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Other non-surgical treatments for liver cancer

Paul Revel-Mouroz[a], *Philippe Otal*[a,*], *Marion Jaffro*[a], *Antoine Petermann*[a], *Olivier Meyrignac*[a], *Pierre Rabinel*[b], *Fatima-Zohra Mokrane*[a]

[a] *Department of Radiology, Rangueil Hospital, 1, avenue du Pr Jean Poulhès TSA 50032, 31059 Toulouse Cedex, France*

[b] *Department of Digestive Surgery and Liver Transplantation, Rangueil Hospital, 1, avenue du Pr Jean Poulhès TSA 50032, 31059 Toulouse Cedex, France*

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ABSTRACT

Interventional radiology plays a major role in the modern management of liver cancers, in primary hepatic malignancies or metastases and in palliative or curative situations. Radiological treatments are divided in two categories based on their approach: endovascular treatment and direct transcapsular access.

Endovascular treatments include mainly three applications: transarterial chemoembolization (TACE), transarterial radioembolization (TARE) and portal vein embolization (PVE). TACE and TARE share an endovascular arterial approach, consisting of a selective catheterization of the hepatic artery or its branches. Subsequently, either a chemotherapy (TACE) or radioembolic (TARE) agent is injected in the target vessel to act on the tumor. PVE raises the volume of the future liver remnant in extended hepatectomy by embolizing a portal vein territory which results in hepatic regeneration.

Direct transcapsular access treatments involve mainly three techniques: radiofrequency thermal ablation (RFA), microwave thermal ablation (MWA) and percutaneous ethanol injection (PEI). RFA and MWA procedures are almost identical, their clinical applications are similar. A probe is deployed directly into the tumor to generate heat and coagulation necrosis. PEI has known implications based on the chemical toxicity of intra-tumoral injection with highly concentrated alcohol by a thin needle.

1. Background

Interventional radiology became a central element in the treatment of liver cancer, providing multiple possibilities for the management of primary hepatic malignancies or metastases. Technological advances of the two past decades have metamorphosed the prognosis of a number of patients, turning palliative situations into curative hopes. Radiological means are attractive through their potential efficiency, their minimally invasive nature and even more by the fact that they can be used in combined treatment strategies, like granting

* *Corresponding author.*
E-mail address: otal.p@chu-toulouse.fr (P. Otal).
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in situ pathways to heighten chemotherapy effect or allowing a surgical resection by increasing the size of the future liver remnant.

The common characteristic of radiological methods is the organ approach which consists of arterial or venous endovascular access, or a direct transcapsular approach either in a percutaneous way or concurrently with a surgical procedure.

In the following sections, we offer an overview of some radiological methods that can be integrated into liver malignancy therapeutic projects, broaching technical principles and leading applications.

Stereotactic body radiation therapy can also be part of this multidisciplinary approach while it has shown to provide promising results in the treatment of hepatocellular carcinoma and liver metastases.[1,2]

2. Endovascular treatments

2.1. *Transarterial chemoembolization (TACE)*

This treatment is based on the following vascular features: the non-tumor liver parenchyma receives two-third of its blood supply from the portal vein and only one-third from the hepatic artery, whereas hepatic tumors are mainly vascularized by branches of the hepatic artery. Through a peripheral arterial access, a selective catheterization of the targeted arterial branch is performed, allowing the injection of a chemotherapeutic molecule combined with an embolic agent. Beside the hepatic artery, it is crucial to search and to treat extrahepatic arterial supplies of the tumor, such as the right inferior phrenic artery, to ensure an optimal effectiveness. Two types of procedures have been described.

2.1.1. *Transarterial oily-chemoembolization*

This procedure employs a mixture of highly concentrated chemotherapy agent with ethiodized oil, marketed as Lipiodol®. The latter combines substantial inherent benefits beyond its carrier nature. Its high iodine concentration makes it opaque to X-ray, which is helpful to adapt flow delivery during the injection to prevent the reflux issue and to control the captation rate of the tumor on CT. Indeed, the degree of Lipiodol® uptake appears to be an independent prognosis factor (Fig. 1).[3,4] Furthermore, it has tumor-seeking properties, its viscosity slows down the washout of the chemotherapy agent, and its oily nature provides tropism to small tumor vessels.[5,6] The most widely used chemotherapy agent is doxorubicin but no scientific proof of its superiority has been established, and cisplatin or epirubicin might be as effective.

Afterwards, an embolic agent is injected causing ischemia and necrosis of the tumor and delaying the drug washout. Multiple embolic agents can be employed, the most widely used is gelatin sponge made of purified porcine-derived gelatin which facilitates repetitive procedures by its resorbability.

In patients with hepatocellular carcinoma (HCC), the frequently underlying cirrhosis narrows therapeutic options since TACE can lead to liver decompensation. Thus, functional hepatic reserve becomes a prerequisite for TACE treatment.[7] Consequently, patients need to be rigorously selected: a panel of experts has determined contraindications including biliary obstruction, decompensated cirrhosis (Child-Pugh B8 or higher), hepatofugal portal flow or portal vein thrombosis, extensive tumor with replacement of both lobes and severe renal insufficiency.[8]

Other complications of TACE include non-target embolization, hepatic abscess and bilioma, facilitated by biliary obstruction, renal failure or variceal bleeding.

The post-embolization syndrome, which is a combination of pain, fever, nausea and vomiting lasts a few hours to a few days and is more of an expected consequence than a complication.

2.1.2. *TACE with drug-eluting beads*

More recently, drug-eluting beads have been developed. These are non-resorbable agents, their chemical structure combines polymeric microspheres doped with sulfonyl groups that provide a reversible ionic binding with polar molecules such as doxorubicin. Benefits reside in a reduced systemic passage of the cytotoxic substances employed, with comparable outcomes to lipiodol (Fig. 2).[9–11] Indeed, the PRECISION V study compared, for a 6 months follow-up, oily-TACE and TACE with DC Beads. The DC Bead group showed non-significantly higher rates of complete response, objective response, and disease control compared with the oily-TACE group (27% vs. 22%, 52% vs. 44%, and 63% vs. 52%, respectively), $P = 0.11$.[11] Nevertheless, the DC Bead group showed improved tolerability, with a reduction in liver toxicity ($P < 0.001$) and a significantly lower rate of doxorubicin-related side effects ($P = 0.0001$).[11]

2.2. *Transarterial radioembolization (TARE)*

This treatment is based on similar principles to TACE, applied to nuclear medicine. TARE selectively delivers high radiations doses to hepatic tumors and minimizes as much as possible the radiation dose received by the non-tumor liver parenchyma and other organs, especially the lungs, stomach and bowel.[12]

For this purpose, quite a few combinations of vectors and radionuclides have been proposed.

2.2.1. *^{131}I-Lipiodol®*

The first example of this strategy is the use of radiopharmaceutical ^{131}I-Lipiodol®. This combination takes advantages of Lipiodol® properties discussed previously and of the gamma rays emitted by this radioisotope. The therapeutic dose is estimated not to exceed the threshold of 30 Gy to the lungs and to the non-tumor liver.

The preliminary step to perform this technique consists of a procedure achieved with a low radiation dose. The aim of this procedure is to quantify the shunting of microparticles to the lungs or the gastrointestinal tract. It is helpful for patient selection because risks of radiation gastritis, enteritis or pneumonia are supposed to be dose-dependent effects. This first phase also allows the evaluation of the dose necessary for treatment.

Subsequently, the treatment is performed via radiologic techniques comparable to TACE (Fig. 3).

Main benefits of this method are: a real-time control of the injection allowed by the radio-opacity of the drug and a simplified evaluation of the efficiency which is correlated to

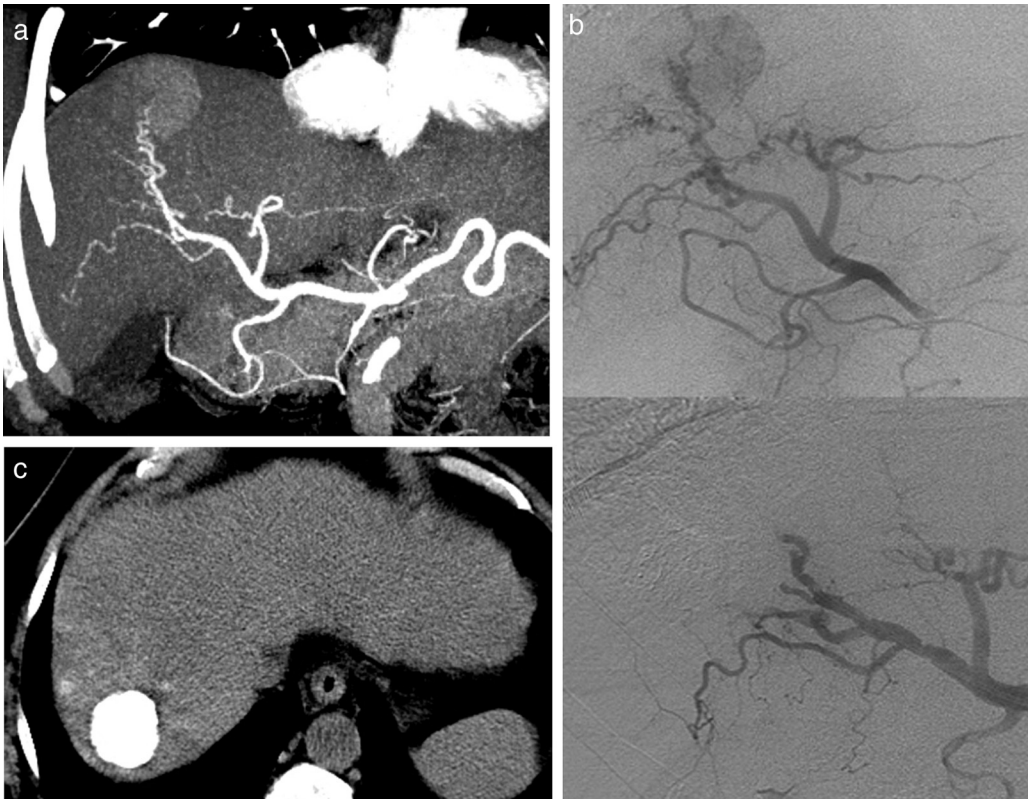

Fig. 1 – Transarterial oily-chemoembolization for hepatocellular carcinoma. (a) Enhanced CT at the arterial phase (same case as in Fig. 3). Hepatocellular carcinoma with arterial enhancement. (b) Corresponding selective angiography of the right branch of the hepatic artery shows tumoral blush (top). Subsequently, a transarterial oily-chemoembolization is performed. The control angiography assessed at the end of the procedure (bottom image) shows the disappearance of the blush. (c) Abdominal non-enhanced CT performed 6 weeks later, shows an homogeneous and intense lipiodol uptake of the tumor.

the tumoral uptake of Lipiodol® on CT. We can describe several limitations: this procedure seems to be less effective for hypovascularized tumors[13] and the biological half-life of ^{131}I is about 8 days and compels a few days of isolation.

2.2.2. *Yttrium-90-labeled microspheres*

There has been a renewed interest for another radioembolic agent. Direct infusion of yttrium-90-labeled microspheres into the hepatic artery via a catheter from a combination of ^{90}Y, which is mainly a beta-emitter, coupled with microspheres, which are non-resorbable embolic agents that eventually lodge into the microvessels of the tumor.[14,15] Two types of microspheres are commercially available: SIR-Spheres® (Sirtex Medical Limited, Australia) and TheraSphere® (Biocompatibles, UK). TheraSphere® has a higher specific activity (2500 Bq) and lower number of spheres (1.2 million microspheres/3 GBq). Conversely, SIR-Sphere® has a lower specific activity (50 Bq) and greater number of spheres (approximately 40–80 million spheres/3 GBq), the injection of the latter is more challenging due to a higher risk of irradiation of non-targeted organs.

This is a technically more challenging procedure than the former one, requiring an accurate mapping of the hepatic arterial vascularization and the embolization of any collateral vessels of the common hepatic artery in order to prevent gastrointestinal irradiation. Furthermore, in the same angiographic time, ^{99m}Tc-labeled macroaggregated albumin is infused into the hepatic artery, which allows the detection and quantification of hepatopulmonary shunting and residual gastrointestinal deposition through a gamma camera (Fig. 4).[16] A fraction of hepatopulmonary shunt greater than 10% represents a contraindication to this procedure. The other procedure consists of a therapeutic injection.[16–18]

2.3. *Portal vein embolization*

This is not an interventional procedure aiming at ablating hepatic tumors but allowing hepatectomy for patients otherwise contraindicated to surgery because of too small remnant liver. Indeed, performing a hepatic resection is a surgical challenge requiring the preservation of liver parenchyma of a sufficient volume with a maintained hepatic artery, biliary duct, portal and hepatic veins. Predicted future liver remnant (FLR) volume is evaluated on a preoperative computed tomography (CT) using volumetric calculations. Because hepatic volume is correlated with patient body surface area, a standardized ratio of FLR volume to the total functional liver volume is more reliable. Threshold ratios allowing surgical resections differ with different conditions and the values are superior to: 40% for cirrhotic liver or patients suffering a chronic biliary obstruction, 30% for patients with hepatic steatosis or exposed to hepatotoxic chemotherapy and 20% for patients with normal

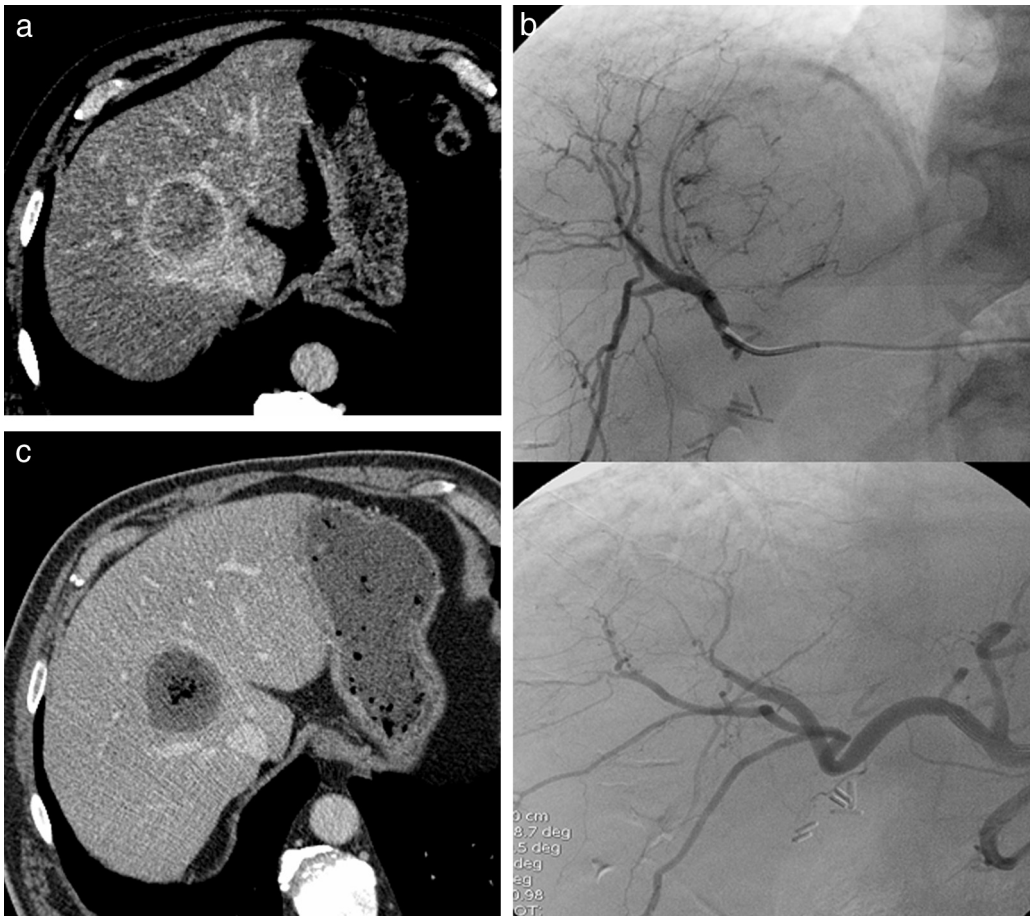

Fig. 2 – Transarterial chemoembolization for hepatocellular carcinoma with drug-eluting beads. (a) Enhanced CT at the venous phase, showing an HCC with wash-out. (b) Selective catheterization and opacification of the right branch of the hepatic artery (top), showing the branches feeding the tumor. The angiography after DC Bead injection (bottom) shows the disappearance of the tumoral blush. (c) Enhanced CT at the portal venous phase 6 weeks later, showing a complete tumoral necrosis.

liver function and no other anomaly.[19–25] Below these values, patients are exposed to severe complications including liver insufficiency, especially during the early postoperative period.

The aim of the portal vein embolization (PVE) is to promote liver regeneration, thus hypertrophy of the FLR. Growth of the FLR is a consequence of hyperplasia occasioned by local and systemic growth factors and cytokines provided by an increased portal flow.[26–28]

From a technical point of view, the PVE procedure is a direct percutaneous approach to either ipsi- or contralateral distal portal branch (Fig. 5). Subsequently, portography facilitates selective catheterization. It is important to embolize the entire portal targeted vessels, even the distal branches, to prevent portoportal shunts.[25] Multiple embolic agents can be used, with a similar efficiency, such as microparticles, n-butyl cyanoacrylate and fibrin glue. The contralateral approach offers the advantage of simpler catheter manipulations and a reduced risk of peritoneal seeding whereas ipsilateral method prevents vascular injury of the FLR. Main indications are represented by right hepatectomy and extended right hepatectomy with an insufficient predicted volume of the FLR (Fig. 6).

Minor complications occur in 25%, while major complications ensue in 5% of cases, including complete portal vein thrombosis, portal hypertension, ipsilateral portal vein thrombus and hemoperitoneum.[29] Expected growth volume of the FLR usually occurs within 4 weeks, normal liver growth rate is 12–21 cm^3 a day, whereas cirrhotic livers have a slower and lower potential of regeneration.[25,30]

3. Percutaneous treatments

3.1. *Radiofrequency thermal ablation*

Radiofrequency thermal ablation (RFA) is a minimally invasive percutaneous strategy for solid malignancies that has been expanding widely in the last decades. RFA may be performed with patients under intravenous sedation or general anesthesia.[31]

During this procedure, the patient is placed in the center of an electromagnetic circuit by means of surface electrodes usually applied on patient's thighs. Then, a thin needle, coupled to a generator, with an insulated shaft and an

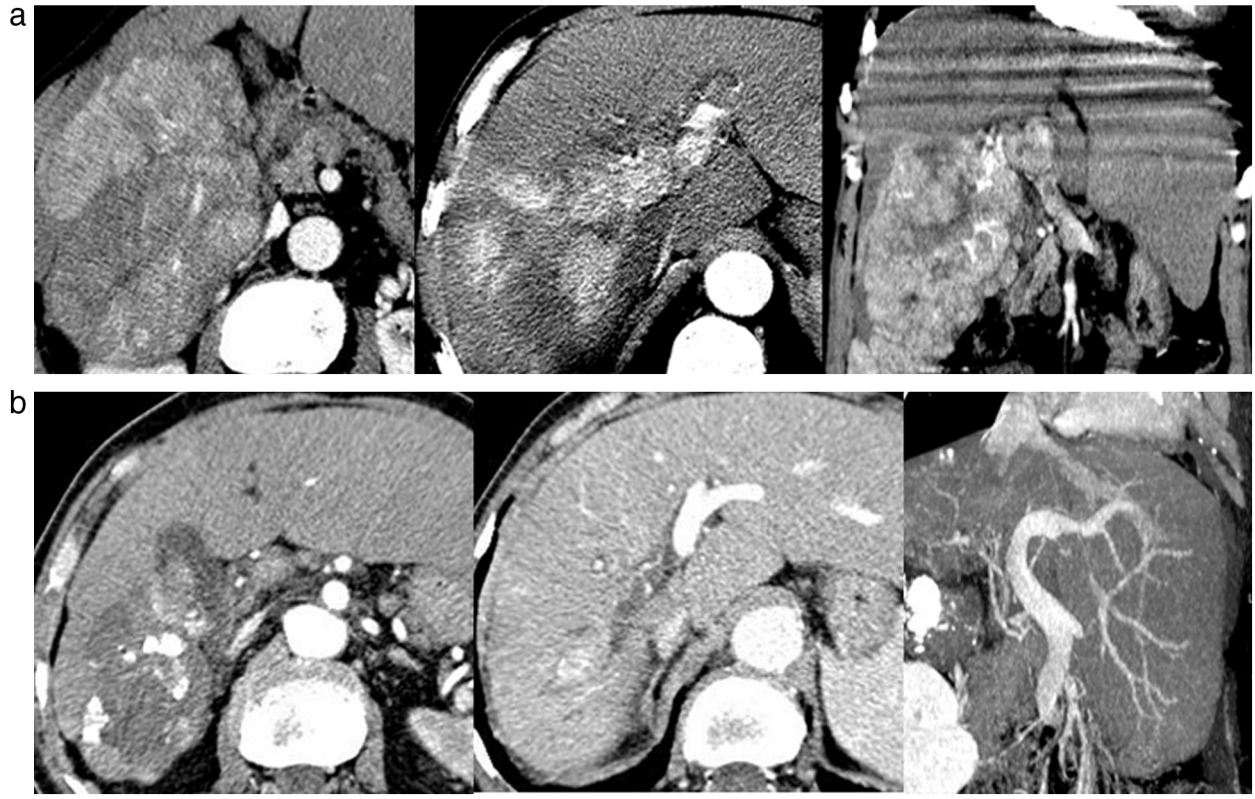

Fig. 3 – Transarterial radioembolization for HCC with ^{131}I-Lipiodol®. (a) Enhanced CT at the arterial phase, MPR reconstructions showing a large heterogeneous hepatocellular carcinoma with marked enhancement. There is a large extension of the tumor into the portal vein (arrow). (b) Enhanced CT at the portal arterial phase, performed 6 weeks after a transarterial radioembolization with ^{131}I-Lipiodol®. MPR reconstructions shows an heterogeneous lipiodol uptake, a shrinkage of the tumor and a substantial reduction of the extension of the tumor into the portal vein.

uninsulated distal tip is introduced and deployed in the tumor, under sonographic, CT or MRI guidance. An alternating current flow generates ionic agitation at the tip of the needle and thus heat in the neighboring tissues. Depending on the size and the shape of the needle's tip, spherical lesions of coagulation necrosis are created, generally from 2 to 5 cm in diameter in about 10 min to half an hour.[32]

It is important to underline two important aspects. On one hand, as much as surgical resection, a 0.5–1 cm depth rim of

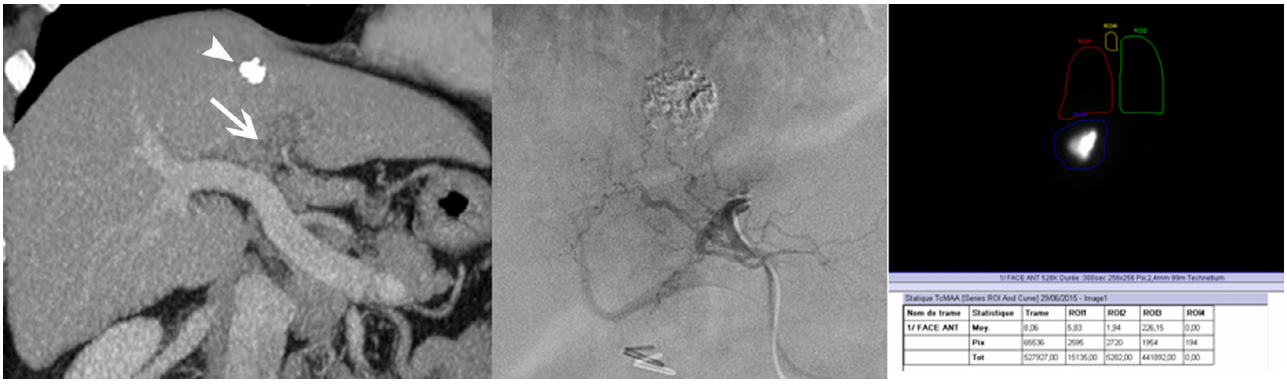

Fig. 4 – Transarterial radioembolization for hepatocellular carcinoma with yttrium-90-labeled microspheres. (a) Enhanced CT at the portal venous phase, performed in order to evaluate the effectiveness of a transarterial chemoembolization for a hepatocellular carcinoma. The primitive tumor shows an incomplete lipiodol uptake (arrowhead) and a portal vein tumor thrombosis (arrow). (b) Selective opacification of the artery feeding the segment IV of the liver, as 1st step of the radioembolization, consisting of the injection of a low dose of ^{99m}Tc-labeled macroaggregated albumin. (c) Immediately after the infusion of the ^{99m}Tc-labeled macroaggregated albumin, a single-photon emission computed tomography is performed, which also allows to plan the therapeutic dose of ^{90}Y after checking the lack of pulmonary and gastro-intestinal shunting.

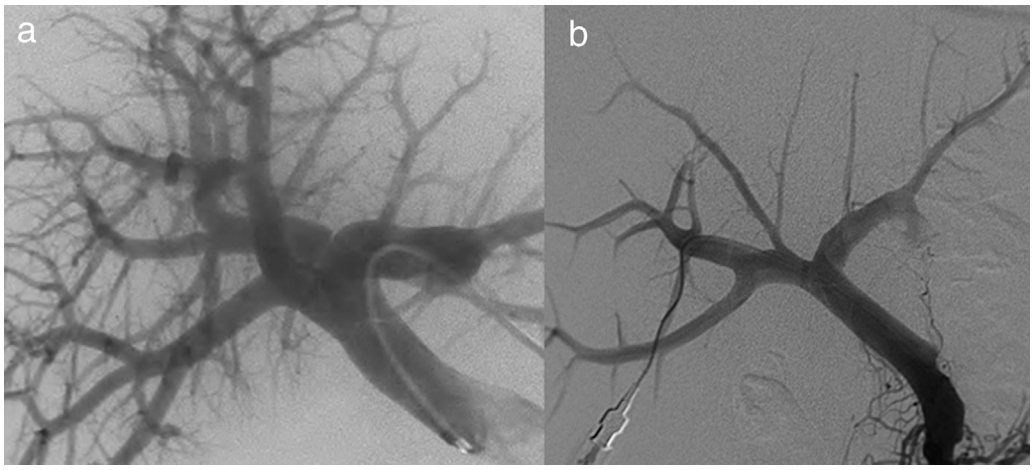

Fig. 5 – Portal vein embolization of the right liver. The procedure can be performed either with a contralateral (a) or a homolateral approach (b).

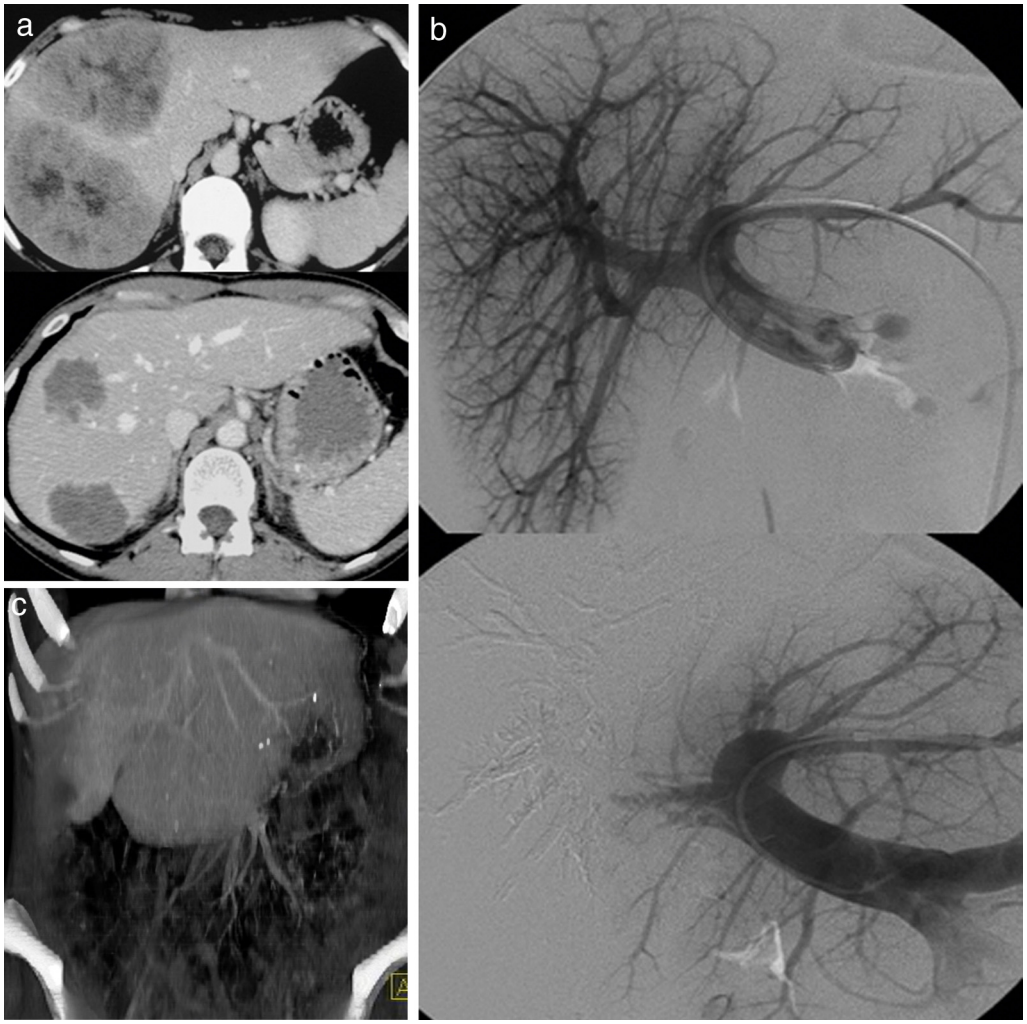

Fig. 6 – Portal vein embolization of the right liver for colorectal cancer metastasis. (a) Enhanced CT at the portal venous phase before (top) and after (bottom) a systemic chemotherapy treatment showing a good response. The patient could be eligible to a curative right hepatectomy provided that the future liver remnant reaches a sufficient volume. (b) Portal vein embolization of the right liver assessed with a contralateral approach. (c) Enhanced CT at the portal venous phase, volume rendering shows a hypertrophied left lobe allowing surgical resection.

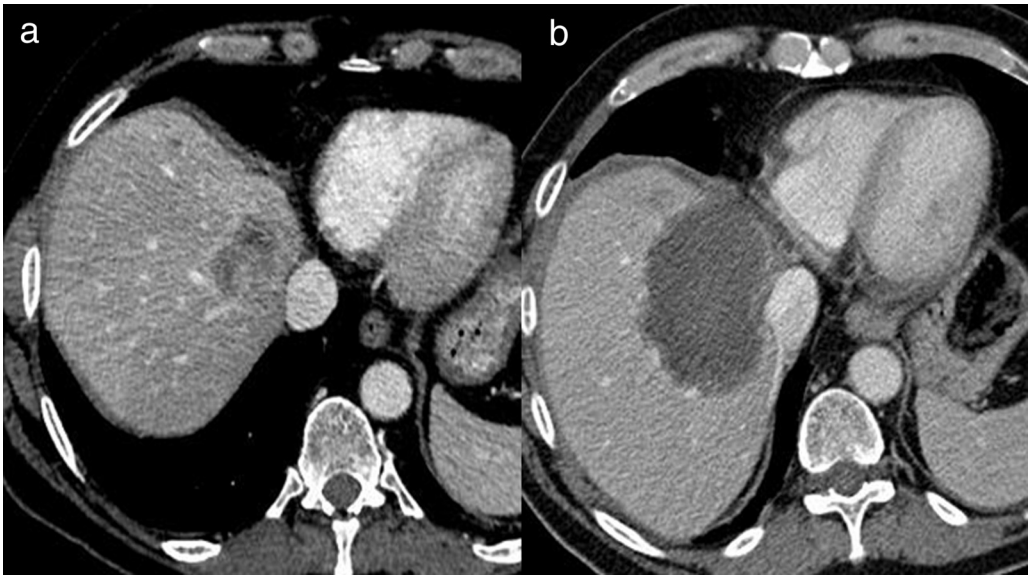

Fig. 7 – Overcoming the heat-sink effect in radiofrequency thermal ablation: a peroperative approach. (a) Enhanced CT at the portal venous phase, showing a colic metastasis in the upper aspect of the right liver, whose posterior aspect has close contact with the right hepatic vein. Patient also required a left lobectomy. Peroperative thermal ablation of the right lesion was performed under Pringle maneuver (clamping of the hepatoduodenal ligament) with a 4-cm diameter needle, to overcome the heat-sink effect. (b) Abdominal CT follow-up at two months shows a complete devascularized thermal lesion, larger than expected.

safety margin has to be respected and, consequently, the size of the needle has to be oversized in relation to the size of the tumor.[31] On the other hand, at the end of the procedure, a slowly managed needle withdrawal has the double benefit of reducing the bleeding risk by a cauterization heat effect and preventing tumor seeding by destroying cells in the needle track.

As the size of lesions increases, its local efficacy is reduced due to a maximum volume of ablation in the range of 4 cm, and in heat loss due to perfusion mediated tissue cooling. The heat-sink effect is a relatively frequent condition that may impair RFA efficiency. Bordering vessels are likely to bring convective cooling effect and reduce the amount of energy locally deposited.[31] Several techniques are available to overcome this barrier (Figs. 7 and 8). When vulnerable organs such as the colon and the stomach are threatened by RFA ballistic, instillation of liquid or gas between the targeted area and this structure is a solution to protect them. This latter technique is called hydro or gas dissection.[31]

An excessive local temperature, reaching 100–110 °C can provide vaporization of the neighboring tissues.[33] Thus, generated gas decreases the volume of tissue destruction.[34] Several technical options are available to prevent this effect, such as monitoring temperature or impedance during treatment or assessing instillations of saline solution.[35]

RFA is a safe technique with very low complication rates. Large studies report 3.5% complications mainly including bile duct injuries (0.7%), liver infarctions (0.5%) and biliomas (0.2%).[36]

Imaging follow-up is performed at 1, 3, 6, 9 and 12 months after treatment and at 6-month interval thereafter.[37] Ablated tumor appears on enhanced imaging (US, CT or MRI) as a non-enhancing area while tumor recurrence shows an irregular nodular enhancement.

3.2. *Microwave thermal ablation*

Microwave thermal ablation (MWA) is an emerging technique that shares multiple common characteristics with RFA. Indeed, technical features of the procedure are almost identical to those of RFA. The differences arise from the physical phenomenon used to generate heat.

While RFA takes advantage of the resistive heating generated by electric current, MWA refers to devices that use physical waves with frequencies superior or equal to 900 MHz.[38] The large majority of the heat is yielded by the agitation of the polar molecules, such as water molecules, induced by microwave pulses; ionic polarization accounts for a much smaller part of the energy deposition.[39–41] Current means are mainly based on two frequency categories: 915 and 2450 MHz. 2450 MHz are the ones most frequently used whereas 915 MHz could present a deeper penetration in the tissues, thus potentially larger ablation zones.[40–42]

MWA presents several theoretical advantages over RFA: it can provide larger areas of coagulation necrosis in shorter times as MWA is less affected by the protection of the neighboring tissues provided by vaporization and charring, and is also much less concerned by the heat-sink effect.[38,41,43] Moreover, it is possible to achieve simultaneously multiple probe deployments.[38,39,43–45] However, this efficiency is counterbalanced by a higher risk of injuring surrounding tissues.

It is important to note that MWA, such as RFA, can be part of combined treatments and potentially give rise to a synergic effect with TACE. It has been proved that interrupting hepatic

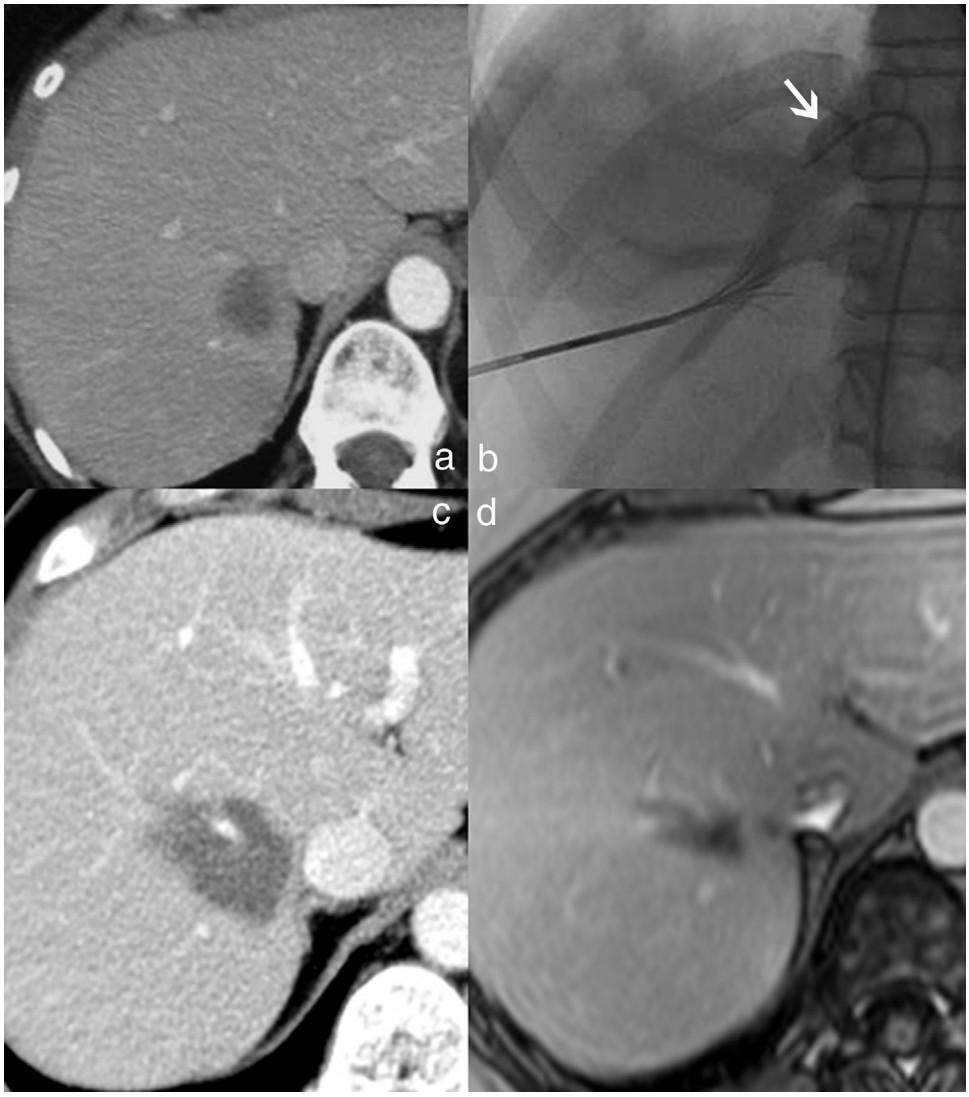

Fig. 8 – Overcoming the heat-sink effect in radiofrequency thermal ablation: a percutaneous approach. (a) Enhanced CT at the portal venous phase showing a breast metastasis whose posterior aspect has close contact with the right hepatic vein. (b) Selective occlusion of the right hepatic vein with a Fogarty balloon during the application of the thermal ablation. (c) Abdominal CT follow-up at three months showing an homogeneous thermal lesion without enhancement. The right hepatic vein remains patent. (d) Liver MRI follow-up at two years, showing the shrinkage of the thermal lesion, without enhancement.

blood flow can increase the thermal ablation zone.[46] Furthermore, TACE might control microscopic intrahepatic tumors unreachable for RFA or MWA.[47]

Despite a relative lack of history for the use of MWA, clinical implications might be similar to RFA indications and can potentially expand to larger tumors than RFA.[48] Adverse events and contraindications are also comparable to those of RFA.

3.3. *Percutaneous ethanol injection*

Percutaneous ethanol injection (PEI) was first described in 1983.[49] It is a local treatment based on the chemical properties of alcohol. Intratumoral injection of highly concentrated ethanol induces protein denaturation, microvascular thrombosis, cellular dehydration and coagulative necrosis of the tumor.[50] Multiple protocols have been reported. The most frequent one is based on direct and repeated percutaneous intratumoral injections via a thin needle under local anesthesia and intravenous sedation. Comparatively to physical ablation techniques, like RFA or MWA, PEI shows several limitations. Firstly, the requirement to repeat multiple PEI procedures may not be tolerated as well. Secondly, intra-tumoral ethanol diffusion is somewhat random or at least less predictable than thermal ablation, probably because the tumoral capsule and septa make it inhomogenous.[51,52] PEI efficiency is comparable to RFA in the treatment of small tumors.[53] However, high tumoral recurrence rates weigh against this method, conferring it worse disease-free and overall survival rates than RFA.[54]

Nevertheless, PEI also presents obvious advantages due to its low cost, its relative simplicity and safety.

Nowadays, the main remaining indications of PEI are HCC located near an anatomical structure with the risk of heat injury or a heat-sink effect near a vessel, metastatic HCC or even patients presenting contraindications to other ablative methods.[55]

4. Therapeutic indications

4.1. *Hepatocellular carcinoma*

Hepatocellular carcinoma represents the third leading cause of deaths from cancer worldwide.[56] In Europe and North America, the Barcelona-Clinical Liver Cancer (BCLC) system is the reference for therapeutic decision in HCC.[57] This system divides HCC into four groups, based on several criteria: number and size of the nodules, the Child-Pugh score, presence or absence of portal hypertension, World Health Organization performance status, symptomatology, vascular invasion and extra-hepatic spread.

According to BCLC system, indications of RFA include early stage HCC[58] with contraindication to orthotopic liver transplantation (OLT) or surgical resection, or as a bridging therapy to those strategies[59] while PEI should be considered with suitable candidates with small HCC, particularly for HCC at difficult-to-treat location for RFA. Although initial small randomized clinical trials (RCTs) have failed to show a survival benefit of TACE treatment for HCC patients, two RCTs published in 2002 proved the survival benefits of conventional TACE compared to the best conservative treatment.[60,61] Nowadays, TACE is recommended as first-line therapy for patients who are not candidates for surgery, transplantation or ablation, i.e., who do not have vascular invasion or extrahepatic spread, the latter can also be part of a bridging therapy to OLT.[62] Though TACE is not considered as a curative therapy, a recent study comparing hepatic radiofrequency thermal ablation, surgical resection and TACE proved that overall survival rate was similar for all groups for small tumors (<3 cm) without vascular invasion, when balancing liver status.[63]

TARE seems to be effective in HCC patients who progressed to TACE, for those in the advanced stage because of portal vein invasion or as a bridge to transplantation for HCC.[64,65] In the largest comparative study, all-type adverse events, response rate and time to progression were better in TARE than in conventional TACE but overall survival was not different.[66] Many clinical studies with TheraSphere® and SIR-Sphere® are ongoing to evaluate feasibility, efficacy and tolerance in primary management of HCC.

4.2. *Liver metastases*

4.2.1. *Colorectal cancer*

Despite the absence of controlled studies, RFA is considered as a curative treatment of liver metastases from colorectal cancer, provided that selection criteria (mainly size and location) are respected.[67,68] RFA can be part of a multimodality treatment strategy, especially for some patients presenting bilobar hepatic metastases that would have been ineligible for a curative treatment. Combination of RFA and surgical resection is a possible solution, sequentially[69] or at once.[70] Moreover, a laparoscopic approach for RFA is sometimes beneficial for hazardous ballistics and provides the advantage of a more accurate intraoperative staging than the percutaneous approach.[71,72]

Trans-arterial chemoembolization with drug-eluting beads loaded with irinotecan, combined with systemic chemotherapy[73] and TARE[74] might be potentially effective for treatment of unresectable colorectal cancer metastases.

4.2.2. *Neuroendocrine tumors*

Surgery resection is the treatment of choice for hepatic metastases but only 10 to 20% of patients are eligible to this treatment, due to the extension of the disease.[75] Eligible patients for these procedures are patients in a metastatic phase, with predominant liver disease, which is judjed not resectable. TACE and TARE are frequently used, especially in patients with refractory, unresectable, or recurrent disease. These treatments are effective both in palliating the hormonal symptoms and achieving objective tumor responses.[76,77] Indeed, in a recent study including 123 patients undergoing an average of 7 TACE cycles each, 62% partial response was seen with overall 3-, 5-, and 10-year survivals of 59, 36, and 20%, respectively, and overall mean survival of 5.47 years.[78] TARE also showed good results in a phase II trial.[79]

4.2.3. *Other liver malignancies*

TACE might be potentially effective for treatment of cholangiocarcinoma, hepatic metastases from gastric, breast and cutaneous origin.[80–83]

Several case series of thermal ablation used to treat metastases from a variety of different primary tumor entities have been reported, including gastric cancer, ovarian cancer, and metastases of unknown primary.[84] Despite the limited size of these series, there is a potential survival benefit from percutaneous ablation treatment in patients who are otherwise not eligible for surgery, especially those with breast cancer.[83]

5. Conclusion

Radiological methods, both endovascular and direct transcapsular approaches, play a determinant role in the modern treatment of liver cancers. Their pros rely on their relative selectivity, safety and their ability to have a synergistic role with surgical, oncological and radiotherapy methods.

Conflict of interest

None declared.

Financial disclosure

None declared.

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