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Radiological treatment of HCC: Interventional radiology at the heart of management

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Abstract  Interventional radiology is involved practically at each stage in the treatment of hepatocellular carcinoma, as recommended in the EASL-EORTC guidelines. It is even becoming more important as technological advances progress and as its long-term efficacy is assessed. Used curatively, thermoablation can obtain five-year survival rates of 40 to 70%, with a survival rate of 30% at 10 years. As there are many tools available in order to be used, it requires a thorough pre-treatment assessment and discussion in a multidisciplinary team meeting. Regular patient reassessment is needed in order to be able to adjust treatment because of the complementarity of the treatments available and the course of the disease.

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Hepatocellular carcinoma (HCC) is the 6th leading cancer in the world by incidence (749,000 new cases annually) and the number of cases of HCC has increased regularly over the last 20 years in all countries. Its annual incidence in France was 12.1/100,000 in 2012 in men and 2.4/100,000 in women (INVS 2013 report www.invs.sante.fr). In 75 to 80% of cases, HCC develops in cirrhosis, which is a pre-malignant situation and contributes to the prognosis of the cancer as it impacts on treatment methods. However, the number of cases of HCC diagnosed in non-cirrhotic patients is continually increasing, mostly due to the prevalence of steatohepatitis.

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The mortality rate, which is directly linked to screening rates in at risk patients and the treatment measures available, varies greatly between countries. Whilst it continues to increase in many countries it appears to have stabilized in France over the last few years [1], (www.invs.sante.fr).

However, the mortality rate from hepatocellular carcinoma remains very high and is the 3rd leading cause of cancer deaths throughout the world. The mismatch between the incidence of the cancer and its mortality rate highlights the importance of advances that still need to be made in its diagnosis and treatment.

Treatments are currently divided somewhat arbitrarily into curative therapies which include liver transplantation, surgical excision and percutaneous ablation methods and treatments deemed non-curative or "palliative", which include chemoembolization, systemic therapies (sorafenib) and, currently under assessment, radioembolization. The survival results obtained in these two treatment groups are extremely different. If curative therapy can be given, the 5-year survival rate is estimated to be 40 to 70% whereas with palliative treatment, the corresponding figure is only 10 to 20% [2]. In the best series, the proportion of patients suitable for curative treatment is no greater than 30 to 40%. A study of practice carried out in France in 2010 [3] showed that only 20% of patients were suitable for curative treatment when the HCC was discovered. It is currently considered that screening for HCC in patients suffering from compensated cirrhosis using six-monthly ultrasound [4] can diagnose HCC in the curative stage in over 70% of cases [2].

Regardless of the stage of the disease, amongst the treatments offered whether curative or palliative, treatments utilising interventional radiology account for a large proportion of the treatment options.

It is therefore important for both interventional radiologists and other practitioners to understand the options, limitations and place of these treatments in the management of HCC. It is important to understand from the outset that these treatments are not exclusive and that a patient must not remain "closeted" within a single type of treatment, but should be able to benefit from the complementarity of the various treatment options available. During the course of the disease, which is largely influenced by the initial treatments, the various therapeutic options can be used alternately. The choice of the most appropriate treatments throughout the course of the disease requires an initial staging assessment and detailed clinical and radiological monitoring, together with regular discussion of these patients in the Multidisciplinary Team Meetings. The staging assessment and treatment decision should not be made by a single specialty but should be the result of a multidisciplinary collegiate decision.

Pre-treatment assessment

The reference diagnostic method for HCC is still histology, although the diagnosis can be made non-invasively in HCC when imaging appearances (CT and MRI) are characteristic, under certain strict technical and interpretation conditions.

The presence of underlying cirrhosis is an essential prerequisite to a non-invasive diagnosis of HCC. The diagnosis of cirrhosis can easily be inferred from clinical, laboratory (PR, platelets, serum albumin, blood markers of fibrosis), elastometric, endoscopic (oesophageal varices), and morphological criteria (hepatic dysmorphism and ultrasound or CT signs of portal hypertension). If patients have no symptoms of cirrhosis, a biopsy of the non-malignant liver is essential to demonstrate the presence of cirrhosis.

In cases of cirrhosis, a liver nodule measuring over 10 mm in diameter exhibiting hypervascularization in the arterial phase followed by washout in the portal or late phase on CT or MRI is deemed to be a hepatocellular carcinoma. It should be noted that in the international guidelines (EASL-EORTC 2012) in non-expert centers, suspect nodules from 10 to 20 mm need to be consistent on CT and MRI in order to confirm the diagnosis. In all other situations and particularly if the diagnosis of cirrhosis is not certain, a needle biopsy should be performed [2]. Generally, however, the merits of biopsy in the future will probably become increasingly to measure prognostic and predictive biomarkers for response to treatment.

It is important to remember that the positive diagnosis of HCC is not sufficient in itself to initiate a discussion on treatment. Various morphological factors need to be considered, including the type, nodular or infiltrative, the number of lesions, their size, their anatomical relationships and loco-regional and extra-hepatic extension (lungs, adrenal glands, etc.). All of these factors should be routinely listed in the radiological investigation report. A standard report for the diagnosis and staging assessment of hepatocellular carcinoma can be found on the Société française de radiologie website (http://www.sfrnet.org).

Morphological imaging data should be combined with all of the clinical and laboratory findings. It is important to understand that in 90% of cases, this cancerous disease occurs on a background of pre-existing disease (cirrhosis or severe fibrosis), the course and prognosis of which need to be considered in the treatment of the HCC. The clinical and laboratory features required to calculate the Child—Pugh score, extent of hepatocellular impairment, portal hypertension and performance status of the patient need to be known in order to consider the treatment strategy.

In practice, the proposal for treatment should be determined in an MDT based on the three criteria of tumor extension, the state of the non-malignant liver and the patient’s general health. There is currently no consensus about the prognostic classification. The BCLC classification produced by the Barcelona group is the one most widely used in France [5]. It is a treatment decision-making aid, which follows an algorithm published in the international guidelines [2]. The treatment decision, however, should not remain strictly bound within these schemas from the international guidelines and information obtained should be used to adapt the treatments for each patient and to choose the techniques available depending on their expected results and limitations.

Interventional radiology techniques for hepatocellular carcinoma treatment

Radiofrequency ablation

Radiofrequency (RF) ablation uses the principle of applying an electrical current of approximately 400 to 450 KHz
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Figure 1. Seventy-year-old man with alcoholic cirrhosis, no longer drinking. Hepatocellular carcinoma in the very upper part of the dome of the liver measuring approximately 25 mm in size; a: attachment of the upper internal part of the lesion with the diaphragm; b: hydrodissection: peritoneal injection of 1.5 L of isotonic dextrose solution in order to completely detach the lesion from the diaphragm; c: multipolar no touch radiofrequency treatment in view of the exophytic nature of the lesion; d: no persistent arterial enhancement following treatment, without damage to the diaphragm.

through an applicator (needle) within the tumor. The ionic agitation produced increases temperature, which beyond 70° causes tissue coagulation necrosis. It should be noted that the electrical conduction around the needle is produced over a diameter of approximately 1 cm and beyond this distance conduction is mostly thermal, explaining some of the limitations of this technique [6].

There are two major application techniques: by far, the widest used technique is monopolar (which uses single, multiple (cluster) or deployable needles) and the multipolar technique (which is less often used as it is more technically complex).

The current indications for RF are a small number of HCC tumors (conventionally less than 3) and small size (3 cm). Size is one of the major limitations of the technique as in order to maintain a safety margin of 0.5 or 1 cm, a 4 or 5 cm ablation is required for a 3 cm tumor. These are the maximum diameters of coagulation necrosis, which can be achieved with a monopolar technique in a single application [7]. At the cost of inserting several needles into the periphery of the tumor, multipolar techniques can be used to achieve larger ablations (5–6 cm) [8].

Repeated monopolar applications to the same tumor make control of necrosis more difficult although there are other technical limitations to RF [9,10]. The heat sink effect, due to the proximity of a large vessel, may be a factor responsible for residual tumor if the area of the tumor close to the large vessel is within the thermal conduction and not electrical conduction area. Some procedures are designed to counter the heat sink effect, such as balloon obstruction of a suprahepatic or portal vein which is affixed to the tumor or clamping the portal trunk if radiofrequency is performed during open surgery. However, removing the vascularization makes it very difficult to predict the coagulation zone obtained.

Subcapsular lesions are a conventional limitation to RF because of the risks of bleeding and tumor seeding [11]. Multipolar techniques can circumvent this difficulty partly using a “no touch” technique, which involves placing the needle on either side of the tumor without actually penetrating it and producing the ablation between the two needles. Another limitation is the proximity of the tumor to the gastrointestinal tract, which carries a risk of gastrointestinal wall necrosis. Techniques for detaching the tumor from the gastrointestinal tract are available by introducing air or dextrose solution (hydrodissection) [12]. Another limiting factor is proximity of the diaphragm but here again interpositioning fluid (controlled ascites) can circumvent this contraindication (Fig. 1). In addition, lack of visualization of the lesions on unenhanced imaging (particularly when visualized only in the arterial phase) or difficulty accessing the lesions is still real limitations. Here again, ancillary techniques can often be used to circumvent these limitations: using lipiodol labelling of the tumor through arteriography with injection of lipiodol into the hepatic artery can visualize the tumor for longer periods of time on CT (Fig. 2). Image fusion techniques can be used for treatments under ultrasound guidance for a lesion only visible in the arterial phases on CT or MRI [13].
Undoubtedly the main contraindication is proximity to the convergence of the biliary tract, as there is no technique, which can circumvent this difficulty. This carries a risk of biliary tract necrosis at the convergence, leading to permanent obstruction with bilateral biliary tract dilation.

The complications of these techniques also include hematomas and abscesses in the coagulation zone, although the risk of large vessel thrombosis is low. Segmental biliary tract dilation due to ischemic necrosis of the ducts close to the coagulation zone occurs relatively commonly but is inconsequential. In a recent literature review, the mortality of RF destruction of HCC was reported to be 0.15%, with a major complication rate of 4.1% [14].

Published results describe 5-year survival rates of 40 to 70% [15, 16] and long-term survival rates (10 years) in the region of 30% [17]. These are similar to results obtained from surgical excision but are associated with a high rate of liver recurrence of approximately 73% at 5 years and 98.5% at 10 years [17].

Few studies have compared radiofrequency ablation to surgical excision. The study by Chen et al. [18] showed no difference in terms of 4-year survival and the study reported by Huang et al. [19] showed survival to be superior at 5 years for excision surgery, although this study contained considerable bias. Finally, the meta-analysis reported by Cho Yun Ku et al. [20] showed no significant difference between the two techniques. More recently a study by Kang et al. on small nodules (BCLC 0 and A) showed no difference between radiofrequency ablation and surgical excision in terms of 5-year survival [21].

The factors found to influence results are relatively consistent in the various studies [22]: size over 3 cm, number of lesions treated, alpha-fetoprotein concentration and the Child–Pugh score. We have recently shown in studies, which have not yet been published that the use of multipolar techniques also reduced the recurrence rate. This supports findings reported by Seror et al., which showed higher levels of necrosis in explanted liver specimens using multipolar compared to monopolar techniques [23].

Two types of treatment combinations have been proposed with radiofrequency tumor ablation to potentiate its effects. Hyperemia around the lesion and stimulation of the production of proangiogenic substances, such as VEGF during RF form the bases for combining targeted therapies or using course of chemoembolization.

Several studies have been conducted with a combination of chemoembolization and sorafenib. These have improved the time to recurrence although none have shown improved survival [24].

Combination of radiofrequency ablation with chemoembolization appears to be more promising and several studies including a recent meta-analysis have shown not only a gain in recurrence rate, but also in terms of survival for intermediary HCC [25–27].

**Microwave tumor ablation**

This is a form of thermoablation based on a similar principle to that of radiofrequency ablation although in this technique, the frequency of the electric current is between 900 megaHz and 2 gigaHz depending on the generator. These frequencies do not produce ionic agitation but rather produce bipolarization of water molecules, movement of which causes very rapid heating. This removes some of the limitations of radiofrequency ablation, in particular the problem of carbonization around the radiofrequency needle when temperatures exceed 110°. Carbonization forms an electrical insulator, which impedes electrical conduction. This effect is not seen with microwave ablation and the temperatures achieved are therefore considerably higher. Electrical conduction is also greater (over a radius of approximately 2 cm). As the temperatures close to the needle are higher, thermal conduction is theoretically greater. These advantages are encumbered by disadvantages, including poor control of thermal conduction and more difficult control of power [28–30].

At present, the potential clinical advantage of the technique is the speed at which the ablation can occur (for a 3 cm tumor, coagulation necrosis is obtained by microwave in approximately 5 minutes compared to 15 to 20 minutes for conventional monopolar radiofrequency ablation). The reduced sensitivity of large vessels to cooling is another theoretical advantage as the electrical conduction zone is greater.

In terms of results, there are no differences published in the literature between radiofrequency and microwave
Ablation techniques [31,32]. Microwave ablation has the same limitations and contraindications to radiofrequency ablation although it probably carries a higher risk of damage to adjacent organs because of the very high temperatures achieved.

Electroporation

Electroporation is not a thermoablation technique. It involves the application of high voltage electrical pulses (1000 to 2000 V), which are very short and damage cellular membrane permeability. This change in permeability is initially reversible and was used in the 1990s to potentiate the effect of chemotherapy (electrochemotherapy). However, above a specific electrical pulse repetition frequency, the damage to permeability becomes irreversible and leads to cell apoptosis. Cell death is therefore gradual, and is not associated with the effects of necrosis, inflammation or fibrous scarring [33]. The major merits of this technique are that they preserve the vascular and biliary structures, explained mostly by the high collagen fiber content of these structures, which are not affected by electroporation effects. Clinically, therefore, irreversible electroporation can be used to treat tumors close to the biliary tract or blood vessels, which until that point were not accessible to percutaneous radiofrequency or microwave therapies without carrying a risk of serious biliary or vascular complications.

The first electroporation series in human beings was reported in 2011 by Thomson et al. [34]. Several studies since then have shown the technique to be feasible with a similar complication rate to other percutaneous ablation techniques and a high technical success rate with complete ablation rates of over 95% [35].

The technique, however, is still subject to numerous limitations, particularly technical ones. Several needles (2 to 6) need to be inserted along parallel paths with fairly strict observation of the distances between the needles (2.2 cm). Application of electrical pulses requires general anaesthesia with curarization and synchronization of the pulses with cardiac function.

Whilst the technique appears to have significant limitations, it can however be used to treat patients in whom other ablation techniques are not possible despite having small tumors.

There are currently no large series in hepatocellular carcinoma, although the method merits being considered.

Chemoembolization

Chemoembolization involves injecting a cytotoxic agent (usually doxorubicin) bound to a vector into the hepatic artery and then carrying out arterial embolization. The effectiveness of this technique is due to the fact that hepatocellular carcinoma is vascularized mostly through the hepatic artery system, unlike the unaffected liver, which is supplied mostly from the portal venous network. The aim of embolization is to create ischemic cellular necrosis, potentiate the action of the cytotoxic agent and slow arterial blood flow to increase the contact time between the cytotoxic agent and the tumor. However, the benefit of combining a cytotoxic agent with embolization remains controversial. It is likely that the effectiveness of the technique is due mostly to the ischemia-producing potential of embolization. Chemoembolization techniques, however, vary greatly between centers and have changed over time. The conventional technique uses a mixture of lipiodol and a cytotoxic agent. Lipiodol is used as the vector to carry the cytotoxic agent to the tumor by binding preferentially to tumor cells and passing through peribiliary spaces to the portal system [36]. This enables a dual arterial and portal approach to the tumor. With this technique, the embolizing agent may be temporary (Curaspon) or permanent (particles). The other major technique involves direct use of particles laden with the cytotoxic agent, which offer more gradual release with less of the drug passing into the systemic circulation [37,38]. Whilst this second technique has been shown to be beneficial in terms of tolerability, particularly in Child B patients, it has not been found to produce any actual gain in terms of survival [39].

The technique is changing towards greater selectivity of treatment, optimally targeting only the tumor(s) or segment containing the tumor. The selectivity of this treatment compared to hemi-hepatic therapy (right lobe/left lobe of liver) improves tolerability and tumor response, although again no change in survival has been found [40]. A trend is also developing towards using smaller embolization particles (100 to 300 microns) in order to increase the tumor necrosis [41,42]. This reduction in microparticle diameter is obviously only possible if the treatment is selective. Finally, the use of drugs, which are more effective than doxorubicin on HCC, may be factor contributing to greater efficacy. Idarubicin has been shown to be a potentially useful cytotoxic agent [43].

The survival results from chemoembolization are still debated widely in the literature. The current use of chemoembolization is based on one positive study [44], and in particular on a meta-analysis [45]. The median survival following lipiodolated chemoembolization in these studies was 20 months although more negative studies are regularly being published [46]. The major problem appears to be with patient selection.

The main limitations and complications of chemoembolization are hepatocellular impairment and potentially worsening pre-existing impairment, which limits its use to patients with preserved hepatic function (Child–Pugh score A or B), without invasion of the portal trunk. This type of contraindication is of course be counterbalanced by the ultraselective nature of the treatment.

As for the technique itself, the morbidity rates of chemoembolization vary greatly in the literature. They depend on the extent of the embolization, selectivity of treatment and the type of embolizing agent used. The post-chemoembolization syndrome, which is a combination of pain and fever lasting approximately 48 hours, is almost always seen. Expected and potentially serious complications include worsening of hepatocellular impairment and decompensation of cirrhosis. Locally, tumor necrosis and abscess formation may occur. The incidence of severe complications was reported to be 5.6% (range 0–50%) with a mortality rate ranging from 0% to 10% in a recent literature review on 18 randomized studies [47].

Conversely, treatment of diffuse HCC, even with small nodules, which requires the entire the liver to be treated needs to be carefully considered as its possible efficacy may
be counterbalanced by severe destruction of non-malignant liver parenchyma [48]. Similarly, treatment of diffuse infiltrated non-hypervascularized tumors remains a subject of debate. Recent studies, however, show that chemoembolization of this type of tumor is beneficial in terms of survival with a low complication rate, provided that patients are well selected [49].

The frequency with which courses are repeated is not clearly defined. In view of the aggressive effect of treatment on the arterial network and non-malignant parenchyma, international guidelines are tending towards recommending treatment based on the results obtained from the first course. Repeating the treatment is only justified if a large amount of residual tumor is present after the first course or if the disease progresses [2]. Criteria to continue or stop treatment after an initial course of chemoembolization (ART criteria) have recently been proposed and are based on measurement of the ALT, the Child–Pugh score and the tumor response after a course of chemoembolization [50]. Recent validation studies for this score, however, have been negative [50,51].

There is a strong rationale to combine chemoembolization with targeted therapy. As a result of the ischemia, which it produces, chemoembolization causes overexpression of VEGF and PDGFR-β. These angiogenesis factors cause a local rebound effect on tumor growth and an increase in their circulating concentrations can promote the growth of new HCC tumors throughout the liver.

Many studies have therefore assessed the combination of chemoembolization with targeted therapies, such as sorafenib, bevacizumab, endostatin or thalidomide [52]. The aim of most of these studies was to examine tolerability and measure the time to progression, which was increased in most studies from an average of 4 to 9 months. None, however, have shown benefit in terms of survival and the tolerability of targeted therapies remains a problem [52,53].

Radioembolization

Like chemoembolization, radioembolization is based on the arterial vascularization of the HCC and involves injection of microspheres labeled with a radioisotope, yttrium 90 ($^{90}Y$) into the hepatic artery. This enables selective internal radiotherapy to be carried out on liver tumors and uses either 20 to 30 μm diameter glass or resin microspheres. $^{90}Y$ is a pure beta minus ($\beta$–) emitter, which has average tissue penetration of 2.5 mm with a maximum penetration of 10 mm. It has a half-life of 64.1 hours. Following injection of the microspheres into the hepatic artery and once they have blocked the tumor microvasculature, emission of $\beta$– particles by $^{90}Y$ irradiates the tumor. In view of the low tissue penetration by the particles emitted by $^{90}Y$, this treatment does not require the patient to be isolated in a lead-lined room and only requires limited radioprotection measures after the treatment has been delivered [54]. Similarly, irradiation of the adjacent non-malignant liver tissue around the tumors, which captured the microspheres, is low.

Preparatory arteriography is required before injecting the radioactive particles into the right or left hepatic artery, depending on the site of the tumor [55]. The purpose of this arteriography is to determine where to inject the $^{90}Y$ labeled microspheres by identifying the main artery supplying the tumor and confirming that there are no arteries arising close to the injection site which could lead to particles being taken up by extra-hepatic organs, primarily the gastrointestinal tract. As such, the right gastric artery usually arises from the common hepatic artery or the origin of the left hepatic artery. Preparatory arteriography can preventatively occlude these arteries with coils. In addition, if the tumor is vascularized by several arteries, some groups propose occlusion of some of these arteries to “monopediculize” the tumor so that there is only a single artery to be embolized. Finally, once the position of the catheter to inject the microsphere has been selected, albu- min particles labeled with $^{99m}Tc$ ($^{99m}Tc$-MAA) are injected, followed by scintigraphy (anterior and posterior images centered on the liver and lungs followed by SPECT-CT images) which ensure that the tumor is correctly targeted, and that there are no sites of extra-hepatic gastrointestinal hyperactivity. In addition, the hepato-pulmonary shunt must remain low, with the objective that the dose being delivered to the lungs is less than 30 Gy per treatment session and a maximum of 50 Gy as a cumulative dose [56] (Fig. 3). If carcinoma is present in both lobes, the treatment is usually delivered sequentially with one injection of $^{90}Y$ labeled microspheres to each lobe of the liver, on each occasion preceded by preparatory arteriography and scintigraphy [55]. It is important, however, to keep in mind the fact that the $^{99m}Tc$-MAA particles are different from the resin or glass particles used in radioembolization and that they behave differently in the arterial blood flow. The distribution of the $^{90}Y$ labeled particles may therefore be different.

Calculation of the activity of the $^{90}Y$ labeled microspheres to be administered varies depending on the type of particle used. The activity calculation for resin microspheres is usually based on body surface area and the percentage of tumor invasion whereas the calculation of activity for glass microspheres is based on the "Medical Internal Radiation Dose" (MIRD) methodology [57]. For glass microspheres, activity is generally calculated to obtain a dose of between 80 and 120 Gy to the perfused liver [56]. Ideally, extensive irradiation of the tumor lesions is sought at the same time maintaining irradiation of the non-malignant parenchyma below a given threshold. In this context, using high performance tools for the planned dosimetry, a recent study showed “intensification” of treatment and administration of higher doses to the tumor without increasing hepatic toxicity [58].

Once the $^{90}Y$ labeled microspheres have been administered, $^{90}Y$ Bremsstrahlung SPECT-CT imaging or a $^{90}Y$ PET-CT imaging (internal pair production of $^{90}Y$) is performed in order to ensure that the spheres are correctly distributed [59].

There are many studies ongoing to assess the efficacy of this new treatment. The first reported [60] showed median survival of 24.4 months, 16.9 months and 10 months for BCLCA, BCLCB and BCLCC patients, respectively in whom no treatment other than systemic chemotherapy was possible. A meta-analysis of 14 studies on the radioembolization treatment of liver tumors showed tumor response rates for HCC ranging from 78 to 89% [61].
In parallel, this treatment is usually well tolerated, better than chemoembolization or targeted therapy. The post-embolization syndrome (nausea, vomiting, abdominal pain and fever) is less common than with chemoembolization. Severe complications have been reported for accidental embolization of non-hepatic organs, including gastrointestinal ulceration, pancreatitis, cholecystitis and radiation-induced pneumonia [62]. Cases of radiation-induced hepatitis have been described [63].

**Indications**

Interventional radiology is involved practically at each stage in the treatment of hepatocellular carcinoma as
recommended in the EASL-EORTC guidelines (Fig. 4). It is even becoming more important as technological advances progress with the long-term assessment of its efficacy [17].

Whilst transplantation remains the treatment, which achieves the best survival rate for BCLC stage A patients, it is only available for a small number of patients. The drop out rate from the transplant list, which is 30% at 1 year for HCC [64,65], requires a bridge treatment. This mostly involves interventional radiology. Whilst chemoembolization has long been the treatment of choice, despite being disputed in terms of efficacy [66], percutaneous ablation is taking on a greater role [64,67].

According to the international guidelines, patients with a single ‘early’ HCC (BCLC classification stage 0) and without liver dysfunction or severe portal hypertension are candidates for excision surgery. In routine practice, however, there is still a question about its use compared to percutaneous ablation depending on the site of the tumor (a central tumor requires wide excision or, compared conversely, to a subcapsular tumor which can easily be resected laparoscopically). Percutaneous ablation is therefore tending to become offered first line for small tumors by many groups, surgery being considered if a percutaneous approach has limitations [2,68,69].

In patients who do not have many (less than 3) HCC which are small (size under 3 cm), percutaneous tumor destruction is the method of choice. At present, the radiofrequency ablation technique is preferred for this, although the availability of multipolar and microwave methods should allow treatment to be potentiated by choosing the appropriate technique. It has become possible to treat multiple tumors with microwave and to treat a lesion lying close to a large vessel. Larger tumors can be treated using the multipolar radiofrequency technique.

Intermediary stage HCC (stage B) accounts for a large proportion of HCC at the time of diagnosis. As the indications for the chemoembolization are very wide, it remains the most commonly used treatment for HCC (20 to 30% of patients with HCC). According to international guidelines, chemoembolization is used for patients with intermediary stage (BCLC B) with multifocal tumors or tumors which are too large to be able to be treated curatively, but who are still in good general health (performance status = 0), without portal thrombosis and with preserved liver function (less than Child B 7). However, this is the most heterogeneous group of patients and for tumors up to 5 cm in size, multipolar radiofrequency ablation, whether or not combined with chemoembolization, can be considered and appears to produce good results [70]. Conversely, for more infiltrative lesions or in patients in poor general health, radioembolization may represent an alternative.

For targeted therapies (sorafenib) represent the current standard for more advanced tumors in patients whose liver function is still satisfactory (Child–Pugh score < B7). If radioembolization were proven from the randomized studies [71], this technique will become an alternative to the systemic therapies [72,73].

Whilst the main principles of treatment are defined in international guidelines (Fig. 4), the situation is not set in stone and each patient’s case should be discussed in light of the available options. It is essential to offer the best treatment at a given time in the course of the disease and to understand the options, together with their possibilities and limitations, as it is important to consider how the treatments are used in succession and sequentially. Patients should have access to several types of treatment and it is likely that over time a combination of the various treatment options will significantly increase patient survival. As an example,
Shon et al. recently showed that RF treatment of residual lesions following chemoembolization could achieve higher survival rates than those usually seen with chemoembolization alone [74]. The 10-year survival rate reported for HCC is not a result of a single treatment but the consequence of combining all of the treatment options, discussed regularly in the MDT.

**Take-home messages**
- In France, only 20% of HCC patients are discovered at a stage allowing curative treatment to be offered.
- The choice of treatment for HCC should be made in a multidisciplinary team meeting after the imaging staging assessment and a full clinical and laboratory assessment.
- Radiofrequency tumor ablation can achieve 10-year survival rates, which are almost equivalent to those of surgical resection for tumors under 30 mm in size.
- Chemoembolization and percutaneous tumor destruction are bridge treatments for liver transplantation.
- Radioembolization is a technique currently being assessed which main gain a significant place in the treatment of intermediary and advanced HCC.
- The various treatments are complementary and should be adapted throughout the course of the disease.

**Clinical case**

A 69-year-old man with metabolic cirrhosis was referred to us for possible treatment of hepatocellular carcinoma. The patient had MR imaging examination after the discovery of a nodule during the six-monthly ultrasound examination (Fig. 5).

**Questions**

1. Without any other information, what treatment(s) would be appropriate for this patient?
   - A. Transplantation
   - B. Surgical resection
   - C. Tumor destruction by monopolar radiofrequency ablation
   - D. Ultra selective chemoembolization with loaded particles
   - E. Sorafenib

2. What additional test and information should be obtained for a discussion about treatment?
   - A. Chest CT scan
   - B. Esophageal endoscopy
   - C. Tumor biopsy
   - D. The portal-suprahepatic gradient
   - E. Measurement of plasma bilirubin

3. The patient is Child stage A with severe portal hypertension and a performance status = 0. What treatments would you offer in the multidisciplinary team meeting?
   - A. Transplantation
   - B. Surgical resection
   - C. Tumor destruction by monopolar radiofrequency ablation
   - D. Microwave tumor destruction
   - E. Selective radioembolization

4. In the event of a single recurrence in the left lobe of the liver 15 mm in diameter within 2 years and the patient’s laboratory and clinical situation is unchanged, what treatment options would you consider?
   - A. Transplantation.
   - B. Salvage surgery.
   - C. Tumor destruction by radiofrequency ablation.
   - D. Selective chemoembolization of the left lobe of the liver.
   - E. Sorafenib.

**Answers**

1 B, C.
2 A, B, E
3 C, D.
4 C.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

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