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The ten commandments of liver ablation: expert discussion and report from Mediterranean Interventional Oncology (MIOLive) congress 2017

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Abstract. – Percutaneous liver ablation has become a cornerstone of the recently developed subspecialty of radiology – that is, interventional oncology. Thermal ablation technology has evolved rapidly during the past decades, with substantial technical and procedural improvements that can help obtain better clinical outcomes and safety profiles. Due to the widespread use of percutaneous ablation, a comprehensive review of the methodologic and technical considerations seems to be mandatory.

This article summarizes the expert discussion and report from Mediterranean Interventional Oncology Live Congress (MIOLive 2017) that was held in Rome, Italy, integrating evidence-reported literature and experience-based perceptions, to assist not only residents and fellows who are training in interventional radiology but also practicing colleagues who are approaching to this locoregional treatment.

Key Words:
Liver, Ablation, HCC, Metastases, Locoregional treatment.

Introduction

The notion of the percutaneous locoregional destruction of a cancer, with minimal morbidity and mortality, has become accepted as part of the modern armamentarium for treating patients with cancer. Radiofrequency ablation (RFA) has become a cornerstone of the developed subspecialty of radiology – that is, interventional oncology. The beginnings of what we now call RFA stretch back over 20 years[1]. Thermal ablation technology has evolved rapidly during the past decades, with substantial technical and procedural improvements that can help obtain better clinical outcomes and safety profiles. The future of ablation should be based on the attempt to expand clinical indications as appropriate, creating the potential for larger areas of ablation, to obtain a more precise control of the ablation area, ensuring the safety of the procedure, and achieving even greater long-term success in the tumours we ablate[2].

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This report summarizes the expert discussion and report from the Mediterranean Interventional Oncology Live Congress (MIOLive 2017) that was held in Rome, Italy in January 2017. The aim of this work is to integrate evidence-reported literature and experience-based perceptions, while attempting to make the information easy to access by using a point format that will assist not only residents and fellows who are training in interventional radiology, but also practicing colleagues who are attempting to gain further expertise with this percutaneous treatment. Accordingly, similar to prior articles on intra-arterial interventional oncologic therapies - chemoembolization and radioembolization, we have organized these principles into a "Ten Commandments" framework[3,4].

Discuss the Case at a Multidisciplinary Tumour Board (MDTB)

The indication for ablation of a liver tumour should come from a MDTB discussion and should be clearly articulated in a concurrent manner by the interventional radiologist, oncologist, hepatologist, and liver surgeon. Multidisciplinary evaluation will take into consideration the clinical specificities beyond liver tumour burden, such as comorbidities, compliance to treatment, general performance status, and natural history of the disease, in order to select the best approach for every patient, following the principles of the precision and personalized medicine.

Hepatocellular carcinoma (HCC), the most common primary liver cancer, in the majority of cases occurs in patients with underlying virus- or alcohol-related cirrhosis. The treatment choice in patients with HCC is therefore driven not only by the tumour staging, as in the great majority of cancers, but also by careful evaluation of liver function and physical status. Image-guided tumour ablation is recommended in patients with very early and early-stage HCC when surgical options, including resection and liver transplantation, are contraindicated. Very early-stage HCC includes patients with a solitary small nodule less than 2 cm in diameter, whereas early-stage HCC includes patients with solitary HCC or up to 3 nodules less than 3 cm in size[5-7].

In the presence of *colorectal cancer liver metastases*, the decision whether a patient has initially resectable or initially unresectable metastatic disease should be made at the first MDTB meeting[8]. The concept of resectability has evolved over time: currently, a liver lesion is considered resectable as long as complete macroscopic resection is feasible, while maintaining at least a 30% future liver remnant, or a remnant liver-to-body weight ratio > 0.5[9-11]. In case of patients with anatomically unfavourable localization of the metastatic lesions, deemed unsuitable for surgical resection, ablative therapies may provide a valid alternative in order to preserve a sufficient future liver remnant. When an oligometastatic disease (localization of the disease to 2/3 sites, with 5 or sometimes more lesions) is present, the role of local treatment becomes relevant in combination with systemic therapy[12]. The goal, in these patients, is not necessarily to cure, but to achieve long-term disease control, potentially contributing to overall survival[8,13]. Finally, ablation may represent a salvage treatment for recurrent disease after hepatectomy[14].

Be Up-To-Date With Available Literature Data

Knowledge of the advantages, limits, and results of ablation procedures according to the best available evidence in the literature is of the utmost importance when proposing and supporting ablation as a therapeutic tool during MDTB meetings. Moreover, especially at the beginning of one's ablative practice, this knowledge will prevent treating the wrong patients and, therefore, facilitate achieving the best results. RFA is currently the ablation modality supported by the largest number of studies, including randomized controlled trials and meta-analyses (2). Microwave ablation (MWA) is gaining growing acceptance in the medical community, and the evidence regarding its greater benefit in comparison to RFA is increasing. While in the European guidelines for the management of HCC[6] only RFA is recommended, in the "toolbox" of liver-directed therapies for the treatment of colorectal cancer liver metastases, both RFA and MWA are included[8]. The decision between different local ablative techniques should be taken by a MDTB based on local experience and expertise, tumour characteristics, and patient preference[8].

In patients with *very early-stage HCC* the complete response rates of RFA approaches 97%, with 5-years survival rates of 68%[15]. Although there has been no robust trial to compare the efficacy of surgery versus RFA, case-control and modelling studies have shown ablation to be non-inferior and more cost-effective for patients with very early-stage HCC[16-18]. It has also been pointed out how individual characteristics, intrinsic to each patient (e.g., whether the tumour is central or peripheral,

close or distant from gallbladder and main bile ducts, occurring in a patient with important comorbidities, who is lean or overweight, in presence or absence of portal hypertension, with platelet count above or below 150,000/μL) influence the result of each treatment, contributing to better- or worse-than-average outcomes[16,17]. Roayaie et al[19] report a 15% mortality risk reduction in ablated patients compared to resected ones, thus endorsing the recommendation to give ablation priority to patients with small tumours that can be effectively and safely ablated[7].

In patients with *early-stage HCC*, resection and transplantation produce the best outcomes, with 60% to 80% of patients surviving for 5 years[2]. Patients who are not suitable for surgery, due to clinically significant portal hypertension or comorbidities, should be considered for ablation treatment. The relative roles of resection and ablation as first-line treatments have been debated, even among HCC patients who would be fit for surgery: three randomized trials have provided conflicting results[20-22]. In particular, limitations in study design reduce the clinical impact of the results. Indeed, the comparison between ablation and resection in nodules more than 3 cm in size is not conceptually correct, as it is well known that in those tumours RFA success rates drop dramatically for technical reasons, whereas resection may offer a better outcome[23]. The failure rate of ablation increases also in case of multinodular HCC and less compensated liver cirrhosis[2]. When RFA was applied in patients with single HCC smaller than 3 cm and Child-Pugh class A cirrhosis, as in a multicenter retrospective comparison of resection and RFA conducted in 15 Italian centres, overall survival rates were similar (74.4% in the resection group and 66.2% in the RFA group; $p = 0.353$)[24]. The results of these studies seem to confirm that when ablation is performed in the appropriate patients, with compensated liver cirrhosis and small solitary HCC, this approach can be offered, as in the case of very early HCC, as a first line treatment option[7].

In patients with *colorectal cancer liver metastases*, unfit for resection due to a poor anatomical localization of the lesions or substantial comorbidities, ablation has been proven as a viable alternative treatment. In cohort studies with long-term follow-up, the 3- and 5-years survival rates were between 38-69% and 22-48%, respectively[25,26]. Results comparable to surgery have been achieved with RFA in solitary colorectal metastases less than 3 cm in size, with tumour size representing one of the main limitations of ablative therapies[27,28]. In patients with oligometastatic disease, the phase II CLOCC trial (chemotherapy plus or minus RFA) suggested an improvement in both progression-free survival and overall survival. At 8-year follow-up, progression-free survival was only 2% in the chemotherapy-only arm, but 22.3% in the chemotherapy plus RFA. Overall survival was 8.9% versus 35.9%, respectively[13]. When applied as a salvage treatment for recurrences after hepatectomy, 3-year survival rates of nearly 40% may be achieved[14].

Do Not Start Performing Liver Ablation With a Difficult Case

When starting an ablation program or testing a new ablative technique, it is advised to choose relatively straightforward, easy cases. It is likely that if the first cases have a smooth course and good results, it will be much easier to propose ablation or new techniques in subsequent MDTBs. On the contrary, if severe complications are encountered at the beginning of one's practice, it likely could become more difficult to continue or increase the ablation practice. A successful clinical outcome is the best advertisement for continued patient recruitment.

Remember You Are Part of a Team

When performing ablation, tight cooperation with the anaesthesiologist, the nurse, and radiographer is strongly recommended, and is indeed the basis for a successful ablation procedure. The anaesthesiologist should know exactly what is required to facilitate the optimal needle placement and to perform the ablation (e.g., if you need the patient to cooperate during the procedure, or to sleep for its entire duration). On the other hand, the anaesthesiologist will provide the best sedation protocol according to the individual features and anaesthesiological risk of the patient[29]. The technician and the nurse should be trained by the interventional radiologist to be ready to provide assistance in all the phases of the procedure.

Liver Tumours Can Be Ablated With Different Techniques

Among ablative modalities, RFA is considered the first-line ablation technique, its advantages and limitations being well known and understood, in large part owing to a number of experimental animal studies and clinical trials[30,31]. MWA is becoming a competitor for RFA. To date, two randomized trials showed equivalent therapeutic effects

and complication rates between MWA and RFA in the treatment of HCC and colorectal cancer liver metastases respectively[32,33]. However, these studies were performed during the initial development of MWA. With further evolution of the technique, comparisons of MWA and RFA have produced inconclusive results in a number of observational studies[34-37]. This lack of agreement may be related to changes in generators/antennas used in the various studies. Despite the theoretical advantages from these improvements in MWA, it remains unclear whether these are associated with actual clinical benefits in terms of outcome. Three recent meta-analyses including available literature concluded that both RFA and MWA are equally effective and safe, but MWA may be more effective, compared to RFA, in preventing local tumour progression when treating larger tumours[37-39]. Given these similar profiles of the two ablative modalities, it is difficult to foresee that a randomized controlled trial will be soon designed and conducted with the aim of comparing differences in overall survival. Instead, some interesting potentially beneficial features of MWA will be analysed in comparison with RFA, including the shorter duration of the procedure and the easy placement of one straight MWA antenna to obtain ablation volumes that would require more than one RFA cooled electrode or expandable electrodes.

A non-chemical non-thermal image-guided ablation technique that is currently available is *irreversible electroporation* (IRE)[40]. IRE induces irreversible disruption of cell membrane integrity by changing the transmembrane potential, resulting in cell death without the need for additional pharmacological injury[40]. Because IRE is a non-thermal technique, issues associated with perfusion-mediated tissue cooling or heating (representing a significant challenge with thermal technique) are less relevant. However, so far, the published data of the technique are mostly represented by case-series including tumours in difficult perivascular or peribiliary locations[41,42].

Consider Different Image Guidance Modalities and Approaches

Image-guided ablation should ensure a precise treatment 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 ultrasound (US), computed tomography (CT), or magnetic resonance (MR) imaging[43]. 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.

The *US* is a widely used tool for imaging-guided procedures in the abdomen, especially in the liver. The US is fast, easily available, allows Real-time imaging, and is characterized by high natural contrast among parenchyma, tumour, and vessels. Because of its high spatial resolution, good contrast, wide field of view, excellent reproducibility, and applicability to bony and air-filled structures, *CT* plays an important role especially in interventions which cannot be adequately guided by US on account of the tumour location, or because gas or bones obstruct the imaging window or needle tract[44]. For example, tumours that are seated high in the liver dome are sometimes inaccessible to successful targeting under US, whereas CT guidance allows access via the transthoracic route, which is impossible with US guidance due to air in the lung that obstructs the imaging window. When tumour visualization and accessibility for targeting are equivalent under both US and CT guidance, the technique of choice should be based upon operator preference or according to the availability of the equipment. Interventional MR systems with an open architecture magnet configuration offer the possibility to use the capabilities of MR imaging during the entire ablation procedure. The open architecture offers adequate patient access and surveillance[45]. MR fluoroscopy using fast gradient echo sequences offers a near Real-time feedback while the RFA applicator is advanced into the target tissue, and is supportive in maintaining the supposed trajectory[45]. Recently, positron emission tomography (PET)/CT has been proposed as a useful tool to provide both guidance and endpoint evaluation, granting an opportunity for repeated interventions, if necessary[46].

In selected cases, a *laparoscopic approach* for ablation may represent the best therapeutic choice[47]. Laparoscopic resection or ablation may be the preferable strategy when the tumour is on the surface of the liver or close to extra-hepatic organs. Increasing evidence has clearly demonstrated that laparoscopic ablation can be performed with high efficacy and safety profiles among patients with absolute or relative contraindications to the percutaneous approach[48]. An alternative approach can be the performing of gas- or hydro-dissection to obtain safe ablation conditions, preserving adjacent organs from thermal damage[43].

Bear in Mind Possible Complications

Knowledge of possible complications will help to avoid them. Each ablative technique can produce complications, which can be classified as puncture- and thermal-related complications.

Puncture-related complications include intraperitoneal bleeding, pneumothorax, and haemothorax, whose rates can be reduced by checking the coagulation status of the patients prior to the procedure, and choosing the most appropriate path to safely reach the nodule. Tumour seeding represents another puncture-related complication, occurring in 0.5% of cases[49-50]. Ablation of the needle track represents a recommended practice to reduce tumour seeding, although admittedly not proven in dedicated trials.

Thermal-related complications include bowel perforation, portal vein thrombosis, liver abscess, bile duct stenosis, and cholecystitis. Bowel perforation can be avoided by applying adjunctive procedures (i.e., gas- or hydro-dissection) to protect the organs at risk of suffering heat-damage. To reduce the risk of liver abscesses and biliary complications, it is recommended not to treat patients with biliary-enteric anastomosis and tumours located less than 1 cm from the main biliary tract[23].

Check Your Overall Results Frequently

Quality improvement (QI) in Interventional Radiology is currently a very hot topic. The Cardiovascular Interventional Radiological Society of Europe (CIRSE) has a specific committee (Standard of Practice Committee) dedicated to develop QI guidelines with the final aim of improving patient care. However, it is strongly recommended to promote QI in interventional radiology in every Department performing ablation, and also on an individual physician basis.

Specific methodologies to design and conduct a practice QI are available and translatable to Interventional Radiology[51]. One of these methodologies is the DMAIC, that stands for "define, measure, analyse, improve control". When defining possible projects, it is advised to select the ones that are meaningful for you and your patients. The projects should have measurable data to be analysed. These data may then be compared with national standards or metrics, as set by Interventional Radiology societies (CIRSE and the Society for Interventional Radiology [SIR]). The SIR has suggested guidelines for establishing a QI program, and these guidelines recommend using threshold values for certain metrics, such that if the value of a metric is beyond the acceptable threshold, not only is the value recorded but a cascade of further investigation is triggered[52]. A systematic analysis of the baseline data is crucial in determining patterns of weakness and areas for improvement. A solution to the problem addressed in the first step can be developed and implemented. The closer the solution is to the root cause of the problem, the more likely it will have a meaningful effect. Finally, consolidation and standardization of changes and new processes into the permanent workflow is needed. No project is too small if it results in better or safer care, more timely service, or decreased costs[51].

Use Combined Therapies When Ablation May Not Be Enough

In patients with solitary HCC >3 and <5 cm, when clinically significant portal hypertension and abnormal bilirubin contraindicate surgical treatment, a combination of transarterial chemoembolization (TACE) followed by RFA has been used to minimise the heat loss due to perfusion-mediated tissue cooling, and increase the therapeutic effect of RFA[53-55]. The results of two meta-analyses, stratified according to tumour size, showed that RFA plus TACE significantly improved the overall survival rates at 1 and 3 years compared to RFA alone in patients with a single HCC >3 cm and <5 cm[56,57]. TACE with drug-eluting beads has also been performed after a RFA procedure to increase tumour necrosis by exposing the peripheral part of the tumour to a higher drug concentration, where only sub-lethal temperatures may be achieved in a standard RFA treatment[58]. 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 (RFA or MWA) is needed. 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[59]. Moreover, several reports seem to suggest that with the use of present MWA devices, percutaneous ablation of HCCs up to 5 cm can be achieved with high efficacy[60,61].

Perform Accurate Imaging Follow-Up After Ablation

Contrast-enhanced CT or MRI are recognized as the standard modalities to assess the treatment

outcome. CT and MRI performed 4-6 weeks after the treatment show successful ablation as a non-enhancing area larger than the treated lesion, with or without a peripheral enhancing rim[62]. 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 (initial reactive hyperaemia and subsequent fibrosis with giant cell reaction). Benign peri-ablation enhancement must be differentiated from irregular, peripheral enhancement due to residual tumour, occurring at the treatment margin. Compared with benign peri-ablation enhancement, residual unablated tumour often grows in scattered, nodular, or eccentric patterns[62-64]. Contrast-enhanced US can be performed after the end of the procedure and may allow initial evaluation of treatment effects, suggesting the need of immediate additional ablation in case of residual viable tumour[43].

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 the next 3 years[62].

Conclusions

Locoregional ablative therapies are minimally invasive procedures with an established role for the management of primary and secondary hepatic tumours.

Factors that contribute to success include: appropriate patient selection, enrolment in a Multidisciplinary Tumour Board (MDTB) management program, a thorough knowledge of all energy-based ablation techniques – including technologies that destroy a tumour either via a thermal (hot or cold) or non-thermal mechanism – as well as of imaging-guiding modalities and assistive techniques for percutaneous treatment. Furthermore, the crucial role of multimodality treatment of patients with liver malignancies by combining ablative and intra-arterial procedures, and the role of follow-up in order to obtain an early detection of local recurrences or new lesions needing prompt treatment must be highlighted.

In conclusion, the mastering of ablative techniques requires familiarization and practice of all these aspects to provide the most optimal, effective, and safe treatment.

Conflict of interest

The authors declare no conflicts of interest.

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