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Estimating Functional Liver Reserve Following Hepatic Irradiation: Adaptive Normal Tissue Response Models

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Abstract

Purpose—To estimate the limit of functional liver reserve for safe application of hepatic irradiation using changes in indocyanine green, an established assay of liver function.

Materials and Methods—From 2005–2011, 60 patients undergoing hepatic irradiation were enrolled in a prospective study assessing the plasma retention fraction of indocyanine green at 15-min (ICG-R15) prior to, during (at 60% of planned dose), and after radiotherapy (RT). The limit of functional liver reserve was estimated from the damage fraction of functional liver (DFL) post-RT $[1 - (\text{ICG-R15}_{\text{pre-RT}} / \text{ICG-R15}_{\text{post-RT}})]$ where no toxicity was observed using a beta distribution function.

Results—Of 48 evaluable patients, 3 (6%) developed RILD, all within 2.5 months of completing RT. The mean ICG-R15 for non-RILD patients pre-RT, during-RT and 1-month post-RT was 20.3%(SE 2.6), 22.0%(3.0), and 27.5%(2.8), and for RILD patients was 6.3%(4.3), 10.8%(2.7), and 47.6%(8.8). RILD was observed at post-RT damage fractions of 78%. Both DFL assessed by during-RT ICG and MLD predicted for DFL post-RT ($p < 0.0001$). Limiting the post-RT DFL to 50%, predicted a 99% probability of a true complication rate $< 15\%$.

Conclusion—The DFL as assessed by changes in ICG during treatment serves as an early indicator of a patient's tolerance to hepatic irradiation.

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Keywords

liver; radiotherapy; indocyanine green; adaptive radiotherapy

INTRODUCTION

Historically, radiotherapy for intrahepatic malignancies has been limited by radiation-induced liver disease (RILD) [1], a clinical constellation that involves anicteric hepatomegaly and ascites and typically occurs within a few months of treatment completion. Although most cases are transient, RILD can be a catastrophic complication leading to irreversible liver failure and death [1, 2].

Recent advances in treatment techniques along with the development of quantitative dosimetric risk assessment models, such as normal tissue complication probability (NTCP) models, have permitted the delivery of higher doses of focal liver irradiation with a low risk of complications [3–9]. There are limitations, however, to current modeling approaches. First, in clinical scenarios where there are few serious adverse events, challenges can arise in fitting the complication probability to the observed complication frequency resulting in notable uncertainties of the complication estimates at critical thresholds (e.g., 10–15%). To overcome this, large numbers of non-event cases can be utilized to model the safe limit of treatment. Secondly, dosimetric models assume the volume of liver is a surrogate for liver function and do not reflect individual patient sensitivity to radiation, which is a crucial factor in determining the individual risk for toxicity. For instance, patients with pre-existing liver disease, such as cirrhosis, or patients who have undergone prior liver-directed treatment are at increased risk for toxicity with high-dose radiotherapy [4, 7, 10]. Thus, individual assessment of liver function in response to radiation during the course of treatment should facilitate individualized adaptive radiation dosing by improving the uncertainty associated with current dosimetric models. Herein we describe a normal tissue response model, using quantitative changes in liver function during the course of radiotherapy along with dosimetric parameters, to estimate the conservative limit of functional liver reserve (i.e. the safe threshold of preserved organ function to prevent a complication).

MATERIALS AND METHODS

Patients

From January 2005 to December 2011, 60 patients undergoing fractionated hepatic irradiation for unresectable intrahepatic tumors (primary or metastatic) were enrolled in this prospective study. Written informed consent was obtained from all patients in accordance with the procedures of the Institutional Review Board of the University of Michigan. Patients were required to have an estimated life expectancy of ≥ 12 weeks, Zubrod performance status of 0 to 2, and adequate hepatic function (INR ≤ 1.3 or correctable by vitamin K, total bilirubin <3 mg/dl in the absence of obstruction). Forty-eight patients were evaluable with pretreatment and during and/or post-treatment measurements of liver function.

Assessment of liver function: indocyanine green

Unlike commonly used static laboratory tests, such as bilirubin and albumin, which provide only indirect measures of hepatic function, the plasma clearance of indocyanine green (ICG), an inert water-soluble compound, provides a direct measure of the functional state of the liver [11–14]. Following intravenous administration, ICG is rapidly bound to plasma protein and is selectively taken up by hepatic parenchymal cells and secreted unchanged into the bile. Because it undergoes no significant extrahepatic or enterohepatic circulation, the plasma clearance rate of ICG serves as a reliable index of dynamic liver function. ICG has been reported to be an early indicator of hepatic dysfunction [11] and has been used preoperatively to plan the extent of partial hepatectomy by predicting the risk of dysfunction after surgery [11, 13, 14].

For quantitative assessment of hepatic function in response to radiotherapy, ICG extraction was performed within 2 weeks prior to the start of radiotherapy, during radiotherapy at 50–70% of the prescribed dose, and at 1 and 2 months after completion of radiotherapy. At each time point, ICG was measured according to the package insert (Akron Inc., Buffalo Grove, IL). In brief, an initial pre-administration blood draw was followed by rapid intravenous (IV) administration of ICG at time 0. Additional blood samples were obtained using a separate IV at 5, 10, 15, and 20 minutes. All patient samples were run in triplicate with absorbance measured spectrophotometrically at 805 nm. Plasma disappearance curves of ICG from plasma to liver were derived, assuming a two-compartment model of ICG elimination. The ICG retention rate at 15 minutes (ICG-R15, %) was calculated based on the distribution phase of the disappearance curve.

Treatment

All patients underwent computed tomography (CT) simulation and were treated with fractionated three-dimensional conformal radiotherapy (3D-CRT). With the exception of whole liver irradiation, radiation treatment planning was individualized to maintain normal tissue dose limits with an associated Lyman NTCP [7] of approximately 10–15%.

Forty-three patients received partial liver irradiation to a median dose of 55 Gy (range 28.8–82.0) with fraction sizes ranging from 1.5–3.3 Gy per fraction. Twenty received concurrent chemotherapy with hepatic arterial floxuridine (n=8), capecitabine/fluorouracil (n=9), or gemcitabine-based regimens (n=3). Five received whole liver radiation, 4 on a dose-escalation study with intravenous amifostine as a radioprotector, to a total dose of 30–38 Gy in 2 Gy fractions, as described previously [15].

Evaluation of radiation- induced liver disease

All patients were prospectively followed for RILD with assessments weekly during therapy and at 1 month, then every 2–3 months after completion of therapy. RILD was defined as the development of either non-malignant ascites and anicteric elevation of alkaline phosphatase of at least twofold of upper normal level (classic RILD) or elevated transaminases of at least fivefold (non-classic RILD), in the absence of documented disease progression [16]. Liver MRI or triphasic CT was routinely performed at 2 and 4 months after treatment with additional scans performed as clinically indicated.

Modeling probability of functional liver reserve

To overcome the uncertainty associated with fitting the complication probability to the observed complication frequency based on small numbers of observations and events, the larger number of non-event cases can be utilized to model the safe limit of functional reserve for a given organ to avoid a complication. Here, we selected the beta distribution [17], which is suitable to model a random variable of a frequency or percentage with an arbitrary distribution and a small number of observations, to estimate the limit of functional liver reserve based upon the ICG-R15 measurements from the cases without complications. First, we consider n_c complication events from n observations. A probability of a true complication rate x from these observations can be estimated by the Beta distribution as: $P(x) \propto (x)^{n_c}(1-x)^{n-n_c}$. An accumulated probability of true complication rates from 0 to R_c can be described by:

$$AP_{\beta}(R_c, n_c+1, n-n_c+1) = \int_0^{R_c} \frac{1}{B(n_c+1, n-n_c+1)} (x)^{n_c} (1-x)^{n-n_c} dx, \quad [1]$$

where B is a normalization constant. Note that the observed complication frequency ($r_c = n_c / n$) may not be equal to the accumulated probability of a true complication rate $< R_c$.

Considering that functional liver exhibits damage after a given amount of radiation, a damage fraction of functional liver (DFL) based upon the ICG-R15 measurements at time t was defined as $DFL_t = 1 - (ICG-R15_{pre-RT} / ICG-R15_t)$. The DFL_t values (ranging 0 to 1 with 0 indicating no damage to liver function) were then divided into seven intervals with a size of 0.143. In each of the seven DFL_t intervals, the number of patients (n), complications (n_c), and observed complication frequency (r_c) were calculated. The lower and upper limits of the 68% of the observed complication frequency ($r_c = n_c / n$) were estimated using the inverse of the accumulated probability density function of the beta distribution as $Inverse_AP_{\beta}(X, n_c+1, n-n_c+1)$ where $X = 0.16$ and 0.84 , respectively. Note that the lower and upper limits of the 68% can be asymmetric from r_c . If $r_c = 0$, the lower bound was set to zero and the upper limit was determined by $Inverse_AP_{\beta}(0.68, n_c+1, n-n_c+1)$.

Based upon current observations, the probability of the true complication rate $< 15\%$ (selected based on a current prospective protocol [18]) was estimated by Eq. 1 for each DFL bin. Extrapolating to target accrual for a planned protocol and assuming future observations following the same distribution of the current observations but four times greater, the probability of the true complication rate $< 15\%$ was also estimated. Using the DFL one month post- RT, the limit of functional liver reserve post-RT was estimated in the DFL bin where no complication occurred, and the probability of the true complication rate $< 15\%$ was estimated. This limit served as a target (upper limit) for developing a response predictive model.

To assess the utility of dosimetric parameters, we applied a similar analysis to the mean liver dose (MLD) as well as to the absolute and fractional volumes of the liver (excluding the GTV) receiving accumulated doses greater than 16, 20, and 24 Gy (V16, V20, V24, and V16%, V20%, V24%, respectively). The dosimetric parameters were calculated based upon

the accumulated doses converted to 2-Gy per fraction equivalents using the linear quadratic approach with an α/β ratio of 2.5 Gy [19].

After estimating the limit of functional liver reserve post-RT, we developed a model to predict the DFL post-RT using the DFL after receiving the initial 60% of planned doses, and dosimetric parameters, e.g., MLD and V20 (or V20%). First, a univariate analysis was performed to select the candidate variables using linear regression. Finally, a multivariate model was developed using multiple linear regression. Since the dosimetric parameters of interest might be correlated, one was selected based upon the results of the univariate analysis. The statistical significance between the univariate model and the multivariate model was compared using F-statistics for the nested models. Statistical analyses were performed using R statistical software [20].

RESULTS

Baseline patient and treatment characteristics are shown in Table 1. Three patients (6%) developed RILD, all within 4–9 weeks of completion of therapy. Of the three RILD patients, two received whole liver radiation for hepatocellular carcinoma and metastatic ocular melanoma, respectively, and one received focal liver irradiation with concurrent hepatic arterial floxuridine for metastatic colon cancer. All RILD patients were Child-Pugh class A and none had received prior liver-directed intervention.

Observed mean values for ICG-R15 are shown in Table 1. Patients who ultimately developed RILD had lower mean pretreatment ICG-R15, indicative of greater hepatic functional reserve, but exhibited a greater than 7-fold elevation in ICG-R15 post-treatment. In comparison, ICG retention rates demonstrated only minor elevation over time in patients without RILD. There was marked individual variation in the DFL as assessed by ICG, both during and after radiation, with the DFL ranging from 0 to 98% one month post-RT (Fig. 1). RILD was observed at post-RT DFLs of 78% or greater while no complications were observed at post-RT DFLs of 64% or less (Fig. 2). However, at 64% of the post-RT DFL, due to the small number of the observations ($n=1$), the probability of a true complication rate $<15\%$ was estimated as 28% and 56% based upon the current and future estimated observations, respectively. At a DFL of 50%, where no complication was observed, the probability of a true complication rate $<15\%$ was 68% and 98% based upon the current and future estimated observations, respectively (Fig. 2). Thus, a post-RT DFL of 50% could be used as a conservative limit of functional liver reserve to maximize safety of treatment.

V16, V20, V24, V16%, V20%, V24% and MLD were all strongly correlated and as such exhibited similar behavior for prediction of post-RT functional liver reserve. Given their similarities, we selected MLD, a commonly used parameter, for modeling. Using MLD alone, all cases of RILD were observed at a MLD of 34 Gy or greater. At a MLD of 31 Gy, where the observed complication frequency was zero, the probability of a true complication rate $<15\%$ was 77% and 99% based upon the current and future estimated observations, respectively (Fig. 2), indicating the probability of the true complication rate at the MLD of 31 Gy could be used *a priori* in clinical trials.

To predict the post-RT DFL at a time point early enough to potentially adapt therapy, we developed models incorporating both the during-RT DFL as assessed by ICG and the planned MLD. Modeling was restricted to the 41 patients with comprehensive ICG measurements (pre-, during-, and post-treatment) and included all patients who developed RILD. In univariate analysis both during-RT DFL and MLD alone predicted post-RT DFL (both $p < 3 \times 10^{-10}$) (Table 2). In the multivariable linear regression model, both during-RT DFL and remaining undelivered planned MLD were significant predictors ($p < 9 \times 10^{-14}$, Table 2). Using F-statistics for nested models, the multiple linear regression model performed significantly better than the univariate models based upon either during-RT DFL alone ($p < 3 \times 10^{-5}$) or MLD alone ($p < 4 \times 10^{-6}$). When the predicted and measured damage fractions of liver function one month post-RT were plotted (supplemental figure), the intercept was not significantly different from zero (univariate or multivariate). As such, these models were fitted with the zero intercept.

In our model pretreatment ICG-R15 did not influence the DFL post-RT. Eight patients had a high-risk pretreatment ICG-R15 level defined as $>39\%$ [14], range 40–61%, but only two of these patients exhibited a post-RT DFL of $>10\%$ (20% and 28%). MLD was not found to inversely correlate with pre-treatment ICG-R15. The two patients exhibiting post-RT DFLs $>10\%$ received a MLD of 23.4 and 24.7 Gy, respectively, which were not found to be high-risk by our NTCP model. Of the six patients with DFLs of 10% or less, the MLDs were 32 Gy ($n=1$), 27–28 Gy ($n=2$), and <20 Gy ($n=3$). In other words, only one patient received the critical threshold dose (MLD 32 Gy) determined by the NTCP model. Thus, the conclusion that the pretreatment ICG-R15 does not significantly affect the DFL has to be limited to the dose levels administered to patients with high-risk pretreatment ICG-R15 levels.

To assess the potential clinical application of the model, the predicted probability distribution of a true complication rate $<15\%$ was calculated using the predicted post-RT DFL as assessed by during-RT ICG and MLD and the accumulated probability density function of the beta distribution based upon population-estimated observations with the same distribution (Fig. 3). The resulting model predicts a 99% probability of a true complication rate $<15\%$ by limiting the DFL to 50%. To meet this limit in clinical practice, the individual complication risk is first estimated based upon the MLD from the NTCP model *a priori*, and then re-estimated based upon dynamic liver function assessment by means of ICG clearance during RT. For instance, consider a scenario in which adequate treatment of a liver tumor required a MLD of 32 Gy. If after receiving 60% of the planned dose, the during-RT DFL was 28% or less, this would lead to a predicted DFL of 47.6% post-RT and the predicted probability of a true complication rate $<15\%$ of 99%. If the during-RT DFL was greater than 28%, the radiation plan could be adjusted to reduce the MLD such that the projected post-RT DFL would remain less than 48%, thereby minimizing the risk of harm.

DISCUSSION

In this study, we estimated the limit of functional liver reserve in patients undergoing radiation for unresectable intrahepatic malignancies. Our results suggest that the damage fraction of liver, as assessed by changes in ICG plasma clearance, serves as a quantitative

indicator of a patient's tolerance to hepatic irradiation. Thus, by incorporating this response measure with dosimetric parameters for initial risk control, we have developed an adaptive model that facilitates estimation of an individual's risk for complication and should aid in the successful application of individualized radiotherapy.

Due to known heterogeneity in pre-existing liver function and variation in normal tissue response, accurate prediction of individual sensitivity to radiation remains a challenge. Several clinical and patient-specific factors may increase susceptibility to RILD, including primary intrahepatic cancer (versus metastatic cancer) [7], preexisting liver dysfunction [4, 10], prior therapy [7, 10], and portal vein thrombosis [10, 21]. NTCP models cannot account for all of these complexities and, as such, lack optimal predictive ability for individuals. Thus, we hypothesized that the measurement of liver function during treatment using ICG would reflect the extent of hepatic damage on an individual basis and thereby permit improved patient-specific evaluation of functional liver reserve. This is particularly important since pre-treatment ICGR15 has not consistently predicted for toxicity [22]. In our model pretreatment ICG-R15 did not influence the DFL post-RT. While no inverse correlation was found between ICG-R15 and MLD, only one of eight patients with a high-risk pre-treatment ICG-R15 level received a MLD above the critical threshold dose (MLD 32 Gy) as determined by the NTCP model. Thus, the conclusion that the pretreatment ICG-R15 does not significantly affect the DFL has to be limited to the dose levels administered to patients with high-risk pretreatment ICG-R15 levels.

In the present study, we estimated the limit of functional liver reserve based upon the DFL obtained from the change in ICG clearance during and after RT. We considered the uncertainty of the observed complication frequency due to the number of observations. We then used the beta probability distribution function to estimate the probability of a true complication rate from both the observed complication frequency and the number of observations. Thus, our approach differs from previous NTCP models, which fit observed complication rates and may result in marked uncertainty of the estimated complication probability if the numbers of the complication events and observations at the critical thresholds are small. In the development of our multivariate response model, we used multiple linear regressions to fit a continuous variable, DFL, rather than multiple logistic regression to fit the three events. In this fitting, all observations can be used, instead of just the three complication events. The estimation of the limit of functional liver reserve can then be easily updated as new data is accumulated, replacing estimated data with true observations.

By incorporating normal tissue response measurements via changes in ICG with established dosimetric parameters, such as MLD, we were able to better predict the post-RT damage fraction of liver during the course of therapy. This combined model has the potential to allow for individualized adaptation, with the goal of delivering the highest, safe dose to each patient. In practice, post-treatment functional liver reserve will be initially estimated at treatment outset based on dosimetric parameters and then re-estimated during the course of radiation based on changes in ICG clearance. This will facilitate adjustments in radiation dosing midway through treatment based upon the individual's sensitivity to RT. This should maximize both the safety and efficacy of treatment for patients, particularly those with

compromised organ function secondary to cirrhosis or prior liver directed therapy who are at increased risk for toxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The observed frequency distributions of the damage fraction of functional liver after receiving the initial 60% of the planned doses and one month after completion of RT.

Figure 2.

The observed complication rates (a, b) and the probability distributions of a true complication rate < 15% (c, d; black line = current observations; gray line = population-estimated observations) as a function of the damage fraction of functional liver function one month post-RT (a, c) and mean liver dose (b, d). Error bars: 68% confidence interval calculated by the inverse beta distribution function. The number of patients in bins from low to high is 12, 8, 6, 6, 1, 5, and 3.

Figure 3.

The predicted probability of the true complication rate < 15% by the predicted damage fraction of functional liver one month post- RT using changes in liver function (indocyanine green clearance) during RT and remaining undelivered mean liver dose.

Table 1

Patient and treatment characteristics

Characteristics	All patients (n = 48)	Patients without RILD (n = 45)	Patients with RILD (n = 3)
Age – yr			
Median	67	68	54
Range	34 – 83	34 – 83	50 – 78
Sex – no. (%)			
Male	37 (77)	34 (76)	3 (100)
Female	11 (23)	11 (24)	0 (0)
Diagnosis – no. (%)			
Hepatocellular carcinoma	21 (44)	20 (44)	1 (33)
Intrahepatic cholangiocarcinoma	14 (29)	14 (31)	0 (0)
Liver metastases	13 (27)	11 (24)	2 (67)
Child-Pugh classification – no. (%)			
A	44 (92)	41 (91)	3 (100)
B	4 (8)	4 (9)	0 (0)
Prior liver-directed therapy – no. (%)	13 (27)	13 (29)	0 (0)
Concurrent chemotherapy – no. (%)	20 (42)	19 (42)	1 (33)
Radiation dose - Gy			
Median	54.5	55.0	38.0
Range	28.8 – 82.0	28.8 – 82	36.0 – 49.5
Interquartile range	49.5 – 63.3	50.0 – 64.0	
Dose per fraction - Gy			
Median	2.0	2.0	2.0
Range	1.5 – 3.3	1.5 – 3.3	1.5 – 2.0
Biocorrected mean liver dose - Gy			
Median	25.7	25.4	38.2
Range	8.7 – 40.9	8.7 – 40.1	34.0 – 40.9
Interquartile range	23.1 – 30.2	22.9 – 28.8	
Liver V _{16 Gy} - %			
Median	57.0	55.2	100.0
Range	15.1 – 100.0	15.1 – 100.0	88.2 – 100.0
Interquartile range	46.6 – 68.9	45.0 – 66.6	
Liver V _{20 Gy} - %			
Median	52.5	51.8	100.0
Range	10.6 – 100.0	10.6 – 100.0	84.3 – 100.0
Interquartile range	40.2 – 64.7	39.2 – 60.3	
Liver V _{24 Gy} - %			
Median	48.5	47.5	100.0
Range	8.6 – 100.0	8.6 – 100.0	80.4 – 100.0
Interquartile range	35.3 – 57.7	34.7 – 55.7	

Characteristics	All patients (n = 48)	Patients without RILD (n = 45)	Patients with RILD (n = 3)
ICG-R15 – %			
Pretreatment – mean (se)	19.4 (2.5)	20.3 (2.6)	6.3 (4.3)
During treatment – mean (se)	21.1 (2.8)	22.0 (3.0)	10.8 (2.7)
1 mo post-treatment– mean (se)	28.9 (2.8)	27.5 (2.8)	47.6 (8.8)
2 mo post-treatment– mean (se)	28.4 (3.6)	24.9 (3.3)	63.5 (11.5)

Abbreviations: RILD: radiation-induced liver disease, ICG-R15: indocyanine green plasma retention at 15 minutes, se: standard error

Table 2

Predictive models to estimate the conservative limit of functional liver reserve following radiation

Univariate Model 1: $DFL_{LMpost} = b_1 \times DFL_{during}$				
	b_1	Estimated Std. Error	t value	p value
DFL_{during}	1.25	0.12	10.7	1.5×10^{-9}
Univariate Model 2: $DFL_{LMpost} = b_2 \times MLD$				
	b_2	Estimated Std. Error	t value	p value
MLD (Gy)	0.015	0.0017	8.7	2.8×10^{-10}
Univariate Model: $DFL_{LMpost} = \beta_1 \times DFL_{during} + \beta_2 \times (1 - f)MLD$ (adjusted $R^2 = 0.82$, $p = 8.2 \times 10^{-14}$)				
	β_i (95% CI)	Estimated Std. Error	t value	p value
DFL_{during}	0.843 (0.53, 1.15)	0.15	5.6	3.3×10^{-6}
$(1 - f)MLD$ (Gy)	0.017 (0.008, 0.027)	0.0047	3.6	9.5×10^{-4}

Abbreviations: DFL: damage fraction of liver, MLD: mean liver dose, CI: confidence interval, β : slope, f: the fraction of delivered planned dose at the time of the ICG measurement during the course of RT.

* The non-zero intercepts were tested in the models but not statistically significant and then the models with zero intercept were fitted.