Review Article | Palliative Medicine and Palliative Care for Serious or Advanced Diseases

Narrative review of management of cirrhosis during the treatment of hepatocellular carcinoma

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Background and Objective: The management of hepatocellular carcinoma (HCC) and cirrhosis are closely linked. HCC most often occurs in the background of cirrhosis and can also lead to decompensation of underlying liver disease. The treatment of complications of cirrhosis is important to help reduce morbidity and mortality and allow for expanded treatment options of HCC.

Methods: We searched PubMed using search terms for cirrhosis and HCC. From this search, we selected references which appeared to be primary studies preferentially within the last 5 years, although also included select landmark studies which have shaped guidelines and recommendations.

Key Content and Findings: The development of HCC and treatment of HCC can both cause decompensation of liver disease and worsening of liver function. For most patients, the development of HCC or progression of disease are the drivers of morbidity and mortality. However, it is important to closely monitor patients for complications of liver disease that develop either as a result of HCC or as a complication of HCC treatment, and this can have important implications on treatment options. Multidisciplinary team involvement including hepatologists, surgeons, radiologists, interventional radiologists, medical oncologists, and palliative care is essential in the care of patients with cirrhosis and HCC to help guide management decisions and treatment.

Conclusions: The management of cirrhosis and HCC are both complex and interrelated. Through a multidisciplinary team approach we can best treat the complications of cirrhosis, allow for expanded treatment options, and improve quality of life through symptom management.

Keywords: Cirrhosis; hepatocellular carcinoma (HCC); treatment

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Introduction

Primary liver cancer is the sixth most common cancer and third leading cause of cancer-related death worldwide; nearly 85% of these cases are hepatocellular carcinoma (HCC) with intrahepatic cholangiocarcinoma accounting for the majority of other cases (1). Mortality from HCC continues to rise (2,3). The greatest risk factor for HCC is the presence of cirrhosis, with nearly 4% of patients with cirrhosis estimated to develop HCC annually (4). There is great regional variation in the leading causes of cirrhosis and HCC worldwide; viral hepatitis (hepatitis B and hepatitis C) is the leading cause of cirrhosis globally, however with rising rates of metabolic syndrome we have seen a parallel rise in metabolic dysfunction-associated steatotic liver disease

Table 1 Search strategy summary

Items	Specification
Date of search	1/31/2023
Databases and other sources searched	PubMed
Search terms used	Cirrhosis, hepatocellular carcinoma, management, treatment
Timeframe	1/1/2000–1/31/2023
Inclusion and exclusion criteria	All studies were published in English, included primary studies and excluded review articles, except for society guidelines published from the AASLD and EASL
Selection process	The authors performed the literature search and selected relevant studies through the process detailed above

AASLD, the American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver.

(MASLD) and MASLD-related HCC (3,5).

Among patients with cirrhosis, the development of HCC can cause a new decompensation in liver disease, manifest by worsening portal hypertension and complications, such as ascites, esophageal varices, or encephalopathy, and can additionally cause worsening liver function. Treatment of HCC can also precipitate worsening liver function, and this can have important implications in treatment options; therefore, the management of cirrhosis and HCC are closely linked. For most patients, the development of HCC or progression of disease are the drivers of morbidity and mortality; however, many patients with HCC will also have morbidity and mortality related to complications of underlying liver disease and cirrhosis (6). It is therefore important to closely monitor patients for these complications to hopefully avoid these potential outcomes. Here we provide a narrative review detailing the management of cirrhosis during the treatment of HCC. We present this article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-23-173/rc).

Methods

We searched PubMed using search terms for cirrhosis and HCC as detailed in the search strategy summary (*Table 1*). From this search, we selected references that were primary studies and preferentially selected studies published within the last 5 years. However, we did also include select landmark studies which have shaped guidelines and recommendations. We additionally referenced guidelines published by the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL).

Treatment of HCC

Once a diagnosis of HCC has been established, treatment options must be weighed. As HCC most often occurs in the presence of cirrhosis, an effective staging system that guides management decisions must take into account not only the status of the tumor [such as the tumor node metastasis (TNM) classification], but also the patient's liver function. Individual treatment options can differentially impact liver function and also have varying efficacies, duration of treatment, and associated morbidity, and these must be considered very carefully.

Treatment options for HCC include surgical resection, liver transplantation (LT), locoregional therapy (LRT), systemic therapy, radiation therapy (RT), or some combination thereof. Goals of therapy can range from complete cure, to a bridge to LT, to palliation. Due to the complexity of managing HCC in cirrhosis, as well as differing center experiences, there is great variation in management patterns between institutions as well as geographically. Several staging systems have therefore emerged, each with their strengths and weaknesses (7-11). The Barcelona Clinic Liver Cancer (BCLC) system (9) links tumor stage, liver function, cancer-related symptoms, and performance status and is favored in American/European hepatology-based guidelines (12,13), while there is more variability in Asia (14).

LT is the only treatment that potentially cures both the underlying cirrhosis and HCC. However, while offering excellent outcomes (15-17), it is largely limited by organ availability, and thus potentially long wait times, which represents risk for tumor progression as well as cirrhosis-related complications. In addition, due to risk of recurrence post-transplant, tumor-based criteria exist to carefully select

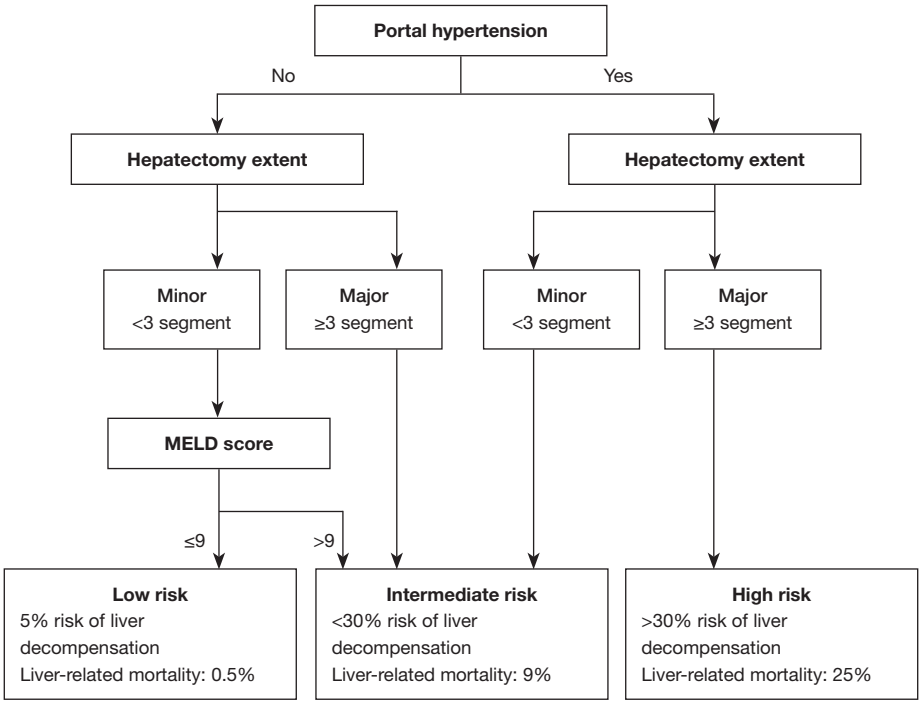

Figure 1 Simplified algorithm for the assessment of risk of live decompensation after LR for HCC in cirrhosis. Similar principles apply for other treatment options including LRT and systemic therapy. Adapted from (13). MELD, model for end-stage liver disease; LR, liver resection; HCC, hepatocellular carcinoma; LRT, locoregional therapy.

candidates for LT (18,19).

Surgical resection also provides excellent outcomes (20,21). However, unlike LT, the patient must rely on their remnant liver for survival and recovery, and the possibility of decompensation of cirrhosis as well as overall mortality must be carefully considered. It is critical to assess liver reserve, typically with the Model for End-Stage Liver Disease (MELD) score and bilirubin value, and degree of portal hypertension via portal pressure measurements, determination of Child-Turcotte-Pugh (CTP) class, or evaluation of surrogate findings such as varices or splenomegaly (22-26). Combined with the extent of hepatectomy, these assessments provide a practical approach to estimating the risk of liver decompensation as seen in this algorithm (*Figure 1*) (13,27). Those with worse liver function or clinically significant portal hypertension should be considered for LT as previously mentioned, or for LRT.

LRT consists of varied interventional radiology treatment modalities such as tumor ablation and arterial embolization. Ablation involves percutaneous chemical (ethanol) or thermal (radiofrequency, microwave) destruction. Embolization includes transcatheter arterial embolization (TAE) involving particle embolization of tumor-feeding blood vessels, transarterial chemoembolization (TACE) with additional infusion of cytotoxic agents, and transarterial radioembolization (TARE) that utilizes radioactive substances (131-Iodine or yttrium-90) instead of chemotherapy. Due to higher recurrence rates but lower hepatic toxicity, these have been historically considered after surgical options, although preferred first-line management in early stage tumors is variable. In early stage HCC based on the BCLC system, a Cochrane review demonstrated that ablation has higher recurrence rates, but equal mortality, decreased adverse events, decreased cost, and decreased length of hospital stay when compared to resection (28). In another study that compared ablation and resection in CTP A patients, there was no difference in survival despite ablation patients being older and having worse liver function (based on MELD score) (29). These studies suggest that liver dysfunction seems to affect prognosis of patients undergoing resection more than those undergoing ablation, even if the patient has compensated cirrhosis as classified by CTP A. Similar safety profiles apply for other locoregional options, including TACE (30), which plays a key role in bridging and downstaging patients prior to LT (12,13), and TARE (31).

Decompensating Event	Acute management	Long-term management
Hepatic encephalopathy	Supportive therapy for AMS, avoid sedatives	Lactulose, rifaximin
Variceal bleed	Supportive therapy for GIB, Vasoactive medication, prophylactic antibiotics, endoscopic therapy, IR therapy, balloon tamponade	Beta blocker initiation, repeat endoscopy
Ascites	Paracentesis to assess for peritonitis and/or symptomatic relief	Low salt diet, diuretics, paracentesis, drainage catheter

Figure 2 Decompensating event in cirrhosis and its associated management. With each event, precipitating cause (i.e., bleeding, infection, thrombosis, medication) must be identified and treated/removed. LT should be considered whenever a patient develops decompensated cirrhosis. AMS, altered mental status; GIB, gastrointestinal bleed; IR, interventional radiology; LT, liver transplantation.

Systemic therapies, which mainly include tyrosine kinase inhibitors (TKIs), antiangiogenic agents, and immune checkpoint inhibitors (ICIs), are typically reserved for patients not eligible for resection, LT, or LRT. All patients enrolled in phase III oncologic trials require preserved liver function, skewing efficacy and safety data toward CTP A or B. Current data suggests a more favorable safety profile with CTP A and early B (32,33), but individualized evaluation is recommended for all patients, especially those with abnormal liver function or decompensation. Due to hepatotoxic effects, similar risk stratification applies to patients undergoing systemic therapies as those undergoing other treatment modalities. While mild worsening of liver function tests may be managed with dose adjustment, significant changes in liver function, CTP score, or the occurrence of decompensating events should lead to treatment interruption and to the identification and treatment of any precipitant factors (34). There are two special issues that bear mentioning; antiangiogenics increase risk of bleeding and require fully treated gastroesophageal varices prior to administration, and use of immunotherapy in patients with autoimmune liver disease (such as autoimmune hepatitis or following LT) requires special caution given their mechanism of action.

RT, especially stereotactic body radiation therapy (SBRT), is another treatment option for HCC. By providing high dose external radiation focused to the tumor, it maintains ablative effects while limiting damage to surrounding liver parenchyma. It has traditionally been considered for tumor control when LRT has been contraindicated, such as in patients with portal vein thrombus or tumor proximity to adjacent organs; however, it has also been used for palliation, including patients with tumor thrombus where RT can decompress portal vein pressures. There is emerging evidence that this may be utilized for bridging patients to LT (35) as well as for advanced HCC in conjunction with systemic therapies (36). While liver decompensation remains a possible adverse event, radiation doses with SBRT can be adapted to liver dysfunction in order to decrease toxicity (37,38).

Overall, it is of utmost importance to have a multidisciplinary team continuously helping to manage patients with cirrhosis and HCC—including hepatology, surgery, interventional radiology, and medical oncology. With the exception of LT, each treatment of HCC has a chance of worsening current liver function and decompensation. Of course, along with survival rates of untreated patients (39), the patient's goals of care need to be fully considered, and there are ongoing studies to evaluate palliative care's benefits in patients with end-stage liver disease, a dynamic population with burdensome symptoms and high risks for hospitalization and death (40).

Complications of cirrhosis

The management of cirrhosis in patients with HCC is similar to that in patients without HCC. This largely includes the management of complications of portal hypertension, which can manifest as hepatic encephalopathy, ascites, and/or esophageal varices (*Figure 2*). Here we review the complications of cirrhosis and the mainstays in management, highlighting some of the nuances to treatment and management in patients with HCC and where that differs from traditional management in patients without HCC.

Ascites is typically the first manifestation of portal hypertension and indication of decompensation of liver disease (41). The mainstays of treatment for ascites include low sodium diet (42-44), diuresis with a combination of loop diuretics and aldosterone antagonists (45-47), and paracentesis for patients with large volume ascites that

are either unable to be controlled with diuretics alone or for whom diuretics are not tolerated due to worsening renal function and/or electrolyte abnormalities (namely hyponatremia). In patients for whom diuretics are not tolerated or are unable to achieve adequate control of ascites, patients can have large volume paracentesis as a means of fluid removal (48,49). In patients who require serial large volume paracentesis at frequent intervals, a transjugular intrahepatic portosystemic shunt (TIPS) procedure is typically considered. This involves placing a stent across the liver to thereby reduce the hepatic venous pressure gradient. TIPS is controversial in patients with HCC and the presence of HCC has traditionally been considered a contraindication given the risk of tumor seeding. However, some recent studies have suggested that TIPS can be effective in carefully selected patients with HCC (50-52), although this management approach has not been widely adopted. The final consideration in patients with refractory ascites is placement of an indwelling peritoneal catheter. This poses a significant risk of infection and is typically not pursued in patients who may be liver transplant candidates. However, especially in patients with HCC and large tumor burden, indwelling peritoneal catheter placement can provide significant improvement in quality of life if it avoids the need for frequent visits to the hospital for large volume paracentesis and more controlled smaller volume fluid removal at home.

The next manifestation of portal hypertension is esophageal varices. Patients with cirrhosis should undergo endoscopic surveillance for esophageal varices at regular intervals (53). Esophageal varices are graded as small, medium, or large based on the endoscopic appearance. For patients with small varices, typically endoscopic surveillance at scheduled intervals is recommended unless the endoscopy shows high risk stigmata for bleeding or the patient is decompensated (54). For patients with medium or large varices, management can include the initiation of a non-selective beta blocker, for which carvedilol is now the preferred agent (55), or alternatively primary prophylactic variceal ligation with banding can be performed (56). There is no clear consensus on the preferred management for primary bleeding prophylaxis except for select patients, such as those with HCC who are planned for receipt of a vascular endothelial growth factor (VEGF) inhibitor (i.e., bevacizumab). This poses an increased bleeding risk and these patients require surveillance endoscopy at least 6 months prior to initiation of treatment; if esophageal varices are present the patient should undergo variceal band ligation to eradication to reduce the risk of bleeding prior to initiation of treatment (57). Patients who present with variceal hemorrhage are typically banded with serial endoscopies scheduled to achieve eradication and also initiated on non-selective beta blockers as secondary prophylaxis (56).

The other main complication of portal hypertension is the development of hepatic encephalopathy, or confusion related to the build-up of ammonia due to impaired hepatic clearance and shunting. The management of encephalopathy consists of administration of lactulose and rifaximin to aid with clearance of ammonia and other gut-derived neurotoxins from the gastrointestinal tract (58). If symptoms persist despite treatment, additional medications such as zinc can be considered (59); given insufficient evidence to support routine use of zinc in treatment of encephalopathy, this therapy is not included in major society guidelines and is mainly considered in patients with zinc deficiency and concomitant encephalopathy. For patients with refractory encephalopathy despite maximal medical therapy, evaluation for the presence of a splenorenal shunt can be performed, and if present shunt embolization can be considered.

There are also complications of cirrhosis that are less directly related to portal hypertension and instead a result of liver dysfunction and/or other complications of liver disease. These can include complications such as development of mesenteric thrombosis, specifically portal vein thrombosis (PVT), as well as systemic symptoms like pruritus. Patients with HCC are at an especially increased risk of developing PVT given their hypercoagulable state. Similar to patients without HCC, determination of chronicity of the thrombus (acute versus chronic) and weighing risks and benefits (namely related to bleeding risk) are important in deciding to initiate therapeutic anticoagulation. Some patients with cirrhosis, in particular those with cholestasis, can experience symptoms of pruritus. This can be a very challenging symptom to manage. The treatment options include bile salt resins, antihistamine therapy, naltrexone, sertraline, and topical agents.

As HCC most often occurs in the background of chronic liver disease, these patients are faced with the burden of symptoms from their cancer and coexisting cirrhosis, as well as navigating the complex interplay of these diagnoses. The involvement of palliative care can be especially helpful for symptom management, aid with advanced care planning, and provide additional support for caregivers and families through the management of both cirrhosis and

HCC. There are not well-described models for the use of palliative care specifically in this population, although its use has been associated with decreased costs and lowered procedure burden during the terminal hospitalization for patients with cirrhosis (60). Furthermore, the American Society of Clinical Oncology (ASCO) recommends routine involvement of palliative care in the clinical care for all patients with cancer (61); given the focus of palliative care on quality of life, it is especially relevant to patients with cirrhosis, including those with and without HCC, given the symptom burden as described above. Involving a multidisciplinary care team in the treatment of patients with HCC has been associated with increased HCC therapy and reduced mortality (62); we therefore recommend the routine and early involvement of palliative care specialists for patients with HCC to help address symptom burden and provide necessary support for patients and their families.

Conclusions

The management of cirrhosis and HCC are closely linked, and each bring their own complexity. It is important to approach the care of patients with HCC and cirrhosis with a multidisciplinary team comprised of hepatologists, surgeons, interventional radiologists, oncologists, and palliative care. It is through this multidisciplinary approach that we can best treat the patient's underlying liver disease and complications of cirrhosis and balance this with oncologic and symptom management.

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Footnote

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