Review Article | Palliative Medicine and Palliative Care for Incurable Cancer

A narrative review of supportive and end of life care considerations in advanced hepatocellular carcinoma※

Irma N. Hashmi[1], Hannah M. Lee[2,3,4], Joel P. Wedd[2,3,4], Richard K. Sterling[2,3,4], Teri E. Dulong-Rae[5], J. Brian Cassel[5], John W. Cyrus[6], James J. Fletcher[7], Danielle M. Noreika[5]

[1]Division of Gastroenterology, Hepatology, and Nutrition, VCU Health System, Richmond, VA, USA; [2]Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, Virginia Commonwealth University, Richmond, VA, USA; [3]Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University, Richmond, VA, USA; [4]Hume-Lee Transplant, Virginia Commonwealth University, Richmond, VA, USA; [5]Division of Hematology, Oncology, and Palliative Care, Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA, USA; [6]Department of Research and Education, VCU Libraries Health Sciences Library, Virginia Commonwealth University, Richmond, VA, USA; [7]Department of Medicine, Michigan State University, East Lansing, MI, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Danielle M. Noreika, MD, FACP, FAAHPM. Division of Hematology, Oncology, and Palliative Care, Department of Internal Medicine, Virginia Commonwealth University, 1101 E Marshall St., Box 980230, Richmond, VA 23298-0230, USA. Email: danielle.noreika@vcuhealth.org.

Background and Objective: Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related deaths, and case numbers continue to rise in the United States. HCC carries a poor prognosis, and management requires a multidisciplinary approach. This narrative review aims to identify opportunities for further integration of palliative care (PC) in HCC care. Given the high symptom burden faced by patients with HCC, early PC consultation can be beneficial for patients.

Methods: A search of PubMed was conducted from inception of the database to March 1, 2023. The search was composed of keywords and controlled vocabulary terms for concepts related to palliative medicine and symptom management in the setting of HCC.

Key Content and Findings: This narrative review finds that although PC has been integrated into HCC guidelines, partnerships between PC and hepatology are still nascent in clinical practice. Treatment-related barriers pose a challenge to timely integration of PC in the care of HCC patients; evaluation or listing for transplantation can be perceived as a barrier to PC consultation, and unpredictable clinical courses make prognostication challenging. Providers may hesitate to pursue PC referral due to a lack of consensus around the role of PC, and for those that are referred, timing of consultation remains an issue, especially for those who are potential liver transplant candidates. There are few studies of PC in HCC, limiting evidence-based recommendations that can be made regarding PC involvement in this patient population.

Conclusions: While PC is not routinely integrated into HCC care, recent guideline recommendations and a growing number of studies may change this over time. Although further evidence is needed, PC and hepatology teams partnering together can explore ways to improve the care of this patient population. PC consultation early in HCC care could assist in management of symptom relief, psychosocial and spiritual support, and caregiver support. Effective communication will be required to set parameters for referral and clarify potential outcomes of consultation. Teams should be prepared for the challenges involved in a culture change and paradigm shift in clinical practice.

Keywords: Hepatocellular carcinoma (HCC); palliative care (PC); supportive care; quality of life

※ Special series on Comprehensive Care for Patients with Hepatocellular Carcinoma: Insights from the 2022 San Antonio Liver Cancer Symposium.

Submitted May 13, 2023. Accepted for publication Aug 08, 2023. Published online Aug 21, 2023.
doi: 10.21037/apm-23-416
View this article at: https://dx.doi.org/10.21037/apm-23-416

Introduction

Background

Hepatocellular carcinoma (HCC) is a form of primary liver cancer, comprising 75–80% of primary liver cases. The remainder of primary liver cancers include cholangiocarcinoma (10–15%) and other rare types of cancer. Most cases of HCC develop in those with cirrhosis from any cause. Chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) are well-known risk factors for HCC, with other risk factors including aflatoxin-contaminated foods, tobacco use, excess alcohol intake, increased body mass index and type two diabetes, which can be associated with non-alcoholic steatohepatitis (NASH). In the United States, the rising burden of liver cancer is now predominantly caused by alcohol-related liver disease and non-alcohol fatty liver disease (NAFLD) (1,2). Significantly, with approximately 830,000 deaths in 2020, HCC remains the third leading cause of cancer-related deaths worldwide (3).

Palliative care (PC) is interdisciplinary by nature and aims to relieve symptom burden and improve quality of life for patients and caregivers through holistic, patient-centered care. PC may be offered concurrently with disease-focused care at any stage and throughout the course of illness (4). Given the high symptom burden faced by patients with HCC, early PC consultation can be beneficial for patients.

Rationale and knowledge gap

Here in the United States, the Surveillance Epidemiology End Results (SEER) program predicts a rising number of cases of HCC through 2030, with the highest prevalence in Hispanic patients, followed by Black patients (5). HCC carries a poor prognosis, with 5-year survival rate at a dismal 20% (6). Importantly, the management of HCC requires a multidisciplinary approach, with input from hepatology, radiology, oncology, and transplant surgery teams, and where available, PC, psychology, social work, and other disciplines. A multi-team approach is required as treatment options range from those offered by interventional radiology to orthotopic liver transplantation (LT), discussed further below (7). Although advances have been made in treatments for HCC, quality of life has been less thoroughly studied, with notable gaps in addressing the burdens experienced by patients (8). The relatively small number of studies on the intersection of HCC and PC limits what evidence-based recommendations can be made at this time and necessitates further study. In general, there are a limited number of publications on symptom management, PC, or hospice in HCC specifically.

Objective

Given the symptom burden faced by patients with HCC as well as that of any underlying cirrhosis, PC consultation in HCC care may be beneficial for many HCC patients who would benefit from more support. Additionally, given the quality-of-life burden in patients with HCC and extrapolating from treatment of other cancers wherein PC has demonstrated benefit, early consultation of PC in HCC care should be actively considered (9,10). Given the common co-occurrence of HCC with cirrhosis as well as the complexities of treatment (including transplant), a summary overview of diagnosis, prognosis and therapeutics salient to symptom management and goals of care is included to give context to discussed PC approaches. We present this article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-23-416/rc).

Methods

A search of Medline via PubMed was conducted from inception of the database to March 1, 2023 and included articles ranging in publication date from 1996–2023. The search for this narrative review was created using the PICO framework and a combination composed of keywords and controlled vocabulary terms for concepts related to palliative medicine and symptom management in the setting of HCC. A summary of the search methods is provided in *Table 1*. A sample search strategy can be found in *Table 2*. Additional articles were identified through other search engines and hand-searching of reference lists.

The screening of articles was conducted by DMN, HML,

Table 1 The search strategy summary

Items	Specification
Date of search	March 1, 2023
Databases and other sources searched	MEDLINE via PubMed
Search terms used	Free text terms: palliative medicine, palliative care, hospice, symptom management, liver transplantation, liver transplant, end stage liver, hepatocellular carcinoma
	Mesh terms: “Palliative medicine”, “Palliative Care”, “Hospice Care”, “Liver Transplantation”, “End Stage Liver Disease”, “Carcinoma, Hepatocellular”
Timeframe	Search not restricted by publication date. Publication dates included articles from 1996 through 2023
Inclusion and exclusion criteria	We selected articles about adult hepatocellular carcinoma and excluded publications based on pediatric populations. We excluded articles which were not in English
Selection process	Authors screened abstracts and full texts to remove those not applicable
Additional considerations	Additional articles were identified through search engines and hand searching of reference lists. Relevant articles and other references included: 65

Table 2 Search strategy for supplemental material

Example search from MEDLINE via PubMed search for palliative care and hepatocellular carcinoma:

1. ("Palliative Medicine"[ti] OR "palliative care"[ti] OR "palliative medicine"[Mesh] OR "palliative care"[Mesh] OR "symptom management"[ti] OR "hospice"[ti] OR "Hospice Care"[Mesh])
2. ("Liver Transplantation"[Mesh] OR "liver transplantation"[ti] OR "liver transplant"[ti] OR "Hepatocellular Carcinoma"[ti] OR "carcinoma, hepatocellular"[Mesh])
3. ("Palliative Medicine"[ti] OR "palliative care"[ti] OR "palliative medicine"[Mesh] OR "palliative care"[Mesh] OR "symptom management"[ti] OR "hospice"[ti] OR "Hospice Care"[Mesh]) AND ("Liver Transplantation"[Mesh] OR "liver transplantation"[ti] OR "liver transplant"[ti] OR "Hepatocellular Carcinoma"[ti] OR "carcinoma, hepatocellular"[Mesh])

INH. Authors excluded articles not in English and those based on pediatric patient populations. Authors screened abstracts and full texts to remove those not applicable to the topic on further review.

Hepatocellular carcinoma

Surveillance and clinical presentation

What makes HCC especially challenging is that preexisting cirrhosis, and the subsequent complications as outlined below, can present concurrently in 80% of cases of HCC (5).

The clinical presentation of HCC can vary based on when HCC is identified. In its early stages, HCC can even be asymptomatic; however, for patients with concurrent decompensated cirrhosis, manifestations including ascites, jaundice, hepatic encephalopathy, variceal bleed may be present. Other symptoms related to HCC include abdominal pain, poor appetite, weight loss, or palpable abdominal mass (11).

Diagnosis and staging

Unlike other malignancies in which biopsy is required, HCC can be formally diagnosed based on imaging, either with multiphase CT or multiphase MRI (5).

Because HCC is often associated with cirrhosis and its complications, staging for HCC reflects the status of malignancy as well as the degree of liver dysfunction. The tumor-node-metastasis classification does not capture the degree of liver dysfunction or the patient’s performance status (PS); therefore, alternative systems such as the Barcelona Clinic Liver Cancer (BCLC) should be utilized. This system “includes an assessment of tumor burden, liver function, and patient PS” (5). Patients are categorized into 0, A, B, C, and D, as illustrated in *Figure 1*.

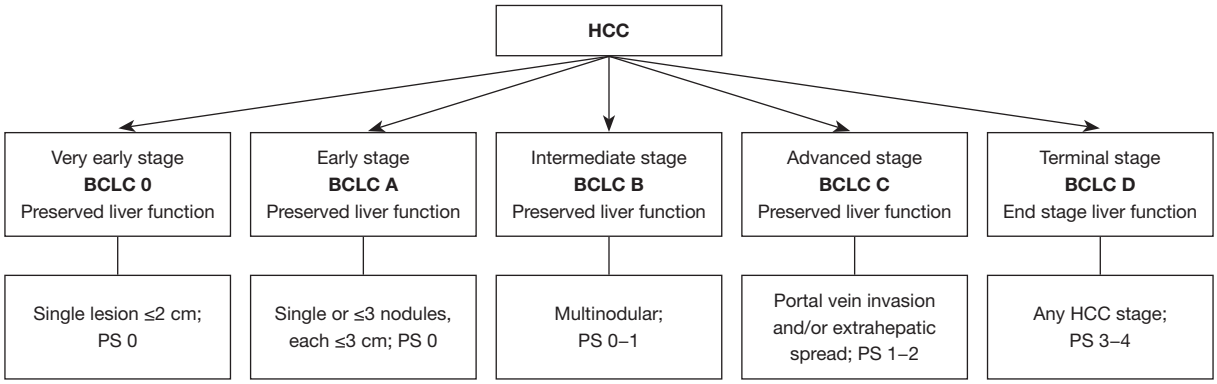

Figure 1 BCLC HCC staging system, 2022. BCLC, Barcelona clinic liver cancer staging system; HCC, hepatocellular carcinoma; PS, performance status score.

Prognosis is likely to be limited for patients with HCC, and courses are often complicated by underlying cirrhosis and decompensations. A review of SEER data of over 11,000 HCC cases noted that patients who died lived an average of 6–10 months depending on the genesis of HCC (with alcohol-related being the shortest) (6). Overall, median survival time ranges from 38 months for BCLC Stage 0 to 6 months for BCLC Stage D (12).

Terminology

In order to further appreciate and understand the patient with HCC, an explanation of commonly used terminology is provided below. Understanding is especially important in consideration of staging and management of patients with HCC.

Compensated versus decompensated cirrhosis

The natural history of cirrhosis can be characterized by a "compensated" phase and "decompensated" phase, also known as end stage liver disease (ESLD). Patients can often be asymptomatic during the compensated phase. In the decompensated phase, the liver develops significant disruption of synthetic function and portal hypertension. Clinical manifestations of decompensation include hepatic encephalopathy, variceal hemorrhage, ascites formation, jaundice, and sarcopenia. The decompensated phase can rapidly progress and develop into further decline such as the development of renal failure (hepatorenal syndrome), worsening encephalopathy, and jaundice, and can further lead to infection and sepsis. Mortality rates shift dramatically from greater than 12 years in patients with compensated cirrhosis to less than 2 years in patients with decompensated cirrhosis (13,14). Without transplant, ESLD is a terminal diagnosis (13).

MELD *vs.* Child-Pugh score

Liver transplant evaluation is indicated when a patient with ESLD develops a Model for End-stage Liver Disease (MELD) score greater than or equal to 15 with or without complications of portal hypertension. Based on a patient's objective data, the MELD score (and revised version MELD-sodium score) includes sodium, total bilirubin, INR, and creatinine to generate an accurate predictor for 90-day mortality. MELD points range from 6 to 40. Conversely, the Child-Turcotte-Pugh (CTP, or Child-Pugh) score, which includes total bilirubin, prothrombin time (PT), and albumin along with the presence or absence of ascites and hepatic encephalopathy, predicts one- and three-year survival. Child-Pugh is graded from A (good hepatic function) to C (worst stage with advanced hepatic dysfunction) (15).

Decompensations, associated infections, or portal hypertension in the form of ascites, hepatic encephalopathy, and/or variceal hemorrhage often trigger a rise in MELD score. Following controversies regarding wait time for organ allocation, the Organ Procurement and Transplant Network (OPTN) determines liver allocation on MELD score, given its sound reproducibility to predict mortality. Waitlisted candidates are prioritized based on MELD score (16).

Criteria for LT

Although transplant increases recipient survival, accurate

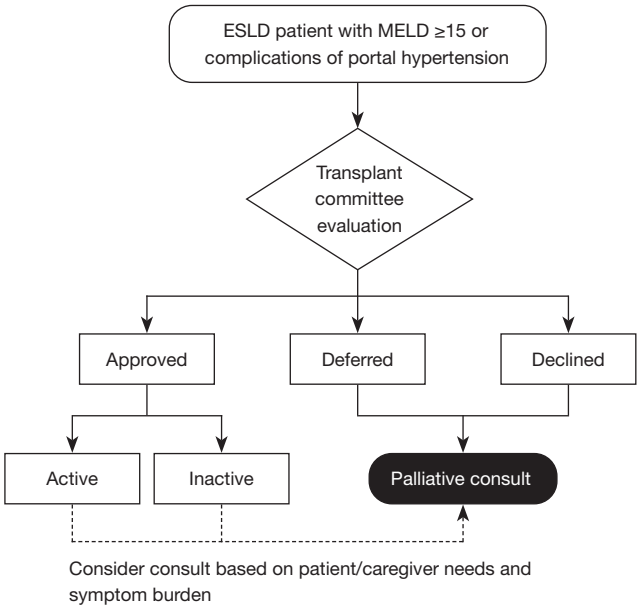

Figure 2 Generic workflow for transplant evaluation and palliative care consultation (may vary by center). This is a sample workflow for transplant committee evaluation and outcomes for patients with HCC. Patients meeting criteria may undergo evaluation by a transplant committee. In general, patients approved for transplant may be active or inactive on the transplant list, or patients may be deferred or declined by the transplant committee. Patient status may change over the course of illness. Palliative care providers should be aware of transplant candidacy status before discussing care planning with patients and referring providers. HCC, hepatocellular carcinoma; ESLD, end-stage liver disease; MELD, model for end-stage liver disease score.

organ allocation also plays an important role in graft survival. To increase the odds of success post-transplant, the patient undergoes a complex, multidisciplinary assessment to ensure adequate candidacy pre-transplant (17). The potential recipient undergoes investigation of cardiopulmonary co-morbidities, screening for age-appropriate malignancies, and consideration of psychosocial factors including social support and history of medical adherence (16,17). There are a number of contraindications to transplant that will be screened for by the transplant team. Insurance approval may also be required prior to placement on the transplant waiting list.

Liver waitlist status

Unlike most other populations referred commonly to PC, ESLD patients represent a unique population subset, as their survival is significantly improved following transplantation. Understanding the patient's transplant candidacy status is necessary for prognostic management (see *Figure 2*).

Following completion of the rigorous protocol of tests and evaluations as noted above, a transplant committee meets to determine the patient's transplant candidacy. This committee comprises transplant surgeons, transplant hepatologists, transplant anesthesiologists, psychologists, psychiatrists, social workers, nurse coordinators, and others who weigh in regarding a patient's acceptability for transplantation. One of several outcomes is determined, noting that terminology and process may be specific to each transplant center. The patient may be approved for transplant, active on the transplant list, deferred or inactive, or declined.

Treatment modalities

The management of HCC is not "cookie cutter" and requires an individualized approach with consideration of several factors for each patient. This includes the state of the liver (cirrhosis *vs.* no cirrhosis); liver function (compensated *vs.* decompensated); staging (size, location, and extent of the cancer); co-morbidities; and functional status of the patient. Because of these complexities, management of HCC benefits from a collaborative, multidisciplinary team approach (including hepatology, radiology, interventional radiology, surgery, medical oncology, radiation oncology, psychology, social work, and others) in an experienced transplant center in order to provide the best treatment options and outcomes (18,19).

Curative approach

Resection, transplantation, and/or ablation

Early stage, BCLC 0/A: in these patients, the first question to ask is whether they are a potential resection or transplant candidate. A resection candidate requires stage BCLC 0/A and Child-Pugh A with no portal hypertension, appropriate tumor location, adequate liver reserve, and liver remnant. Partial hepatectomy is a potentially curative therapy for patients with a solitary tumor of any size with no evidence of gross vascular invasion and is associated with a five-year survival rate of approximately 70% (20-22). However, recurrence rates at five years following liver resection have been reported to exceed 70% (23,24).

If unresectable, then LT should be considered if the tumor(s) is within Milan Criteria (UNOS T2) with one lesion between 2–5 cm or up to 3 lesions, each no greater than 3 cm, with no macrovascular involvement or extrahepatic disease. AFP cannot be 1,000 ng/mL. LT is a potentially curative treatment option for early HCC, as it removes both detectable and undetectable HCC lesions and the underlying cirrhosis. The 4-year overall survival and recurrence-free survival rates were 85% and 92%, respectively, in the landmark study evaluating patients within Milan Criteria and have similar rates to patients undergoing LT for ESLD without HCC (25). If LT and resection is not feasible, HCC lesions up to 3 cm may receive ablation [radiofrequency ablation (RFA)/microwave ablation (MWA)] alone as a potential curative treatment; ablation is associated with survival outcomes similar to resection (26-28).

Non-curative approach (non-resectable, or patient is not a transplant candidate)

Systemic therapy (palliative/tumor control)

Advanced stage, BCLC-B/C: these patients generally present either with BCLC B (diffuse infiltrative, extensive bilobar liver involvement) having failed LRT or with BCLC C with vascular invasion or metastatic disease. Both groups still have preserved liver function and reasonable functional status (PS ≤2) and should be considered for systemic therapy. Systemic therapy regimens provide superior survival benefit compared to sorafenib (29,30).

Multikinase inhibitors (sorafenib and lenvatinib) are recommended as first-line systemic therapy when immunotherapy is contraindicated. If first line immunotherapy has failed, other immunotherapy regimens or multikinase inhibitors could be considered as alternative treatments. SBRT may be considered for symptom control and/or prevention of complications from metastatic HCC lesions in bone or brain (31).

Supportive and end of life care considerations

Symptoms and management

As with other cancers, symptom burden although not extensively studied has been noted not only from HCC but also the underlying cirrhosis, which is then compounded by the potential for side effects of the treatments previously discussed (32).

Palliative intervention may improve quality of life and assist in management of symptom relief. Symptoms reported range from physical (pain, fatigue, and nausea) to psychological (depression, anxiety) which can lead to reduced function (33,34). Notably, patients with depression and anxiety pre-transplant are more likely to display depression post-transplant (17). Palliative management can also provide recommendations on management of disease burden in patients with refractory ascites and dosing regimen of pain medications, especially in patients with hepatic encephalopathy, which can be precipitated with the use of opioids and anxiolytics (35).

As noted above, palliative teams caring for HCC patients will often manage symptoms of both HCC and ESLD. One systematic review and meta-analysis on ESLD patients notes that the most frequent symptoms reported are pain, dyspnea, muscle cramping, insomnia, and mental health issues (36). Pain can be seen in HCC patients and when present requires a thoughtful approach as some of these patients will have co-existing substance use disorders (34). Fatigue is often related to a number of underlying physical and psychological factors, and multimodal treatments may lead to the best outcomes. Anorexia and cachexia, as in many cancers, is often a late stage finding and benefits from a thorough assessment of underlying contributors (37). The additive nature of multiple symptoms was found to be common and was noted to negatively impact quality of life and ability to function (38). Given the co-occurrence of symptoms and barriers to management, focus of future study and guidelines on the confluence of effects for HCC and ESLD have been recommended (39).

Psychosocial burdens are pronounced in HCC and may be an ideal target for PC interventions. A meta-analysis of qualitative studies in HCC found multiple quality-of-life burdens not only from symptoms and psychosocial distress but additionally from noting that patients believed HCC and cirrhosis were “stigmatizing” diseases (40).

Quality of life

Quality of life is an important aspect of care in every illness, and caring for the HCC patient is no exception. Many aspects of HCC contribute to the need for complete assessment of quality of life, including physical symptoms, psychological well-being, social aspects, and spirituality. A recent review noted that a low percentage of studies on HCC considered this topic or its components, especially for

patients with advanced HCC (8).

Recognizing that some patients with HCC may present with decompensated cirrhosis either at initial presentation or later on in their clinical course, it is worth considering the high symptom burden and frequent utilization rates for decompensated cirrhosis, which include frequent hospitalization and, at least in one study of hundreds of cirrhotic patients, a notation of 80% of patients dying in the hospital, most frequently in the ICU (41). Decompensation could be caused by progression of tumor, natural history of liver disease progression, or as the result of treatment.

Given the potential for both curative options, such as LT, and non-curative, palliative-based treatments (for tumor control/life prolongation) for these patients, it may not be realistic for PC to reach goals of decreasing utilization for some of these patients. Indeed, one recent scoping review noted high utilization rates in the last weeks of life for patients with HCC, which the presence of PC did not seem to alter (42). Additionally, one study that compared HCC to all other cancer deaths found HCC patients were more likely to die in medical facilities (43).

PC opportunities in HCC

Specialist PC in the US is distinct from hospice. While hospice usually requires a <6-month prognosis and usually cannot be provided until disease-focused care ceases, PC is not tied to a specific prognosis and is meant to be concurrent with other care. PC teams are multidisciplinary with physicians, advance practice providers, nurses, social workers, and chaplains, as well as others involved. PC focuses on assessment and management of severe symptoms; prognostication; patient and family discussions of goals of care and the benefits and burdens of treatment options; and assistance navigating care choices for patients with advanced disease. Specialist PC teams exist in most hospitals in the US, and most academic cancer centers have outpatient PC services for cancer patients (44,45).

In addition to PC consultation, HCC patients would benefit from the addition of primary PC approaches to their overall care. This would involve training hepatologists and their teams in comprehensive symptom assessment and management skills to help improve quality-of-life outcomes in lieu of PC referral. This has been shown to be feasible and tolerable to hepatologists and has the potential to impact care in the long-term (46).

Another area where PC can be helpful, especially when well-integrated into the hepatology and transplant teams, is in terms of helping families process information. As noted previously, the treatment regimens surrounding HCC are complex, and with a wide range of treatment options potentially ranging from transplant all the way to hospice, patients and families will have much to consider. In addition to the complexity of information, the clinical course is often unpredictable, the combination of which has led family caregivers in multiple studies to note deficits in information when surveyed (47). Caregiver burden is a significant concern in the management of patients with ESLD. Therefore, providing caregiver support through PC resources will be critical in improving patient quality of life and overall care.

The role of PC will vary according to patient and caregiver psychosocial and spiritual needs, severity of cirrhosis, decompensation, and HCC stage. *Figures 3*,*4* demonstrate sample trajectories of clinical courses and potential for involvement of PC for patients with HCC. Patients with HCC eligible for transplant may experience decline in functional status and liver function, which may be attributed to treatment side effects or natural history. PC involvement should increase from the time of presentation and may vary over the clinical course, given unpredictability and fluctuations in decompensation and recovery after the time of transplant (see *Figure 3*). Patients followed by PC who undergo successful LT and recover may no longer require follow-up with PC secondary to the reversal of their prior terminal illness and symptom burden. Patients with HCC not eligible for transplant may experience varying degrees of decline in functional status and liver function over time, ultimately leading to decompensation and death. PC involvement may vary but should be considered concurrently with disease-focused care for HCC as well as hospice at end of life (see *Figure 4*).

Referral criteria and timing

The AASLD guidelines for cirrhosis suggest referral for PC as an option that can be considered anywhere in the course of treatment, including for those who are transplant candidates; however, HCC populations are not specifically mentioned (48). There are no references that recommend a standard approach to timing of referral, and in many centers, this would be a topic of discussion amongst hepatology, transplant, and palliative teams to determine concrete expectations. One set of circumstances that could be readily agreed upon would be HCC patients with incurable disease who are not transplant candidates,

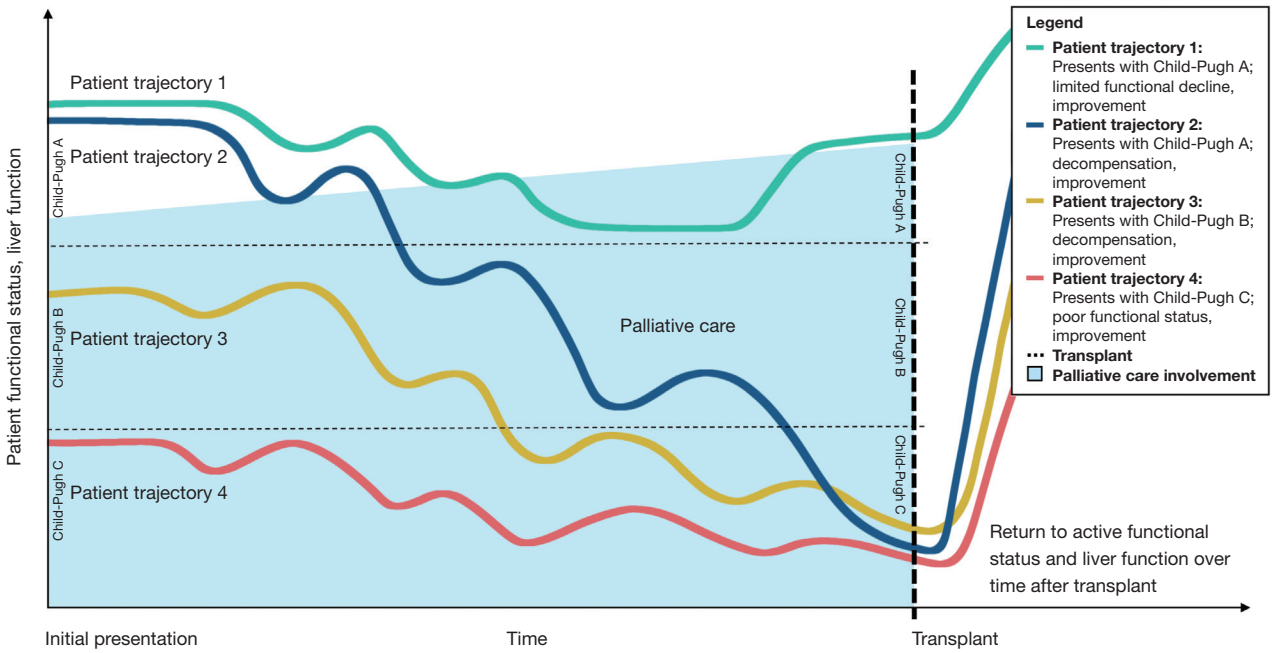

Figure 3 Patients with HCC eligible for transplant: escalation of palliative care with decline in functional status, liver function; concurrent with disease-focused treatment and transplant. Examples of potential courses of patients presenting with HCC and varying Child-Pugh scores for cirrhosis, eligible for transplant. Decline of functional status and liver function may be attributed to side effects of treatment or natural history of liver decompensation over time. Palliative care involvement increases from time of presentation and may vary given unpredictable clinical course with fluctuations in decompensation and recovery through time of transplant. Palliative care role will also vary according to patient and caregiver psychosocial and spiritual needs, severity of cirrhosis, decompensation, and HCC stage. Patients may subsequently return to an active functional status in a curative pathway. HCC, hepatocellular carcinoma.

but prior literature has shown referral rates are low in this subset of the population as well (49). Currently, the majority of referrals in PC when completed are inpatient (49), although the benefits to patients and families are likely to be more pronounced with access to outpatient support.

Hospice

Referral to hospice has been noted to have similar findings of low rates of use and late referrals consistent with those of palliative. When patients are referred, this appears to decrease utilization, whereas PC referral as above may not have proven similar effects to this point. One study exploring SEER data noted that there were on average $10,000 less in inpatient charges for HCC patients enrolled in hospice versus not (50). Length of stay in hospice has been noted to be short for HCC patients, with one study of Medicare beneficiaries noting an average enrollment of less than 2 weeks (51). One point of interest in a publication in the *Journal of Clinical Oncology* on SEER Medicare patients with HCC is that hospice use was more common when hematology/oncology was consulted in contrast to gastroenterology (52).

Settings of PC consultation

It has been noted previously in this review that most of the specialty PC that is currently provided to HCC patients is completed in the inpatient setting and mostly near end of life. There are few authors who have noted delivery of PC in the outpatient space with varying degrees of success. One group embedded a PC-trained nurse practitioner and social worker in a hepatology clinic that agreed to screen appropriate patients for referral as well as have PC participation in weekly interdisciplinary team meetings. After one year of work with particular focus on social determinant of health barriers, they were able to show statistically significant improvement in

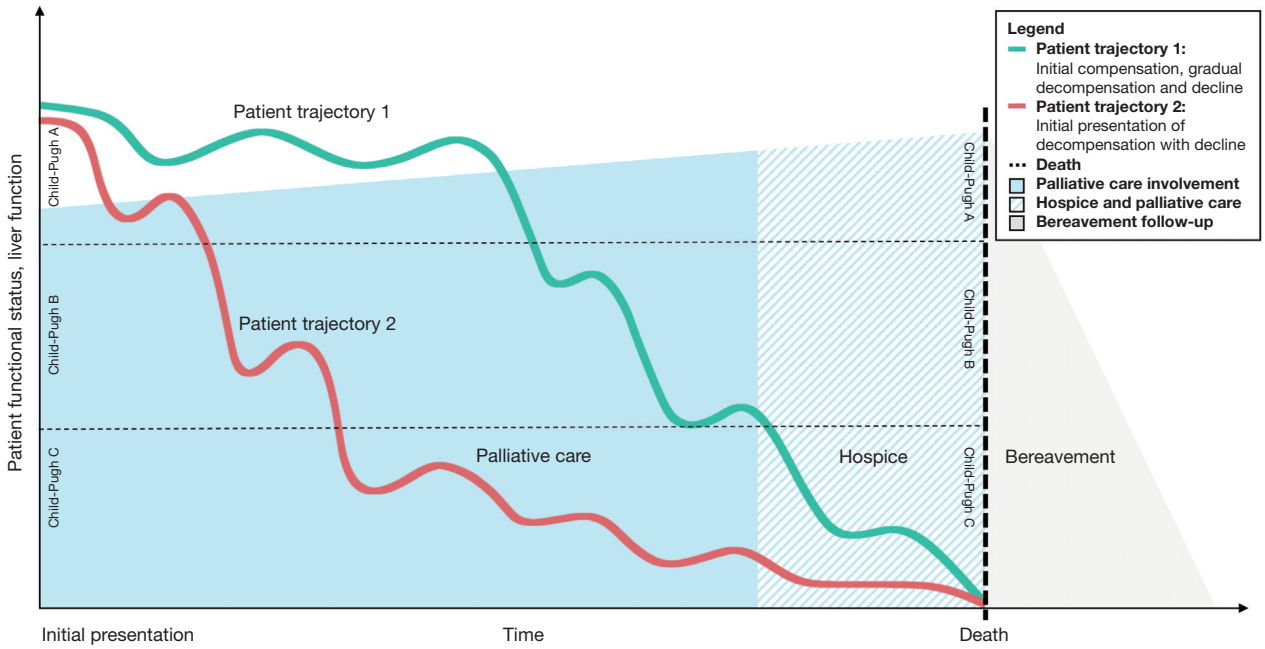

Figure 4 Patients with HCC not eligible for transplant: increasing involvement of palliative care and hospice as patient functional status declines. Examples of potential courses of patients presenting with HCC, not eligible for transplant, experiencing decline over time in functional status and liver function, ultimately leading to decompensation and death. Palliative care involvement may vary given unpredictable clinical course with fluctuations in decompensation and recovery from initial presentation while receiving concurrent disease-focused care for HCC. Involvement of hospice care prior to death. Bereavement follow-up. HCC, hepatocellular carcinoma.

advance care planning (ACP) documentation, psychosocial assessments, and hospice use (53). Another approach that has been utilized is to create a post-discharge clinic for non-transplant eligible patients to discuss ACP, which in a small collection of patients did not change utilization outcomes (54). Finally, a very recent publication reported on over 100 patients with HCC who were randomized to a control group versus intermittent visits from a PC provider outpatient with notation of feasibility of the model and a trend towards improvement in quality-of-life assessments for the intervention group (55).

Disparities

Disparities are a feature noted throughout the literature on HCC, LT, and cirrhosis. Since HCC most often arises in the setting of cirrhosis, screening is recommended for early detection and management. However, it has been noted that the prevalence of screening varies in national data by race, zip code, and socioeconomic factors (56). There are also inequities noted once HCC is diagnosed including differences in receipt of HCC-directed curative therapy and LT for HCC (57). Inequities in access to LT in relation to race, age, gender, and insurance coverage have been an ongoing challenge. Additionally, overlaid on these gaps are regional disparities related to LT (58). These disparities are also noted in the treatment of HCC itself, where authors of one review noted that in Texas, Hispanic and African American patient populations were shown to have lower utilization of invasive treatment strategies and overall higher rates of mortality (59). There are few papers that comment on inequities in PC use in HCC. One recent publication reviewed a national cancer database for HCC patients and found that higher educational level and insurance status increased the likelihood of PC referral (60).

Barriers to PC and hospice

There are a number of barriers that may be present when considering integration of PC in the care of HCC patients. Depending on the treatment plan for the patient, evaluation or listing for LT can be perceived as a

potential barrier to PC consultation. A 2015 survey of liver transplant programs noted that of the respondents (70% response rate) only 2 programs included PC consultation preoperatively (61). Another consideration is the clinical course for these patients, which may make it difficult to elucidate optimal timing for PC introduction. Since a majority of these patients also have underlying cirrhosis, pathways with unpredictable clinic courses including recurrent decompensations and improvements are common and often make prognostication challenging. This barrier is further exacerbated by challenges at the provider level where GI, hepatology, and/or transplant surgery teams may have hesitancy in pursuing PC referral due to lack of understanding of the role of PC. This is a common issue when considering consultation of PC (62). Another potential barrier is the lack of standardized approach to measuring quality of life in patients with HCC that would create a prompt for palliative referral. In one study that summarized quality-of-life outcomes for locoregional therapies there were 13 different scales that were recognized to be included ranging in incidence of use from 5% to 36% (63). In addition to barriers to PC, studies have shown similar barriers to hospice use in this population. One review of hundreds of patients in the VA system noted that 26% of HCC decedents did not use hospice at all, with a number of factors including supplemental insurance, age, race, and location being significantly associated with hospice use (64).

Reflections on integrating PC in management of HCC

The authors of this paper are a mix of PC and transplant hepatology with specialty in HCC care based in the United States. We have observed that despite incorporation of supportive PC into guidelines, partnerships between palliative and hepatology teams are still nascent in clinical practice. For clinicians who wish to build this partnership to improve patient-centered, supportive care in their own setting, and in the absence of evidence that speaks directly to this topic, the authors recommend several considerations in practice.

Given the gaps in evidence regarding this topic, there is less guidance than for other patient populations to suggest optimal integration of PC into this patient population. Therefore, clear communication and expectations will be paramount to ensure that all parties (including transplant surgeons) are aware of parameters for referral and potential outcomes of consultation.

Provider education will be crucial for all involved. This will include not only the nuances of HCC disease course and treatment modalities for PC specialists, but also creating a new framework for hepatology or transplant colleagues that referral to PC is not akin to stopping active therapies/disease-directed therapies. *Figure 5* provides several examples of approaches to integrating PC in HCC management with these considerations in mind.

PC teams interested in working more closely with hepatology and transplant specialists may face a significant learning curve regarding the complexities of HCC, cirrhosis, and myriad treatment modalities. It may be prudent for PC teams to ensure that at least one PC provider has sufficient expertise in the clinical course and treatments for HCC (and cirrhosis), including transplantation, to ensure that they are effective collaborators in care.

Finally, all teams involved who are initiating this new clinical model of practice should be prepared for the inevitable challenges that occur: a paradigm shift and culture change in clinical practice at one's institution. This may take many forms: (I) hepatologist may be asked to consider goals of care earlier on than would be culturally considered standard; (II) PC specialists may have to consider how advance care planning discussions may be different for patients in whom transplantation and cure are a potential care plan; and (III) PC consultation early on in the diagnosis of HCC regardless of the state of liver function, whether treatment plan is curative or non-curative therapy, in order to provide patient-centered supportive care for both patient and caregivers. PC integration into the care of HCC patients has the potential to improve quality of patient care and patient quality of life while also supporting patients, families and care teams involved. For this to be successful, open-minded collaboration and thoughtful approaches to partnership from all teams involved will be essential.

Limitations and future directions for research

As the scope of this topic is broad, the focus of this paper was a narrative review and therefore does not offer a complete review of the literature on this topic as a systematic review would have revealed. We did not include other databases such as Embase, CINAHL, or other international databases, which may limit the generalizability of our results. Additionally, selection of studies to be included was performed manually by the authors to narrow the focus and is therefore subject to bias. One final barrier of note is the small pool of studies in PC in HCC to this

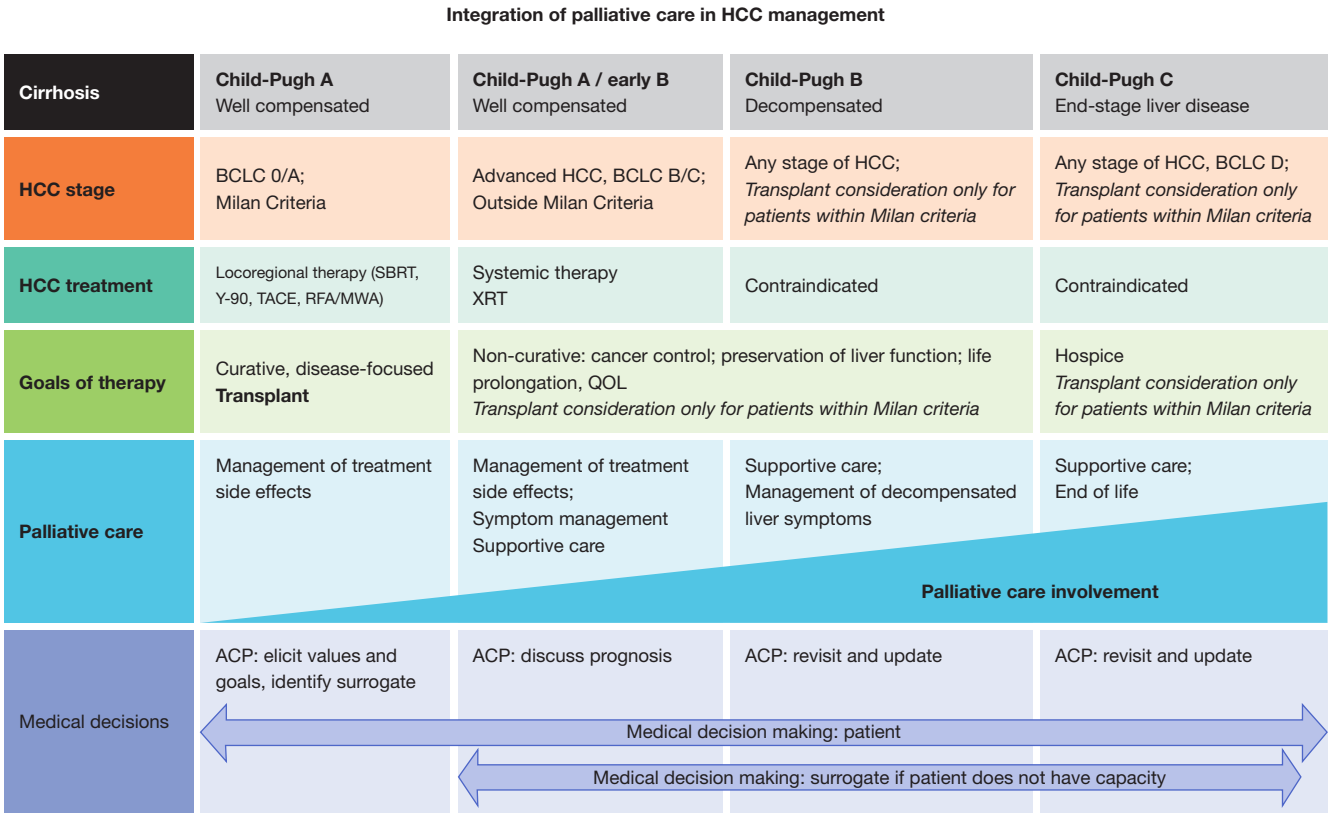

Figure 5 Integration of palliative care in HCC management. Examples of cirrhosis stage, HCC stage, treatment, goals of treatment, and involvement of palliative care in patients with varying Child-Pugh scores and severity of decompensation and disease state. Palliative care consultation and involvement should increase with severity of cirrhosis and decline in patient functional status. Palliative care role will vary according to patient and caregiver psychosocial and spiritual needs, severity of cirrhosis, decompensation, and HCC stage. ACP, advance care planning; BCLC, Barcelona clinic liver cancer staging system; HCC, hepatocellular carcinoma; Milan Criteria, UNOS T2 HCC lesion criteria (a) one lesion greater than or equal to 2 cm and less than or equal to 5 cm in size; or (b) two or three lesions each greater than or equal to 1 cm and less than or equal to 3 cm in size; QOL, quality of life; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; UNOS, United Network for Organ Sharing; XRT, external beam radiation therapy.

point, especially outside of those who meet the traditional criteria of BCLC-D disease, thus limiting evidence-based recommendations that can be made regarding palliative involvement in this patient population at this time (65). Additional research is needed to further develop and implement appropriate referral criteria, determine timing of PC intervention, and track outcomes in patients with HCC receiving PC over the course of treatment.

Further research on the involvement of PC specialists in the care of HCC patients is much needed. Interventions are needed to increase PC referrals during hospitalizations and for ambulatory consultations. Increased referrals can provide further elucidation on what parameters may trigger PC referrals and the timing of these referrals. More studies are needed to further evaluate PC involvement and how this adds to the process of care for HCC patients. This can provide better understanding of the characteristics of patients receiving PC, the interplay between PC care and disease-focused care, the timing of PC referral, and overall outcomes. As at least one study has noted, outcomes of interest might not include subsequent hospital utilization or costs of care (42). Rather, patient-centered outcomes would be more relevant at this time, including experience of care, quality of life, symptom burden, function, psychosocial distress for patients and caregivers, and existential or spiritual distress. At the same time, research on the relationship between HCC specialists and PC specialists could elucidate perceptions of potential collaboration

including trust, the need for cross-training or education, and thoughts on interdiscplinary/specialty boundaries.

Conclusions

HCC is a cancer with high morbidity and mortality, unfortunately often presenting in the setting of underlying cirrhosis. Secondary to this, symptoms and quality-of-life burdens are prevalent, as is the need for end-of-life care for those who are not curable. Many patients with HCC are either primarily managed or co-managed by hepatology, given the underlying cirrhosis as well as the potential for liver transplant as a treatment modality. Given this confluence of factors, PC is not routinely integrated into HCC care, although recent guideline recommendations and further research may change this over time. Although further evidence is needed, palliative and hepatology teams could partner together with open communication to explore ways to improve the care of this patient population. Through these partnerships, patients and families can access the care and support they need as they journey through the challenges of the unpredictable and "roller coaster" trajectory of HCC.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Sukeshi Patel Arora and Sherri Rauenzahn Cervantez) for the series "Comprehensive Care for Patients with Hepatocellular Carcinoma: Insights from the 2022 San Antonio Liver Cancer Symposium" published in *Annals of Palliative Medicine*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-23-416/rc

Peer Review File: Available at https://apm.amegroups.com/article/view/10.21037/apm-23-416/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-23-416/coif). The series "Comprehensive Care for Patients with Hepatocellular Carcinoma: Insights from the 2022 San Antonio Liver Cancer Symposium" was commissioned by the editorial office without any funding or sponsorship. R.K.S. reports that he received grants from Roche, AbbVie, Abbott, Gilead and is a leadership on the ABIM GI/Hepatology Board and AASLD Foundation Research Committee; R.K.S. participates with Pfizer, AskBio; he also received payment/honoraria from Practical Reviews in Gastroenterology. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. BMJ 2018;362:k2817.
2. Estes C, Razavi H, Loomba R, et al. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology 2018;67:123-33.
3. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
4. Center to Advance Palliative Care [Internet]. [cited 2023 Jul 31]. About Palliative Care. Available online: https://www.capc.org/about/palliative-care/
5. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723-50.
6. Brar G, Greten TF, Graubard BI, et al. Hepatocellular

Carcinoma Survival by Etiology: A SEER-Medicare Database Analysis. Hepatol Commun 2020;4:1541-51.
7. Naugler WE, Alsina AE, Frenette CT, et al. Building the multidisciplinary team for management of patients with hepatocellular carcinoma. Clin Gastroenterol Hepatol 2015;13:827-35.
8. Firkins JL, Tarter R, Driessnack M, et al. A closer look at quality of life in the hepatocellular carcinoma literature. Qual Life Res 2021;30:1525-35.
9. Mathews J, Hannon B, Zimmermann C. Models of Integration of Specialized Palliative Care with Oncology. Curr Treat Options Oncol 2021;22:44.
10. Hui D, Hannon BL, Zimmermann C, et al. Improving patient and caregiver outcomes in oncology: Team-based, timely, and targeted palliative care. CA Cancer J Clin 2018;68:356-76.
11. Bialecki ES, Di Bisceglie AM. Diagnosis of hepatocellular carcinoma. HPB (Oxford) 2005;7:26-34.
12. Laube R, Sabih AH, Strasser SI, et al. Palliative care in hepatocellular carcinoma. J Gastroenterol Hepatol 2021;36:618-28.
13. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217-31.
14. Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017;65:310-35.
15. Tsoris A, Marlar CA. Use Of The Child Pugh Score In Liver Disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 May 3]. Available online: http://www.ncbi.nlm.nih.gov/books/NBK542308/
16. Freeman RB Jr. Model for end-stage liver disease (MELD) for liver allocation: a 5-year score card. Hepatology 2008;47:1052-7.
17. Golfieri L, Gitto S, Vukotic R, et al. Impact of psychosocial status on liver transplant process. Ann Hepatol 2019;18:804-9.
18. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol 2022;76:681-93.
19. Benson AB, D'Angelica MI, Abbott DE, et al. Hepatobiliary Cancers, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021;19:541-65.
20. Truty MJ, Vauthey JN. Surgical resection of high-risk hepatocellular carcinoma: patient selection, preoperative considerations, and operative technique. Ann Surg Oncol 2010;17:1219-25.
21. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999;30:1434-40.
22. Poon RT, Fan ST, Lo CM, et al. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg 2002;235:373-82.
23. Kianmanesh R, Regimbeau JM, Belghiti J. Selective approach to major hepatic resection for hepatocellular carcinoma in chronic liver disease. Surg Oncol Clin N Am 2003;12:51-63.
24. Bruix J, Sherman M; . Management of hepatocellular carcinoma. Hepatology 2005;42:1208-36.
25. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-9.
26. Cho YK, Kim JK, Kim WT, et al. Hepatic resection versus radiofrequency ablation for very early stage hepatocellular carcinoma: a Markov model analysis. Hepatology 2010;51:1284-90.
27. Cucchetti A, Piscaglia F, Cescon M, et al. Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. J Hepatol 2013;59:300-7.
28. Doyle A, Gorgen A, Muaddi H, et al. Outcomes of radiofrequency ablation as first-line therapy for hepatocellular carcinoma less than 3 cm in potentially transplantable patients. J Hepatol 2019;70:866-73.
29. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905.
30. Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. NEJM Evid [Internet]. 2022 Jul 26 [cited 2023 May 4];1(8). Available online: https://evidence.nejm.org/doi/10.1056/EVIDoa2100070
31. Soliman H, Ringash J, Jiang H, et al. Phase II trial of palliative radiotherapy for hepatocellular carcinoma and liver metastases. J Clin Oncol 2013;31:3980-6.
32. Muzellec L, Bourien H, Edeline J. Patients' Experience of Systemic Treatment of Hepatocellular Carcinoma: A

Review of the Impact on Quality of Life. Cancers. 2021 Dec 30;14(1).
33. Gandhi S, Khubchandani S, Iyer R. Quality of life and hepatocellular carcinoma. J Gastrointest Oncol 2014;5:296-317.
34. Poonja Z, Brisebois A, van Zanten SV, et al. Patients with cirrhosis and denied liver transplants rarely receive adequate palliative care or appropriate management. Clin Gastroenterol Hepatol 2014;12:692-8.
35. Potosek J, Curry M, Buss M, et al. Integration of palliative care in end-stage liver disease and liver transplantation. J Palliat Med 2014;17:1271-7.
36. Peng JK, Hepgul N, Higginson IJ, et al. Symptom prevalence and quality of life of patients with end-stage liver disease: A systematic review and meta-analysis. Palliat Med 2019;33:24-36.
37. Sun VC, Sarna L. Symptom management in hepatocellular carcinoma. Clin J Oncol Nurs 2008;12:759-66.
38. Norman EML, Weil J, Philip J. Hepatocellular carcinoma and its impact on quality of life: A review of the qualitative literature. Eur J Cancer Care (Engl) 2022;31:e13672.
39. Mudumbi SK, Bourgeois CE, Hoppman NA, et al. Palliative Care and Hospice Interventions in Decompensated Cirrhosis and Hepatocellular Carcinoma: A Rapid Review of Literature. J Palliat Med 2018;21:1177-84.
40. Drott J, Björnsson B, Sandström P, et al. Experiences of Symptoms and Impact on Daily Life and Health in Hepatocellular Carcinoma Patients: A Meta-synthesis of Qualitative Research. Cancer Nurs 2022;45:430-7.
41. Ufere NN, Halford JL, Caldwell J, et al. Health Care Utilization and End-of-Life Care Outcomes for Patients With Decompensated Cirrhosis Based on Transplant Candidacy. J Pain Symptom Manage 2020;59:590-8.
42. Tian T, Guo J, Hu JL, et al. Advanced hepatocellular carcinoma and palliative care: a scoping review. BMJ Support Palliat Care 2022. [Epub ahead of print]. doi: 10.1136/spcare-2022-003798.
43. Truitt K, Khan SS, Gregory DL, et al. Deaths from hepatocellular carcinoma are more likely to occur in medical facilities than deaths from other cancers: 2003-2018. Liver Int 2021;41:1489-93.
44. Calton BA, Alvarez-Perez A, Portman DG, et al. The Current State of Palliative Care for Patients Cared for at Leading US Cancer Centers: The 2015 NCCN Palliative Care Survey. J Natl Compr Canc Netw 2016;14:859-66.
45. Rogers M, Meier DE, Morrison RS, et al. Hospital Characteristics Associated with Palliative Care Program Prevalence. J Palliat Med 2020;23:1296-9.
46. DeNofrio JC, Verma M, Kosinski AS, et al. Palliative Care Always: Hepatology-Virtual Primary Palliative Care Training for Hepatologists. Hepatol Commun 2022;6:920-30.
47. Woodrell CD, Hansen L, Schiano TD, et al. Palliative Care for People With Hepatocellular Carcinoma, and Specific Benefits for Older Adults. Clin Ther 2018;40:512-25.
48. Rogal SS, Hansen L, Patel A, et al. AASLD Practice Guidance: Palliative care and symptom-based management in decompensated cirrhosis. Hepatology 2022;76:819-53.
49. Mazzarelli C, Prentice WM, Heneghan MA, et al. Palliative care in end-stage liver disease: Time to do better? Liver Transpl 2018;24:961-8.
50. Rice DR, Hyer JM, Diaz A, et al. End-of-Life Hospice Use and Medicare Expenditures Among Patients Dying of Hepatocellular Carcinoma. Ann Surg Oncol 2021;28:5414-22.
51. de Avila V, Paik JM, de Avila L, et al. Hospice care utilisation among elderly patients who died with hepatocellular carcinoma in the United States. JHEP Rep 2021;3:100236.
52. Sanoff HK, Chang Y, Reimers M, et al. Hospice Utilization and Its Effect on Acute Care Needs at the End of Life in Medicare Beneficiaries With Hepatocellular Carcinoma. J Oncol Pract 2017;13:e197-206.
53. van Zyl C, Storms AD, van Deen W, et al. A Pilot Study of a Palliative Care Service Embedded in a Hepatology Clinic at a Large Public Hospital. J Palliat Med 2023;26:776-83.
54. Najafian N, Sack JS, DeLisle AM, et al. Advance Care Planning for Patients with Cirrhosis in a Structured Inpatient/Outpatient Hepatology Program. J Palliat Med 2019;22:1445-8.
55. Verma M, Kalman R, Horrow J, et al. Feasibility of a Palliative Care Intervention within Routine Care of Hepatocellular Carcinoma: A Pilot Randomized Controlled Trial. J Palliat Med 2023;26:334-41.
56. Kim AK, Singal AG. Health disparities in diagnosis and treatment of hepatocellular carcinoma. Clin Liver Dis (Hoboken) 2015;4:143-5.
57. Guo A, Pomenti S, Wattacheril J. Health Disparities in Screening, Diagnosis, and Treatment of Hepatocellular Carcinoma. Clin Liver Dis (Hoboken) 2021;17:353-8.
58. Wahid NA, Rosenblatt R, Brown RS Jr. A Review of the Current State of Liver Transplantation Disparities. Liver Transpl 2021;27:434-43.
59. Ha J, Chaudhri A, Avirineni A, et al. Burden of

hepatocellular carcinoma among hispanics in South Texas: a systematic review. Biomark Res 2017;5:15.
60. Alterio RE, Ju MR, Wang SC, et al. Socioeconomic and racial/ethnic disparities in receipt of palliative care among patients with metastatic hepatocellular carcinoma. J Surg Oncol 2021;124:1365-72.
61. Semer NB. Awaiting Liver Transplantation. Transplantation 2015;99:e48.
62. Abasseri M, Hoque S, Slavica Kochovska BA, et al. Barriers to palliative care in hepatocellular carcinoma: A review of the literature. J Gastroenterol Hepatol 2023;38:1047-55.
63. Das A, Gabr A, O'Brian DP, et al. Contemporary Systematic Review of Health-Related Quality of Life Outcomes in Locoregional Therapies for Hepatocellular Carcinoma. J Vasc Interv Radiol 2019;30:1924-1933.e2.
64. Zou WY, El-Serag HB, Sada YH, et al. Determinants and Outcomes of Hospice Utilization Among Patients with Advance-Staged Hepatocellular Carcinoma in a Veteran Affairs Population. Dig Dis Sci 2018;63:1173-81.
65. Gofton C, Agar M, George J. Early Implementation of Palliative and Supportive Care in Hepatocellular Carcinoma. Semin Liver Dis 2022;42:514-30.

Cite this article as: Hashmi IN, Lee HM, Wedd JP, Sterling RK, Dulong-Rae TE, Cassel JB, Cyrus JW, Fletcher JJ, Noreika DM. A narrative review of supportive and end of life care considerations in advanced hepatocellular carcinoma. Ann Palliat Med 2023;12(6):1260-1274. doi: 10.21037/apm-23-416

