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Editorial

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Multidisciplinary treatment of hepatocellular carcinoma in 2023: Italian treatment guidelines

Piera Federico, Bruno Daniele

Medical Oncology Unit, Ospedale del Mare, Napoli 80147, Italy.

Correspondence to: Piera Federico, MD, Medical Oncology Unit - Ospedale del Mare -via Enrico Russo snc, Napoli 80147, Italy. E-mail: pierafederico@yahoo.it

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INTRODUCTION

The Italian multi-society guidelines for Hepatocellular Carcinoma (HCC) were drawn up by the Scientific Societies involved in the management of patients with HCC, along with a patient association, to provide multidisciplinary guidance, standardize and optimize "clinical practice" and offer the patient a nationwide standard of care.

The latest version focuses on patients with liver cirrhosis, as this tumor appears in the context of a cirrhotic liver in over 90% of cases[1].

MULTIDISCIPLINARY APPROACH

HCC is one of the main causes of tumor death in Italy and its therapeutic management is extremely complex due to its peculiarities compared to most solid tumors[2].

The guidelines recommend that patients with HCC should be managed by a multidisciplinary team of experts in view of the frequent occurrence of two equally important diseases, cancer and cirrhosis, and of the variety of therapeutic approaches to be applied during the natural history of the disease, based on tumor stage, liver function and patient's comorbidities.

This is precisely why, prior to any active treatment, the prognosis of patients with HCC on cirrhotic liver must be assessed with a staging system that takes into account both the tumor stage and the degree of liver dysfunction. Italian guidelines suggest the use of the CLIP score as a prognostic tool and the use of the BCLC staging system as a treatment algorithm. The close correlation between BCLC stage and proposed treatment, coupled with differences in clinical practice due to the heterogeneity of patients, prompted the development of the ITA.LI.CA system which is based on the ITAlian LIver CAncer database. The system is validated in populations of different ethnicities and tumor etiologies (Italian and Taiwanese) and has proven to have the best prognostic accuracy among the most widely used systems. It proposes, for each stage, therapeutic alternatives, chosen based on the "therapeutic hierarchy" which, in turn, relies on the effectiveness demonstrated by various treatments in the polycentric management practice of a large cohort of patients[3,4].

This editorial describes the Italian recommendations regarding curative locoregional interventions (liver transplant, liver resection, percutaneous ablation), palliative measures (chemoembolization, radioembolization, radiotherapy) and systemic treatments (molecular targeted therapies and immunotherapy), contextualizing their use in relation to cancer staging and liver function, drawing upon evidence from the scientific literature.

RADICAL TREATMENT OF SINGLE SMALL HEPATOCARCINOMA - THE ROLE OF ABLATION

In Child-Pugh A cirrhotic patients with single HCC, the panel recommends hepatic resection over percutaneous ablation, except for patients with HCC ≤ 2 cm, for which it suggests ablation. In fact, compared to surgical resection, ablation carries a lower burden of morbidity and mortality, leads to a shorter duration of hospitalization and reduced health costs while maintaining comparable survival rates[5].

The guidelines emphasize that, in patients meeting the Milan criteria, liver transplantation remains the ideal treatment. However, due to the limited availability of grafts and the effectiveness of therapeutic alternatives to transplantation, resection surgery and thermoablation are also being considered first-line options, with transplantation reserved for cases of relapse/progression (referred to as "salvage" transplantation)[6,7] [Figure 1].

SURGICAL RESECTION FOR INTERMEDIATE-SIZED HCC AND MULTINODULAR HCC

For single HCC of 2.1-3 cm, the choice between surgery and thermoablation should be made on a case-by-case basis, bearing in mind that resection offers greater prospects of radicality.

For single HCC > 3 cm (3-5 cm), liver resection is the first option[8]. If unresectable, only in selected cases, combined/sequential transarterial chemoembolization (TACE)-ablation treatment can be an alternative to radiofrequency ablation (RFA) with multiple insertions, although the certainty of the evidence was found to be very low and therefore not adequate to draw solid conclusions.

Notably, the only RCT included in the selection had a significantly small sample size (37 patients)[9,10]. For patients with HCC who are ineligible for surgical and/or ablative treatment (specifically, those deemed technically unresectable due to vascular relationships and/or location necessitating excessive surgical removal and those ineligible for ablation due to tumor site and/or size), the panel suggests considering TACE followed by radiotherapy as opposed to TACE alone. However, this recommendation applies only to centers with extensive experience in liver radiotherapy and adequate technical equipment, given the possibility of radiation-induced liver disease (RILD)[1,11].

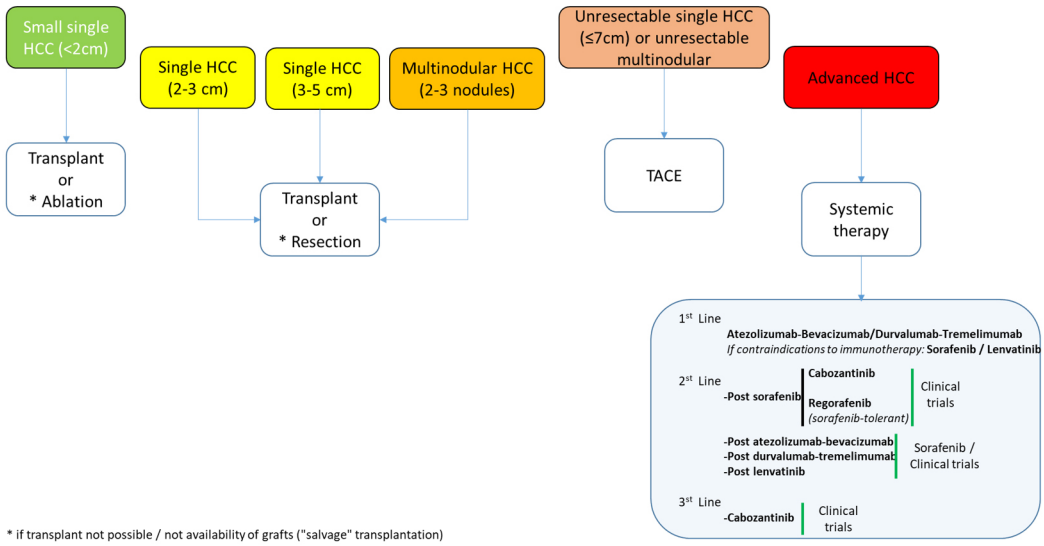

Figure 1. Treatment strategy for HCC by Italian Guidelines. HCC: hepatocellular carcinoma; aHCC: advanced HCC; TACE: transarterial chemoembolization.

In cirrhotic patients with good liver function and multinodular/oligonodular HCC, ranging from 2 to 3 nodules that are anatomically close (such as satellites), resection surgery can be performed if there is sufficient functioning residual liver. The panel recommends liver resection over TACE because it provides better overall survival which outweighs the tendency for increased major complications post-treatment. However, it is evident that the feasibility of the procedure will be conditioned by the patient's tolerance to the extent of parenchymal mutilation required to achieve radicality[12].

When possible, anatomical liver resection (segmentectomy or subsegmentectomy) is preferred. The laparoscopic approach is associated with a lower risk of postoperative liver decompensation.

Advanced age is not in itself a contraindication to liver resection.

Resection is generally reserved for patients with a Child-Pugh score of up to 6 (class A). Child A is the precondition for resection, possibly with no sign of portal hypertension.

In the context of multidisciplinary discussion, hepatic resection can be considered even for a very small group of superselected Child-Pugh B patients, provided that radicality involves limited parenchyma removal.

For patients with compensated cirrhosis and HCC technically eligible (by size and number of lesions) for surgical treatment, but excluded due to other contraindications, the panel suggests using stereotactic body radiation therapy (SBRT) compared to alternative therapies (TACE, TARE or systemic therapy). SBRT has the advantage of delivering ablative doses on tumor nodules while sparing the surrounding nontumorous (cirrhotic) tissue. The strength of the recommendation is assessed as being conditional in favor of radiotherapy but with very low certainty in the evidence. The outcomes from treatments, in fact, are from propensity score analysis rather than prospective comparative trials. Despite the lack of randomized phase III trials proving its efficacy, it appears to be an effective treatment alternative to TACE/RFA and is associated with long-term local control in most treated patients with similar survival rates[13,14]. However,

given this benefit, the choice for radiotherapy should be made with great caution and, as mentioned above, in expert centers considering the further damage induced, especially in the cirrhotic liver (RILD)[15]. So, maintaining the balance between the risk of toxicity and tumor control is the key.

For patients with Child-Pugh A cirrhosis, suffering from single, large HCC (≤ 7 cm) or unresectable multifocal HCC, with neither ascites nor portal invasion or extrahepatic extension, the panel suggests not to carry out the transarterial radioembolization (TARE). The introduction of this recommendation is based on the results of the retrospective multicenter study LEGACY[16], where there is no information on the multinodularity of HCC and most patients (over 90%) had a single nodule of 3 to 5 cm in diameter.

In cirrhotic patients with HCC, without portal neoplastic thrombosis and without extrahepatic neoplastic extension, but beyond Milan criteria, the panel recommends liver transplantation over alternative treatments without transplantation (resection, locoregional and systemic treatments)[17]. For patients with HCC beyond the oncological transplantability criteria adopted by the center, the panel recommends, therefore, the downstaging procedure in order to try to make the patient eligible for liver transplantation. Great caution is needed when making this decision, avoiding the selection of patients well beyond the threshold of transplantability[18,19].

In this regard, the age limit for eligibility for transplantation in Italy is 70 years. However, age itself, both for transplantation and resection, is not an absolute criterion for deciding on the possibility of intervention as it is worked out by various specialists on the basis of general conditions and the presence of concomitant diseases (pulmonary, cardiac, systemic)[17].

INTERMEDIATE-SIZED HCC AND MULTINODULAR HCC NOT ELIGIBLE FOR CURATIVE TREATMENTS

TACE and TAE are the treatments to be considered for patients with liver cirrhosis (maximum Child-Pugh B7) with unresectable multifocal HCC without portal invasion or extrahepatic extension. They may also find a place as a down-staging strategy in transplant candidates. The ideal candidate is the patient with Child-Pugh class A and PS = 0, but these treatments can also be performed in patients with Child-Pugh class B7 and PS = 1[20] [Figure 1].

ADVANCED HCC

The patient with advanced HCC (presence of neoplastic vascular thrombosis and/or metastases) with good liver function (Child-Pugh A) and performance status (PS) 1-2 is a candidate for systemic therapy. Based on the BCLC staging system, systemic treatments also apply to the intermediate stage (BCLC B), Child-Pugh A, with PS > 0 (PS 1-2), to BCLC B, PS 0 patients who failed treatment with TACE and/or BCLC B patients ineligible for TACE because of extensive liver involvement.

The drugs reimbursed in Italy for first-line systemic treatment are sorafenib, lenvatinib, and the combination therapies atezolizumab-bevacizumab and durvalumab-tremelimumab[21]. For the second line, all positive studies were conducted after sorafenib. Therefore, patients with advanced HCC who progress during treatment with combined therapy or manifest intolerance-toxicity to it, yet maintain good performance status and Child-Pugh A liver function, remain eligible for systemic treatment. In such cases, treatment with sorafenib or evaluation for second-line clinical trials is recommended. Similarly, sorafenib is the only second-line therapy reimbursed for patients receiving either lenvatinib or durvalumab-tremelimumab in the first line. Patients progressing after first-line therapy with sorafenib and not intolerant to sorafenib itself may be candidates for second-line therapy with regorafenib or with cabozantinib, as

demonstrated by the RESORCE and CELESTIAL studies, respectively. In addition, cabozantinib can also be administered in the third line (after sorafenib-regorafenib; after lenvatinib-sorafenib; after atezolizumab-bevacizumab/sorafenib; after durvalumab-tremelimumab/sorafenib) [Figure 1]. Ramucirumab in patients with high alfa-fetoprotein values is not reimbursed in Italy.

PALLIATIVE THERAPY

In the multidisciplinary team, the oncologist bears primary responsibility for the patient under treatment; he/she oversees systemic therapy (both targeted therapy and immunotherapy) and refers the patient to the specialist for the most appropriate curative (surgical resection, liver transplantation, and ablation therapy) or palliative treatment.

Palliative therapies aim to alleviate symptoms, improve the quality of life and extend survival for such patients[22].

Palliative care includes: surgical palliation (biliary decompression), palliative systemic therapy, regional therapies (TACE and palliative radiotherapy) and pain management therapies (including radiotherapy for bone metastases)[23]. Paracetamol and opioids are the safest drugs for pain control in patients with HCC associated with liver cirrhosis, while nonsteroidal anti-inflammatory drugs should be avoided because of the increased risk of bleeding and renal failure and the possible development of ascites resistant to diuretic therapy. A state of malnutrition is also commonly observed in these patients, especially those with decompensated cirrhosis, with loss of weight and muscle tissue. Assessment of nutritional status is important in patients with HCC, and it has been observed that the Prognostic Nutritional Index is predictive of the survival of patients with HCC[24]. However, it should also be considered that low albumin serum concentration is a negative prognostic marker for both surgical and systemic palliative therapy[25].

In conclusion, the Italian multi-society guidelines emphasize that HCC management is complex yet can yield success through the implementation of a multidisciplinary patient-centered approach.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Federico P, Bruno D

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Not applicable.

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Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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