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Reena Salgia

Henry Ford Health, rsalgia1@hfhs.org

Vivek Mendiratta

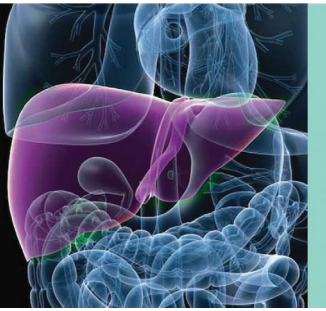
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The Multidisciplinary Management of Hepatocellular Carcinoma

Reena Salgia, and Vivek Mendiratta

Hepatocellular carcinoma (HCC) is the sixth most common cause of cancer worldwide and the third most common cause of cancer mortality.¹ The global incidence and mortality of HCC continues to rise, currently being the fastest-growing cause of cancer-related deaths in the United States.² Clinical presentation can be variable, with symptom onset often late in the disease course. As such, HCC presents a unique set of challenges in diagnosis and treatment, necessitating integration of multiple medical specialties to ensure high-quality care resulting in the best possible patient outcomes.

Approximately 90% of HCC cases arise in the background of cirrhosis, and thus gastroenterologists play a pivotal role in the initial screening process.³ Moreover, precise radiological and tissue assessment by diagnostic radiologists and pathologists often aid in diagnosis and staging. Optimal treatment for HCC is determined based on a complex interplay of factors, including tumor size, number, location, and patient characteristics, such as underlying liver function and performance status. With recent advances in liver-directed and systemic therapies, the landscape for treatment continues to evolve and increase in complexity. Therefore, determining the most effective treatment plan is often challenging, requiring

expertise in the various therapeutic modalities from a number of different specialties, including hepatology, hepatobiliary surgery, transplant surgery, radiation oncology, medical oncology, interventional radiology, and palliative care specialists, among others.⁴ Curative treatment options for HCC include liver transplantation, surgical resection, or thermal ablation for early-stage HCC.⁵ Yet nearly 70% of patients are not surgical candidates at presentation, and thus alternate treatment options must be considered.⁶ For intermediate-stage and some advanced-stage patients, these treatment modalities include locoregional treatment, such as thermal ablation, transarterial chemoembolization, transarterial radioembolization, and stereotactic body radiotherapy.⁷ These rely on the expertise of hepatobiliary surgery, interventional radiology, and radiation-oncology. Systemic therapies are most commonly used in the setting of advanced-stage HCC and often managed by medical oncologists and/or hepatologists with expertise in this area. It is common for multiple treatment modalities to be used sequentially or in concert with one another in an attempt to downstage patients for transplant eligibility or to achieve more durable responses. The best results are achieved through frequent communication among the multidisciplinary team of care providers.

Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; MDC, multidisciplinary care; MTB, multidisciplinary tumor board; OR, odds ratio.

From the Gastroenterology, Henry Ford Health System, Detroit, MI.

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The involvement of physicians of multiple disciplines has long been posited to be the most effective approach to cancer treatment in today's dynamic and complex health care landscape.⁸ The standard method of sequential cancer care with serial referrals in a stepwise process can lack efficiency with studies depicting poorer adherence and patient outcomes.⁹ Multiple different models for multidisciplinary care (MDC) exist, the most common of which is a regularly scheduled meeting where cases are briefly presented to a group of physicians of multiple disciplines with subsequent real-time review of radiology, pathology, and clinical and patient parameters relevant to treatment. These multidisciplinary tumor boards (MTBs) facilitate patient access to the expertise of multiple subspecialties in a timely and cost-effective manner (Fig. 1).⁴

Patients are commonly excluded from these discussions to ensure unbiased case review. At a time thereafter, the physician-to-patient discussion ensues regarding the group consensus treatment recommendations.¹⁰ As a result of the lack of active patient interaction with this model, close oversight and coordination of the postdiscussion care and follow-up are essential.¹¹ Evidence supporting the utility of MTBs initially began when the United Kingdom mandated tumor boards as part of national care guidelines for breast cancer in the early 2000s.¹² More recently, Freytag et al.¹³ showed that patients of 15 different tumor entities at the University of Bonn had significantly better overall survival if discussed at three or more MTBs compared with matched patients who were not discussed at any tumor boards.¹⁴ Data supporting the benefit of HCC-specific MTBs continue to evolve, with one recent study at the University of

Wisconsin showing that patients discussed at MTBs were associated with significantly improved likelihood of treatment (odds ratio [OR]: 2.80, 95% confidence interval [CI]: 1.71-4.59; $P < 0.0001$), greater median overall survival (19.1 ± 2.5 versus 7.6 ± 0.9 months; $P < 0.0001$), reduced hazard ratio (HR) for mortality (HR: 0.716, 95% CI: 0.551-0.931; $P = 0.012$), and higher likelihood to undergo liver transplantation (24% versus 14%) (Table 1).¹⁵

Similarly, Sinn et al.¹⁶ retrospectively reviewed 6619 patients with newly diagnosed HCC, of which the 738 patients discussed at MTBs had significantly higher stage-for-stage survival rates (71.2% versus 49.4% at 5 years), with an adjusted HR of 0.47 (95% CI: 0.41-0.53).¹³ The benefit of MTBs within this cohort was greatest in patients with poor liver function, intermediate or advanced Barcelona Clinic Liver Cancer stage (stage B or C), or high alpha-fetoprotein levels (≥ 200 ng/mL).¹³ Moreover, recent studies have also shown that MTB frequently leads to changes in imaging interpretation, thus impacting potential treatment recommendations. One study at the University of South Carolina showed that radiologists identified new findings in 61% of cases discussed at MTB, while Masch et al.¹⁷ showed that nearly 30% of radiology reports are discordant to tumor board radiology interpretation, of which 22% are considered major discrepancies that would change overall patient recommendations.^{16,18}

Another MDC model is a centralized group clinic model, in which patients see appropriate providers concurrently. Although a dedicated physical space would allow for optimal in-person interaction, appointments can also be held virtually to allow for timely care coordination.¹¹ This MDC model allows for a patient-centered approach in which care is unified and team oriented with long-term longitudinal follow-up through the evolution of the patient's cancer care. Moreover, patients are actively participating in the discussion of their care with such a system generally receiving more favorable reviews.^{12,17} Yopp et al.¹⁰ showed that the establishment of a multidisciplinary HCC clinic led to improved clinical outcomes, including earlier stage of tumor presentation, shorter time to treatment, and improved survival (13.2 versus 4.8 months; $P = 0.005$).¹⁸ Similarly, Chang et al.²⁰ showed that the formation of an HCC-specific multidisciplinary clinic at a Veterans Affairs (VA) improved stage-for-stage overall survival.¹⁹ Furthermore, multidisciplinary HCC care has been shown to have fewer treatment-related complications and higher rates of curative treatments.^{20,21} The far-reaching positive



FIG 1 The MDC team.

TABLE 1. IMPROVED OUTCOMES FOR PATIENTS DISCUSSED AT MTB¹⁴

Variables	MTB (N = 306)	Non-MTB (N = 349)	PValue
Multifocal disease	78 (26%)	123 (35%)	0.008
Extrahepatic disease	33 (11%)	97 (28%)	<0.0001
Rate of treatments	230 (75%)	187 (61%)	<0.0001
Survival	19.1 ± 2.5 months	7.6 ± 0.9 months	<0.0001

effects of MDC go beyond treatment benefits with studies showing a positive impact on patient satisfaction, specifically in communication and physician confidence.^{22,23} Serper et al.²² showed that receiving care at an academically affiliated Veterans Administration hospital (OR: 1.97, 95% CI: 1.60-2.41) or a multispecialist evaluation (OR: 1.60, 95% CI: 1.15-2.21) was associated with higher likelihood of receiving active HCC therapy, while review by an MTB within 30 days of HCC diagnosis was associated with reduced mortality (HR: 0.83, 95% CI: 0.77-0.90).

In today's evolving landscape with newly available cancer treatments readily available, the importance of an integrated multidisciplinary approach to HCC care is vital. Although multiple challenges to effective implementation of MDC exist, including time, workforce resources, and funding, MDC success has been depicted in resource-scarce regions. Litton et al.²³ showed successful implementation of MDC to a smaller community environment. Important factors to a successful MDC, such as administrative support, effective leadership, and team dynamics, are implementable and can bring providers across sites together through teleconferencing.

CORRESPONDENCE

Reena Salgia, Gastroenterology, Henry Ford Health System, Detroit, MI. E-mail: rsalgia1@hfhs.org

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