Review

Radiation induced liver disease: A clinical update

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Abstract Radiation-induced liver disease (RILD) or radiation hepatitis is a sub-acute form of liver injury due to radiation. It is one of the most dreaded complications of radiation which prevents radiation dose escalation and re-irradiation for hepatobiliary or upper gastrointestinal malignancies. This complication should be kept in mind whenever a patient is planned for irradiation of these malignancies. Although, incidence of RILD is decreasing due to better knowledge of liver tolerance, improved investigation modalities and modern radiation delivery techniques, treatment options are still limited. In this review article, we have focussed on patho-physiology, risk factors, prevention and management of RILD.

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Contents

Introduction ............................................................................ 8
Patho-physiology .................................................................. 8
Risk factors ................................................................. 8
Prevention ................................................................. 9
Dose volume constrains for prevention ................................ 9
Role of radio protectors .................................................. 9
Onset and symptoms ...................................................... 9
Investigation and diagnosis ........................................... 10
Treatment .................................................................... 10
Conclusion ............................................................... 10
Conflict of interest ....................................................... 10
Disclosure ................................................................. 10

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Introduction

Radiation induced liver disease (RILD) is one of the important complications of radiation therapy (RT). RILD typically occurs 4–8 weeks after completion of RT but has been described as early as 2 weeks and as late as 7 months after radiation. It is a major factor that limits radiation dose escalation and re-irradiation for tumors that are situated in the close vicinity of the liver. However, in recent years, modern radiation treatment planning has allowed modest dose escalation for these tumors. Various dosimetric constraints have been given to predict toxicity. Mean dose of 30 Gy is usually considered as safe but radiation tolerance of the liver is lesser in patients with deranged liver function. These patients are more susceptible for development of RILD. Clinical manifestations of RILD are non-specific. There are two types of RILD, classical (patients without underlying liver disease) and non-classical (patients with underlying liver disease). Patients with classical RILD usually present with fatigue, abdominal pain, increased abdominal girth, hepatomegaly, anicteric ascites and isolated elevation of alkaline phosphatase out of proportion to other liver enzymes. In contrast, patients with non-classical RILD present with jaundice and markedly elevated serum transaminase. Non-invasive imaging findings are nonspecific. RILD is a diagnosis of exclusion and other common causes must be ruled out first. Computed tomography (CT) may reveal well demarcated area of reduced enhancement as compared to surrounding normal liver [1]. However, recently it has been reported that functional imaging techniques like single photon emission computed tomography (SPECT) are more reliable options to detect RILD [2]. There are no specific guidelines for the management of RILD and patients are managed in the same way as non irradiated population.

Patho-physiology

Reed and Cox were the first to describe the patho-physiology of RILD and suggested that retrograde congestion is the main culprit [3]. Liver biopsy of a patient with RILD may show endothelium swelling, terminal hepatic venule narrowing, sinusoidal congestion, parenchymal atrophy of zone and proliferation of collagen [4]. These abnormalities are similar to that of veno-occlusive disease and are predominantly evident around the central vein. Formation of micro thrombi due to hepatic venule endothelial damage also contributes to the outflow obstruction. Animal studies have shown dose dependent increased expression of transforming growth factor-beta-1 (TGF-ß1) in the liver of irradiated rats which may be an important factor in the development of RILD in humans also [5]. Hepatic stellate cells are responsible for regeneration of hepatocytes, secretion of lipoproteins and growth factors. Activation of these cells may be an early event in patients with severe congestive changes of classic RILD [6].

Risk factors

The risk of developing RILD is about 5–10% when the whole liver is irradiated up to 30–35 Gy. But the radiation dose to control most of the solid malignancies is around 50–70 Gy. Thus the use of radiation for management of upper gastrointestinal (GI) and hepatobiliary malignancies may result in high chance of RILD. Dawson et al. tried to evaluate dose-volume tolerance for RILD using the Lyman–Kutcher–Burman normal tissue complication probability model in their study involving 203 patients treated with conformal liver radiotherapy and concurrent hepatic arterial chemotherapy [7]. They found that no cases of RILD were observed when the mean liver dose was kept below 31 Gy in partial liver irradiation. It was concluded that the liver exhibits a large volume effect for RILD and partial liver irradiation is feasible by keeping the liver mean dose within tolerance limits [8]. Xu et al. compared the Michigan model and the modified Lyman NTCP model for predicting the risk of RILD [9]. The study included 109 patients of primary hepatocellular carcinoma (HCC) treated with hypofractionated 3-dimensional conformal radiotherapy (3D-CRT). They found that the Michigan model was probably not good to predict RILD and the modified Lyman NTCP model for RILD should be used instead.

With the availability of Intensity modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT) and image guidance in radiation treatment planning, high tumor ablative doses of radiation can be delivered to the tumors without compromising normal liver functions [10].

The baseline liver function, background hepatic cirrhosis and volume of liver in the PTV are important factors for developing RILD [11]. The Child-Pugh Grading is useful in assessing the baseline liver function in patients with chronic liver disease [11]. However, Indocyanine green clearance test is a more sensitive test than Child-Pugh grading in assessing liver functions. Indocyanine green is delivered systemically and the hepatic retention is measured at 15 min. When the retention rate is 10–19%, the function of liver is considered very well and even a lobectomy can be done. Though most of the data on Indocyanine green clearance test is on liver resection, it can be helpful in considering patients for liver irradiation also. Some studies have shown that Child-Pugh class may be a more important parameter than Indocyanine green retention test for predicting RILD [12].

Dose per fraction is another important factor in the development of RILD. The tolerance of liver parenchyma to hypofractionated and accelerated radiotherapy is much lower than that of conventional 2 Gy per fraction. This must be kept in mind especially when planning hypofractionated regimens for the treatment of liver malignancies.

There is an additional risk of RILD by concurrent administration of hepatotoxic chemotherapy to radiation and irradiating a patient who has already received hepatotoxic chemotherapy prior to radiation. Though there are no specific guidelines, this factor should be considered whenever a patient.
is planned for radiotherapy. Care must be taken in patients receiving other hepatotoxic drugs also.

Other risk factor that may be associated with a higher risk of RILD includes prior trans-catheter arterial chemo-embolization presence of portal vein tumor thrombosis, tumor stage and male sex [13–15]. Patients with primary hepatobiliary malignancies have a lower tolerance to liver radiation than the patients with liver metastases.

**Prevention**

Since there is no effective treatment for RILD, the most effective measure is prevention. Appropriate assessment of the patient before starting the radiation treatment is very important.

The functional reserve of liver can be assessed by Child-Pugh Grading and Indocyanine green clearance tests. The development in treatment delivery has led to better sparing of the normal liver while providing the desired dose to the tumor. Image guided radiotherapy and stereotactic targeting are useful in reducing setup uncertainty [16]. Regular breathing can result in liver tumor displacement up to 2 cm. Use of respiratory motion management techniques (abdominal compression, shallow breathing, breath holding, gating and tracking) can be useful in reducing the volume of liver irradiated and there by the incidence of RILD [17]. During radiation treatment, patients should be monitored by physical examination and blood chemistry every week. After completion of the radiation, these examinations should be repeated every 2 or 3 months.

**Dose volume constrains for prevention**

Investigators from the university of Michigan are one of the pioneers in the work related to dose constrains and incidence of RILD. When the whole liver is irradiated by conventional fractionation, a dose of 30 Gy is likely to produce a 5% risk of RILD [18]. The threshold dose for RILD may be lower in hypo-fractionated or accelerated radiotherapy. The incidence of RILD was 10% in a RTOG study where accelerated hyper fractionated hepatic radiotherapy of 33 Gy (1.5 Gy separated by 4 h or longer) was given for the management of liver metastasis [19]. There are some clinical situations where the entire liver receives the prescribed dose of radiation and these are whole abdominal irradiation for advanced stage Wilms tumor, some ovarian malignancies and total body irradiation. The radiation dose for Wilms tumor is within the tolerance limit for the whole liver. Whole liver irradiation can also be used in a palliative setting in patients with multiple incurable liver metastases, especially in palliation of pain [20]. The above dose limits must be kept in mind when whole liver irradiation is planned for these patients.

Radiobiologically, liver parenchyma has parallel architecture in which individual functional units work independently. This allows for high-dose treatment to small volumes of the liver as long as the mean dose of the normal liver is kept within tolerance limit. The tolerance of partial liver volumes can be higher (up to 80 Gy). The two main constrains that must be kept in mind are the mean dose to the liver and volume of liver receiving 30 Gy. The volume that must be taken should be liver minus gross tumor. The mean dose should be kept below 28 Gy and 32 Gy in conventional fractionation for primary HCC and liver metastases respectively [15,17]. The volume of liver receiving 30 Gy should be less than 60% of the liver volume [21].

Liang et al. investigated for dosimetric predictors for RILD after hypo fractionated conformal radiotherapy [22]. The study included 114 patients of primary HCC (with Child-Pugh Grade A cirrhosis) treated with hypo fractionated conformal radiotherapy. They found that the volume receiving 20 Gy (V20) was a unique significant dosimetric predictor for RILD in these patients.

The dose constrains are different when SBRT is used. The mean dose must be kept less than 13–18 Gy for three fractions and less than 15–20 Gy for six fractions SBRT. Another important constrain that may be used is to keep the volume of liver receiving 15 Gy to less than 700 mL in three to five fractions SBRT. Jung et al. investigated the clinical and dosimetric parameters that predict the risk of RILD for patients with HCC treated with SBRT [23]. They found that Child-Pugh B class was a significant parameter for predicting grade 2 or higher RILD. Son et al. evaluated the incidence of hepatic complications in 47 patients treated with SBRT for small unresectable primary HCC using Cyber Knife [24]. They found that the factors associated with significant hepatotoxicity were Child-Pugh class and total liver volume receiving a dose less than 18 Gy.

Radio-embolization with yttrium-90 (90Y) is a popular method of treating extensive liver metastasis and HCC. Young et al. investigated the clinical and dosimetric parameters that predict the risk of liver injury in patients of HCC undergoing radio-embolization [25]. They found that compared to Okuda stage II, stage I patients tolerate higher cumulative radiation dose with 90Y and liver toxicity increases with an increase in dose: 222 Gy (no toxicity) versus 390 Gy ($> or = 1$ toxicity, $p < 0.005$).

**Role of radio protectors**

Animal studies have shown that the use of amifostine protects hepatocytes from ionizing radiation without compromising tumor control [26]. In a phase I study, Feng et al. evaluated the role of amifostine as a radio protector in dose-escalated whole liver radiation therapy [27]. The study included 23 patients and a maximum dose of 40 Gy was used. This was compared with previously treated patients by logistical regression model. It was observed that the use of amifostine increased the liver tolerance by 3.3 $+/- 1.1$ Gy. Animal studies have also shown that antioxidant $\alpha$-tocopherol (Vitamin E) may reduce the incidence of RILD by reducing liver lipid peroxidation and maintaining the endogenous liver antioxidant defense [28]. But the use of these radio protectors in routine clinical practice is still investigational due to lack of clinical trials. The question of whether or not these agents reduce the tumor control also needs to be tested before its use as radio protectors.

**Onset and symptoms**

Symptoms of RILD usually occur 2–8 weeks after completion of radiation treatment [29]. A high index of clinical suspicion is very important in early diagnosis. The symptoms are usually
non-specific with fatigue and right upper quadrant pain being the most common symptoms. Examination findings may resemble Budd-Chiari Syndrome with massive ascites and hepatomegaly. Jaundice is unlikely to be present in a patient with RILD. If jaundice develops during or following radiotherapy treatment, ascending cholangitis must be considered as a possible cause. Profound thrombocytopenia may be seen which is caused by splenic sequestration from portal hypertension due to the obstruction of the hepatic veins. The irradiation of the liver may also lead to the reactivation of hepatitis B.

Investigation and diagnosis

In classical RILD, alkaline phosphatase increases more than two times the normal level but level of transaminase, bilirubin and ammonia remain normal. In contrast to classical RILD, patients with underlying liver disease present with jaundice and markedly elevated serum transaminase, more than five times the upper limit of normal [22]. Common toxicity criteria for adverse events (CTCAE) criteria for elevations of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin should be used to report toxicity. Hepatic viral markers, serum bilirubin, serum protein and prothrombin time should be investigated.

Ultrasound of the abdomen reveals massive ascites and hepatomegaly. It may also help in excluding other causes of ascites. Doppler studies may show the direction of flow in the portal vein, and any possible thrombosis. Contrast enhanced computed tomography (CT) usually reveals a sharp demarcation line between the normal enhancing lesion and the hypo attenuation ["straight-border sign," along the trajectory of the radiation beam [30]. RILD may present as demarcated areas of hypo or hyper attenuation in a non-anatomic distribution [31]. One of the limitations of dynamic CT is that even though it may show blood flow, it gives very little idea of the hepatocellular function [32]. Magnetic resonance imaging usually shows low signal intensity on T1-weighted images and high signal on the T2-weighted image as it has increased water content [33].

Paracentesis of ascites may be useful in the diagnosis of RILD as it rules out other possible causes of ascites (RILD is a diagnosis of exclusion) [11]. Cytopathologic evaluation of the ascitic fluid is usually negative for malignancy. The analysis of the fluid generally shows features of transudate with the serum-ascites albumin gradient > 1.1. Diagnostic laparoscopy may reveal mottled appearance of the liver with bluish and dark areas [4]. Liver biopsy helps in confirming the diagnosis of RILD.

Acute hepatic toxicity may also occur during radiation. Patients may present with elevated transaminases. Usually no severe long term consequences are seen if appropriate therapy is given on time. Radiation discontinuation may be required in some cases.

Treatment

No therapy has been shown to prevent or to modify the natural course of the disease. Treatment is mainly directed at control of symptoms. The drugs used for supportive care include diuretics for fluid retention, paracentesis for ascites, correction of coagulopathy, and steroids to reduce hepatic congestion [32]. The use of anticoagulants and thrombolytics may be helpful in relieving hepatic vein thrombosis. Other agents that have been approved for the management of hepatic veno-occlusive disease may be tried in RILD also.

Conclusion

Radiation induced liver disease is a diagnosis of exclusion. Indicators of liver function status like Child-Pugh score and Indocyanine green clearance test are important parameters to predict the toxicity. Mean radiation dose of 30 Gy is considered as safe but radiation tolerance of liver decreases in the presence of deranged liver functions. Prevention is the key as there are no specific treatment guidelines. Attempt should be made to keep the mean dose below tolerance level. Role of radio-protectors is doubtful. Although newer techniques of radiation have reduced the incidence of RILD, more extensive research is required to structure guidelines for prevention and management.

Conflict of interest

None.

Disclosure

None.

Acknowledgment

None.

References

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