

Asian Conference on Tumor Ablation Guidelines for Hepatocellular Carcinoma

Shuichiro Shiina^a Ryosuke Tateishi^b Joon Il Choi^c So Yeon Kim^d
Zhiqiang Meng^e Lujun Shen^f Sheng-Nan Lu^g Jen-I. Hwang^h
Maki Tobari^a Hitoshi Maruyama^a Terguunbileg Batsaikhan^{a,i} Qing Deng^{a,j}
Lariza Marie Canseco^{a,k} Yoshinari Asaoka^l Shi-Ming Lin^m Kai-Wen Huangⁿ
Hyunchul Rhim^o Ping Liang^p Uei Pua^q Masatoshi Tanaka^r Peihong Wu^s

^aDepartment of Gastroenterology, Juntendo University, Bunkyo, Japan; ^bDepartment of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Bunkyo, Japan; ^cDepartment of Radiology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea; ^dDepartment of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; ^eDepartment of Integrative Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; ^fDepartment of Medical Imaging and Interventional Radiology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Sun Yat-sen University, Guangzhou, China; ^gDepartment of Gastroenterology and Hepatology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; ^hDepartment of Radiology, Taichung Veterans General Hospital, Taichung, Taiwan; ⁱDepartment of Interventional Radiology, National Cancer Center of Mongolia, Ulaanbaatar, Mongolia; ^jDepartment of Ultrasound Imaging, Renmin Hospital of Wuhan University, Wuhan, China; ^kSection of Gastroenterology, Department of Internal Medicine, De Los Santos Medical Center, Quezon City, Philippines; ^lDepartment of Medicine, Teikyo University School of Medicine, Itabashi, Japan; ^mDepartment of Gastroenterology and Hepatology, Taipei and Linkou Chang Gung Memorial Hospital, Taoyuan City, Taiwan; ⁿDepartment of Surgery, National Taiwan University Hospital, Taipei, Taiwan; ^oDepartment of Radiology, Samsung Medical Center, Seoul, South Korea; ^pDepartment of Ultrasound, Chinese PLA General Hospital, Beijing, China; ^qDepartment of Diagnostic Radiology, Tan Tock Seng Hospital, Singapore, Singapore; ^rHepatology and Clinical Research Center, Yokokura Hospital, Fukuoka, Japan; ^sDepartment of Medical Imaging and Interventional Radiology, Sun Yat-sen University Cancer Center, Guangzhou, China

Keywords

Hepatocellular carcinoma · Ablation · Guidelines

Abstract

Globally, the incidence and associated mortality of primary liver cancer have been steadily increasing. Currently, 80% of cases are found in Asia. Curative resection is applicable in

only 20% of patients; therefore, various nonsurgical treatment modalities have been developed. Image-guided percutaneous liver tumor ablation is regarded as the best option for treating early-stage hepatocellular carcinoma (HCC). However, skills and knowledge in ablation can vary among operators. Furthermore, Asia has the highest number of ablation procedures for HCC and the largest number of doctors performing ablation worldwide. Thus, the Asian

Conference on Tumor Ablation has developed guidelines for HCC. These guidelines will discuss indications, pre-ablative diagnosis and planning, techniques, peri-ablative management, evaluation of therapeutic effectiveness, complications, post-ablative follow-up, prevention of recurrence, and treatment of recurrence for HCC.

© 2025 The Author(s).

Published by S. Karger AG, Basel

Introduction

Primary liver cancer is the third leading cause of cancer-related death worldwide and one of the few cancers still increasing in mortality rate because of growing incidence and poor prognosis. A total of 865,269 were diagnosed worldwide in 2022 with a mortality of 757,948 [1]. The most common type of primary liver cancer is hepatocellular carcinoma (HCC). Currently, around 75% of deaths from HCC are found in the Asia-Pacific region [2, 3].

Only 20% of HCC patients are candidates for surgical resection [4]. Furthermore, recurrence is frequent even after apparently curative resection [5]. Liver transplantation, which is the best therapeutic option in some patients as it can be a treatment for both HCC and cirrhosis, plays a limited role due to organ donor shortage. Thus, various nonsurgical therapies have been developed [6, 7].

Among nonsurgical therapies, image-guided percutaneous ablation is considered the best for treating early-stage HCC. The proportion of early stage cancer among all HCC patients has been increasing because of surveillance on high-risk patients for developing HCC. Ablation includes ethanol injection [8–10], microwave ablation (MWA) [11], radiofrequency ablation (RFA) [12, 13], etc. It can be potentially curative, is minimally invasive, and is easily repeatable in cases of recurrence. As ablation becomes more widely used and various procedures are performed, standardization has been sought for optimal patient care. Additionally, skills and knowledge in ablation are different from country to country and from institution to institution.

The Guideline Committee of Asian Conference on Tumor Ablation (ACTA) has developed these guidelines (hereinafter referred to as the Guidelines) comprising 47 recommendations, with the aim of ensuring the appropriate clinical introduction of image-guided tumor ablation for HCC (Table 1). To achieve optimal outcomes in ablation, it is essential to acquire expertise in the following: indications, pre-ablative diagnosis and planning, techniques, peri-ablative management, evaluation of therapeutic effectiveness, complications, post-ablative follow-up, prevention, and treatment of recurrence.

The development of these guidelines is crucial as Asia performs the highest number of ablation procedures for HCC and has the largest number of doctors specializing in ablation in the world.

Methods

Members of the ACTA Guideline Committee discussed each guideline, which was developed after a comprehensive review of various studies, including randomized controlled trials, meta-analyses, case-control studies, expert opinions, and case series. Each guideline was ultimately established through a consensus agreement, supported by both literature reviews and our collective experiences. The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Table 2) [14, 15].

Indication for Ablation

Basic Principles in Determining Indication of Ablation

Recommendations

1. The indication must be determined from two aspects: effectiveness and safety (A1).
2. Satisfactory long-term prognosis is required to justify expanding the indications for ablation (A1).
3. Ablatability should be determined not only by tumor-related and patient-related factors but also resource-related factors (B1).
4. The intent of the ablation – whether it is performed as a curative measure or to reduce tumor burden – should be determined in advance (B1).
5. When ablation is performed in oncologically resectable cases, it needs to be curative and aimed at eradicating the entire tumor. Ablation should be repeated until no viable cancer tissue remains (B1).
6. In some cases, ablation can be used in combination or sequentially with other treatment modalities, such as vascular intervention and pharmacotherapy (B2).

Effectiveness and Safety

When determining the indication for ablation, it is essential to evaluate both effectiveness and safety. In cases where the risks outweigh the benefits – such as when a patient's general condition is extremely poor – it is recommended to forgo the treatment. Before proceeding, a thorough evaluation of the patient's general condition and comorbidities is necessary, and informed consent must be obtained.

Generally, ablation has been indicated for cases with three or fewer tumors, each 3 cm or less in diameter [16]. Recent innovations and advanced instruments may allow

Table 1. List of recommendations of ACTA guidelines for HCC

Topic		Recommendations
Indication	Basic principles	1. The indication must be determined from two aspects: effectiveness and safety (A1) 2. Satisfactory long-term prognosis is required to justify expanding the indications for ablation (A1) 3. Ablatability should be determined not only by tumor-related and patient-related factors but also resource-related factors (B1) 4. The intent of the ablation – whether it is performed as a curative measure or to reduce tumor burden – should be determined in advance (B1) 5. When ablation is performed in oncologically resectable cases, it needs to be curative and aimed at eradicating the entire tumor. Ablation should be repeated until no viable cancer tissue remains (B1) 6. In some cases, ablation can be used in combination or sequentially with other treatment modalities, such as vascular intervention and pharmacotherapy (B2)
	Tumor-related factors	1. When ablation is indicated, it is essential to take into account not only tumor size and number but also tumor location and conspicuity as tumor-related factors (A1) 2. Under favorable conditions, ablation may be applied beyond the conventional indication of three or fewer tumors, each 3 cm or less in diameter, in carefully selected cases (A2) 3. Risks and difficulties related to tumor location or conspicuity may be mitigated by applying techniques, such as artificial ascites, artificial pleural effusion, multimodality fusion imaging, and CEUS (B2)
	Patient-related factors	1. Not only liver function but also ECOG performance status, peri-procedure risk, and past history of upper abdominal surgeries should be evaluated as patient-related factors for indication of ablation (B1)
	Resource-related factors	1. Institutional volume, the operator's skills and experience, paramedical staff training, ablation equipment, equipment to assist ablation, and others should be evaluated as resource-related factors when determining the indications for ablation (B1) 2. Improving resource-related factors is essential for achieving better outcomes (B1)
Pre-ablation	Diagnosis	1. HCC can be diagnosed based on imaging criteria in high-risk groups for developing the disease (A1) 2. The interval between pre-treatment imaging and the actual procedure ideally should not exceed 1 month (A1) 3. Liver tumor biopsy is unnecessary in high-risk groups for developing HCC when imaging techniques reveal the hallmark features of HCC (B1) 4. Measurement of tumor markers is essential as changes in tumor marker levels are useful for assessing the efficacy of ablation in elevated cases (B1)
	Planning	1. Pre-ablative planning, including evaluation of all imaging studies and careful US examination, should be conducted to identify target tumors and determine access routes (A1) 2. It is essential to understand the relationship between the tumor and surrounding structures, such as vessels and vital organs, to prevent complications (A1) 3. Before the procedure, it is important to determine the optimal patient position for each target tumor and assess whether artificial ascites or artificial pleural effusion will be necessary (B1) 4. In cases with multiple target tumors, the order of ablation should be determined during the pre-ablative planning phase (B1)

Table 1 (continued)

Topic		Recommendations
Techniques	Choice of modalities	1. RFA is recommended for most cases of small tumors (≤ 3 cm) due to well-established evidence supporting its short-term and long-term efficacy (B2) 2. MWA may offer advantages over RFA for the treatment of larger tumors (B2)
	Image guidance	1. US guidance serves as the primary method for ablation due to its significant advantages, such as real-time monitoring and convenience (B1) 2. CT or MR guidance can serve as complementary or alternative techniques in cases where US guidance has limitations (B1) 3. Fusion imaging enhances the detection and targeting of inconspicuous tumors on US as well as demonstrate 3-dimensional relationship between tumors and the surrounding structures (B1) 4. CEUS is valuable not only for guidance but also for evaluating ablated areas (B1)
	Procedural techniques	1. In order to eradicate possible occult metastasis adjacent to a target tumor, we need to ablate not only the tumor itself but also some amount of the surrounding liver tissue all around the tumor (A1) 2. For tumors of over 3 cm in diameter, to achieve complete tumor necrosis with an adequate safety margin, it is essential to use an ablation system capable of generating a large ablation volume. If this is not feasible, employing an overlapping technique or using multiple applicators becomes mandatory (B1) 3. A stepwise increment of output is recommended to prevent or delay popping, which may lead to tumor cell dispersion or bleeding (B2)
Peri-ablative management	Bleeding and thrombotic risks	1. Thrombopoietin receptor agonists or platelet transfusion should be administered in patients with severe thrombocytopenia undergoing ablation (A1) 2. Generally, ablation should not be performed on patients with prothrombin activity below 50% due to advanced cirrhosis (B1) 3. Regarding antithrombotic medication, a careful balance must be maintained between the risk of clot formation upon discontinuation and the risk of bleeding if the medication is continued (B1)
	Prophylactic antibiotics	1. Prophylactic antibiotics should be tailored to each patient. Prolonged use of prophylactic antibiotics is generally not recommended (B2) 2. Patients with papillary sphincter dysfunction are at risk of developing liver abscess following ablation (A1)
	Monitoring, sedation, analgesia, and substitution or cancellation	1. Patients undergoing ablation require regular monitoring of vital signs throughout the procedure (B1) 2. Sedatives and analgesics are necessary for patients undergoing ablation (B1) 3. Implement rules for substituting operators or canceling the procedure if the ablation cannot be carried out smoothly (A1) 4. Operators must be aware of potential procedure-related complications to ensure prompt detection and management (B1)
Evaluation of therapeutic effectiveness		1. The target tumor should be completely covered by the ablation zone (A1) 2. Appropriate post-treatment evaluation is essential to minimize local tumor progression and overall recurrence (A1) 3. An adequate safety margin is necessary to reduce local tumor progression, while excessive ablation may deteriorate liver function and negatively affect long-term survival (B1)

Table 1 (continued)

Topic	Recommendations
	4. The safety margin needs to be adjusted based on gross pathological type of HCC, the tumor's relationship with nearby structures, and liver function (B1)
Complications	1. To reduce serious complications in ablation, it is essential to evaluate risk factors and implement preventive measures (A1) 2. Upon the occurrence of a complication, early detection and management are critical to prevent a fatal outcome (A1) 3. Sharing knowledge and experience regarding complications is vital, given the low frequency of each complication in ablation procedures (B1)
Post-ablation	1. Even after curative ablation, patients are at extremely high risk of developing HCC. Rigorous follow-up is recommended after ablation (A1) 2. Screening with imaging, such as dynamic CT or MRI, along with tumor marker tests, should be conducted every 3–4 months (A1)

Table 2. Grading of evidence and recommendations (adapted from the GRADE system [15, 16])

Notes		Symbol
<i>Grading of evidence</i>		
High quality	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain	C
<i>Grading of recommendation</i>		
Strong recommendation	Factors influencing the strength of the recommendation included the quality of the evidence, presumed important patient outcomes, and cost	1
Weak recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty; higher cost, or resource consumption	2

for a broader application of this technique. However, satisfactory long-term prognosis is required to justify expanding the indication.

Concept of Ablatability
Understanding “ablatability” for image-guided tumor ablation is essential, similar to the concept of resectability in surgical resection, even though resectability lacks a standard definition [17–21]. “Ablatability” should be determined by tumor-related factors, patient-related factors, and resource-related factors as will be discussed later (Table 3).

In many guidelines for HCC, such as AASLD guidelines [18], EASL guidelines [22], and APASL guidelines [23],

treatment is determined only by tumor-related factors and liver-related factors, which is the main consideration among patient-related factors. However, ablation is highly operator-dependent. Thus, it is imperative to consider resource-related factors as well. “Ablatability” differs from operator to operator and from institution to institution because of the resource-related aspect.

Curative Intent or Debulking Intent
It should be determined prior to the procedure whether ablation will be performed for curative or for debulking intent. In cases in which ablation is performed with curative intent, all tumors detected by imaging modalities must be eradicated. While ablation is less

Table 3. Factors influencing indications for ablation

Tumor-related factors	• Size • Number • Location • Conspicuity
Patient-related factors	• Liver function • ECOG performance status • ASA Physical Status Classification
Resource-related factors	• Institutional volume • Operator's skills and experience • Paramedical staff training • Ablation system • Equipment to assist ablation (US, CT, MRI, US probe, fusion imaging, CEUS, table for treatment, and more)

invasive than surgical resection and can be more easily repeated in cases of recurrence, it is important to avoid local tumor progression as this is associated with poorer outcomes. If there is a possibility of viable residual tissue, ablation should be repeated until entire necrosis is achieved.

Conversely, ablation can also be used for reducing tumor burden to control tumor progression and improve prognosis. In cases treated with debulking intent, the main tumors should be ablated safely and efficiently. For such patients, ablation can be combined with vascular intervention or pharmacological therapies to optimize outcomes.

Tumor-Related Factors

Recommendations

1. When ablation is indicated, it is essential to take into account not only tumor size and number but also tumor location and conspicuity as tumor-related factors (A1).
2. Under favorable conditions, ablation may be applied beyond the conventional indication of three or fewer tumors, each 3 cm or less in diameter, in carefully selected cases (A2).
3. Risks and difficulties related to tumor location or conspicuity may be mitigated by applying techniques, such as artificial ascites, artificial pleural effusion, multimodality fusion imaging, and contrast-enhanced ultrasound (CEUS) (B2).

Tumor-related factors that determine the indications for ablation should include not only tumor size and number but also tumor location and conspicuity. In many treatment algorithms, tumor number and size are the primary factors considered. However, it is indisputable that tumor location and conspicuity also significantly influence the level of technical difficulty associated with ablation.

The indications for ablation could be expanded, under favorable conditions for tumors larger than 3 cm and/or for cases involving more than three tumors in carefully selected cases. Cases of three or fewer tumors, each 3 cm or less in diameter, have been the most widely accepted indication of ablation. However, this 3-3 rule was introduced almost 40 years ago, in the era of ethanol injection. Since then, ablation techniques have evolved from ethanol injection to RFA and MWA. Additionally, various methods have been introduced to assist with ablation, such as artificial pleural effusion, artificial ascites, CEUS, and multimodality fusion imaging [24–29]. Although the prognosis for HCC patients gradually worsens with increasing tumor size and number, no clear threshold has been identified for the diameter or number of nodules.

In the real world, ablation for tumors larger than 3 cm and/or for more than three nodules is widely performed. In fact, there are guidelines which recommend ablation as the treatment of choice for tumors exceeding 3 cm in size [30, 31].

Tumor Size

Conventional Indications. A tumor size of up to 3 cm is a conventional indication for ablation [16, 22, 23, 32]. The criterion of 3 cm or smaller in diameter and three or fewer nodules was proposed for ethanol injection in HCC patients nearly 40 years ago [8, 10]. In ethanol injection, the local tumor progression rate was higher when the tumor diameter exceeded 3 cm [33], primarily because the spread of injected ethanol is significantly influenced by the capsule or septa of the lesion [34]. Its effectiveness remains unreliable even after several sessions of injection [35, 36]. For tumors of 2 cm or less, ablation has achieved comparably good results to surgical resection. According to EASL Clinical Practice Guidelines, RFA may be considered as first-line option [22], while surgery is reserved for patients with nodules unsuitable for RFA or those who fail treatment. For tumors of 2.1–3.0 cm, thermal ablation procedures, such as RFA and MWA, may prove more reliable than ethanol injection.

Expanded Indications. Tumor size of 3.1–5.0 cm is already an expanded indication for ablation [31, 37]. However, overlapping techniques are essential as a single ablation may not adequately cover tumors of this size. Using multiple applicators – by inserting a few applicators to ensure the merging of ablation zones – can cover the entire tumor with a sufficient safety margin. Tumors larger than 5.0 cm represent an exceptional indication [38]. Ablation of such tumors could be a treatment of choice only in high-volume centers with advanced expertise. In such cases, combination therapy with transarterial chemoembolization (TACE) or pharmacotherapy may be

considered. The feasibility should be assessed by a multidisciplinary team [39].

A study showed that the prognosis of patients treated with RFA worsened gradually as tumor size increased. No apparent threshold in the diameter, however, was detected [40]. It concluded that ablation can be applied beyond the conventional indications of 3 cm or smaller in diameter.

Tumor Number

A tumor number of three or fewer is the conventional indication for ablation [16, 22, 23, 32]. Many patients with four or more tumors likely have micrometastases that are too small to be detected by ultrasound (US), CT, or MRI. Since ablation is a local treatment, it is not effective for micrometastases outside of the ablated area. Consequently, many patients with multiple tumors develop recurrence shortly after ablation. However, ablation of tumors detected by imaging modalities may significantly reduce tumor burden and prolong survival. A study showed that although the prognosis of patients treated with RFA worsened gradually as tumor number increased, no clear threshold was identified [40]. In favorable circumstances, ablation may be considered for select cases of more than three tumors.

A multicenter randomized controlled trial was conducted across 49 Japanese institutions to evaluate the efficacy of surgery versus RFA for small HCC (SURF trial). The results revealed that neither overall survival nor recurrence-free survival differed significantly between surgery and RFA for small HCC (≤ 3 cm) and three or fewer tumors [41].

In addition to the size and number of tumors, gross pathological type, including nodular, confluent multinodular, and infiltrative types, should also be considered when determining the indications for ablation (Fig. 1) [42]. In cases of confluent multinodular or infiltrative types, other treatment modalities, such as hepatic resection, may be more appropriate if conditions permit. However, if the patient's liver function and overall condition do not permit surgery, or if the patient declines surgical treatment, ablation can still serve as an alternative option. In such cases, achieving a larger ablative margin is crucial.

Tumor Location

Tumor location may be a crucial factor in determining the indication for ablation. Tumor location is closely related to safety and the risk of complications. Tumors located near major vessels or extrahepatic organs are considered risky to ablate because unexpected extension of the ablation zone may injure these structures [43, 44]. Ablation of Glisson's

sheath can lead to hepatic infarction in the perfusion area, while ablation of a hepatic vein may result in hepatic congestion in the drainage area. Intrahepatic bile ducts are more susceptible to thermal injury than vessels, and injury to these ducts may manifest as focal strictures, diffuse dilation of peripheral bile ducts, bilomas, or liver parenchymal atrophy [45]. In terms of adjacent organs, the intestines are more vulnerable to thermal injury compared to the stomach, gallbladder, or other structures, which may result in perforation or penetration. Tumor location also influences whether a safe applicator path exists [44]. Puncture of Glisson's sheath can lead to hemobilia or aneurysm, while puncture of vital organs may result in complications such as bleeding, pneumothorax, and perforation.

Tumor location significantly influences therapeutic efficacy. Tumors adjacent to large vessels or extrahepatic organs are considered difficult to ablate [43, 44]. Insufficient ablation can result in residual viable tumor tissue, while excessive ablation may damage adjacent structures. The heat sink effect – caused by cooling from blood flow in large vessels – reduces the thermal effect and may lead to incomplete ablation [46]. Additionally, tumors in certain locations may not be detectable by US due to liver atrophy resulting from advanced cirrhosis or deformities caused by previous surgical or nonsurgical treatments. Risks and difficulties associated with tumor location may be mitigated by employing techniques such as artificial pleural effusion [26], artificial ascites [24], and multimodality fusion imaging [25].

Tumor Conspicuity

Tumor conspicuity may also influence the decision to ablate a tumor, considering both the efficacy and safety of the procedure. Obscure tumors are difficult to puncture and ablate, which can result in ineffective and risky treatment. Various factors can affect tumor conspicuity, including the echogenicity and presence or absence of a tumor capsule, the homogeneity or heterogeneity of the surrounding liver tissue, the depth of the tumor, liver deformities due to advanced cirrhosis or prior surgical and nonsurgical treatments, and the patient's body shape.

Tumor conspicuity can be enhanced using techniques such as CEUS [27], artificial ascites [24], artificial pleural effusion [26], and others. Even ultrasonographically invisible tumors can be accurately ablated if their location is definitively identified using multimodality fusion imaging [25].

Extrahepatic Spread and Vascular Invasion

Extrahepatic spread or vascular invasion cases are not traditionally considered indications for ablation [18, 22, 23] as these conditions generally preclude curative treatment. However, ablation might still be considered in

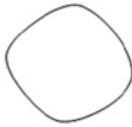
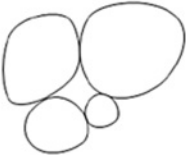
Indistinct margin	Clear margin			Irregular margin
				
Small nodular type with indistinct margin	Simple nodular type	Simple nodular type with extranodular growth	Confluent multinodular type	Infiltrative type

Fig. 1. Schematic representation of gross pathological types of HCC (reproduced with permission from the Liver Cancer Study Group of Japan [42]). HCC, hepatocellular carcinoma.

select scenarios where it could achieve substantial tumor debulking, which may offer survival benefits [47, 48]. Compared to surgical resection, ablation is significantly less invasive, allowing its use even when curative outcomes are unattainable. Reducing tumor burden in cases of extrahepatic spread or vascular invasion might contribute to better outcomes by mitigating tumor progression and its associated complications. In patients with extrahepatic spread, the majority succumb to uncontrolled liver lesions due to either tumor progression or hepatic decompensation [49]. Therefore, achieving control of intrahepatic lesions is critical. Furthermore, extrahepatic lesions may also be addressed using ablation in select cases [50]. In the context of vascular invasion, studies have reported that ablation, in combination with TACE or systemic therapies, has shown improved outcomes in well-selected patient groups [51]. However, due to the lack of robust evidence, the application of ablation in such cases should be approached with caution and confined to experienced centers as part of a comprehensive multimodal treatment strategy.

Patient-Related Factors

Recommendations

1. Not only liver function but also ECOG performance status, peri-procedure risk, and past history of upper abdominal surgeries should be evaluated as patient-related factors for indication of ablation (B1).

Patient-related factors may include not only liver function but also ECOG performance status, the American Society of Anesthesiologists (ASA) Physical Status Classification, and others. These factors impact the safety of ablation. Special attention should be given to patients’ histories of upper abdominal surgeries as adhesions may increase the risk of injury to adjacent organs.

Liver Function

The most widely used method for assessing liver function is the Child-Pugh classification. In general, ablation is indicated for patients classified as Child-Pugh A or B [18, 22, 23]. The survival benefit of ablation may decrease in proportion to the deterioration of liver function, while the risk of procedure-related adverse events (AEs) may increase as liver function declines. In patients classified as Child-Pugh C, there is considerable variability in clinical status, ranging from those who are almost asymptomatic to those who are near the end of life. Thus, the decision to perform ablation in Child-Pugh C patients should be made after carefully weighing the benefits and risks of treatment. For those in whom ablation is expected to significantly prolong survival, the procedure should be performed. However, in those for whom ablation is unlikely to improve prognosis – such as patients who are more likely to die from liver failure rather than HCC, ablation is not indicated. In patients with Child-Pugh C, the median survival time is approximately 16 months [52]. For candidates awaiting

liver transplantation for more than 3 months, including selected Child-Pugh C patients, ablation may be considered as bridging therapy [53]. Ablation is used to prevent tumor progression beyond the transplant eligibility criteria that would disqualify the patient from the transplant list. These criteria, including tumor size, tumor number, and other factors, may vary between institutions [54, 55]. The risk of complications and periprocedural mortality may be higher in patients with Child-Pugh C cirrhosis, so careful consideration of the indications, as well as the risks and benefits of ablation, is essential for this patient group.

ECOG Performance Status

ECOG performance status is an independent prognostic predictor, with long-term survival tending to be worse in patients with progressively poor performance status in HCC as well as other malignancies [56]. Performance status should be considered in determining the indication for ablation, although there have been few studies in which indication for ablation is analyzed from the viewpoint of performance status.

Peri-Procedure Risk Evaluation

Estimating periprocedural risks is essential as most patients with HCC have underlying cirrhosis. There are many periprocedural risk predictors for surgical treatments, including the Child-Pugh classification (Child-Turcotte-Pugh score) [57], the Model for End-Stage Liver Disease (MELD) score [57], ASA Physical Status Classification [58], Charlson Comorbidity Index (CCI) [59], and cardiopulmonary exercise tests (CPET) [60]. However, none of these predictors have been well evaluated in the context of ablation. This may be due to the significantly lower mortality and morbidity rates associated with ablation compared to surgical resection or even TACE [61].

History of Upper Abdominal Surgeries

Many patients with a history of upper abdominal surgery face challenges in undergoing ablation. First, past upper abdominal surgeries may cause adhesion formation between the abdominal wall or gastrointestinal tract and the liver, making it difficult to produce artificial ascites, also known as hydrodissection. Such surgeries include hepatectomy, gastrectomy, cholecystectomy, and others. The artificial ascites or hydrodissection technique is useful for displacing adjacent organs away from the target tumor, thereby making percutaneous ablation safer. This technique also helps reduce pain during or after ablation by

preventing heat transmission to the parietal peritoneum or diaphragm. Second, previous upper abdominal surgeries often result in liver deformity, which complicates tumor detection and the safe insertion of an applicator.

Resource-Related Factors

Recommendations

1. Institutional volume, the operator's skills and experience, paramedical staff training, ablation equipment, equipment to assist ablation, and others should be evaluated as resource-related factors when determining the indications for ablation (B1).
2. Improving resource-related factors is essential for achieving better outcomes (B1).

Resource-related factors may include institutional volume, the operator's skills and experience, paramedical staff training, ablation equipment, equipment to assist ablation, and others. These factors affect both the efficacy and safety of ablation. While tumor-related and patient-related factors are unchangeable, resource-related factors can be improved.

Institutional Volume

Institutional volume may affect efficacy and safety in ablation, namely, the indication. High-volume institutions are often able to perform ablation more effectively and safely, leading to broader indications. The association between institutional volume and outcomes may be attributed to learning curve effects and standardization of practices. Although there are few reports analyzing institutional volume and outcomes in minimally invasive procedures [62], this scarcity may be due to their low morbidity and mortality rates [63, 64]. In surgical treatments, numerous studies have evaluated the association between institutional volume and treatment outcomes [65, 66]. Notably, in-hospital mortality rates are significantly better in high-volume hospitals compared to low-volume ones [64, 67].

Operator's Skills and Experience

Ablation is highly operator-dependent. Skills and outcomes may be notably different from operator to operator and from institution to institution. A notable learning curve has been reported in RFA for liver tumors [68]. The risk of HCC recurrence can be substantially reduced by experienced RFA operators [69].

Paramedical Staff Training

The skills and experience of paramedical staff are crucial for ensuring the smooth execution of ablation procedures. Training for ultrasonographers, medical engineers, and nurses involved in ablation is essential.

Ablation Equipment

The ablation equipment used significantly impacts both efficacy and safety. Chemical ablation and energy-based ablation are different. Within energy-based ablation, RFA and MWA are also distinct from one another. These topics will be discussed in detail later under the section on Techniques.

Equipment to Assist Ablation

US, CT, and MRI equipment are crucial for image-guided procedures. For instance, tumor conspicuity can vary significantly depending on the quality of US machines. Moreover, image-guided ablation is facilitated by US transducers designed specifically for interventional procedures and dedicated procedure tables. Image fusion and navigation systems that integrate multiple modalities, such as US, CT, and MRI, are widely utilized for tumor targeting [70]. Additionally, CEUS can enhance tumor conspicuity in certain cases [27].

Pre-Ablative Diagnosis and Planning

Confirmation of Diagnosis of HCC

Recommendations

1. HCC can be diagnosed based on imaging criteria in high-risk groups for developing the disease (A1).
2. The interval between pre-treatment imaging and the actual procedure ideally should not exceed 1 month (A1).
3. Liver tumor biopsy is unnecessary in high-risk groups for developing HCC when imaging techniques reveal the hallmark features of HCC (B1).
4. Measurement of tumor markers is essential as changes in tumor marker levels are useful for assessing the efficacy of ablation in elevated cases (B1).

The high-risk group for developing HCC includes patients with chronic hepatitis B, chronic hepatitis C, or cirrhosis. US is the most widely used modality for HCC screening and surveillance. However, US alone is insufficient to confirm a diagnosis of HCC due to the overlapping imaging features of benign and malignant cirrhotic nodules.

In cases where nodules are detected by US, dynamic CT or MRI should be considered as diagnostic tools for confirmation [71, 72]. In high-risk groups, nodules can be

diagnosed as HCC based on typical imaging findings, specifically the presence of arterial enhancement followed by washout of the tumor in the portal venous or delayed phases on dynamic CT or MRI [73]. Gd-EOB-DTPA-enhanced MRI can improve the detection of HCC; a definitive diagnosis can be made for a hypervascular nodule that exhibits venous washout or hypointensity in the hepatobiliary phase [74, 75]. Additionally, CEUS using microbubble contrast agents and low mechanical index contrast-specific imaging techniques has proven useful for characterizing liver tumors (Fig. 2) [76, 77]. CEUS can be employed to characterize US-detected liver nodules and diagnose HCC in patients for whom contrast-enhanced CT or MRI are contraindicated due to renal dysfunction or allergy to contrast agents.

Liver tumor biopsy is unnecessary in the high-risk group for developing HCC when imaging techniques reveal the hallmark features of HCC. Biopsy carries potential risks, including bleeding and seeding [78, 79]. Therefore, it should be performed only in cases where imaging techniques do not show the typical findings of HCC.

Tumor marker measurement is necessary before ablation. Changes in tumor marker levels from the baseline value serve as effective indicators of treatment outcomes in elevated cases [80–82]. Chest CT, bone scintigraphy, and FDG-PET are unnecessary in most situations where ablation is considered [83]. Although the presence or absence of extrahepatic metastasis is a critical factor in determining the indication for ablation, extrahepatic spread is relatively rare at the time of initial diagnosis of HCC [84]. Surveillance for extrahepatic metastasis is necessary only in cases with extremely high tumor marker levels [85] or findings suggestive of extrahepatic lesions [86].

Pre-Ablative Planning

Recommendations

1. Pre-ablative planning, including evaluation of all imaging studies and careful US examination, should be conducted to identify target tumors and determine access routes (A1).
2. It is essential to understand the relationship between the tumor and surrounding structures, such as vessels and vital organs, to prevent complications (A1).
3. Before the procedure, it is important to determine the optimal patient position for each target tumor and assess whether artificial ascites or artificial pleural effusion will be necessary (B1).
4. In cases with multiple target tumors, the order of ablation should be determined during the pre-ablative planning phase (B1).

Pre-ablative planning is crucial for the smooth execution of ablation. Understanding the patient's clinical history related to HCC, including details about any

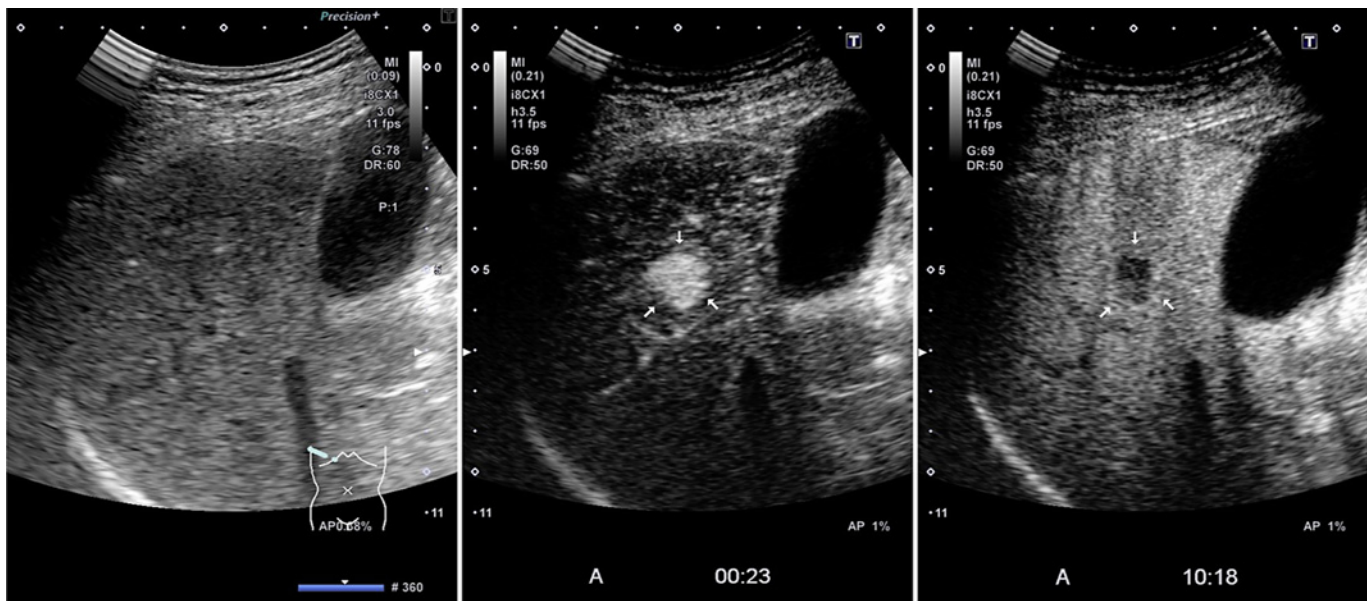


Fig. 2. CEUS image of a typical HCC. The US contrast agent Sonazoid demonstrates hypervascularity during the arterial phase (middle) and washout during the late vascular phase (right), compared to the non-contrast B mode image of the tumor (left).

previously resected or ablated liver segments, is essential. All imaging studies should be evaluated [87]. A careful US examination should be performed to identify target tumors and determine access routes [88]. During the US examination, CT and/or MRI images should be displayed for reference at any time. It is vital to understand the relationship between the tumor and surrounding structures, such as vessels and adjacent organs, to prevent complications. Identifying adjacent Glisson's sheaths is particularly important as puncturing them may lead to hemobilia or pseudoaneurysm. Additionally, ablation can cause hepatic infarction or biliary complications, such as stricture and biloma. Intrahepatic bile ducts are more susceptible to thermal injury than blood vessels. Thus, it is important to identify on which side of a Glisson's sheath a bile duct runs. Ablation can be performed relatively safely on the side opposite to a bile duct compared to the side closer to it. The intestines are also more vulnerable to thermal injury than the stomach, gallbladder, or kidneys. Fusion imaging can provide a 3-dimensional relationship between a tumor and adjacent intrahepatic and extrahepatic structures.

It is essential to determine the optimal patient position for each target tumor prior to the procedure: supine, right hemilateral (low, moderate, high), left hemilateral (low, moderate, high), upright, or 180° bed rotation with a left intercostal approach. Additionally, it is important to

assess whether artificial ascites or artificial pleural effusion will be necessary. In cases with multiple target tumors, the order of ablation – deciding which tumor to treat first, second, and so on – should be determined during the pre-ablative planning phase. As a general rule, tumors located in risky sites or those that are difficult to access should take priority for treatment.

Techniques

Choice of Ablation Modalities

Recommendations

1. RFA is recommended for most cases of small tumors (≤ 3 cm) due to well-established evidence supporting its short-term and long-term efficacy (B2).
2. MWA may offer advantages over RFA for the treatment of larger tumors (B2).

Several thermal and nonthermal ablation modalities are available for the treatment of HCC, including RFA, MWA, cryoablation, high-intensity focused ultrasound, laser ablation, irreversible electroporation, and chemical ablation (ethanol and acetic acid). Among these, thermal ablations, such as RFA and MWA, are the most widely used procedures.

RFA remains the most commonly used treatment for small liver malignancies due to its extensive study and widespread clinical application. Two types of monopolar equipment, designed as a straight cooled-tip electrode and multi-tined electrodes, have been available for over 2 decades [89]. Hepatic neoplasms less than 3 cm can be completely ablated in more than 90% of patients [13]. Using multiple electrodes (2–3) based on impedance and a power pulsing algorithm to expand the ablation zone may yield better outcomes for tumors ranging from 3 to 5 cm [90]. Additionally, some reports suggest that combining TACE with RFA may have a synergistic effect, potentially improving survival outcomes for tumors larger than 5 cm [91].

MWA ablates cancer tissue through dielectric heat generated by microwave energy emitted from an inserted bipolar-type applicator. The first-generation MWA system was introduced into clinical practice in the 1990s [11]. However, it has been replaced by RFA due to its smaller ablation volume and higher complication rates associated with the heated shaft of the applicator [92]. Recently, new-generation MWA systems of high-power generation and incorporating antenna cooling have been developed and received attention [93]. These systems may produce a more predictable ablation zone, create a larger ablation volume in a shorter procedure time, and have a lower heat-sink effect [94]. It is not easy to compare RFA and MWA because there are variations in both treatments. Generally, MWA is more expensive. Unlike RFA, MWA does not require grounding pads. The MWA antenna has a larger diameter than the RFA electrode, so extra caution is needed to prevent bleeding. MWA is more powerful and suitable for treating larger tumors. However, MWA still lacks sufficient clinical data, particularly long-term data, compared to RFA.

Cryoablation can effectively treat tumors near vulnerable structures, such as central bile ducts, as it creates well-defined ablation zone [95]. However, a rare but potentially fatal complication known as cryoshock may occur, and HCC patients with liver cirrhosis face an increased risk of bleeding [96]. There have been insufficient data on cryoablation for HCC. Clinical data on high-intensity focused ultrasound are still limited, preventing meaningful conclusions. Chemical ablation is now more commonly used as an adjunct in treating tumors that are difficult to address with thermal therapies alone. Examples include tumors that abut major bile ducts or are adherent to the bowel [97].

Image Guidance

Recommendations

1. US guidance serves as the primary method for ablation due to its significant advantages, such as real-time monitoring and convenience (B1).
2. CT or MR guidance can serve as complementary or alternative techniques in cases where US guidance has limitations (B1).
3. Fusion imaging enhances the detection and targeting of inconspicuous tumors on US as well as demonstrates 3-dimensional relationship between tumors and the surrounding structures (B1).
4. CEUS is valuable not only for guidance but also for evaluating ablated areas (B1).

In image-guided tumor ablation of HCC, most procedures are performed under US guidance [88, 98, 99]. US offers advantages in real-time monitoring, flexibility, and cost-effectiveness compared to CT and MRI. However, US guidance has some limitations. A primary limitation is the isoechogenicity of tumors. Isoechogenicity can sometimes be mitigated by using higher-resolution US machines or CEUS. Moreover, even isoechoic tumors that are not detectable by US may still be ablated using a fusion imaging system. Fusion imaging may be able to identify the location of the tumors accurately. Thus, even when US does not visualize the tumor, it may still be possible to ablate it precisely as shown in Figure 3. Another limitation arises from tumor invisibility due to the effects of air in the lungs, bones, omentum, or other tissues covering the liver's surface. Blind areas on US include the lateral end of the left lobe and the posterior-inferior segment of the right lobe. This invisibility can often be addressed by optimal patient positioning or by utilizing artificial ascites or pleural effusion (Fig. 4). CEUS and fusion imaging may further help resolve this issue. Additionally, gas bubbles produced by heat during ablation can obscure US images, complicating the following insertion of the applicator. Waiting for 5–15 min can often reduce the impact of these gas bubbles and improve US imaging in many cases. These limitations may be addressed by using CT or MRI guidance, or by combining CT/MRI with US in certain situations [100].

CT guidance is not the primary method for liver tumor ablation. However, in CT-guided tumor ablation, the position of the applicator and its relation to adjacent organs are clearly visualized due to CT's high resolution. This imaging technique allows for almost all organs to be seen without interference from bones or gas. Some investigators suggest that CT guidance may have advantages for tumors located beneath the diaphragm, near bones, or at the edges of the left lateral segment and posterior segment. Nevertheless, with the use of artificial ascites or pleural effusion, most of these tumors can be

effectively identified and ablated under US guidance by experienced operators. In certain cases, ablation is performed following TACE to enhance local control of the tumors. In such scenarios, CT guidance may be beneficial since the tumor can be clearly visualized through the Lipiodol deposit. Traditional CT guidance requires a slow, slice-by-slice process to confirm the updated position of the applicator. In contrast, fluoroscopic CT enables the operator to continuously monitor the trajectory of the applicator during insertion, simplifying the CT-guided interventional procedure [101]. However, it is important to note that CT-guided interventions expose patients to radiation.

MRI is the least commonly used imaging modality for percutaneous ablation, [102, 103], although it has been considered as a versatile and suitable option for guidance [104]. Compared to both US and CT guidance, MR guidance is more expensive and time-consuming. However, MRI offers excellent soft tissue resolution and the ability to image in arbitrary planes. It provides near real-time imaging, which facilitates the characterization and tracking of anatomical motion while eliminating radiation exposure. Additionally, MRI can monitor temperature changes in the ablation zone, helping to assess the extent of tumor destruction.

Fusion imaging is a system that merges real-time US with previously acquired CT or MRI images [105, 106]. In this technique, a virtual image constructed from CT or MRI data is displayed alongside the real-time US image on a single monitor. The virtual image aligns with the same plane and moves synchronously with the real-time US image. This capability enhances the accurate targeting of inconspicuous tumors on US without using CT or MRI equipment. Fusion image is also useful for demonstrating the 3-dimensional relationship between the tumor and surrounding structures.

Fusion imaging may serve as an alternative to CT or MRI guidance for patients with tumors that are poorly visualized on US. Additionally, three-dimensional US can be fused with real-time US for the percutaneous ablation of liver tumors that require overlapping ablation.

CEUS is an US examination that utilizes gas-filled microbubbles to provide sensitive information about blood flow and tissue perfusion [27, 107]. CEUS is beneficial for guiding the insertion of an applicator into inconspicuous tumors on US. Additionally, it is effective for evaluating ablation areas to determine whether any viable tumor portions remain [108]. Unlike CT and MRI, which provide only static images, CEUS offers real-time, continuous dynamic imaging of tumors. The unique intravascular properties of microbubbles enable CEUS to

characterize malignant tumors with increased vascular permeability. Furthermore, CEUS is not affected by motion artifacts, making it a safe and easily performed technique that does not involve ionizing radiation or pose a risk of nephrotoxicity. It is suitable for patients with renal dysfunction, allowing for multiple microbubble injections and repeated observations of tumor enhancement patterns during a single examination. However, CEUS does have specific limitations, including blind spots, particularly in areas located more than 10 cm from the body surface, in addition to the inherent blind areas of US. In some situations where percutaneous ablation is not feasible due to anatomical constraints or poor tumor visibility, laparoscopic or open approaches may serve as alternatives [109, 110].

Procedural Techniques

Recommendation

1. In order to eradicate possible occult metastasis adjacent to a target tumor, we need to ablate not only the tumor itself but also some amount of the surrounding liver tissue all around the tumor (A1).
2. For tumors of over 3 cm in diameter, to achieve complete tumor necrosis with an adequate safety margin, it is essential to use an ablation system capable of generating a large ablation volume. If this is not feasible, employing an overlapping technique or using multiple applicators becomes mandatory (B1).
3. A stepwise increment of output is recommended to prevent or delay popping, which may lead to tumor cell dispersion or bleeding (B2).

It is important to recognize that a sufficiently ablated area does not merely refer to a large volume of ablation. To eliminate potential occult metastases adjacent to a targeted tumor, it is essential to ablate not only the tumor itself but also some surrounding liver tissue [34]. To ensure an adequate ablation zone, overlapping ablation is necessary in many cases.

Protocol for RFA

Single-needle type electrodes generate an ablated area that typically resembles a prolate spheroid or rugby ball shape. The size and shape of this ablation zone can be unpredictable. The dimensions of the minor axis often vary unpredictably, likely due to the cooling effect of adjacent vessels, which restricts the spread of the ablated area. In contrast, the size of the major axis remains relatively stable. Expandable type electrodes can create an oblate spheroid-shaped ablation zone, characterized by a wider horizontal axis compared to the vertical axis.

Regarding the output mode, the stepwise increment of output is widely used in Asian countries [36, 111]. This gradual increase is implemented to prevent or delay

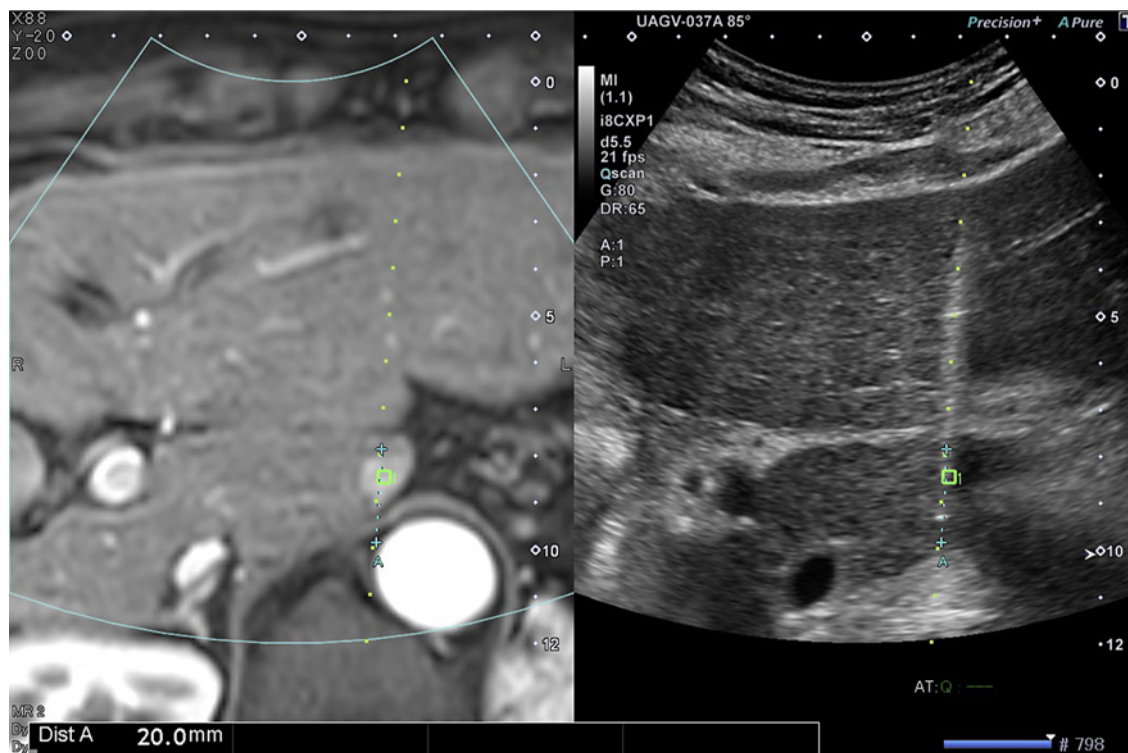


Fig. 3. Fusion image guidance during ablation. Fusion imaging combines real-time US images with previously acquired cross-sectional images, such as CT or MRI. By synchronizing the two imaging modalities, it allows the operator to view both the high-resolution, static images from CT or MRI alongside the real-time,

dynamic US images. Caution: while fused images of MRI/CT and US appear similar, they are not identical. Therefore, during ablation, points are marked on the real-time US image. As a result, the line may appear differently on the fused MRI/CT image, as shown in these figures.

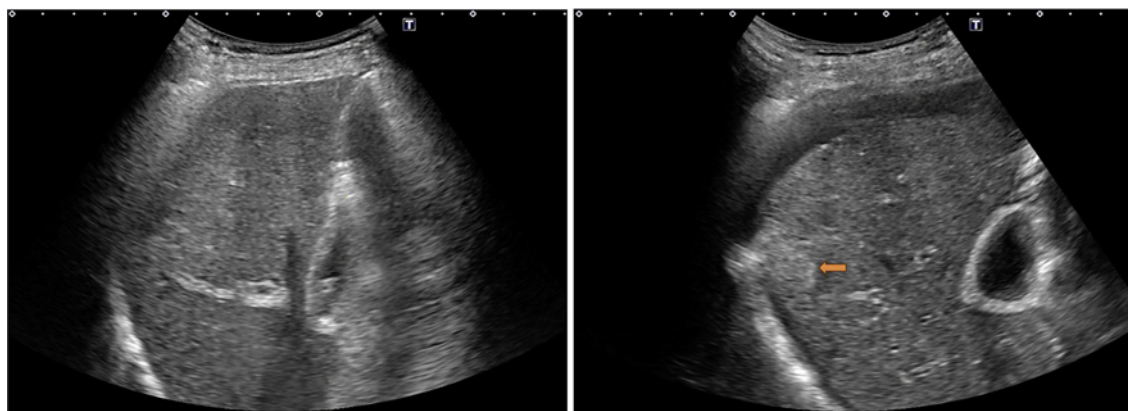


Fig. 4. Artificial ascites and artificial pleural effusion allow a tumor located beneath the diaphragm, which would otherwise be obscured by lung air, to become visible on US. Additionally, artificial ascites, as seen in this image, creates space between the diaphragm and the ablated area, helping to reduce pain during and after the procedure by minimizing heat conduction to the diaphragm.

“popping,” a form of explosive tissue disruption resulting from a rapid rise in intra-tissue pressure. Such popping can lead to tumor cell dispersion or bleeding [112].

We should avoid popping, especially in cases where the target tumor is located on the liver surface, as this may lead to malignant dissemination into the peritoneal cavity

[113]. Additionally, popping should be avoided when the target tumor is adjacent to a hepatic vein or the inferior vena cava as it could increase the risk of pulmonary metastasis [86, 114]. However, if popping does occur, the procedure should be continued until complete ablation is achieved. In RFA, popping is typically followed immediately by an impedance out or “break,” which interrupts the ablation process in most cases. In contrast, in MWA, the procedure continues for the scheduled duration required to achieve the planned ablation size. Notably, once popping occurs, intra-tissue pressure does not increase further due to the tissue disruption. Overall, popping should be avoided whenever possible as it may lead to complications such as bleeding or tumor cell dispersion.

Protocol for MWA

Most microwave antennas produce a pear-shaped ablated area, which elongates along the antenna shaft. However, a more spherical and less elongated ablated zone can enhance ablation precision and reduce complications. Several advanced technologies have been developed to create a more spherical ablation zone, including dual-slot antennas [115], paired antennas [116], an antenna with thermal control, field control, and wavelength control [117]. The stepwise increment of output is also used in MWA to prevent popping, which carries the risk of hemoperitoneum or malignant seeding.

Peri-Ablative Management

Peri-ablative management is fundamental for conducting ablation procedures smoothly and safely. Preparation is essential to minimize AEs, such as bleeding and infection. In many hospitals, ablation is performed on an inpatient basis as severe AEs can occur even more than 8 h post-procedure. Continuous observation is crucial for the timely detection of any complication.

Management of Bleeding and Thrombotic Risks

Recommendations

1. Thrombopoietin receptor agonists or platelet transfusion should be administered in patients with severe thrombocytopenia undergoing ablation (A1).
2. Generally, ablation should not be performed on patients with prothrombin activity below 50% due to advanced cirrhosis (B1).
3. Regarding antithrombotic medication, a careful balance must be maintained between the risk of clot formation upon discontinuation and the risk of bleeding if the medication is continued (B1).

Control of bleeding disorder is important in ablation because image-guided percutaneous ablation precludes the operator from direct visualization and management of bleeding at the procedure site. Ablation carries the risk of bleeding. On the other hand, some patients who undergo ablation have thrombotic risks and thus are under antithrombotic medication. These agents are increasingly utilized by clinicians to reduce thromboembolic events in conditions like cardiac arrhythmia, coronary artery disease, valvular heart disease, deep vein thrombosis, various other vascular occlusions, and hypercoagulable states. Antithrombotic medications can be classified into two main categories: antiplatelet agents and anticoagulants. Commonly used antiplatelet agents include aspirin (acetylsalicylic acid) and thienopyridines (clopidogrel, prasugrel, ticlopidine, ticagrelor), while anticoagulants include warfarin and direct oral anticoagulants (DOACs).

Risk stratification for ablative procedure has been defined by the American Society of Gastrointestinal Endoscopy and the Society of Interventional Radiology guidelines [118, 119]. These guidelines are designed to assist clinicians in their decision-making processes rather than serve as rules to follow. The final decision for antithrombotic management should also be patient tailored.

Severe Thrombocytopenia

Low platelet count is relevant to the risk of bleeding events during and after invasive procedures [120]. In patients with severe thrombocytopenia (platelet count below 50,000/ μ L), many institutions administer platelet transfusions before ablation. However, platelet transfusions might be associated with febrile nonhemolytic and allergic reactions, risk of infection, and platelet refractoriness. Alternatives are splenectomy or partial splenic arterial embolization, which carry considerable complications. Thrombopoietin receptor agonists such as lusutrombopag [119, 121] and avatrombopag [122] may be a treatment of choice in ablation for severe thrombocytopenic patients. They can increase the platelet count effectively in most cases.

Severe Coagulopathy

Many patients with HCC have coagulopathy due to comorbid liver cirrhosis. In most institutions, ablation is performed in patients with prothrombin activity of 50% or higher [88, 98]. In general, ablation should not be performed on patients with advanced cirrhosis whose prothrombin activity is below 50% as liver failure, rather than HCC, is likely to be the primary factor that would shorten life expectancy. Additionally, replacement therapy tends to have only short-term efficacy.

Antiplatelet Agents

Antiplatelet agents are widely used for the primary and secondary prevention of thrombotic cerebrovascular and cardiovascular diseases. Because of lack of robust evidence, such as randomized controlled trials, the management of antithrombotic agents has resulted in considerable variety in clinical practice. Regarding antithrombotic medication, it is essential to weigh the risk of clot formation from stopping the medication against the risk of bleeding from continuing it during or after ablation in each case [123]. For some patients who are at high risk of thrombosis, we may consider switching to an antiplatelet drug with a shorter half-life. The decision should be aligned with each institutional standard or consensus. We generally stop aspirin (acetylsalicylic acid) and other antiplatelet agents such as thienopyridines (clopidogrel, prasugrel, ticlopidine, ticagrelor) a week before ablation.

Anticoagulants

Anticoagulants, such as warfarin and DOACs, are used in patients with atrial fibrillation, mechanical heart valves, and deep vein thrombosis, among other conditions. Anticoagulant therapy can prevent the formation or growth of dangerous clots. Temporarily interrupting anticoagulation increases the risk of thromboembolic events, while continuation raises the risk of bleeding associated with ablation. The decision regarding anticoagulant interruption must be evaluated as a balance between the benefits and risks in each case. Bridging therapy may be required for patients with a high risk of thromboembolic events [118]. Patients with atrial fibrillation should be evaluated using the CHA2DS2-VASc score, and the type of mechanical valve should be assessed for those with valvular heart disease. The risk of thromboembolic events when warfarin is interrupted for 4–7 days is approximately 1% [124, 125]. DOACs are increasingly used in various clinical indications to replace warfarin. Generally, discontinuation of DOACs 1–2 days prior to ablation is recommended; however, a longer duration of drug interruption may be necessary in cases of renal impairment [118, 126].

Prophylactic Antibiotics

Recommendations

1. Prophylactic antibiotics should be tailored to each patient. Prolonged use of prophylactic antibiotics is generally not recommended (B2).
2. Patients with papillary sphincter dysfunction are at risk of developing liver abscess following ablation (A1).

Any invasive procedure carries the risk of infection. According to the literature, 0.3–2.4% of patients develop infections, such as liver abscess and cholangitis, after ablation [127–130]. Most operators use prophylactic antibiotics for ablation not based on robust evidence but rather on personal or anecdotal experience, or on ablative or surgical literature [131–135]. Currently, there is no consensus on the first-choice antibiotic agent. The lack of randomized controlled trials has led to the routine use of antibiotic prophylaxis as a perceived standard of care. However, it is essential to use prophylactic antibiotics judiciously, considering the costs of antibiotic therapy, the increasing incidence of antibiotic resistance, and the potential complications from nosocomial infections. Further investigations are necessary to clarify the role of prophylactic antibiotics in ablation [136].

In patients with papillary sphincter dysfunction due to enterobiliary anastomosis, sphincterectomy, biliary drainage, or stent placement, the incidence of liver abscess following ablation can be as high as 22–100% [127, 137, 138]. Papillary sphincter dysfunction is considered a significant risk factor for the development of liver abscess and is generally regarded as a contraindication for liver tumor ablation [130, 138–140]. In addition to papillary sphincter dysfunction, other risk factors for developing liver abscess include larger ablation volumes, porta hepatis tumors, diabetes mellitus, and advanced liver cirrhosis.

Monitoring, Sedation, Analgesia, and Substitution or Cancellation

Recommendations

1. Patients undergoing ablation require regular monitoring of vital signs throughout the procedure (B1).
2. Sedatives and analgesics are necessary for patients undergoing ablation (B1).
3. Implement rules for substituting operators or canceling the procedure if the ablation cannot be carried out smoothly (A1).
4. Operators must be aware of potential procedure-related complications to ensure prompt detection and management (B1).

Patients undergoing ablation under sedation or general anesthesia require regular monitoring of vital signs – including blood pressure, heart rate and rhythm, pulse oximetry, and airway status – throughout the procedure. Assistant operators, anesthesiologists, and nursing staff must be sufficiently skilled to manage any emergent situations that may arise during sedation or anesthesia. Emergency cart, oxygen tank, and other

resuscitative equipment should be readily available. Vital signs recorded prior to the procedure can help screen for potential underlying conditions that may be exacerbated during sedation or general anesthesia. Post-procedure monitoring is also important for the prompt management of potential AEs resulting from sedatives or the ablation itself. Sedatives and analgesics are necessary because ablation can be painful, and patients often experience anxiety and discomfort. Anesthetic agents not only relieve pain but also reduce the risk of patient injury caused by movement during the procedure.

In cases where the operator encounters difficulty before or during the ablation and is not able to finish the procedure, he/she should request a substitute or cancel the procedure. In some patients with multiple tumors, the procedure may be divided between two operators. Tumors that are easier to ablate may be treated by a less experienced operator, while those that are more difficult to ablate should be handled by a more experienced operator. For large tumors, the portions that are easier or less risky to ablate can be addressed by the less experienced operator, while the more challenging or risky areas should be managed by the more experienced operator.

During post-procedural recovery, attention should be given to the recovery of consciousness, spontaneous respiration, hemodynamics, and urinary retention. Reversal agents such as naloxone for opioids and flumazenil for benzodiazepines may be administered in cases of prolonged sedation. Urinary retention should be monitored, particularly in elderly patients. An indwelling Foley catheter may be used when necessary. In the event of cardiorespiratory depression, advanced airway management and resuscitative medications should be administered by medical professionals with Advanced Cardiovascular Life Support qualifications.

Despite the low rate of major complications, operators must be vigilant about potential procedure-related problems for prompt detection and management [111, 129, 141]. Immediate post-procedural care should focus on hemorrhages, ground-pad thermal injury, pneumothorax, visceral damage, reactive pleural effusion, and ascites. Hemorrhagic complications are the most frequently encountered and most devastating if neglected. A study identified several risk factors for bleeding [120]. Recognizing high-risk procedures prevent delayed diagnosis. Post-procedural observation is mandatory as some complications may take hours to days to manifest obvious symptoms.

Evaluation of Therapeutic Effectiveness

Recommendations

1. The target tumor should be completely covered by the ablation zone (A1).
2. Appropriate post-treatment evaluation is essential to minimize local tumor progression and overall recurrence (A1).
3. An adequate safety margin is necessary to reduce local tumor progression, while excessive ablation may deteriorate liver function and negatively affect long-term survival (B1).
4. The safety margin needs to be adjusted based on gross pathological type of HCC, the tumor's relationship with nearby structures, and liver function (B1).

Evaluation of therapeutic effectiveness is critical for understanding the efficacy of ablation and assessing technical success. This assessment is commonly performed using contrast-enhanced imaging studies (CT or MRI) with a slice thickness of 5 mm within 6 weeks post-ablation [142, 143]. If feasible, early imaging a day after the procedure may be beneficial for assessing technical success and detecting any complications promptly. Multiphasic contrast-enhanced CT may be preferred due to its cost-effectiveness and convenience [144]. Technical success is defined by a target tumor completely covered by the ablation zone [145]. Appropriate post-treatment evaluation is associated with a reduction in local tumor progression and an improvement in overall recurrence rates [146]. If an unsatisfactory safety margin is identified, salvage ablation should be arranged timely. A study using enhanced CT or MRI for safety margin assessment showed comparable ability to predict local tumor progression [147]. The safety margin is conventionally assessed through visual examination of contrast-enhanced images taken before and after the ablation. However, some studies indicated that using software for safety margin assessment was superior to visual evaluation, effectively identifying patients at risk for local tumor progression [148, 149]. CEUS may be beneficial for patients with allergies to contrast agents or renal dysfunction, serving as a complementary tool to assess therapeutic response and safety margin [150], although safety margin could not be determined in 34.8% of the cases.

The concept of safety margin arose from a histopathologic study of resected specimen treated by ethanol injection [34], which revealed residual viable cancer tissue remains in the peripheral area of the nodule or in the extracapsular growth. The 5 mm safety margin was derived from the formula relating the volume of ethanol injected to the tumor size [32]. The safety margin must be adjusted for each case or each tumor. The safety margin needs to be modified based on gross pathological type of HCC as shown in Figure 1 [42]; a larger ablative margin is

necessary in the simple nodular type with extranodular growth and the confluent multinodular type compared to small nodular type with indistinct margins and the simple nodular type. The safety margin should also be modified based on the tumor's relationship with nearby structures. The hepatic artery, portal vein, and hepatic vein are less vulnerable to thermal injury compared to the intrahepatic bile duct. Particular attention should be paid to the intrahepatic bile duct running parallel to the portal vein; the anatomy of their relationship must be recognized, like whether the intrahepatic bile duct runs along a shallower or deeper portion of the portal vein. The hepatobiliary phase of an EOB-MRI can show the relationship between the portal vein and the parallel-running intrahepatic bile duct in certain cases. There was a report indicating that ablation covering the entire tumor blood drainage area improved survival in patients with HCC [151].

An adequate safety margin around the tumor is necessary to minimize the risk of local tumor progression, while also considering that excessive ablation of surrounding liver parenchyma may deteriorate liver function and negatively affect long-term survival. In some cases, a challenging decision must be made regarding the sacrifice of the Glisson's sheath. Sacrificing it can lead to hepatic infarction or intrahepatic bile duct dilatation, resulting in subsequent atrophy of the peripheral liver parenchyma. Alternatively, preserving the Glisson's sheath may increase the likelihood of residual viable cancer tissue remaining. The safety margin should be tailored in terms of liver function.

Complications

Basic Principles regarding Complications

Recommendations

1. To reduce serious complications in ablation, it is essential to evaluate risk factors and implement preventive measures (A1).
2. Upon the occurrence of a complication, early detection and management are critical to prevent a fatal outcome (A1).
3. Sharing knowledge and experience regarding complications is vital, given the low frequency of each complication in ablation procedures (B1).

Ablation procedures can pose potential risks; however, when performed correctly and with appropriate safety systems, complications can be minimized. Two types of safety systems are employed: active and passive. Active safety systems aim to prevent complications by evaluating factors associated with risk and implementing preventive measures. Conversely, passive safety systems are designed to mitigate the consequences of complications if they occur.

Early detection and management of complications are essential to prevent fatal outcomes. While there are various complications associated with ablation, the frequency of each is relatively low. Therefore, sharing knowledge and experiences related to these complications is crucial.

Grade of Complications

The Society of Interventional Radiology (SIR) proposed a classification system for AEs, categorizing them into five levels: mild AE, moderate AE, severe AE, life-threatening or disabling event, and patient death or unexpected pregnancy termination [152]. The SIR AE Severity Scale is designed to align with the surgical Clavien-Dindo scale [153] and the National Cancer Institute Common Terminology Criteria for Adverse Events scale [154]. All AEs occurring within 30 days of a procedure should be included in the AE description and analysis, regardless of their causality, to ensure objectivity.

Hemorrhage

Bleeding is a common complication associated with all types of locoregional ablation that use needle-type devices. These bleeding complications can be further classified into hemoperitoneum, hemothorax, and hemobilia [120]. Hemoperitoneum or intraperitoneal hemorrhage typically results from injuries to intrahepatic or abdominal wall vessels caused by needle devices. Patients with HCC are at a higher risk of bleeding complications since most are in the state of coagulopathy because of underlying chronic liver disease. Risk factors for hemoperitoneum include a longer needle tract to the target tumor and lower platelet counts, among others. A longer needle tract increases the likelihood of injuring vessels along the puncture route, thereby heightening the risk of bleeding. Theoretically, the risk of bleeding increases with greater needle thickness and the number of insertions required to achieve tumor destruction. Additionally, bleeding is more frequent in cryoablation compared to RFA and MWA, which inherently possess hemostatic effects. Notably, these procedures can also be employed to control bleeding by coagulating the bleeding site.

Hemothorax, a rarer complication than hemoperitoneum, occurs due to injury to the intercostal vessels. However, the mortality rate associated with hemothorax is higher than that of hemoperitoneum as spontaneous hemostasis is rarely achieved in cases of arterial bleeding. Additionally, bleeding into the pleural cavity can lead to reactive pleural effusion and, in some cases, a systemic inflammatory response syndrome, resulting in respiratory failure. An interventional radiological procedure is

typically required to manage hemothorax. If the intervention is ineffective, surgical options should be considered.

Hemobilia occurs when a needle device simultaneously penetrates an intrahepatic portal vein or artery and a bile duct. Unlike other bleeding complications, hemobilia is rarely associated with hypovolemic shock. Instead, it typically presents as obstructive jaundice. Hemobilia can be identified by the presence of a clot in the gallbladder, known as the hemobilia sign [155]. Since hemobilia is generally self-limiting, endoscopic intervention should be deferred unless patients develop an infection as a subsequent complication. This is because intervention can sometimes promote rebleeding and infection [156].

Liver Abscess

Liver abscess is typically associated with transbiliary bacterial translocation. Consequently, a history of biliary intervention that leads to enterobiliary reflux is a significant risk factor for developing a liver abscess following locoregional ablation. Specifically, a history of enterobiliary anastomosis should be considered a contraindication for RFA or MWA due to the extremely high risk (exceeding 50%) of abscess formation after these procedures [138].

Intrahepatic Biliary Injury

Intrahepatic biliary injury, characterized by intrahepatic bile duct dilatation, is more prevalent in RFA and MWA compared to cryoablation. The heat produced by RFA or MWA can more easily injure the intrahepatic bile ducts compared to blood vessels as the cooling effect of bile flow is less than that of blood flow. In most cases, biliary injury is asymptomatic, typically indicated by elevated alkaline phosphatase and gamma-glutamyl transferase levels. However, injury to a major intrahepatic bile duct can lead to segmental atrophy of the liver parenchyma, resulting in long-term deterioration of liver function [45]. There have been some reports that intraductal chilled saline perfusion during ablation may be useful to reduce biliary complications [157]. Irreversible electroporation may be a preferable option when the target tumor is located in the liver hilum as it is less likely to damage the biliary structures [158].

Ischemic and Congestive Complications

Hepatic infarction is an ischemic complication, resulting from the simultaneous occlusion of both intrahepatic arterial and portal blood flow [159]. Hepatic venous congestion is caused by the occlusion of the hepatic vein. Both complications are characterized by

massive parenchymal loss with highly elevated liver enzyme levels and subsequent inflammatory response syndrome, which can result in high fever and potentially fatal outcomes. To mitigate the risk of these complications, careful electrode placement along with minimized ablation power and duration are recommended.

Neoplastic Seeding

Neoplastic seeding is classified as a late-onset complication that can occur up to 5 years after ablation [160]. While some instances of neoplastic seeding may be amenable to surgical resection, the prognosis is generally poor in cases involving intraperitoneal dissemination. Factors associated with an increased risk of neoplastic seeding include tumor location on the surface of the liver, poorly differentiated tumor characteristics, and multiple treatment sessions [160, 161]. Additionally, a preceding tumor biopsy has been linked to neoplastic seeding [162]. No-touch ablation using multiple electrodes placed around the target tumor is a method to avoid puncturing the target tumor directly [163].

Post-Ablative Follow-Up, Prevention of Recurrence, and Treatment of Recurrence

Post-Ablative Follow-Up

Recommendations

1. Even after curative ablation, patients are at extremely high risk of developing HCC. Rigorous follow-up is recommended after ablation (A1).
2. Screening with imaging, such as dynamic CT or MRI, along with tumor marker tests, should be conducted every 3–4 months (A1).

Approximately 70%–80% of patients with HCC develop recurrence within 5 years, even after curative resection or ablation, due to occult metastasis or metachronous multicentric (de novo) carcinogenesis [164, 165]. Early detection of recurrence is crucial as most recurrences can be treated curatively with another ablation, unlike many other solid tumors [88]. Comprehensive post-treatment surveillance is essential for improving prognosis after ablation. A combination of dynamic CT or MRI and tumor marker tests is recommended for follow-up, similar to the surveillance protocol for patients at extremely high risk for developing HCC. Screening should be conducted every 3–4 months. The interval should be tailored based on tumor marker level trend and others [166].

Extrahepatic recurrence following ablation is uncommon. Therefore, imaging modalities such as CT, MRI, FDG-PET, or bone scintigraphy should be considered only when patients have symptoms of extrahepatic metastasis or when intrahepatic recurrence is not detected despite a gradual increase in tumor marker levels.

Incidentally, ablation is theoretically associated with a higher recurrence rate compared to surgical resection. Local tumor progression can occur following incomplete ablation. Additionally, ablation may result in more frequent distant recurrences from the initial target tumor than resection due to the smaller volume of surrounding tissue that is ablated.

Prevention of Recurrence

Recommendations

1. It is not recommended to use pharmacotherapy for preventing recurrence and improving survival after curative ablation (B2).
2. Antiviral treatment for hepatitis is recommended to prevent recurrence, maintain and improve liver function, and ultimately improve survival (A1).

Preventing the recurrence of HCC is crucial for long-term survival. One primary reason for recurrence is the presence of microscopic residual tumors. Notably, even small tumors measuring 2 cm or less were found to have portal vein invasion in 27% of cases and intrahepatic metastasis in approximately 10% [167]. Theoretically, adjuvant chemotherapy may reduce or delay such recurrences, but few cytotoxic anticancer drugs have been effective against HCC while many of them may be hepatotoxic. This may result in poor prognosis because of worsening liver function.

Adjuvant sorafenib after surgical resection and ablation for HCC did not provide additional benefit in terms of recurrence-free survival in the STORM trial [168]. The Phase 3 IMbrave 050 trial initially demonstrated that adjuvant atezolizumab with bevacizumab improved recurrence-free survival compared to placebo, but it failed to show a sustained benefit in overall survival or recurrence-free survival [169, 170]. Several ongoing trials are investigating the role of adjuvant targeted therapies for HCC. These include the EMERALD-2 trial on durvalumab alone or in combination with bevacizumab versus placebo, the KEYNOTE-937 trial on pembrolizumab versus placebo, and the trial on nivolumab versus placebo as adjuvant therapies after curative resection or ablation [171–173]. To date, there has been no conclusive evidence that pharmacotherapy can reliably prevent recurrence or improve survival after curative resection or ablation of

HCC. While certain treatments, such as targeted therapies or immunotherapy, have been explored, their effectiveness in reducing recurrence and improving long-term survival remains unproven in large-scale clinical trials.

Furthermore, antiviral treatment may help prevent recurrence, maintain and enhance liver function, and ultimately improve survival in patients with HCC associated with hepatitis B virus (HBV) or hepatitis C virus (HCV) [174, 175]. Interferon has been shown to improve survival, although it does not significantly increase the recurrence-free survival rate in HBV-related HCC [176]. Nucleos(t)ide analogs are effective in reducing the risk of recurrent HBV-related HCC. Recurrence is particularly frequent in HCV-related HCC, with a substantial proportion of these recurrences – especially in the later stages – thought to represent metachronous, multicentric hepatocarcinogenesis. Both direct-acting antiviral therapies and interferon-based treatments may reduce the risk of recurrence and improve survival in patients with HCV-related HCC [175].

Alcohol abuse is another main cause of HCC. Therefore, for these patients, alcohol abstinence is a critical issue following curative liver resection or ablation. Alcohol abstinence may reduce recurrence of HCC and improve overall survival [177, 178].

Treatment of Recurrence

Recommendations

1. Curative treatment should be performed for recurrent HCC whenever possible, similar to primary HCC (A1).
2. Local tumor progression should be ablated carefully to eradicate the entire viable portion, using CEUS and/or fusion imaging when feasible (B1).
3. Salvage surgery should be considered for cases where local tumor progression is extensive and/or accompanied by satellite nodules (B1).
4. Similar strategies should be used for recurrent HCC as for primary HCC (B1).

HCC frequently recurs even after curative locoregional treatment. Unlike other tumors, however, most recurrent HCC can be treated curatively similar to primary HCC. With rigorous post-treatment surveillance, up to 89% of initial recurrences were treated by iterative RFA [88]. Ablation is easily repeatable for recurrences due to its minimal invasiveness. In contrast, only 11–30% of recurrent HCC cases following hepatectomy can be treated with repeat hepatectomy.

In general, local tumor progression is more difficult to treat than the primary tumor. The most important thing is to ensure that the primary HCC is treated in a definitively curative manner to prevent local tumor progression. The second priority is rigorous surveillance to detect any local tumor progression at an earlier stage. When ablation is

used for local tumor progression, it should be performed carefully to eradicate the entire viable portion. To facilitate detection of the viable portion, CEUS and/or fusion imaging should be used. Surgical resection may be the preferred treatment for cases with extensive local tumor progression and/or more than three satellite lesions [179]. While some reports suggest that the efficacy of hepatectomy and ablation for local tumor progression is not significantly different [37, 180], we should not hesitate to pursue salvage surgery if necessary.

Most recurrences that are distant from the primary tumor can be treated with ablation, similar to the primary treatment approach. Surgical options, vascular interventions, radiation therapy, and pharmacological therapies should be chosen based on the individual case. Generally, the same strategies used for primary HCC should be applied to recurrent HCC.

According to a nationwide follow-up survey of primary liver cancer in Japan, the cumulative survival rate for patients treated with surgical resection improved significantly in the 1990s compared to the 1980s. On the other hand, the recurrence-free survival did not improve significantly. This indicates that advancements in the treatment of recurrent HCC play a crucial role in improving long-term prognosis [181].

Limitations of These Guidelines

These guidelines have potential limitations. Despite an exhaustive review of available literature, only a small number of relevant randomized controlled trials and

meta-analyses met the criteria and could be included in the guidelines. Consequently, some of the recommendations in these guidelines are based on expert opinion and limited data. Future randomized controlled trials and meta-analyses are essential to validate these recommendations and provide stronger evidence for clinical practice.

Acknowledgments

The authors thank Dr. Yasuyuki Komiyama, Dr. Hsin-Yi Chen, and Dr. Javkhlan Maikhuu for their invaluable time and effort to the guidelines.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

Funding Sources

The authors have no funding source.

Author Contributions

Conceptualization and design: S.S., R.T., J.I.H., Z.M., L.S., J.-I.C., S.-N.L., S.Y.K., and P.W.; data curation and drafting of the manuscript: Y.A., S.-M.L., K.-W.H., H.R., P.L., U.P., M.T., T.B., and Q.D.; and review and editing of the manuscript: M.T., H.M., and L.M.C. The final version of this manuscript was approved by all the authors.

References

- Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229–63. <https://doi.org/10.3322/caac.21834>
- Sarin SK, Kumar M, Eslam M, George J, Al Mahtab M, Akbar SMF, et al. Liver diseases in the asia-pacific region: a lancet gastroenterology & hepatology commission. *Lancet Gastroenterol Hepatol.* 2020;5(2):167–228. [https://doi.org/10.1016/S2468-1253\(19\)30342-5](https://doi.org/10.1016/S2468-1253(19)30342-5)
- Mak LY, Liu K, Chirapongsathorn S, Yew KC, Tamaki N, Rajaram RB, et al. Liver diseases and hepatocellular carcinoma in the Asia-Pacific region: burden, trends, challenges and future directions. *Nat Rev Gastroenterol Hepatol.* 2024;21(12):834–51. <https://doi.org/10.1038/s41575-024-00967-4>
- Borie F, Bouvier AM, Herrero A, Faivre J, Launoy G, Delafosse P, et al. Treatment and prognosis of hepatocellular carcinoma: a population based study in France. *J Surg Oncol.* 2008;98(7):505–9. <https://doi.org/10.1002/jso.21159>
- Pompili M, Saviano A, de Matthaeis N, Cucchetti A, Ardito F, Federico B, et al. Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma 3 cm. Results of a multicenter Italian survey. *J Hepatol.* 2013; 59(1):89–97. <https://doi.org/10.1016/j.jhep.2013.03.009>
- Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet.* 2003;362(9399): 1907–17. [https://doi.org/10.1016/S0140-6736\(03\)14964-1](https://doi.org/10.1016/S0140-6736(03)14964-1)
- Bruix J, Sherman M, Practice Guidelines Committee; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology.* 2005;42(5):1208–36. <https://doi.org/10.1002/hep.20933>
- Sugiura N, Takara K, Ohto M, Okuda K, Hirooka N. Ultrasound image-guided percutaneous intratumor ethanol injection for small hepatocellular carcinoma. *Acta Hepatologica Japonica.* 1983;24:920.
- Livraghi T, Festi D, Monti F, Salmi A, Vettori C. US-guided percutaneous alcohol injection of small hepatic and abdominal tumors. *Radiology.* 1986;161(2):309–12. <https://doi.org/10.1148/radiology.161.2.3020612>
- Shiina S, Yasuda H, Muto H, Tagawa K, Unuma T, Ibukuro K, et al. Percutaneous ethanol injection in the treatment of liver neoplasms. *Am J Roentgenol.* 1987;149(5): 949–52. <https://doi.org/10.2214/ajr.149.5.949>

- 11 Seki T, Wakabayashi M, Nakagawa T, Itho T, Shiro T, Kunieda K, et al. Ultrasonically guided percutaneous microwave coagulation therapy for small hepatocellular carcinoma. *Cancer*. 1994;74(3):817–25. [https://doi.org/10.1002/1097-0142\(19940801\)74:3%3C817::aid-cnrcr2820740306%3E3.0.co;2-8](https://doi.org/10.1002/1097-0142(19940801)74:3%3C817::aid-cnrcr2820740306%3E3.0.co;2-8)
- 12 Rossi S, Di Stasi M, Buscarini E, Cavanna L, Quaretti P, Squassante E, et al. Percutaneous radiofrequency interstitial thermal ablation in the treatment of small hepatocellular carcinoma. *Cancer J Sci Am*. 1995;1(1):73–81.
- 13 Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology*. 1999;210(3):655–61. <https://doi.org/10.1148/radiology.210.3.r99fe40655>
- 14 Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924–6. <https://doi.org/10.1136/bmj.39489.470347.AD>
- 15 Brozek JL, Akl EA, Jaeschke R, Lang DM, Bossuyt P, Glasziou P, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines: Part 2 of 3. The GRADE approach to grading quality of evidence about diagnostic tests and strategies. *Allergy*. 2009;64(8):1109–16. <https://doi.org/10.1111/j.1398-9995.2009.02083.x>
- 16 Ebara M, Okabe S, Kita K, Sugiura N, Fukuda H, Yoshikawa M, et al. Percutaneous ethanol injection for small hepatocellular carcinoma: therapeutic efficacy based on 20-year observation. *J Hepatol*. 2005;43(3):458–64. <https://doi.org/10.1016/j.jhep.2005.03.033>
- 17 Jones RP, Hamann S, Malik HZ, Fenwick SW, Poston GJ, Folprecht G. Defined criteria for resectability improves rates of secondary resection after systemic therapy for liver limited metastatic colorectal cancer. *Eur J Cancer*. 2014;50(9):1590–601. <https://doi.org/10.1016/j.ejca.2014.02.024>
- 18 Singal AG, Llovet JM, Yarrow C, Mehta N, Heimbach JK, Dawson LA, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology*. 2023;78(6):1922–65. <https://doi.org/10.1097/HEP.0000000000000466>
- 19 Yoh T, Ishii T, Nishio T, Koyama Y, Ogiso S, Fukumitsu K, et al. A conceptual classification of resectability for hepatocellular carcinoma. *World J Surg*. 2023;47(3):740–8. <https://doi.org/10.1007/s00268-022-06803-7>
- 20 Kawamura Y, Akuta N, Shindoh J, Matsumura M, Okubo S, Tominaga I, et al. Newly established borderline resectable 1 (BR1) category is one of the favorable candidates for selecting the use of multidisciplinary combination therapy in patients with advanced hepatocellular carcinoma treated with systemic therapy. *Hepatol Res*. 2024;55(2):275–82. <https://doi.org/10.1111/hepr.14114>
- 21 Nakamura I, Yoh T, Nishimura T, Okuno M, Okamoto T, Sueoka H, et al. A classification model for resectability in hepatocellular carcinoma patients. *Hepatol Res*. 2024;55(1):94–105. <https://doi.org/10.1111/hepr.14108>
- 22 European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182–236. <https://doi.org/10.1016/j.jhep.2018.03.019>
- 23 Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int*. 2017;11(4):317–70. <https://doi.org/10.1007/s12072-017-9799-9>
- 24 Kondo Y, Yoshida H, Shiina S, Tateishi R, Teratani T, Omata M. Artificial ascites technique for percutaneous radiofrequency ablation of liver cancer adjacent to the gastrointestinal tract. *Br J Surg*. 2006;93(10):1277–82. <https://doi.org/10.1002/bjs.5374>
- 25 Crocetti L, Lencioni R, Debeni S, See TC, Pina CD, Bartolozzi C. Targeting liver lesions for radiofrequency ablation: an experimental feasibility study using a CT-US fusion imaging system. *Investig Radiol*. 2008;43(1):33–9. <https://doi.org/10.1097/RLI.0b013e31815597dc>
- 26 Kondo Y, Yoshida H, Tateishi R, Shiina S, Kawabe T, Omata M. Percutaneous radiofrequency ablation of liver cancer in the hepatic dome using the intrapleural fluid infusion technique. *Br J Surg*. 2008;95(8):996–1004. <https://doi.org/10.1002/bjs.6058>
- 27 Claudon M, Dietrich CF, Choi BI, Cosgrove DO, Kudo M, Nolsøe CP, et al. Guidelines and good clinical practice recommendations for Contrast Enhanced Ultrasound (CEUS) in the liver - update 2012: a WFUMB-EF-SUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. *Ultrasound Med Biol*. 2013;39(2):187–210. <https://doi.org/10.1016/j.ultrasmedbio.2012.09.002>
- 28 Maruyama H, Minami Y, Sugimoto K, Funaoka A, Numata K. Ablation manual for liver cancer. *J Med Ultrason*. 2025;52(1):27–53. <https://doi.org/10.1007/s10396-024-01499-9>
- 29 Minami Y, Aoki T, Hagiwara S, Kudo M. Tips for preparing and practicing thermal ablation therapy of hepatocellular carcinoma. *Cancers*. 2023;15(19):4763. <https://doi.org/10.3390/cancers15194763>
- 30 Surveillance group; Diagnosis group; Staging group; Surgery group; Local ablation group; TACE/TARE/HAI group, et al. Management consensus guideline for hepatocellular carcinoma: 2016 updated by the Taiwan Liver Cancer Association and the Gastroenterological Society of Taiwan. *J Formos Med Assoc*. 2018;117(5):381–403. <https://doi.org/10.1016/j.jfma.2017.09.007>
- 31 Zhou J, Sun H, Wang Z, Cong W, Wang J, Zeng M, et al. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (2019 edition). *Liver Cancer*. 2020;9(6):682–720. <https://doi.org/10.1159/000509424>
- 32 Shiina S, Tagawa K, Unuma T, Terano A. Percutaneous ethanol injection therapy for the treatment of hepatocellular carcinoma. *Am J Roentgenol*. 1990;154(5):947–51. <https://doi.org/10.2214/ajr.154.5.2157329>
- 33 Ishii H, Okada S, Nose H, Okusaka T, Yoshimori M, Takayama T, et al. Local recurrence of hepatocellular carcinoma after percutaneous ethanol injection. *Cancer*. 1996;77(9):1792–6. <https://doi.org/10.1016/j.jfma.2017.09.007>
- 34 Shiina S, Tagawa K, Unuma T, Takanashi R, Yoshiura K, Komatsu Y, et al. Percutaneous ethanol injection therapy for hepatocellular carcinoma - a histopathologic study. *Cancer*. 1991;68(7):1524–30. [https://doi.org/10.1002/1097-0142\(19911001\)68:7%3C1524::aid-cnrcr282068071%3E3.0.co;2-o](https://doi.org/10.1002/1097-0142(19911001)68:7%3C1524::aid-cnrcr282068071%3E3.0.co;2-o)
- 35 Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma or =4 cm. *Gastroenterology*. 2004;127(6):1714–23. <https://doi.org/10.1053/j.gastro.2004.09.003>
- 36 Shiina S, Teratani T, Obi S, Sato S, Tateishi R, Fujishima T, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology*. 2005;129(1):122–30. <https://doi.org/10.1053/j.gastro.2005.04.009>
- 37 Kariyama K, Nouse K, Hiraoka A, Toyoda H, Tada T, Tsuji K, et al. Treatment options for solitary hepatocellular carcinoma 5 cm: surgery vs. ablation: a multicenter retrospective study. *J Liver Cancer*. 2024;24(1):71–80. <https://doi.org/10.17998/jlc.2023.09.11>
- 38 Xu Y, Shen Q, Wang N, Liu P, Wu P, Peng Z, et al. Percutaneous microwave ablation of 5-6 cm unresectable hepatocellular carcinoma: local efficacy and long-term outcomes. *Int J Hyperthermia*. 2017;33(3):247–54. <https://doi.org/10.1080/02656736.2016.1239842>
- 39 Oh JH, Sinn DH. Multidisciplinary approach for hepatocellular carcinoma patients: current evidence and future perspectives. *J Liver Cancer*. 2024;24(1):47–56. <https://doi.org/10.17998/jlc.2024.02.27>
- 40 Tateishi R, Shiina S, Ohki T, Sato T, Masuzaki R, Imamura J, et al. Treatment strategy for hepatocellular carcinoma: expanding the indications for radiofrequency ablation. *J Gastroenterol*. 2009;44(Suppl 19):142–6. <https://doi.org/10.1007/s00535-008-2247-9>

- 41 Kudo M, Hasegawa K, Kawaguchi Y, Takayama T, Izumi N, Yamanaka N, et al. A multicenter randomized controlled trial to evaluate the efficacy of surgery versus radiofrequency ablation for small hepatocellular carcinoma (SURF trial): analysis of overall survival. *J Clin Oncol*. 2021; 39(15_Suppl 1):4093. https://doi.org/10.1200/JCO.2021.39.15_suppl.4093
- 42 Japan TILCSGo. The general rules for the clinical and pathological study of primary cancer (6th ed, Revised version). Tokyo: Kanehara (in Japanese). 2019.
- 43 Teratani T, Yoshida H, Shiina S, Obi S, Sato S, Tateishi R, et al. Radiofrequency ablation for hepatocellular carcinoma in so-called high-risk locations. *Hepatology*. 2006; 43(5):1101–8. <https://doi.org/10.1002/hep.21164>
- 44 Rhim H, Lim HK, Kim YS, Choi D, Lee WJ. Radiofrequency ablation of hepatic tumors: lessons learned from 3000 procedures. *J Gastroen Hepatol*. 2008;23(10):1492–500. <https://doi.org/10.1111/j.1440-1746.2008.05550.x>
- 45 Kondo Y, Shiina S, Tateishi R, Arano T, Uchino K, Enooku K, et al. Intrahepatic bile duct dilatation after percutaneous radiofrequency ablation for hepatocellular carcinoma: impact on patient's prognosis. *Liver Int*. 2011;31(2):197–205. <https://doi.org/10.1111/j.1478-3231.2010.02415.x>
- 46 Pillai K, Akhter J, Chua TC, Shehata M, Alzahrani N, Al-Alem I, et al. Heat sink effect on tumor ablation characteristics as observed in monopolar radiofrequency, bipolar radiofrequency, and microwave, using ex vivo calf liver model. *Medicine*. 2015; 94(9):e580. <https://doi.org/10.1097/MD.0000000000000580>
- 47 Yan G, Zhang K, Yan L, Zhang Y. Long-term survival outcomes following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal metastasis of hepatocellular carcinoma patients. *World J Surg Oncol*. 2024;22(1):144. <https://doi.org/10.1186/s12957-024-03426-1>
- 48 Leigh N, Solomon D, Pletcher E, Labow DM, Magge DR, Sarpel U, et al. Is cytoreductive surgery and hyperthermic intraperitoneal chemotherapy indicated in hepatobiliary malignancies? *World J Surg Oncol*. 2020;18(1):124. <https://doi.org/10.1186/s12957-020-01898-5>
- 49 Graf D, Vallböhmer D, Knoefel WT, Kröpil P, Antoch G, Sagor A, et al. Multimodal treatment of hepatocellular carcinoma. *Eur J Intern Med*. 2014;25(5):430–7. <https://doi.org/10.1016/j.ejim.2014.03.001>
- 50 Umakoshi N, Matsui Y, Tomita K, Uka M, Kawabata T, Iguchi T, et al. Image-guided ablation therapies for extrahepatic metastases from hepatocellular carcinoma: a review. *Cancers*. 2023;15(14):3665. <https://doi.org/10.3390/cancers15143665>
- 51 Ding X, Sun W, Chen J, Li W, Shen Y, Guo X, et al. Percutaneous radiofrequency ablation combined with transarterial chemoembolization plus sorafenib for large hepatocellular carcinoma invading the portal venous system: a prospective randomized study. *Front Oncol*. 2020;10:578633. <https://doi.org/10.3389/fonc.2020.578633>
- 52 Genda T, Ichida T, Sakisaka S, Tanaka E, Mochida S, Ueno Y, et al. Survival in patients with Child-Pugh class C cirrhosis: analysis of the liver transplant registry in Japan. *Hepatol Res*. 2017;47(11):1155–64. <https://doi.org/10.1111/hepr.12855>
- 53 Lamarque C, Segaux L, Bachellier P, Buchard B, Chermak F, Conti F, et al. Evaluation of a delayed liver transplantation strategy for patients with HCC receiving bridging therapy: the DELTA-HCC study. *J Hepatol*. 2024;81(2):278–88. <https://doi.org/10.1016/j.jhep.2024.03.019>
- 54 Xu X, Lu D, Ling Q, Wei X, Wu J, Zhou L, et al. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria. *Gut*. 2016;65(6):1035–41. <https://doi.org/10.1136/gutjnl-2014-308513>
- 55 Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334(11):693–9. <https://doi.org/10.1056/NEJM199603143341104>
- 56 Hsu CY, Lee YH, Hsia CY, Huang YH, Su CW, Lin HC, et al. Performance status in patients with hepatocellular carcinoma: determinants, prognostic impact, and ability to improve the Barcelona Clinic Liver Cancer system. *Hepatology*. 2013;57(1):112–9. <https://doi.org/10.1002/hep.25950>
- 57 O'Leary JG, Friedman LS. Predicting surgical risk in patients with cirrhosis: from art to science. *Gastroenterology*. 2007;132(4):1609–11. <https://doi.org/10.1053/j.gastro.2007.03.016>
- 58 Saklad M. Grading of patients for surgical procedures. *Anesthesiology*. 1941;2(3):281–4. <https://doi.org/10.1097/0000542-194105000-00004>
- 59 Schmolders J, Friedrich MJ, Michel R, Strauss AC, Wimmer MD, Randau TM, et al. Validation of the Charlson comorbidity index in patients undergoing revision total hip arthroplasty. *Int Orthop*. 2015;39(9):1771–7. <https://doi.org/10.1007/s00264-015-2810-y>
- 60 Thompson AR, Peters N, Lovegrove RE, Ledwidge S, Kitching A, Magee TR, et al. Cardiopulmonary exercise testing provides a predictive tool for early and late outcomes in abdominal aortic aneurysm patients. *Ann R Coll Surg Engl*. 2011;93(6):474–81. <https://doi.org/10.1308/003588411X587235>
- 61 Sato M, Tateishi R, Yasunaga H, Horiguchi H, Yoshida H, Matsuda S, et al. Mortality and morbidity of hepatectomy, radiofrequency ablation, and embolization for hepatocellular carcinoma: a national survey of 54,145 patients. *J Gastroenterol*. 2012; 47(10):1125–33. <https://doi.org/10.1007/s00535-012-0569-0>
- 62 Yamamoto H, Hashimoto H, Nakamura M, Horiguchi H, Yasunaga H. Relationship between hospital volume and hemorrhagic complication after percutaneous renal biopsy: results from the Japanese diagnosis procedure combination database. *Clin Exp Nephrol*. 2015;19(2):271–7. <https://doi.org/10.1007/s10157-014-0986-x>
- 63 Bertot LC, Sato M, Tateishi R, Yoshida H, Koike K. Mortality and complication rates of percutaneous ablative techniques for the treatment of liver tumors: a systematic review. *Eur Radiol*. 2011;21(12):2584–96. <https://doi.org/10.1007/s00330-011-2222-3>
- 64 Sato M, Tateishi R, Yasunaga H, Matsui H, Fushimi K, Ikeda H, et al. Association between hospital volume and in-hospital mortality following radiofrequency ablation for hepatocellular carcinoma. *BJS Open*. 2017;1(2):50–4. <https://doi.org/10.1002/bjs5.9>
- 65 Yasunaga H, Horiguchi H, Matsuda S, Fushimi K, Hashimoto H, Ohe K, et al. Relationship between hospital volume and operative mortality for liver resection: data from the Japanese diagnosis procedure combination database. *Hepatol Res*. 2012; 42(11):1073–80. <https://doi.org/10.1111/j.1872-034X.2012.01022.x>
- 66 Ogura K, Yasunaga H, Horiguchi H, Ohe K, Shinoda Y, Tanaka S, et al. Impact of hospital volume on postoperative complications and in-hospital mortality after musculoskeletal tumor surgery: analysis of a national administrative database. *J Bone Joint Surg Am*. 2013;95(18):1684–91. <https://doi.org/10.2106/JBJS.L.00913>
- 67 Lu LC, Shao YY, Kuo RNC, Lin ZZ, Yeh YC, Shau WY, et al. Hospital volume of percutaneous radiofrequency ablation is closely associated with treatment outcomes for patients with hepatocellular carcinoma. *Cancer*. 2013;119(6):1210–6. <https://doi.org/10.1002/cncr.27800>
- 68 Poon RT, Ng KK, Lam CM, Ai V, Yuen J, Fan ST, et al. Learning curve for radiofrequency ablation of liver tumors: prospective analysis of initial 100 patients in a tertiary institution. *Ann Surg*. 2004;239(4):441–9. <https://doi.org/10.1097/01.sla.0000118565.21298.0a>
- 69 Lee TY, Lin JT, Ho HJ, Wu MS, Wu CY. Evaluation of the effect of cumulative operator experience on hepatocellular carcinoma recurrence after primary treatment with radiofrequency ablation. *Radiology*. 2015;276(1):294–301. <https://doi.org/10.1148/radiol.15141864>
- 70 Abi-Jaoudeh N, Kruecker J, Kadoury S, Kobeiter H, Venkatesan AM, Levy E, et al. Multimodality image fusion-guided procedures: technique, accuracy, and applications. *Cardiovasc Interv Radiol*. 2012;35(5):986–98. <https://doi.org/10.1007/s00270-012-0446-5>

- 71 Choi JY, Lee JM, Sirlin CB. CT and MR imaging diagnosis and staging of hepatocellular carcinoma: Part I. Development, growth, and spread: key pathologic and imaging aspects. *Radiology*. 2014;272(3):635–54. <https://doi.org/10.1148/radiol.14132361>
- 72 Hanna RF, Miloushev VZ, Tang A, Finklestone LA, Brejt SZ, Sandhu RS, et al. Comparative 13-year meta-analysis of the sensitivity and positive predictive value of ultrasound, CT, and MRI for detecting hepatocellular carcinoma. *Abdom Radiol*. 2016;41(1):71–90. <https://doi.org/10.1007/s00261-015-0592-8>
- 73 Kim TK, Lee KH, Jang HJ, Haider MA, Jacks LM, Menezes RJ, et al. Analysis of gadobenate dimeglumine-enhanced MR findings for characterizing small (1–2-cm) hepatic nodules in patients at high risk for hepatocellular carcinoma. *Radiology*. 2011;259(3):730–8. <https://doi.org/10.1148/radiol.11101549>
- 74 Kobayashi S, Matsui O, Gabata T, Koda W, Minami T, Ryu Y, et al. Gadolinium ethoxybenzyl diethylenetriamine penta-acetic Acid-enhanced magnetic resonance imaging findings of borderline lesions at high risk for progression to hypervascular classic hepatocellular carcinoma. *J Comput Assist Tomogr*. 2011;35(2):181–6. <https://doi.org/10.1097/RCT.0b013e3182026f3b>
- 75 Ichikawa T, Sano K, Morisaka H. Diagnosis of pathologically early HCC with EOB-MRI: experiences and current consensus. *Liver Cancer*. 2014;3(2):97–107. <https://doi.org/10.1159/000343865>
- 76 Kim TK, Jang HJ. Contrast-enhanced ultrasound in the diagnosis of nodules in liver cirrhosis. *World J Gastroenterol*. 2014;20(13):3590–6. <https://doi.org/10.3748/wjg.v20.i13.3590>
- 77 D'Onofrio M, Crosara S, De Robertis R, Canestrini S, Mucelli RP. Contrast-enhanced ultrasound of focal liver lesions. *Am J Roentgenol*. 2015;205(1):W56–66. <https://doi.org/10.2214/AJR.14.14203>
- 78 Silva MA, Hegab B, Hyde C, Guo B, Buckels JA, Mirza DF. Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. *Gut*. 2008;57(11):1592–6. <https://doi.org/10.1136/gut.2008.149062>
- 79 Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD; American Association for the Study of Liver Diseases. Liver biopsy. *Hepatology*. 2009;49(3):1017–44. <https://doi.org/10.1002/hep.22742>
- 80 Tateishi R, Shiina S, Yoshida H, Teratani T, Obi S, Yamashiki N, et al. Prediction of recurrence of hepatocellular carcinoma after curative ablation using three tumor markers. *Hepatology*. 2006;44(6):1518–27. <https://doi.org/10.1002/hep.21408>
- 81 Tsai MC, Wang JH, Hung CH, Kee KM, Yen YH, Lee CM, et al. Favorable alpha-fetoprotein decrease as a prognostic surrogate in patients with hepatocellular carcinoma after radiofrequency ablation. *J Gastroenterol Hepatol*. 2010;25(3):605–12. <https://doi.org/10.1111/j.1440-1746.2009.06115.x>
- 82 Yao CC, Wang JH, Chen CH, Hung CH, Yen YH, Kee KM, et al. Short half-life of des-gamma-carboxy prothrombin is a superior factor for early prediction of outcomes of hepatocellular carcinoma treated with radiofrequency ablation. *Diagnostics*. 2023;13(4):696. <https://doi.org/10.3390/diagnostics13040696>
- 83 Koneru B, Teperman LW, Manzarbeitia C, Facciuto M, Cho K, Reich D, et al. A multi-center evaluation of utility of chest computed tomography and bone scans in liver transplant candidates with stages I and II hepatoma. *Ann Surg*. 2005;241(4):622–8. <https://doi.org/10.1097/01.sla.0000157267.27356.80>
- 84 Natsuizaka M, Omura T, Akaike T, Kuwata Y, Yamazaki K, Sato T, et al. Clinical features of hepatocellular carcinoma with extrahepatic metastases. *J Gastroenterol Hepatol*. 2005;20(11):1781–7. <https://doi.org/10.1111/j.1440-1746.2005.03919.x>
- 85 Bae HM, Lee JH, Yoon JH, Kim YJ, Heo DS, Lee HS. Protein induced by vitamin K absence or antagonist-II production is a strong predictive marker for extrahepatic metastases in early hepatocellular carcinoma: a prospective evaluation. *BMC Cancer*. 2011;11:435. <https://doi.org/10.1186/1471-2407-11-435>
- 86 Kanda M, Tateishi R, Yoshida H, Sato T, Masuzaki R, Ohki T, et al. Extrahepatic metastasis of hepatocellular carcinoma: incidence and risk factors. *Liver Int*. 2008;28(9):1256–63. <https://doi.org/10.1111/j.1478-3231.2008.01864.x>
- 87 Han S, Sung PS, Park SY, Kim JW, Hong HP, Yoon JH, et al. Local ablation for hepatocellular carcinoma: 2024 expert consensus-based practical recommendation of the Korean Liver Cancer Association. *J Liver Cancer*. 2024;24(2):131–44. <https://doi.org/10.17998/jlc.2024.08.04>
- 88 Shiina S, Tateishi R, Arano T, Uchino K, Enooku K, Nakagawa H, et al. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. *Am J Gastroenterol*. 2012;107(4):569–78. <https://doi.org/10.1038/ajg.2011.425>
- 89 Ahmed M, Brace CL, Lee FT Jr, Goldberg SN. Principles of and advances in percutaneous ablation. *Radiology*. 2011;258(2):351–69. <https://doi.org/10.1148/radiol.10081634>
- 90 Lee FT Jr, Haemmerich D, Wright AS, Mahvi DM, Sampson LA, Webster JG. Multiple probe radiofrequency ablation: pilot study in an animal model. *J Vasc Interv Radiol*. 2003;14(11):1437–42. <https://doi.org/10.1097/01.rvi.0000096771.74047.c8>
- 91 Takaki H, Yamakado K, Nakatsuka A, Fuke H, Murata K, Shiraki K, et al. Radiofrequency ablation combined with chemo-embolization for the treatment of hepatocellular carcinomas 5 cm or smaller: risk factors for local tumor progression. *J Vasc Interv Radiol*. 2007;18(7):856–61. <https://doi.org/10.1016/j.jvir.2007.04.022>
- 92 Shiina S, Teratani T, Obi S, Hamamura K, Koike Y, Omata M. Nonsurgical treatment of hepatocellular carcinoma: from percutaneous ethanol injection therapy and percutaneous microwave coagulation therapy to radiofrequency ablation. *Oncology*. 2002;62(Suppl 1):64–8. <https://doi.org/10.1159/000048278>
- 93 Lubner MG, Brace CL, Hinshaw JL, Lee FT Jr. Microwave tumor ablation: mechanism of action, clinical results, and devices. *J Vasc Interv Radiol*. 2010;21(8 Suppl 1):S192–203. <https://doi.org/10.1016/j.jvir.2010.04.007>
- 94 Facciorusso A, Di Maso M, Muscatiello N. Microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma: a systematic review and meta-analysis. *Int J Hyperthermia*. 2016;32(3):339–44. <https://doi.org/10.3109/02656736.2015.1127434>
- 95 Lee FT Jr, Chosy SG, Litttrup PJ, Warner TF, Kuhlman JE, Mahvi DM. CT-monitored percutaneous cryoablation in a pig liver model: pilot study. *Radiology*. 1999;211(3):687–92. <https://doi.org/10.1148/radiology.211.3.r99jn29687>
- 96 Kerkar S, Carlin AM, Sohn RL, Steffes C, Tyburski J, Litttrup P, et al. Long-term follow up and prognostic factors for cryotherapy of malignant liver tumors. *Surgery*. 2004;136(4):770–9. <https://doi.org/10.1016/j.surg.2004.07.001>
- 97 Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology*. 2005;41(6):1313–21. <https://doi.org/10.1002/hep.20701>
- 98 Kim YS, Lim HK, Rhim H, Lee MW, Choi D, Lee WJ, et al. Ten-year outcomes of percutaneous radiofrequency ablation as first-line therapy of early hepatocellular carcinoma: analysis of prognostic factors. *J Hepatol*. 2013;58(1):89–97. <https://doi.org/10.1016/j.jhep.2012.09.020>
- 99 Lin SM. Local ablation for hepatocellular carcinoma in taiwan. *Liver Cancer*. 2013;2(2):73–83. <https://doi.org/10.1159/000343843>
- 100 Kim JE, Kim YS, Rhim H, Lim HK, Lee MW, Choi D, et al. Outcomes of patients with hepatocellular carcinoma referred for percutaneous radiofrequency ablation at a tertiary center: analysis focused on the feasibility with the use of ultrasonography guidance. *Eur J Radiol*. 2011;79(2):e80–4. <https://doi.org/10.1016/j.ejrad.2011.03.090>
- 101 Takaki H, Yamakado K, Nakatsuka A, Yamada T, Shiraki K, Takei Y, et al. Frequency of and risk factors for complications after liver radiofrequency ablation under CT fluoroscopic guidance in 1500 sessions: single-center experience. *Am J Roentgenol*. 2013;200(3):658–64. <https://doi.org/10.2214/AJR.12.8691>

- 102 Corradini S, Alongi F, Andratschke N, Belka C, Boldrini L, Cellini F, et al. MR-guidance in clinical reality: current treatment challenges and future perspectives. *Radiat Oncol.* 2019;14(1):92. <https://doi.org/10.1186/s13014-019-1308-y>
- 103 Maybody M. An overview of image-guided percutaneous ablation of renal tumors. *Semin Interv Radiol.* 2010;27(3):261–7. <https://doi.org/10.1055/s-0030-1261784>
- 104 Rempp H, Clasen S, Pereira PL. Image-based monitoring of magnetic resonance-guided thermoablative therapies for liver tumors. *Cardiovasc Interv Radiol.* 2012; 35(6):1281–94. <https://doi.org/10.1007/s00270-011-0227-6>
- 105 Ahn SJ, Lee JM, Lee DH, Lee SM, Yoon JH, Kim YJ, et al. Real-time US-CT/MR fusion imaging for percutaneous radiofrequency ablation of hepatocellular carcinoma. *J Hepatol.* 2017;66(2):347–54. <https://doi.org/10.1016/j.jhep.2016.09.003>
- 106 Mauri G, Cova L, De Beni S, Ierace T, Tondolo T, Cerri A, et al. Real-time US-CT/MRI image fusion for guidance of thermal ablation of liver tumors undetectable with US: results in 295 cases. *Cardiovasc Interv Radiol.* 2015;38(1):143–51. <https://doi.org/10.1007/s00270-014-0897-y>
- 107 Wilson SR, Greenbaum LD, Goldberg BB. Contrast-enhanced ultrasound: what is the evidence and what are the obstacles? *Am J Roentgenol.* 2009;193(1):55–60. <https://doi.org/10.2214/Ajr.09.2553>
- 108 Lekht I, Gulati M, Nayyar M, Katz MD, Ter-Oganesyan R, Marx M, et al. Role of Contrast-Enhanced Ultrasound (CEUS) in evaluation of thermal ablation zone. *Abdom Radiol.* 2016;41(8):1511–21. <https://doi.org/10.1007/s00261-016-0700-4>
- 109 Jiang C, Feng Q, Zhang Z, Qiang Z, Du A, Xu L, et al. Radiofrequency ablation versus laparoscopic hepatectomy for hepatocellular carcinoma: a systematic review and meta-analysis. *World J Surg Oncol.* 2024;22(1): 188. <https://doi.org/10.1186/s12957-024-03473-8>
- 110 Wang X, Sun X, Lei Y, Pei J, Ma K, Feng K, et al. Open radiofrequency ablation combined with splenectomy and pericardial devascularization vs. Liver transplantation for hepatocellular carcinoma patients with portal hypertension and hypersplenism: a case-matched comparative study. *J Invest Surg.* 2023;36(1):1–7. <https://doi.org/10.1080/08941939.2022.2130482>
- 111 Tateishi R, Shiina S, Teratani T, Obi S, Sato S, Koike Y, et al. Percutaneous radiofrequency ablation for hepatocellular carcinoma. An analysis of 1000 cases. *Cancer.* 2005;103(6):1201–9. <https://doi.org/10.1002/cncr.20892>
- 112 Ishikawa T, Hasegawa I, Hirose H, Honmou T, Sakai N, Igarashi T, et al. An investigation of popping during radiofrequency ablation after lenvatinib administration for hepatocellular carcinoma. *Vivo.* 2023;37(2):836–40. <https://doi.org/10.21873/invivo.13150>
- 113 Spiliotis J, Nikolaou G, Kopanakis N, Vasiliadou D, Terra A, Efstathiou E. Hepatocellular carcinoma peritoneal metastasis: role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). *Gulf J Oncolog.* 2017;1(24):20–3.
- 114 Iida H, Aihara T, Ikuta S, Yamanaka N. Effectiveness of impedance monitoring during radiofrequency ablation for predicting popping. *World J Gastroenterol.* 2012;18(41):5870–8. <https://doi.org/10.3748/wjg.v18.i41.5870>
- 115 Chiang J, Hynes KA, Bedoya M, Brace CL. A dual-slot microwave antenna for more spherical ablation zones: ex vivo and in vivo validation. *Radiology.* 2013;268(2):382–9. <https://doi.org/10.1148/radiol.13122128>
- 116 Lubner MG, Ziemlewicz TJ, Hinshaw JL, Lee FT, Sampson LA, Brace CL. Creation of short microwave ablation zones: in vivo characterization of single and paired modified triaxial antennas. *J Vasc Interv Radiol.* 2014;25(10):1633–40. <https://doi.org/10.1016/j.jvir.2014.06.032>
- 117 Alonzo M, Bos A, Bennett S, Ferral H. The Emprint™ ablation system with Thermosphere™ technology: one of the newer next-generation microwave ablation technologies. *Semin Interv Radiol.* 2015;32(4):335–8. <https://doi.org/10.1055/s-0035-1564811>
- 118 ASGE Standards of Practice Committee; Acosta RD, Abraham NS, Chandrasekhara V, Chathadi KV, Early DS, et al. The management of antithrombotic agents for patients undergoing GI endoscopy. *Gastrointest Endosc.* 2016;83(1):3–16. <https://doi.org/10.1016/j.gie.2015.09.035>
- 119 Davidson JC, Rahim S, Hanks SE, Patel IJ, Tam AL, Walker TG, et al. Society of interventional radiology consensus guidelines for the periprocedural management of thrombotic and bleeding risk in patients undergoing percutaneous image-guided interventions-Part I: review of anticoagulation agents and clinical considerations: endorsed by the Canadian association for interventional radiology and the cardiovascular and interventional radiological society of europe. *J Vasc Interv Radiol.* 2019;30(8):1155–67. <https://doi.org/10.1016/j.jvir.2019.04.016>
- 120 Goto E, Tateishi R, Shiina S, Masuzaki R, Enooku K, Sato T, et al. Hemorrhagic complications of percutaneous radiofrequency ablation for liver tumors. *J Clin Gastroenterol.* 2010;44(5):374–80. <https://doi.org/10.1097/MCG.0b013e3181b7ed76>
- 121 Tateishi R, Seike M, Kudo M, Tamai H, Kawazoe S, Katsube T, et al. A randomized controlled trial of lusutrombopag in Japanese patients with chronic liver disease undergoing radiofrequency ablation. *J Gastroenterol.* 2019;54(2):171–81. <https://doi.org/10.1007/s00535-018-1499-2>
- 122 Terrault N, Chen YC, Izumi N, Kayali Z, Mitrut P, Tak WY, et al. Avatrombopag before procedures reduces need for platelet transfusion in patients with chronic liver disease and thrombocytopenia. *Gastroenterology.* 2018;155(3):705–18. <https://doi.org/10.1053/j.gastro.2018.05.025>
- 123 Yeung LYY, Sarani B, Weinberg JA, McBeth PB, May AK. Surgeon's guide to anticoagulant and antiplatelet medications part two: antiplatelet agents and perioperative management of long-term anticoagulation. *Trauma Surg Acute Care Open.* 2016;1(1): e000022. <https://doi.org/10.1136/tsaco-2016-000022>
- 124 Blacker DJ, Wijedicks EF, McClelland RL. Stroke risk in anticoagulated patients with atrial fibrillation undergoing endoscopy. *Neurology.* 2003;61(7):964–8. <https://doi.org/10.1212/01.wnl.0000086817.54076.eb>
- 125 Garcia DA, Regan S, Henault LE, Upadhyay A, Baker J, Othman M, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch Intern Med.* 2008;168(1):63–9. <https://doi.org/10.1001/archinternmed.2007.23>
- 126 Jaffe TA, Raiff D, Ho LM, Kim CY. Management of anticoagulant and antiplatelet medications in adults undergoing percutaneous interventions. *Am J Roentgenol.* 2015;205(2):421–8. <https://doi.org/10.2214/AJR.14.13342>
- 127 Choi D, Lim HK, Kim MJ, Kim SJ, Kim SH, Lee WJ, et al. Liver abscess after percutaneous radiofrequency ablation for hepatocellular carcinomas: frequency and risk factors. *Am J Roentgenol.* 2005;184(6): 1860–7. <https://doi.org/10.2214/ajr.184.6.01841860>
- 128 Livraghi T, Solbiati L, Meloni MF, Gazelle GS, Halpern EF, Goldberg SN. Treatment of focal liver tumors with percutaneous radiofrequency ablation: complications encountered in a multicenter study. *Radiology.* 2003;226(2):441–51. <https://doi.org/10.1148/radiol.2262012198>
- 129 Rhim H, Yoon KH, Lee JM, Cho Y, Cho JS, Kim SH, et al. Major complications after radio-frequency thermal ablation of hepatic tumors: spectrum of imaging findings. *Radiographics.* 2003;23(1):123–36; discussion 34–6. <https://doi.org/10.1148/rg.231025054>
- 130 Shibata T, Yamamoto Y, Yamamoto N, Maetani Y, Shibata T, Ikai I, et al. Cholangitis and liver abscess after percutaneous ablation therapy for liver tumors: incidence and risk factors. *J Vasc Interv Radiol.* 2003; 14(12):1535–42. <https://doi.org/10.1097/01.rvi.0000099532.29957.4f>
- 131 Bhatia SS, Spector S, Echenique A, Froud T, Suthar N, Lawson I, et al. Is antibiotic prophylaxis for percutaneous radiofrequency ablation (RFA) of primary liver tumors necessary? Results from a single-center experience. *Cardiovasc Interv Radiol.* 2015;38(4):922–8. <https://doi.org/10.1007/s00270-014-1020-0>

- 132 McWilliams JP, Yamamoto S, Raman SS, Loh CT, Lee EW, Liu DM, et al. Percutaneous ablation of hepatocellular carcinoma: current status. *J Vasc Interv Radiol*. 2010; 21(8 Suppl 1):S204–13. <https://doi.org/10.1016/j.jvir.2009.11.025>
- 133 Venkatesan AM, Kundu S, Sacks D, Wallace MJ, Wojak JC, Rose SC, et al. Practice guidelines for adult antibiotic prophylaxis during vascular and interventional radiology procedures. Written by the standards of practice committee for the society of interventional radiology and endorsed by the cardiovascular interventional radiological society of europe and Canadian interventional radiology association [corrected]. *J Vasc Interv Radiol*. 2010;21(11):1611–31; quiz 31. <https://doi.org/10.1016/j.jvir.2010.07.018>
- 134 McDermott VG, Schuster MG, Smith TP. Antibiotic prophylaxis in vascular and interventional radiology. *Am J Roentgenol*. 1997;169(1):31–8. <https://doi.org/10.2214/ajr.169.1.9207497>
- 135 Gervais DA, Goldberg SN, Brown DB, Soulen MC, Millward SF, Rajan DK, et al. Society of Interventional Radiology position statement on percutaneous radiofrequency ablation for the treatment of liver tumors. *J Vasc Interv Radiol*. 2009;20(1):3–8. <https://doi.org/10.1016/j.jvir.2008.09.007>
- 136 Nakagomi R, Tateishi R, Mikami S, Wake T, Kinoshita MN, Nakatsuka T, et al. Infectious complications related to radiofrequency ablation of liver tumors: the role of antibiotics. *PLoS One*. 2021;16(11):e0259641. <https://doi.org/10.1371/journal.pone.0259641>
- 137 de Baère T, Risse O, Kuoch V, Dromain C, Sengel C, Smayra T, et al. Adverse events during radiofrequency treatment of 582 hepatic tumors. *Am J Roentgenol*. 2003; 181(3):695–700. <https://doi.org/10.2214/ajr.181.3.1810695>
- 138 Iida H, Aihara T, Ikuta S, Yamanaka N. Risk of abscess formation after liver tumor radiofrequency ablation: a review of 8 cases with a history of enterobiliary anastomosis. *Hepatogastroenterology*. 2014;61(135):1867–70.
- 139 Crocetti L, de Baere T, Lencioni R. Quality improvement guidelines for radiofrequency ablation of liver tumours. *Cardiovasc Interv Radiol*. 2010;33(1):11–7. <https://doi.org/10.1007/s00270-009-9736-y>
- 140 Elias D, Di Pietroantonio D, Gachot B, Menegon P, Hakime A, De Baere T. Liver abscess after radiofrequency ablation of tumors in patients with a biliary tract procedure. *Gastroenterol Clin Biol*. 2006; 30(6–7):823–7. [https://doi.org/10.1016/s0399-8320\(06\)73327-9](https://doi.org/10.1016/s0399-8320(06)73327-9)
- 141 Fonseca AZ, Santin S, Gomes LG, Waisberg J, Ribeiro MA Jr. Complications of radiofrequency ablation of hepatic tumors: frequency and risk factors. *World J Hepatol*. 2014;6(3):107–13. <https://doi.org/10.4254/wjh.v6.i3.107>
- 142 Forner A, Ayuso C, Varela M, Rimola J, Hessheimer AJ, de Lope CR, et al. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? *Cancer*. 2009;115(3):616–23. <https://doi.org/10.1002/cncr.24050>
- 143 Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*. 2010;30(1): 52–60. <https://doi.org/10.1055/s-0030-1247132>
- 144 Westwood M, Joore M, Grutters J, Redekop K, Armstrong N, Lee K, et al. Contrast-enhanced ultrasound using SonoVue® (sulphur hexafluoride microbubbles) compared with contrast-enhanced computed tomography and contrast-enhanced magnetic resonance imaging for the characterisation of focal liver lesions and detection of liver metastases: a systematic review and cost-effectiveness analysis. *Health Technol Assess*. 2013;17(16):1–243. <https://doi.org/10.3310/hta17160>
- 145 Ahmed M, Solbiati L, Brace CL, Breen DJ, Callstrom MR, Charboneau JW, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria: a 10-year update. *Radiology*. 2014;273(1): 241–60. <https://doi.org/10.1148/radiol.14132958>
- 146 Teng W, Liu KW, Lin CC, Jeng WJ, Chen WT, Sheen IS, et al. Insufficient ablative margin determined by early computed tomography may predict the recurrence of hepatocellular carcinoma after radiofrequency ablation. *Liver Cancer*. 2015;4(1): 26–38. <https://doi.org/10.1159/000343877>
- 147 Koda M, Tokunaga S, Fujise Y, Kato J, Matono T, Sugihara T, et al. Assessment of ablative margin after radiofrequency ablation for hepatocellular carcinoma; comparison between magnetic resonance imaging with ferucarbotran and enhanced CT with iodized oil deposition. *Eur J Radiol*. 2012;81(7):1400–4. <https://doi.org/10.1016/j.ejrad.2011.03.004>
- 148 Koda M, Tokunaga S, Miyoshi K, Kishina M, Fujise Y, Kato J, et al. Ablative margin status by magnetic resonance imaging with ferucarbotran in radiofrequency ablation for hepatocellular carcinoma can predict local tumor progression. *J Gastroenterol*. 2013; 48(11):1283–92. <https://doi.org/10.1007/s00535-012-0747-0>
- 149 Yoon JH, Lee JM, Klotz E, Woo H, Yu MH, Joo I, et al. Prediction of local tumor progression after Radiofrequency Ablation (RFA) of hepatocellular carcinoma by assessment of ablative margin using pre-RFA MRI and post-RFA CT registration. *Korean J Radiol*. 2018;19(6):1053–65. <https://doi.org/10.3348/kjr.2018.19.6.1053>
- 150 Zhou P, Kudo M, Minami Y, Chung H, Inoue T, Fukunaga T, et al. What is the best time to evaluate treatment response after radiofrequency ablation of hepatocellular carcinoma using contrast-enhanced sonography? *Oncology*. 2007;72(Suppl 1):92–7. <https://doi.org/10.1159/000111713>
- 151 Hirooka M, Koizumi Y, Tanaka T, Sunago K, Nakamura Y, Watanabe T, et al. Radiofrequency ablation covering the entire tumor blood drainage area improves survival in hepatocellular carcinoma. *Hepatol Commun*. 2021;5(7):1300–9. <https://doi.org/10.1002/hep4.1703>
- 152 Khalilzadeh O, Baerlocher MO, Shyn PB, Connolly BL, Devane AM, Morris CS, et al. Proposal of a new adverse event classification by the society of interventional radiology standards of practice committee. *J Vasc Interv Radiol*. 2017; 28(10):1432–7.e3. <https://doi.org/10.1016/j.jvir.2017.06.019>
- 153 Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009;250(2):187–96. <https://doi.org/10.1097/SLA.0b013e3181b13ca2>
- 154 Baerlocher MO, Nikolic B, Sze DY. Adverse event classification: clarification and validation of the society of interventional radiology specialty-specific system. *J Vasc Interv Radiol*. 2023;34(1):1–3. <https://doi.org/10.1016/j.jvir.2022.10.011>
- 155 Obi S, Shiratori Y, Shiina S, Hamamura K, Kato N, Imamura M, et al. Early detection of haemobilia associated with percutaneous ethanol injection for hepatocellular carcinoma. *Eur J Gastroenterol Hepatol*. 2000; 12(3):285–90. <https://doi.org/10.1097/00042737-200012030-00005>
- 156 Sasahira N, Tada M, Yoshida H, Tateishi R, Shiina S, Hirano K, et al. Extrahepatic biliary obstruction after percutaneous tumour ablation for hepatocellular carcinoma: aetiology and successful treatment with endoscopic papillary balloon dilatation. *Gut*. 2005;54(5):698–702. <https://doi.org/10.1136/gut.2003.038331>
- 157 Ohnishi T, Yasuda I, Nishigaki Y, Hayashi H, Otsuji K, Mukai T, et al. Intraductal chilled saline perfusion to prevent bile duct injury during percutaneous radiofrequency ablation for hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2008;23(8 Pt 2): e410–5. <https://doi.org/10.1111/j.1440-1746.2007.05091.x>
- 158 Seror O. Ablative therapies: advantages and disadvantages of radiofrequency, cryotherapy, microwave and electroporation methods, or how to choose the right method for an individual patient? *Diagn Interv Imaging*. 2015;96(6):617–24. <https://doi.org/10.1016/j.diii.2015.04.007>
- 159 Wake T, Tateishi R, Nakagomi R, Fujiwara N, Kinoshita MN, Nakatsuka T, et al. Ischemic complications after percutaneous radiofrequency ablation of liver tumors: liver volume loss and recovery. *Hepatol Res*. 2019;49(4):453–61. <https://doi.org/10.1111/hepr.13302>

- 160 Imamura J, Tateishi R, Shiina S, Goto E, Sato T, Ohki T, et al. Neoplastic seeding after radiofrequency ablation for hepatocellular carcinoma. *Am J Gastroenterol.* 2008; 103(12):3057–62. <https://doi.org/10.1111/j.1572-0241.2008.02153.x>
- 161 Francica G. Needle track seeding after radiofrequency ablation for hepatocellular carcinoma: prevalence, impact, and management challenge. *J Hepatocell Carcinoma.* 2017;4:23–7. <https://doi.org/10.2147/JHC.S106558>
- 162 Livraghi T, Lazzaroni S, Meloni F, Solbiati L. Risk of tumour seeding after percutaneous radiofrequency ablation for hepatocellular carcinoma. *Br J Surg.* 2005;92(7):856–8. <https://doi.org/10.1002/bjs.4986>
- 163 Hocquet A, Aubé C, Rode A, Cartier V, Sutter O, Manichon AF, et al. Comparison of no-touch multi-bipolar vs. monopolar radiofrequency ablation for small HCC. *J Hepatol.* 2017;66(1):67–74. <https://doi.org/10.1016/j.jhep.2016.07.010>
- 164 Shiina S, Tateishi R, Arano T, Uchino K, Enooku K, Nakagawa H, et al. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. *Am J Gastroenterol.* 2012;107(4): 569–78. <https://doi.org/10.1038/ajg.2011.425>
- 165 Tsimiligras DI, Bagante F, Moris D, Hyer JM, Sahara K, Paredes AZ, et al. Recurrence patterns and outcomes after resection of hepatocellular carcinoma within and beyond the barcelona clinic liver cancer criteria. *Ann Surg Oncol.* 2020;27(7):2321–31. <https://doi.org/10.1245/s10434-020-08452-3>
- 166 Han S, Sung PS, Park SY, Kim JW, Hong HP, Yoon JH, et al. Local ablation for hepatocellular carcinoma: 2024 expert consensus-based practical recommendations of the Korean liver cancer association. *Korean J Radiol.* 2024;25(9):773–87. <https://doi.org/10.3348/kjr.2024.0550>
- 167 Nakashima O, Sugihara S, Kage M, Kojiro M. Pathomorphologic characteristics of small hepatocellular carcinoma: a special reference to small hepatocellular carcinoma with indistinct margins. *Hepatology.* 1995; 22(1):101–5. <https://doi.org/10.1002/hep.1840220116>
- 168 Bruix J, Takayama T, Mazzaferro V, Chau GY, Yang J, Kudo M, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* 2015;16(13):1344–54. [https://doi.org/10.1016/S1470-2045\(15\)00198-9](https://doi.org/10.1016/S1470-2045(15)00198-9)
- 169 Qin S, Chen M, Cheng AL, Kaseb AO, Kudo M, Lee HC, et al. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial. *Lancet.* 2023;402(10415):1835–47. [https://doi.org/10.1016/S0140-6736\(23\)01796-8](https://doi.org/10.1016/S0140-6736(23)01796-8)
- 170 Yopp A, Kudo M, Chen M, Cheng AL, Kaseb AO, Lee HC, et al. LBA39 Updated efficacy and safety data from IMbrave050: phase III study of adjuvant atezolizumab (atezo) + bevacizumab (bev) vs active surveillance in Patients (pts) with resected or ablated high-risk Hepatocellular Carcinoma (HCC). *Ann Oncol.* 2024;35:S1230. <https://doi.org/10.1016/j.annonc.2024.08.2279>
- 171 Goyal L, Vogel A, Zhu A, Cheng A-L, Yau T, Zhou J, et al. P024 KEYNOTE-937 trial in progress: adjuvant pembrolizumab for hepatocellular carcinoma and complete radiologic response after surgical resection or local ablation. *Gut.* 2021;A22.1. <https://doi.org/10.1136/gutjnl-2021-basl.33>
- 172 Knox J, Cheng A, Cleary S, Galle P, Kokudo N, Lencioni R, et al. A phase 3 study of durvalumab with or without bevacizumab as adjuvant therapy in patients with hepatocellular carcinoma at high risk of recurrence after curative hepatic resection or ablation: EMERALD-2. *Ann Oncol.* 2019;30:iv59–60. <https://doi.org/10.1093/annonc/mdz155.216>
- 173 Exposito MJ, Akce M, Alvarez J, Assenat E, Balart L, Baron A, et al. Abstract No. 526 CheckMate-9DX: phase 3, randomized, double-blind study of adjuvant nivolumab vs placebo for patients with hepatocellular carcinoma (HCC) at high risk of recurrence after curative resection or ablation. *J Vasc Intervent Radiol.* 2019;30(3): S227–8. <https://doi.org/10.1016/j.jvir.2018.12.607>
- 174 Minami T, Tateishi R, Shiina S, Nakagomi R, Kondo M, Fujiwara N, et al. Comparison of improved prognosis between hepatitis B- and hepatitis C-related hepatocellular carcinoma. *Hepatol Res.* 2015;45(10):E99–107. <https://doi.org/10.1111/hepr.12468>
- 175 Fukumoto T, Minami T, Moriyama M, Yamada T, Wake T, Kinoshita MN, et al. Improved prognosis of hepatitis C-related hepatocellular carcinoma in the era of direct-acting antivirals. *Hepatol Commun.* 2022;6(9):2496–512. <https://doi.org/10.1002/hep4.2010>
- 176 Zhang W, Song TQ, Zhang T, Wu Q, Kong DL, Li Q, et al. Adjuvant interferon for early or late recurrence of hepatocellular carcinoma and mortality from hepatocellular carcinoma following curative treatment: a meta-analysis with comparison of different types of hepatitis. *Mol Clin Oncol.* 2014; 2(6):1125–34. <https://doi.org/10.3892/mco.2014.386>
- 177 Rodríguez M, González-Diéguez ML, Varela M, Cadahía V, Andrés-Vizán SM, Mesa A, et al. Impact of alcohol abstinence on the risk of hepatocellular carcinoma in patients with alcohol-related liver cirrhosis. *Am J Gastroenterol.* 2021;116(12):2390–8. <https://doi.org/10.14309/ajg.0000000000001399>
- 178 Shirai D, Shinkawa H, Takemura S, Tanaka S, Amano R, Kimura K, et al. Impact of alcohol abstinence on survival after hepatic resection for hepatocellular carcinoma in patients with alcohol-related liver disease. *Ann Med Surg.* 2021;68:102644. <https://doi.org/10.1016/j.amsu.2021.102644>
- 179 Okusaka T, Okada S, Ueno H, Ikeda M, Shimada K, Yamamoto J, et al. Satellite lesions in patients with small hepatocellular carcinoma with reference to clinicopathologic features. *Cancer.* 2002;95(9):1931–7. <https://doi.org/10.1002/cncr.10892>
- 180 Zhang C, Gao R, Guo S, Ning C, Li A, Wang X, et al. Anatomic resection versus radiofrequency ablation with an ablative margin ≥ 1.0 cm for solitary small hepatocellular carcinoma measuring 3 cm: Comparison of long-term outcomes using propensity score matching analysis. *Eur J Radiol.* 2022;155:110498. <https://doi.org/10.1016/j.ejrad.2022.110498>
- 181 Taura K, Ikai I, Hatano E, Fujii H, Uyama N, Shimahara Y. Implication of frequent local ablation therapy for intrahepatic recurrence in prolonged survival of patients with hepatocellular carcinoma undergoing hepatic resection: an analysis of 610 patients over 16 years old. *Ann Surg.* 2006;244(2):265–73. <https://doi.org/10.1097/01.sla.0000217921.28563.55>