Editorial

Management of hepatocellular carcinoma

Received: 21 September 2021; **Accepted:** 6 October 2021;

Published: 08 October 2021.

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DOI: https://doi.org/10.52378/mhae1978

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Hepatocellular carcinoma (HCC) is a heterogeneous disease that develops most of the time in the diseased liver. Early diagnosis and management are the best options for patients, so screening programs are mandatory for those at risk of developing HCC. Despite the challenges of management of HCC, there is hopeful management for HCC as the field of primary liver cancer has moved quickly.

Keywords: hepatocellular carcinoma, management, epidemiology, immune checkpoint inhibitors.

1-New trends in epidemiology and surveillance of HCC: virally induced tumors will soon become less frequent, alcohol-related cirrhosis is a stably prevalent pre-neoplastic condition, fatty liver disease is a growing cause of HCC even in the absence of cirrhosis[1].

2- Pathogenesis: Recent technological breakthroughs such as next-generation sequencing have enabled the sequencing of a whole tumor exome, genome, or transcriptome in a few hours. Sequencing data have highlighted the main signaling pathways altered in HCC (e.g., Telomere, cell cycle, epigenetic)[1]. These data helped understand the link between genetic alterations clinical and pathological features of HCC[2], [3]. Telomerase activation, viral insertions, chromosome translocation, or gene amplification are the most frequent driver gene alterations in ~80% of HCC[4].

3- **Trends in Diagnosis:**

The fraction of AFP bound to lectin [5], des-gamma-carboxyprothrombin[5], Golgi protein-73 [6], glypican-3 [7], or Dickkopf-1[8] present the same drawbacks as the AFP and cannot compete with the reliability of the ultrasonography.

Dynamic imaging study (CT or MRI): The difference between 'dynamic' and 'time-lapse' can be considered a smooth motion picture and a stop motion animation. The advantage of performing dynamic CT is achieving uninterrupted, real in situ experiments.

The use of contrast ultrasound has been proposed as a second-rate test in the latest update of the EASL[9] guidelines.

PET is of poor performance for diagnosing HCC. *^{11} C-Choline* shows promising initial results, but not comparable with CT or MRI[10].

4-**Resection of HCC and liver transplantation:** the times when cirrhosis was considered an absolute contraindication for liver resection are over. Vibert et al. summarize the recent advances in the surgical treatment of HCC.[11] Lower morbidity rates associated with the laparoscopic approaches, and personalized prognostication based on the volume and quality of the future liver remnant, the degree of portal hypertension, and the risk of tumor recurrence have changed the way surgery is considered in the treatment of HCC[12].

Adjuvant or neoadjuvant treatment: Tumor recurrence complicates 70% of cases 5 years after surgical resection. Checkpoint inhibitors(ICIs) could reduce recurrence and increase early survival after curative treatment[13]. Many programs propose using AFP levels and response Neoadjuvant treatment (downstaging) as markers of good biological behavior to be included in the selection criteria [14]. The “compound criteria” that, in addition to the size and number of nodules, provide information on tumor biology (e.g., AFP) and include tumor evolution and response to previous treatments, could replace the criteria in the future.

5-**Locoregional treatment:** Palmer et al. summarize the significant issues of TACE, including risk stratification for patient selection, the transition from TACE to systemic therapy, and the use of TACE or other locoregional medicines (e.g., TARE) for patients with the earlier-stage disease (for downsizing)[15]. Data from clinical trials of combinations of TACE and systemic therapy for BCLC stage B or C patients are under evaluation [16].

Ablation techniques as laser[17], cryoablation[18], high-intensity focused ultrasound[19], or irreversible electroporation[20] are not superior to RFA.

Radiomics: CT-guided electromagnetic navigation systems and image fusion are available, allowing refinement of percutaneous ablation. They provide precise and safer punctures, reduce the operator-dependent factor, and allow access to hard-to-reach locations.

The safety and efficacy of **synthetic microspheres** loaded with adriamycin [drug-eluting bead] - TACE) are promising. The charged particles achieve vascular occlusion with a slow release of chemotherapy at the intratumoral level. This allows less passage of chemotherapy to the systemic circulation and thus reduces the potential toxicity of chemotherapy once the particles are injected[21]. The immunotherapy combination with ablation has been suggested to increase survival for several years[22].

Radiation therapy techniques such as three-dimensional conformal radiation therapy, intensity-modulated radiation therapy, image-guided stereotaxic radiation therapy, or proton beam radiation allow high doses of radiation to the tumor without damaging the surrounding tissue. The results reported in HCC and recurrent HCC are promising, but efficacy needs to be confirmed [23],[24].

6-**Assessment of radiological response:** Modified Response Evaluation Criteria in Solid Tumors has served its purpose since being included in clinical practice guidelines[25] for the Management of HCC. Using AI techniques to aid traditional diagnostic procedures is promising (diagnosis, evaluation of recurrence, survival)[26].

7- **Selection of cells expressing the cell surface epithelial cell adhesion molecule** (EpCAM): used for circulating tumor cells (CTC) enrichment as it has little or no expression on leukocytes and is expressed by most epithelial-derived cancers. The FDA-cleared Cell Search platform uses CTC enrichment by EpCAM targeting immunomagnetic selection. *Liquid biopsy* is a procedure based on identifying tumor components released into biological fluids, particularly blood. CTC, circulating tumor nucleic acids, DNA and RNA, and extracellular vesicles[27].

8-**Immunotherapy (immune checkpoint inhibitors(ICIs) and tyrosine kinase inhibitors(TKIs) as mono or combined):** *TKIs:* After a decade of struggling with negative results from randomized trials of drug therapy for advanced HCC, data emerging over the past three years has transformed the management landscape [28]. Faivre et al. provide an overview of targeted therapies for advanced HCC, including Sorafenib and lenvatinib in the first-line setting and regorafenib, cabozantinib, and Ramucirumab in the second-line setting[29]. Sorafenib and lenvatinib improve survival in HCC patients compared to the first-line placebo. Second-line, regorafenib improves survival in patients who progress and are tolerant to Sorafenib, cabozantinib in patients who are candidates for second and third-line treatments, and Ramucirumab in patients who are candidates for second-line treatments who present an AFP value ≥ 400 ng / dL. Ramucirumab is a monoclonal antibody that binds VEGFR-2.

ICIs:

ICIs were the first agents, other than tyrosine kinase inhibitors, to be approved for the treatment of HCC[30],[31].

Combinations of ICIs targeting the programmed cell death-1 (PD-1) pathway and anti-angiogenic therapy have become the mainstream of combination therapy trials for HCC[32],[33, 34]. A combination of atezolizumab and bevacizumab was the first treatment shown to improve the benefit of Sorafenib [35]. Atezolizumab is a PD-L1 inhibitor, and bevacizumab is a monoclonal antibody against VEGF[36].

A combination of nivolumab and ipilimumab (cytotoxic associated lymphocyte-associated protein 4) will be approved soon. Cheng et al. discuss advances in developing predictive biomarkers[37]. In addition, they discuss the further development challenges of different immunotherapy-based combination therapies[37],[38]. Although ICIs are well tolerated, they can result in life-threatening toxicities[39]. The management of such toxicities in patients with HCC, who usually suffer from advanced chronic liver disease, is challenging[40], specific recommendations for liver toxicities were formulated [41].

Adoptive cellular therapy: A recent review summarizes chimeric antigen receptor T cell(CAR-T) therapy targets HCC and current obstacles [42].

Footnotes

Citation of this article: *Mohamed SY. Management of hepatocellular carcinoma. African journal of gastroenterology and hepatology [Internet]. Egypt's Presidential Specialized Council for Education and Scientific Research; 2021 Oct 8;4(1):19-25. Available from: http://dx.doi.org/10.52378/mhae1978.*

Peer-reviewers: Mohamed Hassan Ali Emara (professor of hepatology, gastroenterology, and infectious diseases), Emad Fawzi Hamed (professor of internal medicine).

E- Editor: Salem Y Mohamed.

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