Strategies for prediction and mitigation of radiation-induced liver toxicity

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ABSTRACT

Although well described in the 1960s, liver toxicity secondary to radiation therapy, commonly known as radiation-induced liver disease (RILD), remains a major challenge. RILD encompasses two distinct clinical entities, a ‘classic’ form, composed of anicteric hepatomegaly, ascites and elevated alkaline phosphatase; and a ‘non-classic’ form, with liver transaminases elevated to more than five times the reference value, or worsening of liver metabolic function represented as an increase of 2 or more points in the Child–Pugh score classification. The risk of occurrence of RILD has historically limited the applicability of radiation for the treatment of liver malignancies. With the development of 3D conformal radiation therapy, which allowed for partial organ irradiation based on computed tomography treatment planning, there has been a resurgence of interest in the use of liver irradiation. Since then, a large body of evidence regarding the liver tolerance to conventionally fractionated radiation has been produced, but severe liver toxicities has continued to be reported. More recently, improvements in diagnostic imaging, radiation treatment planning technology and delivery systems have prompted the development of stereotactic body radiotherapy (SBRT), by which high doses of radiation can be delivered with high target accuracy and a steep dose gradient at the tumor–normal tissue interface, offering an opportunity of decreasing toxicity rates while improving tumor control. Here, we present an overview of the role SBRT has played in the management of liver tumors, addressing the challenges and opportunities to reduce the incidence of RILD, such as adaptive approaches and machine-learning-based predictive models.

Keywords: radiation-induced liver disease; liver toxicity; SBRT; radiation; stereotactic body; hepatic function

INTRODUCTION

Radiation therapy is playing an increasing role in treatment in both primary and secondary liver tumors due to a number of factors: (i) the majority of primary liver cancers, which mainly include hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), are unresectable at diagnosis; (ii) improving radiation technology that allows higher and more ablative doses of radiation to be delivered safely; and (iii) the recognition of an oligometastatic disease state in patients with liver metastases that may benefit from liver-directed therapy.

Historically, hepatic radiation has been challenging due to the radiosensitivity of the liver [1, 2]. Previous studies, before the development of 3D conformal radiotherapy (3D-CRT), have reported high rates of hepato-biliary (HB) toxicity with liver irradiation [3, 4]. Despite advancements in technology, significant rates of liver toxicity have been observed, mostly in patients with prior underlying liver dysfunction, common among HCC patients [5–7]. This observation prevented the development of radiation as a major modality for liver-directed local treatment, while other techniques, such as ablative and intra-arterial chemotherapy options, became standard of care [8, 9].

Technical developments on imaging acquisition, radiotherapy treatment planning and dose delivery have allowed higher target precision and conformity, offering the possibility of giving higher doses of radiation while maximally sparing adjacent normal tissues. Stereotactic body radiotherapy (SBRT) is a treatment technique that exploits the benefits of a sharp dose fall-off beyond the target to deliver ablative doses of radiation safely, and this has led to high rates of local control [10–19].
While the literature generally shows that liver SBRT is well tolerated, high-grade toxicities have been reported, and the mechanisms driving the development of liver toxicity with hypofractionation are still being investigated. In this review, we discuss the predisposing factors implicated in the development of radiation-induced liver toxicity, with a special focus on SBRT, and present alternatives for adequate prediction and reduction of risk.

Biologic mechanisms of radiation-induced liver injury
The seminal work undertaken at Stanford University in the early 1960s described the clinicopathological syndrome of radiation-induced liver damage [20, 21]. Investigators examined liver tissue samples from 12 patients who had their whole liver irradiated with doses between 30 and 59 Gy and found that radiation injury to the liver was present. They suggested that radiation injury to the liver was caused by a veno-occlusive process. A spectrum of histologic injury ranged from the appearance of a few fibrils within the lumen to a complete obliteration of small central hepatic vein branches by collagenous tissue, which increased with increasing time from radiation therapy (RT) [21].

The morphologic features of this progressive fibrotic process were further described by Fajardo et al., who demonstrated by electron microscopy the appearance of fibrin accumulation in the lumen of small central veins and adjacent sinusoids of liver tissue samples from patients irradiated with total doses up to 40.5 Gy. The authors hypothesized that the causal effect of radiation-induced injury to the liver was damage to the endothelial cells of small centrilobular veins, exposing the subendothelial basal membrane and leading to platelet activation and aggregation [22]. The accumulation of fibrin in the central veins and sinusoids was followed by reticulin and collagen deposition by fibroblasts, with further erythrocyte aggregation and sinusoidal congestion, culminating in an increase in portal system pressure [23]. Later, Shulman et al. reinforced this hypothesis by demonstrating through immunohistochemical staining the presence of collagen types I, III and IV deposits in the sinusoids of patients with veno-occlusive disease [24]. Necrosis in proximity to the central vein (zone 3) has also been described, potentially resulting from sinusoidal congestion, with hypoxic cell death of centrilobular hepatocytes [23, 25].

Although the morphologic characteristics are well described, the pathogenesis of the veno-occlusive process induced by radiation is not completely understood. One of the early events following injury to the hepatic parenchyma is stellate cell proliferation in the affected sites and posterior myofibroblastic transformation contributing to the repair response to liver damage [26, 27]. This process is regulated by the production of growth factors and other cytokines, many of which have been thought to participate in the pathogenesis of veno-occlusive disease, such as tumor necrosis factor alpha (TNF-α) and transforming growth factor beta (TGF-β), known to stimulate fibroblasts that would then migrate to the regions of hepatic injury, causing collagen deposition [28–30]. TNF-α produced by Kupffer cells was shown to sensitize hepatocytes to radiation in vitro, thus contributing to the centrilobular atrophic process seen in patients with veno-occlusive disease [31]. A combination of all these components may contribute to the development of the veno-occlusive disease, but the cardinal event is attributed to injury of sinusoidal endothelial cells, which is followed by a series of biologic processes that ultimately lead to circulatory compromise of centrilobular hepatocytes, fibrosis, and obstruction of liver blood flow [32].

Clinical manifestations of radiation-induced liver injury
As previously described, a veno-occlusive process induces an increase in the pressure of the portal system, which may manifest clinically as anicteric hepatomegaly, ascites, weight gain, fatigue and elevation of alkaline phosphatase. Thrombocytopenia caused by splenic sequestration from portal hypertension may also be observed. This collection of clinical signs is considered the classic form of radiation-induced liver disease (RILD), also referred to as a sub-acute ‘hepatitis’ without significant liver transaminases elevation [20, 22]. The severity of RILD may vary depending on the received dose, volume of liver irradiated and underlying liver dysfunction, with some patients developing fulminant liver failure. Until now, no grading system has been described to categorize RILD. Clinical signs of classic RILD can be evident as early as 2 weeks and may occur up to 6 months following treatment [22, 25, 33].

Another clinical manifestation of radiation-induced liver injury is ‘non-classic RILD’, where patients present with liver transaminases elevation $5x$ greater than the laboratory reference value (20x if baseline values were already $5x$ above the reference), or a worsening of liver function represented by an increase of 2 or more points in the patient’s Child–Pugh (CP) score. Non-classic RILD is defined as the occurrence of these events within the 3 months following irradiation and in the absence of classic RILD features. In addition, non-classic RILD is usually accompanied by total bilirubin serum levels elevation (Table 1). Non-classic RILD has been more commonly observed in

| Table 1. Clinical manifestations of radiation-induced liver toxicity |
|------------------|------------------|------------------|
| **Classic RILD** | **Non-classic RILD** | **cHBT toxicity** |
| ▪ Anicteric hepatomegaly | ▪ Transaminases elev. ($5x$) or | ▪ Alkaline phosphatase elev. |
| ▪ Ascites | ▪ Increase ≥2 points in CP score | ▪ Total bilirubin elev. |
| ▪ Alkaline phosphatase elev. ($2x$) | ▪ Absence of classic features | ▪ Cholangitis |

Can be accompanied by weight gain, fatigue and abdominal right upper quadrant pain.

Commonly presenting with total bilirubin elevation and low albumin values.

Usually caused by central biliary tract inflammation/stricture, more common in presence of biliary stent.

RILD = radiation-induced liver disease, cHBT = central hepatobiliary tract, $x$ = times the reference laboratory value, CP = Child–Pugh.
patients with baseline liver dysfunction, such as HCC patients, and is thought to be caused by hepatocyte loss and dysfunction along with hepatic sinusoidal endothelial injury. Self-limited mild elevation of liver transaminases (<5x the reference value) due to acute inflammation is frequently observed after partial organ irradiation, and this tends to resolve within 1–2 months after treatment and should not be interpreted as non-classic RILD [33, 34].

Prognostic factors for radiation-induced liver injury
For patients with underlying liver dysfunction, lower radiation doses can be sufficient to induce liver toxicity [35–38]. Among 109 patients treated for primary liver cancer with hypofractionated 3D-CRT, 9 out of 16 (56%) CP class B patients developed RILD, compared with 8 out of 93 (9%) CP class A patients, and severity of liver dysfunction was the only independent predictor of RILD on multivariable analysis [38]. Patients with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection commonly present with compromised liver function, and have been associated with an increased sensitivity to radiation [39–41]. In a study from South Korea including 48 HCC patients with chronic HBV who received radiation, those treated with prophylactic antiviral therapy with lamivudine had a lower rate of RILD compared with those who were not treated with lamivudine (12.5 vs 21.8%, P = NS). In addition, those treated with antiviral therapy had significantly lower rates of HBV hepatitis reactivation (0 vs 21.8%, P = 0.047) [39]. Similarly, a retrospective study that included 69 patients with chronic HBV treated with 3D-CRT for HCC reported a 17.4% incidence rate of RILD (12/69), 10.1% (7/69) as classic RILD and 7.3% (5/69) as non-classic RILD. Moreover, there was a 21.7% rate of HBV reactivation-induced hepatitis [41]. For patients with untreated HCV, adjuvant antiviral therapy is usually recommended after SBRT for HCC treatment, since it has been shown to reduce the risk of HCC recurrence and prolong survival [42].

Other clinical factors that may increase the probability of RILD are the administration of concurrent systemic therapy, prior liver-directed therapies such as transarterial chemoembolization (TACE) and transarterial radioembolization (TARE), small hepatic reserve as a result of prior partial hepatectomy and portal vein (PV) thrombosis [36, 38, 43, 44]. More recently, the sole presence of tumors within healthy liver parenchyma was associated with an increased risk for development of veno-occlusive disease [45].

Radiation-induced liver toxicity after conventionally fractionated RT
One of the first descriptions of a dose–effect correlation with liver toxicity was reported by Ingold et al. from Stanford University, who noted signs of what was ultimately described as classic RILD in 1 out of 8 patients (12.5%) who received 30–35 Gy and in 12 of 27 patients (44%) who received 35 Gy [20]. Since then, additional data has shown that conventionally fractionated RT (CFRT) doses above 30 Gy to the whole liver have a probability of 5–10% of developing classic RILD in patients with normal liver function [25, 34]. Clinical experience and normal tissue complication probability (NTCP) models demonstrate that partial liver irradiation to high doses, that became possible with the advent of 3D-CRT, is safe, as long as a sufficient volume of normal liver parenchyma is spared from high doses [46–49]. A comprehensive review in the early 1990s by Emami et al. estimated CFRT doses for one-third, two-thirds and the whole liver to incur in a 5% risk of RILD at 5 years (TDS/5) were 50 Gy, 35 Gy and 30 Gy, respectively [49]. Data from the University of Michigan using NTCP modeling and the ‘effective volume’ (Veff) DVH reduction scheme in the 1990s led to a more quantitative understanding of the partial organ tolerance of the liver, setting the basis for future clinical trials that explored focal dose escalation to portions of the organ, resulting in increased local control rates while maintaining a low incidence of RILD [47, 50–61].

Radiation-induced liver toxicity after SBRT
In the SBRT era, the dose constraint of sparing ≥700 cm³ from receiving >15 Gy in 3 fractions has emerged as a safe threshold, with low rates of toxicity in patients treated for liver metastases [62, 63]. This liver constraint has been used in other Phase I and II trials, with similarly low toxicity rates [12, 64–66]. In the setting of underlying cirrhosis, toxicity rates have been higher [34–38]. In addition, patients with worse liver function (CP Class B) seem to have worse tolerance for radiation [5, 37, 67, 68].

Assessment of non-classic RILD has been classically computed using the CP score or by the Common Terminology Criteria for Adverse Events. Assessment of liver function by the Model for End-stage Liver Disease (MELD) and MELD-Na have been shown to be superior alternatives, with the former being an independent prognostic factor in patients diagnosed with HCC [33, 69, 70]. Another scoring for liver function assessment is albumin–bilirubin (ALBI) scoring. ALBI is a simpler tool for assessing liver function, considering only serum albumin and total bilirubin, thus eliminating the need for subjective clinical criteria [71, 72]. The ALBI grade has been shown to more precisely predict worsening of liver function and survival in HCC patients following SBRT, compared with CP class [37, 73, 74, 75, 76]. A recent study that included 152 patients with HCC treated with SBRT demonstrated that both baseline ALBI grade and CP class correlated with liver toxicity, but ALBI grade showed a superior discriminatory and predictive power for toxicity estimation compared with CP class, especially considering cases of CP class A [74]. The simplicity, objectivity and predictive capabilities of ALBI grade should be further explored on future prospective clinical trials on liver SBRT.

Central hepatobiliary tract toxicity
Efforts to reduce the risk of RILD (classic or non-classic) have focused primarily on sparing a sufficient amount of liver parenchyma or by limiting the mean liver dose [33, 52]. However, recent data suggest that toxicity may be derived from the dose to the central liver, where the bile duct and venous vasculature coalesce [77]. A dosimetric analysis of 96 patients treated with liver SBRT was conducted at Stanford University. Of the 96 patients, 45 had liver metastases, 31 had HCC, and 20 had CCA [78]. The central hepatobiliary tract (cHBT) was defined as a 15 mm isotropic expansion from the portal vein (PV), starting at the confluence of the superior
mesenteric and splenic vein until the second bifurcation of the right and left PV (Fig. 1). The 15 mm expansion from the PV was empirically chosen, since radiographic and surgical series have revealed that the central biliary tract runs in close proximity to the PV, and the expected common bile duct diameter in both normal and pathological states tends to be between 5 and 15 mm. A significant dose-dependent relationship was identified between the cHBT volumes and Grade ≥3 liver toxicities. In total, 23 patients (24.0%) had Grade ≥2 and 18 patients (18.8%) had Grade ≥3 liver toxicity, most frequently for those with CCA (55%), followed by HCC patients (13%). The most common G3 toxicity observed was biliary stricture or infection. The strongest predictors on multivariable analysis were V72 and V66, with dose converted to BED_{10}.

In a subsequent analysis of 130 total patients, a significant dose-response relationship again was seen between the dose to the cHBT and the risk of liver toxicity, but only for patients treated for HCC and CCA, not for patients with liver metastases. The strongest predictors for liver toxicity were V40 < 37 ml, V30 < 45 ml, and the mean cHBT dose < 25 Gy, (all doses in BED_{10}), while mean liver dose was not predictive on multivariate analysis. In addition, a nomogram was created to predict the probability of Grade ≥3 liver toxicity, using significant parameters on multivariate analysis, including baseline liver function assessed by ALBI score, primary liver cancer histology (HCC vs CCA) and cHBT15, V40 [79]. An online nomogram calculator is available at (http://web.stanford.edu/~akoong/nomogram.html).

**Hepatitis B virus reactivation**

Patients treated for HCC that present chronic HBV infection are at risk for hepatitis reactivation with the use of immunosuppressive and liver-directed therapies [80, 81]. The rate of HBV reactivation after systemic therapy for patients who are HBsAg-positive has been reported to be as high as 68%, while for those with resolved infection (HBsAg-negative, anti-HBc-positive, HBV DNA-negative) it can reach up to 10% [81]. Clinical presentation ranges from mild aminotransferase elevations to acute liver failure. HBV reactivation is usually defined as an increase in HBV DNA levels to more than 10 times the baseline level, and hepatitis due to HBV reactivation as an abrupt increase in serum alanine aminotransferase to more than 3 times the baseline level in the presence of HBV reactivation [82].

Radiation therapy is also known to have immunosuppressive potential, and coupled with hepatocyte-directed injury, becomes a risk for HBV reactivation, with data suggesting a radiation dose effect [39, 40, 83]. RILD and HBV reactivation were reported after adjuvant chemoradiation in patients with gastric cancer. Of 62 patients treated, 8 (13%) developed Grade ≥3 liver toxicity, with HBV status being the only independent factor associated with liver toxicity (P < 0.001). Moreover, of six HBV carriers that developed RILD, four showed evidence of HBV reactivation, with two of them progressing to liver failure [84]. Other investigators have reported HBV reactivation after liver irradiation with 3D-CRT, with one study suggesting that IL-6 produced from endothelial cell damage was implicated in HBV reactivation through bystander effect [40, 85]. A prospective study that enrolled 205 patients with HCC demonstrated that concurrent, more intensive therapies and higher HBV DNA levels (>10^4 copies/ml) were independent predictors of HBV reactivation, ultimately recommending prophylactic antiviral therapy for all patients with high levels of HBV DNA, irrespective of the modality chosen for HCC treatment [86].

Monitoring of HBV DNA levels prior to and after treatment is recommended for chronic HBV patients (HBsAg positive or negative), especially in the context of HCC that is usually accompanied by liver dysfunction. Despite the lack of high-level evidence, prophylactic antiviral therapy with nucleoside and nucleotide analogues has been generally recommended. Prophylactic lamivudine use was associated with a significantly reduced rate of HBV reactivation in patients treated for HCC with 3D-CRT compared with patients without prophylaxis, including a lowered incidence of RILD (12.5% vs 21.8%), although this difference did not reach statistical significance [39]. Currently, there is a paucity of data on the ideal approach to prevent HBV reactivation in the context of liver SBRT.

Fig. 1. Volumetric reconstructions of (A) the portal vein and (B) the central hepatobiliary tract (cHBT) surrogate structure. Note: in brown = liver; in yellow = portal vein, including segments of the splenic and superior mesenteric vein; in green = segment of the portal vein used to construct the cHBT structure; and in light blue = central hepatobiliary tract (cHBT) surrogate structure created by a 15 mm expansion from the portal vein region between red arrows. (Adapted from Osmundson EC, Wu Y, Laxton G et al. Predictors of toxicity associated with stereotactic body radiation therapy to the central hepatobiliary tract. Int J Radiat Oncol Biol Phys 2015;7:986–94, Copyright (2015), with permission from Elsevier.)
Adaptive approaches based on liver function estimation

Functional liver imaging

Recent studies have investigated the utility of functional imaging and direct measures of liver function in predicting RILD. A group from the University of Washington used quantitative imaging of liver function to identify areas within the normal liver parenchyma with higher or lesser functional activity using $^{99m}$Tc sulfur colloid (SC) single-photon emission computed tomography (SPECT)/CT. A feasibility study first confirmed the correlation of SC SPECT/CT metrics with liver function assessed by CP score, demonstrating that the volume of functional liver above a predefined threshold correlated with overall survival after adjusting for CP class [87]. Later, the same group conducted a retrospective analysis of 47 HCC patients treated with SBRT or proton therapy, correlating dosimetric data with volumetric functional liver parameters. These investigators reported that patients with higher risk of non-classic RILD had baseline functional liver volume of <400 cm$^3$ or <30% of uninvolved liver, showing that functional liver volume normalized by the spleen uptake ratio was independently predictive of RILD-specific survival [88].

Biomarkers of liver function

Indocyanine green (ICG) is a compound that can only be cleared from the circulation by liver metabolism, thus serving as a direct measurement of dynamic liver function, and it has been used for assessing post-hepatectomy liver function in surgical planning [89, 90]. This concept has been applied in radiotherapy as well [91, 92]. Feng et al. recently reported the results of a Phase II trial in which 90 patients with liver tumors (77% HCC) were treated with an adaptive SBRT regimen based on liver function estimation using ICG clearance [92]. Prior to SBRT, all patients underwent measurement of ICG retention rate at 15 min for a baseline liver function assessment. A five-fraction SBRT plan was then generated, with a maximum predicted risk of RILD of 15% based on a NTCP model. After the first three SBRT fractions were delivered, a 4-week treatment break was given to all patients, and this was followed by a repeat ICG retention measurement. The dose of the final two fractions was adapted based on the estimated liver function change. For cases where the estimated liver function was too low, a second 4-week break was offered and treatment continuation allowed only if an improvement in function was observed on a third ICG test after the second break. Using this protocol, the SBRT course was adapted for 52 (45%) of 116 tumors, with 26 receiving only three fractions. Using this adaptive approach, a significantly lower decline in liver function was observed compared with the predicted function decline if no adaptation was used. Only 6% (7%) patients presented a worsening ≥2 points in CP score, with a LC of 99 and 95% at 1 and 2 years, respectively.

Other alternatives for mitigating the impact of radiation on liver function are currently under investigation, including systemic agents acting as radioprotectors, such as pentoxifylline, glibenclamide, ursodeoxycholic acid (UDCA) and low-molecular-weight heparin; agents involved in hepatic fibrosis such as C-X-C chemokine receptor type 4 (CXCR4); as well as hepatocytes transplantation [93–96].

Machine learning for toxicity prediction after radiotherapy

Machine learning can help in liver SBRT planning through computerized image analysis and toxicity prediction models. Computerized analysis involves registration of CT, MR and PET pre-treatment images, and detection and segmentation of tumors and organs-at-risk (OARs) surrounding tumors. Toxicity prediction models utilize machine learning for identification and selection of pretreatment features and for detecting consistent patterns among such features associated with post-treatment toxicities.

Machine learning-based liver imaging analysis

Segmentation of the target tumor and surrounding OARs is required for accurate dose calculation of dose–volume histograms during liver SBRT planning. When performed manually, segmentation is negatively affected by intra- and interobserver variability and the likelihood of inaccuracies. In addition, this task is time-consuming, which reduces efficiency and increases expense. Machine learning–based solutions have the potential to replace manual contouring, and improve the quality and accuracy of the segmentation process, and a number of computerized methods have been proposed for liver image segmentation.

Various convolution neural network (CNN) architectures have successfully addressed problems of detection and segmentation of both liver tumors and various OARs [97–100]. The recently reported volume agreement between manual and CNN-based liver segmentation is nearly 95% [100]. The maximal segmentation accuracy is usually achieved when CNNs are augmented with conditional random fields, graph cuts, and shape models [100–102].

Machine learning–based methods have been developed for automated analysis of the majority of OARs that may be involved in liver SBRT. Because of the availability of a public database and unified evaluation software, liver segmentation has been receiving considerable attention in the literature [100, 101, 103–110]. The existing machine learning–based methods exhibit liver segmentation accuracy of from 67 to 97.3%, measured in terms of Dice coefficient, and ~5% of volume disagreement from that obtained with manual segmentation [107, 108]. This level of agreement is impressive, considering the interpatient anatomical variability, and these methods will certainly take the place of major radiotherapy planning steps currently done manually in the near future. Top-performing liver segmentation methods utilize CNNs with convolution–deconvolution architecture and augment CNNs with shape model or conditional random fields (Fig. 2) [100, 107]. Machine learning–based segmentation of liver tumors represents a unique challenge due to highly variable tumor appearance in CT and MR image modalities, and the presence of fiducial markers that compromise tumor border identification. For segmentation of liver tumors from CT images, the accuracy of machine learning–based methods varied from 77 to 93% of the Dice coefficient.

We have observed a strong movement in the abdominal image analysis field towards the utilization of modern deep-learning algorithms in both segmentation and registration problems. Particularly, success has been observed when deep learning is augmented with...
We must note that machine learning is not limited to abdominal image segmentation and registration, and is, for example, used for liver motion estimation, which is also of importance for accurate dose delivery [111].

**Machine learning–based models for toxicity prediction**

While much of the focus on predicting liver toxicity risk has been on liver dosimetry, toxicity is clearly influenced by non-dosimetric factors as mentioned previously. Consequently, toxicity prediction requires analyzing complex and non-trivial relationships that exist between features of both dosimetric and non-dosimetric nature, making the problem challenging to solve with simple statistical models. There is growing confidence that such relationships can be effectively studied by machine-learning approaches [112, 113]. However, most of the machine learning–based toxicity predictors of RT were developed for the prostate and lung, and toxicity prediction after liver SBRTs remains an understudied field.

Toxicity prediction with machine learning requires the identification of features that may potentially contribute to toxicity manifestation, and selection of an appropriate machine-learning algorithm that can successfully identify consistent patterns among features, associating them with toxicities. For prediction of RT-induced toxicity, dosimetric features tend to exhibit the highest correlation potential with toxicity, as demonstrated in prediction of radiation-induced pneumonitis, rectal toxicities and gastrointestinal toxicities [114–120].

The history of comorbidities and previously treated diseases also plays an important role in toxicity prediction. For example, the diffusion capacity of the lungs for carbon monoxide, and chronic obstructive pulmonary disease were found to be contributing features by machine-learning predictors for pulmonary toxicity [116, 119]. Finally, studies have shown that chemotherapy given concurrently and surgical interventions performed near the time of RT may increase the risk of radiation pneumonitis and lung injury; therefore, these other treatment modalities should be analyzed together with dosimetric and other clinical features [114, 119, 121].

Methodologically, random forests and neural networks are the most commonly selected approaches for toxicity prediction [112, 116, 117, 119, 121–123]. Computational models to predict drug-induced liver toxicity have been previously reported, but to our knowledge, there is lack of evidence on RILD prediction using machine-learning methods [124, 125]. We suggest that toxicity prediction after liver SBRT should be multifactorial, involving analysis of doses delivered to the liver and surrounding OARs; liver comorbidities such as cirrhosis, HCV and HBV infections; radiogenomic features; concurrent and prior liver-directed therapies; as well as baseline liver metabolic function (Fig. 3). Research on the development of machine-learning models capable of predicting RILD after SBRT is warranted.
CONCLUSIONS
Despite advancements in understanding the biological mechanisms involved in the development of radiation-induced liver injury, and identification of specific clinical syndromes, prognostic factors and dosimetric parameters associated with an increased toxicity risk, RILD remains an entity of great clinical concern for oncologists and patients. Machine-learning–based and adaptive approaches based on estimated liver function offer the possibility of increasing the accuracy of treatment-related toxicity prediction, allowing for a radiation treatment planning tailored to the patient’s malignancy, anatomy, inherent liver function and risk factors, ultimately delivering an individualized radiation therapy.

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