

HCC Management: Detection, Treatment, and Precision Medicine

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Introduction

The early detection of hepatocellular carcinoma (HCC) is of paramount importance for enhancing patient outcomes, necessitating a comprehensive strategy that encompasses risk stratification and regular surveillance, particularly for individuals at high risk such as those with chronic hepatitis B or C, or cirrhosis from any cause. This approach often involves sensitive imaging techniques like ultrasound, frequently augmented by alpha-fetoprotein (AFP) measurements, to identify the disease in its nascent stages. Current clinical management paradigms for HCC are predominantly dictated by the tumor stage, the patient's liver function status, and their overall performance status, guiding the selection of appropriate interventions. For patients diagnosed with early-stage disease, curative treatment modalities are prioritized, including surgical resection, liver transplantation, and radiofrequency ablation, offering the best chance for long-term survival and disease eradication. As the disease progresses to more advanced stages, palliative treatment options become the mainstay, such as transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and systemic therapies, including tyrosine kinase inhibitors and immunotherapy, to manage symptoms and prolong life. The growing recognition of the heterogeneity of HCC has driven an increasing emphasis on personalized treatment approaches, where therapy is tailored based on molecular profiling and the patient's response to ongoing treatment, aiming for more effective and individualized care. Surveillance strategies are particularly crucial for patients diagnosed with cirrhosis, serving as a primary method for early detection of HCC, although the sensitivity of ultrasound alone can be limited in certain scenarios. Combining ultrasound with AFP measurements has demonstrated some improvement in detection rates, but the occurrence of discordant results remains a common challenge that necessitates further investigation and refinement of diagnostic protocols. Research is actively pursuing the identification of more sensitive and specific biomarkers that can aid in the early detection of HCC, addressing the current limitations and improving diagnostic accuracy. The benefits derived from surveillance, as well as the determination of its optimal frequency, are subjects of ongoing research and are critical areas for guideline refinement to ensure the most effective patient management. Liver transplantation stands as a curative treatment for patients presenting with early-stage HCC and preserved liver function, offering the most promising avenue for long-term survival and complete disease remission. Current selection criteria, exemplified by the Milan criteria, are designed to identify suitable candidates for transplantation, yet efforts are underway to broaden these criteria to encompass a larger patient population while striving to maintain favorable treatment outcomes. The intricate management of HCC within the context of liver transplantation involves meticulous staging of the disease and the implementation of bridging therapies to prevent tumor progression while the patient awaits a suitable donor organ. Surgical resection continues

to be a foundational treatment for early-stage HCC in patients possessing adequate liver reserve, with the primary objective being the complete removal of the tumor while ensuring clear surgical margins to minimize the risk of recurrence. Preoperative assessment of liver function, utilizing metrics such as indocyanine green retention and liver stiffness measurements, is indispensable for predicting postoperative outcomes and mitigating the potential risk of liver failure, a critical consideration in surgical planning. Recurrence of HCC following surgical resection is a relatively common occurrence, underscoring the necessity for lifelong surveillance protocols to monitor for any signs of disease reappearance and to intervene promptly if necessary, thereby optimizing long-term patient management. Radiofrequency ablation (RFA) and microwave ablation (MWA) represent effective minimally invasive therapeutic options for early-stage HCC, particularly beneficial for smaller tumors or for patients who are not candidates for surgical intervention. These loco-regional therapies function by ablating the tumor tissue through the application of heat generated by radiofrequency or microwave energy, offering a less invasive alternative to traditional surgical methods. The efficacy of RFA and MWA has been shown to be comparable to that of resection and transplantation for carefully selected patients, providing significant advantages in terms of reduced invasiveness and a generally faster recovery period, enhancing the patient's quality of life post-treatment. In the management of intermediate-stage HCC, transarterial chemoembolization (TACE) remains a well-established and standard treatment option, demonstrating significant clinical utility in this patient group. TACE operates by delivering chemotherapeutic agents and embolic materials directly into the tumor vasculature via the hepatic artery, effectively starving the tumor of its blood supply and delivering a high concentration of chemotherapy precisely where it is needed most. Its efficacy in prolonging survival and facilitating tumor downstaging for potential resection or transplantation is well-documented, making it a critical component of the treatment algorithm for many HCC patients. Various TACE techniques and combinations of chemotherapeutic agents are continually being evaluated and refined to optimize treatment outcomes and address potential limitations, reflecting the dynamic nature of oncological treatment strategies. Systemic therapy for advanced HCC has undergone substantial evolution, marked by the introduction of targeted agents and novel immunotherapeutic approaches, significantly expanding the treatment armamentarium. Tyrosine kinase inhibitors (TKIs), such as sorafenib and lenvatinib, have consistently demonstrated improvements in overall survival, establishing themselves as important therapeutic options for patients with advanced disease. More recently, immune checkpoint inhibitors (ICIs), particularly when administered in combination with anti-angiogenic agents, have emerged as a frontline treatment modality, offering enhanced response rates and improved progression-free survival for a select group of patients, thereby revolutionizing the treatment landscape for advanced HCC. Biomarker-driven selection of therapy is a rapidly advancing area of interest, promising to further refine treatment strategies and personalize care for individual patients, leading to more

effective and targeted interventions. The role of biomarkers in the comprehensive management of HCC is progressively expanding beyond the traditional use of AFP, with ongoing investigations into novel markers for enhanced early detection, more accurate risk stratification, improved prediction of treatment response, and more effective monitoring for recurrence. These emerging biomarkers encompass a diverse range, including microRNAs, circulating tumor DNA, and sophisticated proteomic signatures, each offering unique insights into the disease's biology and progression. The integration of these advanced biomarkers into routine clinical practice holds substantial promise for enabling more personalized and ultimately more effective care for individuals affected by HCC, optimizing treatment outcomes and improving patient prognoses. Despite significant advancements in diagnostic and therapeutic strategies, several challenges persist in the effective management of HCC, including inherent diagnostic limitations in accurately distinguishing HCC from benign regenerative nodules, the complex management of HCC in patients with coexisting liver diseases, and the development of resistance to various therapeutic interventions, posing ongoing clinical hurdles. The implementation of multidisciplinary team management, which involves the collaborative efforts of hepatologists, surgeons, oncologists, radiologists, and pathologists, is absolutely essential for ensuring optimal patient care and facilitating informed, evidence-based decision-making, thereby enhancing the overall quality of care provided to HCC patients. The landscape of hepatocellular carcinoma management continues its dynamic evolution, characterized by persistent research efforts directed towards the development of improved surveillance tools, the discovery and implementation of novel therapeutic agents, and the sophisticated personalization of treatment strategies to meet the unique needs of each patient. Precision medicine approaches, which integrate comprehensive genomic and proteomic data, are anticipated to play an increasingly pivotal role in the future of HCC treatment, enabling the tailoring of therapies to individual patients based on their specific molecular profiles, with the ultimate goal of significantly improving survival rates and enhancing the overall quality of life for those affected by this challenging disease.

Description

The early detection of hepatocellular carcinoma (HCC) is crucial for improving patient outcomes, and this is achieved through a multi-faceted approach involving risk stratification and regular surveillance in high-risk individuals, such as those with chronic hepatitis B or C, or cirrhosis from any cause. The utilization of sensitive imaging techniques like ultrasound, often complemented by alpha-fetoprotein (AFP) measurements, plays a key role in identifying the disease at its earliest stages. Current clinical management strategies for HCC are largely guided by the tumor stage, liver function, and patient performance status, dictating the course of treatment. For individuals with early-stage disease, curative treatments including surgical resection, liver transplantation, and radiofrequency ablation are the preferred options. As the disease progresses, palliative approaches such as transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and systemic therapies like tyrosine kinase inhibitors and immunotherapy become the primary modes of treatment. The trend towards personalized approaches is gaining momentum, with treatment decisions being increasingly tailored based on molecular profiling and response to therapy, aiming for more effective patient care. Surveillance strategies are particularly vital for patients with cirrhosis, serving as a primary modality for the early detection of HCC, although the sensitivity of ultrasound alone can be a limiting factor in some instances. The combination of ultrasound with AFP measurement has shown some enhancement in detection rates, yet discordant results are common, highlighting the need for ongoing research and refinement. Efforts are actively underway to identify more sensitive and specific biomarkers for the early detection of HCC, aiming to overcome the current diagnostic limitations and improve accuracy. The benefits derived from

surveillance, along with the determination of its optimal frequency, remain subjects of active research and are critical for the refinement of clinical guidelines to ensure optimal patient management. Liver transplantation represents a curative treatment option for patients with early-stage HCC and preserved liver function, offering the best potential for long-term survival and complete disease eradication. Current selection criteria, such as the Milan criteria, are employed to identify suitable candidates for transplantation, though initiatives are being made to expand these criteria to include more patients while maintaining good outcomes. The management of HCC in the context of liver transplantation is complex, requiring careful staging and the application of bridging therapies to prevent tumor progression while awaiting a donor organ. Surgical resection remains a cornerstone in the management of early-stage HCC for patients with adequate liver reserve, with the primary goal being complete tumor removal with clear margins to minimize recurrence. Preoperative assessment of liver function, including parameters like indocyanine green retention and liver stiffness measurements, is critical for predicting postoperative outcomes and reducing the risk of liver failure. Recurrence after surgical resection is a common event, necessitating lifelong surveillance to monitor for disease progression. Radiofrequency ablation (RFA) and microwave ablation (MWA) are effective minimally invasive treatments for early-stage HCC, particularly suited for smaller tumors or patients unsuitable for surgery. These loco-regional therapies aim to ablate tumor tissue using heat generated by radiofrequency or microwave energy, offering comparable efficacy to resection and transplantation for selected patients with advantages in reduced invasiveness and faster recovery. For intermediate-stage HCC, transarterial chemoembolization (TACE) remains a standard treatment, delivering chemotherapeutic agents and embolic materials directly to the tumor via the hepatic artery to starve it of blood supply and deliver high chemotherapy concentrations. Its efficacy in prolonging survival and enabling downstaging for potential resection or transplantation is well-established, with ongoing evaluation of various TACE techniques and agent combinations. Systemic therapy for advanced HCC has advanced significantly with targeted agents and immunotherapy; tyrosine kinase inhibitors (TKIs) like sorafenib and lenvatinib have shown survival benefits. More recently, immune checkpoint inhibitors (ICIs), often combined with anti-angiogenic agents, are a first-line option, improving response rates and progression-free survival for some patients, with biomarker-driven therapy selection being a key area of development. The role of biomarkers in HCC management is expanding beyond AFP, with research focused on novel markers for early detection, risk stratification, treatment response prediction, and recurrence monitoring, including microRNAs, circulating tumor DNA, and proteomic signatures. Integrating these biomarkers into clinical practice promises more personalized and effective HCC care. Despite advances, challenges persist in HCC management, including diagnostic limitations in distinguishing HCC from regenerative nodules, managing HCC in patients with coexisting liver disease, and overcoming treatment resistance. Multidisciplinary team management, involving hepatologists, surgeons, oncologists, radiologists, and pathologists, is essential for optimal patient care and decision-making. The management of hepatocellular carcinoma continues to evolve, with ongoing research focused on improved surveillance tools, novel therapeutic agents, and personalized treatment strategies. Precision medicine approaches, incorporating genomic and proteomic data, are expected to play an increasingly important role in tailoring treatment to individual patients, ultimately aiming to improve survival rates and quality of life.

Conclusion

Hepatocellular carcinoma (HCC) management emphasizes early detection through risk stratification and surveillance, employing tools like ultrasound and AFP. Treatment strategies vary based on disease stage, with curative options for early stages (resection, transplantation, ablation) and palliative measures for advanced stages

(TACE, systemic therapies). Personalized medicine, guided by molecular profiling, is becoming increasingly important. Biomarkers beyond AFP are being explored for better detection, prognostication, and treatment response prediction. Challenges include diagnostic accuracy and treatment resistance, necessitating multidisciplinary team approaches. Ongoing research aims to improve surveillance, develop novel therapies, and implement precision medicine for better patient outcomes.

Acknowledgement

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Conflict of Interest

None.

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