Review Article

Position paper of the Italian Association for the Study of the Liver (AISF): The multidisciplinary clinical approach to hepatocellular carcinoma

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ARTICLE INFO

ABSTRACT

Patients with hepatocellular carcinoma should be managed with a multidisciplinary approach framed in a network where all the diagnostic techniques and therapeutic resources are available in order to provide the optimal level of care.

Given this assumption, the Coordinating Committee of the Italian Association for the Study of the Liver nominated a panel of experts to elaborate practical recommendations for the multidisciplinary management of hepatocellular carcinoma aiming to provide: (1) homogeneous and efficacious diagnostic and staging work-up, and (2) the best treatment choice tailored to patient status and tumour stage at diagnosis.

The 2010 updated American Association for the Study of Liver Disease Guidelines for hepatocellular carcinoma were selected as the reference document. For each management issue, the American Association for the Study of Liver Disease recommendations were briefly summarised and discussed, according to both the scientific evidence published after their release and the clinical expertise of the Italian centres taking care of these patients. The Italian Association for the Study of the Liver expert panel recommendations are finally reported.

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1. Introduction

Patients with hepatocellular carcinoma (HCC) should be managed with a multidisciplinary approach framed in a network where all the diagnostic techniques and therapeutic resources are available in order to provide the optimal level of care.

Given this assumption as the pre-requisite to adequately approach all patients with known or suspected HCC, the following recommendations of the Italian Association for the Study of the Liver (AISF) aim at providing: (1) homogeneous and efficacious diagnostic and staging work-up, and (2) the best treatment choice tailored to patient status and tumour stage at diagnosis.

The AISF Coordinating Committee nominated a panel of experts, mainly composed by the Scientific Committee of the AISF Monothematic Conference on HCC held in Taormina, Italy, in 2009, with the scope to elaborate practical recommendations for the multidisciplinary clinical approach to HCC.

The 2010 updated American Association for the Study of Liver Disease (AASLD) HCC Management Guidelines [1] were selected as the reference document, because they were the most recent guidelines applied to Western populations available at the time of drafting this document. We believe that several aspects in the HCC management need to be revised according to both the scientific evidence published after their release and the clinical expertise of the Italian centres taking care of these patients. Thus, for each management issue, the main AASLD recommendations are briefly summarised and discussed, outlining the reasons for their modifications whenever useful, followed by the presentation of the relevant AISF recommendations.

The level of evidence and strength of recommendation were graded according to the March 2009 updated version of the Oxford Centre for Evidence-Based Medicine Level (www.cebm.net) and reported in parentheses for each statement [2]. The concordance rate between operators in assigning the levels of evidence was >90%.

2. Epidemiology of HCC in Italy

Epidemiology of primary liver cancer in Italy is based upon data derived from clinical practice and may therefore suffer from mis-classification of metastatic tumours in the liver. According to the 2009–2011 report of the Italian Association of Tumor Registry, covering 50% of the Northern, 25% of Central, and 18% of the Southern Italian/Italian Islands population, the most common primary liver cancers in the period 1998–2002 were HCC (79%), cholangiocarcinoma (6%), carcinoma (5%), adenocarcinoma (4%), and malignant tumours (2%) [3]. The diagnosis of primary liver cancer was based on histology in 31% of cases.

Primary liver cancer represents the 7th most common tumour in males (4% of all cancers) and the 13th most common tumour in females (2.3% of all cancers), with a prevalence of 53/100,000 in males and 22/100,000 in females (male-to-female ratio = 2:1). The lifetime (up to 74 years of age) risk of diagnosis of HCC is 17‰ in men (1/59) and 5‰ in women (1/199). Primary liver cancer is the 5th cause of mortality in men (3rd in subjects 50–69 years old) and the 7th in women (4.5% of malignancy-related mortality).

According to recent estimates based on the World Health Organization report, the age-adjusted mortality rate for HCC in Italy in 2009 was 4/100,000 in men and 1/100,000 in women, with a 34% and 41% decrease as compared to the year 2000, respectively [4]. The incidence/mortality ratio of primary liver cancer in both men and women is close to 1.0 (approximately 1.3), thus emphasising the short-term lethality of this tumour. In Italy, the 5-year age-standardised relative survival of patients with primary liver cancer is 15% with a rather homogenous distribution within the country [3].

In most cases, HCC develops in patients with cirrhosis and therefore the risk factors for HCC and chronic liver disease are overlapping. According to the Italian Liver Cancer (ITA.LI.CA.) database, the most common cause of HCC in Italy in the period 2002–2008 was hepatitis C virus (HCV) infection (49%), followed by alcohol abuse (21%), mixed viral hepatitis plus alcohol abuse (12%), and hepatitis B virus (HBV) infection (13%) [5].

3. Surveillance

3.1. Target population

3.1.1. Summary of 2010 AASLD guidelines

Patients at risk of developing HCC should be enrolled in surveillance programmes for early tumour diagnosis. The annual incidence of HCC that triggers a favourable cost/efficacy surveillance programme is 0.2% in chronic hepatitis B and 1.5% in cirrhosis. These thresholds are reached by all cirrhotic patients and by some categories of patients with chronic HBV and HCV infection. Among HCV patients who have obtained a sustained virological response (SVR) to antiviral treatment, cirrhotic patients should continue surveillance, while non-cirrhotic individuals should not undergo surveillance because they have a low risk of developing HCC. Surveillance of patients on liver transplantation (LT) waiting list is recommended because HCC provides transplant priority, and the identification of tumours exceeding the accepted limits for LT would result in de-listing.

3.1.2. AISF expert panel comments

The fundamental pre-requisite for surveillance is the absence of contra-indication to curative and palliative treatment of HCC. Therefore, among cirrhotic patients, surveillance should be performed in Child-Pugh class A and B patients, and class C patients

Table 1
Adult patients at risk of developing hepatocellular carcinoma in whom surveillance is recommended.

- Cirrhotic patients, Child–Pugh class A and B (evidence 2b, strength B)
- Cirrhotic patients, Child–Pugh class C awaiting liver transplantation (evidence 5, strength D)
- Non cirrhotic patients with chronic hepatitis B or inactive hepatitis B carriers with viraemia >2000 UI/ml (evidence 3b, strength B for Western patients; evidence 1b, strength A for Asian patients)
- Non cirrhotic patients with chronic hepatitis C and liver fibrosis ≥F3 Metavir (o ≥10 kpa at transient elastography [Fibroscan®]) (evidence 5, strength D for Western patients; evidence 3b, strength B for Asian patients)
- Successfully treated patients with chronic hepatitis B and C (undetectable viraemia), but belonging to any of the previous at risk categories prior to starting antiviral treatment (*evidence 5, strength D*)

N.B.: surveillance is recommended for all the above patients if they do not have contraindications to radical and effective palliative treatments.

who are on LT waiting list, as surveillance is not associated with increased survival in class C patients not amenable to LT [6]. Besides the categories proposed by the AASLD, the AISF panel of experts felt that among non-cirrhotic patients with HBV and HCV there are some sub-categories where the probability of developing HCC is high enough to make surveillance cost-effective (Table 1).

3.2. Surveillance tests and interval

3.2.1. Summary of 2010 AASLD guidelines

Surveillance is based on repeated liver ultrasound at 6-month intervals. Ultrasound sensitivity for HCC is 94% but decreases to 63% for early tumours, defined as one nodule <5 cm or three nodules each <3 cm, without macrovascular invasion [7]. Sensitivity for early tumours improved by only 6% with the concurrent assessment of alpha-fetoprotein [7]. At present, there is no role for alpha-fetoprotein or other oncomarkers in HCC surveillance. In some subjects, the visibility on ultrasound may be inadequate, but there are no sufficiently tested strategies to overcome this technical limit. The performance characteristics of computed tomography (CT) scanning in the surveillance setting are unknown, and therefore this technique cannot be recommended as an alternative to ultrasound in such patients.

The 6-month surveillance interval is supported by several evidences: (a) the mean doubling time of tumour volume is around 6 months [8]; (b) semiannual surveillance offered a better survival as compared with care on demand in a randomised prospective trial [9]; (c) this interval was superior to the 12 month interval in both a prospective and a retrospective study [10,11] and in a meta-regression analysis [7].

3.2.2. AISF expert panel comments

Liver ultrasound is the recommended HCC surveillance test, and the recommended surveillance interval is 6 months. The increase in surveillance sensitivity of the combination of ultrasound and alpha-fetoprotein (6–8%) as compared to ultrasound alone is off-set by an increase in false positives (from 2.9% to 7.5%) and costs (from 2000 USD to 3000 USD *per* tumour identified) [7,10], thus this combination is not recommended also by the AISF panel of experts.

The diagnostic accuracy of ultrasound is highly dependent on both operator's expertise and patient's characteristics (*e.g.*, body mass index, ascites, intestinal gas, thoraco-abdominal malformations, coarse liver echo-pattern, patient compliance with breathing commands). Thus, ultrasound should be performed by a trained operator in liver ultrasound [12]. When technical issues limit its accuracy, this should be highlighted in the report and the possible

integration of ultrasonography with a radiological contrast-enhanced technique (CT, magnetic resonance imaging [MRI]) should be considered [12–14]. In those patients who are awaiting LT and present a coarse liver echo-pattern, which may impair identification of small tumours, surveillance can be performed with CT or MRI every 6 months, taking into account that the expected surveillance duration is rarely longer than 1 year and it has been reported that these techniques are associated with a better cost/efficacy ratio [12].

The 6-month surveillance strategy is preferred to the 12-month schedule because: (1) identifies smaller lesions; (2) is associated with increased survival (even after adjustment for the lead-time bias) through identification of tumours at an earlier stage, which are more often amenable to curative treatment; (3) is the best cost/efficacy strategy independently of aetiology of liver disease [11,13,15].

Shortening the surveillance interval to 3 months does not lead to a better outcome in terms of: (1) cumulative incidence of HCC diagnosed with a size of either ≤3 cm or ≤2 cm; (2) feasibility of HCC treatment; (3) liver-related death; and (4) rate of recall procedures and surveillance-associated costs [16].

3.2.3. AISF expert panel recommendations

- **Patients at risk of HCC development (Table 1) should be enrolled in surveillance programmes for early tumour detection (*1a-A*). Candidates for liver transplantation should be screened regardless of Child-Pugh class, in order to detect tumours exceeding conventional criteria and modify priority in the waiting list (*5-D*).**
- **Surveillance should be based on periodic liver ultrasound (*2a-B*) performed by an experienced operator (*5-D*). In the presence of conditions clearly limiting the accuracy of ultrasound, CT scan or MRI may be proposed as supplementary imaging techniques (*5-D*). In patients awaiting liver transplantation and presenting a coarse liver echo-pattern, surveillance should be carried out with CT or MRI (*5-D*).**
- **The measurement of alpha-fetoprotein is not indicated as a surveillance tool as its use, alone or in combination with ultrasound, does not improve the cost/efficacy ratio of surveillance (*2b-B*).**
- **A surveillance interval of 6 months is recommended (*2a-B*). Shortening the interval to 3 months, even in patients at higher risk of developing HCC (*5-D*), is not associated with any prognostic improvement and may worsen the cost/efficacy ratio of surveillance (*1b-A*).**

4. Recall procedures

4.1. Summary of 2010 AASLD guidelines

The detection of any new focal lesion during ultrasound surveillance should immediately prompt a diagnostic recall strategy that varies according to the size of the lesion. The recall strategy for lesions ≥1 cm is based on contrast-enhanced imaging techniques with use of vascular contrast media. The lesion should be assessed prior to contrast injection and after contrast injection in the arterial, portal and venous phases (dynamic contrast imaging) at either CT or MRI. A diagnosis of HCC can be established when the typical vascular pattern is observed, that is a contrast uptake (hyper-enhancement) in the arterial phase ("wash-in") followed by "wash-out" (the lesion becomes hypo-enhancing) in the portal or venous phase. If the radiological behaviour is not typical for HCC, the lesion should be assessed by the alternative imaging technique (either CT or MRI) or undergone biopsy. Bioptic samples
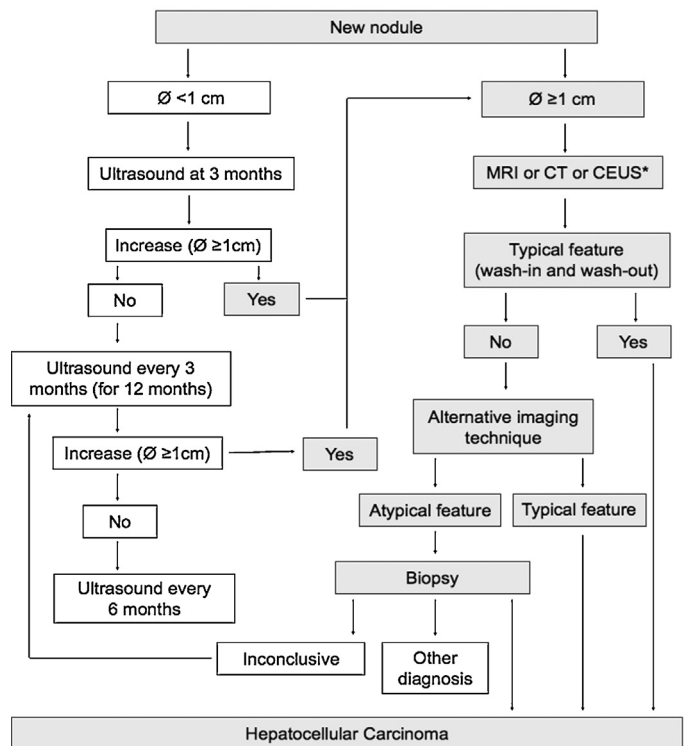

Fig. 1. Diagnostic algorithm and recall policy for cirrhotic patients with a new nodule detected during ultrasound surveillance. *Since magnetic resonance imaging (MRI) or computed tomography (CT) would be performed for hepatocellular carcinoma staging after detection of a nodule by ultrasonography, the most cost-effective approach is to prescribe in first line MRI or CT and to resort to contrast-enhanced ultrasonography (CEUS) in case of inconclusive diagnosis at MRI and/or CT.

should be assessed by a pathologist expert in the evaluation of liver lesions, and the histological evaluation should include the use of tissue markers to increase the diagnostic yield. Lesions <1 cm should be entered into an enhanced follow-up programme based on ultrasound repetition at 3–6 months interval, as the probability of achieving a definitive diagnosis at this stage is small, due to high rate of non-diagnostic imaging and difficulties in obtaining appropriate tissue sampling. If the size of such lesions does not increase over a 2-year period, the semiannual surveillance can be restored.

Alpha-fetoprotein should not be used as a diagnostic test due to the possibility of elevated levels in patients with non-HCC malignancies and non-malignant diseases.

4.2. AISF expert panel comments

The proposed recall strategy for nodules identified during surveillance is similar to that of AASLD guidelines (Fig. 1). In the AASLD algorithm contrast-enhanced ultrasound (CEUS) was not included among the imaging techniques for the diagnosis of HCC of a lesion detected during surveillance. This exclusion has been related to report of few cases in which the "wash-in/wash-out" pattern was found to occur in histologically proven intra-hepatic cholangiocarcinoma (ICC) [17–19]. Conversely, the AISF expert panel considers the available scientific evidence not sufficient to remove CEUS from the diagnostic tools since a CEUS pattern typical for HCC has a positive predictive value >95% [13,18]. Furthermore, ICC currently accounts for 1–2% of all new nodules detected in cirrhosis [17,18] and, among them, only half shows the typical HCC pattern at CEUS [19,20]. The wash-in/wash-out pattern at CEUS of a nodule in cirrhosis should be regarded specific for malignancy and, unless highly discordant findings with MRI or CT are observed (namely ring arterial enhancement and/or progressive increase in

contrast uptake in delayed CT/MRI vascular phase), it should be considered indicative of HCC, without the need for biopsy. However, due to the need of CT or MRI for tumour staging, use of CEUS as first line approach, despite possible, does not appear to be the most cost-effective strategy [21].

MRI has higher sensitivity than other imaging techniques for the detection of the typical vascular pattern in HCC <2 cm [10,22,23]. MRI is also superior for the detection of hypovascular HCC (lacking arterial hyper-enhancement) when hepatocyte-specific contrast agents and post-vascular phase assessments are employed [24]. A pre-contrast hyperintensity in T2 acquisitions with the diffusion-weighted technique, and an enhancement defect in the post-vascular (hepato-biliary) phase with hepatocyte-specific contrast agents support the diagnosis of malignant lesion. However, these features alone are not accepted as markers of HCC in the absence of the typical vascular pattern [25]. The minimal technical requirements of contrast-enhanced CT and MRI for the diagnosis of HCC are reported online in Supplementary Materials.

Considering that the main goal of surveillance is to identify very small HCC (<2 cm) that carries much lower risk of satellite nodules and microvascular invasion as compared to larger lesions [26,27], and that some HCCs may have a doubling time of approximately 30 days [8], the AISF expert panel suggests that the most appropriate interval for surveying nodules <1 cm or larger nodules with a biopsy negative for malignancy is 3 months.

Although Eastern guidelines propose that a serum level of alpha-fetoprotein >400 ng/mL is diagnostic for HCC within the frame of a recall strategy in patients at risk [14,28], the AISF expert panel does not support its use, considering the possibility of false positive results in patients with non-malignant diseases or malignancies other than HCC.

4.3. AISF expert panel recommendations

- **Any new nodule identified during ultrasound surveillance in patients at risk for HCC should be regarded as HCC until otherwise demonstrated, prompting recall procedures that should be performed within a reasonable time interval in order to allow definite diagnosis and treatment when tumour is small (<2 cm)** (Fig. 1, *2b-A*).
- **In patients not included in the categories at risk for HCC listed in** Table 1, **the *a priori* probability that a focal liver lesion is HCC is unknown, and the final diagnosis must be based on histology (*3b-B*).**
- **When hepatic nodule(s) and the underlying liver disease are simultaneously identified, the criteria for HCC diagnosis are the same adopted for nodules identified during surveillance if the patient belongs to one of the categories at risk for HCC reported in** Table 1.
- **Alpha-fetoprotein should not be considered a diagnostic test for HCC (*3b-B*).**
- **If available, any previous diagnostic imaging should be reviewed by an expert radiologist at the Institution where the patient will be managed (*5-D*). Otherwise, the appropriate diagnostic technique should be repeated. CEUS performed by operators with specific expertise in liver diseases can be used to characterise nodules presenting in cirrhotic livers (*1b-A*).**
- **The non-invasive diagnosis of HCC is based on typical features (homogeneous hyper-enhancement of the lesion in the arterial phase, followed by hypo-enhancement in the venous or delayed phase) at dynamic contrast-enhanced imaging techniques (CT, MRI, or CEUS) (*2b-B*). Multiphasic MRI with hepatocyte-specific contrast medium may provide additional clues to the diagnosis of HCC (*1a-A*) and is superior to CT for intra-hepatic staging of the tumour (*2b-A*). A global "wash-in" followed by a very rapid (<60 s) and marked "wash-out"**

at CEUS should be regarded as not completely typical for HCC and as potential indicator of non-hepatocellular malignancy (*e.g.*, intrahepatic cholangiocarcinoma) (*5, D*).
- **Histological assessment of the nodule should be performed by pathologists expert in liver tumours (*5-D*).**
- **If biopsy is negative for malignancy, a strict monitoring at 3-month intervals is recommended. The diagnostic recall strategy should be restarted if the lesion changes in size or morphology (*5-D*).**

5. Staging

5.1. Summary of 2010 AASLD guidelines

Tumour stage, residual liver function, patient performance status (PS), and the impact of treatment on survival should be taken into account in order to comprehensively stage a patient with HCC. The Barcelona Clinic Liver Cancer (BCLC) staging system is the only staging system that includes all these parameters, its main advantage being the possibility to link patient stage to treatment and to assess prognosis on the basis of the survival rates reported by the literature for each treatment option [29].

5.2. AISF expert panel comments

There is not an universal accepted and optimal staging system for HCC, as the accuracy of each staging system becomes suboptimal when applied to populations showing a different prevalence of HCC stages from that observed in the population where the staging system was developed. Although the AISF expert panel endorses its use, the BCLC staging system carries some limitations represented by: (1) a unique treatment option for each stage; (2) absence of indications regarding second-line or combined/sequential treatments; (3) inclusion of a very heterogeneous population in the intermediate stage (BCLC B) in terms of liver function and tumour burden; (4) assignment to the advanced stage (BCLC C) of all patients with a PS 1. In the ECOG scale, PS1 refers to patients restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, *e.g.*, light house work, office work; the panel of experts does not consider this condition a contraindication for HCC treatments.

The utility of alpha-fetoprotein as prognostic marker is still debated, and several prognostic systems do not incorporate this variable. However, over time changes of serum alpha-fetoprotein may be useful to assess response to loco-regional and systemic treatments in patients with baseline values >200–400 ng/mL, and to evaluate the risk of drop-out from LT waiting list [30–32].

The AASLD Guidelines do not provide recommendations on how to assess global tumoral burden and to identify extra-hepatic metastases. The AISF expert panel suggests the use of "panoramic" imaging techniques, such as CT or MRI, with the latter being preferred due to its greater accuracy for hepatic nodules <2 cm of diameter [10,22,23]. However, the advantages of greater accuracy is maximal in patients in the early stage, where detection of additional HCC tiny nodules may produce a stage migration and where the small size of nodules make diagnosis of HCC more challenging. Conversely, in the intermediate and advanced BCLC stages, the detection of additional intrahepatic nodules usually does not affect the treatment strategy. Moreover, as the likelihood of extra-hepatic spread becomes higher at the latter stages, a chest and bone investigations are more strongly recommended. To this end, the slightly lower accuracy of CT for intrahepatic nodules detection in comparison to MRI is largely outbalanced by the possibility of obtaining both an abdominal and chest investigations (plus

additional bone study for the structures contained in these regions) in the same session, at much cheaper costs and shorter times.

A bone nuclear scan is requested only upon clinical suspicion of bone involvement not solved by the already available imaging techniques.

Positron emission tomography (PET) scan is not useful for staging because it has a lower resolution as compared to CT and MRI, and some HCCs do not show increased glucose up-take [12].

Finally, the presence of esophageal varices should be always assessed by upper digestive endoscopy in cirrhotic patients as it represents an independent predictor of death [33].

5.3. AISF expert panel recommendations

- **The BCLC is the recommended staging system for HCC (*1b-A*).**
- **Patients should not be included in the advanced stage (BCLC C) when assignment is solely due to the presence of a PS 1 (*5-D*) and the relationship between symptoms and the tumour is uncertain.**
- **In patients with markedly elevated or progressively increasing levels, alpha-fetoprotein may provide useful prognostic information to assess the response to loco-regional and systemic treatments and the risk of drop-out from LT waiting list (*2b-B*). Thus, the AISF expert panel recommends assessment of alpha-fetoprotein levels prior to commencing any treatment for HCC. However, it cannot be used to guide therapeutic decisions based on the best scientific evidence currently available.**
- **Intra-hepatic staging of HCC should be assessed by MRI whenever the patient appears to be a potential candidate to surgical or ablative treatments, as this radiological technique is more accurate, though more expensive, than CT (*4-C*). CT can be preferred when the availability of MRI may delay diagnosis and staging or if the MRI results may be affected by technical limitations (*5-D*).**
- **HCC staging should include a chest CT scan when the patient is a candidate to surgery or HCC is beyond the Milan criteria (*4-C*). In the latter instance, abdominal + chest CT might be considered the most convenient approach for tumour burden assessment. However, in candidates to resection with HCC <2 cm, CT scan of the chest is not mandatory, due to the very low probability of extra-hepatic spread, and may be replaced by a chest X-ray film.**
- **Staging of patients with cirrhosis and HCC should include the assessment of portal hypertension-related bleeding risk (*4-C*).**

6. Treatment

The BCLC is the only staging system that proposes a therapeutic algorithm for HCC. However, the AISF expert panel points out that BCLC treatment allocation should be considered as a "general frame" indicating the most beneficial treatment option for most patients included in each stage of the disease according to available trials. The definitive therapeutic choice should be personalised at the individual level, taking into account several clinical variables and regional organisational settings that may lead to combined/sequential treatments (*5-D*). Inclusion of patients into therapeutic trials is suggested in the case of contra-indications to conventional treatment or treatment failures (*5-D*).

6.1. Surgical resection

6.1.1. Summary of 2010 AASLD guidelines

Patients presenting with a single HCC may benefit from hepatic resection in the absence of cirrhosis or, in patients with cirrhosis, if they have normal serum bilirubin and no clinically significant portal hypertension (hepatic venous pressure gradient <10 mmHg). The

risk of HCC recurrence after resection exceeds 70% at 5 years. Recurrence includes both dissemination, which typically occurs within the first 3 years, and *de novo* occurrence of cancer, which is the most common cause of HCC recurrence, usually at sites distant from the resected area. Predictors of recurrence are microvascular invasion and the presence of satellite lesions. There are currently no treatments capable of preventing HCC recurrence after resection. In this setting, neo-adjuvant and adjuvant therapies are not recommended.

6.1.2. AISF expert panel comments

There is solid evidence that liver resection can be successfully carried out also in patients with portal hypertension and multiple hepatic lesions, when properly selected [34,35].

The size of the nodule ("single large HCC") has a lesser impact for resection than for loco-regional therapies [36–38] and, therefore, these tumours should be firstly considered for surgical resection.

In the presence of multinodularity, portal hypertension or hyperbilirubinemia surgery may be proposed in strictly selected cases on the basis of multidisciplinary evaluation of the patient. Variables to be assessed in order to minimise the risk of postoperative hepatic irreversible decompensation include number and location of the nodules, extent of the resection necessary for radical surgery, possibility of a laparoscopic approach, Model for End-stage Liver Disease (MELD) score, serum sodium, comorbid illnesses, and patient general conditions [34,35,39–41].

For patients with HCC arising in a non-cirrhotic liver, who often present with large tumours (average size 8 cm), surgical resection is the first line therapy since they tolerate large surgical parenchymal sacrifice [42].

Based on the observed risk of developing an irreversible liver failure after hepatic resection, two promising selection protocols, derived from large case-series, have been proposed. Japanese authors have based the case selection on serum bilirubin level, indocyanine green retention rate at 15 min and expected extension of surgical resection [43], whereas an Italian protocol relies on MELD score, serum sodium level, and expected extension of hepatectomy [34]. However, before their implementation in clinical practice, the AISF expert panel considers necessary an external validation.

Some studies report 5-year survival rates after surgery >20–30% in selected HCC patients with peripheral vascular invasion (portal branches of II and III order) [36,44]. Nonetheless, the AISF Committee recommend that this advanced surgery should be considered only in the setting of a multidisciplinary evaluation of the patient and in controlled prospective studies aimed at identifying individually tailored therapies for advanced HCC.

Laparoscopic HCC resection in cirrhotic patients is now practiced in highly specialised centres with results comparable to those of conventional resection, but with less morbidity and at lower costs [45].

For neo-adjuvant and adjuvant therapy see Section 6.4.

6.1.3. AISF expert panel recommendations
- **For patients with solitary HCC and preserved liver function without evidence of portal hypertension, liver resection is a first choice treatment. This is particularly true for HCC 2–5 cm, whereas for smaller HCC (<2 cm) the clinical outcome of surgery is comparable to radiofrequency thermal ablation (RFTA) if this can be safely and effectively performed (see also Section 6.3.2). As the only available radical treatment for single HCC > 5 cm is surgical resection, the feasibility of this option should be always assessed also in these patients, preferably in a multidisciplinary setting. (*3b-B*).**
- **In the presence of portal hypertension, hyperbilirubinemia, or multinodularity, patients must be evaluated by a**

multidisciplinary team with great expertise, and the surgical option must be accurately weighed against the risk of decompensation after surgery (*4-C*).

- **Considering the current evidence, the utility of resection in patients with peripheral portal invasion should be validated in comparative clinical studies with the standard palliative treatment which, should be carried out in centres where highly qualified liver surgeons are available.**
- **Liver resection is the treatment of choice in patients with HCC arising in a non-cirrhotic liver (*3b-B*).**
- **After surgical resection, diagnostic imaging should be repeated quarterly during the first 2 years. Thereafter, clinical and imaging assessment could take place twice a year (*5-D*). Radiological assessment 1 month after surgery is considered optional and should be carried out in relation to the individual oncological profile (*5-D*).**

6.2. Liver transplantation

6.2.1. Summary of 2010 AASLD guidelines

Transplantation is an effective treatment option for HCC patients who meet the Milan criteria, and currently no recommendations can be made regarding the opportunity to expand these criteria. A pre-transplant treatment for HCC is considered appropriate if a waiting list period exceeding 4–6 months is expected.

Regarding living donor liver transplant (LDLT), decision-analysis models suggest that its cost-effectiveness becomes favourable if the waiting list time exceeds 7 months. However, LTLD is a very complex procedure that should be performed only by highly skilled surgeons, in order to ensure the lowest possible risk of morbidity (20–40% in different series) and mortality (0.3–0.5%) to the donor.

There are insufficient data to recommend or discourage the use of specific immunosuppressive therapies in order to reduce the growth of extra-hepatic tumour lesions not diagnosed before LT.

6.2.2. AISF expert panel comments

In patients with HCC and decompensated cirrhosis, treatments for HCC are limited/prevented by the advanced stage of the cirrhotic disease [34,39–41]. Therefore, LT represents the therapy of choice in these patients when the tumour burden falls within the Milan criteria [46–48].

LT can provide excellent results even in patients with cancer exceeding the Milan criteria, provided they meet other criteria, such as those proposed by the University of San Francisco [49], the "up-to-seven" criteria (sum of largest nodule size in centimetres *plus* number of nodules ≤7) [50], or considering the "total tumour volume" (maximum total tumour volume ≤115 cm^3) [51]. Moreover, promising results have been obtained with the "down-staging" treatment strategy [52,53]. In patients outside the Milan criteria, tumour size seems to be the most important prognostic factor for the recurrence risk, whereas the impact of nodule number is controversial [51,52,54]. In any case, vascular invasion and presence of extra-hepatic spread are absolute contraindications to LT due to the extremely high risk of death from HCC recurrence.

Patients with a tumour burden close to the accepted limits for inclusion in the waiting list have a high risk of being excluded for disease progression, even when the waiting period is ≤6 months. Therefore, they could benefit from neo-adjuvant therapy. However, there is yet not strong evidence of the usefulness of loco-regional therapies (ablation, trans-arterial chemioembolisation [TACE]) in reducing the risk of drop out from waiting list [55]. From a prognostic point of view, there are pre-operative indicators of biological aggressiveness of the tumour, such as serum alpha-fetoprotein, the rate of uptake of the standardised ^{18}F-fluoro-deoxyglucose

by the tumour, and poor histological differentiation at biopsy [56,57].

The AASLD guidelines do not provide indications about the issue of transplant list priority. Assigning a fixed arbitrary extra-points to the biochemical MELD score of HCC patients may cause an imbalance in the probability of receiving the graft favouring HCC with respect to non-HCC candidates. Therefore, while awaiting more solid evidence, list priority should take into account not only the tumour progression risk, but also the response to neo-adjuvant therapy and the biochemical MELD score [58,59].

As compared to cadaveric LT, LDLT does not increase the risk of tumour or viral disease recurrence, and has a potential advantage especially in patients with MELD score >15, although it should be offered only by centres with significant experience in surgical resection and split LT [60,61].

As far as immunosuppression is concerned, a retrospective study reported a lower HCC recurrence rate in patients receiving either a low dose of calcineurin inhibitors or mTOR inhibitors as immunosuppressive regimen [62]. A retrospective study based on a large series of the "Scientific Registry of Transplant Recipients" found improved survival with the use of sirolimus in patients transplanted for/with HCC, and an opposed tendency in patients without cancer [63]. The validity of mTOR inhibitors to reduce the risk of post-LT HCC recurrence is still under investigation.

6.2.3. AISF expert panel recommendations

- **LT is a well established treatment for HCC patients, and the Milan criteria represent the benchmark for patient selection (*1a-A*).**
- **LT listing should be considered even in patients with intermediate stage HCC (BCLC B) slightly beyond Milan criteria. These patients should be (re)-evaluated at transplant centres adopting "expanded criteria" or "down-staging" protocols (*4-C*). Tumour vascular invasion and metastases always are absolute contraindications to LT (*4-C*). Due to the limited accuracy of the available indicators of recurrence, patients with non conventional criteria should be considered eligible for LT only in centres with well-established interventional algorithms or in the context of clinical trials (*5-D*).**
- **The decision to start neo-adjuvant (or "bridge") therapy while awaiting LT should be taken on a case-by-case basis and in a multidisciplinary setting (*5-D*). Neo-adjuvant therapy is generally desirable in the absence of contra-indications, and particularly for patients with an expected waiting time exceeding 6 months or with a tumour burden close to LT feasibility limits (*5-D*).**
- **The use of "fixed" arbitrary extra points to the biochemical MELD of HCC patients does not seem appropriate (*2b-B*). While awaiting more reliable tools, each transplant centre should standardise the priority given to HCC patients on the basis of the "urgency" principles, such as biochemical MELD, tumour extension, alpha-fetoprotein values and response to neo-adjuvant therapy (*3b-B*). Nonetheless, each transplant centre should periodically evaluate the transplant probability for listed patients with and without HCC, in order to correct any imbalance between the different patient categories (*5-D*).**
- **LDLT offers an additional option for improving survival of HCC patients, but it should be performed in highly qualified centres for liver resection and split LT. (*3b-B*). LDLT may be a good procedure for testing the results of transplant with extended criteria in controlled clinical trials as the use of a living donor does not harm patients with HCC within the Milan criteria as well as patients without HCC listed for cadaveric donation (*5-D*).**

- **Immunosuppressive therapy in patients undergoing LT with/for HCC should not differ from that adopted for non-tumoral patients when the tumour meets the Milan criteria and lacks aggressive biological features (high degree of de-differentiation, micro- or macro-vascular invasion). In patients with aggressive HCC, the use of mTOR inhibitors (sirolimus and everolimus) should be considered, given their anti-neoplastic properties together with the opportunity to reduce or eliminate the use of calcineurin inhibitors and their associated risks (*3b-B*).**

6.3. Ablation techniques

6.3.1. Summary of 2010 AASLD guidelines

Percutaneous ablation of HCC is a safe and efficacious treatment for patients with small HCC, who are not suitable for surgery or as a "bridging" therapy to LT. Percutaneous ethanol injection (PEI) and radiofrequency thermal ablation (RFTA) can be equally efficacious for lesions up to 2 cm. However, the necrotising effect of RFTA is more predictable and significantly better than with PEI for larger lesions. The evaluation of response to ablation techniques must be assessed with contrast-enhanced imaging techniques, and there are no data to prefer the use of either CT or MRI for this purpose. Although the optimal interval to assess response is not clearly defined, it is often suggested to evaluate response at approximately 1 month and thereafter every 3–4 months after the procedure. After 2 years of recurrence-free follow-up, this interval can be prolonged. In cases with increased alpha-fetoprotein before ablation and a serological response to treatment, an increase of this oncomarker during follow-up may suggest HCC recurrence. Nevertheless, alpha-fetoprotein assessment cannot replace radiological surveillance follow-up.

6.3.2. AISF expert panel comments

Three randomised studies on percutaneous ablation *versus* surgical resection have shown no overall and recurrence-free survival advantage with surgery [64–66]. A fourth randomised study carried out in 230 patients with HCC meeting the Milan criteria showed a superiority of surgery (with null peri-operative mortality) as compared to RFTA, regardless of size and number of HCCs [67]. Conversely, the most recent randomised controlled study did not show differences in the 3-year mortality rate between hepatic resection and RFTA in patients with a HCC <4 cm and up to two nodules, although the recurrence rate was greater in non surgical patients (42% *vs.* 32%) [68]. Lastly, a comparative study between surgery and RFTA carried out in patients with very early and early HCC (BCLC 0 and A) showed no survival difference after adjustment for confounding factors and the recurrence-free survival advantage provided by surgery was offset by RFTA repeatability [38]. A multi-centre, prospective study carried out in patients with single HCC ≤2 cm reported a complete tumoral necrosis (confirmed during follow-up) of 97%, with RFTA, without treatment-related mortality and negligible morbidity. Moreover, in the subgroup of patients without contra-indications to surgery, the 5-year survival rate was 68% [69]. Finally, a Markov model-based analysis has shown that "rescue" resection after incomplete HCC necrosis with RFTA offers a survival chance equivalent to that of patients treated with surgery as first-line approach. The same study also estimated that initial RFTA followed by "rescue" surgery would be the most appropriate approach when surgical mortality is >1% and the risk of persistence/recurrence after RFTA is <1.9% [70]. The AISF expert panel believes that any patient failing percutaneous ablation should be reassessed by a multidisciplinary team to choose the alternative treatment with the highest safety/radicality ratio, considering at first surgery unless definitively excluded

from resection already before percutaneous ablation. As compared to surgical resection, percutaneous ablation is associated with lower morbidity and mortality, shorter length of hospitalisation, and lower sanitary costs [65,67,68]. In patients not suitable to a percutaneous approach, ablation can be performed using a video-laparoscopic route, resulting a safe and efficacious method [71,72].

Meta-analyses of randomised controlled trial of comparative studies showed that RFTA is associated with lower local recurrence rates and longer survival than PEI [73,74]. However, complications of RFTA are more frequent and severe, and contra-indications are more frequent.

Percutaneous microwave ablation is increasingly being used in clinical practice for the treatment of HCC. The safety profile appears good, although specific confirmation in larger series of cirrhotic patients is still awaited [75]. In the only comparative study with RFTA, microwave ablation showed equivalent efficacy but required more therapeutic sessions [76].

Beside CT and MRI, CEUS has been successfully used for the assessment of response to ablation techniques [77–79].

6.3.3. AISF expert panel recommendations

- **For HCC ≤2 cm, in the setting of a multi-disciplinary evaluation, RFTA can be considered the first-line treatment when performed in expert centres (*3b-B*).**
- **For HCC of 2.1–3 cm, the choice between surgery and RFTA should be made on a case-by-case after a multi-disciplinary evaluation (*5-D*)**
- **Patients with nodules >3 cm should be treated with surgery, when feasible (*5-D*).**
- **In case of failure of percutaneous ablation, patients should be reassessed by a multidisciplinary team for the most appropriate treatment modality, at first considering surgery if feasible.**
- **When technically feasible, RFTA should be preferred to PEI due to better efficacy and predictability of treatment result (*2a-B*).**
- **In non-resectable cases where RFTA is not feasible (due to insufficient ultrasound visibility or proximity to hollow organs or coagulopathy), video-laparoscopic RFTA, performed in expert centres, should be considered (*5-D*).**
- **Response to ablation can be assessed with CEUS, MRI, or CT approximately 1 month after treatment, and every 3–4 months thereafter up to 2 years of follow-up. In this setting, CT or MRI should be performed every 6 months. After 2 years of follow-up without recurrence, the usual semiannual ultrasound surveillance programme can be re-started (*5-D*).**

6.4. Adjuvant therapy after radical treatment (surgery and ablation)

6.4.1. Summary of 2010 AASLD guidelines

Adjuvant or neo-adjuvant treatments are not recommended by the AASLD guidelines. However, there is evidence that these treatments may be able to reduce recurrence rates and improve recurrence-free survival after surgery or ablation. These treatments include acyclic retinoids, immunotherapy with autologous activated lymphocytes, lipodol-I^{131}-transcatheter arterial radio-embolisation (TARE), capecitabine, antiviral therapy (especially interferon) [80–83].

6.4.2. AISF expert panel comments

The AISF expert panel considers that adjuvant treatments were inconsistently associated with an increase in overall survival, and the evidence supporting their use was provided by small studies without external validation.

More solid data coming from the results of meta-analyses showed a survival benefit for adjuvant antiviral therapy with interferon in HCV infected patients [84–88].

6.4.3. AISF expert panel recommendations

- **Adjuvant therapy after surgery or ablation cannot be suggested on a routine basis but should be tested in prospective studies (*5-D*).**
- **When possible, antiviral therapy should always be considered, taking into account its favourable impact on the progression of liver disease and non-HCC-related mortality (*5-D*).**

6.5. Transcatheter arterial techniques

6.5.1. Summary of 2010 AASLD guidelines

Transcatheter arterial chemoembolisation (TACE) relies on the infusion into the arterial branches feeding the tumour of a chemotherapeutic agent suspended in Lipiodol, followed by an arterial occlusion with embolising agents, most often Gelfoam particles. Epirubicine, doxorubicine and cis-platinum are the chemotherapeutic agents most frequently used. An embolisation not coupled with infusion of a chemotherapeutic agent is defined transcatheter arterial embolisation (TAE).

TACE is the first-line treatment for patients with large, multifocal, unresectable tumours, in the absence of macrovascular invasion and extra-hepatic spread (BCLC stage B). Patients with Child-Pugh class B and C are not good candidates for TACE. The treatment is scheduled "*on demand*" or at fixed intervals, as there is no prospective comparison to support one or other strategy. TACE with Drug-Eluting Beads (DEB-TACE) reduces the frequency/severity of the post-TACE syndrome. A complete response to TACE is uncommon and cannot be ascertained by using the standard RECIST criteria.

Transcatheter arterial radio-embolisation (TARE) with lipiodol-I^{131} or Ittrium^{90} has tumoricidal effect and an acceptable risk profile but its impact on patients survival has not been ascertained, and therefore this technique cannot be considered standard of care.

6.5.2. AISF expert panel comments

Performing selective/super-selective TACE optimises treatment results, as confirmed by a pathologic study in explanted livers, showing complete response in 92% of tumours smaller than 3 cm [89]. In clinical practice, TACE is also used in some Child-Pugh B patients if not decompensated, since a few of these patients were included in the trials selected for the TACE meta-analysis showing a survival benefit [90]. Survival of Child-Pugh A and B7 patients treated with TACE is indeed similar, but it significantly declines in Child-Pugh B8-9 cases [91]. The results of TACE and TAE are not significantly different, despite a trend towards better results for TACE, while a complete response to TACE and TACE-like procedures is observed in $44 \pm 30\%$ of cases [92]. TACE can induce a liver damage, albeit generally not severe, but in 5–7% of the cases this procedure causes liver failure with a 30 days mortality of 2.4% [92]. Moreover, the frequent (>60% of cases) post-embolisation syndrome may worsen the quality of life, for weeks [92].

An European multicenter randomised study has shown that DEB-TACE is more effective than cTACE in terms of radiological response only in patients with more advanced disease (Child-Pugh B, ECOG 1, bi-lobar or relapsing HCC)) [93]. A small non-randomised study demonstrated a survival advantage with DEB-TACE as compared to conventional TACE (cTACE) [94], whereas a randomised trial did not confirm this result in patients with limited tumour burden [95].

The modified Response Evaluation Criteria in Solid Tumour (mRECIST) should be used to evaluate treatment response after TACE and, in this setting, MRI is more efficient than CT, especially
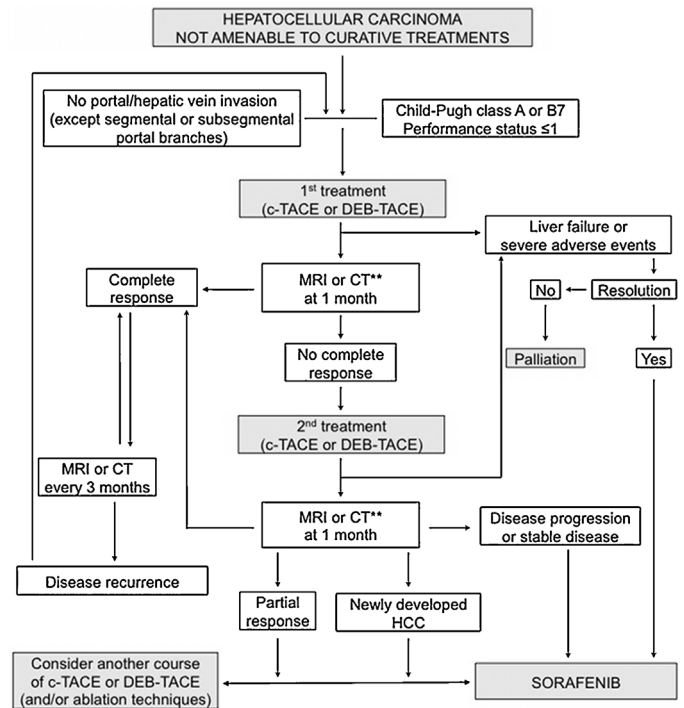
Fig. 2. Treatment algorithm for patients with hepatocellular carcinoma (HCC) undergoing transcatheter arterial chemoembolisation (TACE). *The therapeutic flowchart is valid for any session of TACE. **Magnetic resonance imaging (MRI) is preferable in case of conventional TACE (cTACE) since Lipiodol uptake causes beam hardening artefacts at computed tomography (CT) and may mask residual tumour tissue. Response to any treatment is defined according to the modified Response Evaluation Criteria in Solid Tumour (mRECIST).

in patients undergoing cTACE due to "beam-hardening" technical artefacts secondary to lipiodol retention [96,97]. CEUS is able to detect the viable portions of the target lesion(s) after TACE [98]. Radiological assessment of the response should be carried out with MRI or CT one month after TACE and every 3 months thereafter [99]. TACE retreatment should be considered useless if no objective response according to mRECIST criteria is observed after two consecutive treatments [99] (Fig. 2).

Two non randomised studies have demonstrated that TACE and TARE are not different in terms of both overall survival and toxicity, while toxic effects were lower with TARE in another large series of patients [100–102]. TARE was reported to be effective and well tolerated in patients with tumour portal vein thrombosis, when TACE is contra-indicated [103].

6.5.3. AISF expert panel recommendations

- **TACE is indicated in BCLC stage B patients, not eligible for surgery or ablation (*1a-A*). The best candidates for TACE are asymptomatic Child-Pugh class A patients (*1b-A*), although those with a Child-Pugh score of B7 or ECOG PS 1 can also be considered (*5-D*). TACE is not indicated in patients with jaundice, untreatable ascites, main or branch portal vein thrombosis, hepatofugal portal blood flow, HCC nodules larger than 10 cm.**
- **TACE can be utilised in patients with early stage HCC, if surgical or ablative techniques are not applicable due to technical conditions and/or comorbidities.**
- **TACE should be carried out with a selective or super-selective (segmental or sub-segmental) technique in order to optimise the risk/benefit ratio and increase the likelihood of complete response of the target lesion(s) (*2b-B*). In the case of bi-lobar HCCs not treatable with a super-selective approach, the option to treat a single lobe *per* session should be considered (*5-D*).**

- **The presence of peripheral, segmental portal invasion is not an absolute contra-indication to TACE (5-D). In these patients, TACE may be associated with systemic treatment, however, in the frame of controlled clinical studies (5-D).**
- **Even though TACE is the most frequently used trans-arterial treatment for HCC, yet there is not convincing evidence in favour of TACE over TAE in terms of patients survival (1a-A).**
- **In the absence of radiologic evidence of disease persistence (complete response), TACE should not be repeated, due to its risks, costs and impact on the patient's quality of life. Therefore, TACE should be repeated "on demand" (5-D).**
- **The AISF expert panel considers failure of TACE the lack of objective response of the treated lesions after two procedures (Fig. 2). Nonetheless, considering bi-lobar distribution, number of lesions and patient tolerability, the number of sessions to define the failure should be established case-by-case in multi-disciplinary decisional setting, and may greatly vary on an individual basis (5-D).**
- **Response to TACE should be evaluated using the mRECIST criteria (5-D). Results of conventional TACE should be preferentially evaluated using MRI if available (4-C), while CT and MRI are equivalent in evaluating results of DEB-TACE (5-D). CEUS can be used to ascertain disease persistence in patients in which the targets are one or two lesions. The first radiologic assessment of TACE results should be performed at 1 month, and thereafter repeated at 3–4 month intervals (5-D).**
- **DEB-TACE may be preferred to conventional TACE in Child-Pugh B or ECOG PS 1 patients, although additional prospective comparisons are needed before this approach can be definitely recommended in the clinical practice (2b-B).**
- **TARE may be indicated in patients with large masses and/or portal thrombosis/invasion, but it should be utilised in the context of prospective studies aimed at ascertaining its cost-effectiveness profile (5, D).**

6.6. Combined locoregional treatments

6.6.1. Summary of 2010 AASLD guidelines
The AASLD guidelines do not address this topic.

6.6.2. AISF expert panel comments
Four small randomised studies did not show an increased survival when combined locoregional treatments were compared to a single technique [104–107], although a significant reduction of tumour recurrence was observed in two of them [104,106]. However, the meta-analysis of these trials, including 199 treated patients, demonstrated a significant better survival in those receiving combined locoregional treatments [108].

The AISF expert panel outlines that the combination of locoregional therapies offers the maximal flexibility which allows an approach tailored to the characteristics of each nodule in each patient. This approach seems to be particularly valuable in patients with multifocal disease.

6.6.3. AISF expert panel recommendations
- **In non-surgical cases, a combined/sequential approach (TACE *plus* PEI, RFTA, or microwave ablation) should be considered, on an individual basis, for multinodular HCCs and for each nodule >3 cm, after a multidisciplinary assessment (2b-B).**

6.7. Systemic treatment

6.7.1. Summary of 2010 AASLD guidelines
Systemic chemotherapy with conventional agents, octreotide, interferon, tamoxifen, external radiation and anti-androgenic

therapy have shown no survival benefit for HCC patients and should therefore be discouraged.

Sorafenib increases the life-expectancy of Child-Pugh class A patients with advanced (BCLC C) stage HCC, and is the recommended treatment for HCC patients with preserved liver function who are not suitable for surgical treatment, loco-regional therapies or non-responding to TACE [109]. Patients with HCC and end-stage liver disease not amenable to LT or with PS >2 do not benefit from any therapeutic option for HCC, and should receive only symptomatic treatment.

6.7.2. AISF expert panel comments
Sorafenib is the recommended treatment for patients with advanced stage HCC and preserved liver function. There is no role for other palliative systemic treatments outside clinical trials. A recent prospective, observational, multi-centre study carried out in patients with advanced (75%) and intermediate (25%) stage HCC and preserved liver function (88% Child-Pugh class A) has shown that patient requiring a decrease in sorafenib dose (400 mg/day for >70% of the therapy period) due to the occurrence of adverse events, retained a good therapeutic efficacy and received treatment for a longer time [110]. Therefore, in patients intolerant to the sorafenib full-dose, the tolerability to lower dosage (400 mg/day) should be pursued before deciding to withdraw the drug.

Sorafenib is reimbursed by the Italian National Health Service only for patients with Child-Pugh class A and until an objective response or a stable disease are maintained or patients are judged to be still obtaining clinical benefit from treatment.

6.7.3. AISF expert panel recommendations
- **Systemic chemotherapy with conventional agents, octreotide, interferon, tamoxifen, and anti-androgenic drugs has no role in HCC treatment (1b-A).**
- **Full dose sorafenib is the recommended treatment for HCC patients with preserved liver function who are not amenable to surgery and loco-regional treatments or in whom TACE failed, according to the Italian National Health Service rules (1b-A). In patients intolerant to full dose sorafenib, the tolerance to a reduced dose (400 mg/day) is to be pursued before definitively suspending the treatment (2b-B).**
- **HCC patients who cannot receive any effective treatment for HCC must receive symptomatic treatment for pain management and nutritional and psychological support (5-D).**

6.8. Treatment of hepatitis virus infection in HCC patients

6.8.1. Summary of 2010 AASLD guidelines
The AASLD guidelines do not address this topic.

6.8.2. AISF expert panel comments
Morbidity and mortality of HCC patients also depend on the development of complications of chronic liver disease such as bleeding, ascites, hepatic encephalopahy and bacterial infections. This risk can be reduced by treatment aimed at curbing the progression of liver disease. The AISF expert panel feels that a comprehensive approach to patients with HCC should consider, when feasible, the treatment of the cause of the underlying liver disease.

There is evidence that hepatic necro-inflammatory activity is a risk factor for the development of HCC and its "*de novo*" appearance after curative treatment [111]. Stopping viral replication reduces the activity of liver disease and decrease HCC risk. In HBsAg positive patients, this risk is indeed reduced by antiviral therapy [112]. In HCV-RNA positive patients, obtaining a SVR with anti-viral therapy decreases the likelihood to develop HCC, and interferon-based antiviral therapy after curative HCC treatment may extend overall

and recurrence-free survival [86]. Moreover, stopping or lowering the progression of liver disease may increase the likelihood to receive curative treatment for HCC recurrences.

Therefore, a favourable impact on prognosis can be expected from: (1) treatment with nucleos(t)ide analogues of HBsAg, HBV-DNA positive patients with HCC; (2) antiviral therapy in HCV-RNA positive patients with HCC and preserved liver function successfully treated with curative modalities (surgery or ablation).

6.8.3. AISF expert panel recommendations

- **All HBsAg and HBV-DNA positive patients should receive antiviral therapy with nucleos(t)ide analogues at the time of and after HCC treatment (*2b-B*).**
- **HCV-RNA positive patients with preserved liver function (Child-Pugh class ≤8) whose HCC has been treated with curative intent should be considered potential candidates to antiviral therapy (*2b-B*).**

Conflict of interest statement

The authors declare the following disclosures:

Paolo Caraceni, Speaker bureau for Gilead; Barbara Coco, Consulting fees from Janssen; Alessia Ciancio, Speaker bureau for BMS, Janssen, Gilead, MSD, Novartis, Roche; Maria Rendina, Speaker bureau for Gilead, Novartis; Giovanni Squadrito, Speaker bureau for BMS, Gilead, MSD, Roche; Raffaele Bruno, Advisory boards, speaker bureau for Gilead, Janssen, MSD; Pierluigi Toniutto, Advisory boards, speaker bureau for BMS, Janssen, MSD, Novartis; Edoardo Giovanni Giannini, Consulting fees, research grants, speaker bureau, travel grants from Bayer, BMS, Gilead, MSD, Novartis, Roche, 4-SC; Massimo Levrero, Advisory boards, speaker bureau for BMS, Gilead, Janssen, Roche; Antonio Craxì Advisory boards, speaker bureau consulting fees, research grants, from Bayer, BMS, Gilead, Novartis, Janssen, MSD, Roche; Fabio Farinati, Research grants from Bayer, 4-SC; Rita Gofieri, Speaker bureau for Bayer, Syrtex; Franco Trevisani, Consulting fees, research grants from Bayer, 4-SC; Giovanni Raimondo, Advisory boards, speaker bureau for BMS, Gilead, Janssen, MSD, Roche, Roche Diagnostics; Massimo Colombo, Advisory boards, speaker bureau, research grants from Bayer, BMS, Gilead, Janssen, MSD, Novartis, Roche.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2013.01.012.

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