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Palliative Care for People with Hepatocellular Carcinoma and Specific Benefits to Older Adults

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Abstract

Purpose—Hepatocellular Carcinoma (HCC), the most common type of primary liver cancer, has a rapidly rising incidence in the United States and a very poor overall rate of survival. This epidemic is driven by the cohort of aging baby-boomers with hepatitis C virus infection and the increasing incidence of non-alcoholic steatohepatitis (NASH) cirrhosis. Because curative options are limited, the disease course creates distressing uncertainty for patients and their families around prognosis and treatment decisions. Older adults are disproportionately affected by HCC and have more co-morbidities, adding to the complexity of the disease. This population would benefit from increased access to palliative care services, which can potentially complement the treatments throughout the disease trajectory. The purpose of this review is to use existing evidence to propose a new model of palliative care integration for HCC patients. Thus, we focus on the HCC stage and the treatment algorithm, and the ways that palliative care can offer support to this population at each stage, as well as elements that can enhance patient and family support throughout the entire disease trajectory, with an emphasis on the care of older adults with HCC.

Methods—This is a narrative review in which we identify evidence-based ways that palliative care can help adults and older adults with HCC, and their families, at each stage of HCC, and throughout the disease trajectory.

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Conflict of Interest Statement

The authors do not have any conflicts of interest to disclose.

Findings—We propose ways to integrate HCC and palliative care based on the existing evidence in both fields. Palliative care offers support of symptom management, advance care planning, and decision making in ways that are specific to each stage of HCC. We also discuss the evidence that illustrates the palliative care needs of HCC patients that span the entire course of illness, including coping with the stigmatization of liver disease, addressing informational needs at different stages, and discussions of quality of life longitudinally. Implications: Integrating palliative care into treatment of patients with HCC has the potential to improve outcomes, although more research is needed to build this evidence base.

Keywords

Hepatocellular carcinoma; palliative care; cirrhosis; supportive oncology; geriatric oncology

Introduction

Hepatocellular carcinoma (HCC) is a dreaded complication of liver disease that has a poor rate of overall survival.[1] Patients undergo many different types of treatments throughout the course of disease.[2] The treatment algorithm can be complex, and patients face considerable uncertainty around treatment and prognosis.[3] Because HCC occurs in the context of underlying liver disease, this population suffers from the symptoms of both end-stage liver disease and cancer.[4, 5] Hepatologists play a central role in HCC management. Multi-disciplinary HCC tumor boards are often led by hepatologists, with the involvement of many different types of specialists to address the different treatment modalities.[6] In addition to the medical complexity of HCC, a diagnosis of HCC is emotionally overwhelming for anyone, but in particular for older adults, who may face additional treatment and symptom challenges due to chronic conditions.[7]

Palliative care, which is specialized interdisciplinary care that focuses on quality of life while living with a serious illness,[8] has the potential to offer additional support to patients with HCC and their families as they navigate life with the disease. However, little is known about the specific palliative care needs of these patients,[9] and particularly older adults with multiple co-morbidities. No HCC-specific models of palliative care delivery have been described, and patients with end-stage liver disease rarely receive palliative care, even at the end of life.[10–12] This narrative review will focus on the aspects of HCC that make it a uniquely complex and distressing illness, and the ways that existing evidence suggests that palliative care can provide support throughout the course of HCC. Specifically, we will review the course of HCC by stage and propose specific, ways that palliative care can be helpful at each stage of HCC, as well as longitudinally throughout the disease course. We will then discuss some of the challenges of integrating palliative care into the HCC treatment landscape, and propose future research directions to address this gap in the healthcare literature.

HCC is a complex disease with an uncertain course

HCC is the most common type of primary liver cancer and the second leading cause of cancer-related mortality worldwide.[2] In the United States (US) approximately 30,000 adults

are diagnosed with HCC each year and 21,000 die.[13] The incidence is rising[14] in the setting of a hepatitis C virus epidemic.[15, 16] Of note, relatively new, highly effective anti-viral hepatitis C treatments are available, but their effect on the rising incidence of HCC is not yet known.[17] The proportion of patients on the liver transplant waiting list for malignancy tripled between 2005 and 2015.[18] In addition, an increasing proportion of those affected by HCC have non-alcoholic steatohepatitis (NASH), which is associated with the obesity epidemic and metabolic syndrome.[19]

HCC affects older adults with chronic liver disease. The risk of developing HCC rises with age, with more than 15-fold increase after 65 years of age among hepatitis C-infected patients.[20] The average age of HCC patients awaiting liver transplant has risen in recent years, from 51.2 to 55.7 years, and the proportion of those waiting who are older than 60 years has more than doubled from 19% to 42%.[21]

HCC develops in the context of chronic liver inflammation or infection, and in most cases, underlying cirrhosis.[2] Thus, because of concurrent liver disease, this cancer has an unpredictable disease course, and the treatment algorithm is uniquely and increasingly complex, with many potential new treatments on the horizon.[22] Treatment modalities include surgical resection, liver transplant, interventional radiology procedures (embolization), chemotherapy,[2] and immunotherapy,[23] in addition to the management of the underlying chronic liver disease. Older adults often face multi-morbidity[24] requiring many medical visits, thus the uniquely complex treatment scheme of HCC for this population is potentially quite burdensome, when added on top of the numerous other visits needed to treat their other medical illnesses. Furthermore, the presence of symptoms of underlying liver disease, like minimal hepatic encephalopathy, can lead to further deterioration of patients' functional status.

A major source of uncertainty within the HCC treatment algorithm is transplant: candidacy is not certain and may change over time with disease progression. HCC may progress, or become more widespread, while patients are on the liver transplant waiting list, thus precluding transplantation. Secondly, in the U.S. the United Network for Organ Sharing (UNOS) policies governing HCC patient placement on the liver transplant waiting list have recently become more stringent. Patients are listed according to their Model for End-Stage Liver Disease (MELD) score,[25] which is calculated from serum bilirubin, prothrombin time, and renal function and ranges from six (less ill, lower waitlist priority) to greater than 40 (gravely ill, higher waitlist priority). HCC patients receive additional points based on time spent on the waiting list. However, HCC patients now have a waiting period before listing and a MELD score cap, and their effects on waiting times and waitlist mortality for HCC patients are not yet known.[18]

Early palliative care would benefit HCC patients

Early and consistent access to palliative care would benefit HCC patients and their families. Palliative care is interdisciplinary care provided to people with a serious illness, and can be offered at any stage of disease and at any age.[8] Palliative care can be delivered concurrently with curative or disease-modifying treatments. The focus of palliative care is on quality of

life, through the management of symptoms, discussion of treatment preferences, provision of psychosocial support, including religion and spirituality, and coordination of care. Palliative care has been shown to reduce patient[26, 27] and family suffering,[28, 29] reduce healthcare utilization,[30, 31] and even improve survival[32, 33] in the context of cancer. The American Society of Clinical Oncology now recommends routine inclusion of palliative care in the care of people with cancer.[34]

The landmark study in 2010 by Temel and colleagues[32] showed that an ambulatory early palliative care intervention for advanced lung cancer patients improved quality of life and symptom control. They also found that the intervention group had longer survival while receiving less aggressive end-of-life care. The content of the visits was tailored to the stage of the patients' disease, with earlier visits focused on building rapport and providing support; discussions around end-of-life care preferences occurred when patients became sicker.[35] A qualitative study of palliative care practitioners revealed that the clinical approach to providing early palliative care for cancer patients has three major themes: (1) symptom management, (2) facilitation of coping, accepting, and planning, and (3) helping to improve medical understanding by the patient.[36]

Table 1 features four domains of palliative care that are relevant to the care of people with HCC, adapted from the clinical guidelines published by the National Consensus Project for Quality Palliative Care.[37] Palliative care practitioners can help manage symptoms in a way that complements management of specialists, including hepatologists, oncologists, or surgical oncologists. The symptoms associated with HCC that are listed in the right column reflect the findings of Hansen *et al.*,[5] Sun and Sarna,[4] and Kaiser *et al.*[38] Pain management is an area where palliative care can complement the management of HCC specialists because of the complexity of dosing analgesics for patients with hepatic impairment (most HCC patients), prevalent history of substance use among patients with chronic liver disease,[39] and the opioid addiction epidemic in the U.S.[40] Since most HCC patients also have cirrhosis, they also have symptoms that reflect their underlying liver dysfunction. Notably hepatic encephalopathy can be very distressing symptom for family members.[41] In addition to the difficulties with metabolism of medications caused by liver disease, older adults may be more susceptible to side effects of medications[4] including delirium related to medications, gait imbalance, urinary retention, and falls.

Advance care planning (table 1) refers to patient preferences about how they receive care and who might make decisions for them if they are unable. Physician (or Medical) Orders for Life-Sustaining Treatment (POLST or MOLST; differs by U.S. State) is available throughout the U.S. and specifies preferences related to care received—e.g., resuscitation, ventilation, artificial nutrition and hydration, hospitalization, and renal replacement therapy.[42] Psychosocial support (table 1) might include referral for religious or faith-based resources, child-life or art therapy, or referral to support groups. Finally, care coordination (table 1) might include functional assessment, identification of needed home based care, and screening for geriatric syndromes, like frailty, fall risk, and polypharmacy.

In addition, inpatient palliative care consultation for advanced cancer patients is associated with reduced cost. Morrison and colleagues have shown that early inpatient palliative care

reduced cost, and that earlier consultation resulted in larger cost savings.[31] They also demonstrated that reduced length of hospital stay had the largest impact on the observed cost reduction.[43] It is important to note that the same group has reported improved patient and family satisfaction by surveying bereaved family members,[29] thus demonstrating that palliative care consultation may reduce cost while also improving patient and family satisfaction.

Reduced healthcare utilization associated with palliative care consultation for people with cirrhosis has been reported by Patel *et al.* in their study of palliative care receipt among Medicare beneficiaries with cirrhosis. Specifically, they showed that palliative care consultation was associated with fewer numbers of procedures at the end of life.[12] The existing evidence for the impact of palliative care on cost focuses on advanced disease (cancer or cirrhosis); little is known about the potential impact of palliative care on the intensity and cost of care received by HCC patients with early stage disease.

The principles of palliative care are especially pertinent to older adults with HCC, who have increased numbers of co-morbid conditions, thus complicating treatment decisions. Hewitt and colleagues reported that cancer survivors with chronic diseases were more likely to report limitations of activities of daily living (e.g., bathing, dressing) or instrumental activities of daily living (e.g., shopping for groceries, managing money) and being unable to work because of a health condition.[44] Among cancer survivors with comorbid chronic conditions the likelihood of poor health and disability was much higher. Four out of five older adults have at least one chronic condition,[24] and multiple chronic conditions are associated with poor functional status and quality of life, and adverse drug events.[45] Among older women with breast cancer for instance, level of symptom burden and number of co-morbidities are strongly associated with physical function.[46] Significant chronic conditions may also compromise treatment effectiveness and treatment adherence.[47] In addition to HCC related symptoms, older adults may have a more complicated symptom presentation because of more co-morbid conditions, adding additional complexity and challenges to an already complex treatment algorithm and symptom profile. Palliative care delivery to older adults with HCC may have an even greater cost saving effect as compared with younger people: Morrison and colleagues found in their analysis impact of palliative care consultation for cancer patients, that cost savings are increased for patients with increased numbers of co-morbidities.[48]

Potential early palliative care interventions, tailored to the needs of people with HCC and their families, should span the course of illness. The role of palliative/supportive care in the care of HCC patients has been suggested previously,[49] Many of the services that palliative care can provide, including symptom management, decisional support, care coordination, and psychosocial support are needed in the early stages of HCC, when curative treatments are still available. However little has been written about the best ways to integrate these services into existing models of HCC care.

Palliative care delivery to HCC patients may ideally be connected to the multi-disciplinary tumor board, as previously described.[50–53] There is observational evidence that patients managed through a multi-disciplinary tumor board have higher rates of therapy and longer

survival.[6, 54] And while improvement of quality-of-life for HCC patients is an important stated objective of the multidisciplinary approach to HCC care, there is a paucity of literature on measured outcomes in this area, and the models do not include palliative care,[53] or a focus on older patients with HCC.[55] HCC is amenable to early palliative care intervention, and the disease-specific triggers and content of the visits need to be tailored to the specific needs of HCC patients and their families.

Palliative care can be helpful to HCC patients in different ways at each stage

Palliative care presents an opportunity to address illness understanding and information sharing at all stages. Palliative care clinicians are uniquely suited to help patients navigate the process of treatment decisions while considering how to best define and maintain quality of life while living with a serious illness like HCC. Here we describe potential roles of palliative care at each Barcelona Clinic Liver Cancer (BCLC) stage. The BCLC staging system is endorsed by major clinical practice guidelines.[56] It is divided into five stages: stage 0, A (early), B (intermediate), C (advanced), and D (terminal). The staging system forms the basis for the HCC treatment algorithm and prognostication. Table 2 outlines a framework to approach the development of palliative care that is tailored to the trajectory of HCC. The first row describes an overview of the clinical features that characterize each stage. Below that, we have listed ways in which palliative care might enhance the care of HCC patients at each stage. The bottom row shows ways in which palliative care can help these patients throughout the course of illness that are specific to HCC.

Barcelona Clinic Liver Cancer (BCLC) stage 0 and A HCC

Patients with very early stage HCC (BCLC stage 0) have a single liver nodule less than 2 cm, while patients with early stage HCC (BCLC stage A) have a single nodule less than 5 cm or three or fewer nodules less than 3 cm.[2] They are eligible for consideration of curative treatments, including ablation, resection, or liver transplant. Transplant candidacy is determined primarily by the Milan Criteria: a single tumor less than 5 cm in diameter, or up to three tumors not larger than 3 cm in diameter, confined to the liver.[57] Median survival for this cohort is more than 5 years with treatment.[2]

Some of the core principles of palliative care can be helpful in supporting patients and families in decision making.[58] Thus, it stands to reason that there are opportunities to address decision making around surgical intervention for early stage HCC patients. As outlined by Mosenthal and colleagues in their recent publication in the *Annals of Surgery*, there are no studies to date that test a surgical palliative care intervention during the perioperative period.[59] Advance care planning before surgical intervention is particularly important for patients who face greater risk of complication, like older adults or patients with significant co-morbidities. Patients with early stage HCC may benefit from discussions about treatment preferences early. Ideally they would have such discussions with a provider (physician, nurse practitioner, or social worker trained in communication techniques) whose skill in communication complements the expertise of the HCC-treating physicians. Patients with BCLC stage A HCC who are listed for liver transplant risk disease progression, making

them ineligible for transplant, and may represent a group of patients with potential unmet palliative care needs. Mehta *et al.* report, in their three-center cohort study of HCC patients listed for liver transplant, a waitlist dropout rate of 18.4% with a median time to dropout of 11.3 months.[60] Similarly, Salvalaggio *et al.* report single center retrospective data that demonstrates a one-year dropout rate of 17.7%.[61] Importantly, they found that patients who dropped out before receiving a transplant did so either because of the severity of their underlying liver disease, or were less likely to respond to embolization therapy and had higher alpha fetoprotein values, suggesting more aggressive disease. These data suggest that the event of waitlist removal may mean patients have a greater need for palliative care, both for their disease severity and resulting symptom burden, and for support during a time of uncertainty and distress over their inability to receive curative therapies. Removal from the transplant waiting list may therefore be an important point in the HCC trajectory for treating physicians to refer their patients to palliative care as an added layer of support. This may also serve as a strategy for triaging patients to palliative care where availability of specialty-level palliative care is more limited, given palliative care staffing shortages.[62]

In addition, within this early-stage group, older adults are particularly vulnerable to prognostic uncertainty. It may be more difficult, or even impossible to undergo surgery or be listed on the liver transplant waiting list and receive a transplant. Older recipient age is associated with higher mortality after liver transplant, as compared with younger recipients.[63] A meta-analysis of HCC treatment for older adults (70 years or more) by Hung and Guy showed similar survival for older adults who underwent resection, as compared with younger individuals, but lower survival for those who underwent ablation.[64]

BCLC stage B HCC

Patients with intermediate stage HCC (BCLC stage B) have multinodular HCC, or tumors outside of Milan Criteria, good functional status, and compensated liver disease.[2] They may receive local anti-neoplastic treatments, including trans-arterial chemo-embolization (TACE)[65] and ^{90}Y-radioembolization.[66] Though they are not eligible for transplantation, their treatment may result in downstaging of their tumors and potential liver transplant candidacy.[67, 68] People with intermediate stage HCC have a median overall survival of 26 months.[2]

The treatment of intermediate stage HCC is notable for the multiple specialists that may be involved in the patients' treatment plan. Intermediate stage patients may be following with, and receiving information from, multiple specialists at this stage: interventional radiology, medical oncology, transplant hepatology, and surgical oncology. Furthermore, for this group, care coordination may be particularly important in addition to decisional, informational, and symptomatic support. Palliative care teams are uniquely skilled in care coordination[69] and could provide support to patients and families as they navigate the different treatment modalities for intermediate stage disease.

BCLC stage C HCC

Patients with advanced HCC (BCLC stage C) have portal invasion, lymph node involvement, metastases, and/or reduced functional status, but compensated liver disease as defined by

Child Pugh A and B,[2] a scoring system that rates severity of liver disease based on presence of underlying symptoms.[70] Chemotherapy has been the mainstay of treatment for patients with advanced HCC for the last ten years.[71] Until recently, no other approved therapies were approved beyond sorafenib (a tyrosine kinase inhibitor), so those who were not able to tolerate or did not benefit had only clinical trials or supportive care as therapeutic options. Within the last year, there have been two major developments in the treatment of advanced HCC. Regorafenib has been approved by the Federal Food and Drug Administration as second line therapy for HCC.[72] Lenvatinib has been submitted to the FDA for approval, as first-line therapy for advanced HCC, given its noninferiority to sorafenib (with respect to overall survival),[73] Both of these medications are kinase inhibitors. These new developments will offer additional treatment options for this group, and will add complexity to their decisions about treatments. Median survival for BCLC C patients is 11 months with treatment.

BCLC stage C HCC

Palliative care can help this group with both symptomatic management and decisional support. In their longitudinal qualitative study of the experience of HCC patients near the end of life, Hansen et al found that more than half of the participants considered stopping cancer treatment at some point during the study.[3] They found that a common theme in this decision making process was a wish to maintain their quality of life, yet their perception of a good quality of life understandably changed with the progression of their disease. Exploration of how a patient defines good quality of life is an important way that palliative care may provide additional support to patients at this advanced stage, as they undergo treatment, and possible disease progression and worsening symptom burden.

Patients with BCLC stage D HCC (often referred to as terminal stage) have impaired liver function (Child Pugh C) and reduced functional status. Lin *et al.* report that HCC patients with Child Pugh C cirrhosis had higher rates of peripheral edema, ascites, dyspnea, jaundice, thrombocytopenia, and hepatic encephalopathy as compared with Child Pugh A and B patients.[74] Disease-directed treatments are not available for patients with terminal HCC, and their median survival is less than three months.[75] Patients with BCLC stage D HCC can be offered supportive care. Palliative care practitioners can help at this stage with treatment of complex symptoms associated with worsening disease[5] and coping with the lifestyle changes that come with patients' progressive disability. Knowledge and support in the provision of end-of-life care may be lacking for HCC patients and families.[41]

Hospice is an important consideration for patients with terminal stage HCC, and palliative care specialists can help with discussion of patient preferences for hospice referral. Hospice is interdisciplinary care that is distinguished from palliative care (which can be delivered at all stages of illness), because it is for people who (1) are close to the end of their lives, generally with a less than six-month prognosis, and (2) are no longer receiving treatments with curative intent. Hospice use is associated with improved quality of care at the end of life.[76]

Like palliative care consultation for advance cancer patients, hospice care at the end of life is associated with reduced healthcare utilization with improved patient satisfaction, and is

therefore an opportunity for reduced costs with care that is aligned with patient preference. Kleinpell *et al.* report that hospice admission during the last six months of life is associated with improved patient satisfaction ratings, better pain control, reduction in hospital days and hospital deaths, and is inversely related with hospital and intensive care unit mortality at the hospital level.[77] For HCC patients specifically, the hospice enrollment rate for Medicare beneficiaries near the end of life is 63%.[78] Hwang *et al.* reported that in Taiwan hospice care for older adults with terminal HCC was associated with improved delivery of symptomatic medications, and was associated with reduced costs.[79] Similarly, a recent publication by Fukui *et al.* demonstrates lower hospitalization costs for Medicare beneficiaries with liver cancer who received hospice care.[80]

Palliative care can be helpful to HCC patients longitudinally, regardless of stage

In order to meet the needs of HCC patients throughout their illness, palliative care should be offered early, and continue longitudinally, and be tailored to the specific needs of patients with a given illness.[81, 82] Designing care delivery models specifically based on disease stage will not meet the needs of all patients, as there is likely to be variation among palliative care needs, particularly among older adults with other chronic conditions. Furthermore, there are specific challenges that span the course of illness that palliative care may help address (bottom-most row of table 2), which are described here.

First, HCC patients' definition of quality of life, and their perceptions of how it is affected by their treatments, change over the course of time with disease progression.[3] Thus, longitudinal involvement of palliative care in the care of these patients will be helpful by providing uniquely skilled practitioners to help define and monitor quality of life over time. Their interaction with palliative care may involve complex symptom management, discussion of treatment preferences, or provision of additional resources to help them cope with their illness, regardless of disease stage.

Second, the stigma around liver disease is an added burden for this population. HCC patients and their family caregivers experience stigma associated with liver disease, and may experience guilt or feel ostracized.[41] HCC almost always arises in the setting of chronic liver disease, and in the US, common causes of chronic liver disease and/or cirrhosis that lead to HCC are viral hepatitis and obesity.[83] In many cases the disease is a direct result of stigmatized behavior or personal characteristic: intranasal or intravenous drug use, sexual intercourse, alcohol use, and obesity. Hansen and colleagues report the experience of one participant who had experienced both breast and liver cancer compared the experiences: she noted that HCC is not one of the "good" cancers, compared leukemia or breast cancer (both cited by the participant with regard to public perception). A recent survey of caregivers for HCC patients, by Bristol-Meyers Squibb,[84] confirms this feeling of isolation and shame: many respondents noted that stigmatization and lack of public awareness make it difficult for HCC patients to find support.

A third potentially unmet need among HCC patients that is amenable to longitudinal palliative care involvement is patient and family caregiver need for more information about

this disease and its course. End-stage liver disease is frequently characterized by unpredictable disease exacerbations, and the treatment algorithm for HCC is complex. In their study of HCC patients' family caregiver experience, Hansen and colleagues found a desire for more information, both in terms of treatment options, and interpreting the significance of symptoms with respect to disease progression. Similarly, the Bristol-Meyers Squibb survey of family caregivers (of HCC patients at both early and late stages) revealed that more than half of respondents felt the need for more information about the disease and its treatments, and 80% did not know where to find additional information.

Challenges in developing HCC-specific palliative care models

Two important factors may play a part in the barriers to integrating palliative care with the medical care of HCC patients: (1) lack of available resources and trained staff and (2) stigmatization of palliative care, particularly in the setting of liver transplant.

First, palliative care is a relatively new field and necessary resources may not be readily available for incorporation into current practice models. A recent report of palliative care growth in the US demonstrated that access to palliative care across health systems remains uneven.[85] Factors that impact availability of hospital-based palliative care include hospital size, tax status, and geographic location. Furthermore, given the rapid growth of the field of palliative care in recent years, there is a relative shortage of specialists offering palliative care in the US.[86, 62] Workforce training in the principles of palliative care for both palliative care and HCC specialists is necessary to address the needs of people facing HCC.

Second, misperceptions that equate palliative care with end-of-life care may impact when and how often HCC patients are referred to palliative care as a complement to disease-directed therapy. A 2014 survey of medical oncologists revealed a belief among some respondents that palliative care is not compatible with cancer-directed treatment.[87] Beck *et al*.[88] performed a survey of liver transplant providers including nurses, physician trainees, and attending physicians at an academic transplant program. Respondents reported that palliative care services benefit patients, even when listed for liver transplant. Nonetheless, solid organ transplantation is sometimes viewed as incongruous with palliative care, usually based on the assumption that palliative care focuses on the provision of end-of-life care, on the part of both physicians and patients/families.[89] Concurrent palliative care and transplant referral has been studied by Navarro and colleagues: they found that end-stage liver disease patients who received palliative care referrals concurrently with liver transplant evaluation had improved symptom control, and notably fewer depressive symptoms.[90]

Recommendations for Future Directions

Given the complexity of HCC care and the lack of research to test the efficacy of models of palliative care delivery in this population, and particularly in older adults with HCC, more research is needed. Palliative care models that incorporate care for patients with all stages of HCC should be tested. It is important to consider measurement tools to be used in a trial of palliative care and quality-of-life focused interventions for this population. There are two HCC-specific quality-of-life questionnaires that have been validated: the European

Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) HCC18,[91] and the Functional Assessment of Cancer Therapy—Hepatobiliary (FACT-Hep) Questionnaire.[92] In addition, qualitative methods should be incorporated into the design of trials that test palliative care interventions for HCC patients. This will allow incorporation of patient and family caregiver voice in real time, as the trial is carried out. Thus, the investigators can detect and respond to unanticipated or otherwise unmeasured effects of the intervention.[93] This will help to inform future studies and create more effective models of HCC care.

There are different types of palliative care interventions that have been tested in cancer patients. Most notably, inpatient palliative care consultation and early/ambulatory palliative care interventions have been shown to improve quality and in some cases quantity of life, and reduce rates of healthcare utilization. Because we believe that continuity of palliative care that dovetails with HCC-specific management, we propose that study of early, outpatient-based palliative care interventions will be central to successful delivery of palliative care for HCC patients. Furthermore, there is evidence that longitudinal palliative care delivery has different patterns of maximal benefit based on the type of primary cancer. Temel and colleagues showed in their 2017 randomized controlled trial of palliative care for patients with lung and gastrointestinal (GI) cancers[94] that patients with lung cancer had significant improvement in quality of life and depressive symptoms at the 12-week time-point. In contrast, those with GI cancers who received palliative care did not show significant improvement over usual care until the 24-week time-point. In order to understand the timing and ways that HCC patients will benefit from palliative care, research should focus on implementation across the spectrum of HCC care.

Enhanced information sharing may benefit this population, so HCC-specific palliative care interventions should include components of information sharing and disease understanding. Prior studies have shown that patients and family caregivers perceive a lack of information about the disease.[3, 41] The unpredictable disease course of HCC is similar to the end-organ failure model of disease trajectory described previously, most extensively in the context of heart failure.[95] These patients often face a course that may be punctuated by disease exacerbations, any one of which could result in death. Furthermore, regardless of whether patients have end-organ failure or cancer, the pattern of disability during the last year of life is uncertain.[96] As recommended for heart failure patients,[97] regularly scheduled visits with their provider that are woven into the HCC treatment algorithm could potentially be helpful in making sure patients and families have a mechanism to receive information and review the disease course and milestones, or when there is an acute need, for instance when the patient is hospitalized unexpectedly. This could help address the lack of information felt by caregivers in previous studies.[41, 84]

Finally, the existing multi-disciplinary model of care for pre- and post-transplant patients is likely more amenable to an embedded palliative care model, rather than a consultative model, such that the palliative care team members are well known to the multi-disciplinary team and regularly care for the patients seen in the liver cancer practice. This model will help build trust and facilitate close communication between providers, while helping HCC patients and families navigate the complex course of this disease.

Conclusion

Patients and their families face unique challenges from HCC, a complex, deadly, and increasingly common disease. As demonstrated in palliative care research for other serious diagnoses, palliative care may offer an added layer of support to the multidisciplinary approach to HCC care, especially in the specific areas of symptom management, psychosocial coping, decisional support, and disease understanding. We propose that integrating palliative care into the multidisciplinary approach to care may be most feasible and effective model. This integration may be accomplished through both provision of specialty level palliative care, particularly at specific points in the disease course, and by incorporating specific elements of palliative care into routine HCC care. Research in this area should focus on testing interventions throughout the course of HCC, with outcomes that include quality of life measures and design that incorporates patient and family voice. HCC is a complex disease, and even more so for older adults with multiple co-morbidities. Thus, we need to better understand the specific needs of HCC patients so that their palliative care needs can be met throughout the disease course. We believe that enhancement of palliative care services that complement the HCC treatment algorithm will significantly improve the care of HCC patients and their families.

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Abbreviations

HCC	Hepatocellular carcinoma
NASH	Non-alcoholic steatohepatitis
US	United States
MELD	Model for end-stage liver disease
BCLC	Barcelona Clinic Liver Cancer
UNOS	United Network for Organ Sharing
MOLST/POLST	Medical/Physician Orders for Life-Sustaining Treatments
TACE	Trans-arterial chemo-embolization
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
FACT-Hep	Functional Assessment of Cancer Therapy—Hepatobiliary

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Table 1

Domains of services that can be delivered by an interdisciplinary palliative care team, and examples of specific interventions within each.

Domain	Specific examples
Symptom management	Pain
	Fatigue
	Diarrhea
	Skin problems
	Anorexia
	Weight loss
	Obstructive Symptoms
	Drowsiness
	Dyspnea
	Nausea
	Depressive symptoms
	Anxiety
	Encephalopathy
Advance care planning	Elicit decision-making preferences
	Identification of healthcare agent
	Completion of advance directives (e.g. MOLST/POLST)
	Discussion of patient's definition of quality of life
Psychosocial support	Identify religious or spiritual needs
	Referral to child-life/art therapy
	Referral to support groups
Care coordination	Functional assessment
	Coordination of services
	Screening for geriatric syndromes (fall risk, polypharmacy, frailty)

Table 2

Elements of palliative care that may be incorporated into HCC treatment by stage, and elements which might span the course of illness.

BCLC Stage	**A**	**B**	**C**	**D**
Defined by	Disease confined to the liver; eligible for curative therapies	Disease Confined to liver; not eligible for curative therapies	Metastatic disease or portal vein invasion; reduced performance status	Decompensated liver function; reduced performance status
Cancer-directed treatments	Resection Liver transplant Ablation	Embolization with intent to control disease or downstage	Chemotherapy/ Immunotherapy	None
Potential role of the palliative care interdisciplinary team	Advance care planning discussion prior to surgery	Symptom management; Decisional support around treatment decisions Care coordination	Symptom management Decisional support around treatment decisions	Symptom management End-of-life care preferences Hospice referral
	Ongoing discussion of quality-of-life throughout the illness course, which will change over time as HCC progresses; Coping with stigmatization of liver disease/liver cancer; Helping to facilitate illness understanding			