

Guidelines

Multidisciplinary Treatment of Hepatocellular Carcinoma in 2023: Italian practice Treatment Guidelines of the Italian Association for the Study of the Liver (AISF), Italian Association of Medical Oncology (AIOM), Italian Association of Hepato-Bilio-Pancreatic Surgery (AICEP), Italian Association of Hospital Gastroenterologists (AIGO), Italian Association of Radiology and Clinical Oncology (AIRO), Italian Society of Pathological Anatomy and Diagnostic Cytology (SIAPeC-IAP), Italian Society of Surgery (SIC), Italian Society of Gastroenterology (SIGE), Italian Society of Medical and Interventional Radiology (SIRM), Italian Organ Transplant Society (SITO), and Association of Patients with Hepatitis and Liver Disease (EpaC) – Part I – Surgical treatments



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ABSTRACT

Worldwide, hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death. The remarkable improvements in treating HCC achieved in the last years have increased the complexity of HCC management. Following the need to have updated guidelines on the multidisciplinary treatment management of HCC, the Italian Scientific Societies involved in the management of this cancer have promoted the drafting of a new dedicated document. This document was drawn up according to the GRADE methodology needed to produce guidelines based on evidence. Here is presented the first part of guidelines, focused on the multidisciplinary tumor board of experts and surgical treatments of HCC.

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1. Introduction

This report summarizes the recommendations of Clinical Practice Guidelines regarding Surgical treatments of Hepatocellular Carcinoma (HCC) [1], drawn up according to the GRADE methodology [2] and promoted by the following scientific societies: Italian Association for the Study of the Liver (AISF), Italian Association of Medical Oncology (AIOM), Italian Association of Hepato-Bilio-Pancreatic Surgery (AICEP), Italian Association of Hospital Gastroenterologists (AIGO), Italian Association of Radiology and Clinical Oncology (AIRO), Italian Society of Pathological Anatomy and Diagnostic Cytology (SIAPeC-IAP), Italian Society of Surgery (SIC), Italian Society of Gastroenterology (SIGE), Italian Society of Medical and Interventional Radiology (SIRM), Italian Organ Transplant Society (SITO), and Association of Patients with Hepatitis and Liver Disease (EpaC).

Current knowledge on treatment of HCC is translated into relevant practical recommendations following the rules and the methodology indicated by the Centro Nazionale per l'Eccellenza delle Cure (CNEC) and the Istituto Superiore di Sanità (ISS).

The guideline developers, designated by the above-mentioned scientific societies, identified key questions that health care providers are frequently faced with in the management of patients with HCC.

2. Background

HCC is a common cause of cancer-related mortality and morbidity worldwide [3,4] with variable, but on average still poor prognosis [5], that in the vast majority of cases occurs in patients with chronic liver disease, usually in the cirrhotic stage [6,7]. Early detection of HCC, increasing the percentage of early-stage tumors,

expands the rate of patients amenable to curative treatments, favorably impacting overall survival [8].

In recent years, the therapeutic armamentarium of HCC has been remarkably enriched with new effective techniques and strategies, leading to the need of a management involving different specialists [9]. Indeed, prediction of outcome and treatment choice are particularly complex as they must consider the underlying liver disease and comorbidities, which condition treatment feasibility and have an inherent competing mortality risk.

3. Methods for developing the guideline

Twenty-two experts indicated by the above-mentioned scientific societies, plus 2 delegates of the EpaC patient association, selected by collegial discussion the key questions and draw up guidelines. This document was arranged according to the rules of the CNEC of the Italian Ministry of Health. The key questions were developed according to the Population, Intervention, Comparison, Outcomes (PICO) acronym. For each PICO question, the literature on MEDLINE/Pubmed, Embase and Cochrane Library databases was systematically searched with both Thesaurus terms and free text. A further hand-search was performed on the bibliography of articles and previously published guidelines.

Recommendations were formulated applying the GRADE approach [2] according to the CNEC manual [10]. All aspects concerning questions, assessment of evidence and conclusions were discussed among panel members and voted. Before voting, members declared their potential conflict of interest (COI) relevant to the PICO question, and only those without COI voted. The online GRADEpro GDT tool was used to develop questions, assess evidence, and make decisions [11]. The certainty of evidence was assessed applying the tool for Risk of Bias in randomized trials (RoB)

Table 1
PICO questions about Surgical treatment, Recommendations, Certainty of evidence, and Strength of recommendation of Clinical Practice Guidelines for the management of Hepatocellular Carcinoma (HCC).

PICO	Recommendation	Certainty of evidence	Strength of recommendation
1	Is management by a multidisciplinary team of experts versus management by a single expert indicated in patients with hepatocellular carcinoma (HCC)?	Moderate	Strong in favor of multidisciplinary management
2	In patients with Child-Pugh class A cirrhosis and single HCC, is hepatic resection indicated compared to the treatment with thermal ablation?	Low	Conditional in favor of resection
3	In cirrhotic patients with good liver function and multinodular HCC, is liver resection indicated compared to transarterial chemoembolization (TACE)?	Low	Strong in favor of resection
4	In cirrhotic patients with good liver function and HCC responsible for intrahepatic macrovascular invasion, is liver resection indicated compared to sorafenib-based systemic therapy?	Very low	Conditional in favor of resection
5	In cirrhotic patients with HCC who are candidates for liver transplantation, is a selection according to the “transplant benefit” criterion indicated compared to other criteria?	Not applicable	Not applicable
6	In cirrhotic patients beyond Milan criteria, but without intrahepatic vascular invasion and extrahepatic tumor spread, is liver transplantation indicated compared to alternative treatments (liver resection, locoregional or systemic therapies)?	Transplant vs. resection: moderate Transplant vs. alternative therapies: very low.	Strong in favor of transplantation
7	In patients with HCC single >2 cm or multifocal (within the centre's transplantability criteria) and treatable with any potentially radical therapy (“first-line” liver transplantation, resection or thermal ablation), is “salvage” transplantation (i.e. transplant performed at the time of cancer recurrence/ progression after resection or thermal ablation) indicated compared to the “first line” transplant?	Low	Conditional in favor of liver resection or thermal ablation followed by “rescue” transplant
8	In patients with HCC beyond the transplant criteria adopted by the center, is the “downstaging” procedure followed by transplantation indicated compared to treatments without subsequent transplantation?	Low	Strong in favor of transplantation

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

as suggested by Cochrane [12], and the Newcastle-Ottawa scale for non-randomized studies [13].

4. PICO questions and recommendations

Table 1 summarizes PICO questions about Surgical treatment, Recommendations, Certainty of evidence, and Strength of recom-

mendation of Clinical Practice Guidelines for the management of Hepatocellular Carcinoma (HCC).

1. Is management by a multidisciplinary team of experts versus management by a single expert indicated in patients with hepatocellular carcinoma (HCC)?

The management of patients with HCC involves multiple professional specialists (Fig. 1), such as the hepatologist, radiologist,

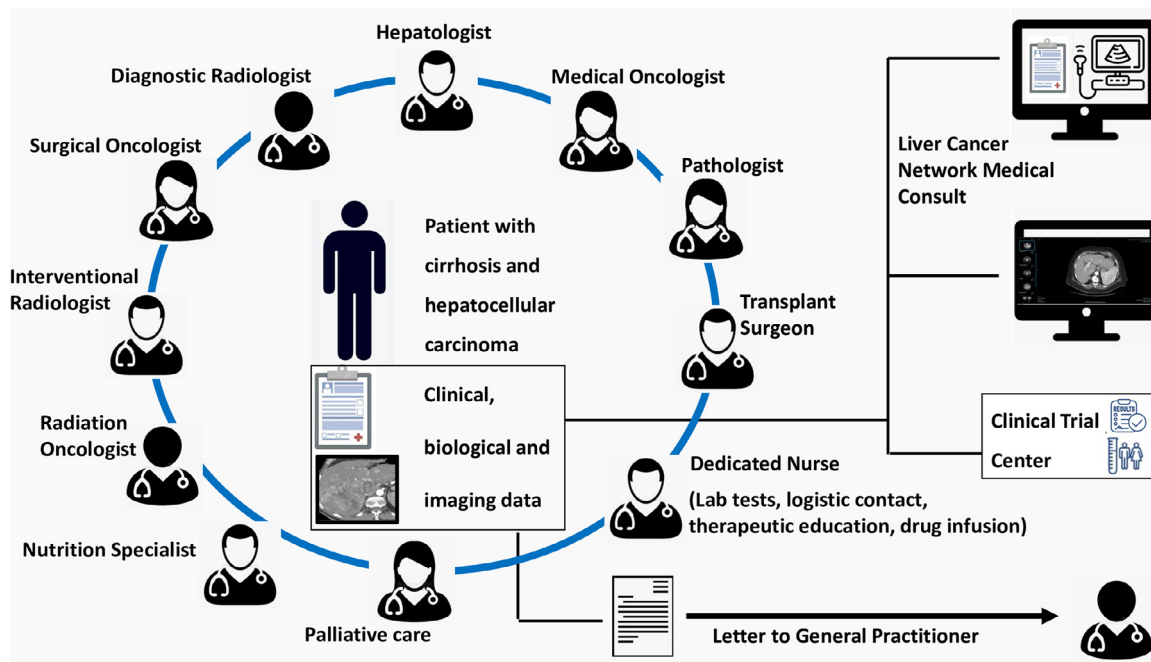


Fig. 1. Multidisciplinary tumor board.

pathologist, surgeon, transplant surgeon, oncologist, radiation oncologist, as well as nurses and experts of palliative care [9,14,15]. The hepatologist represents the pivotal figure and the link between the other professional figures in all phases of the patient's journey [15], while the other specialists assume a fundamental role at different times, depending on the tumor stage and the therapeutic strategy adopted.

Patients with HCC have two peculiar features which necessitate of a multidisciplinary vision [9,16,17]: 1) HCC is associated with the presence of chronic liver disease in the vast majority of cases, most frequently in the cirrhotic stage (>90% of cases), which affects itself both the applicability of many therapies and the survival of patients, and whose management requires specialized knowledge; 2) numerous modalities of therapy are available, also including liver transplantation, a very peculiar case among solid tumors.

In this line, good liver function is generally defined as Child-Pugh class A (without ascites) and MELD score <10, also considering the grade of portal hypertension. However, it is important to consider that assessing liver function reserve before treatment and during follow-up is complex and multifaceted. So, also other scores are usually used as the model for end-stage liver disease (MELD) score, MELD-sodium score, albumin-bilirubin grade, and indocyanine green test.

The goal of a multidisciplinary approach is therefore to improve the patient's outcome by defining, in an individualized basis, the best diagnostic approach and the best therapeutic option applicable through a common unified discussion, where specialists examine together the individual case. Multidisciplinary teams are increasingly common, particularly in referral centers, replacing the referral of the patient to individual consultations with specific relevant specialists for the given stage of the tumor. Nevertheless, the available evidence demonstrating that the multidisciplinary approach improves the prognosis of patients with HCC remains relatively weak, resulting from retrospective studies and comparisons with historical control groups [18,19]. In particular, 7 retrospective studies with a control group and an analysis adjusted for confounders were found and scrutinized [20–26]. Of them, 3 included historical controls and 4 contemporary controls.

When pooled, these studies reported a statistically significant reduction in mortality in patients managed by the multidisciplinary tumor board (MDT) compared to controls (HR 0.55, 95% CI 0.38–0.80).

Recommendation: For patients with HCC, the panel recommends that the evaluation of the diagnostic and therapeutic workup be carried out by a multidisciplinary team of experts rather than by a single expert.

Certainty in evidence: Moderate.

Strength of recommendation: Strong in favor of multidisciplinary management.

2. In patients with Child-Pugh class A cirrhosis and single HCC, is hepatic resection indicated compared to the treatment with thermal ablation?

Although liver transplantation remains the ideal treatment for all cirrhotic patients with HCC [8], the limited availability of grafts and the growing and improved efficacy of therapeutic alternatives to transplantation have led to consider resection and thermal ablation as first-line options for some of these patients [9,16,27–33].

Even if liver resection has long been the treatment of choice, radiofrequency or microwave thermal ablation have gained widespread use thanks to its less invasiveness and lower risk of complications, high reproducibility, adequate oncological efficacy and feasibility even in patients with a moderate liver dysfunction [34–36]. However, outcomes the feasibility of both resection and thermal ablation are affected by several features, such as underlying liver dysfunction, tumor diameter and position (superficial/deep, adjacent to hollow organs or vascular-biliary structures), general patient conditions (including comorbidity, frailty and Performance Status), that should be evaluated in a multidisciplinary context [37–44], and that are also considered in other Western HCC guidelines [16,27,28].

A total of 27 studies were included in the analysis, 6 randomized controlled trials (RCTs) [38–43] and 21 observational studies [44–64]. RCTs did not demonstrate a difference in overall survival between patients undergoing liver resection and those undergoing thermal ablation at 1, 3 and 5 years, while observational studies

showed a survival advantage for surgery at 3 and 5 years. Observational studies also reported a higher recurrence free survival with resection with respect to thermal ablation. However, the long-term benefit of resection was not confirmed in the subgroup of patients with single HCC ≤ 2 cm. Therefore, as the two treatments were oncologically equivalent in these patients, but thermal ablation has a lower risk of complications and a better cost-effectiveness, this choice should be preferred for treating HCC ≤ 2 cm whenever the tumor is clearly identifiable and adequately approachable [65,66].

Finally, in a multiparametric evaluation process, particularly when percutaneous thermal ablation procedures are considered unfeasible, it is important to consider the possibility of adopting a mini-invasive approach (laparoscopic or robotic).

Recommendation: In patients with Child-Pugh class A cirrhosis and single HCC, the panel suggests preferring liver resection over thermal ablation, except for patients with HCC ≤ 2 cm, for whom the panel suggests thermal ablation.

Certainty in evidence: Low.

Strength of recommendation: Conditional in favor of resection.

3. In cirrhotic patients with good liver function and multinodular HCC, is liver resection indicated compared to transarterial chemoembolization (TACE)?

Approximately 35–40% of HCCs are multinodular at diagnosis [67,68]. The term multinodular includes extremely heterogeneous diseases, from oligo-nodular (2 or 3 nodules) to diffuse miliary disease, which require different treatments. Some proposals for the re-classification of multinodular HCC have been advanced [69–73] which, however, have not yet found correspondence with standard of care therapeutic indications.

The EASL guidelines [16] and AASLD guidance [28] recommend, as first-line treatment for multinodular HCC, transarterial chemoembolization (TACE) or, in oligo-nodular cases, percutaneous thermal ablation if liver transplantation is not feasible according to the selection criteria of the transplant center. This preclusion to resective surgery, especially for patients with 2–3 nodules, is not shared by both the Eastern [29,30] and Italian multisociety [31] guidelines and is not accepted by centers expert in liver surgery [9,67,68,33,74–76]. It should be noted that the BCLC update [77] and AASLD guidance [28], although excluding liver resection as first-line treatment for patients with intermediated stage (multinodular) HCC, consider not only TACE but also liver transplantation (LT) and systemic treatment.

The literature search identified 9 studies, consisting of 1 RCT [78] and 8 observational studies [67,79–85]. The RCT demonstrated a longer survival following liver resection than TACE at 1 year (76% vs 52%, RR 1.47, 95% CI 1.16–1.86), 3 years (64% vs 35%, RR 1.80, 95% CI 1.30–2.50) and 5 years (51% vs 18%, RR 2.90, 95% CI 1.75–4.79). In agreement, observational studies [67,79–85] demonstrated a better survival after liver resection than after TACE at 1 year (5 studies, 2511 patients: 88% vs 79%, RR 1.12, 95% CI 1.08–1.16), 3 years (6 studies, 2775 patients: 54% vs 34%, RR 1.59, 95% CI 1.31–1.92) and 5 years (7 studies, 4875 patients: 53% vs 31%, RR 1.70, 95% CI 1.41–2.04).

The panel highlights that 90% of the patients included in the studies evaluated had 2–3 nodules: therefore, this represents the population in which liver resection may outperform TACE. Moreover, it is important to consider that the certainty of the evidence is highly conditioned by a series of limitations of the studies including heterogeneous inclusion criteria, high prevalence of hepatitis B virus etiology and heterogeneous residual liver function at baseline. Hence, due to the low level of evidence, the members of the Panel reiterate the importance of a multidisciplinary treatment evaluation on a case-by-case basis.

Recommendation: In well selected cirrhotic patients with good liver function and oligo-nodular (2–3 nodules) HCC, and

after multidisciplinary board evaluation, the panel recommends liver resection over TACE.

Certainty in evidence: Low.

Strength of recommendation: Strong in favor of resection.

4. In cirrhotic patients with good liver function and HCC responsible for intrahepatic macrovascular invasion, is liver resection indicated compared to sorafenib-based systemic therapy?

Approximately 10–15% of patients with HCC present with macroscopic vascular invasion (MVI) at diagnosis [68,86,87] with a median survival of 8–11 months [16,88]. The EASL guidelines [16] and AASLD guidance [28] consider MVI a contraindication to hepatic resection, proposing the systemic therapy as the unique option for these patients. Conversely, Eastern guidelines [29,30] consider the possibility of performing liver resection in selected patients, considering the results of numerous studies that have demonstrated the feasibility of the resection even in the presence of MVI, with acceptable postoperative mortality rates (3–6%) and survival at 3 and 5 years (17–49% and 10–39%, respectively) [75,87,89,90]. Similar position has been taken by the Italian multi-societal recommendations [31].

These patients are frequently candidates for a large hepatectomy to obtain surgical radicality [30,87], particularly in presence of MVI of large vessels and, therefore, require an accurate evaluation of the hepatic functional reserve and of the residual liver volume in order to minimize the risk of postoperative liver failure.

There is a clear association between the site of portal MVI and prognosis, and the prognosis is better for MVI of peripheral branches [86,91]. For this reason, portal invasion has been categorized into 4 classes [86,91]: Vp1, invasion of segmental or sectoral portal branches; Vp2, invasion of right or left portal branch; Vp3, invasion extending to the portal trunk; Vp4, invasion extended to the superior mesenteric vein. A survival advantage after surgery compared to nonsurgical treatment has been reported only in the presence of a MVI not extending to the portal trunk [87,92–94]. The association between the site of invasion and prognosis has been reported even for MVI of hepatic veins [86,90]. Surgery may offer a survival benefit in patients with intrahepatic MVI, but not in those with the tumoral invasion of the inferior vena cava [90].

Four observational studies were identified [95–98]. They enrolled a total of 1143 patients, 618 of whom were treated with liver resection and 525 with systemic therapy. Among these studies, 3 had sorafenib as a control, while the fourth did not specify the systemic therapy used. These studies report a better survival after liver resection at 1 year (3 studies, 879 patients: 65% vs 41%, RR 1.60, 95% CI 1.12–2.29), 3 years (one study, 639 patients: 68% vs 18%, RR 3.82, 95% CI 2.92–5.00,) and 5 years (one study, 639 patients: 56% vs 13%, RR 4.35, 95% CI 3.14–6.03). The improved survival of surgery compared to sorafenib-based systemic therapy was demonstrated both in studies that included only patients with portal invasion and in those that included patients with portal and hepatic vein invasion.

However, it is important to note that the overall certainty of the evidence was judged by the Panel to be very low, as it derives from observational studies, and with important limitations such as the risk of bias, imprecision, and poor generalizability. Therefore, their results should be interpreted with great caution particularly considering the impact in term of survival of the new systemic therapies (i.e., combinations based on immunotherapy) compared to sorafenib [99–101]. Hence, new comparative studies are warranted.

Recommendation: In cirrhotic patients with good liver function and HCC responsible for intrahepatic macrovascular invasion, the panel suggests preferring liver resection versus sorafenib-based systemic therapy.

Certainty in evidence: Very low.

Strength of recommendation: Conditional in favor of resection.

5. In cirrhotic patients with HCC who are candidates for liver transplantation, is a selection according to the “transplant benefit” criterion indicated compared to other criteria?

In conditions of insufficient organ donation, the selection of patients to be included in the waiting list for liver transplantation (LT) and the intervention priority to assign to each patient (“prioritization”) should follow the “transplant benefit” (TB) principle, which integrates the elements of urgency and utility [9,102–108].

The TB is calculated as the difference of the predicted survivals achievable with transplantation and alternative treatments. The major criticality inherent in the application of the TB concept derives from the lack of RCT comparing LT and alternative therapies, stratified by tumor stage, liver function [109,110] and downstaging therapies [111].

TB is also high for patients who suffer an early recurrence (within 2 years) of HCC after potentially radical treatments (resection or thermal ablation), especially if the tumor is multifocal and/or in the presence of deterioration of liver function, as this condition is burdened with an unfavorable prognosis [112].

Recently, Lai et al. [113] have created models of *Intention-to-treat* (ITT) survival with LT and with loco-regional therapies by a retrospective analysis of a large cohort of patients (2103 patients) waiting for LT. They showed that MELD score <13, response to locoregional therapy according to mRECIST criteria (either complete or absent with disease progression), alpha-fetoprotein levels >1000 ng/ml and T1-T2 stages were able to reduce the TB-ITT.

Although there is no broad international agreement, the Italian transplant community considers TB as the reference to select patients for LT and to calculate the priority for intervention [114–117]. In line with the principle of TB, recent cost-efficacy studies have shown that LT is cost-effective only for some categories of patients outside the Milan criteria and, hence, without effective therapeutic alternatives [103], but not for patients eligible for potentially radical alternative therapies such as resection or thermal ablation [118,119].

For all these reasons, the Panel agreed to formulate a Good Practice Statement [120,121] on the importance of adopting the principle of TB as a selection criterion for LT.

Indication of good clinical practice: The Panel believes that the criterion of “transplant benefit” instead of that of “transplant utility” should be used for the selection of candidates for transplantation, taking into account that the potential transplantability must consider overall health, comorbidity, nutritional status and age (although without a defined and universally accepted cut-off), in addition to the tumor burden.

6. In cirrhotic patients beyond the Milan criteria, but without intrahepatic vascular invasion and extrahepatic tumor spread, is liver transplantation indicated compared to alternative treatments (liver resection, locoregional or systemic therapies)?

It is well established that liver transplantation (LT) can provide excellent results also in patients who exceed the oncological limits established by the Milan criteria [122], provided they respect other validated “extended” criteria [123].

The “extended” criteria were established through observational studies that demonstrated that, adopting these criteria, post-transplant overall survival and cancer recurrence-free survival were comparable to those obtained using the Milan criteria [123]. Some extended criteria are purely morphological (largest tumor diameter, number of nodules, total tumor volume), such as the University of California San Francisco criteria [124,125], or the Asian criteria

[126,127]. Others combine morphological and biological (alpha-fetoprotein level or tumor grade) features, such as the Alpha-fetoprotein model [128,129], the Total Tumor Volume plus Alpha-fetoprotein criteria [130], the Metroticket 2.0 criteria [131], and the Padova-Toronto criteria [132,133]. All these extended criteria produced consistent “indirect” evidence that LT can guarantee excellent survival profiles (>70% at 5 years) even beyond the Milan criteria. Notably, these survival figures cannot be achieved with any therapy alternative to transplant [33].

Also, direct evidence about comparing LT and non-transplant therapies in patients beyond Milan criteria has been searched for. For the comparison between LT and liver resection, the Panel analyzed a systematic review, including 6 retrospective cohort studies, for evaluating the desired effects [134] and 2 studies for evaluating the undesirable effects [135,136].

Moreover, 3 cohort studies were considered for comparing LT and non-surgical therapies, one comparing LT vs. Sorafenib [137] and 2 comparing LT vs. transarterial chemoembolization (TACE) [138,139].

Observational studies [134] clearly showed a better overall survival (HR 0.83, from 0.68 to 1.01) and recurrence-free survival (0.45, from 0.37 to 0.56) after LT than after resection. Only slightly higher perioperative mortality and undesirable effects were detected after LT [135,136].

A significant long-term survival advantage in favor of LT was also confirmed by observational studies comparing LT with Sorafenib [137] or TACE [138,139].

Clinical recommendation: In potentially transplantable (comorbidities, nutritional status and age) cirrhotic patients with HCC beyond the Milan criteria, but without intrahepatic vascular (and biliary) invasion and extrahepatic tumor spread, the Panel recommends considering liver transplantation rather than alternative treatments (resection, locoregional treatments and systemic treatments).

Certainty in evidence: Transplant vs. resection: Moderate. Transplant vs. alternative therapies: Very low.

Strength of recommendation: Strong in favor of transplantation.

7. In patients with HCC single >2 cm or multifocal (within the centre’s transplantability criteria) and treatable with any potentially radical therapy (“first-line” liver transplantation, resection, or thermal ablation), is “salvage” transplantation (i.e., transplant performed at the time of cancer recurrence/progression after resection or thermal ablation) indicated compared to the “first line” transplant?

The analysis of the role of the so-called “salvage liver transplant” (SLT), performed at the time of tumor recurrence after potentially radical treatments (resection or thermal ablation) is complex [140,141] due to the various factors that can influence the result, including: a) characteristics of the first tumor; b) type of recurrence (early or late, single or multifocal, local or intrahepatic distant); c) applicability of therapies alternative to LT; d) waiting times in list for SLT; e) availability of living transplant donors (LDLT). Due to this complexity, there are no randomized controlled trials comparing SLT with “front-line” transplantation.

Importantly, the option of SLT is in line with the principle of the “transplant benefit” aimed at providing grafts to the patients not amenable to therapeutic alternatives potentially radical [142–145]. Therefore, the possible loss of accessibility to SLT at the time of HCC recurrence represents the main drawback of this strategy.

Five systematic reviews were identified [146–150]. The most up-to-date and methodologically rigorous of them includes a total of 9879 patients [149]. The studies reviewed by this review showed:

Mortality:

- Mortality at an average follow-up of 1 year: moderately in favor of the SLT strategy (OR 0.86, 95% CI 0.75 - 0.98);
- Mortality at an average follow-up of 3 years: moderately in favor of the SLT strategy (OR 0.85, 95% CI 0.76 - 0.96);
- Mortality at an average follow-up of 5 years: moderately in favor of the SLT strategy (OR 0.85, 95% CI 0.76 - 0.96);
- Recurrence at a mean follow-up of 1 year: moderately in favor of the SLT strategy (OR 0.86, 95% CI 0.75 - 0.99);
- Recurrence at a mean follow-up of 3 years: in favor of the SLT strategy (OR 0.56, 95% CI 0.39 - 0.81);
- Recurrence at a mean follow-up of 5 years: in favor of the SLT strategy (OR 0.75, 95% CI 0.66 - 0.86).

However, the results of this meta-analysis should be viewed with great caution as they do not consider patients who dropped out due to death or progression before receiving the SLT.

Adverse events:

- Biliary tract complications: slightly against SLT (OR 1.14, 95% CI 0.94 - 1.40);
- Sepsis: slightly against SLT (OR 1.14, 95% CI 0.63 - 2.06);
- Post-operative bleeding: against SLT (OR 1.32, 95% CI 1.03 - 1.71);
- Vascular complications: against SLT (OR 1.35, 95% CI 0.98 - 1.85);
- Operative mortality: against SLT (OR 2.00, 95% CI 1.21 - 3.31).

Two cost-effectiveness studies were identified [151,152]. In the first one, SLT after partial hepatectomy led to a longer life expectancy and quality-adjusted life expectancy at a lower cost than front-line transplantation [151]. In the second study, first-line transplantation was superior and dominant over SLT performed after both liver resection and RFA [152].

Information regarding the average time spent on the transplant waiting list and the number of delisting before the intervention was also checked. The analysis of data from 10 studies [135,153–161] showed no significant differences between SLT and front-line transplant.

Clinical recommendation: In patients with HCC single >2 cm or multifocal (within the centre's transplantability criteria) and treatable with any potentially radical therapy, the panel suggests performing liver resection or thermal ablation followed, in case of cancer recurrence, by "salvage" transplantation.

Certainty in evidence: Low.

Strength of recommendation: Conditional in favor of liver resection or thermal ablation followed by "rescue" transplant.

8. In patients with HCC beyond the transplant criteria adopted by the center, is the "downstaging" procedure followed by transplantation indicated compared to treatments without subsequent transplantation?

A crucial aspect of the "downstaging" concerns the access criteria, i.e., the characteristics of the patients to whom downstaging is offered [162]. In fact, the access criteria can influence two important outcomes: a) the downstaging *failure rate* and the subsequent risk of dropout due to tumor progression while waiting for liver transplant (LT) [163]; b) the *outcomes of LT* and, in particular, the risk of death due to recurrence of HCC [162].

It is also worth noting that, if the outcome LT after downstaging is evaluated with the "intention to treat" method (i.e., the start of the follow-up coincides with the start of downstaging procedures), the overall survival is greatly reduced by the high percentage (21–50%) of cases who do not complete the downstaging program due to lack of response to therapy - and consequent tumor progression

- or worsening liver function or other causes [164]. Besides the entry criteria, the AFP value, and the Child-Pugh class [165,111] can affect the success rate of the downstaging.

An Italian consensus conference on the allocation criteria for LT [166] and a recent "position paper" of the Italian Association for the Study of the Liver [167] did not report criteria of eligibility for the downstaging. What was considered utmost important is the complete or at least partial response to loco-regional or systemic therapies (absolute or biological downstaging), after which patients can be allocated to the category with the highest priority for LT, given the relatively good prognosis after surgery and the temporariness of the results of locoregional treatments to contain the tumor [166].

The term "downstaging" refers to the attempt to reduce the tumor burden throughout liver resection, locoregional therapies such as transarterial chemoembolization (TACE) followed by resection or ablation [112,163,111,168–180] or transarterial radioembolization [181,182] or even systemic therapy, in order to bring back the patient within the transplant criteria adopted by the reference transplant center.

The downstaging can be distinguished in "relative" and "absolute". Relative downstaging has the purpose of bringing the patient back into the transplant criteria adopted by the center. Most of the studies which used this criterion (also defined as "morphological") included the patients in advanced or intermediate stage and without vascular or biliary invasion who were considered transplantable when downstaging reported the tumor within the Milan criteria (Milano-in) [168–171].

A seminal retrospective study by Otto et al. [179] indicated that patients with partial response to TACE had a 5-year survival after LT comparable to that of *ab initio* Milano-in controls, regardless of they met the Milan criteria. Subsequent studies confirmed that the response to locoregional therapies is a key factor to guide the selection of candidates for LT, being able to identify those patients with a favorable tumor biology which, in turn, leads to low post-transplant recurrence rates [112,111,180]. Therefore, a good radiological response to locoregional therapy *before* listing (downstaging) or *while waiting LT* (neoadjuvant therapy) detect the cases for which good medium- and long-term results can be expected. In fact, the good response to treatment is often associated with histopathological markers of good prognosis, such as the absence of micro-vascular invasion and a medium-low degree of tumor undifferentiation [170,182].

Furthermore, to better understand the degree of aggressiveness of the neoplasm, the majority of downstaging protocols adopt the so-called "time test", i.e., the presence of a "stability" of the result achieved with loco-regional therapies for a certain time (usually at least 3 months). The good response to therapy and its "stability" make downstaging (relative or absolute) a better selection system than morphological stage classification [112].

Moreover, a recent American study [172] has highlighted the prognostic role of alpha-fetoprotein (AFP) in patients undergoing downstaging, showing that the reduction of AFP levels below pre-defined values (for example, 500 or 100 ng/mL) heralds LT results similar to those obtained with *ab initio* Milano-in patients. Such an information underlines the importance of considering, besides the radiological response to therapy, the treatment-induced changes in biological indicators of tumor aggressiveness [18].

Of note, the unique randomized controlled study available on this topic [112] included 45 patients with HCC beyond the Milan criteria, no macrovascular invasion or extrahepatic tumor extension, good liver function (Child-Pugh class A–B7) and estimated post-transplant survival of at least 5 years, who had responded to downstaging with locoregional, surgical or systemic therapy and had received sorafenib for at least 3 months. The mean age was 57, 98.5% they were male. Patients were then randomized to receive LT

or to continue to receive locoregional, surgical (liver resection, ablation, TACE and SIRT in various combinations) or systemic therapy. The mortality (with a mean follow-up of 5 years) was remarkably lower in transplanted patients than in the counterpart (HR 0.32, 95% CI 0.11 – 0.92). Even the progression-free survival was clearly in favor of LT (HR 0.20, 95% CI 0.07 – 0.57).

A prospective observational study [174] conducted in China included 66 patients with intermediate HCC that met the following selection criteria for downstaging: single tumor <8 cm or 2–3 tumors <5 cm and total diameter <8 cm, without vascular invasion and who had responded to locoregional downstaging therapy (TACE and/or thermal ablation). The patients underwent resection (n. 35) if they had cirrhosis and preserved liver function or LT (n. 31) if resection was not feasible for anatomical reasons and a live or deceased donor liver was available (n. 31). The mean age was 44 years; males were 60%. The baseline characteristics of patients were similar in the two groups. The study showed a mortality tendentially but not non significantly lower after LT compared to successful resection (HR 0.72, 95% CI 0.32 – 1.62).

Therefore, although most of the evidence currently available regarding the downstaging comes from uncontrolled studies, they would indicate that this procedure, when succeeds in reducing tumor mass, is associated with a post-transplant survival similar to that obtained in patients who *ab initio* respect to the selection criteria for transplantation adopted by the center [168–180,183].

Even recurrence-free survival appears to be often superimposable, although a recent work reports a non-significant increase in recurrences in the downstaging group compared to controls at 5-year (18). Similarly, an Italian single-center study including 43 patients who successfully underwent downstaging (transition from stage T3 to T2) reports a lower 5-year survival of down-staged patients (although not significantly) compared to patients initially in stage T2 (62% vs 76%) and a higher rate of tumor recurrence (20.9% vs 7.6%) [184].

Clinical recommendation: In patients with HCC beyond the oncological transplant criteria adopted by the center, the panel recommends to perform the downstaging procedure aimed at bringing the patient back to the adopted transplant criteria compared to all other therapies without transplantation.

Certainty in evidence: Low.

Strength of recommendation: Strong in favor of transplantation.

5. Future perspective

Future studies and up-dated treatment guidelines should: 1) evaluate the role of systemic therapies in conversion strategies [9] in a perspective of a forthcoming evolution in the management of advanced HCC; 2) evaluate the impact of adjuvant strategies [185–187]; 3) better define the role of pre-planned combined treatment strategies; 4) assess the surrogacy of intermediate radiological endpoints across different HCC stages and treatments; 5) include liver-related evolutionary events [187–191] to better understand competing risks with survival.

Given the complexity of the disease and the large number of potentially useful therapies, it is not surprising that the expertise of many physicians is required to provide optimal care to patients with HCC; so, patients diagnosed with liver cancer on cirrhosis should be referred to multidisciplinary teams. Finally, the role of *expert multidisciplinary tumor board*, able to adopt a personalized therapeutic approach tailored to the characteristics of each patient, should be further evaluated, and emphasized.

Conflict of interest

The authors declare that there are no conflicts of interest.

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