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REVIEW

Radiation-Induced Liver Injury: An Overview

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Abstract: Radiation therapy is one of the main methods of tumor treatment, with over 50% of patients opting for it during treatment. The optimal regimen of radiation therapy aims to increase the dose in the target area while decreasing the dose in normal tissue. Radiotherapy for liver tumors has seen significant development in recent years. Despite the technological progress and improved accuracy of radiotherapy, the path of radiation reaching the target area still passes through normal tissues. Although there is tolerance doses as a reference parameter for normal liver exposure in planning, radiation damage still occurs. In addition, when combination of radiation therapy with chemotherapy, targeted therapy and immunotherapy has been widely used in recent years, the occurrence of RILD still affects the implementation of other treatment programs. In this review, latest research results of RILD are discussed to better understand the mechanism and provide research directions for optimizing radiotherapy.

Keywords: radiation-induced liver injury, radiation therapy, tolerance doses, normal tissue toxicity, radiotherapy optimization

Introduction

According to global cancer statistics, there were nearly 20 million new cases of cancer in 2022, and 9.7 million deaths from cancer. In addition to the most common lung cancer and female breast cancer, colorectal cancer, prostate cancer, stomach cancer and liver cancer are the main types of cancer with high incidence and/or high mortality.[1] Radiation therapy plays an important role in the process of tumor treatment. More than 50% of cancer patients received radiation therapy, benefiting from both radical and palliative treatment effects.[2] Although current precision radiotherapy, such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), stereotactic body radiation therapy (SBRT), radioembolization, etc, has optimized the dose to organs at risk (OARs) to the greatest extent, normal tissue damage by radiation remains one of the important factors affecting the therapeutic effect. Radiation induced liver injury (RILD) is not only the biggest obstacle to liver tumor radiotherapy, but also an important indicator to consider the dose of abdominal radiotherapy. Exploring the mechanism of RILD and its intervention lays the foundation for prevention and following treatment. Therefore, with RILD as the focus, the review discusses its molecular mechanisms and common interventions in recent years.

Diagnosis Criteria of RILD

There are two types of RILD, classic RILD and non-classic RILD. Classic RILD manifested as anicteric hepatomegaly, ascites, elevated alkaline phosphatase (>2 X ULN [upper limit of normal] or baseline value), typically occurring 2 weeks to 3 months after therapy.[3] Non-classic RILD is identified when meeting one of the following conditions: 1) Elevated liver transaminases >5 ULN; 2) CTCAE Grade 4 with>5 ULN baseline values within 3 months after completion of radiotherapy; 3) Child-Pugh score increasing ≥2 scores. The conditions above were all in the absence of classic RILD, typically occurring one week to three months after therapy.[4]

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In clinical practice, it is often challenging to differentiate between liver dysfunction caused by disease progression and RILD, particularly in patients with advanced disease or pre-existing poor liver function. The effective liver volume would shrink as a result of tumor progression, failing to compensate for normal liver function, thus leading to abnormal liver function. In addition, tumor invasion of the portal vein may lead to portal vein tumor thrombus (PVTT), causing obstruction in normal liver blood supply, which also induces abnormal liver function. Moreover, for patients who take oral antiviral drugs to treat viral hepatitis and achieve negative in virus tests, there is a possibility of viral reactivation after radiotherapy, which can also result in abnormal liver function and interfere with the diagnosis of RILD.

Pathological Changes in RILD

The mechanism of RILD is complex, and the main pathological changes are a combination of endothelial cell edema, terminal hepatic venule narrowing, sinusoidal congestion, zonal parenchymal atrophy, accumulation of collagen in the subendothelial space (space of Disse) and secondary hepatocyte necrosis.[4,5] Typical pathological manifestation of RILD includes damage to hepatocytes, hepatic stellate cells (HSCs), Kupffer cells (KCs) and other hepatocytes.[6] Oxidative stress, hepatocyte senescence, apoptosis, and fibrosis all play important roles in the development of RILD.[7,8]

Radiation directly damages hepatocytes through oxidative stress and inflammatory responses, initiating a cascade of liver injury. This injury is further amplified by the activation of Kupffer cells (KCs) and the recruitment of circulating immune cells, which exacerbate inflammation and fibrosis.[9] As specialized liver macrophages, KCs originate from blood monocytes adhering to hepatic sinusoids and function to clear foreign particles and damaged erythrocytes via phagocytosis. Following irradiation, KCs secrete tumor necrosis factor-alpha (TNF-α) in a dose-dependent manner, which promotes hepatocyte apoptosis when co-cultured with irradiated hepatocytes.[10] In vivo studies in rats demonstrate that KC inhibition reduces pro-inflammatory cytokine production (IL-1β, IL-6, IFN, and TNF-α), thereby alleviating acute RILD.[11] Additionally, selective KC inhibition mitigates radiation-induced SEC apoptosis, offering protection against RILD.[12] Concurrently, injured sinusoidal endothelial cells (SECs) undergo apoptosis and release TNF-α, further driving hepatocyte apoptosis and KC activation.[9] SEC dysfunction also leads to erythrocyte extravasation and fibrin deposition in central veins, contributing to sinusoidal obstruction.[9] Notably, hepatocytes and SECs engage in reciprocal regulation through TLR4 and TNFR1 signaling pathways.[13] HSCs play a pivotal role in both classic and non-classic RILD, contributing not only to hepatocyte regeneration but also to the secretion of lipoproteins, growth factors, and cytokines that modulate inflammation and fibrosis.[9,10,13,14] Their activation is a critical step in the development of radiation-induced liver fibrosis (RILF), a hallmark of late-stage RILD. Activated KCs secrete transforming growth factor-beta (TGF-β), the primary profibrogenic cytokine, which drives HSC activation and subsequent fibrogenesis[9] (Figure 1).

Radiological Changes in RILD

The hepatomegaly and ascites as diagnostic criteria of RILD can be observed in imaging tests. After focal irradiation of the liver, the irradiated hepatic parenchyma, compared with the surrounding non-irradiated hepatic parenchyma, typically shows hypo-attenuation on plain CT and hyper-attenuation on contrast-enhanced CT.[6] Tomoki Kimura et al[15] reported that dynamic CT imaging can be classified into 3 types after stereotactic body radiotherapy: type 1, hyper-density in all enhanced phases; type 2, hypodensity in arterial and portal phases; type 3, iso-density in all enhanced phases. Further analysis found that half of the type 2 or 3 findings significantly changed to type 1, particularly in patients belonging to Child-Pugh classification A. After 3–6 months, patients of Child-Pugh B classification mainly presented the type 3 pattern. To sum up, dynamic CT results could be classified into 3 patterns and those of Child-Pugh A patients mostly changed over time into the enhancement group (type 1). Irradiated liver parenchyma area in magnetic resonance (MR) typically exhibits a sharply defined wide band of hypo-intensity on T1-weighted images (T1WI), hyperintensity on T2WIs, slight hyperintensity on diffusion-weighted imaging (DWI), with low apparent diffusion coefficient (ADC) values corresponding to the radiation port.[16,17] Poonam Yadav et al[18] transferred 10 Gy-70 Gy treatment isodose lines in increments of 1 Gy from the planning scans to the follow-up diagnostic MR scans and they found that a median dose of 35 Gy correlated most closely with the visible RILD. It is necessary to distinguish between RILD and metastasis in CT and MR imaging,[19] as well as the uptake and accumulation of F-18-fluorodeoxyglucose (18F-FDG) and F-18-labeled fibroblast-activation protein inhibitor (18F-FAPI) in PET/CT imaging that are caused by RILD or other conditions in

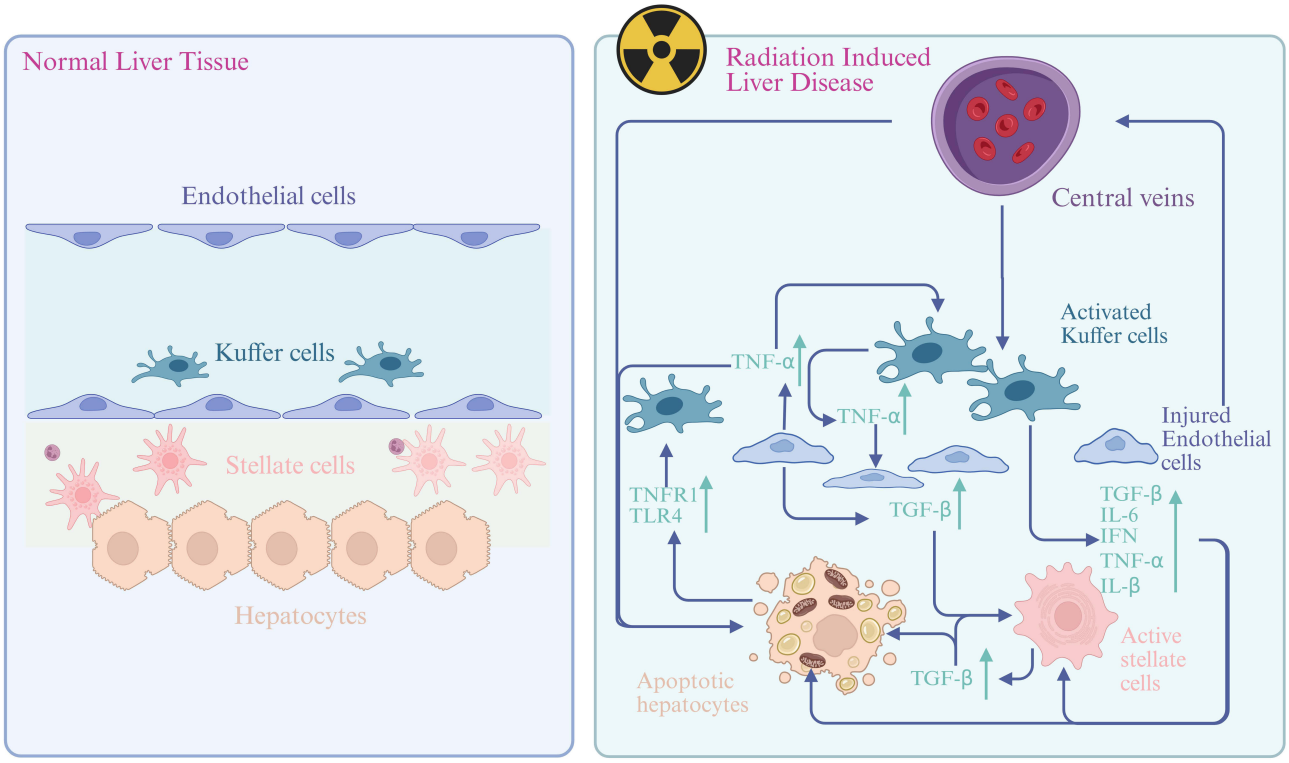

Figure 1 Radiation-induced cellular changes and inflammatory crosstalk in the liver.

clinic settings.[20,21] Enoch Chang et al[22] conjectured that liver-directed radiotherapy can be safely delivered at high doses when incorporating functional SPECT into the radiation treatment planning process, which may enable sparing of lower volumes of liver than traditionally accepted in patients with preserved liver function.

We performed gadoxetic acid-enhanced MRI (EOB-MRI) on 32 post-treatment patients, and the imaging findings of the targeted area and surrounding areas before and after radiation therapy were shown in Figure 2.

Related Research of RILD

Ionizing radiation can induce oxidative damage to DNA, lipids, proteins, and metabolites in both tumor and normal cells. The accumulation of DNA damage and reactive oxygen species (ROS) can trigger cell death via various mechanisms, such as apoptosis, necrosis, necroptosis and ferroptosis. Additionally, ionizing radiation can lead to senescence and autophagy.[23] In recent years, several fundamental studies on RILD have been conducted, encompassing in-vitro cell experiments and in-vivo animal studies (Table 1), with the RILD modeling methods detailed in Table 2. The results revealed that RILD is a complex process that can cause changes in a variety of signal pathways. In addition, some in-vivo animal studies also found that hepatobiliary secretion of bile acids[24] and fibrinogen-like 1(FGL1) upregulation[25] may serve as a potential biomarker for acute and sub-acute radiation exposure to the liver. In the early stages, our research team successfully established a RILD model using New Zealand white rabbits and SD rats (Figure 3), irradiated with a CyberKnife system. The success of modeling provided a guarantee for later mechanism research.

In recent years, numerous studies on RILD have initially identified differences in clinical samples and subsequently validated these findings through animal experiments to enhance the objectivity of the research. Zeng ZC et al[39,40] found that compared with non-irradiated samples, expression of STING and interleukin-1β in kupffer cells (KCs) and non-parenchymal cells (NPCs) increased in clinical human normal liver tissue samples collected after irradiation. Targeting and inhibiting STING alleviated irradiation-induced liver injury in mice, indicating its therapeutic potential in RILD. Su TS et al[41] reported that Akt/mTOR participates in liver regeneration after RILD in human specimens, then they found that the Akt activator-carbamazepine and mTOR inhibitor-temsirolimus both could enhance liver regeneration in rats.

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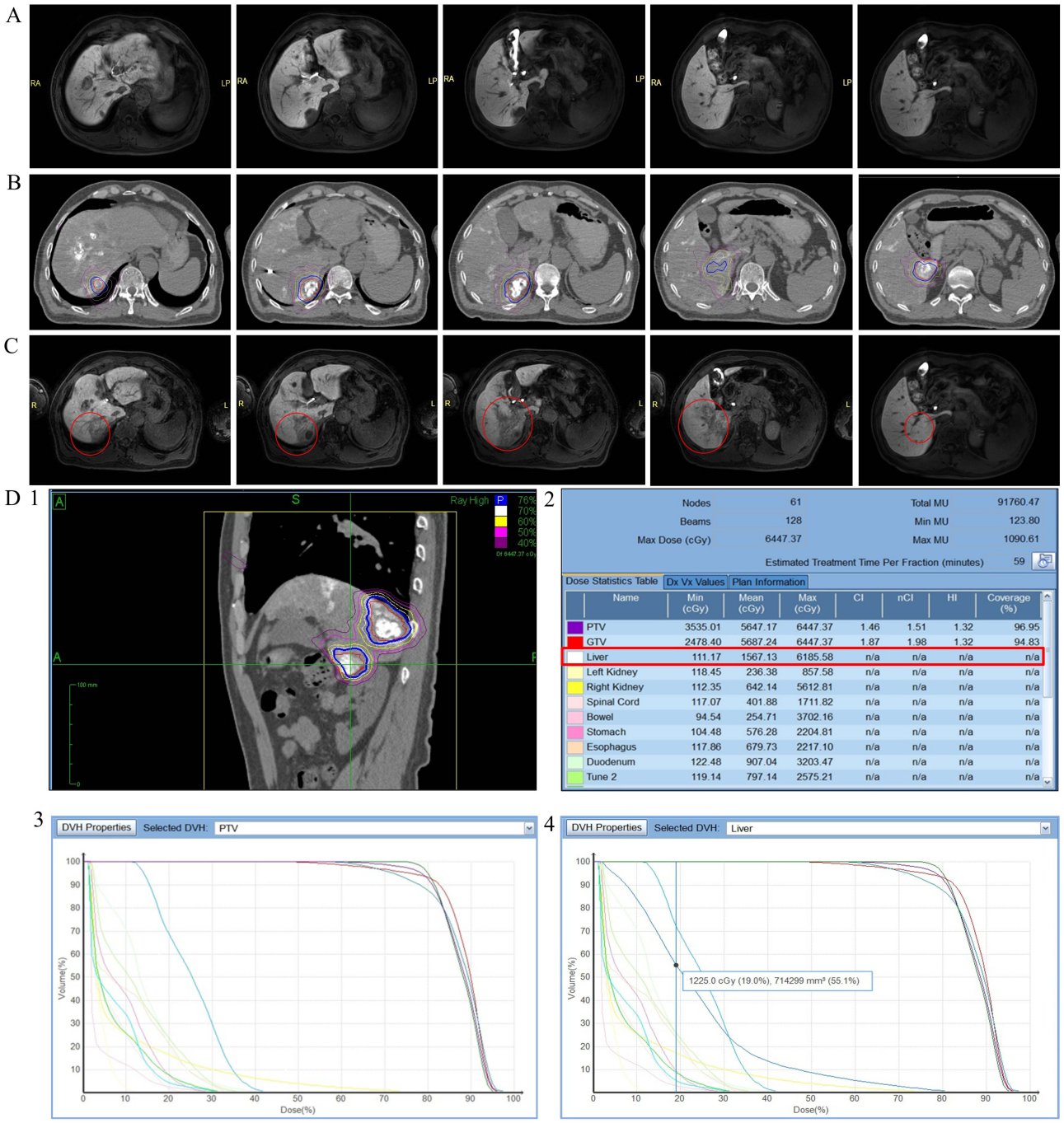

Figure 2 Radiation-induced liver injury on gadoxetic acid-enhanced MRI (EOB-MRI, 18–20min) at 3 months post-radiotherapy along with treatment planning details, where (**A**) shows pretreatment liver MRI, (**B**) displays the radiation dose distribution, (**C**) presents the hepatobiliary phase (18–20 min) of MRI. The hypointense regions within the red circles correspond to the irradiated areas, and (**D**) presents treatment planning parameters including prescription isodose distribution (D1), Liver dose-volume metrics (D2; mean dose of 1567.13cGy, maximum dose of 6185.58cGy, and minimum dose of 111.17cGy within the red box), and dose-volume histogram (DVH, D3), with 714 mm^3 of liver volume receiving 12.25 Gy radiation dose (D4).

Clinical Influence Factors of RILD

Some researchers have investigated parameters such as radiotherapy dose using various techniques, aiming to identify high-risk factors and reduce the incidence of RILD. The Child-Pugh classification has been widely recognized as a significant factor influencing the development of RILD.[42,43] Clinical studies on radiation therapy for liver cancer and corresponding incidence of RILD over the past five years are shown in Table 3. One of our previous studies

Table 1 In-vitro and in-vivo Studies of RILD

Study	Signaling Pathway	Intervening Measure	Functioning Cells/ Animal Tests
Liu Y et al[26]	AdipoRon/AdipoR1/ AMPKα	AdipoRon 1.2 mg/kg via tail vein injections Qod	Hepatocytes (HHL-5)
Yuhan C et al[27,28]	MicroRNA-146a-5p/TLR4		HSCs and hepatocytes Male C3H/HeN mice
Lei Xiao et al[29]	PI3K/Akt signaling pathway		HSCs (HSC-T6) Male SD rats
Wei Li et al[30]	NF-κB signaling pathway	Curcumina via intragastric administrated dose of 30 mg/kg Qd	SD mouse
Liu Q et al[31]	Nrf2/ HO-1	Phycocyanin	C57BL/6 mice
Shereen M Shedid et al[7]		Betaine (400mg/kg/d, oral), after the first radiation dose	Male Wistar albino rats
Nicolas Melin et al[32]	p53 pathway		BALB/c female mice (8 weeks old)
Bing-Shen Huang et al[33]	KLF4 signaling pathway	BPC157: In-vitro cell tests: 1μg/mL BPC157; In-vivo animal tests: BPC157 (10μg/kg, 5 mL/kg, oral)	Rat liver clone 9 cells C57BL/6 mice
Rania A Gawish et al[34]	JAK/STAT pathway	Ferulic acid (50mg/kg, oral for seven days).	Male rats
Li HY et al[35]		*p*-coumaric acid (100 mg/kg) for 4 consecutive days	C57BL/6 male mice
Asmaa A Hassan et al[36]	TNF-α/NF-κB signaling pathway, Pro-Fibrotic Factor TGF-β1	Mangosteen (500 mg/kg, oral)	Male Wistar albino rats

Table 2 Experimental Methods for Establishing RILD Models

	Animal Species	RILD Modeling Scheme
Shereen M Shedid[7]	Male Wistar albino rats (150–180g)	The whole-body was exposed to 3 fractions of 3 Gy/wk (total dose of 9Gy)
Nicolas Melin[32]	BALB/c female mice of 6 weeks	1% of the liver volume received the full 50 Gy dose, IGRT
Bing-Shen Huang[33]	C57BL/6 mice of 7 weeks (20–25g)	The whole abdomen (from xyphoid to pubis) and dose was 12Gy/1f
Li W et al[30]	Sprague-Dawley (SD) (180–220 g)	The lead block covered the left lung and mediastinum, 12Gy/3f, F992AT type 500 mA X-ray
Rania A Gawish et al[34]	Adult male rats (220–250 g)	The whole-body gamma irradiation of 6Gy by Cesium-137 source
Li HY et al[35]	C57BL/6 male mice	The total body X-ray (Simens company, Munich, Germany) irradiation of a single dose of 4 Gy
Kristoffer Kjærgaard et al[24]	Göttingen minipigs	The whole-liver, 14 Gy/1f, SBRT (Varian, Trilogy)
Asmaa A Hassan et al[36]	Wistar albino rats (150 ± 20 gm)	The whole-body gamma irradiation of 6Gy by Cesium-137 source
Na-Kyung Han[25]	Male BALB/c mice (18.2±2.1 g)	30 Gy of liver IR encompassing over 80% of the liver volume, XRAD-SmART
Lu JK[37]	Male Kunming mice of 6 weeks	The whole-body irradiation of 4 Gy at 1Gy/min by a ^{60}Co irradiator
Cagin YF[38]	Female Wistar albino rats (220g)	A single 800 cGy dose of radiation to the entire abdomen

demonstrated that platelet count is a critical factor in predicting RILD prognosis.[44] Reflecting the degree of liver cirrhosis, platelet count may have similar impact as Child-Pugh classification on RILD. Various studies have indicated that prolonged pre-treatment prothrombin time, hepatitis virus positivity, a higher number of tumors, tumors located at the hepatic hilum, elevated albumin-bilirubin scores, and increased body mass index are all contributing factors to RILD.[42,45–48] In addition to the well-known effective liver volume ≥700mL, several planning parameters have been reported as related to the occurrence of RILD, including the mean dose on normal liver, V15, V25, V30, etc.[42,43,45]

In Asia, many patients with liver cancer have cirrhosis due to hepatitis B or C infection, and their liver cell function differs significantly from that of non-cirrhotic patients. However, until now, there has been no liver tolerance dose standard specifically for patients with cirrhosis. Therefore, for these patients with an effective liver volume of around 700cc, clinical experience is very important when designing radiation therapy plans. Our clinical observations revealed that in HCC patients treated with SBRT, with an effective normal liver volume of 700cc and a maximum BED_{10} of 102.6Gy (DT: 54Gy/6f), the primary factors influencing RILD were baseline liver function parameters, including platelet count, white blood cell count, and albumin levels (Clinical Trails NCT: 03295500, other results are not shown here). Our

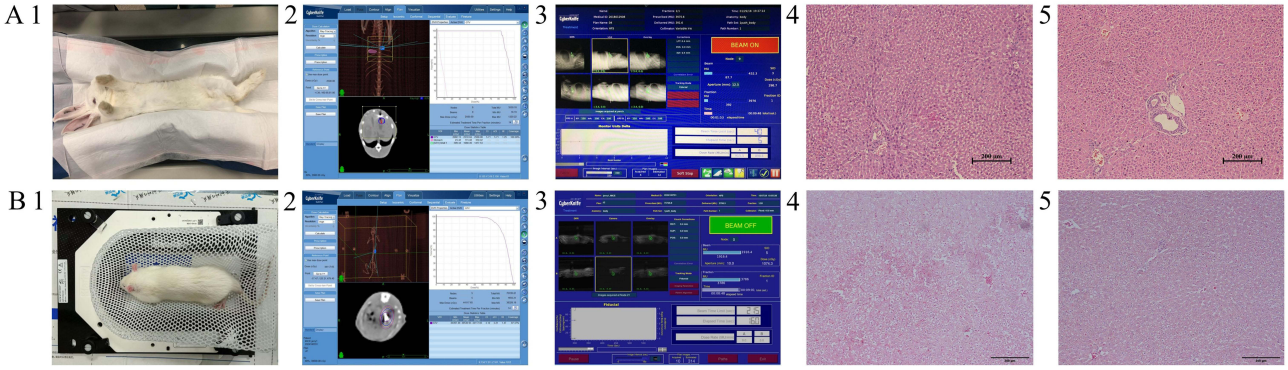

Figure 3 Prior to radiotherapy, fiducial markers were percutaneously implanted into the liver of New Zealand white rabbits/SD mouse under CT guidance. (**A**) RILD model using New Zealand white rabbits. A1, immobilization achieved using vacuum cushions. A2, followed by dose delivery. A3, Histopathological evaluation compared irradiated liver tissue. A4, with untreated controls (A5), through HE staining (200× magnification). Pre-radiotherapy liver function tests showed ALP 25 IU/L, AST 27 IU/L, and ALT 28 IU/L, which increased to 357 IU/L (ALP), 426 IU/L (AST), and 228 IU/L (ALT) post-radiotherapy, indicating significant hepatic injury. (**B**) RILD model using SD mouse. B1, immobilization achieved using thermoplastic mask immobilization. B2, treatment planning was conducted using CyberKnife Multiplan system (version 4.0.2). B3, followed by dose delivery. B4, histopathological evaluation compared irradiated liver tissue with untreated controls (B5) through HE staining (200× magnification). Pre-radiotherapy liver function tests showed ALP 72 IU/L, AST 32 IU/L, and ALT 45 IU/L, which increased to 223 IU/L (ALP), 222 IU/L (AST), and 126 IU/L (ALT) post-radiotherapy, indicating significant hepatic injury.

team referred AAPM TG-101,[61] Timmerman's Standard[62] and QUANTEC[63] for liver radiation therapy tolerance when treating liver tumors with SBRT and IMRT, without additional classification of liver function based on Child-Pugh scores. Our center has been treating liver tumors with radiotherapy for fifteen years with an acceptable incidence rate of RILD and no deaths due to RILD. Matthew M cousins et al[64] found that elevated plasma soluble TNFα receptor (sTNFR1) was associated with liver injury after radiotherapy, suggesting that elevated inflammatory cytokine activity was a predictor of RILD.

Table 3 Incidence of Radiation-Induced Liver Disease in Clinical Practices

Study	Radiation Technique	Number of Patients	Dose Schedule	RILD
Marco Lorenzo Bonù, 2024[49]	Protons or Photons	178 patients (213 lesions)	Photon: 60 Gy/3 fractions; Proton: 58–67.5 Gy/15f	Proton: 1 case; Photon: 1case.
Ahmed Allam Mohamed, 2024[50]	SBRT	52 HCC patients (a total of 62 lesions)	40 (24–66) Gy/5 (3–12) fx	4 cases were diagnosed with non-classic RILD
Zhang RJ, 2023[51]	IMRT or VMAT	96 unresectable HCC: 30 cases underwent RT + PD1;66 patients underwent RT alone. After PSM, 30 cases were in each group.	51.0 Gy (47.5–60.0 Gy), 3.0 Gy (2.4–4.0 Gy) per fraction	7 patients were diagnosed with non-classic RILD in each group after PSM
Rodney Cheng-En Hsieh, 2023[52]	Protons or Photons	159 HCC patients (>5cm)	Proton: 72.6 CGE[a]/22f for central tumors and 66 CGE/10f for peripheral tumors; Photon: 50, 45 or 40 Gy/5f.	Proton: 12 cases (11.4%); Photon: 16 cases (29.6%)
Won Il Jang, 2023[53]	IMRT	1755 HCC patients (most patients had advanced-stage HCC and combined treatment)	51 Gy (42–62 Gy), 1.8–6Gy per fraction	The occurrence rates of classic RILD, non-classic RILD and hepatic toxicity ≥ grade 3 were 2%, 4%, and 4%, respectively.
Karl Bordeau, 2023[54]	MRgRT	56 primary liver tumors (seventy-two lesions)	50Gy/5f	None
Chen Bo, 2021[55]	IMRT	76 eligible patients who underwent narrow-margin resection	50-60 Gy/25-30f; Mean dose of whole liver ≤24 Gy	None

(*Continued*)

Table 3 (Continued).

Study	Radiation Technique	Number of Patients	Dose Schedule	RILD
Hiromitsu, 2021[56]	Image-Guided Proton Therapy	71 elderly patients with HCC	Peripheral tumor 66Gy/10f (forty-seven cases); Central tumor 72.6Gy/22f (twenty- four cases).	1 case was diagnosed with Grade 3 RILD
Ying-Fu Wang, 2021[57]	CyberKnife-SBRT	14 advanced HCC patients (a total of 25 HCC lesions)	28-60Gy/4-5f	1 case was diagnosed with non-classic RILD
Munire Abulimiti, 2021[58]	IMRT	82 HCC patients: 36 cases underwent IMRT+ sorafenib; 46 cases underwent IMRT alone.	40-62.5 Gy, 2–2.5 Gy per fraction	None
Won Il 2020[59]	SBRT	74 unresectable HCC	45Gy-60Gy/3f	1 case was diagnosed with Grade 3 RILD
Stephanie K. Schaub, 2020[60]	Intensity-modulated proton therapy (IMPT)	25 HCC patients with large tumors near OARs	Median mean and minimum dose delivered to the GTV was 64.0 Gy (54.3–69.6) and 45.1Gy (33.4–67.7), respectively. Median mean dose to liver minus GTV was 15.0 Gy (8.2–19.6).	2 cases were diagnosed with RILD

Note: [a]CGE: Relative biologic effectiveness was set to 1.1 for cobalt Gy equivalent.

Future Prospects of RILD

In conclusion, RILD is a major limiting factor in radiation therapy for abdominal tumors, especially liver cancer. Although the diagnostic criteria for RILD are well-defined, it remains essential to differentiate RILD from liver dysfunction caused by tumor progression or viral hepatitis reactivation in advanced-stage patients. Research utilizing in-vitro cell experiments and in-vivo animal models provides an effective approach to elucidating the underlying mechanisms of RILD. For patients with advanced liver tumors, the emergence of targeted and immunotherapy has provided them with more treatment options, but it has also concurrently increased the risk of liver injury. As the current treatment paradigm for most patients with advanced hepatocellular carcinoma involves a combination of local therapy and systemic anti-tumor therapy, greater emphasis must be placed on the potential for the co-occurrence of drug-induced liver injury (DILI) and RILD. Although advances in radiotherapy have effectively lowered radiation exposure of liver and the risk of liver damage, fully understanding the mechanism of RILD and developing new therapeutic agents to reduce RILD are essential to improve patients' survival rates.

Ethics Approval Statement

The Ethics Committee Board of the Fifth Medical Center of PLA General Hospital approved this review and waived the requirement for patient consent (Case in Figure 2). This study was conducted in compliance with the Declaration of Helsinki. We confirm that all procedures strictly adhered to relevant laws and regulations, and no patient personal information was disclosed to unauthorized individuals or organizations, ensuring the confidentiality and security of patient data.

All animal experiments were approved by the Ethics Committee Board of the Fifth Medical Center of PLA General Hospital and performed in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals. Animals were housed in a controlled environment with a 12-hour light/dark cycle and provided with ad libitum access to food and water. Surgical procedures were performed under anesthesia, and postoperative analgesia was administered to minimize pain and distress. Every effort was made to reduce the number of animals used while maintaining the statistical validity of the results.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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