Cardiovasc Intervent Radiol (2020) 43:951–962
https://doi.org/10.1007/s00270-020-02471-z

CIRSE STANDARDS OF PRACTICE

CIRSE Standards of Practice on Thermal Ablation of Liver Tumours

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Received: 24 September 2019 / Accepted: 27 March 2020 / Published online: 7 May 2020

Abstract This CIRSE Standards of Practice document reviews current literature and provides best practices for image guided thermal ablation of liver tumours, including radiofrequency, microwave and cryoablation techniques.

Keywords Liver tumour · Ablation · Radiofrequency · Microwave · Cryoablation

Introduction

Image-guided thermal ablation is currently widely offered as part of the modern armamentarium for treating patients with primary and secondary malignancies of the liver. Thermal ablation technology has evolved rapidly during the past several decades, with substantial technical and procedural advancements that have improved clinical outcomes and safety profiles. The increasing knowledge of technology and the experience gained prompted a broadening of the clinical use of ablative therapies. Nevertheless, in order to maintain safety profiles and optimise outcomes of ablation that are needed for recognition in a multidisciplinary clinical setting, it is of the utmost importance to be aware of the best available evidence in the field and to move towards standardisation of ablation in clinical practice.

A summary of key points can be found in Table 1.

Methodology

The need for an updated Standards of Practice document on liver tumour ablation was identified by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Standards of Practice Committee. A working group comprised of international experts was established to carry out the task of producing this document. An in-depth literature search and a critical review of peer-reviewed articles were performed with regard to the study methodology, results, and conclusions. Conflicting or weak evidence was presented to the working group members for review and comments.

Definitions

Ablative Margin

This is the region ablated beyond the borders of the tumour to achieve complete tumour destruction [1]. Ideally, it should measure 0.5–1.0 cm in its smallest width depending on tumour histotype [2, 3].

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Table 1 Summary of key points

Liver tumour ablation: key points
The indication for ablation of a liver tumour should come from a multidisciplinary tumour board evaluation
State-of-the-art pre-treatment imaging (according to tumour histology) is needed
Tumour size (< 3 cm) and lesion location are the most important technical factors affecting ablation success
Grade 2–6 complications (formerly major) are rare, in the range of 2–3%
Survival outcomes are significant, about 70% at 5 years in most favourable histologies (HCC, NETs metastases)

Complete Ablation

On contrast-enhanced imaging modalities, there is a non-enhancing area at the site of the treated tumour which includes the tumour and the ablative margin [1].

Complications

Complications can be stratified on a 6-grade scale on the basis of outcome by using the CIRSE standard table [4]. The CIRSE classification system for complications combines outcome, presence of complication, effect upon hospitalisation, and severity of a specific complication and sequelae in a patient's everyday life.

Cryoablation

This is a treatment for destroying tissue by the application of freezing temperatures (around -160 °C), alternated with thawing or slight heating. Cryoprobes are used to freeze (and actively thaw) tissues [1].

Hydro/Gas Dissection

This is the instillation of liquid (dextrose 5%, sterile water, saline) or gas (air, carbon dioxide) between the targeted area and the structure vulnerable to thermal damage [5].

Incomplete Ablation

This is the presence of residual unablated tumour, which is seen as peripheral irregular enhancement at first control imaging. It often grows in a scattered, nodular, or eccentric pattern [5].

Local Tumour Progression

This is the appearance at follow-up of foci of untreated disease in tumours that were previously considered to be completely ablated [1, 5].

Microwave (MW) Ablation

This is tumour destruction from electromagnetic energy sources using devices with frequencies from 300 MHz to 300 GHz. Currently available microwave ablation devices function at frequencies of 915 MHz or 2.45 GHz, designated for industrial, scientific, and medical (ISM) use. MW applicators are called antennas [1].

Perfusion-mediated tissue cooling (or heating)

This refers to both the effects of the larger heat sinking vessels (> 3 mm), as well as the substantial effects of capillary level microperfusion. It can negatively affect the extent of induced coagulative necrosis because it can potentially remove heat (or freezing) by convection before complete tumour ablation is achieved [1].

Radiofrequency (RF) Ablation

This is coagulation induction from all electromagnetic energy sources with frequencies < 30 MHz. For tumour ablation purposes, the frequency is usually in the range of 375–500 kHz. RF applicators are named electrodes [1, 5].

Technical Success

This is considered when treatment of the tumour was performed according to protocol and complete tumour coverage is assessed either during or immediately after the procedure [5].

Pre-treatment Imaging

Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma can be diagnosed non-invasively in patients with liver cirrhosis and specific imaging criteria, relying on the contrast-enhanced imaging for lesion characterisation. The typical vascular hallmarks of HCC are represented by hypervascularity in the arterial phase, with

Table 2 Summary of indications for thermal ablation of liver tumours

Indications
Hepatocellular carcinoma
Single nodule < 2 cm (even in surgical patients)
Single or up to 3 nodules ≤ 3 cm in non-surgical patients (alternative to surgical resection based on technical factors)
Colorectal liver metastases
Up to 5 metastases, ≤ 3 cm
'Un-fit' patient
'Fit' patients with initially resectable patient, poor lesion anatomical location or substantial comorbidities
'Fit' patients with initially non resectable patient, as an adjunct to systemic therapy
Intrahepatic cholangiocarcinoma
Single nodule ≤ 3 cm in non-surgical patients
Liver metastases from neuroendocrine tumours
Alternative to systemic therapy in oligonodular disease
Metastases from other primaries
Personalised approach, after multidisciplinary tumour board, tailored on features of the patient, of the disease and of liver sites

washout in the portal venous or delayed phase in a nodule of > 1 cm diameter using contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) [7]. Biopsy of the lesion is indicated when the imaging-based diagnosis remains inconclusive [6, 7].

Colorectal liver metastases

CT scans are routinely used for primary staging and disease surveillance in patients with colorectal cancer (CRC). Although practice varies between treatment centres, the evidence suggests that the best methods for detecting liver metastases from CRC are CT and MRI [8].

Other primary and secondary liver malignancies

Ablation may be considered as a treatment option in selected patients with other primary tumours (intrahepatic cholangiocarcinoma—iCCA) or secondary tumours from non-colorectal carcinomas (neuroendocrine, breast, thyroid cancer, melanoma and in oligometastatic disease controlled with systemic treatment). In these cases, careful pre-treatment imaging is needed to confirm liver only or oligometastatic disease [9–13].

Indications for Treatment and Contraindications

Indications

The indication for ablation of a liver tumour should come from a multidisciplinary tumour board discussion and should be clearly articulated in a concurrent manner by the interventional radiologist, oncologist, hepatologist and liver surgeon, in order to select the best approach for the individual patient following the principles of precision medicine [14].

Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma is the most common primary liver cancer, often occurring in patients with underlying virus-related, alcohol-related or dysmetabolic cirrhosis. The treatment choice in patients with HCC is therefore driven not only by tumour staging, as in the great majority of cancers, but also by careful evaluation of liver function and physical status. In patients with very early stage HCC (solitary small nodule less than 2 cm in diameter), image-guided tumour ablation is recommended as a first-line therapy even in surgical candidates. In patients with early-stage HCC, solitary HCC (any size), or up to 3 nodules less than 3 cm, the choice of ablation as an alternative to surgical resection is based on technical factors (location of the tumour), hepatic and extrahepatic patient conditions (Levels of Evidence 1) [15]. Presently, thermal ablation also has a significant role as a neo-adjuvant therapy before liver transplantation, as a 'bridge' to prevent patient dropout from the waiting list [16]. Considering current technical limitations in the production of large volumes of necrosis, a tumour up to 3 cm should be treated by ablation [5, 15] (Table 2).

Colorectal liver metastases

The general condition and performance status of a patient are strong prognostic and predictive factors for systemic treatments. Whether a patient is classified as 'fit' or 'unfit' is now used to determine whether or not they will be

assigned to a more intensive (a combination of 2 or 3 cytotoxic drugs with a biological) or less intensive treatment approach. The classical drivers of treatment choice are tumour, patient and treatment characteristics [17]. According to current European guidelines, 'unfit' patients are candidates for supportive care and palliative treatment [17]. In this clinical sub-setting, the role of ablation has yet to be defined, but it seems reasonable that 'unfit' patients with limited liver tumour burden are candidates for ablative modalities, in view of their tolerability and low invasiveness [14]. 'Fit' patients have then to be stratified into patients with initially resectable or initially unresectable metastatic disease at the first meeting of the multidisciplinary tumour board [14, 17]. Currently, liver disease is considered resectable as long as complete macroscopic resection is feasible while maintaining at least 30% future liver remnant or a remnant liver to body weight ratio of > 0.5 [19]. In the case of patients with poor anatomical localisation of their metastases for resection, ablative therapies may provide an alternative to resection, or can be used in combination with resection, in order to retain sufficient future liver remnant [19]. When an oligometastatic disease (usually defined as 2–3 sites of disease and up to 5 metastases) is present, the role of local treatment becomes relevant in combination with systemic therapy [20]. The goal in these patients is not necessarily to cure, but to achieve long-term disease control with a non-evaluable disease, potentially contributing to overall survival [17–21]. Finally, ablation may represent a salvage treatment for recurrences after hepatectomy [22]. Ablation of metastases larger than 3 cm presents a high risk of failure, regardless of the technology used [5, 14, 19] (Table 2).

Other primary and secondary liver malignancies

iCCA—Locoregional treatments should be reserved for patients with non-resectable iCCA; as there are no established first-line locoregional therapeutic options for these patients [9]. Ablation approaches may be considered for small, single lesions < 3 cm if surgery is not an option, but additional clinical trials are needed to establish its role in this population (Table 2) [9].

Liver metastases from NETs

In the absence of any large comparative trials of different locoregional or ablative therapies or systemic treatment, the choice of treatment is based on individual patient features (e.g. size, distribution and number of liver lesions, vascularisation, proliferative index) and local physicians' expertise [23]. According to the 2012 European Neuroendocrine Tumor Society Consensus Guidelines, the management of metastatic NET surgery with curative intent and/or locoregional or ablative therapies should be considered at initial diagnosis and during the course of the disease, as an alternative approach to systemic therapies (Table 2) [10]. It has been recommended that patients with NETs be premedicated with somatostatin analogues prior to ablation to avoid a carcinoid crisis, secondary to the release of vasoactive hormones during ablation [24].

Liver metastases from other primaries

Similarly to liver metastases from NETs, indication for ablative treatment is tailored by characteristics of the patient (age, performance status), the disease (genetic profile, proliferative index, response to chemotherapy, etc.) and liver sites (number and location). Evidence is available for ablative treatments of breast, melanoma and thyroid cancer liver metastases [11–13, 25–28] (Table 2).

Contraindications

Contraindications for thermal ablation are as follows [5]:

1. Tumour located < 1 cm from the main biliary duct—due to risk of delayed stenosis or perforation of the main biliary tract unless a specific manoeuvre, such as bile duct cooling, is performed
2. Significant ascites interposed along the applicator path
3. Exophytic location of the tumour when direct puncture of the tumour cannot be avoided—due to the risk of tumour seeding (especially for undifferentiated HCC)
4. Untreatable/unmanageable coagulopathy (Table 3).

Patient Preparation

Pre-procedural clinical and laboratory assessment

The interventional radiologist that will perform the ablation procedure needs to see the patient as an outpatient clinic prior to the date of the procedure. The purpose of the visit is to describe the treatment that will be performed, including imaging ablation modality, benefits and risks, any ancillary procedures that may be required, and to obtain informed consent from the patient following national laws and institutional forms. Alternative options, when available, should be discussed with the patient. In addition, during the visit the radiologist needs to assess the general condition of the patient, investigate comorbidities and discuss the anaesthesia requirements of the patient [14].

Pre-procedural laboratory test should include clotting function tests (platelet count, and international normalised

Table 3 Summary of contraindications for thermal ablation of liver tumours

Contraindications
1. Tumour located < 1 cm from the main biliary duct, due to risk of delayed stenosis of the main biliary tract
2. Significant ascites interposed along the applicator path
3. Exophytic location of the tumour when direct puncture of the tumour cannot be avoided—due to the risk of tumour seeding
4. Untreatable/unmanageable coagulopathy

ratio—see "Evaluation of bleeding risk and correction of coagulopathy" section), full blood count, and biochemistry tests evaluating liver and kidney function.

Evaluation of bleeding risk and correction of coagulopathy

Values of international normalised ratio inferior to 1.5 and platelet count superior to 50,000/μL are required in order to proceed [29]. When possible, antiplatelet/anticoagulation medications should be discontinued before the procedure. When a cessation is problematic, risks and benefits should be carefully evaluated [30], and patients should be informed of potential increased risk of bleeding. It has to be taken into consideration that, in comparison with a biopsy, the applicator track can be coagulated during thermal ablation. Recommendations about bleeding risk evaluation and management in liver thermal ablation according to the Society of Interventional Radiology (SIR), Canadian Association for Interventional Radiology and CIRSE are summarised in Table 4.

Peri-procedural manoeuvres and medications

Patients should be fasting for 4–6 h prior to the procedure. A peripheral venous access (18–20 Gauge) should be obtained. The risk of contamination is low, as the procedure is performed under sterile conditions. The routine use of prophylactic antibiotics is recommended. Although bacterial seeding is uncommon, the large amount of necrotic material created during ablation poses a risk of bacterial seeding during percutaneous access, and the use of a single agent targeted to skin flora (i.e. cefazolin, 1–2 g IV) may be reasonable [31, 32]. In high-risk patients, such as those with history of bilio-enteric anastomosis, cirrhosis, diabetes, more specific regimens are advised. In patients with bilio-enteric anastomosis, it is advised to proceed with a regimen that includes oral levofloxacin 500 mg/d + oral metronidazole 500 mg twice daily beginning 2 days before and continuing for 14 days after ablation + neomycin 1 g and erythromycin base 1 g orally at 1, 2, and 11 PM on the day before ablation. For other high-risk patients, 1.5 g ampicillin/sulbactam IV or vancomycin or clindamycin for Gram positive coverage and gentamicin for Gram negative coverage is advised [32, 33].

Table 4 Summary of recommendations about bleeding risk evaluation and management in liver thermal ablation according to the Society of Interventional Radiology (SIR), Canadian Society of Interventional Radiology and CIRSE (modified from [30])

Pre-procedural laboratory testing	
PT/INR	Routinely recommended
Platelet count/Haemoglobin	Routinely recommended
Fibrinogen	Recommended in patients with chronic liver disease
Management	
INR	Correct to ≤ 1.5–1.8;
	Correct to < 2.5 in patients with chronic liver disease
Platelets	Transfusion recommended for count < 50,000/μL
	Transfusion recommended for count < 30,000/μL in patients with chronic liver disease
Fibrinogen	Correct to > 100 mg/dL in patients with chronic liver disease
Clopidogrel	Withhold for 5 days before procedure
Aspirin	Withhold for 3–5 days
Fractionated heparin	Withhold for 24 h or up to two doses if therapeutic dose; withhold 1 dose if prophylactic
Warfarin	Withhold 5 days until target ≤ INR1.8; consider bridging for high thrombosis risk cases; if stat or emergent, use reversal agent

PT prothrombin time, *INR* international normalised ratio

Checklist

The CIRSE IR checklist should be completed before starting the procedure. The checklist for IR was produced to avoid human error and ensure that key steps in patient preparation, intraprocedural care, and postoperative care are not forgotten [34].

Anaesthesiology care and patient monitoring

Thermal ablation is usually performed with the patient under intravenous sedation or general anaesthesia, depending on operator or institutional preference. The American Society of Anesthesiologists (ASA) score can be used to assess the patient's physical status before thermal ablation. Patients with ASA $\leq$ III score can be treated [5, 35]. Local anaesthesia is additionally provided by injecting 5–10 mL of local anaesthetics (e.g. lidocaine) from the skin to the liver capsule along a specified insertion route. When general anaesthesia is used, high-frequency jet ventilation may help with tumour targeting.

Equipment Specifications

Radiofrequency ablation

One or multiple electrodes are inserted directly into the tumour to deliver RF energy current (see "Definitions" section). Electrodes can be monopolar or bipolar, and they can have different designs (multi-tined expandable, internally cooled, open perfused) [5, 36].

- Monopolar electrodes have a single active electrode applicator, with current dissipated at one or several return grounding pads.
- Bipolar electrodes consist of two electrode applicators or a single array containing both the active and return electrodes.
- Multi-tined expandable electrodes have multiple electrode tines that expand from a larger needle cannula.
- Internally cooled electrodes have an internal lumen that is perfused by saline without coming into direct contact with patient body tissue. Monopolar electrodes are usually internally cooled.
- Open perfused electrodes have a small aperture(s) that allows the fluid (usually saline) to come in contact with the tissue.

Microwave ablation

In the case of MW ablation, differences between devices are not related as much to the morphology of the applicators (which are, in all cases, straight needles without hooks), but rather to the following characteristics [1, 37]:

- MW frequency emission used is either 915 MHz or 2450 MHz.
- Antenna calibre varies between 11 and 18 G.
- Maximum available generator power varies between 60 and 195 W, and a certain amount of power is lost between the generator and the antenna tip along the linking coaxial line. Due to this power loss, the maximum power at the antenna differs from the power at the generator.
- The number of antennas that can be used simultaneously with a single generator is 1–4. The simultaneous use of several applicators determines a more uniform and larger ablation area.
- The methods of energy delivery (manual or automatic, continuous or pulsed).

Cryoablation

Cryoablation systems use the Joule–Thomson effect of expanding gases within a needle-like cryoprobe. As the cryogen (typically argon) moves from an internal feed line into an internal expansion chamber at the tip of the needle, it produces a heat sink near the antenna tip that cools the probe to temperatures of -160 °C or colder. Heat transfer from the tissue into the cryoprobe takes place through passive thermal diffusion. In liver tissue, the threshold for lethal cellular damage is -40 °C. As a result, the surface area of the cryoprobe limits cooling efficiency; smaller cryoprobe diameters are associated with lower cooling capacity and, consequently, smaller ablation zones. Therefore, several cryoprobes are required to treat most tumours in clinical practice, and ablation times are typically 25–30 min [38]. Cryoprobe size ranges from 17 to 8 G. In ultrasound (US), the ice ball is seen as a hyperechoic line representing the proximal edge of the ice ball with posterior acoustic shadow. The ice ball is identified as a low-attenuation ($\sim$ 0 HU) region on CT and signal-void region on MRI [38]. Cauterisation of the needle track by means of thermal energy is available in the latest versions of some vendors' cryoprobes.

Procedural Features and Variations of the Technique(s)

Imaging guidance

Image-guided ablation should ensure a precise ablation therapy leading to a complete coagulation of the tumour tissue with an ablative safety margin, and without injury of

critical structures during applicator positioning or energy delivery. Targeting of the index tumour can be performed using US, CT, or MR imaging [39–41]. The guidance system is chosen largely on the basis of operator preference and local availability of dedicated equipment, such as cone beam-CT or open MR systems. Recently, positron emission tomography (PET)/CT performed with dedicated protocols has been proposed as a useful tool to provide both guidance and endpoint evaluation, allowing an opportunity for repeat intervention if necessary [42]. Laparoscopic ablation may be the preferable strategy when the tumour is on the surface of the liver or close to extra-hepatic organs [43].

Adjunctive procedures

Although minimally invasive, thermal ablation carries a risk of thermal injury to sensitive structures in the vicinity of the ablation zone. Several different thermo-protective techniques have been developed in order to expand indications for thermal ablation while limiting the risk of complications [44].

- Injection of fluid or gas between lesions and vulnerable structures is an effective, inexpensive method of thermal protection. The type of hydrodissection fluid is carefully selected depending on ablation modality. Due to its intrinsic electrical conductivity, saline should not be used with RF, and instead 5% dextrose in water is preferred. Saline may be safely used in combination with MW and cryoablation, since these modalities do not risk conduction of electrical current. CO_2 is preferred to injection of room air due to a lower risk of symptomatic gas embolism [44].
- Endoluminal cooling/warming is to instil fluid (generally saline) through an existing anatomic hollow/tubular organ adjacent to the ablation zone, in order to prevent thermal injury and avoid secondary perforation and/or stricture. This can be applied in liver thermal ablation in the case of peribiliary lesions through the placement of a nasobiliary or biliary drainage [44].

Combination with intra-arterial approach

In patients with solitary HCC $>$ 3 cm and $<$ 5 cm, when clinically significant portal hypertension and abnormal bilirubin contraindicate surgical treatment, a combination of transarterial chemoembolisation (TACE) followed by RF has been used to minimise heat loss due to perfusion-mediated tissue cooling and to increase the therapeutic effect of RF [45]. Recently, the results of two meta-analyses, stratified according tumour size, showed that RF plus conventional-TACE significantly improved the overall survival rates at 1 and 3 years, compared with RF alone in patients with a single HCC $>$ 3 cm and $<$ 5 cm [46, 47]. Despite a plethora of literature on the topic, due to the inhomogeneity in enrolled patient population and treatment protocols, further research to determine optimal methods of combining chemotherapeutic regimens (agent, route of administration, time interval between TACE and ablation or vice versa) with ablation (RF or MW) is needed [48]. It has been suggested that a single-step 'combined' approach, with both procedures performed in the same session, makes it possible to obtain and amplify the synergistic effects of ablation and TACE [49].

Side effects and complications

Side effects

Post-ablation syndrome is characterised as a self-limited flu-like illness with low-grade fever, malaise, nausea, and/or vomiting [50], and it is thought to be mediated by an inflammatory response to the necrotic tissue that results from ablation [51]. Another frequently reported side effect of thermal ablation is pain at the treatment site or right shoulder [52]. It is usually not severe and resolves in a few days. Ablation size and proximity to the liver capsule have been related to frequency and intensity of post-ablation pain [52]. Symptomatic treatment is advised for side effects.

Complications

Each ablative technique can produce complications, which can be classified as puncture- and thermal-related complications. Overall grade 2–6 (formerly major) complication rate ranges from 2.2 to 3.1% [4, 14].

Puncture-related complications include intraperitoneal bleeding, pneumothorax, and haemothorax, the rates of which can be reduced by checking the coagulation status of the patients and choosing the most appropriate path to safely reach the nodule. Tumour seeding represents another puncture-related complication occurring in 0.5% of cases [14]. Ablation of the needle track is a recommended practice to be performed to reduce tumour seeding.

Thermal-related complications include bowel perforation, portal vein thrombosis, liver abscess, bile duct lesions, and cholecystitis. Bowel perforations can be avoided by applying adjunctive procedure (i.e. gas- or hydrodissection) to protect the organs at risk of damage by heating. To reduce the risk of biliary complications, it is recommended not to treat patients with tumours located less than 1 cm from the main biliary tract, unless biliary cooling is provided [5, 14]. A specific complication of cryoablation is cryo-shock. Although cryotherapy of liver tumours is generally considered a safe procedure, a syndrome of

coagulopathy and fatal multiorgan failure (acute renal failure and adult respiratory syndrome) has been observed in some patients and is called the cryo-shock phenomenon. The risk of occurrence is proportional to the amount of treated liver. Mediators similar to those in septic shock may be involved in this syndrome [53].

Post-procedural Imaging and Follow-up

Immediate post-procedural imaging, despite being affected by some early benign findings such as periablational enhancement (see below), is essential to demonstrate sufficient ablative margins that are strongly related to local control [2, 3]. The availability of software platforms to register pre- and post-ablation CT or MR scans allows for the assessment in 2 and 3 dimensions the presence and the extent of the ablative margins [54].

Contrast-enhanced CT and MRI are recognised as the standard modalities to assess treatment outcome. CT and MRI results obtained *4–6 weeks after treatment* show complete ablation as a non-enhancing area larger than the treated lesion with or without a peripheral enhancing rim [1]. The enhancing rim, that may be observed along the periphery of the ablation zone, appears to be a relatively concentric, symmetric, and uniform process in an area with smooth inner margins. This transient finding represents a benign physiologic response to thermal injury (reactive hyperaemia initially and subsequent fibrosis and giant cell reaction). Benign periablational enhancement must be differentiated from irregular peripheral enhancement due to residual tumour that occurs at the treatment margin. Compared with benign periablational enhancement, residual unablated tumour often grows in scattered, nodular, or eccentric patterns [1].

Later follow-up imaging studies should be aimed at detecting local tumour progression, development of new hepatic lesions, or emergence of extrahepatic disease. A recommended follow-up protocol includes CT or MRI studies at 3, 6, 9, and 12 months after treatment and at 6-month intervals thereafter, for at least 3 years [1].

Outcomes

Hepatocellular Carcinoma (HCC)

In patients with cirrhosis and *very early and early stage HCC,* the complete response rate of RF ablation is above 95%, with 5 years survival rates in 62–68% of cases [55, 56]. Few studies regarding comparison between RF and MW ablation in the treatment of early HCC are available. The only randomised controlled trial available is a phase II, regarding the comparison of RF and MW for the treatment of HCC. In this study, MW was not more effective than RF ablation in patients with HCC lesions of 4 cm or smaller, with no difference between the two groups of patients in the proportion of lesions with local tumour progression after 2 years of follow-up (respectively 6% for MW and 12% for RF) [57]. At the moment, therefore, there is not enough evidence to support MW over RF in HCC < 3 cm. Ease of use, reproducibility and size of volumes of ablation, together with short procedural times make MW ablation widely used and often the preferred thermal ablation modality.

There have been a limited number of studies comparing outcomes including overall survival and liver cancer-specific survival in patients treated with cryoablation or RF ablation. A recent systematic review attempted to address this gap by analysing 7 geographically diverse prospective studies (3 from Europe, 3 from USA, and 1 from China). The authors found that there was no significant difference in overall survival between RF ablation and cryoablation at 6 months (OR = 1.00, 95% CI: 0.68–1.49) [58].

CRC liver metastases

In patients with *CRC liver metastases* who are unfit for resection due to poor anatomical localisation of the lesions or substantial comorbidities, ablation has been proven a viable alternative treatment. In cohort studies of non-surgical patients treated with thermal ablation, the 5-year survival rates were in the range of 25–55% [59].

Results comparable to surgery have been reached with RF ablation in solitary CRC metastases less than 3 cm in size, with tumour size representing one of the main limitations of ablative therapies [59]. In patients with oligometastatic disease, the phase II CLOCC trial compared chemotherapy alone versus chemotherapy with percutaneous or intraoperative RF ablation upfront in patients with up to 10 metastases. This trial reported an improvement in both progression-free survival and overall survival. At the 8-year follow-up, progression-free survival was only 2% in the chemotherapy only arm, but 22.3% in the combined group with chemotherapy plus RF ablation. Overall survival was of 8.9% versus 35.9%, respectively [21].

Several cohort studies have been published regarding the role of MW ablation in the treatment of CRC liver metastases. They reported a 3-,4- and 5-year overall survival for MW ablation between 35–79%, 35–58% and 17–18% [59].

Other primary and secondary tumours

iCCA

A recent meta-analysis evaluated 7 RF ablation studies including 84 iCCAs and reported pooled 1-year, 3-year,

Table 5 Summary of outcomes of ablation of liver tumours

Histology	Grade 2–6 complications	Local tumour progression	Survival	
			3 years	5 years
HCC				
Very early/early stage	2–3%	1–14%	80–89%	62–68%
Colorectal liver metastases				
Unresectable patients	0–5%	3–41%*	37–77%	25–55%
Other histotypes				
iCCC	0–1%	22%	44–47%	24–32%
Neuroendocrine liver metastases	NA	6%	88–100%	57–84%

*Nodules < 3 cm

NA Not available

and 5-year overall survival rates of 82%, 47% and 24%, respectively [60]. MW ablation was not associated with lower rates of local tumour progression when compared to RF in a study that reported a median overall survival of 23.6 months in patients treated for iCCAs with thermal ablation [61].

Liver metastases from NETs

Patients submitted to RF ablation for liver metastases from NETs demonstrated a median survival of 10.3–11 years, with 5-year overall survival rate of 57–84% [62].

Breast, melanoma, thyroid liver metastases

The results of a surgical series on *breast* metastasis resection show that despite metastatic breast cancer being a systemic disease, local therapies have the potential to improve survival. In the case series, the median survival of patients with liver metastases treated with RF ablation was in the range of 30–60 months [63–66].

RF ablation has also been utilised in the treatment of metastatic uveal *melanoma*. There have been studies evaluating surgical resection as compared with RF (with or without surgery) for liver metastases from uveal melanoma. These studies showed no significant difference in the median overall survival for either group [25, 27]. Large series addressing ablation treatments in liver metastases from *thyroid cancer* are substantially lacking. Similar to the hepatic metastases from CRC, liver metastases from thyroid cancer can be reasonably treated with ablation, providing that the tumour size is < 3 cm and coupled with large margins of ablation [65].

A summary of outcomes for the most common indications of ablation of liver tumours is reported in Table 5.

Conclusion

The indication for ablation, or even resection, of a liver tumour should come from a multidisciplinary tumour board evaluation that will take into consideration the clinical specificities beyond liver tumour burden, in order to select the best approach for the individual patient following the principles of precision medicine. These specificities include comorbidities, compliance to treatment, general performance status, and history of the disease. Some specific features make ablation a valuable and irreplaceable tool in the management of liver tumours. Ablation is minimally invasive and can be combined with other treatment options, including systemic therapies, intra-arterial approaches and surgical treatments. Moreover, in the presence of local or distant relapse of the disease it can be repeated in most cases.

Established indications for percutaneous thermal ablation are very early and early stage HCC and oligometastatic CRC. However, selected patients with oligometastatic disease of non-colorectal origin may benefit from an early ablation therapy. Tumour size and tumour location are critical factors that affect treatment choice, in particular regarding technique (RF ablation vs MW ablation versus cryoablation) and guidance/approach (percutaneous US/CT guided, open, video laparoscopic).

Funding This study was not supported by any funding.

Compliance with ethical standards

Conflict of interest T. de Baére has received speaker honoraria from Medtronic and BTG and is a Grant recipient and has received speaker honoraria from Terumo. P. Pereira is a Grant recipient and has received speaker honoraria from Medtronic and Terumo Corporation and has received financial support from Angiodynamics. All other authors declare that they have no conflict of interest.

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