Published in final edited form as:
Semin Radiat Oncol. 2011 October ; 21(4): 256–263. doi:10.1016/j.semradonc.2011.05.003.

Hepatic Radiation Toxicity: Avoidance and Amelioration

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Abstract

The refinement of radiation therapy and radioembolization techniques has led to a resurgent interest in radiation-induced liver disease (RILD). Awareness of technical and clinical parameters that influence the chance of RILD is important to guide patient selection and toxicity minimization strategies. “Classic” RILD is characterized by anicteric ascites and hepatomegaly, and is unlikely to occur after a mean liver dose of approximately 30 Gy in conventional fractionation. By maintaining a low mean liver dose and sparing a “critical volume” of liver from radiation, stereotactic delivery techniques allow for the safe administration of higher tumor doses. Caution must be exercised for patients with hepatocellular carcinoma or pre-existing liver disease (e.g., Child-Pugh score of B or C), since they are more susceptible to RILD that can manifest in a non-classic pattern. Although no pharmacologic interventions have yet been proven to mitigate RILD, preclinical research demonstrates the potential for therapies targeting TGF-β and for transplantation of stem cells, hepatocytes, and liver progenitor cells as strategies that may restore liver function. Also, in the clinical setting of veno-occlusive liver disease following high-dose chemotherapy, agents with fibrinolytic and antithrombotic properties can reverse liver failure, suggesting a possible role in the setting of RILD.

INTRODUCTION

Recent technological advances in the planning and delivery of radiation therapy in a more tightly focused manner have provided a means to treat primary and metastatic liver cancer much more safely and effectively than in previous decades. There is also growing interest in radioembolization, also called selective internal radiation therapy, which involves hepatic arterial infusion of Yttrium-90 microspheres to deliver a higher radiation dose to the tumor vasculature relative to surrounding normal parenchyma. As a result of the heightened interest in both of these forms of treatment, it remains important to understand the types of toxicity that have been observed and their predisposing clinical factors, so that the risk of serious radiation-induced hepatic toxicity may be minimized. Furthermore, a burgeoning body of evidence characterizing the pathophysiologic mechanisms of radiation injury to the liver might soon lead to new biological or pharmacological interventions that can relieve or reduce hepatic dysfunction in the setting of primary or treatment-induced liver dysfunction.

Radiation injury to the liver following conventionally fractionated radiotherapy was first described several decades ago, and it was soon thereafter recognized to have the histopathologic features of veno-occlusive disease (VOD) [1, 2]. In a modern context, the same normal tissue changes have been described following high dose-per-fraction stereotactic body radiation therapy (SBRT) [3].

Currently the generally accepted best means of treating radiation injury to the liver is to try to avoid it entirely by limiting the volume of normal liver exposed to potentially injurious radiation doses. Here, the available data concerning the relationship between radiation dose to liver and risk of liver toxicity are reviewed, and dose volume parameters associated with a reduced risk of toxicity are described. Finally, preclinical and pilot studies of novel approaches that may mitigate radiation induced liver toxicities are discussed.

Clinical Syndromes and Endpoints for Radiation Induced Liver Toxicity

The clinical scenario commonly called “classic” radiation induced liver disease (RILD) occurs typically within 4 months following hepatic radiation therapy. The patient presents with fatigue, weight gain, increased abdominal girth, hepatomegaly, anicteric ascites, and an isolated elevation in alkaline phosphatase out of proportion to other liver enzymes. The characteristic initial finding is relatively normal liver function tests and normal bilirubin and ammonia levels [4].

In contrast to this “classic” RILD, patients with underlying chronic hepatic disease such as cirrhosis and viral hepatitis may present with liver function abnormalities that do not match the criteria above, including jaundice and/or markedly elevated serum transaminases (> 5 times the upper limit of normal) within 3 months of completion of hepatic RT [5–7]. All these hepatic toxicities have been included under the umbrella label of “non-classic RILD”.

Hepatic VOD, or combined modality induced liver damage, CMILD, has also been seen as part of a spectrum of multi-organ failure syndromes that occur within 3 weeks of completion of a preconditioning regimen of high-dose chemotherapy with or without radiation therapy (RT) for **allergenic** bone marrow or hematopoietic stem cell transplantation [8–10]. These patients usually present with hyperbilirubinemia ≥ 2mg/dl within 21 days of stem cell transplantation and at least two of the following symptoms or signs: painful hepatomegaly, ascites and/or weight gain >5% of the baseline. Profound thrombocytopenia, due to splenic sequestration from portal hypertension and/or consumption through endothelial injury, is also seen [11].

With the approval of sorafenib in the treatment of advanced hepatocellular carcinoma [12,13] there have been efforts to combine RT with this agent [14,15]. RT has also been combined with sunitinib in the treatment of liver cancer, and there appears to be limited hepatic toxicity from the combination of sunitinib and hypofractionated partial liver RT to a dose of 52.5 Gy in 15 fractions [16]. However, the possibility of observing CMILD has to be considered while planning phase I/II trials of liver RT with these and other new biologic agents, whose full spectrum of potential toxicity in combination with RT might not yet be known. Such toxicity could manifest as a combination of sinusoidal endothelial and hepatocellular injury with signs of VOD and liver function abnormality as seen in patients receiving stem cell transplantation.

The Child-Pugh scoring system (based on ascites, encephalopathy, albumin, bilirubin and international normalized ratio (INR) for the prothrombin time) and the Cancer Therapy Evaluation Program, Common Terminology Criteria for adverse events (CTCAE), version 3.0, have been used to grade the prognosis of RILD in the radiation literature [17]. It has recommended that the baseline Child-Pugh score and changes following radiation therapy be

recorded as a crude indicator of liver function. However, a better measure of liver function and prognosis might be the Model for End-Stage Liver Disease (MELD) score. The MELD score is calculated from the serum bilirubin, creatinine and the INR, and has been used for determining the prognosis of patients with hepatocellular carcinoma and cirrhosis, especially those who are on the liver-transplant waiting list [18,19]. The MELD score has been further modified to include the serum sodium concentration as a key prognosticator in patients with end-stage liver disease [20] [21]. Since the MELD-Na score has been shown to be an independent prognostic factor of survival in hepatocellular carcinoma [22], we recommend MELD-Na score to be measured in patients with liver injury following RT and/or chemotherapy.

Pathophysiology of Radiation Induced Liver Toxicity

The pathological hallmark of RILD, VOD, is characterized by complete obliteration of central vein lumina by erythrocytes trapped in a dense network of reticulin and collagen fibers that crisscross the lumen of the central veins, sublobular veins, and centrilobular sinusoids [2,23,24]. Collagen proliferates along the hepatic sinusoids and produce mild congestion in peri-portal areas. Centrilobular hepatocytes are largely absent, presumably due to hypoxic cell death secondary to vascular congestion. After approximately four months, vascular congestion resolves as the liver begins to gradually heal.

Based upon these findings, it was postulated that radiation injury to sinusoidal endothelial cells and central vein endothelium initiates activation of the coagulation cascade, leading to accumulation of fibrin and formation of clots in the central veins and hepatic sinusoids [4]. The fibrin serves as a scaffold for the deposition of reticulin and collagen, which eventually occludes the vessel. The trapping of erythrocytes produces vascular congestion and decreased oxygen delivery to the central zone. This hypoxic milieu presumably results in death of centrilobular hepatocytes and atrophy of the inner hepatic plate, producing the hepatic dysfunction observed clinically in RILD.

Recently, the term sinusoidal obstructive syndrome (SOS) has been proposed as a better description of the pathology of liver injury seen after administration of chemotherapy with or without RT [25]. The earliest morphological change in SOS is edematous widening of the subendothelial space of central and sublobular veins by fragments of erythrocytes and cellular debris [26–28], accompanied by sinusoidal dilatation and engorgement, erythrocyte penetration into the space of Disse, and necrosis of perivenular hepatocytes [25]. The sinusoidal pathology and subsequent hepatocellular damage in SOS is typically more prominent than the central vein changes, an important difference from classic RILD. In addition to endothelial cell damage, hepatic stellate cell activation is noted in patients with severe congestive changes of classic RILD [29]. Stellate cells **and** have multiple functions, including, participation in the regeneration of hepatocytes, secretion of lipoproteins, growth factors, and cytokines that play a key role in modulating inflammation and fibrosis [30,31]. Of these cytokines, transforming growth factor beta (TGF-β) has been implicated in the subendothelial and hepatic fibrosis in RILD. Anscher et al. described the radiation dose dependence of the level of TGF-β in irradiated rat liver [32]. The same group reported that patients who developed VOD following induction chemotherapy and bone marrow transplantation had significantly higher levels of pre-transplantation TGF-β as compared to patients who did not develop VOD and to normal controls [33].

In the non-classic RILD syndromes, hepatocellular loss and dysfunction along with hepatic sinusoidal endothelial death and stellate cell activation is noted. This pathology could be secondary to radiation-induced mitotic catastrophe of regenerating hepatocytes in cirrhotic livers and reactivation of Hepatitis B virus in patients with chronic viral hepatitis. These patients develop elevated serum transaminases rather than elevated alkaline phosphatase and

nonmalignant ascites, indicating severe radiation-induced injury to the hepatocytes [34]. Patients with Hepatitis B Virus carrier status have been shown to have an increased risk of this toxicity, compared to the non-carrier group. Chou et al. demonstrated that the HBV reactivation is due to a bystander effect, whereby IL-6 is released from endothelial cells after irradiation, which acts upon infected hepatocytes to stimulate HBV replication [35].

PREVENTION OF RADIATION-INDUCED LIVER TOXICITY

Dose-complication relationships after whole liver irradiation

The topic of whole liver tolerance to external beam radiation therapy is well analyzed in the QUantitative Assessment of Normal Tissue Effects in the Clinic (QUANTEC) project review [17]. Widely credited with the first report of a dose-response relationship for severe toxicity to the liver are Ingold and colleagues, who noted ascites and hepatomegaly in 1 of 8 patients who received 30–35 Gy over 3–4 weeks versus 12 of 27 patients who received >35 Gy [1]. Later, in the landmark 1991 report by Emami and colleagues, the whole liver tolerance dose expected to yield a 5% risk of liver failure 5 years after treatment (TD 5/5) for whole liver radiation was estimated to be 30 Gy in 2 Gy fractions [36]. Subsequent prospective studies yielded results largely concordant with this estimate: in the RTOG 84–05 dose escalation study of accelerated hyperfractionation for liver metastases, none of the 122 patients who received 27–30 Gy in twice daily 1.5 Gy fractions of whole liver radiation therapy experienced severe radiation-induced liver disease (RILD), whereas 5/51 who received 33 Gy in 1.5 Gy fractions developed RILD [37].

In the treatment of primary and metastatic hepatic malignancies via Yttrium-90 microsphere radioembolization, the normal liver parenchyma is exposed to a variable dose of radiation depending on the total activity infused and patient-specific characteristics of hepatic arterial blood flow. Kennedy and Salem reviewed the published literature on radioembolization and extracted a rate of grade 2–3 RILD of 0–4% across the studies reviewed, though a dose-risk relationship was not provided [38]. The characteristics of RILD described included progressive ascites, elevation of alkaline phosphatase and other liver enzymes with or without elevated total bilirubin.

A substantially higher rate of serious toxicity was reported by Strigari and colleagues in a recent study not included in the Kennedy-Salem review [39]. Among 73 patients with hepatocellular carcinoma treated by Yttrium-90 radioembolization, grade 2 liver toxicity (medically significant but not immediately life-threatening; mild encephalopathy; varices or ascites; hospitalization indicated; disabling; limiting self-care activities) was observed in 11% (8/73) of patient, and grade 3 liver toxicity (hepatic coma, life-threatening encephalopathy; urgent intervention indicated) in 9% (7/73). Grade 4 (fatal) liver toxicity was observed in 11% (8/73) of the patients. The authors estimated that the delivered mean dose to normal liver associated with a 50% risk of grade 2 or higher toxicity was 52 Gy, which corresponds to a biological equivalent dose (BED) of 93 Gy, assuming linear-quadratic (LQ) formalism with an alpha/beta ratio of 2.5 Gy for normal liver. Direct comparisons to published external beam treatment series are challenging given the very heterogeneous dose deposition with radioembolization and different toxicity grading scales employed.

Radiobiological architecture of the liver: implications for partial liver irradiation

The liver parenchyma is arranged in a radiobiologically parallel architecture that allows for high dose treatment to subvolumes of the liver as long as the mean dose the non-tumorous regions is low enough to minimize the risk of global functional compromise. Furthermore, the liver can regenerate to some extent, providing an additional opportunity for functional

recovery. This notion is supported by surgical series including non-cirrhotic patients, for whom extensive resections of 75–80% of the normal liver can be safely performed [40].

Clinical data supporting the parallel architecture model for liver parenchyma include the experience accumulated at the University of Michigan using a hyperfractionated split course regimen. In one of the group's initial reports, the Lyman normal tissue complication probability (NTCP) model was applied to characterize the risk of RILD, as a function of the delivered dose-volume histogram analysis of normal liver. Here, RILD was defined as Radiation Therapy Oncology Group Grade 3 or higher toxicity developing within 4 months following treatment (classic RILD requiring treatment, at least 2 times elevation of serum alkaline phosphatase, non-malignant anicteric ascites) [41]. No RILD was observed when the mean liver dose was <31 Gy (corrected to 2 Gy fraction equivalent doses using the linear-quadratic model). The corrected mean liver dose in 1.5 Gy fractions, associated with a 5% risk of RILD was higher for patients treated for liver metastases (37 Gy) than for hepatobiliary cancer (32 Gy), consistent with numerous reports demonstrating a higher risk of toxicity among patients with worse baseline liver dysfunction [5,6,42,43]. It should be noted that all patients in this series were treated with hepatic arterial infusion of fluorodeoxyuridine or bromodeoxyuridine, and the radiotherapy scheduled included a planned break after 2 weeks of treatment. Patients treated with bromodeoxyuridine had an increased risk of toxicity compared to those treated with fluorodeoxyuridine.

Studies involving patients treated with hypofractionated stereotactic body radiation therapy (SBRT) have rarely included any occurrences of classic RILD for patients who have intact baseline liver dysfunction (i.e. liver metastases and no cirrhosis). The dominant reason for the typical low risk of RILD after SBRT is likely the substantial difference in normal liver dose distribution, including a lower mean dose and minimization of dose to larger volumes of the normal liver. For example, Schefter and colleagues applied a "critical volume" constraint in a Phase I dose escalation study of liver SBRT whereby 700 cc of liver was required to receive 15 Gy in 3 fractions or less [44]. No symptomatic liver toxicity was observed, and the dose to the planning target volumes was safely escalated to 60 Gy in 3 fractions when adhering to this guideline. It is not possible to know whether the safety was a result of this critical volume constraint per se or simply the fact that the uncorrected mean dose to uninvolved liver ranged from 3–24 Gy (median, 15 Gy in 3 fractions). However, independent support for the critical volume approach is provided in the study of SBRT for hepatocellular carcinoma reported by Son and colleagues [45]. Among 36 evaluable patients treated with SBRT for small unresectable hepatocellular cancer to a dose of 30–39 Gy in 3 fractions, only 1 patient (3%) experienced classic RILD, but 4 patients (11%) experienced a progression in Child-Pugh class, consistent with other reports of hepatocellular carcinoma patients. A multivariate analysis revealed that the only dosimetric parameter significantly associated with the risk of worsened Child-Pugh class was the volume of liver that received 18 Gy or less. The authors recommended that the volume receiving less than 18 Gy should be at least 800 cc to minimize the risk of Child-Pugh class progression.

Regarding the difficulty of comparing dose limits that are tolerated with SBRT to dose limits that are tolerated using conventionally fractionated RT, it should be appreciated that although the prescription dose per fraction differs, for both strategies the majority of normal liver tissue receives a dose per fraction substantially lower than the prescription dose, since multiple beams and/or dynamic conformal arcs are used to minimize the high dose volume, steepen the dose falloff outside the PTV, and avoid dose hotspots outside the PTV. It is unknown whether traditional linear quadratic modeling is appropriate to relate the biological effect of high dose per fraction schedules into equivalent low dose per fraction effects, and alternative models have been proposed [47]. A thorough discussion of this topic is beyond the scope of the present review.

One other important caveat regarding the use of SBRT for hepatocellular cancer is that just as with conventionally fractionated schedules, patients with severe underlying baseline liver disease are at higher risk for radiation-induced liver toxicity. Cardenes and colleagues conducted a multi-institutional phase I dose escalation study of SBRT given in 3 fractions for HCC [46]. Patients with either Child-Pugh Class A or B disease were eligible. The prescription dose was escalated to 48 Gy (16 Gy/fraction) in Child-Pugh class A patients without any dose-limiting toxicity. But despite the same constraint that seems to serve well for Child-Pugh Class A patients, namely requiring that at least 700 cc of uninvolved liver received less than 15 Gy, 2 patients with Child-Pugh class B disease developed CTCAE grade 3 hepatic toxicity at the 42 Gy (14 Gy/fraction) level. As a result, the investigators reduced the prescription dose for Child-Pugh Class B patients to 40 Gy in 5 fractions; 5 patients then received this dose without any SBRT-attributable grade 3 toxicity, and it was thus suggested to be the maximum tolerated dose by the study's supervising data safety and monitoring board.

Table 1 summarizes the suggested dose limits put forth by the QUANTEC upper abdomen study group for the treatment of primary or metastatic cancers in the liver using external beam radiation therapy. The group did not comment on dose limits after hepatic arterial radioembolization. The recommendations were intended as conservative guidelines for off-protocol treatments, subject to refinement and individualization as more published data accumulate. The ALARA (as low as reasonably achievable) principal always holds.

AMELIORATION OF LIVER INURY

Potential biomarkers for liver toxicity

Although biomarkers of radiation related liver toxicity have not been systemically investigated, various markers of sinusoidal endothelial cell injury have been investigated to predict VOD in patients with bone marrow transplantation [10]. Elevations in plasminogen activator inhibitor (PAI-1), probably produced by activated stellate cells and damaged endothelial cells [48], confirmed the diagnosis of VOD, particularly when associated with hyperbilirubinemia [49]. Serum levels of hyaluronic acid are also elevated in patients with VOD [50] and have been shown to be a marker of sinusoidal endothelial injury in rodents after liver irradiation [51]. Elevation of tissue factor pathway inhibitor, soluble tissue factor, thrombomodulin, P- and E-selectin have also been seen in these patients indicating ongoing endothelial stress [10]. Since stellate cell-mediated hepatic subendothelial fibrosis is ongoing in RILD and VOD, markers of fibrosis, such as TGF-β [33], collagen propeptide and N-terminal peptide of type III procollagen remain elevated [52, 53]. Multifactorial defects in the coagulation system, as suggested by low levels of protein C and anti-thrombin III, may contribute to the pathogenesis of VOD[54]. Another interesting marker that could predict the occurrence of VOD is the von Willebrand factor-cleaving protease, ADAMTS13, which is solely synthesized by the liver. Plasma ADAMTS13 activity was significantly reduced in VOD patients, even before the conditioning regimen was administered [55].

Imaging of liver toxicity

Characterizing RILD by non-invasive imaging has been challenging, and the techniques are evolving. CT findings within the irradiated portion of the liver after conventionally fractionated radiotherapy consist of a reversible, generally well demarcated region of reduced enhancement compared with the corresponding liver, possibly representing increased water or fat content in the irradiated liver [56–58]. Likewise, a similar initial hypodense reaction is seen on CT scans following high dose stereotactic treatment [59]. There can be eventual atrophy of the irradiated segment and hypertrophy of the untreated

liver. However, these radiographic findings do not correlate with clinical manifestation of RILD.

Portal perfusion is reduced secondary to radiation-induced hepatic SOS; therefore, noninvasive quantitation of liver perfusion may predict induction of RILD [60]. Cao et al, performed dynamic contrast-enhanced CT and an indocyanine green (ICG) clearance study to measure liver perfusion and function, following hepatic RT [61]. This study demonstrated a decrease in portal perfusion post-RT, indicating radiation-induced SOS. Not unexpectedly, there was substantial variability in the individual sensitivity to hepatic radiation injury and there was a significant correlation between ICG clearance and the mean of the estimated portal vein perfusion. A limitation of CT perfusion studies is that although they show blood flow, they provide little if any information regarding hepatocellular function.

Asialoglycoprotein receptor (ASGPR) uptake scans using non-invasive single-photon emission computerized tomography (SPECT) have the potential to quantify hepatocyte function. ASGPRs are receptors found on the sinusoidal surface of hepatocytes that mediate the removal of serum glycoproteins, lipoproteins, fibronectin, and apoptotic cells. Iguchi et al have shown ASGPR SPECT correlates well with liver fibrosis [62]. The uptake and subsequent endocytosis of labeled asialoglycoproteins can be imaged to distinguish functional regions of hepatocytes from non-functional zones.

Similar to CT, MRI demonstrates changes following liver radiation. Decreased signal intensity on T1-weighted images, increased signal intensity on T2-weighted images, and increased signal intensity on proton spectroscopic imaging of irradiated liver lobes suggests that the irradiated liver has increased water content [57]. Hepatic irradiation inhibits the phagocytic capacity of Kupffer cells in rodents [51]. Superparamagnetic iron oxide (SPIO) is a particulate MR contrast agent that is selectively taken up by the Kupffer cells and SPIO-enhanced T2-weighted gradient echo (GRE) imaging could be used to detect subclinical RILD. This imaging technique was recently used to detect subclinical SOS induced by oxaliplatin [63].

Treatment of radiation-induced liver toxicity

No pharmacologic therapy is currently available to relieve radiation-induced liver toxicity. In the late 1970s, Lightdale and colleagues observed an apparent protective benefit from the use or anticoagulation with warfarin in a small group of Hodgkin’s disease patients [64]. Supportive care in established VOD involves the use of diuretics for fluid retention, analgesics for pain, paracentesis for tense ascites, correction of coagulopathy, and steroids to prevent hepatic congestion. Based upon the presence of clots in central veins, treatments have been designed to promote thrombolysis by tPA with or without anticoagulation therapy using heparin. In the largest study of anticoagulation, 12 out of 42 patients (29%) with severe VOD who received tPA and concomitant heparin responded to the therapy [65]. However, the authors concluded that tPA/heparin should be given early during the course of VOD and should be avoided in patients with multi organ failure.

Glutathione plays a protective role in preventing SOS caused by irradiation and chemotherapeutic agents [66, 67]. The protective effect of glutathione against SOS was confirmed by the demonstration that continuous GSH or N-acetylcysteine infusion into the portal vein of Sprague-Dewey rats prevented the development of SOS after administration of monocrotaline [68]. More recently, Gençel and colleagues proposed that the combination of selenium and vitamin E might offer a means of protection against injury, based on pre-clinical data showing less liver degeneration in rats given these agents prior to a 7 Gy exposure relative to control animals [69].

The most notable recent development in the treatment of VOD seen in patients undergoing stem cell transplantation is the use of Defibrotide (Gentium SpA, Como, Italy), a polydisperse oligonucleotide derived from bovine or porcine mucosa that has fibrinolytic and antithrombotic properties [70]. Defibrotide has specific aptameric binding sites on adenosine receptors, A1 and A2, located on endothelial cell surface [71]. It mobilizes beta-fibrogen growth factor (bFGF) from extracellular matrix and stimulates proliferation of microvascular endothelial cells [72]. In a multi-institutional study of defibrotide in 88 patients with severe VOD and multisystem organ failure, complete resolution of VOD was seen in 36% of the patients [73]. Decrease in mean serum creatinine and plasminogen activator inhibitor-1 levels during defibrotide therapy predicted better survival. A randomized phase II dose-finding trial confirmed the efficacy of defibrotide in patients with severe VOD and identified a dose of 25 mg/kg/day for future phase III clinical trials [74]. Investigations of defibrotide appear warranted, therefore, in the setting of radiation-induced liver injury.

Future prospects

Various strategies are being investigated to inhibit stellate cell activation and reverse fibrosis in RILD. Anti-TGF-β therapy with monoclonal antibodies against TGF-β and several small molecular agents that inhibit the kinase activity of TGF-β receptors are being investigated to reverse chronic liver fibrosis [75]. Further studies reveal that Connective Tissue Growth Factor (CTGF) mediates TGF-β-induced fibroblast collagen synthesis and that blockade of CTGF reduces TGF-β-induced granulation tissue formation by inhibiting collagen synthesis and fibroblast accumulation [76]. Mouse models of fibrosis have been successfully treated with an antibody to human CTGF [77]. Successful completion of a phase I trial with this antibody, FG-3019 (Fibrogen Inc, San Francisco, CA) in patients with diabetic renal disease has been promising [78].

Besides fibrosis, cell-based therapies have been proposed as treatment of liver injury in end-stage liver diseases. Cell therapies, including, the transplantation of bone marrow-derived stem cells [79], adult hepatocytes and liver progenitor cells [80, 81] have all been investigated. In a recent report, Li et al. demonstrated that intravenous injection of G-CSF-mobilized CD34+ hematopoietic stem cells engrafted in irradiated mouse liver and promoted tissue repair and ameliorated RILD in this model [82]. This raises a unique opportunity of hematopoietic stem cell mobilization by G-CSF and/or plerixafor, a chemokine receptor-4 (CXCR4) inhibitor for the treatment liver injury, including hepatic radiation injury [82, 83]. Finally, in a rodent model of RILD, intra-splenic or intra-portal transplantation of adult primary hepatocytes ameliorated RILD and improved survival of rats treated with high-dose liver RT after partial hepatectomy [84]. The transplanted hepatocytes engrafted and extensively repopulated to maintain normal physiological function in a heavily irradiated rat liver. This raises hope that application of autologous cell transplantation strategy using bone marrow-derived stem cells or adult hepatocytes or iPS-derived hepatocytes [85–88] might be useful in the amelioration of RILD following definitive (chemo) radiation therapy of liver cancer.

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Table 1

QUantitave Analysis of Normal Tissue Effects in fhe Clinic (QUANTEC) recommendations for dose constraints during external beam radiation therapy (RT) to the liver.

	Liver metastases	Primary Liver cancer	comment
Whole liver RT	≤ 30 Gy, 2 Gy/F 21 Gy/7 F	≤28 Gy, 2 Gy/F 21 Gy/7 F	Whole organ prescription dose
Partial liver RT, conventional fractionation	≤ 32 Gy	≤ 28 Gy	Mean normal liver * dose for tumor dose ≤ 2 Gy/F
SBRT, 3–6 F	< 15 Gy/3F < 20 Gy/6 F	< 13 Gy/3F < 18 Gy/6F CP B: < 6 Gy/4-6F	Mean normal liver * dose
	At least 700 cc normal liver < 15 Gy/3F		Critical volume model
	At least 800 cc normal liver < 18 Gy/3F		Only for Child-Pugh class A

* Normal liver refers to the total volume of liver minus the gross tumor volume.

SBRT = Stereotactic body radiation therapy; F = fraction; GTV = gross tumor volume; CP = Chld-Pugh class. Modified from Pan et al [17].