Radiotherapy and Oncology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Estimating functional liver reserve following hepatic irradiation: Adaptive normal tissue response models

Matthew H. Stenmark [a,d,*,1], Yue Cao [a,b,c,1], Hesheng Wang [a], Andrew Jackson [e], Edgar Ben-Josef [f], Randall K. Ten Haken [a], Theodore S. Lawrence [a], Mary Feng [a]

[a] Department of Radiation Oncology; [b] Department of Radiology; [c] Department of Biomedical Engineering, University of Michigan Health System; [d] Veterans Affairs Medical Center, Ann Arbor; [e] Memorial Sloan Kettering Cancer Center, New York; and [f] University of Pennsylvania, Philadelphia, United States

ARTICLE INFO

Article history:
Received 30 January 2014
Received in revised form 24 March 2014
Accepted 7 April 2014
Available online xxxx

Keywords:
Liver
Radiotherapy
Indocyanine green
Adaptive radiotherapy

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 to 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 $\geqslant$78%. Both DFL assessed by during-RT ICG and MLD predicted for DFL post-RT ($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.

Published by Elsevier Ireland Ltd. Radiotherapy and Oncology xxx (2014) xxx–xxx

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

* Corresponding author. Address: University of Michigan Medical Center, 1500 E Medical Center Dr., Ann Arbor, MI 48109-5010, United States.
E-mail address: stenmark@umich.edu (M.H. Stenmark).
[1] Contributed equally to this work.

http://dx.doi.org/10.1016/j.radonc.2014.04.007
0167-8140/Published by Elsevier Ireland Ltd.

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 $\geqslant$12 weeks, Zubrod performance status of 0 to 2, and adequate hepatic function (INR $\leqslant$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 catheter at 5, 10, 15, and 20 min. 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 min (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 to 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:

$$\mathrm{AP}_\beta(R_c, n_c+1,\ n-n_c+1) = \int_0^{R_c} \frac{1}{B(n_c+1,\ n-n_c+1)}(x)^{n_c}(1-x)^{n-n_c}\mathrm{d}x, \quad (1)$$

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 $\mathrm{DFL}_t = 1 - (\mathrm{ICG\text{-}R15}_{\text{pre-RT}}/\mathrm{ICG\text{-}R15}_t)$. 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 $\mathrm{Inverse\_AP}_\beta$ (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 $\mathrm{Inverse\_AP}_\beta$ (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

Please cite this article in press as: Stenmark MH et al. Estimating functional liver reserve following hepatic irradiation: Adaptive normal tissue response models. Radiother Oncol (2014), http://dx.doi.org/10.1016/j.radonc.2014.04.007