is an attractive technique for assessing risk of RILD because it is noninvasive, reproducible, objective, and convenient for patients who require an MR evaluation for assessment and/or RT planning.[11,12] Other novel imaging techniques are being explored for pretreatment assessment of patients with liver tumors and/or metastasis, including sulfur colloid single photon emission computed tomography, indocyanine green clearance on MR, and Eovist® (Bayer, Whippany, NJ) enhancement on MR.[17-19] One significant development is the use of ALBI grade instead of CP score for prediction of RILD and overall survival. Compared with CP score, which requires subjective assessment of encephalopathy and ascites and is impacted by the use of warfarin, ALBI grade relies on only objective measures and has been shown to be more predictive of overall survival and RILD than CP score.[20,21]

Limitations of the study include the retrospective nature of data collection and analysis and a heterogeneous cohort in terms of patient and treatment characteristics. For measurement of RILD, we applied change in CP score to noncirrhotic patients as has been done in other series,[5,6] although this has not been rigorously evaluated. Moreover, we considered change in ALBI score for a measure of liver dysfunction as well; however, only 43 patients had sufficient information, limiting analysis and utility. Finally, the overall sample size and number of RILD events limits our multivariate model in determining the most significant independent factors associated with development of RILD.

Conclusion

Elevated pre-RT LS measured by MRE was associated with an increased risk of RILD as measured by change in CP score in patients receiving SBRT and hypofractionated RT for primary liver tumors and liver metastasis. Further work is needed to validate whether MRE has independent predictive ability for RILD, incorporating other known risk factors.

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