Hepatic Dysfunction Following Radiotherapy and Management

21

Do Young Kim

Abstract

Although proper selection of patients with liver cancer minimizes the probability of occurrence of hepatic dysfunction, radiotherapy for patients with underlying liver diseases such as cirrhosis or chronic hepatitis B might lead to classic or non-classic radiation-induced liver disease. Clinically, hepatic dysfunction includes ascites, jaundice, variceal hemorrhage, hepatorenal syndrome and hepatic encephalopathy. Several factors such radiation dose, residual liver function, and treatment other than radiotherapy are involved in the development of hepatic dysfunction. Ascites is the most common manifestation of hepatic dysfunction after radiotherapy in patients with liver cancer. A strict adherence to a low-salt diet and medical therapies including diuretics and therapeutic paracentesis can control ascites. In patients with refractory ascites, liver transplantation should be considered if tumor extent after radiotherapy is decreased within usual criteria for transplantation. When patients develop jaundice during or after radiotherapy, radiation oncologists or hepatologists differentiate between obstructive jaundice and hepatocelluar jaundice, which often implies poor prognosis. Esophageal or gastric variceal bleeding is a medical emergency requiring intensive fluid resuscitation and endoscopic or interventional treatment. To prevent rebleeding from esophageal varices, endoscopic variceal ligation combined with pharmacologic therapy is necessary. Hepatic encephalopathy is a neurological or psychiatric manifestation of hepatic dysfunction resulting from inability to detoxify endogenous or exogenous compounds. Hepatic encephalopathy usually occurs late during hepatic dysfunction, requiring liver transplantation when tumor control is enough. It is essential for radiation oncologists and hepatologists to cooperate to properly manage liver cancer patients with radiation therapy.

Keywords

Radiation · Liver cancer · Hepatic dysfunction

21.1 Introduction

The survival of patients with liver cancer is substantially affected by not only tumor status but also liver function. Therefore, physicians and radiation oncologists should be alert to hepatic dysfunction

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that might occur during and after radiation treatment for liver cancer. This is because the liver is often not healthy, i.e., infected by hepatitis B virus (HBV) or hepatitis C virus (HCV) or cirrhotic, even though it is known to have a high regenerative potential. In spite of pretreatment selection of patients with liver cancer who are feasible for radiotherapy, a proportion of patients develop hepatic dysfunction including jaundice, ascites, variceal hemorrhage, and so on. In addition to appropriate selection of patients for radiotherapy, close monitoring during treatment and optimal management for patients with hepatic dysfunction are essential to improve patient survival. For successful radiation therapy for liver cancer patients, a multidisciplinary team approach and collaboration between radiation oncologists and hepatologists are crucial. Antiviral therapy for patients with HBV infection must be considered before radiation therapy since radiation might cause reactivation of HBV, resulting in liver injury and hepatic dysfunction [1].

21.1.1 Radiation-Induced Liver Disease

Traditionally, radiation therapy has not been frequently applied because of the relatively low tolerance of the whole liver to radiation [2]. However, technological advances including intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and stereotactic body radiotherapy (SBRT) have made it possible for high doses of radiation to conform to the target volume safety [3]. Nevertheless, patients may experience liver damage such as transaminase elevation, jaundice, prolongation of prothrombin time, and aggravation of portal hypertension during or after radiation therapy. Radiation therapy causes these liver injuries for various reasons. The most important factors in avoiding radiation toxicity are the estimation of pretreatment residual liver function indicated by Child-Pugh score, accurate calculation of radiation dose, and precise targeting. Radiation-induced liver disease (RILD) is the terminology used to assess liver toxicity caused by radiation when there is an association between radiation therapy and liver disease, and it is diagnosed mainly based on clinical manifestations or laboratory findings.

21.1.1.1 Pathogenesis of RILD

The pathogenesis of RILD includes complex and multicellular responses related to vascular changes, increased collagen synthesis, and sequential activation of key growth factors and cytokines, such as tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), and hedgehog (Hh), which are important regulators in repair responses to liver damage [4]. Upon irradiation to the liver, subendothelial cells (SECs) are injured, undergo apoptosis and release TFN-α, which promotes hepatocyte apoptosis and Kupffer cell activation. Furthermore, injured SECs induce the penetration of red blood cells and activate fibrin deposition in central veins, resulting in sinusoidal obstruction. The ensuing hypoxic environment leads to the death of hepatocytes and the activation of Kupffer cells. Activated Kupffer cells release TGF-β, the major profibrogenic cytokine, which promotes the transdifferentiation of quiescent hepatic stellate cells (HSCs) into myofibroblast-like HSCs (MF-HSC). Apoptotic hepatocytes also produce Hh ligands, which trigger the proliferation of Hh-responsive cells, such as HSCs. MF-HSCs accumulate and promote the deposition of extracellular matrix proteins, leading to liver fibrosis [5].

21.1.1.2 Classification of RILD

RILD can be classified into two kinds of radiation toxicity. The first is classic RILD, which was historically the dose-limiting complication of liver radiation with onset two weeks to four months after whole hepatic radiation to 30–35 Gy using conventionally fractionated regimens. The underlying mechanism of liver damage is veno-occlusive disease secondary to fibrosis [6]. The clinical manifestations are comprised of anicteric hepatomegaly, ascites, and elevated liver enzymes, particularly alkaline phosphatase. Risk factors related with classic RILD are known to be high mean liver dose, primary liver cancer, male gender, and hepatic intra-arterial chemotherapy [6]. With technological advances, classic RILD is

currently rare. Non-classical RILD is much more common, and the signs and symptoms are markedly elevated serum transaminases (>5× upper limit of normal) and jaundice. The most vulnerable populations affected by non-classic RILD are patients with underlying liver disease such as chronic hepatitis B or cirrhosis [7–9]. The mechanism of non-classic RILD is less well-understood but may involve the loss of regenerating hepatocytes and reactivation of hepatitis [8]. The most commonly used criteria for non-classic RILD are an increase in Child-Pugh score ≥2 in cirrhotic patients and a ≥5× increase in transaminases or change in albumin–bilirubin (ALBI) score in noncirrhotic patients. Table 21.1 shows the comparisons of several characteristics between classic and non-classic RILD.

Table 21.1 Characteristics of classic and non-classic RILD

Characteristics	Classic RILD	Nonclassic RILD
Onset	2 weeks to 4 months	
Underlying mechanism	Veno-occlusive disease	Loss of regenerating hepatocytes
Clinical manifestations	Anicteric hepatomegaly, liver enzyme elevation	Transaminase elevation, jaundice
Risk factors	High mean liver dose, male, primary liver cancer	Cirrhosis, Hepatitis B virus infection

21.1.2 Hepatic Dysfunction Following Radiation Therapy

21.1.2.1 Ascites

Ascites is the most common complication of cirrhosis, with 5–10% of patients with cirrhosis developing this complication. As a significant proportion of patients who receive radiation therapy for liver cancer have underlying cirrhosis, ascites manifests as the most frequent hepatic dysfunction following radiotherapy (Fig. 21.1). Development of ascites is due to portal hypertension according to progressive loss of functioning hepatocytes and aggravated liver fibrosis. Excessive accumulation of sodium, i.e., renal sodium retention, is explained by arterial splanchnic vasodilation. The resulting decrease in effective arterial volume activates vasoconstrictor and sodium-retaining systems such as sympathetic nervous system and renin-angiotensin-aldosterone system. Finally, renal sodium retention leads to expansion of extracellular fluid volume and formation of ascites [10]. When ascites develops, patients complain of abdominal discomfort, increase in abdominal girth, weight gain, and reduced food intake. With increasing amount of ascites, edema of the lower legs or scrotum in males might occur. The mainstays of first-line treatments for patients with ascites which occurs following radiotherapy include education regarding dietary sodium restriction (80–120 mmol/day) and oral diuretics

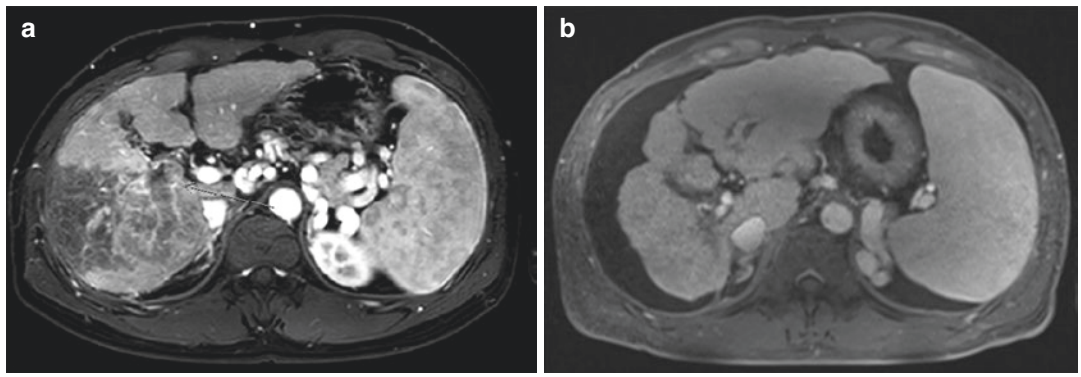

Fig. 21.1 Occurrence of ascites after radiotherapy for a 43-year-old patient with hepatocellular carcinoma. (**a**) Contrast-enhanced MRI showing advanced liver cancer with portal vein thrombosis. (**b**) Following concurrent chemoradiation therapy viable tumor substantially decreased with liver atrophy and ascites formation.

[11, 12]. More stringent dietary sodium restriction is not recommended to prevent a reduced caloric intake, which could aggravate malnutrition already present in patients with liver cancer. Fluid loss and weight change are directly related to sodium balance in patients with portal hypertension-associated ascites. It is sodium restriction, not fluid restriction, that results in weight loss, as fluid follows sodium passively [13]. It is not easy for patients with liver cancer and ascites to eat a low-salt diet because they have decreased appetite related with cancer and treatment.

21.1.2.2 Diuretics

The usual strategy of using diuretics consists in the simultaneous administration of spironolactone and furosemide starting with 100 mg/day 40 mg/day, respectively [11, 12]. Previously, single-agent spironolactone was advocated, but hypokalemia and the long half-life of this drug have resulted in its use as a single agent only in patients with minimal fluid overload [14]. Eventually most patients require combination treatment of spironolactone and furosemide. Starting both drugs appears to be the preferred approach in achieving rapid natriuresis and maintaining normokalemia. The doses of both oral diuretics can be increased simultaneously every three to five days (maintaining 100 mg:40 mg ratio) if weight loss and natriuresis are inadequate. Usual maximum doses are 400 mg/day of spironolactone and 160 mg/day of furosemide [11, 12]. Patients with parenchymal renal disease or post-liver transplantation may tolerate less spironolactone than usual because of hyperkalemia. Single morning dosing maximizes compliance. Dosing more than once daily reduces compliance and can cause nocturia. Amiloride (10–40 mg/day) can be substituted for spironolactone in patients with tender gynecomastia. Other diuretics such as torasemide must be proven to be superior to current drugs before the expense can be justified. The goal of diuretic treatment is to achieve a loss of body weight between 300 and 500 mg/day in patients without peripheral edema. Greater weight loss may be safe in patients with concomitant peripheral edema but may be associated with complications in patients without edema [15].

21.1.2.3 Measures to Maintain Blood Pressure

Since blood pressure in patients with ascites is supported by elevated levels of vasoconstrictors such as vasopressin, angiotensin, and aldosterone, which compensate for the vasodilatory effect of nitric oxide (NO) [16], drugs that inhibit the effect of these vasoconstrictors would be expected to lower blood pressure, which might worsen survival. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers should be avoided or used with caution in patients with cirrhosis and ascites. In the unusual situations in which they are used, blood pressure and renal function must be monitored carefully to avoid rapid development of renal failure. Propranolol, which is used for reducing portal pressure, has been shown to shorten survival in patients with refractory ascites in a prospective study [17]. This could be due to its negative impact on blood pressure and the increase in the rate of paracentesis-induced circulatory dysfunction that is seen in patients who are taking propranolol in the setting of refractory ascites. Prostaglandin inhibitors such as nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce urinary sodium excretion in patients with cirrhosis and can induce azotemia [18]. Thus, NSAIDS should be cautiously used in cirrhotic patients who are receiving various treatments including radiation for liver cancer.

21.1.2.4 Therapeutic Paracentesis

A prospective study has demonstrated that a single 5-liter paracentesis can be performed safely without post-paracentesis colloid infusion in patients with diuretic-resistant tense ascites [19]. Larger volumes (>5 L) of fluid have been safely removed with the administration of intravenous albumin (8 g/L of fluid removed) in patients with tense ascites whether it was diuretic-resistant or not [20]. A single large-volume paracentesis followed by diet and diuretic therapy is appropriate treatment for patients with tense ascites [19, 20]. In the outpatient clinic, body weight, blood pres-

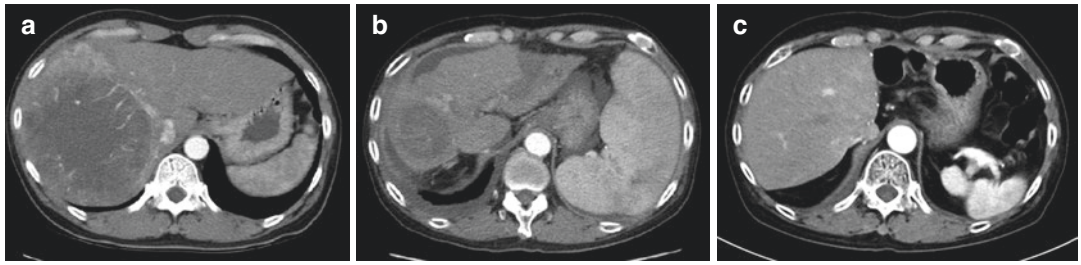

Fig. 21.2 A case of patient who underwent liver transplantation after radiotherapy for hepatocellular carcinoma. (**a**) contrast-enhanced CT scan showing a huge tumor with thrombus in inferior vena cava. (**b**) The tumor markedly decreased after concurrent chemoradiation therapy, but ascites and liver dysfunction developed. (**c**) Living donor liver transplantation was performed and there was no recurrence of tumor.

sure, orthostatic symptoms, serum electrolytes, urea, and creatinine are monitored. If weight loss is inadequate, a random spot urine sodium/potassium ratio or 24-h urine sodium can be measured. Patients who are excreting urine sodium/potassium greater than 1 or 24-h urine sodium greater than 78 mmol/day and not losing weight are consuming more sodium in their diet than 88 mmol/day (2000 g/day) and should be counseled further about dietary sodium restriction [21].

21.1.2.5 Management of Refractory Ascites

Refractory ascites is defined as fluid overload that is unresponsive to a sodium-restricted diet and high-dose diuretic treatment (400 mg/day of spironolactone and 160 mg/day of furosemide), or that recurs rapidly after therapeutic paracentesis [22]. Once ascites becomes refractory to medical treatment, the median survival of cirrhotic patients is approximately six months [23]. Therefore, the survival is expected to be much less than six months in patients with liver cancer and refractory ascites. There are several options in these patients. Serial therapeutic paracenteses are effective in controlling ascites. Even in patients with no urine excretion, paracentesis performed approximately every two weeks controls ascites [11, 12]. The treatment options for cirrhotic patients with refractory ascites are: large-volume paracentesis (LVP), defined by drainage of more than five liters of ascites, insertion of transjugular intrahepatic portosystemic shunt (TIPS), and liver transplantation (LT). In patients with liver cancer and ascites who received radiotherapy, LT might be an effective and life-saving treatment if tumor burden does not exceed the usual criteria defined, for example, by the Milan criteria (Fig. 21.2). Frequently, TIPS is technically unavailable in these patients because of portal vein tumor thrombosis, which is contraindication of this procedure.

21.1.3 Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is an acute ascitic fluid infection, and clinically suspected when patients with cirrhosis and ascites have symptoms of fever and abdominal pain. SBP is the most frequent bacterial infection in cirrhotic patients. Diagnosis is based on paracentesis with a polymorphonuclear leukocyte count $\geq$250 cell/mm^3 in ascitic fluid, with or without positive ascitic culture, in the absence of other causes of peritonitis [24]. Patients diagnosed as SBP should receive empirical antibiotic therapy. Meanwhile, the ascitic fluid needs to be cultured in a blood culture bottle. Delaying treatment until the ascitic fluid culture grows bacteria may result in the death of the patient from overwhelming infection. Relatively broad-spectrum antibiotic therapy is warranted in patients with suspected ascitic fluid infection until the results of susceptibility testing are available. Cefotaxime or a similar third-generation cephalosporin appears to be the best choice for suspected SBP; it used to cover 95% of the flora, including the three most common isolates: *Escherichia coli*, *Klebsiella*

Pneumoniae, and *Streptococcal pneumoniae* [25]. After sensitivities are known, the spectrum of coverage can usually be narrowed. Oral ofloxacin (400 mg bid for an average of eight days) has been reported in a randomized controlled trial to be as effective as parenteral cefotaxime in the treatment of SBP in patients without vomiting, shock, grade II (or higher) hepatic encephalopathy, or serum creatinine greater than 3 mg/dl [26]. Norfloxacin 400 mg/day orally has been reported to successfully prevent SBP in patients with low-protein (<15 g/L) ascites and patients with prior SBP [27, 28].

21.1.4 Jaundice

Jaundice (from the French *jaune* meaning yellow), refers to the yellowish discoloration of the skin, sclera, and mucous membranes that accompanies deposition of bilirubin in tissues [29]. It develops when serum bilirubin levels are elevated above 34 mmol/L (2 mg/dl), with yellow discoloration of the sclera being the site where jaundice is detected earliest due to high elastin content of sclera and its strong binding affinity for bilirubin [30]. Clinically and pathophysiologically, jaundice is classified as either hepatocellular jaundice or obstructive jaundice. Hepatocellular jaundice is due to hepatocyte dysfunction, resulting in failure of secretion of bilirubin into the bile duct. Obstructive jaundice, previously known as surgical jaundice, is a manifestation of cholestasis. Cholestasis is defined as impairment in the formation of bile or bile flow out of the porta hepatis through the biliary ducts into the duodenum. Cholestasis often results in conjugated hyperbilirubinemia and may or may not be accompanied by clinical jaundice. The main symptoms of cholestasis or jaundice are fatigue, pruritus, and indigestion. When physicians or radiation oncologists observe jaundice in patients who underwent radiotherapy, the first step is to differentiate hepatocellular jaundice (intrahepatic cholestasis) from obstructive jaundice (extrahepatic cholestasis). Cholestasis from bile duct obstruction is generally identified by abnormal findings on biochemical tests of the liver, such as elevated alkaline phosphatase (ALP) and ɣ-glutamyl transferase (ɣ-GT) levels and variable levels of bilirubin and prothrombin time. However, elevated ALP levels are not completely specific for cholestasis; the levels are often elevated even in patients with hepatocellular jaundice. The levels of enzyme can be elevated by less than three times the normal limit in virtually any type of liver disease. Once cholestasis is identified by the liver function tests, it should be determined whether the cholestasis is intrahepatic or extrahepatic. Radiologic imaging plays an important role in evaluating the etiology of cholestasis and determining treatment strategies. In patients with liver cancer, extrahepatic cholestasis can be caused by extrinsic compression of bile ducts or invasion by tumors. Causes of intrahepatic cholestasis in patients with liver cancer who received radiotherapy include reactivation of hepatitis B or significant damage or lost of functioning hepatocytes.

21.1.4.1 Management of Jaundice

When patients with liver cancer develop intra or extrahepatic cholestasis due to compression of bile duct by mas, radiation therapy itself is sometimes useful for relieving obstructive jaundice. If other treatment modalities are not available because of jaundice or poor liver function, radiation therapy might be optimal. In liver cancer patients who underwent radiation therapy, the management of jaundice depends on the etiology of cholestasis. However, since patients usually have a significant tumor burden and underlying liver disease, manifestation of jaundice implies a dismal prognosis irrespective of the etiology of cholestasis. Supportive care with liver pills including ursodeoxycholic acid (UDCA) or silymarin is recommended in patients with intrahepatic cholestasis. Interventional or endoscopic palliation, such as percutaneous transhepatic biliary drainage (PTBD) or endoscopic retrograde cholangiopancreatography (ERCP) with stenting, might be provided to patients with obstructive jaundice (Fig. 21.3).

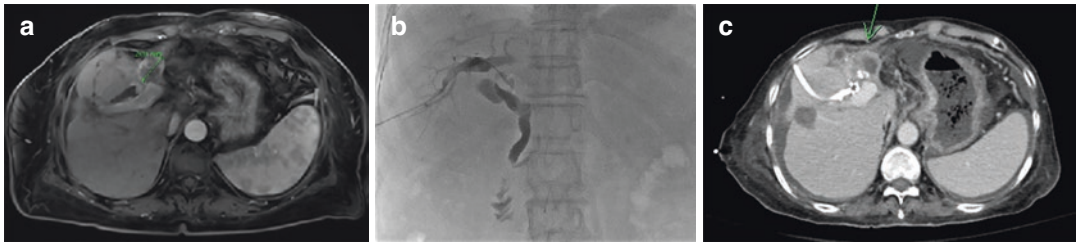

Fig. 21.3 Recurrent hepatocellular carcinoma after resection obstructing bile duct treated with radiotherapy. (**a**) A 2.7 cm recurrent tumor with bile duct dilatation at the margin of resection is observed. (**b**) Percutaneous transhepatic biliary drainage (PTBD) was performed to decompress biliary trees. (**c**) Post-radiation follow-up CT scan showing stable tumor and decompressed bile duct.

21.1.5 Portal Hypertension and Variceal Hemorrhage

Portal hypertension (PH) is defined as an increase of blood pressure in the portal venous system. Hepatic venous pressure gradient (HVPG) measurement is the gold-standard method to assess the presence of PH [31]. Based on portal pressure, patients with compensated cirrhosis can be divided into those with mild portal hypertension (HVPG >5 but <10 mmHg) and those with clinically significant PH (CSPH), defined by an HVPG ≥10 mmHg. CSPH is associated with an increased risk of developing varices and other cirrhotic complications [32–34]. As described above, radiation therapy may increase portal pressure by increasing deposition of extracellular matrix from hepatic stellate cells. Patients with gastroesophageal varices have, by definition, CSPH, because patients with GEV have an HVPG of at least 10 mmHg [35, 36]. Portal pressure increases initially as a consequence of increased intrahepatic resistance to portal flow attributed to structural mechanisms. This "structural" component, which explains around 70% of the increased intrahepatic resistance, could be targeted by treating the etiology of cirrhosis, the use of antifibrotic agents, and even anticoagulants [37]. However, at least one-third of the increased intrahepatic resistance is attributed to increased intrahepatic vascular tone, which, in turn, is attributed to endothelial dysfunction resulting mostly from reduced nitric oxide (NO) bioavailability [38]. Another factor that has been shown to contribute to the worsening of PH is the translocation of bacterial or bacterial products from the intestinal lumen into the systemic circulation [39].

21.1.5.1 Management of Acute Esophageal Variceal Bleeding

In patients with liver cancer who underwent radiation therapy, esophageal variceal hemorrhage (VH) implies poor prognosis because it is closely associated with HVPG ≥20 mmHg. Moreover, it is a life-threatening complication if hemostasis is not done urgently and completely. The precise prognosis of a patient with esophageal varices depends on whether the patient presents as an isolated decompensating event or whether the patient presents with other complications of cirrhosis such as ascites or encephalopathy [40]. New-onset or aggravation of portal vein thrombosis accompanied by hepatocellular carcinoma (HCC) could increase portal pressure and lead to VH. Therefore, imaging studies should be considered after emergent management for VH. The immediate goal of therapy in these patients is to control bleeding, to prevent early recurrence (within five days) and prevent six-week mortality, which is considered the main treatment outcome [41]. Acute VH is a medical emergency requiring intensive care. As in any patient with any hemorrhage, it is essential to first assess and protect the circulatory and respiratory status of the patient. Volume resuscitation should be initiated to restore and maintain hemodynamic stability. Packed red blood cell transfusion should be performed with a target hemoglobin level of

between 7 and 8 g/dl [42]. Regarding correction of coagulopathy, correcting the international normalized ratio (INR) by the use of fresh frozen plasma or factor VIIa is not recommended. No recommendations can be given regarding platelet transfusion in patients with VH. Patients with cirrhosis presenting with GI hemorrhage are at a high risk of developing bacterial infections, and the use of antibiotic prophylaxis has been shown, in randomized controlled trials, to lead to a decrease in development of infections, recurrent hemorrhage, and death [43, 44]. Regarding the type of antibiotic, intravenous ceftriaxone has been shown to be more effective in preventing infection compared to oral norfloxacin [45]. Therefore, the antibiotic of choice is intravenous ceftriaxone at a dose of 1 g every 24 h. Duration of antibiotic prophylaxis is short term, for a maximum of seven days. Vasoactive drugs should be started as soon as variceal bleeding is suspected, ideally before endoscopy. Vasoactive drugs (terlipressin, somatostatin, octreotide) should be used in combination with endoscopic therapy and continued for up to five days [46]. Endoscopy is done as soon as possible and not more than 12 h after presentation. Endoscopic variceal ligation (EVL) is the recommended form of endoscopic therapy for acute esophageal variceal hemorrhage. Endoscopic therapy with a tissue adhesive (e.g., N-butylcyanoacrylate) is recommended for acute bleeding from gastric varices. The diagnosis VH is considered certain when active bleeding from a varix is observed or when a sign of recent bleeding, such as a "cherry red," is observed (Fig. 21.4). Early TIPS placement within 72 h improves survival in high-risk patients with acute variceal bleeding. However, in most patients with liver cancer who underwent radiotherapy, TIPS procedure is not technically available because of tumor or portal vein thrombosis. If rebleeding is modest, a second session of endoscopic therapy can be attempted. Up to 20% of VH episodes can be refractory to standard therapy and are associated with a high mortality. A "bridge" therapy may be necessary to acutely control hemorrhage until a more definitive therapy, such as TIPS, can be performed. Balloon tamponade is still used as bridge therapy and provides hemostasis in up to 80% of patients but is associated with high rate of severe adverse events and a mortality rate near 20% [47]. Balloon tampodade should not exceed 24 h.

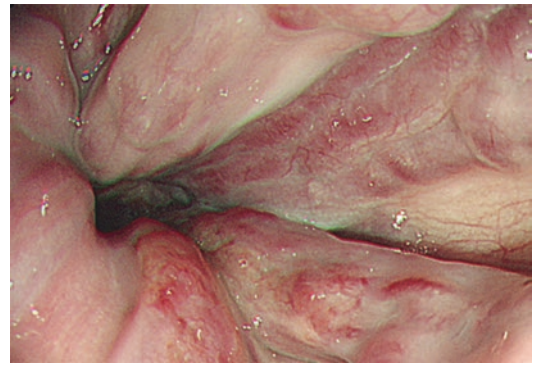

Fig. 21.4 Endoscopic appearance of esophageal varices with cherry red sign suggesting impending variceal rupture.

21.1.5.2 Prevention of Rebleeding of Esophageal Varices

Patients who recover from the first episode of VH have a high rebleeding risk, with a mortality of up to 33%. Therapy to prevent rebleeding is therefore mandatory in these patients and should be instituted before the patients are discharged from the hospital. First-line therapy for patients who received EVL is the combination of non-selective beta blocker (NSBB), either propranolol or nadolol. A recent meta-analysis comparing combination therapy to monotherapy with EVL or drug therapy has demonstrated that combination therapy (EVL + NSBB) is significantly more effective than EVL alone in preventing all-source GI hemorrhage. However, use of NSBB in patients with refractory ascites is not recommended because it might lower patient survival.

21.1.6 Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is defined as a deterioration of kidney function that takes place in the context of severe chronic liver diseases, such as advanced cirrhosis or acute liver failure [48]. It is characterized by functional circulatory changes

in the kidneys that overpower physiologic compensatory mechanisms and lead to reduced glomerular filtration rate (GFR). Re-establishment of adequate renal blood flow leads to improvement in renal function and is achieved by liver transplantation or vasoconstrictor drugs. The diagnosis of HRS is essentially one of exclusion of other causes of renal failure. The pathophysiology associated with HRS includes vasodilation in the splanchnic arterial bed and low cardiac output. There are two types of HRS. Type 1 HRS, now termed HRS-acute kidney injury (AKI), is a rapidly progressive acute renal failure that frequently develops in temporal relationship with a precipitating factor for a deterioration of liver function together with deterioration of other organ function. It is characterized by rapid deterioration caused by precipitating events that leads to the failure of one or more organs, aggravating the patient's central hypovolemic state [49]. Conventionally, HRS-AKI is only diagnosed when the serum creatinine increases more than 100% from baseline to a final level of greater than 2.5 mg/dl. Type 2 HRS, now termed HRS-non-AKI (HRS-NAKI), occurs in patients with refractory ascites and there is a steady but moderate degree of functional renal failure, often with avid sodium retention. HRS-NAKI is defined by estimated GFR rather than serum creatinine [48]. NAKI is divided into HRS-acute kidney disease (HRS-AKD) if the eGFR is less than 60 mL/min/1.73 m^2 for less than three months and HRS-chronic kidney disease (HRS-CKD) if it is less than this for more than three months.

21.1.6.1 Drug Therapy

The management of HRS starts with a fluid challenge of 20–25% intravenous albumin at 1 g/kg/day for two days and withdrawal of diuretics. This is not only needed to rule out pre-renal azotemia but also promotes early plasma volume expansion in the setting of reduced effective arterial blood volume. The specific treatment of HRS-AKI comprises vasoconstrictors in combination with albumin infusion and reversal of precipitating factors. Among the vasoconstrictors used, those that have been investigated more extensively are the vasopressin analogues, particularly terlipressin [50]. The rationale for the use of vasopressin analogues in HRS is to improve the markedly impaired circulatory dysfunction by causing a vasoconstriction of the extremely dilated splanchnic vascular bed and increasing arterial pressure [51, 52]. Terlipressin shows greater efficacy in reversal of HRS-AKI in patients with a systemic inflammatory response [53], which may relate to indirect vasopressin mediated anti-inflammatory effects [54]. Response to terlipressin therapy is generally characterized by a slowly progressive reduction in serum creatinine, and an increase in arterial pressure, urine volume, and serum sodium concentration. Median time to response is 14 days and usually depends on pre-treatment serum creatinine, the time being shorter in patients with lower baseline serum creatinine [55]. The most frequent side effects of treatment are cardiovascular or ischemic complications, which have been reported in an average of 12% of patients treated [51].

21.1.6.2 TIPS

Transjugular intrahepatic portosystemic shunt has been reported to improve renal function in patients with HRS-AKI [56]. However, the applicability of TIPS in this setting is very limited because many patients have contraindications to the use of TIPS including portal vein tumor thrombosis. TIPS has also been shown to improve renal function and the control of ascites in patients with HRS-NAKI [57].

21.1.6.3 Renal Replacement Therapy

Renal replacement therapy (RRT) may be indicated for patients with HRS-AKI unresponsive to drug treatment and with volume overload, uremia, or electrolyte derangement. However, RRT does not improve survival in HRS, and it should be reserved for use as a bridge to LT [58, 59]. Short-term mortality in patients with cirrhosis and AKI who are ineligible for transplantation approaches 90% regardless of the cause of AKI [60, 61].

21.1.6.4 Liver Transplantation

The functional nature of HRS means that improvement in renal function is expected with

LT. Accordingly, LT is the treatment of choice for both HRS-AKI and HRS-NAKI, with survival rates of approximately 65% in HRS-AKI [62]. The lower survival rate compared to patients with cirrhosis without HRS is a result of renal failure being a major predictor of poor outcome after transplantation. Kidney recovery is not universal and is dependent of multiple factors, particularly duration of kidney injury [63]. Moreover, patients with HRS-AKI have a high mortality while on the waiting list and ideally should be given priority for transplantation. In patients with liver cancer who underwent radiation therapy and have no or minimal tumor burden (i.e., within Milan criteria), LT should be considered for HRS-AKI and HRS-NAKI.

21.1.7 Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a prevalent complication of portal hypertension and cirrhosis that is seen in 50–70% of patients [64]. It manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations such as reduced awareness to coma. In patients with liver cancer who underwent radiation therapy, HE may occur because of diminishing functioning hepatocytes or aggravation of portosystemic shunt. The incidence and prevalence of HE are associated with the severity of the underlying liver insufficiency [65, 66]. In its lowest expression, HE is not overt. Instead, there is only abnormal behavior on psychometric tests oriented toward attention, working memory, psychomotor speed [67, 68]. As HE progresses, personality changes, frequent falls, incompetent driving, and fatigue may occur, and obvious alterations in consciousness and motor function occur. Disturbances of the sleep-wake cycle with excessive daytime sleepiness are frequent [69], whereas complete reversal of the sleep-wake cycle is less consistently observed. Patients may develop progressive disorientation to time and space, inappropriate behavior, and an acute state of confusion with agitation or somnolence, stupor, and finally, coma [70]. Asterixis or "flapping tremor" is often present in the early to middle stages of HE that precede stupor or coma and is not a tremor, but a negative myoclonus consisting of loss of postural tone. It is easily elicited by actions that require postural tone, such as hyperextension of the wrists with separated fingers or the rhythmic squeezing of the examiner's fingers. However, asterixis can be observed in other areas, such as the feet, legs, arms, tongue, and eyelids. Asterixis is not pathognomic of HE because it can be observed in other diseases such as hypercarbia and uremia [71].

21.1.7.1 Diagnosis of HE

Currently, there are no gold-standard laboratory markers that can be used to diagnose HE. Hepatologists have graded the severity of HE according to the West Haven criteria [72]. However, these are subjective tools with limited interobserver reliability, especially for grade I HE, because slight hypokinesia, psychomotor retardation, and a lack of attention can easily be overlooked in clinical examination. Diagnosing cognitive dysfunction is not difficult. It can be established from clinical observation as well as neuropsychological or neurophysiological tests. The difficulty is to assign them to HE. For this reason, HE remains a diagnosis of exclusion in the patient population that is often susceptible to mental status abnormalities resulting from medications, alcohol abuse, drug use, effects of hyponatremia, and psychiatric disease. Thus, as clinically indicated, exclusion of other etiologies by laboratory and radiological assessment for a patient with altered mental status in HE is warranted. Although increased blood ammonia levels often are found in HE in large population studies, in an individual patient it often is not useful as a diagnostic test [73]. On the contrary, a normal ammonia level that occurs in a cirrhotic patient with altered mental status should lead the physician to question the diagnosis of HE [74]. Computed tomography (CT), magnetic resonance (MR), or other modality scans do not contribute diagnostic or grading information. However, the risk of intracerebral hemorrhage is at least five time higher in this patient group [75], and the symptoms may be indistinguishable. A brain scan is usually, therefore, part of the diagnostic

workup of first-time HE and on clinical suspicion of other pathology including brain metastasis during or after radiotherapy for liver cancer.

21.1.7.2 Treatment of HE

The goal of therapy for HE episodes are to diagnose and treat the inciting factor because up to 90% of patients will have a precipitant [76]. Lactulose is the most used disaccharide for the treatment of HE. This nonabsorbable disaccharide has laxative effects and change the gut microbiome to non-urase-producing bacteria, reducing intestinal ammonia production [77]. Lactulose is usually administered as an oral syrup with dosages titrated for a goal of 2–4 soft bowel movements a day. Lactulose also can be given rectally (300 mL in 700 mL of saline), which is preferred in patients in whom oral administration is contraindicated [78]. Common side effects of lactulose include flatulence, abdominal discomfort, and diarrhea. There is a danger that overuse of lactulose will lead to complications such as aspiration, dehydration, hypernatremia, and severe perianal skin irritation, and overuse can even precipitate HE [79]. Rifaximin has been used for the therapy of HE in a number of trials comparing it with placebo, other antibiotics, nonabsorbable disaccharides, and in dose-ranging studies [80]. These trials showed that the effect of rifaximin was equivalent or superior to the compared agents with good tolerability. L-ornithine-L-aspartate can reduce blood ammonia levels via stimulating both the urea cycle and glutamine synthesis [81]. Liver transplantation remains the only treatment option for HE that does not improve on any other treatment.

21.1.7.3 Prevention of HE

Data for nonabsorbable disaccharides for the secondary prevention of HE have been sparse. However, it is still widely recommended and practiced. An open-label RCT showed that lactulose was able to prevent recurrent HE in patients with cirrhosis [82]. Another RCT supports lactulose as prevention of HE subsequent to upper gastrointestinal bleeding [83]. Rifaximin added to lactulose is the best-documented agent to maintain remission in patients who have already experienced one or more bouts of HE.

21.2 Conclusions

Patients with liver cancer are regarded to have not one disease, but two: cancer and underlying liver disease. In some patients, even a large or advanced tumor can be cured by treatments including radiotherapy. However, most patients may suffer from hepatic dysfunction resulting in occurrence of ascites, jaundice, or variceal bleeding that requires LT. Fortunately, sophisticated application of radiation therapy with high technology significantly reduced the incidence of liver dysfunction in patients with liver cancer compared to the past. Nevertheless, radiation oncologists and hepatologists must be cautious of possible hepatic dysfunction in these patients.

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