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Radiation-Induced Liver Toxicity

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The advent of highly conformal radiation therapy (RT) has defined a new role for RT in the treatment of both primary and metastatic liver cancer. Despite major advances in how RT is delivered, radiation-induced liver disease (RILD) remains a concern. Classic RILD, characterized by anicteric ascites and hepatomegaly, is unlikely to occur if treating to doses of $\leq$30 Gy in 2 Gy per fraction in patients with baseline Child-Pugh A liver function. On the other hand, nonclassic RILD is a spectrum of liver toxicity, including a general decline in liver function and elevation of liver enzymes. It is less well defined and less predictable, especially in patients with underlying liver disease. Scoring and quantifying RILD remains a challenge. The Child-Pugh score has been the most consistently used parameter. Other scoring systems such as the albumin-bilirubin score provide further discrimination in patients with hepatocellular carcinoma, although their value in patients treated with RT remains to be established. Many serum and imaging biomarkers of liver function are currently being investigated, and they will provide further useful information in the future for local and global liver function assessment, for planning optimization, and for treatment adaptation. To date, no pharmacological therapies have provided consistent results in mitigating RILD once it has manifested clinically. Numerous promising treatment strategies including TGFβ inhibition, Hedgehog inhibition, CXCR4 inhibition, hepatocyte transplantation, and bone marrow-derived stromal cell therapy, have potential to be helpful in the treatment of RILD in the future.
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Introduction

Radiation-induced liver disease (RILD) remains a limitation in the use of radiation therapy (RT) to effectively treat hepatobiliary malignancies and liver metastases. Classic RILD has been well described and can for the most part be prevented if enough of the liver is spared from RT. In contrast, nonclassic RILD is a spectrum of liver toxicity, including a general decline in liver function and elevation of liver enzymes. It is less well defined and less predictable, especially in patients with underlying liver diseases.

Recent technological advances in planning and delivery of RT, including the advent of liver stereotactic body RT (SBRT), have provided means to treat primary and metastatic liver cancers and achieved promising tumor control and overall survival. A wide range of rates of RILD have been reported, mostly due to variable patient selection for treatment. Patient heterogeneity is important to consider when assessing the risk of developing this life-threatening complication. In this review, patient, tumor and treatment factors associated with both classic and nonclassic RILD will be reviewed. Since the last review in this journal,[1] several advances in biomarkers for RILD have occurred, and our understanding of RILD continues to improve. However, many of the proposed clinical and dosimetric factors associated with toxicity, as well as promising serum and imaging surrogate biomarkers need further validation in larger patient cohorts.

Characterization of RILD

The first described form of RILD is known as "classic" RILD, occurring within 4 months generally following whole (or near whole) hepatic RT. Patients present with rapid weight gain, increased abdominal girth, hepatomegaly, anicteric ascites, occasional right upper quadrant discomfort, and an isolated

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elevation in alkaline phosphatase out of proportion to the other liver enzymes. Initially, liver function tests, including bilirubin and ammonia levels, are normal.[2] RILD is generally defined in the absence of intrahepatic cancer progression. Patients with underlying chronic hepatic disease such as viral hepatitis or cirrhosis, tend to develop hepatic toxicity that presents differently than classic RILD, with either a general decline in liver function, markedly elevated transaminases (at least 5 times the upper limit of normal) or jaundice within 3 months of completing hepatic RT, termed "non-classic" RILD. Both classic and nonclassic RILD can potentially be life threatening.

Several confounding factors make the characterization of RILD and the definition of a high-risk population challenging. Previous exposure to systemic treatment, particularly cytotoxic chemotherapy, has been associated with liver damage.[3,4] Previous surgical resection can substantially limit hepatic reserve; 25% of patients with bilobar liver metastases who were initially planned for a 2-stage hepatectomy could not undergo the second stage due to inadequate liver hypertrophy after portal vein embolization and a predicted inadequate liver remnant.[5] In many patients with hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHCC), hepatic reserve is directly impaired by the tumor at the time of diagnosis. It has been demonstrated that patients with liver cirrhosis are at a higher risk of developing RILD.[6,7] Central biliary toxicity that may occur following central hepatic irradiation should be considered as a different entity from RILD, presenting with acute biliary edema and obstruction or late biliary stricture or secondary infection. Recently, multiple dose-volume endpoints of the central hepatobiliary tract as independent predictors of hepatobiliary toxicity after liver SBRT have been described,[8] although challenges exist in distinguishing toxicity from potential disease progression, especially in patients with biliary malignancies.

Cellular and Molecular Pathophysiology of RILD

The morphologic appearance of classic RILD in humans is that of veno-occlusive disease (VOD), which 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 hepatic veins, and centrilobullar sinusoids, with sparing of the periportal areas, larger hepatic veins, and hepatic arterial vasculature. Centrilobular hepatocytes are largely absent, presumably because of hypoxic cell death secondary to vascular congestion.[9] Approximately 4 months after the injury, vascular congestion resolves, but there is still persistent fibrosis of the central veins, fibrous tracts bridging portal and central veins, and unrepaired lobular collapse remains prominent in the affected region. These same findings have also been described following high-dose per fraction SBRT.[10]

Subclinical or ongoing infection with hepatitis B virus (HBV) contributes to some presentations of nonclassic RILD. Hepatic venulitis can be seen as part of the pathologic findings in viral hepatitis, as well as other causes of severe hepatitis, leading to loss of affected venules and sinusoidal congestion. Although the exact mechanism of HBV reactivation remains unknown, an endothelial cell-mediated "bystander effect" has been postulated. Chou et al[11] demonstrated that direct irradiation of both normal or HCC-derived hepatocytes did not reactivate HBV; however, conditioned medium from irradiated endothelial cells that contains high levels of IL-6 resulted in HBV DNA expression, suggesting that HBV reactivation might be in part due to a bystander effect of elevated IL-6 originating from endothelial cells.

Transforming growth factor beta (TGF-β) is implicated in the fibrogenesis leading up to RILD. Although TGF-β is not necessarily associated with radiation injury, it is present in many types of liver diseases, such as cirrhosis and chronic hepatitis. Anscher et al[12] reported a dose-dependent increase in TGF-β1 expression confining primarily to hepatocytes in the pericentral region in the liver of irradiated rats 9 months after, and a significant correlation between the percentage of strongly TGF-β1 positive hepatocytes and the extent of fibrosis. In the early period after partial liver irradiation in rats, the levels of TGF-β1 mRNA increase up to 3.6-fold of the control by 1 month with no significant fibrosis in serial biopsies, implying that TGF-β1 is activated long before fibrosis appears.[13]

Recently, Hedgehog (Hh) signaling has been recognized as a potential factor involved in the liver response to radiation.[14] Hh signaling plays a significant role in liver fibrosis and regeneration after liver injury.[15] The production of Hh ligands increases and levels of hedgehog interacting protein decreases after liver injury, allowing for ligand-receptor interaction and activation of the Hh pathway.[16] Wang et al[17] showed an increase in steatosis and in Hh signaling 6 and 10 weeks after liver irradiation in mice, resulting in the proliferation of myofibroblastic hepatic stellate cells and progenitors, and thereby contributing to liver fibrosis and the repair response after irradiation.

Challenges With Preclinical Models

The pathogenesis of RILD has proven hard to investigate because of a lack of suitable animal models. In xenograft models where HCC tumors are formed by injecting human cancer cells, often subcutaneously, into immunocompromised mice, it is not possible to assess the effect of the immune system and tumor-stromal interactions (eg, mouse endothelial cells and fibroblasts in tumor xenografts vs human endothelial cells and fibroblasts in clinical human tumors) on liver fibrosis following radiotherapy. In nonxenograft murine HCC models, chronic chemical exposure is used to induce liver disease and HCC formation. Many chemical agents have been used for this purpose including thioacetamide,[18] carbon tetrachloride,[19] among others. These models do mimic the injury-cirrhosis-malignancy cycle seen in humans, providing a similar tumor microenvironment resembling human patients with HCC, and the tolerance of the injured murine liver may be more comparable with that of a cirrhotic human liver. The use of genetically modified mouse models expressing HBV genes may