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REVIEW

Multidisciplinary meetings specific to hepatocellular carcinoma: How to proceed?

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KEYWORDS
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Guidelines

Summary The French ''cancer plan'' has created a framework for good practice in the course of care for cancer patients. Decisions must be made in a multidisciplinary team meeting (MDM) and an individualized care plan (ICP) is to be established for each patient. Hepatocellular carcinoma (HCC) is a common cancer with complex treatments that warrant a dedicated meeting. Cancer coordination centers (3C) ensure the organization and the functioning of MDMs. Multidisciplinary, standardized and systematic assessment of HCC patients allows for personalized management and orients them toward treatment that is either curative (transplantation, surgical resection, ablathermy) or palliative (chemoembolization, radiotherapy, systemic treatment, supportive care). MDMs bring together all the professionals treating the disease, and who are tasked with producing an enforceable document effective that justifies decisions and is often an essential step toward inclusion of patients in a clinical trial. It must be carried out according to a systematic schema in an approach applied from initial diagnosis to treatment outset and throughout the treatment. Numerous advances in HCC treatments have rendered their management complex, with the possibility of liver transplantation, twhose access is regulated by the Biomedicine Agency requiring the submission of MDM reports. MDMs must meet specific quality criteria to ensure effective management based on general guidelines and yet specifically tailored to each patient.

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Introduction

Key points
- Multidisciplinary meetings (MDMs) are of paramount importance in decision-making regarding cancer patient treatment.
- MDMs are enforceable.
- The purpose of MDMs is to exchange views on diagnosis and on treatment to be chosen in accordance with updated guidelines adapted to the needs of individual patients, who may in some cases be proposed for inclusion in trials.
- An MDM is a difficult undertaking with major consequences for a patient. Its efficacy has got to be regularly monitored. Delayed treatment outset and inappropriate decisions secondary to a lack of information on patient presentation are the two main factors having an influence on survival.
- An MDM dedicated to hepatocellular carcinoma (HCC) is justified by frequent occurrence of the disease and the complexity of treatments necessitating highly specialized skills in hepatic surgery, transplantation, hepatology and interventional radiology.
- HCC is the only solid cancer for which transplantation is indicated, in the strictly regulated framework of the French biomedicine agency, which requires validation of the indication in a multidisciplinary meeting (MDM).

The French cancer plan has defined a certain number of key points for good practice in the treatment and management of cancers. The multidisciplinary team meeting (MDM) is of paramount importance from diagnosis through treatment. While MDMs may have to do with any and all digestive cancers, given their high number and wide-ranging specificities as well as today's hyper-specialization (in terms of organ and of the different professionals involved), MDMs have grown correspondingly specific and individualized. Multidisciplinary meetings dedicated to hepatocellular carcinoma (HCC) are a representative example.

MDM regulation

Regulatory framework

MDMs fall within the objectives of the 2002 French Plan Cancer (measure 31). In Appendix 2 of circular DHOS/SDO/2005/101, the guiding principles and modalities of functioning of MDMs are defined.

Cancerology health networks and health facilities are responsible for their implementation. Cancerology coordination centers (3C), which federate the different MDMs, are in charge of the organization of multidisciplinarity.

The multidisciplinary meeting is a necessary precondition for the initiation of chemotherapy, radiation therapy and cancer surgery as well as health care involving cancer treatment in health care facilities (decree No. 2007-389 of 21 March 2007).

The MDMs can be local, regional or national according to cancer occurrence. In the HCC framework, they can be local (at the echelon of a university hospital) or regional. A decision made at a MDM meeting is enforceable in the event of a dispute.

Scientific framework

The French definition is somewhat different from the European definition. In France, according to the National Health Authority (HAS), ''Multidisciplinary team meetings (MDMs) bring together professionals from different disciplines whose skills are indispensable when making a decision providing patients with the best treatment in accordance with the state of science at a given time''.

The European definition emphasizes treatment based on the data of Evidence Based Medicine and introduces the notion of patient participation in a therapeutic project. ''Multidisciplinary teams (MDTs) are an alliance of all medical and health care professionals related to a specific tumour disease whose approach to cancer care is guided by their willingness to agree on evidence-based clinical decisions and to co-ordinate the delivery of care at all stages of the process, encouraging patients in turn to take an active role in their care''[1].

Justification of an MDM dedicated to HCC

The different objectives of an MDM are built around the imperative of offering better treatment to the cancer patient. With this in mind, is necessary to bring together all the professionals possessing the skills required during each diagnostic and therapeutic step, the objectives being to reach a decision on initial treatment and to reassess the situation at each stage while identifying the patients liable to be included in phase II or phase III therapeutic trials.

Given the following facts, it has become necessary to set up an HCC-specific MDM:
- HCC incidence continues to increase, and it is presently the 3rd most frequent digestive cancer in France and the 5th in the world. It is the third cause of cancer death in the world [2];
- Complex treatment necessitates the following specific skills:
  - In HCC diagnosis, histological proof is recommended but not mandatory. Iconographic diagnosis requires specific radiological skills. Peeraphatdit T et al. [3] have shown that without hepatic MRI and discussion in HCC-specific MDMs, the rate of diagnosis and treatment is reduced. Gaba RC et al. [4] showed that presentation in HCC-specific MDMs increased the rates of positive HCC diagnosis, of curative treatment (resection, ablation, transplantation) and of survival,
  - Therapeutic possibilities are multiple. Even if guidelines exist, treatment must be individualized. Existing HCC treatments range from transplantation to chemoembolization and may also be ablative or systemic. Moreover, treatments may be combined or sequential. Therapeutic choice is in many cases far from ''unicast'' and depends on non-tumoral factors such as the usual underlying liver disease. While guidelines have been established in the form of decision trees, they need to be tailored to the patient; given the therapeutic advances of the last 10 years, they have correspondingly evolved [5–7]. In parallel to HCC approaches, treatment of liver disease is part and parcel of overall treatment and must be incorporated into the therapeutic regimen;

- The substantial development of therapeutic trials. Randomized studies of the different treatments are accessible in clinical research centers concentrating a large number of patients and thereby modifying disease prognosis. Indeed, Barbare JC et al. [8] have shown that patients in expert centers had greater access to therapeutic trials. One mission of an MDM consists in identifying the patients liable to benefit from these protocols. Several therapeutic trials are ongoing or will be activated over the coming months. For the most part, they evaluate the interest of systemic treatment in cases where locoregional treatment is impossible. Tyrosine kinase inhibitors (TKI) and immunotherapies are mainly studied alone or in association. Successive lines of systemic treatment make it possible to envisage prolongation of survival for more than two years in cases of compensated cirrhosis; it is consequently vitally important to provide patients with access to newly developed treatments (Box 1).

While there exist few publications underlining the interest of MDMs specific to HCC, it is possible to draw an analogy with treatment of hepatic metastases, for which it has been shown that organization of an MDM involving hepatic surgery professionals can bring about a heightened rate of curative treatment [9]. Engstrand J et al. [10] showed in their study of 272 patients with hepatic metastases of colorectal origin that discussion in specialist MDMs led to the conclusion that an additional 13% were potentially resectable. Thillai K et al. [11] similarly underlined high potential for increased resection (15%).

The participants in an HCC MDM

It is recommended that an MDM take place at least twice a month. However, it may be weekly so as to reduce the number of files submitted and to devote closer attention to each file, to simplify organization and to reduce waiting times prior to treatment.

The file should preferably be presented by the physician in charge of the patient, who will contribute clinical elements essential to the decision-making process. This doctor should inform the patient of the MDM decision and, after having obtained his or her consent, to explain its implementation.

Box 1: Ongoing therapeutic trials in France.

- Phase I/II study FGF401X2101: FGF401 in association with an anti-PD1, PDR001 in second-line treatment. ClinicalTrials.gov Identifier: NCT02988440.
- Phase 3 randomized, open label study comparing Pexa-Vec (Vaccinia GM-CSF/Thymidine Kinase-Deactivated Virus) associated with Sorafenib and Sorafenib alone in patients presenting with advanced HCC who have yet to receive systemic treatment (PHOCUS). ClinicalTrials.gov Identifier: NCT02562755.
- Phase I/Ia study assessing the morbidity and effectiveness of association of Pexa-Vac (Vaccinia GM-CSF/Thymidine Kinase-Deactivated Virus) with nivolumab (anti-receptor PD-1) as first-line treatment of advanced HCC. ClinicalTrials.gov Identifier: NCT03071094.
- Hymalaya study: Durvalumab (anti-PDL1) and tremelimumab (anti-CTLA4) as first-line treatment of hepatocellular carcinoma. ClinicalTrials.gov Identifier: NCT03298451.
- Prospective randomized controlled study comparing response and recurrence rates after microwave treatment and percutaneous radiofrequency ablation in patients with chronic liver disease complicated by hepatocellular carcinoma. ClinicalTrials.gov Identifier: NCT02859753.
- Phase 1/2a study aimed at assessing tolerability profiles and determining the dose of le GNS561 to be recommended for patients with advanced malignant tumors such as HCC.
- Study of ramucirumab (LY3009806) versus placebo in hepatocellular carcinoma patients with elevated alpha-fetoprotein levels (REACH-2). ClinicalTrials.gov Identifier: NCT02435433.
- Phase 1-2 study of 188RE-SSS Lipiodol in treatment of hepatocellular carcinomas (LIP-RE-I) ClinicalTrials.gov Identifier: NCT01126463.
- Phase 3 randomized, double blind study, nivolumab adjuvant versus placebo in patients with hepatocellular carcinoma at high risk of recurrence following hepatic resection or curative ablation. (CheckMate 9DX). ClinicalTrials.gov Identifier: NCT03383458.
- Phase 1 study to assess the safety, tolerance, pharmacokinetics, pharmacodynamics and preliminary efficacy of BLU-554 in hepatocellular carcinoma patients. ClinicalTrials.gov Identifier: NCT02508467.
- Open-label, multicenter phase Ib/II study of INC280 in association with PDR001 or PDR001 Single Agent in cases of advanced hepatocellular carcinoma. ClinicalTrials.gov Identifier: NCT02795429.
- Open-label, multi-center phase 2 study of the efficacy, safety and pharmacokinetics of the monoclonal antibody anti-PD-1 BGB-A317 in previously treated patients with unresectable hepatocellular carcinoma. ClinicalTrials.gov Identifier: NCT03419897.
- Phase I-II study of NBTXR3 activated by stereotaxic radiation therapy (SBRT) in liver cancer treatment. ClinicalTrials.gov Identifier: NCT02721056.
- Open-label, multicenter phase 1/2 study aimed at determining the doses optimally assessing the safety, tolerability and preliminary efficacy of CC-122 in association with nivolumab in patients with unresectable hepatocellular carcinoma (HCC) subsequent to failure of first-line treatment. ClinicalTrials.gov Identifier: NCT02859324.
- Transarterial chemoembolization (TACE) versus stereotaxic radiation therapy in cases of hepatocellular carcinoma (TENDANCE). ClinicalTrials.gov Identifier: NCT02470533.
- Open-label, multicenter, phase I/II study on oral FGF401 in adult patients with hepatocellular carcinoma or solid malignant tumors characterized by positive expression of FGFR4 and KLB. ClinicalTrials.gov Identifier: NCT02325739.

A coordinator

The team meeting is multidisciplinary. A ''conductor'' highly invested in the decision-making process is tasked with making sure that all participants are advised of the date and time of the meeting and that all necessary material equipment and resources are available. Last but not least, he must make sure that all participants sign in and that those whose presence is indispensable attend regularly.

In an MDM, the hepatologist, the oncologist or the hepatic surgeon may be the coordinator. He must be present at all the meetings; when this is not possible, he has got to preliminarily designate a substitute chairman.

The other participants

The medical team must be composed of at least three specialists:

- a hepatologist skilled in oncology and transplantation;
- a hepatic surgeon who should at best, have competence as a transplant surgeon or, at least, be cognizant of the rules as regards indications and feasibility;
- a radiologist specialized in HCC diagnosis and percutaneous treatments [12,13].

In addition to this indispensable trio, the other intervening participants are: a pathologist, a radiotherapist (indications for radiation therapy, radiation therapy tests), a nuclear medicine physician (PET-TDM) and a psychiatrist (an addictologist, specialized if possible in pre-transplant check-up).

Practitioners from outlying and private centers can be invited to present their patients. Agreements between centers must be concluded to officialize their collaboration.

MDMs in university centers present an educational dimension inasmuch as they involve residents, registrars, assistants and medical students.

A secretariat

The secretariat is fundamental, ensuring production and distribution of meeting reports and, ideally, making the appointments through which decisions are implemented. The secretariat also functions as guarantor of reasonable waiting time prior to treatment. Charriere B et al. [14] have demonstrated that excessive waiting time prior to treatment explains decreased opportunities to contain tumoral progression.

How an HCC interdisciplinary team meeting proceeds

It is indispensable to record patient data and discussion reports on a standardized document, the MDM form, validated by the participants and the 3C office.

Proceedings are premised on the international guidelines of the Barcelona Clinic Liver Consensus (BCLC), the European Association of the Study of the Liver-European Organization for Research and Treatment of Cancer (EASL-EORTC) and the American Association for the Study of the Liver Disease (AASLD); the most recent recommendations were issued in 2018 [5,7,15]. However, the decision tree stemming from them fails to translate all clinical situations, moreover, it is not a subject of consensus, particularly as concerns indications for medical resection [16]. Today's experts have a major role to assume in orienting as many patients as possible toward curative treatment, possibly outside the recommendations [7].

Box 2: Criteria for positive, non-invasive HCC diagnosis.

[•]Cirrhotic patient.

- Four-stage technique of imagery by scanner or MRI (without injection, arterial phase, portal phase and late phase).
- Tumor > 1 cm with arterial enhancement washout (hypodensity/hypointensity compared to the rest of the liver during the portal or late stage.

Presentation of a new patient

Ideally, presentation of the patient should be carried out by the physician managing his case.

Numerous elements need to be put together in view of optimizing the MDM decision-making process (Fig. 1):

- the patient's complete civil status;
- the patient's correspondents' names;
- the patient's clinical data: performance status (PS), comorbidities, ongoing treatments;
- data on the patient's hepatic disease and tumoral disease: underlying disease, portal hypertension (PHT), Child-Pugh score, number and size of nodules, HCC site, alpha-fetoprotein score (AFP), vascular spread and metastasis;
- previously initiated treatments and their effectiveness.

The data must be exhaustively gathered and recorded on an MDM form (Fig. 2) so that even when the practitioner in charge of the patient is absent, a standardized and reliable analysis remains possible.

First and foremost, the MDM must affirm or validate the diagnosis.

The radiologist is the central figure in the diagnostic phase; he is called upon:

- to ensure the satisfactory quality of the tests and their recentness (less than 3 months). If these conditions are not fulfilled, the MDM can call for a new presentation aimed at providing complementary information;
- to identify the indirect radiological characteristics of the cirrhosis;
- determine whether the non-invasive iconographic diagnostic criteria indicating HCC are met and, if not, point out the need for a biopsy (Box 2);
- to determine the number, size and location of the different nodules;
- determine whether or not an extra-hepatic extension exists.

The hepatologist is called upon:

- to discuss the cirrhosis diagnosis, particularly the supposed need for biopsy of a non-tumoral liver;
- to characterize the underlying hepatic disease, to determine its etiology and to underline the need for treatment.

At this stage, the pathologist assumes an important role with his commentaries on the detailed results of the biopsy of the tumorous liver (HCC presence, differentiation, vascular spread, peritumoral nodule) and the non-tumorous liver (cirrhosis activity, fibrosis grade).

The MDM then organizes a discussion on the suitable therapeutic step.

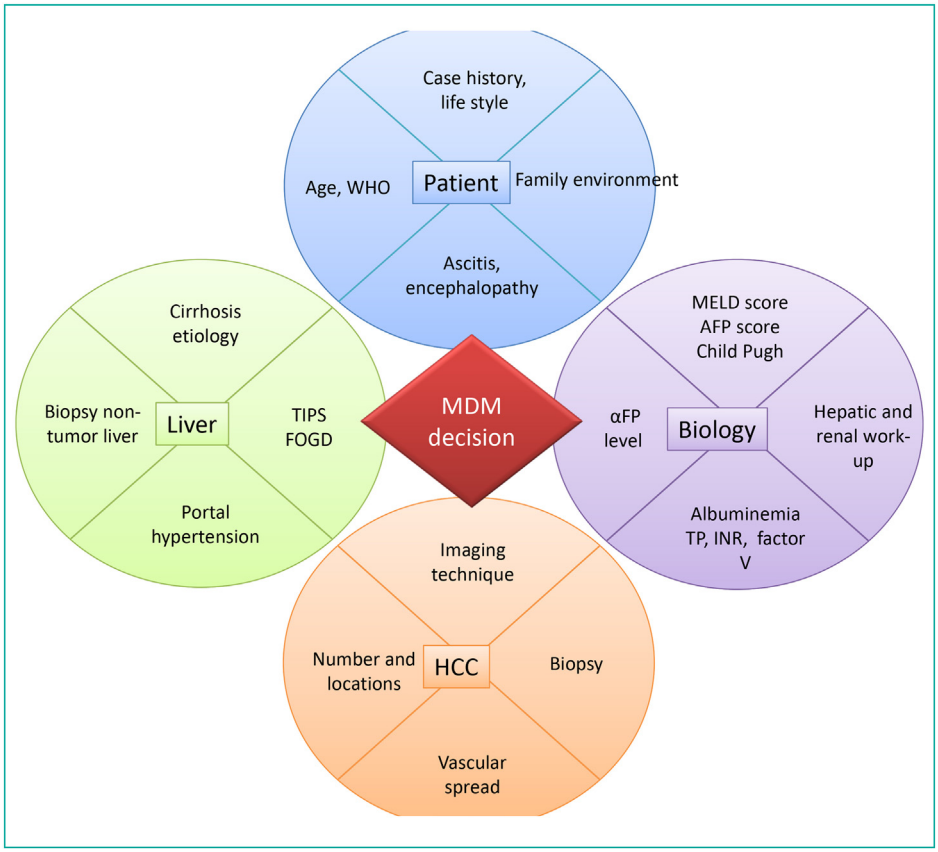

Figure 1. The decision made during a multidisciplinary team meeting (MDM) stems from the confrontation of clinical, morphological and biological elements with the recommendations and guidelines issued by learned societies and the expertise of participants specialized in hepatocellular carcinoma.

The primary therapeutic objective of the MDM consists in deciding whether to orient the patient toward curative or toward palliative treatment and, subsequently, in determining the optimal treatment based on existing recommendations and according to patient characteristics. The order of questions is systematized and begins with a general assessment of the patient followed by analysis of the hepatic disease and the tumor disease, after which the course of treatment is decided upon (Fig. 3).

Orientation must be reviewed and revised following each treatment.

Possible curative treatments are to be initially considered during an MDM

Curative treatments are limited to patients without metastases and who have conserved satisfactory overall physical condition; they consist in: liver transplantation (LT), surgical resection and ablation methods.

Liver transplantation (LT) is the first option to be discussed. HCC is the one cancer for which a validated organ transplant indication exists. It should be considered initially in cases of early or intermediate HCC. The French *Agence de Biomédecine* (ABM) has established strict indications for transplantation and makes its graft allotment decisions according to what is known in French as the *Score Foie*, which is largely based on the Model of End-stage Liver Disease (MELD). One advantage of transplantation consists in its treating the tumor disease and, more precisely, in its addressing the underlying hepatopathy, which is the main cause of HCC occurrence, and thereby possibly leading to a definitive cure. On the other hand, Sasaki K et al. [17] have shown that subsequent to surgical resection of HCC, the risk of HCC recurrence on the remaining hepatic parenchyma is 13% per year over 5 years (as opposed to 6% per year over 5 years with a healthy liver, $P = 0.003$).

Several strategies for access to transplantation are currently applied, and the rules for graft allocation are regularly revised. While waiting for a graft, patients can be registered on a list following imagery and alpha-fetoprotein assay every three months, and they may be entitled to bridge therapy. When, having been treated, they develop a recurrence, they are not only registered on a list, but are also given access to salvage transplantation, the strategy adopted by the ABM.

HT is limited to HCCs having met the criteria of the alpha-fetoprotein score (AFP), which must be lower than or equal to 2. This rule is based on work by the French team of Duvoux et al. [18], who reported a recurrence rate at 5 years of 13% and an overall survival rate of 70%. Access to transplantation is currently predicated on the AFP score, which has become the central pillar of the decision-making process (Table 1).

The AFP score is applied to stage T2 HCC (one nodule from 2 to 5 cm, or up to 3 nodules of less than 3 cm). In the setting of salvage strategy, a curative approach by resection or ablation is proposed as first-line treatment; when it is impossible to apply any of the above techniques, the HCC is deemed incurable and the patient is given access to a graft within a period not exceeding 9 months.

Patients presenting with a very small HCC classified T1 (one nodule < 2 cm) cannot be registered for HCC treatment, and the *Score Foie* will not take into account the presence

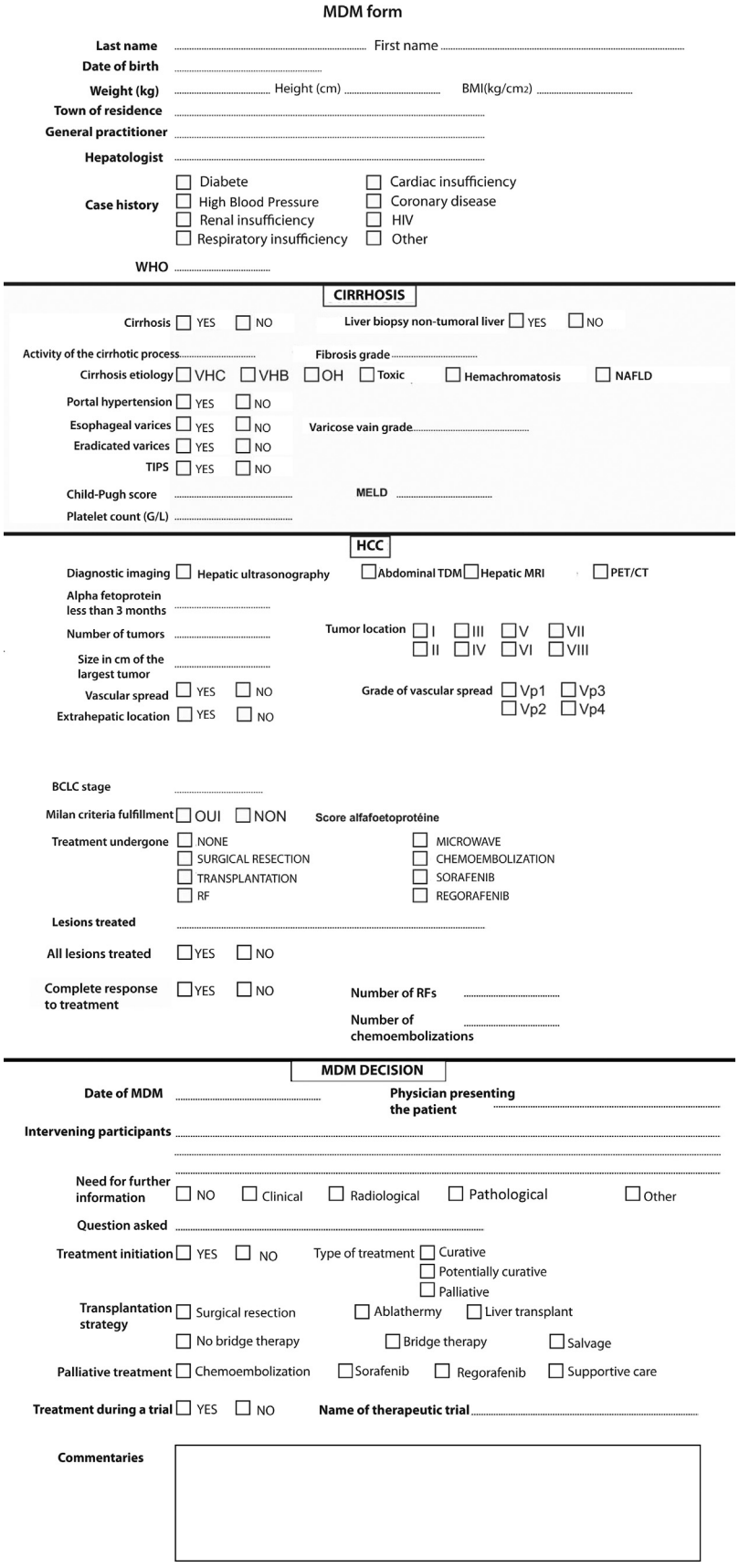

Figure 2. A standardized form proposed for use in a multidisciplinary team meeting dedicated to hepatocellular carcinoma.

of the tumor. In fact, only cirrhosis severity will be taken into account, the objectives being to privilege other curative treatments and to avoid ''futile'' HT. In such cases, access to liver graft is determined by the MELD score (see above).

In general, it involves patients with well-compensated liver disease whose MELD score is lower than 12, and for whom first-line treatment will consist in surgical resection or ablation (see Fig. 4).

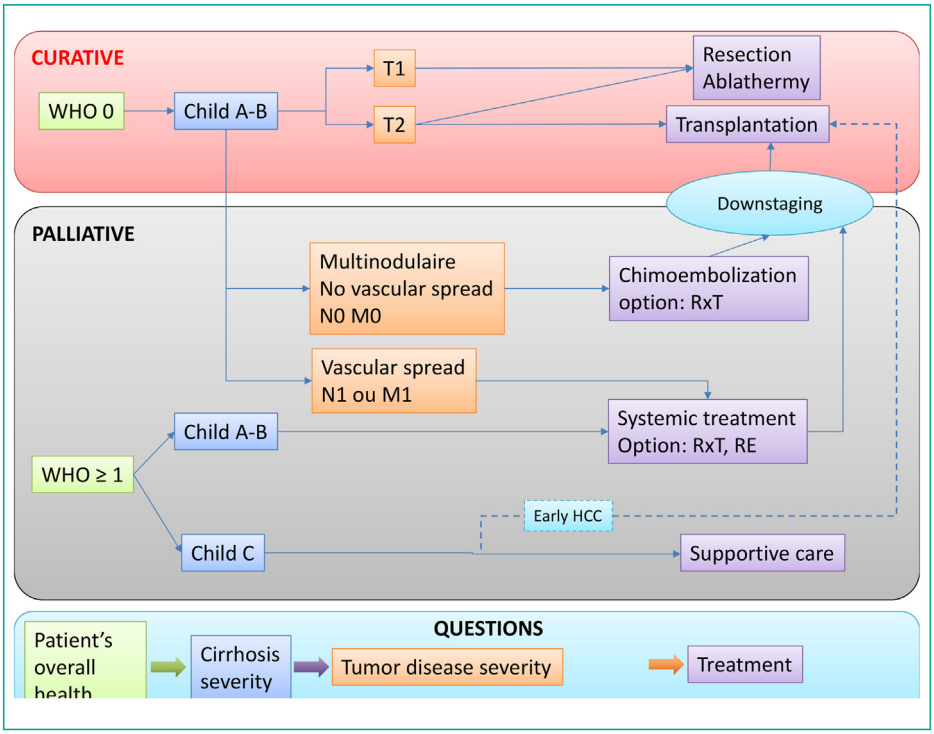

Figure 3. A decision at a multidisciplinary team meeting is the result of a logical and standardized series of questions, which are presented in accordance with current treatment guidelines. While this schema covers most clinical situations, a few peculiar situations are not represented and are exterior to the recommendations justifying the creation of a specialized MDM. RxT: radiation therapy; RE: radioembolization.

Table 1 Alpha-fetoprotein score (AFP) [18].

Factors		Points
Number of tumors	≤ 3	0
	≥ 4	2
Tumor size in cm	≤ 3	0
	3—6	1
	> 6	4
Alpha-fetoprotein level in ng/mL	≤ 100	0
	100—1000	2
	> 1000	3

When a patient presents with an AFP score higher than 2, discussion will revolve around the possibility of downstaging as a transition prior to LT. For these patients, one particularity can consist in the use of grafts ''out of turn'', that is to say having been turned down by 5 transplantation teams, in which case they may be used regardless of the AFP score when they can be beneficial for patients.

In the event that the AFP score increases during the waiting period, patients are removed from the list and contraindicated for transplantation; they are said to have ''dropped out''.

These graft allocation rules for HCC patients have been put into place due to a penury of grafts and so as to ensure equality of opportunity concerning LT access.

Surgical resection is systematically considered as first-line treatment whenever LT is not indicated or found to be impossible.

The essential role of the hepatic surgeon consists in determining the possibility of resecting a tumor in a given patient and in specifying the necessary invasive or non-invasive tests and interventions: transparietal biopsy of liver without tumor, transjugular biopsy and pressure gradient measurement, volumetry, portal vein embolization...

The patient's overallgeneral condition, cirrhosis severity, portal hypertension, vascular spread and residual liver volume are the parameters of reference when deciding upon an indication for surgery. It is according to these parameters that the EASL has calculated the risks of hepatic insufficiency and post-operative mortality.

While anatomical resection is the rule, in cases where parenchymal volume remains insufficient, atypical resection with a margin of 2 cm can be performed [19,20].

Once the resection has been validated, the physician responsible for the patient must make sure that no time is wasted before consulting a hepatic surgeon.

One interest of presentation in an expert center consists in its enabling BCLC stage B patients not having the aforementioned AFP score to undergo surgical resection even though it is not explicitly recommended. Assessment of the surgical risk/oncological benefit ration necessitates substantial experience. Cucchetti et al. [21] showed that for carefully selected BCLC stage B patients, risk of death from post-operative hepatic insufficiency was lower than risk of death due to progression of the disease. Glantzounis et al. [22] reevaluated 2412 patients from 23 studies and reported heightened survival after resection, even in cases of distal deep vein thrombosis. High-powered studies corroborating these results remain necessary.

Ablathermy methods are indicated when there is no indication for transplantation or when surgical resection is impossible, and they consist mainly in radio frequency (RF) and microwaves. As regards RF, while its effectiveness in cases of HCC of less than 2 cm is identical to that of surgical resection, it entails a higher risk of recurrence [23].

Since the emergence of ablathermy, ethanol injection has been less and less frequently used; in fact, it is limited to

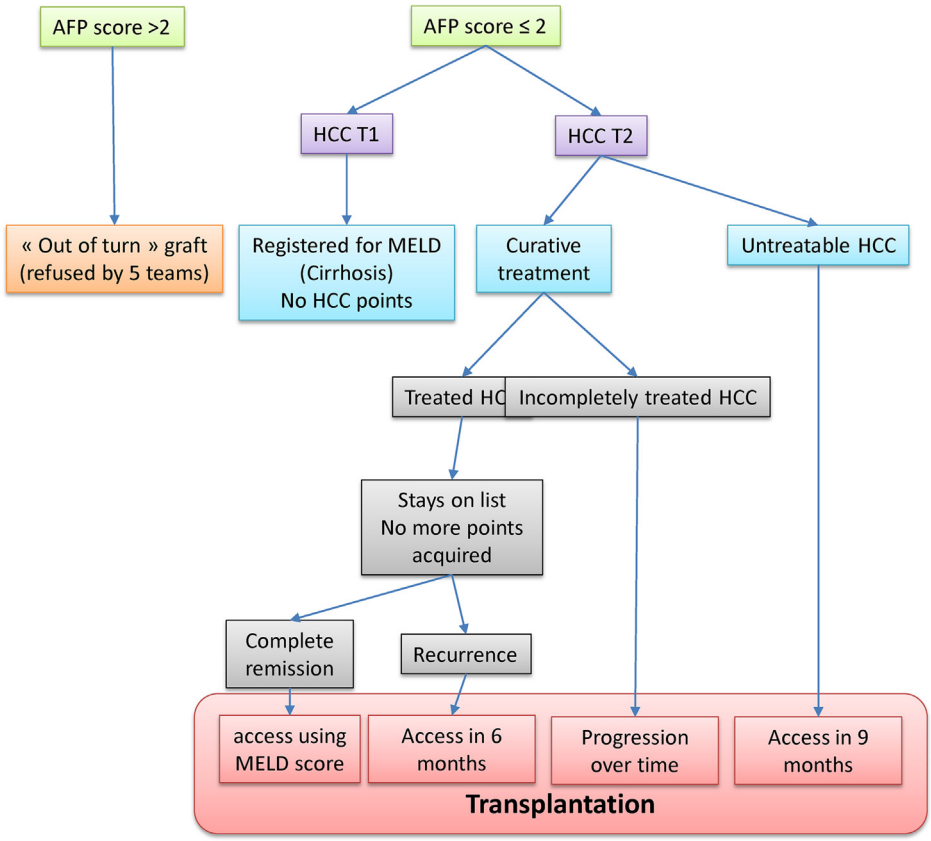

Figure 4. Strategy of treatment and management according to the Alpha Fetoprotein (AFP) score. An AFP score higher than 2 represents a contraindication for liver transplantation (LT). However, in the event of a good general condition, absence of vascular or extra-hepatic spread and when the patient is less than 65 years old, HT may be envisaged using a marginal graft considered as ''out of turn'' after having been turned down by 5 medical teams. A T2 tumor that has been totally resected or considered as sterilized in control images subsequent to ablathermy is eligible for LT only in the event of recurrence. While waiting, the patient remains on the list but no longer moves forward, except when recurrence reactivates advancement toward LT eligibility.

patients with a tumor of less than 2 cl who are not eligible for surgical resection or ablathermy.

When no curative treatment is chosen, palliative treatments are envisaged

Palliative treatments include Trans-Arterial Chemo Embolization (TACE) and systemic treatments by targeted therapy (tyrosine kinase inhibitor: sorafenib, regorafenib).

Chemoembolization is indicated for patients with multiple or infiltrative lesions for whom curative treatment is not feasible [5,7].

Association of TACE with radiofrequency ablation (RF) is dan feasible. It seems beneficial as concerns overall survival and non-recurrence in patients in a palliative situation, particularly for tumors larger than 3 cm [24].

Even though TACE is considered as palliative treatment, it can permit downstaging in patients who may be reoriented toward a curative project through LT [25,26].

Multi-targeted tyrosine kinase inhibitors inhibit the signaling pathways of cellular proliferation. While they allow for slightly increased survival, they frequently entail severe adverse effects (10%) [27]. They are nonetheless indicated for patients in good general condition presenting with HCC but ineligible for a specific treatment (LT, surgical resection, percutaneous destruction, TACE) or having relapsed subsequent to a specific treatment [28].

All in all, specialized professionals assume an indispensable role at this stage of therapeutic discussion.

The hepatic surgeon is the leading actor during this phase; his role is:

- to determine the possibility of resecting the tumor and the ''transplantability'' of a given patient;
- if possible, to propose therapeutic trials.

The role of the interventional radiologist is:

- to determine whether or not ablathermy and TACE are possible;
- to assess the effectiveness of treatments being or having been performed (mRECIST and RECIST1.1 criteria). This is a difficult task, particularly following application of the ablative method [7]. For example, in a given transplantation project a response considered as complete will contraindicate use of grafts prior to recurrence, and it has been shown that in 20% of the cases under consideration, the tumor remained active [29].

The role of the hepatologist is:

- to determine indications for treatment of the underlying hepatic disease, treatment that is not presently an object of consensus, particularly in the setting of a transplantation project [30];
- to indicate palliative treatments, especially the systemic ones;
- if possible, to propose therapeutic trials.

Monitoring and evaluating of previously presented patients

As patients need to be reassessed at each therapeutic step, a major portion of MDMs is dedicated to following up on the decisions having been made during previous MDMs. In case of good tumor response, teh patient can be sometimes reorientated from a palliative management toward a curative project; this is known as ''downstaging''.

The practitioner responsible for the patient assesses his tolerance of and compliance with the treatment.

The radiologist assesses treatment efficacy and diagnoses possible intra-hepatic or distant recurrences.

The hepatic surgeon reassesses the possibilities of surgical resection or transplantation. Updating of the computerized ''Cristal'' file has got to be carried out once every three months for patients in a transplantation project. Even when downstaging is not present in the BCLC guidelines, it remains a reality, and if feasible, it must be possible for a patient to receive curative treatment. It has been estimated that 40% of BCLC B patients should be able to undergo curative treatment subsequent to treatment by TACE, stereotactic radiation therapy, radioembolization or sorafenib and optimized management of cirrhosis complications [31].

The hepatologist determines whether the underlying disease remains active or has been cured, and is also called upon to reassess the indication for systemic treatments.

In the event of toxic hepatopathy, the opinion of an addictologist is necessary, particularly when there exists a transplantation project.

To sum up, in its meeting report an MDM specifies the objectives and checkpoints in a patient's PPS [personalized health plan). All of the practitioners involved in treatment are kept informed by means of the report.

A multidisciplinary team meetings dedicated to HCC has got to be assessed

MDMs represent a difficult exercise, especially insofar as the decisions made will have major repercussions on a patient's life. It is important that each step be approached with the utmost rigor. We previously exposed which MDM elements remains essential, at the organizational as well as the medical levels.

Establishment of an HCC-specific MDM can markedly improve treatment and management. Ottevanger et al. [32] have shown that MDM quality criteria are more optimally fulfilled in an organ-specific than in a ''generalist'' MDM, the reason often being that meetings are held in an expert center.

It is important to formalize quality criteria allowing for systemized procedures and feedback control through regularly programmed self-assessment (Box 3). The processes that improve or worsen MDM quality need to be identified (Box 4).

The MDM is the cornerstone in comprehensive care of the cancer patient; that is why more and more publications have been addressing the issue of MDM quality assessment. Indeed, quality practice has been growing in industrial as well as institutional settings, even though it remains a difficult exercise.

Soukup T et al. [33] carried out an excellent review of the literature on the topic and identified not only the elements necessitating quality control, but also the factors undermining or enhancing decision-making quality. The structural quality of an MDM can be measured in terms of decision-making process, collegiality and time devoted to each medical file. Lamb et al. [34] showed that files presented at the end of a meeting were less frequently associated with a conclusion and that when a decision was made, it was less frequently elaborated by the entire team. Moreover, the quality of a given decision can be measured in terms not only of oncological outcome, but also as regards applicability. Charriere et al. [14] demonstrated that noncompliance with MDM decisions reduced patient survival. Reasons for treatment modification included: poor evaluation of the patient impeding or even preventing application of a prescribed treatment; overly delayed initiation of the

Box 3: Quality criteria and control process.

The team:

- Quality and experience des participants: hepatologist, hepatic surgeon, interventional radiologist, radiotherapist/oncologist.
- Assiduity.
- Coordinator: non-medical skills.
- Team spirit — respect.

Logistics = secretariat +++:

- Preparation of the meeting: mailing list, reminder note, patient list.
- Dedicated MDM form, dedicated data base.
- Organization of the meeting: attendance taking/sign-in, practicalities (food and beverages)...
- Decision-making management: writing up a meeting report (minutes), appointment making, contacting physicians responsible for patients.

Infrastructure:

- Venue: dedicated, calm, ergonomic.
- Equipment: computer, internet...

Organization:

Frequency: ideally weekly, if possible.

Quality control:

- Treatment application.
- Oncological results.
- Percentage of decisions exterior to guidelines or protocol.
- Time devoted to each medical file.

Box 4: Continuous improvement process and situations to avoid.

To promote:

- MDM form prepared in advance.
- Coordinator with experience in MDM.
- Presence of an anesthesiologist to consider possibilities of surgery.
- Limit to number of patients to have enough time to discuss each individual case.
- Rapid validation of decisions corresponding to a recommendation.

To avoid:

- Incomplete information on the tumoral or hepatic disease.
- Incomplete information on a patient's comorbidities and general status
- Absence of essential participants.
- Absence or poor quality of imaging
- Logistical problems (computer, network...).

treatment, delay often largely due to inadequate communication of the MDM conclusions to the physician responsible for the patient.

Numerous assessment scores have been proposed. As an example, Jalil R et al. [35] have developed a tool evaluating an MDM coordinator's management entitled ATLAS (A Tumor Leadership Assessment inStrument). Most of the 2000 MDM participants responded that a team leader's medical or surgical skills were not the main required qualities. Indeed, the 12-item score makes reference to forms of competence ranging from MDM punctuality to personality and conflict management. Overall, the advantage of these different scores resides in their reminding the medical and non-medical skills needed in MDM leaders and participants.

Conclusion

MDMs provide rigorous assessment of each patient, offering him the best chance to benefit from the treatment best suited to his pathology, including participation in therapeutic protocols. MDM quality must be regularly assessed in terms of number of medical files presented, frequency of consultation of the relevant recommandations, number of patients included in trials, etc... Due to the establishment of computerized records compiling all patient data, it has become possible to conduct prospective assessments. MDMs dedicated to HCC are largely justified by the complexity of treatment of HCC patients, with highly diversified therapeutic options taking into account not only HCC characteristics, but also the underlying hepatopathy. A standardized form has been proposed herein (see Fig. 2).

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] European Partnership Action Against Cancer consensus group, Borras JM, Albreht T, et al. Policy statement on multidisciplinary cancer care. Eur J Cancer 2014;50(3):475—80.

[2] Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Abera S, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the Global Burden of Disease Study 2015. JAMA Oncol 2017;3(12):1683—91.

[3] Peeraphatdit T, Naksuk N, Phatharacharukul P, et al. Adherence to diagnostic guidelines of hepatocellular carcinoma: 12-year experience in a veterans affairs medical center. Eur J Gastroenterol Hepatol 2015;27(7):846—52.

[4] Gaba RC, Kallwitz ER, Parvinian A, et al. Imaging surveillance and multidisciplinary review improves curative therapy access and survival in HCC patients. Ann Hepatol 2013;12(5):766—73.

[5] Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67(1):358—80.

[6] Blanc J, Barbare J, Boige V. Carcinome hépatocellulaire. Thésaurus National de Cancérologie Digestive 2017 [Disponible sur: http://www.tncd.org].

[7] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69(1):182—236.

[8] Barbare J-C, Franco D, André T, et al. Should cases of hepatocellular carcinoma be discussed by non-specialized multidisciplinary team meetings? Bull Cancer 2014;101(6):558—63.

[9] Jones RP, Vauthey J-N, Adam R, et al. Effect of specialist decision-making on treatment strategies for colorectal liver metastases. Br J Surg 2012;99(9):1263—9.

[10] Engstrand J, Kartalis N, Strömberg C, et al. The impact of a Hepatobiliary Multidisciplinary Team Assessment in patients with colorectal cancer liver metastases: a population-based study. Oncologist 2017;22(9):1067—74.

[11] Thillai K, Repana D, Korantzis I, et al. Clinical outcomes for patients with liver-limited metastatic colorectal cancer: arguing the case for specialist hepatobiliary multidisciplinary assessment. Eur J Surg Oncol 2016;42(9):1331—6.

[12] Shah SA, Tan JCC, McGilvray ID, et al. Accuracy of staging as a predictor for recurrence after liver transplantation for hepatocellular carcinoma. Transplantation 2006;81(12):1633—9.

[13] Davenport MS, Khalatbari S, Liu PSC, et al. Repeatability of diagnostic features and scoring systems for hepatocellular carcinoma by using MR imaging. Radiology 2014;272(1):132—42.

[14] Charriere B, Muscari F, Maulat C, et al. Outcomes of patients with hepatocellular carcinoma are determined in multidisciplinary team meetings. J Surg Oncol 2017;115(3):330—6.

[15] Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet Lond Engl 2018;391(10127):1301—14.

[16] Garancini M, Nespoli S, Romano F, et al. Surgical management of hepatocellular carcinoma within and beyond BCLC indications in a middle volume center. J Visc Surg 2018;155(4):275—82.

[17] Sasaki K, Shindoh J, Margonis GA, et al. Effect of background liver cirrhosis on outcomes of hepatectomy for hepatocellular carcinoma. JAMA Surg 2017;152S(3):e165059.

[18] Duvoux C, Roudot-Thoraval F, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012;143(4):986—94.e3 [quiz e14—15].

[19] Cucchetti A, Qiao G-L, Cescon M, et al. Anatomic versus nonanatomic resection in cirrhotic patients with early hepatocellular carcinoma. Surgery 2014;155(3):512—21.

[20] Marubashi S, Gotoh K, Akita H, et al. Analysis of recurrence patterns after anatomical or non-anatomical resection for hepatocellular carcinoma. Ann Surg Oncol 2015;22(7):2243—52.

[21] Cucchetti A, Sposito C, Pinna AD, et al. Competing risk analysis on outcome after hepatic resection of hepatocellular carcinoma in cirrhotic patients. World J Gastroenterol 2017;23(8):1469—76.

[22] Glantzounis GK, Paliouras A, Stylianidi M-C, et al. The role of liver resection in the management of intermediate and advanced stage hepatocellular carcinoma. A systematic review. Eur J Surg Oncol 2018;44(2):195—208.

[23] Majumdar A, Roccarina D, Thorburn D, et al. Management of people with early- or very early-stage hepatocellular carcinoma: an attempted network meta-analysis. Cochrane Database Syst Rev 2017;3:CD011650.

[24] Ni J, -Y, Liu S, et al. Meta-analysis of radiofrequency ablation in combination with transarterial chemoembolization for hepatocellular carcinoma. World J Gastroenterol 2013;19(24):3872—82.

[25] Chapman WC, Majella Doyle MB, Stuart JE, et al. Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. Ann Surg 2008;248(4):617—25.

[26] San Miguel C, Muffak K, Triguero J, et al. Role of transarterial chemoembolization to downstage hepatocellular carcinoma within the milan criteria. Transplant Proc 2015;47(9):2631—3.

[27] Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359(4):378—90.

[28] Boige V, Barbare J-C, Rosmorduc O, et al. Use of sorafenib (Nexavar) in the treatment of hepatocellular carcinoma: PRODIGE AFEF recommendations. Gastroenterol Clin Biol 2008;32(1 Pt. 1):3—7.

[29] N'Kontchou G, Aout M, Laurent A, et al. Survival after radiofrequency ablation and salvage transplantation in patients with hepatocellular carcinoma and Child-Pugh A cirrhosis. J Hepatol 2012;56(1):160—6.

[30] Anand AC. Potential liver transplant recipients with Hepatitis C: should they be treated before or after transplantation? J Clin Exp Hepatol 2017;7(1):42—54.
[31] Parikh ND, Waljee AK, Singal AG. Downstaging hepatocellular carcinoma: a systematic review and pooled analysis. Liver Transpl 2015;21(9):1142—52.
[32] Ottevanger N, Hilbink M, Weenk M, et al. Oncologic multidisciplinary team meetings: evaluation of quality criteria. J Eval Clin Pract 2013;19(6):1035—43.
[33] Soukup T, Lamb BW, Arora S, et al. Successful strategies in implementing a multidisciplinary team working in the care of patients with cancer: an overview and synthesis of the available literature. J Multidisciplinary Healthc 2018;11: 49—61.
[34] Lamb BW, Sevdalis N, Benn J, et al. Multidisciplinary cancer team meeting structure and treatment decisions: a prospective correlational study. Ann Surg Oncol 2013;20(3): 715—22.
[35] Jalil R, Soukup T, Akhter W, et al. Quality of leadership in multidisciplinary cancer tumor boards: development and evaluation of a leadership assessment instrument (ATLAS). World J Urol 2018;36(7):1031—8.