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Review

Comprehensive Management of Hepatocellular Carcinoma: A Review of Current Surgical, Locoregional, and Systemic Therapies

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ABSTRACT

The most frequent primary liver cancer is called hepatocellular carcinoma (HCC), which presents serious clinical difficulties because of its aggressiveness and frequently late-stage diagnosis. A significant health burden in Egypt is associated with hepatitis C virus (HCV) infection, which is highly prevalent. Liver resection and liver transplantation are two possibilities for curative treatment; each has advantages and disadvantages of its own. For tiny tumors, local ablative therapies including cryoablation, microwave ablation, and radiofrequency ablation (RFA) work well. Systemic therapies including sorafenib, lenvatinib, and immunotherapy are essential for advanced stages of HCC, while locoregional therapies, such as transarterial chemoembolization (TACE) and transarterial radioembolization (TARE), target intermediate-stage HCC. Novel approaches, like gene therapy and combination medicines, demonstrate the

continuous progress in HCC treatment. In order to improve patient outcomes, effective therapy requires a multidisciplinary strategy that includes supportive and palliative care. Improving prognosis requires early discovery using diagnostic imaging and biomarkers, as well as screening programs. In order to maximize HCC management and patient care, it is crucial to comprehend the intricate interactions between staging systems, prognostic variables, and therapeutic modalities.

Keywords: Hepatocellular carcinoma, Liver resection, Transarterial chemoembolization and Immunotherapy.

1. Introduction

1.1. Hepatocellular Carcinoma

The most prevalent primary liver cancer, known as hepatocellular carcinoma (HCC), develops from hepatocytes, the basic liver function cells (1). It usually occurs in the context of cirrhosis and chronic liver disease, and because of its aggressive character and frequent late-stage detection, it poses a serious treatment challenge (2). A significant amount of liver cancer instances worldwide are HCC cases, which are particularly common in Egypt and other specific regions (3).

Egypt is home to one of the highest frequencies of HCC in the world, making the disease a major health burden there (4). The high frequency of hepatitis C virus (HCV) infection is primarily responsible for this high incidence (5). About 70–80% of instances of liver cancer in Egypt are liver cancers (6). Over the past few decades, Egypt has seen an increase in the prevalence of HCC; according to recent studies, there are roughly 21.9 instances of the disease per 100,000 people year for men and 10.2 cases per 100,000 people annually for women (5). The higher rates of HCC in the region are largely caused by the high prevalence of HCV, especially genotype 4, as well as additional risk factors such as hepatitis B virus (HBV) infection and aflatoxin exposure (3).

1.2. Etiology and Risk Factors

The majority of instances globally are caused by chronic infections with hepatitis viruses, specifically HCV and HBV, which are the main etiological causes of HCC (7). Because of Egypt's historically high prevalence of HCV infection from previous risky medical practices, chronic HCV infection is the main risk factor for HCC in Egypt (8). The development of HCC is

also greatly influenced by chronic HBV infection, especially in areas where HBV is endemic (8). Aflatoxin exposure (mycotoxins produced by Aspergillus species present in contaminated food supplies), non-alcoholic fatty liver disease (NAFLD), chronic alcohol usage, and specific genetic abnormalities are additional etiological factors (9).

Liver cirrhosis, irrespective of the cause, is a risk factor for HCC because it fosters a carcinogenic environment (10). Although chronic alcohol consumption is less common in Egypt than viral hepatitis, it can induce liver cirrhosis, which can lead to HCC (11). Metabolic syndrome, diabetes, and obesity-related NAFLD are becoming a major risk factor for HCC (12). Diabetes and obesity alone, as well as genetic and metabolic conditions including hemochromatosis and alpha-1 antitrypsin deficiency, raise the risk of HCC (9). The risk of HCC is further increased by lifestyle choices like smoking and exposure to specific chemicals and poisons in the workplace and environment, such as thorium dioxide and vinyl chloride (13).

1.3. Importance of Early Detection and Diagnosis

Because early-stage HCC is more responsive to potentially curative treatments such as surgical resection, liver transplantation, and local ablative therapy, early detection and diagnosis of HCC are essential for improving patient outcomes (14). Early detection of the disease improves the prognosis for HCC, underscoring the significance of routine screening and surveillance in high-risk populations (15).

For high-risk patients, such as those with cirrhosis, chronic HBV or HCV infection, and other predisposing factors, screening programs for HCC are advised (16). Every six months, an abdominal ultrasound and an alpha-fetoprotein (AFP) level assessment is part of routine screening (17). One commonly available, non-invasive, and reasonably priced screening method is abdominal ultrasonography (18). Serum biomarker AFP is frequently raised in HCC patients; however, due to its weak sensitivity and specificity, elevated levels of this biomarker require additional diagnostic confirmation (19).

1.4. Diagnostic Imaging and Biomarkers

Additional diagnostic imaging is required to describe a lesion found during screening and validate the diagnosis of HCC (20). Comprehensive imaging of liver abnormalities can be obtained by multiphasic computed tomography (CT) scans, which include arterial and venous phases. HCC usually exhibits arterial phase amplification and venous phase washout (21). HCC can be distinguished from other liver lesions using magnetic resonance imaging (MRI), which is

very sensitive and specific for the condition when liver-specific contrast agents are used (22). Contrast-enhanced ultrasonography (CEUS) helps characterize HCC by providing a real-time assessment of lesion vascularity, which improves the diagnostic potential of traditional ultrasound (23).

In addition to AFP, several biomarkers and molecular tests are being investigated for the diagnosis and prognosis of HCC (24). PIVKA-II, also known as des-gamma-carboxy prothrombin (DCP), is another serum biomarker linked to HCC that is utilized in conjunction with AFP to increase diagnostic precision (25). Research is being done on Glypican-3 (GPC3), a cell surface proteoglycan that is overexpressed in HCC, as a possible target for diagnosis and treatment (26). As non-invasive biomarkers for early identification and prognosis, microRNAs (miRNAs) exhibit variable expression in HCC (27). By examining circulating tumor DNA (ctDNA) and other blood components, liquid biopsy techniques provide a potential means of detecting and tracking HCC early on (28).

Improving patient outcomes requires an understanding of the epidemiology, etiology, and risk factors of HCC as well as the value of early detection and the resources available for screening and diagnosis (1). A key component of managing this difficult disease is the implementation of focused screening programs, along with advancements in diagnostic imaging and biomarkers, particularly in places such as Egypt where the incidence of HCC is very high (5). The study aims to offer a guide for doctors to different HCC therapies to achieve maximum effectiveness while minimizing adverse events.

2. Methods

This study focuses on a thorough examination of hepatocellular carcinoma (HCC), covering a range of clinical circumstances and patient demographics. Important patient populations are individuals with cirrhosis, non-alcoholic fatty liver disease (NAFLD), hepatitis C and hepatitis B virus (HBV) infections, and HCC diagnosed at various stages, from early to advanced. The review focuses on individuals from areas with high incidence of HCC, especially Egypt, where the prevalence of HCV is the main cause of the country's significant liver cancer burden.

2.1. Literature Search and Selection Criteria: Using databases including PubMed, Scopus, and Web of Science, a comprehensive literature search was carried out to find pertinent papers, clinical trials, and reviews on HCC. The keywords included "hepatocellular carcinoma", "liver resection", "liver transplantation", "local ablative therapies", "transarterial chemoembolization",

"transarterial radioembolization", "systemic therapies", "immunotherapy", "early detection", "screening programs", along with "diagnostic imaging." From 2000 to 2024, English-language articles were taken into consideration. Studies that provided information on treatment plans, indications, results, benefits, drawbacks, and prognostic factors were the main emphasis of the inclusion criteria. Case reports, small cohort studies with fewer than ten patients, and studies without well-defined outcome measures were among the exclusion criteria.

2.2. Data Extraction and Synthesis: Patient demographics, disease stage, treatment modalities, results, and complications were all collected from the data. Data on different approaches to treatment were divided into four categories: systemic therapies, locoregional therapies, local ablative therapies, and surgical techniques. Indications, benefits, drawbacks, and precise usage guidelines were covered in detail for each category. A summary of innovative and experimental treatments, the function of interdisciplinary teams, and supportive care was also provided.

2.3. Evaluation of Early Detection and Diagnostic Methods: The review evaluated the significance of using biomarkers and diagnostic imaging along with screening programs to achieve early detection and diagnosis. The usefulness of abdominal ultrasonography, AFP levels, CT, MRI, CEUS, and other newly discovered biomarkers was assessed in pertinent research.

2.4. Staging Systems and Prognostic Factors: Various staging systems were assessed, such as the Child-Pugh score, the Tumor-Node-Metastasis (TNM) staging system, and the Barcelona Clinic Liver Cancer (BCLC) staging system. In order to comprehend their influence on patient outcomes and treatment choices, prognostic parameters including tumor size, number, vascular invasion, liver function, performance status, alpha-fetoprotein (AFP) levels, genetic and molecular markers, and therapy response were studied.

2.5. Multidisciplinary Approach and Supportive Care: The review emphasized the importance of managing HCC through a multidisciplinary strategy combining surgeons, radiologists, oncologists, hepatologists, and pathologists. The improvement of HCC patients' quality of life through supportive and palliative care—which includes symptom management techniques, nutritional assistance, psychiatric counseling, and social support—was also covered. This review attempts to provide a thorough overview of current and new treatment techniques for HCC by combining data from a wide range of sources. It emphasizes the significance of early identification, precise staging, and a multidisciplinary approach to enhance patient outcomes.

3. Staging Systems and Prognostic Factors

3.1. Staging Systems

HCC staging systems are essential for directing therapy choices, forecasting results, and standardizing patient care. There are several widely used staging systems, and they all take into account different clinical and pathological aspects (29).

The widely used Barcelona Clinic Liver Cancer (BCLC) staging system incorporates liver function, performance status, tumor features, and available treatments (30). Very early (stage 0), early (stage A), intermediate (stage B), advanced (stage C), and end-stage (stage D) are the five stages into which HCC is classified. Treatment recommendations vary depending on the stage of the disease; in the early stages, curative treatments such as liver transplantation and resection are recommended, while in the later stages, palliative care is recommended (31).

The American Joint Committee on Cancer (AJCC)-endorsed Tumor-Node-Metastasis (TNM) staging system uses the size of the main tumor (T), the involvement of regional lymph nodes (N), and the existence of distant metastases (M) to classify hepatocellular carcinoma (HCC). The main applications of this technology are prognostication and decision-making in surgery. The T component measures vascular invasion, tumor size and quantity, lymph node involvement, and distant metastases; the N component takes these factors into account (32).

The Child-Pugh score evaluates liver function and aids in determining prognosis and treatment options, even though it is not a staging system for HCC in and of itself. Bilirubin, albumin, prothrombin time, ascites, and hepatic encephalopathy are the five parameters that are assessed. Child-Pugh grades A, B, or C correspond to well-compensated disease, substantial functional compromise, and decompensated disease, respectively, in patients (33).

The Cancer of the Liver Italian Program (CLIP) score integrates tumor morphology, Child-Pugh stage, AFP levels, and portal vein thrombosis. Other staging systems include the Okuda staging system, which takes into account tumor size, ascites, serum albumin, and bilirubin levels. The Japanese Integrated Staging (JIS) score combines the Child-Pugh classification with TNM staging (34).

3.2. Prognostic Factors

To forecast patient outcomes and customize treatment regimens, prognostic variables for HCC are crucial. Tumor features, liver function, performance status, AFP levels, genetic and

molecular markers, cirrhosis presence, treatment response, extrahepatic dissemination, and nutritional status are important prognostic variables (34).

Tumor features that are important to consider include size, number, and vascular invasion. A worse prognosis is linked to larger tumors, numerous nodules, and macrovascular invasion (involvement of the hepatic or portal veins) (35). Poorly differentiated tumors also indicate a more aggressive disease course. Liver function has a major influence on prognosis; worse outcomes are correlated with worse liver function, as measured by the Child-Pugh score and the more recent Albumin-Bilirubin (ALBI) grade (36).

Another important prognostic marker is performance status, which is determined by the Eastern Cooperative Oncology Group (ECOG) performance status scale. Reduced functional status, as indicated by higher ECOG values, is linked to a worse prognosis. Alpha-fetoprotein (AFP) values above 400 ng/mL are associated with worse outcomes and more aggressive illness (37). Furthermore, prognosis and treatment outcomes are influenced by particular genetic mutations and molecular markers, such as those found in the TP53, CTNNB1, and TERT promoter genes (38).

The prognosis is greatly impacted by the existence and severity of cirrhosis since it might restrict available treatments and raise the risk of liver failure (31). Long-term results and overall survival are also influenced by the patient's reaction to initial treatment techniques, such as resection, ablation, TACE, or systemic therapy (39). The prognosis is considerably worsened and treatment choices are limited in cases of extrahepatic dissemination, or metastasis to other organs (40).

Lastly, poorer outcomes for HCC patients are linked to nutritional status, which includes elements like malnutrition and sarcopenia (loss of muscle mass). To effectively care for and manage patients with HCC, doctors must have a thorough understanding of these prognostic markers. This knowledge will enable them to make well-informed judgments about treatment plans and make accurate patient outcome predictions (41).

4. Curative Treatment Options (Surgical Interventions)

4.1. Liver Resection: For individuals with early-stage HCC who have preserved liver function and no appreciable portal hypertension, liver resection is the main curative procedure (31). Liver resection is indicated when there is just one tumor, no significant vascular invasion,

and sufficient residual liver after surgery (42). Liver resection techniques range from non-anatomical resections, which preserve more liver tissue but are less accurate, to anatomical resections, which adhere to the liver's normal segmental structure (43). The size of the tumor, the existence of cirrhosis, and the underlying liver function all have a major impact on the outcome of liver resection (42). Although 5-year survival rates of 50–70% after surgical excision suggest potentially curative outcomes, recurrence rates are still substantial, requiring continuous postoperative surveillance and maybe adjuvant therapy (44).

4.2. Liver Transplantation: For HCC patients with early-stage tumors and advanced cirrhosis, liver transplantation is thought to be the only effective curative treatment that can treat both the tumor and the underlying liver disease (45). Candidates are often chosen using the Milan criteria, which stipulate that patients must have a single tumor measuring ≤5 cm or up to three nodules, each measuring ≤3 cm, free of extrahepatic dissemination or vascular invasion (46). Living donors are frequently transplanted to shorten waiting periods. Donor selection involves either deceased or living donors (47). Immunosuppressive medication to stop rejection, frequent recurrence monitoring, and problem management are all part of post-operative care. Liver transplant results are generally good, with 5-year survival rates above 70%; nonetheless, immunosuppressive effects and the possibility of recurrence continue to be major risks (48).

5. Local Ablative Therapies

5.1. Radiofrequency Ablation (RFA): Using high-frequency electrical currents, radiofrequency ablation (RFA) produces heat that kills cancer cells (49). Patients who are not candidates for surgery and have small tumors (usually less than 3 cm) may benefit from it. RFA is carried out via open surgery, laparoscopic, or percutaneous methods, under the guidance of imaging modalities like CT or ultrasound (50). When it comes to early-stage HCC, RFA is quite successful. Its local control rates are similar to those of surgical resection for tiny tumors, and it has fewer side effects (51).

5.2. Microwave Ablation (MWA): Similar to RFA, Microwave Ablation (MWA) produces heat using microwave energy, enabling quicker and more even heating. MWA provides a wider ablation zone and is useful for treating bigger tumors up to 5 cm in size. It has a low risk of complications and a good rate of local control when done percutaneously under imaging guidance (52).

5.3. Cryoablation: Using cryoprobes that circulate argon gas, tumor tissue is frozen during the cryoablation process. This method creates ice crystals and causes vascular damage to cause cell death. Larger lesions can be treated using cryoablation, which is useful for cancers that respond less well to heat-based treatments. On the other hand, there is an increased chance of problems like bleeding and harm to nearby structures (53).

5.4. Percutaneous Ethanol Injection (PEI): By directly injecting ethanol into the tumor to cause coagulative necrosis, a procedure known as percutaneous ethanol injection (PEI) is used. PEI is less frequently used these days since more sophisticated ablation procedures are available, and it is best suited for tiny tumors (<3 cm). In environments with limited resources, it is still a cost-effective choice, although its recurrence rate is higher than that of RFA and MWA (53).

6. Locoregional Therapies

6.1. Transarterial Chemoembolization (TACE): When patients with intermediate-stage HCC are not candidates for curative therapy, TACE, is recommended. Chemotherapeutic drugs are infused selectively into the hepatic artery, causing ischemia and cytotoxicity inside the tumor, before embolic particles are injected. Chemotherapy is released continuously with the help of drug-eluting beads (DEB-TACE), which also lessen systemic toxicity (54).

Patients with intermediate-stage HCC have longer median survival periods (26–40 months) after receiving TACE. Post-embolization syndrome (fever, discomfort, nausea), liver malfunction, and infrequently, more serious side effects such as liver abscess or biliary damage are common consequences (55).

6.2. Transarterial Radioembolization (TARE) / Selective Internal Radiation Therapy (SIRT): By injecting radioactive microspheres—typically Yttrium-90—directly into the hepatic artery that supplies the tumor, transarterial radioembolization (TARE)/selective internal radiation therapy (SIRT) provides targeted radiation therapy. This method spares the surrounding liver parenchyma while specifically irradiating the tumor tissue. Patients with portal vein thrombosis, for whom TACE is contraindicated, benefit most from it (56).

TARE has shown effective in both palliating advanced cases and downstaging malignancies to enable curative treatments. When compared to traditional medicines, it has a lower systemic toxicity and a better safety profile. On the other hand, dangers include exposure to non-target radiation and liver damage brought on by radiation (57).

6.3. Stereotactic Body Radiotherapy (SBRT): High-dose radiation is precisely delivered to the tumor via stereotactic body radiotherapy (SBRT), sparing the surrounding healthy tissue SBRT has a high local control rate and is recommended for individuals with tiny, localized tumors who are not candidates for surgery or ablation. Studies show 70–90% local control rates after two years, which makes it a useful substitute for some patients (58).

Patients with impaired liver function can benefit from SBRT because it is a non-invasive treatment with fewer procedural hazards than TACE and TARE. Nevertheless, it calls for specific tools and knowledge (56).

7. Systemic Therapies

7.1. Molecular Targeted Therapies

7.1.1. Sorafenib: As a multi-kinase inhibitor, sorafenib inhibits the growth and angiogenesis of tumors by targeting the Vascular endothelial growth factor (VEGFR), Platelet-derived growth factor receptors (PDGFR), and Rapidly Accelerated Fibrosarcoma (RAF) kinase pathways. Medicated for advanced HCC, sorafenib has tolerable side effects and increases median survival above placebo by almost three months (59).

7.1.2. Lenvatinib: Another multi-kinase inhibitor that targets Fibroblast growth factor receptors (FGFR), VEGFR, and other pathways is called lentinanib. With varying safety profiles, lenvatinib has demonstrated non-inferiority to sorafenib in terms of overall survival and has been approved for use as the first-line treatment of advanced HCC (60).

7.1.3. Regorafenib: After sorafenib, regorafenib is used as second-line therapy. It inhibits several kinases that are involved in angiogenesis and tumor growth. In individuals who respond well to sorafenib, it increases survival. In advanced HCC, further Tyrosine kinase inhibitors (TKIs) such as cabozantinib and ramucirumab are also beneficial (61).

7.2. Immunotherapy

7.2.1. Immune Checkpoint Inhibitors: Pembrolizumab and nivolumab, for example, prevent PD-1/PD-L1 interactions and hence boost the body's defenses against cancer. Following sorafenib failure, they are approved for advanced HCC and, in a subgroup of patients, provide lasting responses (62).

7.2.2. Combination Therapies: In first-line treatment, the anti-PD-L1 antibody atezolizumab and the anti-VEGF antibody bevacizumab have shown improved efficacy over sorafenib, improving overall survival and progression.-free existence (63).

7.2.3. Chemotherapy: Because HCC is generally resistant to cytotoxic drugs, its effectiveness is limited. Still, some regimens like FOLinic acid, Fluorouracil, and OXaliplatin (FOLFOX) might be applied in particular circumstances. Clinical studies are more likely to employ chemotherapy in conjunction with other treatments (64).

8. Combination Therapies

8.1. Combining Systemic and Locoregional Treatments: There are benefits to combining locoregional therapies (like TACE, and TARE) and systemic therapies (such as TKIs, and immunotherapies), such as increased survival and synergistic effects on tumor control. Clinical data demonstrates that certain combinations enhance patient outcomes (65).

8.2. Gene Therapy and Precision Medicine: Through the customization of medicines to specific tumor features and genetic abnormalities, personalized treatment techniques are made possible by advancements in genetic and molecular profiling. Although still in its preliminary stages, gene therapy may be able to specifically address the genetic flaws that cause HCC (66).

8.3. Multidisciplinary Approach and Supportive Care: A multidisciplinary strategy combining hepatologists, oncologists, radiologists, surgeons, and pathologists is necessary for the effective care of HCC. This cooperative endeavor guarantees all-encompassing care, encompassing diagnosis, treatment planning, and follow-up (67).

8.4. Supportive and Palliative Care: The goals of supportive and palliative care are to enhance quality of life while controlling symptoms and therapeutic adverse effects. This addresses the patients' complete requirements and includes pain management, dietary assistance, psychiatric therapy, and social support (68). Table 1 shows different treatment modalities for HCC patients.

Table 1: Treatment Modalities

Treatment	Mechanism
Surgical Resection	For patients with early-stage HCC and well-preserved liver function, surgical resection may be considered. This involves the removal of the tumor and part of the surrounding healthy tissue.
Liver Transplantation	Liver transplantation is a curative option for individuals with HCC and cirrhosis who meet specific criteria. This approach addresses both the cancer and the underlying liver disease.
Ablation Therapy	Ablation techniques, such as radiofrequency ablation, microwave ablation, and ethanol injection, are used to destroy cancerous tissue. These minimally invasive procedures are suitable for small tumors and are often employed in patients who are not candidates for surgery.
TACE	TACE involves the injection of chemotherapy drugs directly into the blood vessels supplying the tumor, followed by the embolization of these vessels to cut off the tumor's blood supply. TACE is commonly used for intermediate-stage HCC.
Targeted Therapies	Several targeted therapies have been developed to inhibit specific molecular pathways involved in HCC progression. Sorafenib and lenvatinib are examples of oral tyrosine kinase inhibitors approved for the treatment of advanced HCC.
Immunotherapy	Immunotherapy, particularly immune checkpoint inhibitors like nivolumab and pembrolizumab, has shown promise in the treatment of advanced HCC. These drugs aim to enhance the body's immune response against cancer cells.
Systemic Chemotherapy	While systemic chemotherapy has limited efficacy in HCC, some chemotherapy agents, such as doxorubicin and cisplatin, may be used in certain cases, especially for patients with advanced disease who do not respond to other treatments.
Radiation Therapy	External beam radiation therapy or stereotactic body radiation therapy may be employed to target HCC tumors. This is often considered for patients with localized disease who are not candidates for surgery or ablation.
Supportive Care	Given the impact of HCC on liver function and the overall health of the patient, supportive care is crucial. This includes measures to manage symptoms, maintain nutritional support, and address complications such as ascites and hepatic encephalopathy.
Palliative Care	In cases where the cancer is advanced and curative options are not feasible, palliative care focuses on improving the quality of life, managing symptoms, and providing emotional support.

Abbreviations: HCC: Hepatocellular carcinoma, TACE: Trans arterial chemoembolization

9. Results

9.1. Surgical Interventions

9.1.1. Liver Resection: For individuals with early-stage HCC who have intact liver function and no appreciable portal hypertension, liver resection is still the recommended course of

treatment (42). Several studies show that these patients have 5-year survival rates ranging from 50% to 70%. Nevertheless, recurrence rates are significant, frequently over 70%, requiring close postoperative monitoring and maybe additional operations like repeat resections, local ablative therapies, or systemic treatments (69–71).

9.1.2. Liver Transplantation: By treating both the malignancy and underlying cirrhosis, liver transplantation offers curative potential, especially for individuals who meet the Milan criteria (a single tumor ≤5 cm or up to three nodules each ≤3 cm, without vascular involvement or extrahepatic dissemination) (46). Five-year survival rates after transplantation are good, approaching 70%. The scarcity of donor organs and the requirement for medication for the rest of one's life, which entails the risk of infection and organ rejection, are obstacles (72).

9.2. Local Ablative Therapies

9.2.1. Radiofrequency Ablation (RFA): Small HCC tumors (usually ≤3 cm) respond well to RFA, which has lower morbidity and comparable local control rates to surgical excisionIt is a less intrusive choice appropriate for individuals who are not surgical candidates. However, larger tumors and those that are close to important structures like huge blood veins lose some of their efficacy (73).

9.2.2. Microwave Ablation (MWA): Compared to RFA, MWA treats tumors up to 5 cm with a wider and more consistent ablation zone since it generates heat using microwave energy. It is appropriate for deeper tumors where RFA may be less effective due to its high local control rates and low complication rates (52).

9.2.3. Cryoablation: Freezing tumor tissue is known as cryoablation, and it is especially helpful for tumors that do not respond well to heat-based treatments. Larger lesions can be treated with it, but there is a higher chance of consequences like bleeding and tissue damage (53).

9.2.4. Percutaneous Ethanol Injection (PEI): Small tumors (less than 3 cm) respond well to PEI, which involves injecting ethanol directly into the tumor to cause necrosis. Concerning its higher recurrence rates, more sophisticated treatments have mostly superseded it despite its cost-effectiveness, however, it is still applicable in situations with low resources (74).

9.3. Locoregional Therapies

9.3.1. Transarterial Chemoembolization (TACE): To cause ischemia and cytotoxicity within the tumor, TACE combines chemotherapeutic medicines with embolic particles in the case of

intermediate-stage HCC (54). This method is improved with drug-eluting beads (DEB-TACE), which offer sustained chemotherapeutic release, increasing efficacy while lowering systemic toxicity. The range of median survival periods following TACE is 26 to 40 months (75). Post-embolization syndrome is one of the sequelae and infrequently, more serious issues such as liver abscess or biliary damage (76).

9.3.2. Transarterial Radioembolization (TARE): By injecting Yttrium-90 microspheres straight into the hepatic artery, TARE, often referred to as Selective Internal Radiation Therapy (SIRT), provides localized radiation therapy. Patients with portal vein thrombosis benefit most from it (77). TARE has proven to be effective in palliating symptoms and downstaging tumors for curative treatments. It also has a better safety profile and less systemic toxicity than traditional medicines (78).

9.3.3. Stereotactic Body Radiotherapy (SBRT): With SBRT, healthy tissue is spared as high-dose radiation is carefully delivered to the tumor. It is recommended for individuals with tiny, localized tumors who are not candidates for surgery or ablation because it yields excellent rates of local control (70–90% at 2 years). SBRT provides a non-invasive treatment alternative with fewer procedural hazards, but it does require specific equipment and experience (79).

9.4. Systemic Therapies

9.4.1. Molecular Targeted Therapies: The standard therapies for advanced HCC are sorafenib and lenvatinib, which increase median survival above placebo by about three months. As a second-line treatment, regorafenib prolongs survival for individuals who do not respond to sorafenib. These treatments have controllable adverse effects by inhibiting many kinases implicated in angiogenesis and tumor growth (80).

9.4.2. Immunotherapy: Nivolumab and pembrolizumab, two immune checkpoint drugs that boost anti-tumor immune responses, are authorized for advanced HCC following sorafenib failure. For some individuals, these treatments result in long-lasting improvements (81). In first-line treatment, the combination of atezolizumab plus bevacizumab has demonstrated greater efficacy over sorafenib, improving both overall and progression-free survival (82).

9.4.3. Chemotherapy: Since HCC generally resists cytotoxic drugs, its response to chemotherapy is limited. Nonetheless, FOLFOX regimens are employed in a limited number of instances, frequently in conjunction with other modalities in clinical trials (83).

10. Discussion

Considering HCC is a heterogeneous disease and is frequently associated with chronic liver diseases, the therapy landscape for the condition is varied and difficult. Although there is still a high recurrence rate after liver resection and a shortage of donor organs for transplantation, surgical procedures, such as liver resection and transplantation, offer curative potential for early-stage HCC.

For early-stage cancers, local ablative therapies like RFA and MWA offer efficient, less invasive solutions; MWA has particular promise for bigger lesions. Though less prevalent, cryoablation and PEI provide additional choices, especially in settings with limited resources.
For the treatment of intermediate-stage HCC, locoregional treatments such as TACE and TARE are crucial, with TARE providing a special advantage to patients with portal vein thrombosis. For circumscribed malignancies, SBRT is a non-invasive option that achieves high control rates with little to no damage to neighboring tissues.

Systemic treatments, which provide better survival and tolerable side effects, are essential for advanced HCC. These include targeted medicines and immunotherapies. A noteworthy development in first-line therapy is the combination of atezolizumab with bevacizumab, which shows how combination medicines can improve results.

It is impossible to overestimate the significance of early diagnosis through screening and sophisticated diagnostic imaging since early-stage HCC is more responsive to curative therapiesOptimizing patient treatment and results requires a multidisciplinary approach combining surgeons, pathologists, radiologists, oncologists, and hepatologists.

To sum up, the treatment of HCC necessitates a multimodal strategy based on the disease stage, liver function, and general health of each patient. For HCC patients to have a higher chance of survival and a better quality of life, ongoing developments in treatment modalities, early detection techniques, and a multidisciplinary approach are essential.

- **Limitations**

  This study has some limitations such as small included studies and short duration.

- **Disclosure of funding**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

- **Conflict of Interest**

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

- **Competing Interest**

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