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Using Indocyanine Green Extraction to Predict Liver Function After Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma

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Abstract

Purpose—To test the hypothesis that mid-treatment measures of the retention of indocyanine green after 15 minutes (ICGR15) would improve the prediction of posttreatment liver function in the setting of hepatocellular carcinoma.

Methods and Materials—Between 2006 and 2015, 144 patients with hepatocellular carcinoma received 175 courses of stereotactic body radiation therapy (SBRT). Patient data, such as age, sex, portal vein thrombosis, cirrhosis, Child-Pugh (CP) score, prior liver-directed therapies, and liver function tests, including albumin-bilirubin (ALBI) and ICG clearance, and dosimetric data, such as tumor volume and radiation dose, were collected. Toxicity was evaluated as a 2-point increase in CP score or a change in ALBI score at 3 months from start of SBRT. Logistic or linear regression was used to build toxicity prediction models based on patient and tumor characteristics and ICG clearance variables. Performance of the models for the binary CP outcome was summarized using area under the curve and receive operating characteristic curves. Likelihood ratio tests were used to evaluate whether the model fit improved after incorporating the ICG variable information.

Results—In multivariable analysis age, baseline ICGR15, and change in ICGR15 were associated with toxicity defined by increased CP score. For the continuous ALBI outcome, being female, having cirrhosis, and increasing radiation dose were associated with increased toxicity. When incorporating ICGR15 into these models, an increase in ICGR15 from baseline to mid-treatment was most consistently significantly associated with an increase in toxicity.

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Conclusions—Incorporation of ICGR15 variables significantly improves the prediction of post-SBRT liver function. The use of ICGR15 can facilitate the delivery of the maximum safe dose of radiation for patients with hepatocellular carcinoma and has the potential to improve uncomplicated tumor control and survival.

Introduction

Hepatocellular carcinoma (HCC) remains a challenge to treat. Stereotactic body radiation therapy (SBRT) has become more widely used as primary treatment or in conjunction with other local therapies, such as transarterial chemoembolization or radiofrequency ablation for unresectable disease or as a bridge before liver transplant (1–3). Most HCC patients also have cirrhosis. Cirrhotic liver disease increases the risk of radiation-induced liver injury, and prior studies in patients with poor Child-Pugh (CP) scores show that great caution must be exercised in delivering SBRT in this population (4).

Optimal radiation treatment planning that maximizes local control at an acceptable risk of toxicity requires accurate prediction of toxicity. Current prediction of liver toxicity is based on dosimetric factors and clinical factors, such as CP score at the time of treatment. The CP score is largely based on parameters reflecting synthetic liver function but also involves the subjective evaluation for hepatic encephalopathy and ascites. Recently, ALBI (a logarithmic function of albumin and bilirubin levels) was shown to be a prognostic measure for overall survival in HCC (5, 6). Complementary to standard laboratory values is indocyanine green (ICG) clearance, which is an objective and direct measure of liver function (7). This measure has been used to assess patients before liver resection and for transplant (8, 9). We have shown that it can be used to assess liver function before radiation therapy (10).

Accurate toxicity measures and modeling can lead to safer dose recommendations for HCC patients and could improve local control. In this study we investigate the use of CP score and ALBI to assess liver toxicity and hypothesize that there will be predictive gains from incorporating ICG clearance into liver toxicity models that already use widely available clinical information. This would be a novel finding, because ICG clearance is not routinely used for assessment of liver function before radiation therapy. If our hypothesis were confirmed, it could permit the safe increase in radiation dose, leading to improved tumor control and, potentially, survival.

Methods and Materials

Patients

Eligible patients included HCC patients treated with SBRT between 2006 and 2015. Some patients did not have ICG measured and were thus included only in the normal tissue complication probability (NTCP) (non-ICG) modeling. Only patients who were enrolled in our institutional SBRT protocols (UMCC 2003.081 and UMCC 2009.053) had ICG data available and were thus included in the ICG-based models. These patients had radiation dose adjusted on the basis of indocyanine green clearance (see below for details).

ICG administration

Indocyanine green was infused intravenously, and blood samples were collected at time 0, 5, 10, 15, and 20 minutes after this infusion. Spectrophotometric measurement of ICG was performed at 805 nm in a Clinical Laboratory Improvement Amendments–certified laboratory, as described previously, and the ICG retention rate at 15 minutes (ICGR15) was calculated (10).

For each patient, 5-fraction SBRT plans were optimized according to an in-house NTCP model of 15% toxicity (11). The CP and ALBI measurements were assessed at baseline (before SBRT) and at 3, 6, 9, and 12 months after completion of SBRT.

For the patients who were enrolled on protocol, ICG was administered before SBRT to obtain a baseline assessment (ICGR15 at time 0). Three fractions were delivered initially, followed by a 1-month break, at which point patients had reassessment of ICG clearance. The goal of the mid-treatment adaptation was to ensure, with high probability, that the final (1 month after the end of SBRT) ICGR15 was less than 44% (a value associated with liver failure after wedge resection [12]). If the ICGR15 was below 44%, patients received an additional 2 fractions but, possibly, at a reduced dose per fraction. Patients who had an ICGR15 above this threshold, indicating highly impaired hepatic function, did not receive additional radiation therapy. For additional details for this adaptive regimen, please refer to the article by Feng et al (13).

Stereotactic body radiation therapy procedure

Subjects treated with SBRT were simulated with contrast-enhanced computed tomography (CT) in the arterial and venous phases, in addition to contrast-enhanced magnetic resonance imaging if possible. Subjects were treated with a controlled breath-hold technique when possible to minimize motion. For subjects who were free-breathing (ie, could not breath-hold), a 4-dimensional CT scan was acquired to generate an internal target volume to account for tumor excursion. In all subjects the CT and magnetic resonance images were co-registered for delineation of gross tumor volume. Expansion of the gross tumor volume to the planning target volume for subjects able to breath-hold was 5 mm in the axial dimension and 8 mm in the cranio-caudal dimension. Slightly larger margins were used at the discretion of the radiation oncologist, depending on the excursion of the tumor in free-breathing subjects. Cone-beam CT was used to maintain image registration across sessions.

Statistical methods

Liver toxicity was defined as a decline in liver function, as assessed by ALBI or CP scores. For the CP measure, we created a binary endpoint as the occurrence of a 2-point increase in CP score (14). The ALBI grades bin the continuous ALBI score into grades 1, 2, and 3. However, modeling an increase in ALBI grade is problematic when some patients begin at the highest grade. Furthermore, using discrete values leads to a loss of information. Additionally, there is no widely accepted threshold value for “toxicity.” Thus, we modeled the change in ALBI scores continuously. However, to allow fitting the classic NTCP model to ALBI outcomes, we also created a binary ALBI endpoint defined as a 0.5-point increase, which was the median change in ALBI for patients who had a 1 change in ALBI grade. All

endpoints were based on the change from baseline to 3 months after completion of SBRT. Other clinical measurements collected from patients were sex, age at SBRT, pretreatment cirrhosis, portal vein thrombosis, number of prior liver-directed therapies, histology status, and mean liver dose (MLD) based on linear quadratic linear correction.

Dose-volume histograms were generated from a planning system for the calculation of NTCP models, to identify the appropriate dose metric to use in the statistical analysis. The Lyman-Kutcher-Burman NTCP model was fit to both of the toxicity outcomes considered. Maximum likelihood estimates for the parameters n , D_{50} , and m were obtained with associated 95% confidence intervals. Mean liver dose was calculated using (Liver – GTV).

There were 144 unique patients. Twenty-seven patients received more than 1 course (range, 2–4) of treatment, producing a total of 175 treatment courses. Multiple treatment courses in the same patient were included separately in the analysis owing to differential baseline CP and ALBI scores, as well as follow-up scores from the end of treatment. Robust standard errors were used to account for within-patient correlation in patients treated more than once at different times (15, 16). Logistic and linear regression models were fit to the CP outcome and continuous change in ALBI score, respectively, and parameter estimation was conducted using maximum likelihood methods. Univariate analysis was conducted to identify dose and clinical factor variables that are associated with each toxicity outcome. Multivariable models were fit and variable selection was performed to identify the best-fitting model using stepwise regression by Akaike Information Criterion, a measure that rewards model goodness-of-fit and penalizes overfitting. We note that such models may contain terms whose P values are $>.05$. We then added baseline ICG (ICG0) and mid-treatment change from baseline (ICG1-ICG0) to these models. The predictive ability of the CP models was evaluated using area under the curve (AUC) from the respective receiver operating characteristic (ROC) curves. For the ALBI continuous outcome, using a multivariable linear regression model, we examine the relationship between predicted change in ALBI at 3 months from start of SBRT and MLD by some baseline covariates. Improvement in model prediction performance after the incorporation of ICG measures for both outcomes was tested using the likelihood ratio test (17). Goodness-of-fit was evaluated using the Hosmer-Lemeshow test for the binary CP outcome models, and R^2 for the continuous ALBI score models. All statistical analyses were conducted using R version 3.2.2 (R Foundation for Statistical Computing, Vienna).

Results

Patient and tumor characteristics

A total of 144 unique patients who received 175 treatment courses were included in NTCP modeling. Toxicity outcomes and baseline data (at the time of treatment) were captured separately for each treatment course and are reported in Table 1. The majority of treatment courses were in patients who were male (79%) and had cirrhosis (85%). The median age at start of SBRT was 64 years (range, 25–86 years), whereas the median number of prior liver-directed therapies was 1 (range, 0–8). The median MLD with linear quadratic linear correction was 10.5 Gy (range, 1.87–36.8 Gy). Data on ICG were available for 91 unique patients, 10 of whom were treated twice, for a total of 101 treatment courses.

Toxicity outcomes

The toxicity outcomes for the 101 patients with ICG data are summarized in Table 2. The median CP score before the start of SBRT was 6 (range, 5–10). At 3 months after treatment completion, 15% of patients had a 2-point change in CP score. The median ALBI score before SBRT was -2.23 (range, -3.19 to -0.74). At 3 months after the end of SBRT, 17% of patients had a change in ALBI score ≥ 0.5 . As shown in Figure 1, there is significant positive correlation between ALBI and CP scores at base-line (Spearman $r=0.77$, $P<.001$). The baseline ICG measurement is also significantly correlated with pre-SBRT ALBI ($r=0.77$, $P<.001$) and CP ($r=0.64$, $P<.001$), with baseline ICG and ALBI being more closely correlated. There was no association between mean increase in CP score or ALBI at 3 months after SBRT and early (within 3 months of SBRT) intrahepatic progression ($P=.62$ and $P=.18$, respectively). The proportion of patients who experienced a 2-point increase in CP also did not differ significantly between patients receiving 3 versus 5 fractions (18% vs 13%, $P=.65$).

NTCP model

Parameter estimates for both NTCP models are presented in Table E1 (available online at www.redjournal.org). If the n parameter is equal to 1, the NTCP model reduces to a function of MLD. The maximum likelihood estimates of n in Table 2 are not significantly different from 1 ($P=.89$ CP; $P=.60$ ALBI score ≥ 0.5), as seen by the inclusion of 1 in the wide 95% confidence intervals for both outcomes. Thus, in the subsequent toxicity modeling, we use MLD as our dose metric. The AUCs for the CP and ALBI score models were 0.55 and 0.67, respectively.

Model for CP

In univariate analysis of the CP toxicity outcome, increased age at SBRT was marginally associated with increased risk of toxicity (odds ratio 1.06; $P=.08$), whereas patients with hepatitis C virus liver disease had decreased risk of toxicity (odds ratio 0.29; $P=.06$) (Table E2; available online at www.redjournal.org). In the multivariable analysis excluding the ICG measures, the best-fitting model contained age and number of prior liver-directed therapies, as shown in Table E3 (available online at www.redjournal.org). When ICG measures were considered for inclusion, both baseline ICGR15 and change in ICGR15 since base-line (ICG1-ICG0) were selected in the best-fitting model. For each 10% increase in baseline ICG, the odds of toxicity increased by a factor of 1.55 ($P=.04$). For each 10% increase in change in ICG, the odds of toxicity increased by a factor of 3.59 ($P=.02$). Figure 2 shows ROC curves based on the CP toxicity models with or without ICG. The predictive power of the model that includes the ICG measures was significantly greater than the model that included only clinical factors (AUC = .86 vs .75; $P=.04$). The Hosmer-Lemeshow test showed no significant evidence of lack of fit.

Model for ALBI

In univariate models, the only clinical factor identified as a significant predictor of ALBI decline was hepatitis C virus liver disease, which was associated with decreased toxicity ($P=.05$) (Table E2; available online at www.redjournal.org). Stepwise linear regression (excluding ICG) identified cirrhosis ($P=.04$), increasing MLD ($P=.04$), and female sex ($P=.04$).

09) as at least marginally significantly associated with increased risk of toxicity, as shown in Table E3 (available online at www.redjournal.org). For every 5-Gy increase in MLD, ALBI is predicted to worsen by 0.05 ($P=.05$). When ICG measures were considered for inclusion, both baseline ICGR15 and change in ICGR15 since baseline (ICG1-ICG0) were selected in the best-fitting model. Adding the ICG measures to the clinical factors model significantly improved model fit ($P=.04$), increasing model R^2 from 0.07 to 0.13. Although statistically significant, this result also highlights that changes in ALBI are difficult to predict accurately, even with ICGR15. Similar to the CP model, mid-treatment change in ICGR15 was a significant predictor of later toxicity ($P=.01$), whereas, in contrast to the CP model, higher baseline ICG values were not significantly associated with toxicity ($P=.22$).

In Figure 3 we further examine the relationship between expected change in ALBI score and MLD by cirrhosis and baseline ALBI grade. In all cases the expected change in ALBI score increases with MLD. From Figure 3a, patients with cirrhosis had, on average, larger increases in ALBI score; however, there was no significant interaction between cirrhosis and MLD, so the effect of increasing MLD was similar for cirrhotic and noncirrhotic patients. In Figure 3b it can be seen that at lower MLD values, ALBI grade 2/3 patients tend to have larger increases in ALBI scores than do grade 1 patients, whereas for higher MLD values, the expected change is similar for all grades.

Discussion

In this study we have found that incorporating ICG measures into toxicity models allows improved prediction of liver function after liver SBRT for HCC patients. In particular, the change in ICG from baseline at the mid-treatment time point was highly predictive of subsequent liver toxicity.

Indocyanine green clearance is well studied in the setting of liver transplant (9, 18, 19). We are among the first to use it to assess liver function and to use it in models of toxicity outcomes for liver radiation. We have previously demonstrated that the damage fraction of functional liver, which is based on a function of ICGR15 before and after radiation, is predictive of patient intolerance to hepatic irradiation (10). We had assumed that baseline ICG may be key to predicting toxicity, and we have adapted SBRT treatment. However, the current model shows that it is the increase in ICGR15 that is pivotal to predicting toxicity.

The CP score is the baseline for the Barcelona Clinic Liver Cancer staging system that has been widely adopted for HCC. Prior liver SBRT studies have shown that patients with borderline or poor liver function according to pretreatment CP scores do experience greater toxicity (4, 20). Culleton et al (20) recently published a study examining the outcomes of patients with Childs B and C liver disease after SBRT, showing that 63% of patients had an increase in CP score 2 at 3 months. Of these patients, those with CP 7 disease had the best outcomes in this study (20). The same group has also shown that baseline CP score and higher liver dose are most predictive of toxicity (14).

The ALBI is a relatively new measure, and its design was meant to remove some of the clinical subjectivity that comes with CP scoring. Further, bilirubin and albumin are both

excellent surrogates of liver synthetic function and are key to the CP system. The ALBI has since been investigated in HCC as being predictive of outcomes in HCC in the setting of stratifying patients for sorafenib therapy as well as surgery (5, 6, 21, 22). It is highly correlated with CP score, and it is an objective measure that predicts survival. A recent study has correlated CP score and ALBI as predictors of toxicity in patients treated with liver SBRT. However, this study included 60 patients, in whom one-third of laboratory values for calculation of these measures were missing, and the population was mixed, with both cholangiocarcinoma and HCC patients analyzed (23).

The few publications that are available on prediction of liver toxicity (endpoint was change in Child-Pugh score) focus mostly on dosimetric factors in the setting of nonadaptive therapy (ie, all patients, regardless of liver function, are treated in an identical fashion). They are also based on a small sample sizes of <50 patients (23–26). This makes our study especially salient because we adapted radiation according to mid-treatment liver function to try to mitigate toxicity. Even with this approach, we observed that 15% of patients showed a worsening of CP status of ≥ 2 . Changes in indocyanine green may be more sensitive to acute liver toxicity than an absolute change in a standard liver function panel.

Indocyanine green is approved by the US Food and Drug Administration for clinical use in the United States for determining cardiac output and hepatic function and for ophthalmic angiography. It is reimbursable as well. Measurement of ICG requires either a noninvasive densitometer (like a pulse oximeter) or blood samples every 5 minutes for 30 minutes to generate a clearance curve. The densitometer is not clinically available in the United States. At our institution we measure blood samples with standard spectrophotometry in a Clinical Laboratory Improvement Amendments–certified laboratory. Calibration of the standard curve and measurement would be implementable in most institutions.

Our study has limitations. Although the data were collected prospectively, the models we present were fit to data from patients treated adaptively. Our approach likely decreased the toxicity compared with that anticipated if patients were treated in a nonadaptive fashion, because the patients with worse or worsening liver function were generally treated with lower doses (27). Thus our models may underestimate toxicity if applied in the context of nonadaptive therapy. At the same time, we expect the key finding regarding the role of ICG as a predictor of later liver function decline to hold for either adaptive or nonadaptive patients.

The present study provides a framework for modeling and mitigating toxicity in HCC patients treated with liver SBRT. Baseline measures of ICG allow more accurate prediction of toxicity than is possible using dose and baseline CP score or ALBI and could be used to calculate an individualized safe dose of radiation therapy. Mid-treatment measures of ICG could be used to adapt patients' radiation therapy treatment plans, to either reduce dose if estimated risk of toxicity is high or to potentially give more dose to patients who may require a boost to achieve local control.

Conclusions

Changes in ICGR15 are highly predictive of toxicity after liver SBRT. Modeling toxicity using ALBI, in addition to the widely accepted CP score, may inform safer SBRT treatments in patients with poorer liver function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Summary

Indocyanine green (ICG) is a direct measure of hepatocyte function. Incorporation of ICG with standard clinical factors significantly improves the prediction of post-stereotactic body radiation therapy (SBRT) liver function when toxicity is defined by an increase of Child-Pugh score ≥ 2 or change in absolute albumin-bilirubin (ALBI) score ≥ 0.5 or ALBI grade ≥ 1 . The use of ICG may facilitate the delivery of the maximum safe dose of radiation for patients with hepatocellular carcinoma and has the potential to improve uncomplicated tumor control and survival.

Fig. 1. Correlations between albumin-bilirubin grade (ALBI), Child-Pugh score (CP), and indocyanine green at baseline (ICG0). *Abbreviation:* SBRT = stereotactic body radiation therapy.

Fig. 2.

Receiver operating characteristic curves for the Child-Pugh score (CP) toxicity models. The increase in area under the curve (AUC) from 0.75 to 0.86 by including indocyanine green (ICG) measures is statistically significant ($P=.04$).

a Predicted change in ALBI score by MLD and Cirrhosis **b** Predicted change in ALBI score by MLD and ALBI Grade **Fig. 3.**

Predicted change in albumin-bilirubin (ALBI) score at 3 months by mean liver dose (MLD) (linear quadratic linear [LQL]) according to (a) cirrhosis status and (b) ALBI grade 1 or 2/3 at baseline. Dashed lines represent 90% confidence intervals.

Table 1

Baseline characteristics

Characteristic	NTCP modeling (n=175)	ICG modeling (n=101)
Age at SBRT (y)	64 (25–86)	65 (25–85)
Sex		
Male	139 (79)	79 (78)
Female	36 (21)	22 (22)
Cirrhosis		
Yes	149 (85)	86 (85)
No	26 (15)	15 (15)
Portal vein thrombosis		
Yes	33 (19)	22 (22)
No	142 (81)	79 (78)
No. of prior liver therapies	1 (0–8)	2 (0–8)
Liver disease		
HCV	86 (49)	43 (43)
Other	89 (51)	58 (57)
Mean liver dose (LQL) (Gy)	10.5 (1.87–36.8)	11.6 (3.33–28.9)

Abbreviations: HCV = hepatitis C virus; ICG = indocyanine green; LQL = linear quadratic linear; NTCP = normal tissue complication probability; SBRT = stereotactic body radiation therapy.

Values are number (percentage) or median (range).

Table 2

Summary of outcomes in patients who received ICG

Outcome	Value
Baseline CP	6 (5–10)
CP at 3 mo	6 (5–11)
CP change (3 mo-baseline)	
0	55 (54)
1	31 (31)
2+	15 (15)
Baseline ALBI score	–2.2 (–3.2 to –0.7)
ALBI score at 3 mo	–2.0 (–3.2 to –0.3)
ALBI score change (3 mo-baseline)	0.2 (–1.0 to 1.5)
ALBI grade change (3 mo-baseline) 1	22 (22)
Pretreatment ICGR15 (ICG0)	29.2 (5.1–77.5)
ICGR15 1 mo after third fraction (ICG1)	36.1 (5.1–83.5)
Mid-treatment change in ICG (ICG1-ICG0)	3.0 (–12.4 to 16.9)

Abbreviations: ALBI = albumin-bilirubin; CP = Child-Pugh score; ICG = indocyanine green; ICG0 = baseline ICG; ICG1 = mid-treatment ICG; ICGR15 = retention of ICG after 15 minutes.

Values are median (range) or number (percentage).