# Role of Multidisciplinary Care in the Management of Hepatocellular Carcinoma

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## **Abstract**

#### **Keywords**

- ► liver cancer
- treatment
- multidisciplinary
- guideline-concordant care
- hepatocellular carcinoma

Despite advances in treatment options for hepatocellular carcinoma (HCC), 5-year survival for HCC remains below 20%. This poor survival is multifactorial but is partly related to underuse of curative treatment in clinical practice. In light of growing treatment options, delivered by different types of providers, optimal management requires input from multiple specialties. A multidisciplinary approach has been evolving over the past couple of decades, bringing different specialists together to develop a therapeutic plan to treat and manage HCC, which significantly increases timely guideline-concordant treatment and improves overall survival. The present review attempts to highlight the need for such a multimodal approach by providing insights on its potential structure and impact on the various aspects of HCC management.

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer deaths worldwide and the fastest-rising cause of cancer mortality in the United States, largely driven by an aging hepatitis C virus (HCV)-infected population and a growing number of persons with nonalcoholic steatohepatitis. Cirrhosis is the strongest risk factor for HCC, with over 90% of HCC arising in the background of cirrhosis and HCC being the leading cause of death in patients with compensated cirrhosis. 2

Early detection of HCC significantly impacts overall survival with curative treatment options available only if patients are diagnosed at an early stage.<sup>3,4</sup> However, prognosis and management decisions for HCC are more complex than many other solid tumors, given it arises in the setting of chronic liver disease, which leads to an inherent competing risk of mortality and inevitably impacts therapeutic decisions. Accordingly, the Barcelona Clinic Liver Cancer (BCLC) system—the most widely accepted HCC staging system

worldwide—includes degree of liver dysfunction and Eastern Cooperative Oncology Group (ECOG) performance status in addition to tumor burden.<sup>5</sup>

The BCLC system has also been linked to a treatment algorithm and subsequent prognosis.<sup>3,6</sup> Patients detected at an early stage (BCLC 0–A) can achieve 5-year survival exceeding 70% with curative treatments, including surgical resection, liver transplantation, and local ablation. In contrast, patients with intermediate or advanced stages (BCLC B or C) are amenable to palliative therapies such as transarterial chemoembolization (TACE), transarterial radioembolization (TARE), or systemic therapy and have a median survival of 1 to 3 years. However, there is marked heterogeneity within each BCLC stage and a single treatment strategy is not optimal for all patients, particularly after accounting for other factors such as age, comorbidities, tumor biology, patient preferences, and center expertise. These considerations highlight the need for a multidisciplinary approach

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with expertise across several disciplines to define optimal treatment choices for each individual patient.

The goal of multidisciplinary care is to review clinical data to verify HCC diagnosis and staging, facilitate provider communication, determine optimal treatments, and thereby improve clinical outcomes. The process is not only dynamic in nature based on a patient's initial HCC presentation but also continues over time with treatment strategies continually evolving based on tumor response and changes in underlying liver dysfunction. Given consistent data demonstrating improved outcomes including increased curative treatment receipt and overall survival, multidisciplinary tumor boards and clinics are increasingly regarded as the standard of care and are being adopted by many high-volume medical centers. In this review, we discuss the rationale for multidisciplinary care, its potential structures and effective ways of implementation, and data supporting improved clinical outcomes.

## **Rationale for Multidisciplinary Care in** Hepatocellular Carcinoma

Patients with HCC are a heterogeneous group as a result of having both underlying chronic liver disease and a concomitant malignancy. Treatment recommendations for HCC depend on several factors including tumor burden (number of lesions, maximum tumor diameter, and the presence of vascular invasion or distant metastases), degree of liver dysfunction (Child Pugh class and degree of portal hypertension), and patient performance status (ECOG status). Based on these factors, curative surgical therapies such as resection and liver transplantation have historically been used for early-stage disease; locoregional therapies such as TACE and TARE for intermediate-stage disease; and systemic therapies including tyrosine kinase inhibitors, monoclonal antibodies, and checkpoint inhibitors for advanced HCC. With evolution of HCC treatment options, there is increased recognition of stage migration and need for transitions between therapies as well as increasing interest in combination therapies, calling into question the validity of a "onesize-fits-all" approach to the management of HCC. This heterogeneity and complexity of treatment options highlight the need for a multidisciplinary team approach, with input from providers of appropriate specialties.

Treatment decisions for some patients are well delineated by guidelines, with likely widespread consensus among providers.<sup>3,6</sup> For example, few would debate surgical resection as treatment of an exophytic HCC in a noncirrhotic liver, liver transplantation for a patient with a Child C cirrhosis and a tumor within Milan's criteria, or systemic therapy for a patient with Child A cirrhosis and metastatic disease. However, there are several situations where the optimal treatment is less clear, for example, in a patient with unifocal HCC and mild portal hypertension, a patient with limited branch tumor thrombus, or a patient with bilobar multifocal HCC. These discussions are increasingly common in light of evolving data, suggesting curative therapies can be effectively offered to patients beyond traditional criteria. For example, liver transplantation was historically limited to patients with Milan's criteria, that is, one tumor  $\leq 5$  cm or two to three tumors, each  $\leq$  3 cm in maximum diameter; however, patients with larger tumors who have been successfully downstaged into Milan's criteria can also achieve good long-term survival, leading to a change in criteria for MELD exception points.<sup>8</sup> Surgical resection has also been historically limited to a unifocal lesion in patients with compensated cirrhosis, but recent data suggest acceptable outcomes can be achieved in patients with mild portal hypertension, limited multifocal disease, or even patients with branch tumor thrombus. 9 Similarly, interventions such as portal vein embolization and TARE can increase functional liver remnant (FLR) and allow resection in patients who are not initially eligible for resection. 10,11 In parallel with expansion of eligibility for curative therapies, there has been improvements in systemic therapy effectiveness, prompting some to advocate for consideration of systemic therapy in patients with multifocal liver-localized HCC, even in the absence of gross vascular invasion or distant metastases. A propensity-weighted analysis by Kudo and colleagues suggested improved survival with use of systemic therapy compared with TACE in patients with HCC beyond up-toseven criteria. 12 Although thought provoking, these data are nonrandomized, prone to residual confounding, and it is unclear if and what would be the optimal tumor burden threshold to consider systemic therapy instead of locoregional therapy. Appropriate patient selection in these cases is critical and must be considered in light of all treatment options. Multidisciplinary formats efficiently facilitate and promote provider communication between different specialties when evaluating and managing patients with HCC.

There is also growing interest in pursuing combination therapies across tumor stages, requiring joint management by providers from different specialties. Locoregional treatment as bridging therapy is commonly used for patients listed for liver transplantation to reduce risk of drop-out from the waiting list, but prior studies had failed to show a benefit of neoadjuvant or adjuvant therapy after resection, ablation, or TACE. However, there has now been renewed interest in this area with ongoing trials evaluating checkpoint inhibitors in combination with resection (both adjuvant and neoadjuvant), ablation, TACE, and stereotactic body radiation therapy. 13 A multidisciplinary team can help increase patient evaluation and recruitment into these clinical trials as well as care pathways when implemented in clinical practice. Multidisciplinary care can facilitate the increased coordination of treatments and communication required to effectively deliver combination treatments.

Similarly, as the number of HCC treatment options have increased, there is increased recognition of stage migration and need for transitions between therapies. These stage migrations have historically been "left to right" shifts, suggesting treatment failure; however, increasing objective response rates have also yielded potential "right to left" shifts and downstaging, allowing receipt of curative therapies in some who initially present with more advanced tumor burden. For example, patients who present beyond

Milan's criteria but within UNOS-DS criteria (i.e., BCLC stage B) can be eligible for exception points if they respond to locoregional therapy and are downstaged to within Milan's criteria. Similarly, objective response rates of approximately 25 to 30% with the introduction of atezolizumab and bevacizumab may allow some patients with advanced HCC to be downstaged for consideration of locoregional therapy. 14

With increasing complexity of treatment options, there is also increasing potential for failure in cancer care delivery. Failures in communication between providers at care transitions can result in delayed treatments, duplication of testing, or incomplete follow-up. 15 Several studies have highlighted the underuse of curative therapies for patients with HCC despite the marked survival benefit of surgical therapies compared with locoregional and systemic therapies. A systematic review of 24 studies found that pooled rates of any HCC treatment and curative treatment were 52.8 and 21.8%, respectively.<sup>16</sup> Among patients diagnosed at an early stage, curative treatment continued to be underused with only 59.0% of patients undergoing curative treatment. The authors also noted disparities in treatment receipt, with lower curative treatment utilization in racial/ethnic minorities and patients of low socioeconomic status. Studies have also highlighted variation in care and deliver of appropriate therapies between health systems, with patients seen at high-volume centers significantly more likely to undergo curative therapies, resulting in improved stage-by-stage survival.<sup>17</sup> Even among those who undergo treatment, some patients experience substantial therapeutic delays, allowing interval tumor growth and resulting in worse

survival. 18 Variations in HCC therapy likely relate to differences in referral patterns, with nearly half of patients with early-stage HCC being referred to see a medical oncologist and over one-fourth never being referred to see a surgeon.<sup>19</sup> Multidisciplinary formats such as tumor boards or co-located clinics enable treatment decisions to be more agnostic to initial referral patterns and curative therapies to be considered in all cases.

# **Models of Multidisciplinary Care**

There are different models for multidisciplinary care, ranging from a multidisciplinary tumor board to a fluid referral system between specialties to a co-located clinic. Multidisciplinary care traditionally started in the form of a tumor board, in which providers could present patients to a broad base on consultants for their consultation. Although historically tumor board presentations were performed retrospectively after patients had already been seen, there is increasing use of prospective treatment planning. In fact, the Commission on Cancer requires 15% of all patients be presented to tumor boards; of those presented, a minimum of 80% must be presented prospectively.<sup>20</sup> Although tumor boards are most often used for new HCC diagnoses, there is also increasing re-presentation when transitions between treatment strategies are being considered.

A multidisciplinary liver tumor board constitutes a core team of experts from different specialties who collaboratively evaluate and design treatment and management plans for patients with HCC (Fig. 1). The core disciplines for an HCC

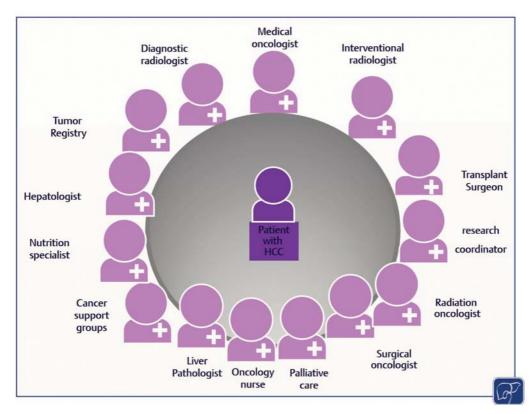


Fig. 1 Multidisciplinary liver tumor board for hepatocellular carcinoma (HCC) patients.

tumor board typically includes transplant hepatologist and surgeons, hepatobiliary surgeons, interventional radiologists, and medical oncologists. With increasing recognition of HCC subtypes as well as combined hepatocellular cholangiocarcinoma, pathologists and translational researchers may also be integrated into multidisciplinary teams. Although not routinely incorporated into an HCC multidisciplinary team, close collaborations with other disciplines such as dermatology, endocrinology, and rheumatology can be helpful for the management of complications of immune checkpoint inhibitors. The disciplines represented on tumor boards are not limited to medical specialties, as nurses, nurse navigators, social workers, and case managers also play vital roles in implementing personalized and effective treatment plans for patients. Involvement of these specialties can be particularly important for patient engagement, increasing treatment adherence, and integrating quality of life and other survivorship considerations into treatment decisions. Strong leadership of the multidisciplinary tumor board is critical to facilitate good relationships and effective communication between team members. Nontechnical skills, such as communication, and clinical expertise have been shown to be two of the key characteristics for an effective tumor board leader.<sup>21</sup> This leadership is also key to including all disciplines in treatment decisions, not having decisions dominated by a single specialty and promoting consistency of clinical decision making over time, while still allowing decisions to incorporate patient singularities and facilitate patient-centered care. Multidisciplinary tumor boards have now largely become standard of care for many cancers, including HCC, in large health systems.

With increased emphasis on multidisciplinary care and coordination, some centers have transitioned from tumor boards to a more interactive multidisciplinary care team structure that continues along the entire HCC treatment pathway. Two key elements that distinguish tumor boards from this form of multidisciplinary care are use of a true "team structure" and inclusion of patients as part of the structure. 15 The latter can be subdivided into two care models: (1) "actual" in which providers are co-located and patients can be attended concurrently by providers from multiple specialties or (2) "virtual" in which providers do not typically meet face to face but operate through a fluid referral system, in which patients can be seen sequentially or as needed by specialists from different disciplines. 15 Specialties included in multidisciplinary clinics parallel those involved in tumor boards but often includes transplant hepatologists and surgeons, hepatobiliary surgeons, interventional radiologists, and medical oncologists.

The concept of co-location places multiple specialties in the same physical space or proximity to facilitate coordination of care and cross-provider communication. Co-located clinics are also referred to as "one-stop shops," as these facilities offer a variety of services within a single practice. HCC patients seeking care from such a multidisciplinary cancer clinic benefit from tailored, collaborative treatment available in one place, and this approach dramatically reduces the stress and inconvenience associated with multiple clinic visits to physicians from different specialties. A meta-analysis examining co-located specialties in primary care, such as behavioral health, diabetes care, infectious disease, geriatrics, nephrology, and cardiology, showed colocation was associated with increased patient satisfaction and quality of life, provider satisfaction, and frequency of specialty and primary care outpatient visits.<sup>22</sup> Co-location models were also associated with reduced per-member-permonth costs for health management organizations and reduced treatment costs to the patients.

In both multidisciplinary care models, a patient coordinator typically gathers information from the patient during an initial intake process and makes appropriate referrals to each specialty. Oncology navigators can play a significant role in care delivery, as they assist with care coordination, provide disease-specific education, and ensure compliance with treatment plans established by the multidisciplinary care teams. In many circumstances, navigators serve as the initial and primary contact person for patients throughout the course of their diagnosis and treatment. Nurse navigation in cancer care has been shown to decrease time from diagnosis to treatment and increase patient satisfaction.<sup>23,24</sup>

The form of multidisciplinary care also facilitates decisions that can be more patient centered, as more team members have met the patient and can take a more holistic approach to decision making, incorporating patient preferences. Decisions that take into account patient comorbidity, performance status, and preferences are typically more clinically appropriate and better accepted by patients. To facilitate a more patient-centered approach, members of the multidisciplinary team can incorporate patient values by asking open questions regarding treatment preferences and discussing treatment options relative to patients' expressed desired outcomes. Inclusion of clinical nurses and navigators as key members of the multidisciplinary team has been shown to increase representation of the patient perspective and promote patient-centered decision making.

Barriers to implementing this type of model primarily include administrative hurdles, for example, considering the challenge of coordinating service delivery by multiple providers. Effective teams require a minimum size to cover necessary disciplines, but larger teams are more difficult to coordinate and can lead to inefficiencies and poorer team performance. As mentioned earlier, strong leadership of the multidisciplinary team is key to facilitating participation from all disciplines and avoiding the conversations being dominated by a single specialty. Although co-located cancer models improve time to treatment and patient satisfaction, they are associated with significant investment of time and finances-both for initiation as well as maintenance. Multidisciplinary tumor boards are typically noncompensated activities in both community and academic settings, and multidisciplinary clinics can create inefficiencies for providers who may see less patients than typical, resulting in lost clinical revenue. In community settings, providers from a variety of specialties may have practice locations that are geographically separated from those of their colleagues, making travel to a centralized location more difficult. In

addition to the concerns regarding clinic visit flow (i.e., sequential vs. concurrent visits with specialists), decisions about who should attend the patients during each visit present an administrative challenge. As several multidisciplinary clinics (MDCs) are incorporating the expertise of ancillary services such as nutrition, social work, and physical therapy, clinic coordinators must make important decisions about the services required for patients and their complex medical needs. Given that tumor board recommendations are typically documented in the medical record, there may be some initial concerns about legal liability, although we are not aware of any lawsuits toward members of a multidisciplinary team not directly involved in the care of a patient. Furthermore, achieving consensus among providers for optimal therapies increases quality of care and should decrease likelihood of negligent care. If consensus is not possible, documenting and discussing the different treatment options with the patient should increase patient-centric care and facilitate shared decision making, thereby increasing patient satisfaction and decreasing likelihood of litigation. Conversely, it is unclear if legal liability for a provider would be increased if he/she decides to now follow a tumor board recommendation.

## **Demonstrated Benefits of Multidisciplinary Care in Patients with Hepatocellular** Carcinoma

Beyond a theoretical rationale for multidisciplinary care, several studies have demonstrated its direct benefits in the management of HCC (►Table 1).

The first step in the management of HCC is establishing a definitive diagnosis, which can be aided by a multidisciplinary tumor board. In contrast to most other cancers, a diagnosis of HCC is typically made by characteristic radiographic cross-sectional imaging with few patients requiring histological confirmation. There has been increased adoption of the LI-RADS criteria as consistent nomenclature for communication between radiologists and clinicians. LR-5 (i.e., definite HCC) is defined by major criteria including size, arterial enhancement, delayed washout, and the presence of a pseudocapsule. 25,26 These lesions have a 97% positive predictive value for being HCC and can be treated as such without requiring a biopsy.<sup>27</sup> In contrast, LR-4 lesions (suspicious but not definite for HCC) and LR-M (worrisome for malignancy, not definitely HCC) can be HCC in 74 and 36% of cases, respectively; however, they typically require either short interval imaging or biopsy to confirm the diagnosis.<sup>27</sup> Although LI-RADS criteria can be highly accurate and improve communication, there can be concerns about inter-reader reliability and misclassification of HCC diagnoses in some cases.<sup>28,29</sup> Beyond diagnosis, radiologists play a critical role in determining intrahepatic tumor burden as well as the presence of any vascular involvement or distant metastases. This can be particularly challenging in patients with possible bland versus tumor thrombus or patients with mildly enlarged lymph nodes, which could be reactive in the setting of liver cirrhosis or early lymph node metastases. Multidisciplinary tumor boards offer a venue for imaging to be presented by radiology and discussed with other members of the multidisciplinary team. In a single-center study among

Table 1 Multidisciplinary care improves outcomes in patients with hepatocellular carcinoma

Study	Country	Period	No. of patients	Outcomes
Yopp et al <sup>32</sup>	USA	Pre: 2006–2010 Post: 2010–2011	Pre: 250 Post: 105	Shorter time to treatment Reduced stage-adjusted mortality
Serper et al <sup>33</sup>	USA	2008–2014	Total: 3,988 Multidisciplinary tumor board (MDT): 1,366 Multidisciplinary care: 2,155	Increased treatment receipt Reduced mortality
Chang et al <sup>31</sup>	USA	Pre: 2000–2003 Post: 2003–2006	Pre: 62 Post: 121	Increased treatment receipt Reduced mortality
Sinn et al <sup>34</sup>	Korea	Pre: 2000–2005 Post: 2005–2013	Pre: 5,881 Post: 738	Reduced mortality
Agarwal <sup>40</sup>	USA	Pre: 2002–2011 Post: 2007–2011	Pre: 349 Post: 306	Increased treatment receipt Reduced mortality
Gashin et al <sup>36</sup>	USA	2009–2010	137	<ul><li>Increased treatment receipt</li><li>Reduced mortality</li><li>Not following MDT decision was a negative prognostic factor</li></ul>
Duininck <sup>41</sup>	USA	Pre: 2009–2012 Post: 2013–2016	Pre: 70 Post: 134	Increased treatment receipt Reduced mortality
Zhang et al <sup>30</sup>	USA	2009–2012	343	<ul><li>Alterations to imaging and pathology</li><li>Interpretation for diagnosis</li><li>Changes in management plan</li></ul>
Charriere et al <sup>35</sup>	France	2006–2013	387	Not following MDT decision was a neg- ative prognostic factor

269 patients with malignant lesions, of whom 95 had HCC, presentation at a multidisciplinary tumor board changed imaging and histological interpretation in 18.4 and 10.9% of patients, respectively. Diagnosis and management plans were altered in 8.4 and 41.7% of patients, respectively.<sup>30</sup>

Increasing data demonstrate multiple benefits of multidisciplinary care on treatment delivery, including increased receipt of any treatment, increased receipt of curative treatments, and improved overall survival. One of the first studies to evaluate the impact of multidisciplinary care on HCC outcomes was from the San Francisco Veterans Affairs (VA) Medical Center.<sup>31</sup> The authors found a fluid referral system between health care providers increased both palliative and curative therapy delivery as well as improved overall survival. Similarly, a study by Yopp and colleagues showed similar findings in a safety-net health system, where establishment of a multidisciplinary co-located clinic involving multiple specialties paired with a multidisciplinary tumor board improved HCC-related outcomes.<sup>32</sup> Compared with patients treated previously, patients seen in the multidisciplinary clinic had increased receipt of curative treatment, shorter time to treatment, and improved stage-by-stage survival. Interestingly, both the studies by Chang et al and Yopp et al also demonstrated a higher proportion of tumors found at an early stage after establishment of the multidisciplinary programs.<sup>31,32</sup> This migration in stage may be secondary to increased provider HCC awareness, resulting in increased surveillance and earlier detection, improved diagnostic accuracy for small HCC tumors given improved radiologic expertise, or greater clinic access with reduced appointment wait times.

A multicenter study by Serper and colleagues analyzing 3,988 patients who underwent HCC treatment across 128 VA centers in the United States found receiving care at an academically affiliated VA hospital and multispecialty evaluation was associated with higher likelihood of receiving HCC therapy.<sup>33</sup> Similarly, subspecialist care by a hepatologist, medical oncologist, or surgeon within 30 days of diagnosis as well as review by a multidisciplinary tumor board were associated with reduced mortality. A singlecenter study from Seoul, Korea, among 6,619 HCC patients seen over an 8-year period similarly found improved 5-year survival in patients who were managed through a multidisciplinary team than those who were managed otherwise, including in a propensity-matched analysis (5-year survival: 71.4 vs. 58.7%).<sup>34</sup> Survival benefit of multidisciplinary care was particularly notable for patients with intermediate or advanced tumor burden (BCLC stages B or C), poor liver function (ALBI grade 2-3), or high AFP levels exceeding 200 ng/mL-subgroups in whom treatment decisions may be particularly difficult with wider variation in treatment practices.

Conversely, nonadherence to multidisciplinary tumor board recommendations may be associated with worse outcomes, although there are a multitude of patient- and provider-related reasons why this may occur in clinical practice.<sup>35</sup> In one single-center study including 419 tumor

board discussions in 137 HCC patients, nonadherence was observed for 145 recommendations in 90 patients. Patient-related reasons included missed appointments, clinical deterioration, and patient choice, whereas provider-related reasons included physician preference and provider believing the patient was not appropriate for the recommended therapy. Although these data highlight that nonadherence may be unavoidable in some cases such as clinical deterioration, they do suggest that nonadherence may be common and should be avoided when possible.

Finally, multidisciplinary care in HCC typically has high acceptance from providers and appears to improve patient satisfaction and quality of life. In a survey at the Dana Farber Cancer Institute, patients expressed high satisfaction with care coordination and convenience.<sup>37</sup> Similarly, more than 90% of providers enjoyed working in multidisciplinary clinics and over three-fourths preferred to attend new patients in this clinic setting, although one-third of physicians expressed frustration with inefficiency, particularly surgeons who felt that MDCs were not as well equipped for surgical patients' needs (e.g., surgical supplies and clinical support staff). Qualitative interviews among 18 patients presenting with advanced-stage HCC to the Philadelphia Veterans Affairs Medical found high patient satisfaction with multidisciplinary care including psychological support helping them with coping.<sup>38</sup> Similarly, members of Temple University Hospital's multidisciplinary team reported improved collaboration and collegiality after implementation of their multidisciplinary program and believe this allows patients and caregivers to obtain a clearer understanding of treatment options and the anticipated treatment pathways.<sup>39</sup> The impact of multidisciplinary care on patient satisfaction, patient's knowledge and acceptance of treatments, quality of life, and caregiver burden is an area in need of continued research.

#### Conclusion

HCC is a heterogeneous tumor with treatment decisions based on a combination of tumor burden, degree of liver dysfunction, and patient performance status. There are a wide range of potential treatment options from surgical therapies to locoregional and systemic therapy options, depending on tumor stage, requiring input from different specialties. Furthermore, increasing transitions between therapies and a growing number of trials evaluating combination therapies require close collaboration and communication between these specialties. Accordingly, multidisciplinary care has been increasingly adopted for HCC management, although it can exist in various forms including multidisciplinary tumor boards, fluid referral systems, or co-located clinics. Studies have demonstrated multidisciplinary care results in high patient satisfaction, improved receipt of timely guideline-concordant care, and increased overall survival, highlighting this should be considered standard of care for the management of HCC patients.

### **Main Concepts and Learning Points**

- · The wide range of treatment options delivered by different provider types, which must be considered at baseline as well as over time, create a strong rationale for the role of multidisciplinary care in management of patients with
- There are different potential models of multidisciplinary care including tumor boards, referral systems between specialties, and co-located clinics.
- · Studies have demonstrated multiple benefits of multidisciplinary care including increased curative treatment receipt, shorter time to treatment, and improved overall survival.

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#### **Conflicts of Interest**

Dr. Singal has served on advisory boards or consultant for Genentech, Bayer, Eisai, Exelixis, BMS, and TARGET PharmaSolutions. None of the other authors have any relevant conflicts of interest to disclose.

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