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Radiation-induced liver disease and modern radiotherapy

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Abstract

Modern radiotherapy techniques have enabled high focal doses of radiation to be delivered to patients with primary and secondary malignancies of the liver. The current clinical practice of radiation oncology has benefitted from decades of research that have informed how to achieve excellent local control and survival outcomes with minimal toxicities. Still, one of the most devastating consequences of radiation to the liver remains a challenge: radiation induced liver disease (RILD). Here, we will review the current understanding of classic and non-classic RILD from a clinical perspective, the evaluation and management of patients who are at risk of developing RILD, methods to reduce the likelihood of RILD using modern radiation techniques, and the diagnosis and treatment of radiation-related liver toxicities.

I. Introduction

Overview

The understanding of the effects of radiotherapy on primary and secondary liver cancers continues to evolve. The radiation delivery techniques that were used decades ago generally treated large volumes and provided cautionary guidance for using radiation for palliative and definitive treatment. In that era, “classic” radiation induced liver disease (RILD) was a devastating consequence of treatment. These old approaches informed our current practice as to the proper radiation dose constraints to use for the liver. Modern radiation delivery techniques now enable the safe delivery of radiotherapy to limited liver volumes in many patients, but challenges remain, especially for patients with advanced cirrhosis. These patients are particularly at high risk of developing “non-classic” RILD. Methods to reduce the risk of radiation-related liver toxicities have emerged, opening new opportunities to help patients who otherwise have limited options for liver-directed therapies. The goals of this article are to review the understanding of classic and non-classic RILD, the management of patients with underlying liver dysfunction, the methods to mitigate toxicities through

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modern radiation techniques, and the evaluation and management of radiation-related liver toxicities.

Radiation Induced Liver Disease (RILD)

Classic RILD—Classic RILD was historically the dose limiting complication of liver radiation with onset 2 weeks to 4 months post whole hepatic radiation to 30–35 Gy using conventionally fractionated regimens. The syndrome is comprised of anicteric hepatomegaly, ascites, and elevated liver enzymes, especially alkaline phosphatase. The incidence described in the 2000s was 5–10% if the above mean liver dose was met. The mechanism of hepatic injury was classically veno-occlusive disease secondary to fibrosis.^{6, 98} Risk factors associated with classic RILD included high mean liver dose, primary liver cancer, male gender and hepatic intra-arterial chemotherapy.⁶ The veno-occlusive nature of RILD correlated with decreased hepatic arterial and portovenous perfusion on MRI.⁷¹ The work on classic RILD was largely based on the experience of the University of Michigan.^{6, 98}

Non-Classic RILD—In the current era of CT based radiation planning, daily image guidance with motion management, and IMRT/VMAT based plans, classic RILD is very rare. Non-classic RILD is much more common and manifests as markedly elevated serum transaminases (>5X upper limit of normal), and jaundice. The most vulnerable populations affected by non-classic RILD are those with underlying liver disease such as patients with hepatitis B or cirrhosis from a variety of causes.^{39, 40, 99} The mechanism for non-classic RILD is less well understood but may involve the loss of regenerating hepatocytes and reactivation of hepatitis.⁴⁰

In an attempt to characterize the outcomes of patients who develop non-classic RILD, which is more akin to acute hepatic decompensation, recent literature has examined the use of Child Pugh score and the more objective ALBI. There have now been a number of publications within the last 3 years detailing various dose thresholds and evaluating the risk of a decline in hepatic function. The most commonly used criteria in cirrhotic patients is an increase in Child Pugh score greater than or equal to 2. In non-cirrhotic patients, a >5X increase in transaminases or change in ALBI (usually decreased albumin) has been reported.

Historical perspective—One of the first reports of radiation to the liver was in 1924. This described the autopsy of a patient who received 200 kVp for 200 milli-ampere minutes showing marked pathological changes in the lymphoid tissue and intrahepatic bile ducts and comparatively mild changes in the hepatocytes¹. In 1966, a report described the acute and chronic pathological findings in the livers of 12 patients who received whole liver irradiation to 30–59 Gy over 6 weeks for metastatic disease, and established the hallmark finding of veno-occlusion in association with classic RILD². The Radiation Therapy Oncology Group (RTOG) conducted studies in the 1970s and 1980s to examine the role of whole liver radiation for hepatic metastases. The RTOG 76–09 study evaluated 109 patients with liver metastases, evaluating various fractionation schemes to the whole liver based on the presence of a single metastasis (30.4 Gy in 19 fractions with or without a 20 Gy boost, or 30 Gy in 15 fractions with or without a 20 Gy boost) or multiple metastases (30 Gy in 15 fractions, 25.6 Gy in 16 fractions, 20 Gy in 10 fractions, or 21 Gy in 7 fractions). No classic

RILD was seen in this study³. The RTOG 84–05 study was a Phase I/II design evaluating the escalation of dose from 27 to 33 Gy at 1.5 Gy twice daily fractionation. Patients who received 30 Gy or lower did not develop RILD, but 10% of patients at 33 Gy developed classic RILD⁴. Classic RILD was also seen in the Gynecologic Oncology Group Study No. 122, with 1% of the patients in the radiation arm undergoing whole abdominal radiation therapy developing grade 4 liver toxicity.

Changing from whole organ treatment to focal radiation of the liver—A shift to partial radiation of the liver was made in the 1980s, and seminal work demonstrated that partial liver volumes could be safely irradiated to high doses. These studies helped to establish dose-response relationships and dosimetric parameters to guide treatment planning. One of the first articles to quantify the dependence of liver toxicity on radiation dose and volume evaluated 79 patients who received protocol-based radiotherapy for intrahepatic malignancies, 9 of whom developed classic RILD. All of the patients who developed toxicity had whole liver radiation to a mean dose >37 Gy. Subsequently, a dose escalation protocol to partial volumes of the liver evaluated the safety of giving the maximum dose possible with a 10% risk of classic RILD, which was estimated using a normal tissue complication model⁵. This prospective study demonstrated that an NTCP model could be used to safely deliver higher doses of radiation to partial volumes of the liver. Further refinement of the model parameters was made in a study of 203 patients who received radiation for liver cancers, 19 of whom developed classic RILD. This study indicated that the mean liver dose would be a useful metric to evaluate liver radiation plans because the liver exhibited a large volume effect for the development of classic RILD⁶.

Stereotactic body radiotherapy emerges as a therapeutic option

As image guidance and conformal radiation techniques improved in the 1990s and early 2000s, it became clear that radiation could be delivered at higher doses to tumors in a shorter time frame. Phase I and II studies for lung and liver cancers demonstrated that stereotactic body radiation therapy (SBRT, also called stereotactic ablative radiotherapy [SABR] when the technique achieves high rates of local control) was an excellent option for small tumors (<5 cm). In a Phase I study of 6 fraction SBRT for patients with Child-Pugh A liver function and unresectable hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma (ICC), the investigators used an individualized dosing approach that was chosen based on the risk of RILD estimated by an NTCP model⁷. The toxicity risk was escalated from 5% to 10% and 20%. This study demonstrated that the treatment was relatively safe, with 7 patients (5 HCC and 2 ICC) having worsening Child-Pugh score from A to B, while achieving a median survival of 11.7 months for HCC and 15 months for ICC. To achieve these results, the investigators used active breath hold to immobilize the liver when feasible and used daily image guidance⁸. The NTCP model to estimate the risk of RILD was based on their prior work.

While SBRT has been safe and effective for the treatment of small hepatic tumors (< 5 cm), delivering SBRT safely to large liver tumors (>7 cm) has been challenging. For example, in a report of sequential phase I and II trials of SBRT for 102 patients with hepatocellular carcinoma (HCC) who were not eligible for other locoregional therapies (median tumor size

7 cm), the locoregional control rate at 1 year was good (87%), but the rate of grade 3 toxicities was high (30%) and 7 patients may have died of treatment-related causes⁹.

One of the challenges with SBRT using photons is the radiation dose to the normal liver. One potential way to overcome this challenge is to use protons. Dosimetric studies have demonstrated that due to the Bragg peak protons can reduce the volume of liver irradiated significantly compared to photons^{10, 11}. In patients at high risk of developing non-classic RILD, such as those with cirrhosis, this may be advantageous. Japanese and American investigators have used hypofractionated proton radiation regimens for HCC with promising local control and overall survival rates^{12–14}. Notably, in a recent Phase II study of hypofractionated proton radiation therapy for patients with HCC and intrahepatic cholangiocarcinoma, a very low rate of worsening Child Pugh score (4%) was noted¹⁵. This observation and the difference in survival results between this proton study and previous SBRT studies were the reasons to conduct an ongoing phase III randomized trial comparing protons and photons for HCC (NRG GI003, NCT03186898).

Beyond radiation types to improve toxicities, fractionation to achieve ablative doses through the use of 15 to 25 treatments for large liver tumors has been associated with a substantial prolongation of survival in patients with intrahepatic cholangiocarcinoma¹⁶. Stereotactic techniques were used to achieve these results. The same principles have been applied to HCC, using either protons or IMRT¹⁷. In the following sections, we will focus on the clinical management and technical treatment principles that are integral to achieving the promising clinical results with modern radiotherapy, while mitigating the risks of RILD.

II. Pre-radiation evaluation and management

Overview

In this section, we review the causes of liver dysfunction in patients prior to irradiation, approaches to multi-disciplinary care, and functional assessment of liver function.

Etiologies of liver dysfunction

We have previously reviewed how baseline liver reserve can impact the susceptibility to RILD¹⁷. Briefly, the underlying causes of liver dysfunction can include underlying liver disease such as non-alcoholic fatty liver disease and cirrhosis (which can have many causes), limited normal liver volumes due to previous resection, compromised liver function due to prior hepatotoxic chemotherapy, and tumor-related dysfunction from vascular or biliary involvement. For a more thorough discussion of these causes of liver dysfunction and how they may impact radiation to the liver, the reader is referred to our previous review. In the evaluation of patients with any of these causes of liver dysfunction, it is important to consider the specific risks and the pre-radiation management for each group.

Risks of radiation according to underlying cause of liver dysfunction

For a given patient who is being considered for hepatic radiation, it is important to understand that patients with advanced cirrhosis demonstrate a higher risk of non-classic RILD, which presents as jaundice and markedly elevated serum transaminase^{18–20}. In

comparing patients with primary versus metastatic liver cancers, the risk of developing non-classic RILD differs considerably, as patients with primary liver cancers have a higher chance of having this toxicity after external beam radiation.²¹ The mechanisms related to higher RILD risk in patients with cirrhosis are hypothesized to be due to signaling in the TGF-beta pathway and activation of hepatic stellate cells^{22, 23}. Another risk in patients with underlying hepatitis B infection is reactivation of the virus²⁴. This can be a fatal consequence of radiation when it occurs.

The risks of RILD in patients with limited liver reserve due to previous hepatectomy or liver-toxic chemotherapies are poorly documented. In patients who have had previous surgical resection of the liver, the effective volume of the liver may be reduced overall, but the liver may compensate through regeneration. In these patients, the mean liver dose of radiation is a critical dose constraint to meet. The treating physician should utilize methods to minimize the mean normal liver dose, including motion management and image guidance, which we review in the subsequent section.

The use of hepatotoxic chemotherapies is increasing, especially for patients with gastrointestinal malignancies that often metastasize to the liver. The modes of liver injury from chemotherapy can include steatosis, steatohepatitis, and hepatic sinusoidal injury²⁵. Steatosis or fatty liver is associated with the receipt of 5-fluorouracil, and is seen in patients with obesity and diabetes. Hepatic steatosis has been associated with a higher operative risk²⁶, but higher risks of radiation-related toxicities are not well-documented. Steatohepatitis is associated with irinotecan. Studies have documented steatohepatitis rates of up to 20% in patients who receive this drug compared to a 4% rate in patients who do not receive it^{27, 28}. There is a significant risk of post-operative mortality in patients who have steatohepatitis^{27, 29}, but, to our knowledge, no reported associations between steatohepatitis and radiation-related toxicities. Specific guidelines for dose constraints to the liver in the setting of different modes of hepatic injury from prior or concurrent hepatotoxic chemotherapies are an area of opportunity for future investigation.

Assessment of liver function prior to radiation therapy

Optimizing clinical status and liver function prior to radiotherapy—Since most primary liver cancers arise in the background of cirrhosis, multidisciplinary medical management plays an important role for these patients. Cirrhosis can cause portal hypertension and hepatic dysfunction, potentially leading to ascites, variceal bleeding, and encephalopathy³⁰. Hence, careful attention needs to be paid to the prevention and treatment of complications from cirrhosis. Ideally, these patients should be referred to a gastroenterologist or hepatologist³⁰ to optimize liver function or clinical status prior to beginning radiation therapy, if feasible. Approaches may include the judicious use of non-selective beta-blockers to reduce portal hypertension in certain patients^{30, 31}, dietary sodium restriction and possibly diuretics to manage ascites^{30, 32}, paracentesis to treat patients symptomatic from large volume or refractory ascites^{30, 32}, endoscopy to identify and treat esophageal and gastric varices³³, and transjugular intrahepatic portosystemic shunt (TIPS) to reduce the risk of variceal bleeding in patients who are refractory to band ligation and beta-blockers³².

Patients with hepatic dysfunction may develop encephalopathy, with symptoms ranging from sleep disturbance, to confusion, drowsiness, and stupor^{30, 32}. Lactulose can be used to treat hepatic encephalopathy, with the dose titrated based on number of bowel movements. The antibiotic, rifaximin, can be used to control ammonia-producing intestinal flora.

Management of viral hepatitis—Many patients with hepatocellular carcinoma (HCC) have chronic hepatitis B or C (HBV or HCV). Patients with HCC and chronic hepatitis B should be considered for treatment with a nucleoside or nucleotide analog, such as entecavir or tenofovir^{32, 34}. A longitudinal study on 780 patients with resected HBV-related HCC showed that patients who received nucleotide/nucleoside analogs had lower rates of early recurrence, and improved liver function³⁵. A meta-analysis on 15 studies with 8060 patients showed that treatment with nucleotide analogs decreased recurrence rates and increased overall survival rates, in patients with HBV and HCC³⁶.

Patients with HCC and chronic HCV should be considered for treatment with direct-acting antivirals (DAA), such as the ledipasvir/sofosbuvir combination^{32, 34}. Direct-acting antivirals can lead to cure rates over 90%, thereby resulting in improved hepatic function, and lower rates of complications such as variceal bleeding³⁴. Some studies have reported higher rates of HCC recurrence in patients treated with DAA, but an analysis of three French prospective cohorts with over 6000 patients, did not show an increased risk of HCC recurrence in patients treated with DAA^{34, 37}.

Clinical systems for liver function assessment—The baseline liver function of patients with chronic liver disease has traditionally been assessed using the Child-Pugh system and the Model for End-stage Liver Disease (MELD) score³⁸. The Child-Pugh score was originally used to predict the operative risk of portosystemic shunt surgery in patients with variceal bleeding, and included ascites, hepatic encephalopathy, nutritional status, total bilirubin and albumin. It was later modified to include the international normalized ratio (INR) and removed nutritional status. Most studies of radiotherapy used this system to gauge baseline cirrhosis^{39, 40}. The MELD is most often used for patients being evaluated for transplant. It was originally calculated from serum bilirubin, creatinine and INR, but modified to include serum sodium concentration (MELD-Na)^{41, 42}. More recently, the albumin-bilirubin (ALBI) score has been developed as an objective measure of liver function⁴³. Data regarding the use of the ALBI in radiation applications is still limited, but retrospective evidence indicates similar performance of the ALBI as with the Child-Pugh score⁴⁴.

In addition to these clinical systems, another important laboratory study to consider in the evaluation of patients is the platelet level. Thrombocytopenia⁴⁵, especially in a patient with cirrhosis and splenomegaly, may be an indicator of portal hypertension. The steps mentioned above in the optimization of liver function and clinical status should be considered prior to initiating radiotherapy.

III. Functional Liver Imaging and Incorporation into Radiation Planning

Overview

Several groups have investigated the use of functional liver imaging to create avoidance sectors in radiation planning to try to mitigate the risk of RILD in patients.

Functional Imaging with ^{99m}Tc -Sulfur Colloid (SC) SPECT-CT

^{99m}Tc -sulfur colloid (Figure 1) is mostly taken up by the reticuloendothelial/Kupffer cells. In a normal healthy liver, 80–85% of this isotope is sequestered in the liver. In patients with cirrhosis or parenchymal liver damage, there is depression of the reticuloendothelial system, leading to decreased uptake of sulfur colloid. This property has made this modality useful for imaging global liver function using SPECT-CT^{46, 47}. There are some technical challenges to the technique including limited spatial resolution, difficulty with registration to CT, and altered distribution based on particle size.⁴⁸ However, these can be overcome to provide meaningful application in radiation planning and evaluation of liver function.⁴⁹ Using this approach, investigators demonstrated a 43% reduction in the amount of functional liver volume defined on the ^{99m}Tc -sulfur colloid SPECT-CT as a percentage of predicted liver volume in patients with Child-Pugh Class B cirrhosis. No advantage of this sparing was seen in patients with Child-Pugh Class A cirrhosis or non-cirrhotic patients.

In one retrospective study using ^{99m}Tc -sulfur colloid SPECT-CT into the treatment planning process to avoid functional areas of the liver, the investigators observed no incidence of RILD, grade 3 or higher hepatic toxicity, or accelerated liver failure in HCC patients with advanced cirrhosis who completed liver SBRT^{50, 51}. The outcomes in these studies are similar to prospective trials evaluating SBRT in HCC without functional treatment planning, where the incidence of grade 3 or higher hepatotoxicity ranged between 5% - 36%^{7, 52, 53}.

Prospective evaluation of treatment planning with functional imaging is being performed in a Phase I trial of hypofractionated radiation for patients with impaired liver function and liver tumors (NCT02626312). Rather than using SBRT, as described above, the study is evaluating the safety of fractionated radiotherapy in 15 or 25 fractions in this high risk patient population for RILD, using the same principles of SBRT of conformal radiation, motion management and daily image guidance.

Changes in ^{99m}Tc -sulfur colloid SPECT-CT have been used to evaluate RILD. Decreased isotope uptake has been noted in patients with fatal radiation hepatitis in the 1980s⁵⁴. More recent work at the University of Washington looking at stereotactic body radiation in cirrhotic patients imaged with ^{99m}Tc -sulfur colloid showed good correlation between change in isotope biodistribution and declining liver function based on ALBI and CP score over a longitudinal period.⁵⁵ This group has also demonstrated that baseline ^{99m}Tc -sulfur colloid SPECT-CT can be used to calculate the total liver function (TLV), a ratio formed by the threshold functional liver volume and the liver/spleen mean, and that higher TLV is correlated with improved overall survival in HCC post SBRT.⁵⁶ There is some suggestion that SPECT-CT can potentially image decreased perfusion and early damage post stereotactic body radiation as one case report showed abrogated ^{99m}Tc -sulfur colloid uptake

following chemoradiation for a metastatic lesion with pathologic correlation to their functional imaging findings.⁵⁷

The University of Washington group has also published a number of planning studies looking at avoidance of high functioning liver using both proton and VMAT photon plans.^{58, 59} Most recently, they have published a series on 87 patients treated with liver SBRT using functional optimization with ^{99m}Tc-sulfur colloid SPECT-CT in which no grade 3 and above toxicity was seen while maintaining excellent local control.⁵¹ Building on these promising results, they currently have a trial open evaluating the role of SPECT-CT for radiation therapy and surgical planning for primary and metastatic liver cancers (NCT02881554).

Indocyanine Green for Evaluation of Global Liver Function

Indocyanine green (ICG) is a dye that when injected into the systemic circulation goes through a significant first pass effect in the normal liver. In healthy individuals, ICG shows a high hepatic extraction rate (above 70%), and toxicity is very low⁶⁰. It is preferentially taken up in hepatocytes. In the non-cirrhotic normal liver, much of this green dye is eliminated from the circulation; hence, blood draws to measure residual ICG using spectrophotometry or noninvasive oximetry measurement should show rapid clearance and disappearance of the dye. Conversely, patients with underlying metabolic liver disease retain high levels of ICG in the circulation as hepatocellular uptake is compromised.^{61–63}

ICG is routinely used in Asia and parts of Europe to evaluate liver function prior to transplant and post transplant, as well as post-hepatic resection residual liver function⁶⁴. It has been shown to be predictive of survival in combination with traditional liver metrics such as Child-Pugh score, albumin, and bilirubin.^{65–68} In interpreting ICGR15 (percentage of retained ICG at 15 minutes), a normal value would be in the range of 4–10%. Most cirrhotic patients have values that exceed this. The addition of the ICGR15 value to standard liver function indices can improve the prediction of hepatic decompensation post radiotherapy in cirrhotic patients.^{69, 70} In particular, an increase in the ICGR15 value post radiotherapy was highly associated with the development of RILD.^{69, 70} While baseline values of ICGR15 may be helpful, the change in this value after radiation therapy appears to be most indicative. This makes it challenging to anticipate the best treatment approach *a priori*. Further, ICG is purely a functional blood test and does not provide any spatial information about liver function itself.

Extrapolating from the surgical literature, the University of Michigan has been evaluating the application of ICG in evaluating radiation induced liver disease. Their group has shown a close correlation between the 1 month post radiation ICG measurement and portal vein perfusion of the liver parenchyma on dynamic contrast enhanced CT and MRI.^{71, 72} Stenmark et al. showed that ICGR15 was highly correlated with RILD, especially when used to characterize the damage fraction of functional liver (DFL) which was essentially a ratio of preRT ICGR15/postRT ICGR15. An independent Japanese study by Kawashima et al. showed a correlation between ICGR15 > 50% and mortality after high dose proton irradiation of unresectable HCC.¹³

Based on these findings, a Phase II study evaluated whether radiotherapy could be adapted based on functional imaging and ICGR15 measurements prior to treatment, at mid treatment, and after treatment. Patients received 3 fractions initially and had a 4 week break. After this break, a mid treatment ICGR15 was used to adapt the final 2 fractions.⁷³ This phase II trial included 90 patients and was completed in 2014 and published recently showing 2 year local control of 95% for both HCC and liver metastases and only an 8% risk of change in CP score > 2 (their definition of hepatic decompensation).⁷⁴ An ongoing trial extends adaptive radiotherapy to patients who have CPB8 and above liver function and patients with CPA/B7 cirrhosis with tumors larger than 3.5 cm (NCT02460835).

Eovist-Based MRI Functional Liver Imaging

Eovist, also known as gadoxetate disodium, is a liver specific gadolinium based contrast agent that is specifically transported into hepatocytes. Patients with impaired liver function, particularly cirrhosis, have altered expression of the membrane transporter proteins that ferry Eovist into hepatocytes. Enhancement with Eovist is also dependent on liver perfusion, vascular permeability, and extracellular diffusion all of which are affected by liver fibrosis and cirrhosis. Thus, Eovist-mediated enhancement of the liver parenchyma can be used to measure functional liver.^{75–77} As a corollary, Eovist enhancement as a measure of liver function is correlated with ICGR15 retention.^{78, 79}

The advantage of Eovist-enhanced MRI is the excellent spatial resolution it provides in mapping out functional pockets within the liver. Changes in Eovist uptake have been correlated with post-radiation liver damage. Various studies have shown a dose threshold in Eovist hypoenhancement (decreased uptake) in the hepatobiliary phase post-SBRT for HCC in cirrhotic patients. Okamoto et al. has described absorbed radiation dose dependent changes in Eovist uptake by analyzing different segments of the liver that received differential radiation dosing.⁸⁰

Jung et al. reported a 20 Gy threshold (after 45 Gy/3 fractions) for D50 and MR Eovist-enhanced liver parenchymal changes.⁸¹ Sanuki et al. proposed that Childs Pugh A patients can have a threshold dose of 30 Gy while Childs Pugh B patients have a threshold dose of 25 Gy based on Eovist enhancement changes post SBRT.⁸² Doi et al. proposed a threshold dose of 40–70 Gy in BED.⁸³ Studies examining brachytherapy in the liver illustrated a timeline of hepatic edema and decreased hepatic Eovist enhancement at 6–12 weeks post radiation corresponding to possible early radiation liver damage.^{84, 85} Universally, these studies show decreased Eovist enhancement in areas subjected to radiation as an early indicator of hepatocyte dysfunction.

The use of functional MR with radiation planning is still in its infancy. There is little published on incorporating Eovist in functional planning. One recently published article used Eovist MR to define functional liver volumes for SBRT planning in HCC patients showing that PTV coverage and OAR constraints could be safely met without compromise.⁸⁶ The University of Michigan has also published on using voxel level gadolinium-based MR perfusion to delineate functional avoidance sectors for optimization of liver radiation planning.^{87, 88} This group proposes a model-based planning algorithm that not only utilizes functional liver imaging but also other clinical measures such as ICGR15, CP score, tumor

size, mean liver dose, and biomarkers to generate a global functional model.⁸⁸ A number of studies are ongoing to incorporate and evaluate the utility of MR based radiation planning including one at the University of Michigan (NCT02460835) and one at Duke University (NCT02722395).

IV. Radiation treatment planning process

Overview

One of the keys to minimizing the risks of radiation treatment to the liver is achieving the proper simulation setup and using advanced technologies to control motion and ensure proper daily alignment. These topics have been previously reviewed¹⁷. Here, we focus on principles of treatment planning.

The Evidence for Liver Constraints

Careful evaluation of the radiation treatment plan is critical for reducing the risk of classic and non-classic RILD. The factors that need to be considered include the radiation dose, fraction size, volume of liver radiated, and hepatic function.

The initial studies on classic RILD were based on whole liver radiation, with a reported risk of 44% at > 35 Gy⁸⁹. In a Radiation Therapy Oncology Group (RTOG) dose-escalation trial of whole liver radiation in 1.5 Gy twice daily fractions, no patient developed classic RILD after treatment with 27–30 Gy, while 10% of patients developed classic RILD after treatment with 33 Gy⁴. The risk of classic RILD was estimated to be 5% when the whole liver was treated with 30 Gy in 2 Gy per fraction^{90,91}.

Contemporary studies have evaluated the risk of RILD after partial liver radiation^{39,90}. Multiple studies have demonstrated an association between RILD and the mean normal liver dose³⁹. Investigators at the University of Michigan have done extensive work on the Lyman normal tissue complication probability (NTCP) model for RILD^{6,39}. In a study on 203 patients treated with conformal liver radiation at the University of Michigan, no patient developed classic RILD when the mean liver dose was <31 Gy⁶. The median value of the mean liver dose was 31.3 Gy in patients who did not develop RILD, compared to 37.0 Gy in patients that developed RILD. Furthermore, patients with primary hepatobiliary cancers had a higher risk of RILD, compared to those with liver metastases, indicating the important role of underlying hepatic function⁶. Based on the Lyman NTCP model, the mean liver dose associated with 5% risk of classic RILD was estimated to be 37 Gy in 1.5 Gy fractions and 32 Gy in 2 Gy fractions for patients with liver metastases, and 32 Gy in 1.5 Gy fractions and 28 Gy in 2 Gy fractions for patients with primary liver cancers⁶.

Multiple other studies have shown an association between hepatic function and RILD³⁹. In a study from China on 109 patients with primary liver cancers, both classic and non-classic RILD were observed after 3D conformal radiation therapy, and the overall rate of RILD was 9% in Childs Pugh grade A patients, and 56% in Childs Pugh Grade B patients²⁰. Among the Childs Pugh A subgroup, the tolerance dose for the normal liver was estimated to be 23 Gy²⁰. Dose constraints for patients with more advanced cirrhosis are not well delineated.

One approach is to risk-adjust the dose constraint based on the Childs Pugh score, reducing the allowable mean liver dose as the degree of hepatic dysfunction worsens (Table).

In patients treated with hypofractionated radiation therapy or with stereotactic body radiation therapy (SBRT), a critical volume of normal liver should be kept below a threshold dose that causes hepatic injury^{39, 92}. In a landmark phase I/II trial of SBRT for liver metastases, a minimum volume of 700 cc of normal liver was required to be kept below a total dose of 15 Gy, based on the assumptions that (1) 15 Gy in 3 fractions would have a lower biologically equivalent dose than that for liver tolerance, and (2) 500 cc of residual liver volume appears sufficient after surgical resection of non-cirrhotic livers⁹². Based on the excellent results from this trial, 700 cc of liver has been widely accepted as an acceptable critical volume of normal liver that should be kept below a threshold dose (DC700cc).

The DC700cc criteria is an especially important metric associated with non-classic RILD. Barry et al. from the Princess Margaret Group recently published a detailed analysis and timeline of radiation liver toxicity within the first 3 months of liver SBRT. In their 81 patient cohort of non-cirrhotic patients post SBRT to liver metastases, they confirmed that DC700 remained the prevailing factor associated with acute transaminitis and reduced albumin. Nearly 50% of patients experienced a transient rise in aminases that resolved by 3 months with very little long term toxicity as long as the DC700 was not violated¹⁰⁶.

In cirrhotic patients, CP score and ALBI are commonly used to delineate post SBRT decompensation. A recent study showed that baseline CP score and higher liver doses (DC700, Veff and mean liver dose) were all strongly associated and predictive of liver function decline 3 months post SBRT in cirrhotic patients.¹⁰⁷ Similarly, when using the more objective ALBI score, the dose to spared liver remained the greatest predictor for hepatic decline with worse post treatment ALBI correlated with poorer overall survival.⁴⁴

In addition to the risk of RILD, radiation therapy to the liver can also lead to central hepatobiliary toxicity, with events such as central biliary obstruction and hepatobiliary infection^{93, 94}. The risk of central hepatobiliary toxicity appears to be correlated to the dose to the central biliary tract, instead of the dose to the liver as a whole⁹³. A study on 130 patients treated with SBRT, showed that the strongest predictors for central hepatobiliary toxicity were V_{BED10}40 and V_{BED10}30⁹³.

A Practical Approach for Treatment Plan Evaluation

Based on the evidence discussed above, at the University of Texas MD Anderson Cancer Center, the following constraints are typically used for treatment plan development and evaluation (Table 1).

During treatment plan evaluation, attention must be paid to the specific isodose distribution, including that for intermediate doses, such as 20–30 Gy. Adjustments in beam arrangement and weighting can help make the 20–30 Gy isodoses more conformal, thus sparing more of the normal liver. For instance, instead of uniformly weighting beams from all directions, preferentially weighting beams that enter through the liver tumor, can help spare more of the normal liver. As discussed above, special attention needs to be paid to the dose at the central

hepatobiliary region. For patients treated with SBRT, the Stanford group recommends a central biliary tract dose of $V_{BED10}40<37$ cc, and $V_{BED10}30<45$ cc⁹³. Treatment plan evaluation should also take into account dose to other normal structures, including the esophagus, stomach, duodenum, other small bowel, large bowel, kidneys, heart, and abdominal/chest wall; however, a detailed discussion of those constraints is outside the purview of this article.

V. Response to liver radiation and management of toxicities

Hypertrophy

The parallel structure of the liver's functional units is a key reason that focal ablation with radiation or other treatments can be safely performed. It has been noted that the liver can compensate for lost functional units through hypertrophy. For example, the degree of hypertrophy after proton beam radiotherapy ranged from -19% to 51% and was associated with the ratio of the planned treated liver volume with the total liver volume.⁹⁵ Left liver hypertrophy has been noted after radioembolization of the right liver with ⁹⁰Y,⁹⁶ and predictors of liver hypertrophy are generally related to patients with better baseline liver function (or surrogates thereof), including small spleen volume, low Child Pugh score, platelet count 100/nl or greater, as well as others.⁹⁷ Predicting this normal liver hypertrophy prior to liver-directed radiotherapy or other treatment is of keen interest, as it would be helpful in surgical and transplantation decision-making. Currently, a clear understanding does not exist for determinants of liver hypertrophy/atrophy and methods to optimize this effect of liver-directed treatments.**RILD**

Once a patient has developed classic or non-classic RILD, best supportive care is generally the only management that can be done. This supportive care may include diuretics or paracentesis for fluid management, analgesics for pain, and steroids for hepatic congestion.⁴⁰ The treatment of veno-occlusive disease after bone marrow transplantation has been investigated with tissue plasminogen activator, showing success in 29% of a small retrospective cohort but with significant risk of hemorrhage.¹⁰⁸ Defibrotide has also been used in this context with some success.¹⁰⁹ The emphasis in the RILD literature is to prevent it or minimize the risk. There have been a small number of prospective trials examining radioprotective agents. Feng et al. reported on the use of amifostine with whole liver radiation for diffuse metastatic disease in the liver, with classic RILD in only 4 of 23 patients despite treating to doses of 40 Gy or more to the whole liver.¹¹⁰ Another group used MR changes as an indication of early radiation induced liver injury and found that low molecular weight heparin, pentoxifylline and ursodeoxycholic acid were protective.¹¹¹ Other proposed targeted therapies including hedgehog inhibitors and CXCR4 inhibitors are currently under investigation.⁹⁹ For cirrhotic patients who are transplant candidates, a new liver may be the only cure after decompensation from liver-directed radiotherapy.

The reactivation of hepatitis B is a well-recognized phenomenon with both radiation¹⁰⁰ and chemotherapy¹⁰¹, and can have devastating consequences. Treatment of the chronic infection prior to radiation may mitigate this risk, as discussed earlier. Central liver toxicity, as mentioned earlier, has also emerged as a concern in the modern era, as biliary obstruction

and hepatobiliary infection can become major challenges in the management of patients, requiring long-term antibiotics as well as biliary drainage solutions⁹³.

Summary

We have reviewed the evolution of radiation to the liver, the multi-disciplinary management principles for patients with primary and secondary malignancies of the liver, the tenets of simulation and treatment of liver cancers, and the approach to managing hepatic toxicities from radiation. The emergence of modern radiotherapy techniques has helped to minimize the toxic side effects of radiation to the liver, and ongoing studies will help refine the clinical indications for radiation treatment for patients with liver tumors.

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Figure 1.

(A) Axial view of a 78 year old male with chronic hepatitis B-related cirrhosis and a large hepatocellular carcinoma. The fused images are from a ^{99m}Tc -sulfur colloid SPECT-CT scan that was performed prior to proton radiation treatment planning. The photopenic area in the liver is the tumor. There is a radio-opaque carbon fiducial at the periphery of the liver, which was used for image guidance along with two other peri-tumoral fiducials.

(B) Coronal view of a proton radiation plan of the same patient who underwent ^{99m}Tc -sulfur colloid SPECT-CT functional imaging prior to planning. The functional liver volume is shown in the white shaded areas, and the radiation dose distribution is shown in the colorwash. The prescribed dose was 6750 cCGE (Cobalt Gray Equivalents) in 15 fractions.

Figure 2.
Immobilization and motion management during CT simulation

Table 1:

Radiation dose constraints based on Childs-Pugh class

Fractionation	Childs Pugh Class	Mean Normal Liver Dose	700 cc Normal Liver Below
Conventional (1.8– 2 Gy daily)	A	28 Gy	28 Gy
Conventional (1.8– 2 Gy daily)	B	24 Gy	24 Gy
Hypofractionation (3–4.5 Gy daily)	A	24 Gy	24 Gy
Hypofractionation (3–4.5 Gy daily)	B	18 Gy	18 Gy
SBRT (3–5 fractions)	A	13–15 Gy	15 Gy
SBRT (5 fractions)	B	10 Gy	15 Gy and at least 500 cc of normal liver below 7 Gy