cancers

MDPI

Review

Locoregional Therapy Approaches for Hepatocellular Carcinoma: Recent Advances and Management Strategies

Mina S. Makary [1,*], Umang Khandpur [1], Jordan M. Cloyd [2], Khalid Mumtaz [3] and Joshua D. Dowell [4]

1 Division of Vascular and Interventional Radiology, Department of Radiology, The Ohio State University Wexner Medical Center, Columbus, OH 43210, USA; umang.khandpur@osumc.edu
2 Division of Surgical Oncology, Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH 43210, USA; jordan.cloyd@osumc.edu
3 Division of Hepatology and Gastroenterology, Department of Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, OH 43210, USA; khalid.mumtaz@osumc.edu
4 Northwest Radiology, Indianapolis, IN 46290, USA; josh.dowell@gmail.com
* Correspondence: mina.makary@osumc.edu; Tel.: +1-614-293-8000

Received: 22 June 2020; Accepted: 14 July 2020; Published: 15 July 2020

Abstract: Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and third leading cause of cancer-related mortality worldwide. While surgical resection and transplantation are the standard first-line treatments for early-stage HCC, most patients do not fulfill criteria for surgery. Fortunately, catheter-directed and percutaneous locoregional approaches have evolved as major treatment modalities for unresectable HCC. Improved outcomes have been achieved with novel techniques which can be employed for diverse applications ranging from curative-intent for small localized tumors, to downstaging or bridging to resection and transplantation for early and intermediate disease, and locoregional control and palliation for advanced disease. This review explores recent advances in liver-directed techniques for HCC including bland transarterial embolization, chemoembolization, radioembolization, and ablative therapies, with a focus on patient selection, procedural technique, periprocedural management, and outcomes.

Keywords: hepatocellular carcinoma; transarterial embolization; chemoembolization; radioembolization; ablation; immunotherapy; TAE; TACE; TARE; SIRT

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy [1]. The prognosis depends on a multitude of clinical, laboratory, and radiologic parameters, but the overall 5-year survival rate for liver cancer remains below 20% [2–4]. Traditional management options for patients with HCC include surgical resection and orthotopic liver transplantation (OLT) [4]. However, in a recent comparative study of more than 8000 HCC cases worldwide, less than 10% of patients fulfilled preoperative criteria for resection [5]. For patients who are not ideal surgical candidates, novel liver-directed strategies are being utilized to treat appropriately selected patients, and in some cases achieve curative effect. Other goals of locoregional approaches include tumor cytoreduction for downstaging or "bridging" to maintain eligibility for transplantation, hypertrophy of hepatic tissue to increase liver function for future major resection, and palliation [6]. Over the past two decades, management approaches that increase overall survival and reduce adverse effects for a wide range of patients have increased with the incorporation of new image-guided techniques and enhanced targeted pharmaco- and radiotherapeutics [7,8]. This review discusses the recent advances in locoregional

therapy for HCC including transarterial embolization (TAE), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and ablative therapies (Table 1).

Table 1. Summary of Locoregional Therapy Options for Hepatocellular Carcinoma.

Modality	Techniques	Clinical Utility	Risks	Benefits
TAE	Particulate or liquid embolic agents	Disease control (BCLC B) and bridging/downstaging to transplant (BCLC A, B).	PES, liver failure, liver abscess/biloma	Improves OS vs. best supportive care. Avoids chemotherapy toxicity. Less expensive than TACE.
TACE	Conventional emulsified chemotherapeutic agent (c-TACE) or drug-eluting beads (DEB-TACE)	Same as TAE. Can combine with portal vein embolization before resection.	PES, liver failure, liver abscess/biloma	Improves OS vs. best supportive care. Simultaneous embolic and chemotherapeutic effects.
TARE	Yttrium-90 radioisotope loaded onto microspheres	Same as TAE/TACE. RS for nonsurgical early stage patients (BCLC 0, A). Can also be used in portal vein thrombosis.	RILD, radiation-induced pneumonitis, PES, liver failure, liver abscess/biloma	Higher quality of life/TTP vs. TACE. RS outcomes comparable to curative-intent treatments (e.g., resection and ablation) at 5 years
Ablation	Microwaves, radiofrequency alternating current, laser, cooling	Early stage HCC < 2–3 cm in non-surgical candidates (BCLC 0, A). Improved outcomes for tumors 3–5 cm when combined with TACE.	PAS, bleeding, adjacent organ injury	Similar outcomes as resection for tumors < 3 cm.

PES—postembolization syndrome. PAS—postablation syndrome. OS—overall survival. RILD—radiation-induced liver disease. CP—Childs-Pugh class. RS—radiation segmentectomy. TTP—time to progression.

2. Transarterial Embolization

2.1. Procedure

Intraarterial therapies are centered on the principle that hepatocellular tumors mainly recruit hepatic artery branches for growth whereas normal liver parenchyma receives dual blood flow primarily via the portal vein [7,9,10]. The goal of transarterial embolization (TAE) is to restrict hepatic artery blood flow to vessels supplying a tumor. This causes ischemia-induced cellular membrane disruption and oncosis resulting in ischemic cell death [11]. Both particulate and liquid materials can be used as embolic agents [12]. TAE is also known as "bland" embolization because the particles themselves are not equipped with additional functions such as chemotherapy or radiation.

During the procedure, identification of key hepatic artery branches supplying the tumor is crucial to maximize treatment effectiveness and avoid collateral ischemia to adjacent liver parenchyma. The targeted tumoral arterial supply is then treated with an embolic agent, most commonly microparticles ranging from 40 to 120 μm in size [13]. Depending on the disease distribution within the liver, the treatment approach can vary including lobar treatment for multifocal disease or targeted segmental treatment for unifocal disease [14]. The procedure is commonly performed in the inpatient setting under moderate sedation, although some patients may require general anesthesia [15–17].

The most common associated risk is that of postembolization syndrome (PES), the severity and duration of which might be correlated with the degree of healthy tissue ischemia and underlying liver function [18,19]. Additional risks include hepatic decompensation, renal injury, biliary injury, infection (abscess), and rarely pulmonary embolization via undetected arteriovenous shunts within the tumor and/or small embolic particle size [20–22]. Lastly, non-target embolization of extrahepatic vascular supply such as the cystic artery to the gallbladder is another risk [23]. Meticulous technique including

the use of novel intraprocedural technologies such as cone-beam CT is utilized to ensure complete tumoral coverage while avoiding non-target embolization [24].

2.2. Periprocedural Management

Prior to the procedure, patients may be administered prophylactic antibiotics for coverage of gram-negative enteric microbes. Watchmaker et al. evaluated the need for infection prophylaxis before hepatic embolization and found that sterile technique of the procedure itself is enough to perform the procedure safely in patients with an intact sphincter of Oddi [25]; however, in patients with previous biliary or bowel interventions leading to altered sphincter function, the risk of postprocedural infection is significantly higher [26]. Thus, antibiotic administration and bowel preparation may be beneficial in these patients. For example, Khan et al. found that 400 mg of oral moxifloxacin given 3 days before and 17 days after hepatic transarterial therapy in patients at high risk for hepatic abscess formation was effective in preventing this complication [27]. Another protocol involves levofloxacin and metronidazole daily for 2 days preceding the procedure and continued for 2 weeks after combined with a bowel regimen of neomycin plus erythromycin at 1, 2 and 11 pm of the day before embolization [28]. Other preprocedural considerations include hydration status, antiemesis, antihistamines, and steroids. Some institutions use dexamethasone and hydrocortisone.

After the procedure, adequate hydration, pain and nausea control, and stable hepatic function tests are key criteria for discharge. PES is the most common complication of embolotherapy and presents with right upper quadrant pain, nausea, fatigue, fever, hypertransaminasemia, and hyperbilirubinemia [18,19,29]. It usually occurs within 72 h of the procedure but is self-limiting in most cases, and completely resolves in 7 to 10 days [29]. Debate exists regarding routine administration of postprocedural antibiotics, and this should be case-dependent until more robust data are available [30]. Specifically, patients with any history of biliary abnormality, bilio-enteric intervention, or dysfunctional sphincter of Oddi should likely continue antibiotics for 2 weeks [27]. Appropriate periprocedural anticoagulation management guidelines should be observed [31,32]. Follow-up imaging and laboratory investigations are conducted 4–6 weeks later and then every 3–6 months thereafter to evaluate treatment success as well as monitor disease progression [10,33]. CT or MRI can be used to confirm tumor necrosis [14].

2.3. Patient Selection

Generally, TAE is reserved for non-surgical candidates with liver-dominant disease. Patient selection for all locoregional therapies including TAE involves clinical and serologic evaluation of the patient including functional status, liver function tests, and clinical indices such as the ALBI (Albumin-Bilirubin), CP (Child-Pugh), MELD (Model for End-stage Liver Disease), and ECOG (Eastern Cooperative Oncology Group) performance status scores for patient stratification and assessment [34–36]. In addition to its role in the diagnosis of HCC, preprocedural imaging is paramount for evaluation of the vascular anatomy, access site patency, and ensuring patency of the portal vein [37]. Studies have demonstrated that patients in class B of the Barcelona Clinic Liver Cancer staging classification system (BCLC) derive the most benefit from this procedure followed by BCLC class C [10,38]. Patients in BCLC class A may undergo TAE to maintain eligibility for transplantation per the Milan and UCSF criteria [38,39]. The contraindications for TAE include decompensated cirrhosis (Child-Pugh B8 or higher), significantly reduced portal venous flow, creatinine clearance < 30 mL/min, high tumor burden, severe comorbidities, untreated esophageal varices, and elevated liver function markers [40]. Figure 1 shows possible treatment strategies stratified by BCLC class.

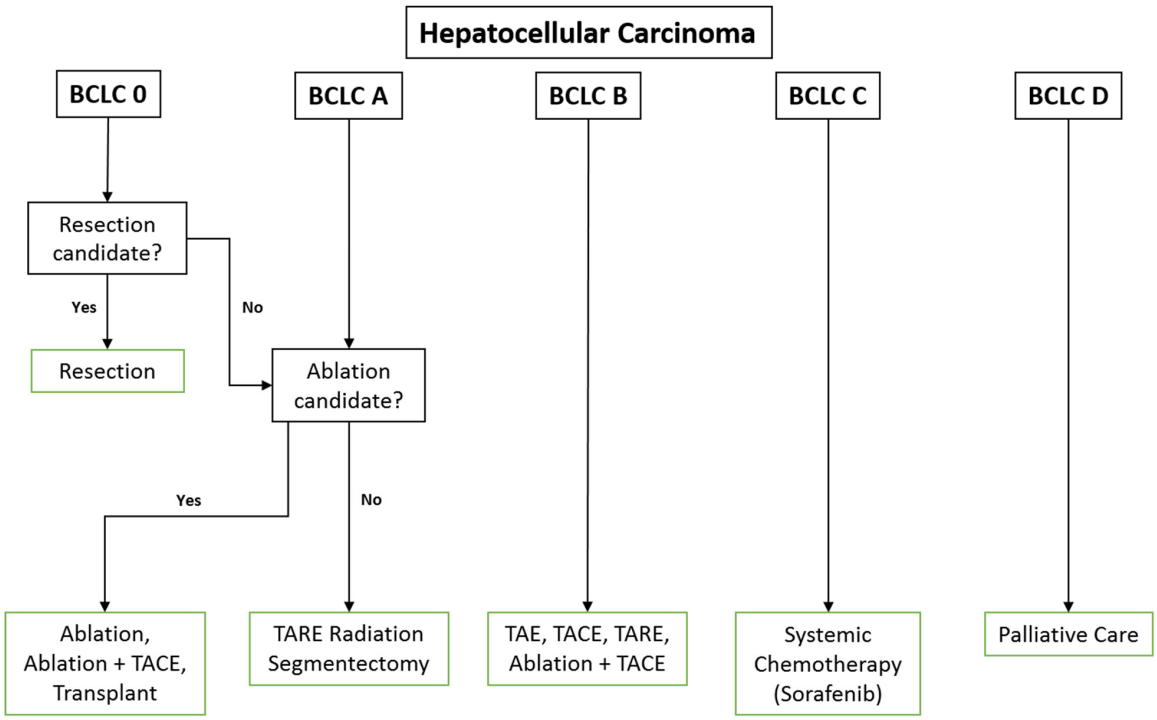

Figure 1. Treatment options for hepatocellular carcinoma stratified by BCLC class. Note that any locoregional approach can be used to maintain or downstage to transplant eligibility. Contraindications to resection include significant portal hypertension, hyperbilirubinemia, multiple nodules, and comorbidities. Contraindications to ablation include lesion > 5 cm, > 4 nodules, and anatomic infeasibility.

2.4. Prognostic Factors and Outcomes

Various clinical staging systems are currently in use for predicting overall survival, progression-free survival, and adverse events after intra-arterial therapy for HCC. Examples include the Okuda system, Cancer of the Liver Italian Program (CLIP) score, Hong Kong Liver Cancer (HKLC) staging system, and the Barcelona Clinic Liver Cancer (BCLC) classification scheme [41,42]. Among specific prognosticators, tumor burden, hepatic reserve, extrahepatic spread, and performance status are most strongly associated with overall survival in HCC [41,43–45]. The gold standard for assessing response to treatment is the 2010 modified Response Evaluation Criteria in Solid Tumors (mRECIST) [46].

Although outcomes comparing locoregional therapy to best supportive care are better characterized for TACE than for bland embolization, embolotherapy as a whole confers significant survival benefit compared to best supportive care [10,47]. Tsochatzis et al. [43] published results from a meta-analysis of six randomized controlled trials comparing TAE with TACE, and none of them revealed significant differences in overall survival [43,48]. Lee et al. [49] summarized evidence from three studies revealing no significant differences in 3-year survival rates, adverse events, or RECIST responses [49–52]. Interestingly, Kluger et al. [50] found that TAE patients were significantly less likely to require retreatment before transplantation than TACE patients. Finally, a 2009 multicenter RCT that compared drug-eluting bead transarterial chemoembolization (DEB-TACE) to TAE found significant improvement in time to progression in the DEB-TACE group, but no change in overall survival [53]. Since induced ischemia from embolotherapy could be the dominant contributor to tumor cell death and bland embolization does spare the cost of chemotherapy and its unfavorable toxicity profile, [54,55] TAE should continue to be offered to appropriately selected patients.

3. Transarterial Chemoembolization

3.1. Procedure and Periprocedural Management

Similar to bland embolization, transarterial chemoembolization (TACE) involves occlusion of tumor feeding vessels. In contrast to TAE, TACE permits the delivery of targeted chemotherapy with the embolic therapy. In the conventional approach (c-TACE), a lipiodolized chemotherapeutic agent is administered into a feeding artery followed by administration of an embolic agent. This theoretically allows for (1) increased pharmacologic concentration and (2) increased effect duration due to decreased washout [7,10]. However, there is considerable variation in technique and drug mixture across institutions, and pharmacokinetic analysis revealed that plasma concentration after c-TACE may approximate systemic chemotherapy drug levels [56]. A newer approach using drug-eluting beads (DEB-TACE) provides better standardization and arguably less hepatotoxicity [57,58]. In DEB-TACE, drug-infused microspheres release chemotherapy in a sustained fashion and serve an embolic role are injected. Doxorubicin is the most widely cited chemotherapeutic agent, but others use a solution adding mitomycin C and cisplatin in c-TACE [59].

Periprocedural evaluation and management is identical to that for TAE (see Section 2.2.). Antimicrobial prophylaxis is recommended as is periprocedural clinical stabilization and laboratory monitoring. PES is common after TACE occurring in up to 80% of patients [60]. Pharmacological treatments include intra-arterial lidocaine, steroids, 5-HT3R antagonists, and antibiotics. Antibiotics seem to be of little clinical utility in managing fever [61], but intra-arterial lidocaine and/or dexamethasone have improved analgesic requirements and hospital length of stay [62,63].

3.2. Patient Selection

The most appropriate candidate for TACE is one with intermediate-stage HCC (BCLC class B, Child-Pugh B or better) without portal vein thrombosis or extrahepatic spread who is ineligible for surgical resection or transplantation [10,64,65]. Numerous studies confirm that TACE can significantly impact survival if patients are selected on the aforementioned factors. For example, Burrel et al. [66] demonstrated a median survival up to 47.7 months after TACE for BCLC B patients with preserved liver function (no higher than Child-Pugh B7), no vascular invasion, extrahepatic spread, nor significant functional impairment [7,66].

BCLC A (early-stage) or BCLC 0 (very early-stage) patients with a solitary nodule and minimal to no underlying liver disease should undergo surgical resection which boasts a favorable prognosis [7]. However, TACE may be indicated in these patients especially if they are ineligible for surgery/ablation or require a "bridge" to maintain transplant eligibility per the Milan/UCSF criteria [38]. TACE can also be combined with unilateral portal vein embolization (PVE) to induce hypertrophy of the contralateral future liver remnant before hepatectomy of the diseased liver [67]. In patients who have portal vein invasion, chemoembolization plus radiotherapy may be beneficial if hepatic compensation is adequate [68,69]. For advanced-stage patients (BCLC C), TACE may still be useful in combination with the systemic drug sorafenib, but definitive evidence is lacking [70,71]. Thus, TACE provides a versatile tool in the arsenal of treatment options for HCC patients.

Absolute contraindications for TACE include decompensated cirrhosis (Child-Pugh B8 or higher), severely reduced portal vein flow, creatinine clearance <30 mL/min, extensive bilobar tumor involvement, and technical infeasibility [40]. Relative contraindications include high tumor burden, severe comorbidities, untreated esophageal varices, and elevated liver function markers [64]. Generally, lobar and selective/segmental TACE may still be performed with a total bilirubin level up to 3 and 4 mg/dL, respectively [72]. In Child-Pugh class C patients, the American Association for the Study of Liver Disease (AASLD) guidelines recommend against TACE if serum bilirubin is above 3 mg/dL or there is main portal vein thrombosis unless segmental treatment is possible [73,74]. However, Luo et al. noted significant survival improvement in patients with either segmental-branch or first-border branch portal vein thrombosis [75].

3.3. Prognostic Factors and Outcomes

As mentioned previously, there are several prognostic models for predicting survival in HCC. The Child-Pugh score may be the most accurate for patients treated with TACE [76]. To determine prognosis for patients undergoing retreatment with TACE (and to decide whether there would be additional benefit after two TACE treatments), the Assessment for Retreatment with TACE (ART) scoring system was developed [8,77].

While the outcomes for both c-TACE and DEB-TACE are more favorable than best supportive care or other conservative management in appropriately selected patients [59,78–83], the superiority of c-TACE versus DEB-TACE remains somewhat controversial. At least 12 studies have investigated superiority between the two techniques, but a significant difference in overall survival remains unconfirmed [6,84]. However, the well-known PRECISION V study did demonstrate significant increase in tumor response, reduction in severe hepatotoxicity, and lower doxorubicin-related adverse events in the DEB-TACE group compared with c-TACE for certain patient populations (Child-Pugh B, ECOG 1, bilobar disease, recurrent disease) [81].

The idea of combining locoregional therapy with systemic chemotherapy has been explored. Sorafenib, the first-line treatment for advanced stage (BCLC class C) HCC patients as established by the SHARP trial [85], is both an inhibitor of the growth and proliferation Raf pathway in tumor cells as well as an inhibitor of the angiogenic VEGFR/PDGFR pathway in endothelial cells [86]. The compensatory angiogenesis from TACE-induced hypoxia could theoretically be attenuated from the antiangiogenic functions of sorafenib. Unfortunately, studies like the SPACE trial that randomized patients into DEB-TACE with sorafenib or DEB-TACE with placebo have not shown significant improvements in time to progression [70].

4. Transarterial Radioembolization

4.1. Procedure and Periprocedural Management

Selective internal radiotherapy (SIRT) for HCC can be performed with transarterial radioembolization (TARE) [10]. This procedure primarily provides its therapeutic effect via radiation instead of embolization [87]. Currently, a radioisotope of yttrium, 90Y, is either loaded onto or embedded within microspheres that are injected into a hepatic artery branch feeding tumor cells [6]. 90Y undergoes beta decay and irradiates surrounding tumor, ultimately damaging repair mechanisms and facilitating cell death [88].

Preprocedural angiographic mapping and evaluation are usually conducted 1–2 weeks prior so that variant anatomy and intrahepatic portosystemic shunts can be identified. Technetium-99m labeled macroaggregated albumin (99mTc-MAA) is used with single-photon emission computed tomography (SPECT) to determine the hepatopulmonary fraction that, if high, may increase the likelihood of radiation pneumonitis after TARE [10,88]. Some patients with advanced hepatobiliary malignancies are prescribed gemcitabine. This chemotherapeutic agent should be held for at least 4 weeks prior to TARE and 2–4 weeks afterwards due to its radiosensitizing effects which increase the risk of radiation-induced liver disease (RILD) [89–91]. The actual TARE procedure is performed in similar fashion to other locoregional endovascular approaches with targeting of the tumoral disease in a lobar or segmental fashion [92,93]. Treatment effect is observed slightly later than with TACE or TAE, so follow-up imaging and labs usually take place 12 weeks after TARE [94].

4.2. Patient Selection

The indications and contraindications for TARE are generally similar to those for the other embolotherapies. A total bilirubin up to 2 mg/dL is acceptable while encephalopathy and prior radiation to the liver are not [93]. A notable contraindication to TARE is significant (>20%) hepatopulmonary or hepato-enteric shunting as unintended radiation to the lungs or gastrointestinal tract may be serious [6]. However, TARE offers a unique application in patients with portal vein thrombosis given the reduced

embolic effect [94,95]. Several series have demonstrated the safety of 90Y-SIRT in cases where tumor infiltrated either a main or lobar portal vein branch [96,97]. Although the BCLC guidelines recommend chemoembolization as first-line therapy for class B patients, expert recommendations from AASLD and NCCN do not posit radioembolization's inferiority in the list of suitable treatments for unresectable intermediate-stage HCC patients [98,99]. For BCLC 0 and A patients, radiation segmentectomy with intraarterial 90Y-SIRT is safe and effective [100,101]. Neoadjuvant radiation lobectomy is also a safe and effective option to increase the function of the contralateral future liver remnant in patients who plan to undergo resection and avoids the alternative risks of portal vein embolization [102,103]. Finally, just like the other embolotherapies, TARE can be used to maintain or encourage transplant/resection eligibility through bridging as well as enhance overall survival in BCLC C patients [104,105].

4.3. Prognostic Factors and Outcomes

Prognosis after TARE is most associated with baseline patient stage (BCLC, Child-Pugh), performance status (ECOG), tumor burden, and extrahepatic disease [10]. According to a 2016 meta-analysis by Lobo et al. [106], overall survival and complication rates for TARE are similar to those of TACE, but the prospective trial PREMIERE demonstrated longer time to progression (TTP) for TARE [107]. Another randomized trial showed higher quality of life scores for TARE patients vs. TACE [108]. In a prospective study, Salem et al. reported excellent outcomes including an overall survival of 47.3 months for Child-Pugh A patients and 27 months in Child-Pugh B patients [109]. With more contemporary approaches such as radiation segmentectomy, response rates, tumor control, and survival outcomes have been comparable to curative-intent treatments (e.g., resection, transplantation, ablation) at 5 years [109,110].

When compared to sorafenib among advanced-stage patients, Hilgard et al. [111] actually demonstrated a survival benefit for TARE (10.7 vs. 16.4 months, respectively). Two randomized controlled trials revealed higher tumor response rates and fewer adverse events with TARE vs. sorafenib for unresectable, treatment-naïve Child-Pugh A patients, although overall survival was similar between the two [112,113]. Considering the side effects of systemic sorafenib therapy, TARE may be an attractive option for these patients [113].

5. Ablation

5.1. Procedure and Periprocedural Management

Ablative techniques for HCC include radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation (CA), irreversible electroporation (IRE), laser-induced interstitial thermotherapy (LITT), and high-intensity focused ultrasound (HIFU). The choice of technique is often based on individual and institutional expertise, but historically the most commonly utilized technology was RFA. In recent years, MWA has gained traction as an alternative modality [114]. CA has also been used regularly in the past, although its use has diminished due to serious complications including cryogenic shock, acute renal failure secondary to myohemoglobinuria, coagulopathy, and cardiac dysrhythmias [115,116].

In RFA, the tumor is heated to high temperatures via frictional heat in water molecules produced by an electrode, which can be with or without hooks, to increase and maximize heat production in the tissue [117]. The ablation zone consists of the original space occupied by the tumor plus a 5-10 mm boundary of ablated adjacent liver parenchyma [118]. Over time, fibrosis causes retraction of the necrotic tissue. A homogenous, non-enhancing, well-circumscribed area is consistent with successful radiographic response [118,119]. Conversely, MWA uses an electrode to deliver thermal energy-induced cellular destruction. MWA may be suitable for larger tumors than RFA is indicated for and highly perfused regions [120]. Moreover, MWA can target multiple tumor sites simultaneously, yields shorter time to threshold temperature, achieves larger ablation treatment zones, results in better delineated ablation zone borders, and is less prone to heat-sink effects from adjacent vascular structures [114,120,121]. While RFA yields smaller ablation zones, less uniform borders, and is more

prone to heat-sink, it does offer the advantage of avoiding energy delivery to tracking structures such as bile ducts or large vessels [122].

All ablative modalities utilize imaging guidance/monitoring during the procedures such as computed tomography (CT) or ultrasound (US), or a combination. New modalities such as contrast-enhanced US (CEUS) have also been utilized as well as novel fused imaging technologies to predict treatment zones [123,124]. Follow-up imaging with CT or MRI every 3–6 months for the first two years with serum alpha fetoprotein (AFP) monitoring is recommended by the NCCN [99]. Serious complications include injury to adjacent organs e.g., diaphragm, gastrointestinal tract, gallbladder [125]. Similar to PES, a postablation syndrome (PAS) may occur with analogous clinical presentation and self-limiting nature [126].

5.2. Patient Selection

Surgical resection or orthotopic liver transplantation is the mainstay of treatment for very early and early-stage (BCLC 0, A) HCC patients [127]. However, most patients are disqualified from surgical intervention due to significant comorbidities, portal hypertension, poor hepatic function, cardiovascular comorbidities, inability to tolerate general anesthesia, or lesion location [5,128]. As such, ablation offers a potentially curative option for these patients with early HCC with some studies demonstrating equivalent survival outcomes to resection even with poorer baseline liver function [129–131]. Ablation with curative intent is an effective alternative to resection, particularly for tumors smaller than 3 cm [114]. For tumors 3–5 cm in diameter, the combination of TACE and ablation demonstrate good outcomes albeit not curative [132–135]. Caution must be exercised when lesions are close to major vessels, biliary structures, diaphragm, and other intra-abdominal organs. Hydrodissection, or artificial ascites, wherein 5% dextrose in water (D5W) fluid is injected between the tumor area and adjacent extrahepatic organ to prevent transmission of thermal energy, helps to separate the tumor and protects against unintentional organ injury [122,136,137]. RFA and MWA can also be considered in advanced stage patients (BCLC C) for downstaging as a bridge to transplantation and in intermediate stage patients (BCLC B) when combined with TACE [98].

5.3. Prognostic Factors and Outcomes

The independent predictors of survival after RFA/MWA from several multivariate analyses were Child-Pugh class, tumor size, and tumor number [138–142]. The overall survival outcomes between RFA and resection are not significantly different at 1 and 3 years [143–145], but MWA may see lower local tumor progression rates than RFA for tumors > 5 cm or > 3 HCC nodules [120]. Complication rates are similar between MWA and RFA [146]. Although there is a relative paucity of high-impact studies pertaining to cryoablation, an RCT by Wang et al. found higher 3-year survival rates (but similar 5-year survival rates) and lower local progression rates (for tumors > 3 cm) in the cryoablation group vs. RFA group [147].

Combination therapy of RFA with chemoembolization has been investigated and has shown improved locoregional control compared to either RFA or TACE alone for BCLC A and B patients [148]. RFA helps to decrease total cellular resistance so that chemotherapy in TACE can yield relatively higher concentrations proximal to the tumor vascular bed at the periphery of the ablated tissue [149]. If TACE is conducted first, peripherally situated tumor cells are preferentially destroyed so that later RFA treatment, typically performed within 4 weeks, undergoes less vascular heat sinking and yields more complete central necrosis particularly for lesions > 3 cm [150]. The optimum parameters for both mechanisms require further exploration. MWA plus TACE has also shown to be effective for lesions between 3–5 cm [133–135]. It should be noted that adjuvant sorafenib therapy following ablation or resection is not effective per results from the STORM trial [151].

6. Future Directions

New developments in drug-eluting bead technology have allowed the loading of tyrosine kinase inhibitors (e.g., sunitinib, vandetanib) and anti-VEGF antibodies (e.g., bevacizumab) in preclinical stages with promising results in halting tumor growth [152–155]. Experiments in immunotherapy such as oncolytic viruses, dendritic cells, and immune checkpoint inhibitors (against CTLA-4, PD-1, PD-L1) are also underway [156,157]. In fact, nivolumab, a PD-1 inhibitor (already FDA approved for sorafenib-refractory HCC) is being directly compared to sorafenib for advanced stage HCC patients [158, 159]. Several combination strategies of innate and adaptive immunotherapies with RFA, MWA, and cryoablation are also be investigated in vitro and in animal models of HCC [160]. Lastly, personalized therapies and prognosticators are being appraised in human subjects research. Several putative histological, epigenetic, and metabolomic biomarkers are being studied to individualize treatments for HCC patients [161]. For example, micro-RNA-122 (miRNA-122) is a tumor suppressor molecule that is often severely reduced in hepatocytes linked to hepatocellular oncogenesis. Therapies that involve reintroduction of miRNA-122 to stabilize cell cycle regulation are being scrutinized for effectiveness and safety [162,163]. Advances in artificial intelligence (AI) are also being applied to HCC management. In addition to improved intra-procedural imaging guidance, AI has been used to construct prediction models for response to locoregional treatment [164,165]. While the role of interventional-based liver-directed techniques continues to expand, additional research is needed regarding the application of these therapies in a neoadjuvant or adjuvant setting to improve the multidisciplinary care of HCC and reduce recurrence rates [166].

7. Conclusions

HCC is the most common primary liver malignancy and the third leading cause of cancer-related mortality worldwide [1]. Although overall survival for this complex disease has improved in recent years, prognosis is still poor particularly for advanced and terminal-stage patients [1]. Surgical extirpation and transplantation remain the curative standard of care for early-stage patients, but there is an expanding role of locoregional therapies in the management of HCC including curative-intent, disease control, bridging to transplant and resection, downstaging patients, and palliation. With the addition of targeted chemotherapy and radiotherapy delivery, the inventory of transarterial hepatic embolization techniques offers major benefit in appropriately selected candidates. Ablative procedures using high frequency alternating currents or microwaves have also developed as excellent therapies for nonsurgical patients, achieving curative results in early-stage patients. Although advanced-stage patients are currently limited to systemic therapy, novel advances in immunotherapy and personalized biomolecular signatures of HCC are paving the way for more robust strategies to tackle this disease.

Author Contributions: All authors have contributed to the writing of this review article, and have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Kim, H.S.; El-serag, H.B. The epidemiology of hepatocellular Carcinoma in the USA. *Curr. Gastroenterol. Rep.* **2019**, *21*, 17. [CrossRef] [PubMed]
2. Howlader, N.; Noone, A.M.; Krapcho, M.; Miller, D.; Brest, A.; Yu, M.; Ruhl, J.; Tatalovich, Z.; Mariotto, A.; Lewis, D.R.; et al. (Eds.) *EEER Cancer Statistics Review, 1975–2016*; National Cancer Institute: Bethesda, MD, USA, 2018. Available online: https://seer.cancer.gov/csr/1975_2016/ (accessed on 1 July 2020).
3. Onaca, N.; Davis, G.L.; Jennings, L.W.; Goldstein, R.M.; Klintmalm, G.B. Improved results of transplantation for hepatocellular carcinoma: A report from the International registry of hepatic tumors in liver transplantation. *Liver Transpl.* **2009**, *15*, 574–580. [CrossRef] [PubMed]

4. Byam, J.; Renz, J.; Millis, J.M. Liver transplantation for hepatocellular carcinoma. *Hepatobiliary Surg. Nutr.* **2013**, *2*, 22–30. [PubMed]
5. Roayaie, S.; Jibara, G.; Tabrizian, P.; Park, J.; Yang, J.; Yan, L.; Schwartz, M.; Han, G.; Izzo, F.; Chen, M.; et al. The role of hepatic resection in the treatment of hepatocellular cancer. *Hepatology* **2015**, *62*, 440–451. [CrossRef]
6. Inchingolo, R.; Posa, A.; Mariappan, M.; Spiliopoulos, S. Locoregional treatments for hepatocellular carcinoma: Current evidence and future directions. *World J. Gastroenterol.* **2019**, *25*, 4614–4628. [CrossRef]
7. Kis, B.; El-Haddad, G.; Sheth, R.A.; Parikh, N.S.; Ganguli, S.; Shyn, P.B.; Choi, J.; Brown, K.T. Liver-directed therapies for Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma. *Cancer Control* **2017**, *24*. [CrossRef]
8. Mokdad, A.A.; Singal, A.G.; Yopp, A.C. Advances in local and systemic therapies for Hepatocellular cancer. *Curr. Oncol. Rep.* **2016**, *18*, 9. [CrossRef]
9. Breedis, C.; Young, G. The blood supply of neoplasms in the liver. *Am. J. Pathol.* **1954**, *30*, 969–977.
10. Gbolahan, O.B.; Schacht, M.A.; Beckley, E.W.; Laroche, T.P.; O'neil, B.H.; Pyko, M. Locoregional and systemic therapy for hepatocellular carcinoma. *J. Gastrointest. Oncol.* **2017**, *8*, 215–228. [CrossRef]
11. Brown, K.T.; Nevins, A.B.; Getrajdman, G.I.; Brody, L.A.; Kurtz, R.C.; Fong, Y.; Blumgart, L.H. Particle embolization for hepatocellular Carcinoma. *J. Vasc. Interv. Radiol.* **1998**, *9*, 822–828. [CrossRef]
12. Vaidya, S.; Tozer, K.R.; Chen, J. An overview of embolic agents. *Semin. Intervent. Radiol.* **2008**, *25*, 204–215. [CrossRef] [PubMed]
13. Rand, T.; Loewe, C.; Schoder, M.; Schmook, M.T.; Peck-Radosavljevic, M.; Kettenbach, J.; Wolf, F.; Schneider, B.; Lammer, J. Arterial embolization of unresectable hepatocellular carcinoma with use of microspheres, lipiodol, and cyanoacrylate. *Cardiovasc. Intervent. Radiol.* **2005**, *28*, 313–318. [CrossRef] [PubMed]
14. Gaba, R.C.; Lokken, R.P.; Hickey, R.M.; Lipnik, A.J.; Lewandowski, R.J.; Salem, R.; Brown, D.B.; Walker, T.G.; Silberzweig, J.E.; Baerlocher, M.O.; et al. Quality improvement guidelines for transarterial chemoembolization and embolization of hepatic malignancy. *J. Vasc. Interv. Radiol.* **2017**, *28*, 1210–1223.e3. [CrossRef]
15. Zheng, N.; Wei, X.; Zhang, D.; Chai, W.; Che, M.; Wang, J.; Du, B. Hepatic resection or transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus. *Medicine* **2016**, *95*, e3959. [CrossRef] [PubMed]
16. Coldwell, D.M.; Loper, K.A. Regional anesthesia for hepatic arterial embolization. *Radiology* **1989**, *172*, 1039–1040. [CrossRef] [PubMed]
17. Makary, M.S.; Kapke, J.; Yildiz, V.; Pan, X.; Dowell, J.D. Conventional versus drug-eluting bead transarterial chemoembolization for neuroendocrine tumor liver metastases. *J. Vasc. Interv. Radiol.* **2016**, *27*, 1298–1304. [CrossRef]
18. Wigmore, S.J.; Redhead, D.N.; Thomson, B.N.J.; Currie, E.J.; Parks, R.W.; Madhavan, K.K.; Garden, O.J. Postchemoembolisation syndrome—Tumour necrosis or hepatocyte injury? *Br. J. Cancer* **2003**, *89*, 1423–1427. [CrossRef]
19. Paye, F.; Farges, O.; Dahmane, M.; Vilgrain, V.; Flejou, J.F.; Belghiti, J. Cytolysis following chemoembolization for hepatocellular carcinoma. *Br. J. Surg.* **1999**, *86*, 176–180. [CrossRef]
20. Chan, A.O.; Yuen, M.F.; Hui, C.K.; Tso, W.K.; Lai, C.L. A prospective study regarding the complications of transcatheter intraarterial lipiodol chemoembolization in patients with hepatocellular carcinoma. *Cancer* **2002**, *94*, 1747–1752. [CrossRef]
21. Garwood, E.R.; Fidelman, N.; Hoch, S.E.; Kerlan, R.K.; Yao, F.Y. Morbidity and mortality following transarterial liver chemoembolization in patients with hepatocellular carcinoma and synthetic hepatic dysfunction. *Liver Transpl.* **2013**, *19*, 164–173. [CrossRef]
22. Wu, G.C.; Perng, W.C.; Chen, C.W.; Chian, C.F.; Peng, C.K.; Su, W.L. Acute respiratory distress syndrome after transcatheter arterial chemoembolization of hepatocellular carcinomas. *Am. J. Med. Sci.* **2009**, *338*, 357–360. [CrossRef] [PubMed]
23. Shah, R.P.; Brown, K.T. Hepatic arterial embolization complicated by acute cholecystitis. *Semin. Intervent. Radiol.* **2011**, *28*, 252–257. [CrossRef] [PubMed]
24. Cornelis, F.H.; Borgheresi, A.; Petre, E.N.; Santos, E.; Solomon, S.B.; Brown, K. Hepatic arterial embolization using cone beam CT with tumor feeding vessel detection software: Impact on hepatocellular Carcinoma response. *Cardiovasc. Intervent. Radiol.* **2018**, *41*, 104–111. [CrossRef] [PubMed]

25. Watchmaker, J.M.; Lipnik, A.J.; Fritsche, M.R.; Baker, J.C.; Mouli, S.K.; Geevarghese, S.; Banovac, F.; Omary, R.A.; Brown, D.B. Are prophylactic antibiotics necessary prior to transarterial chemoembolization for hepatocellular carcinoma in patients with native biliary anatomy? *J. Surg. Oncol.* **2018**, *117*, 1312–1317. [CrossRef]
26. Song, S.-Y.; Chung, J.W.; Han, J.K.; Lim, H.G.; Koh, Y.H.; Park, J.H.; Lee, H.-S.; Kim, C.Y. Liver abscess after transcatheter oily chemoembolization for hepatic tumors: Incidence, predisposing factors, and clinical outcome. *J. Vasc. Interv. Radiol.* **2001**, *12*, 313–320. [CrossRef]
27. Khan, W.; Sullivan, K.L.; McCann, J.W.; Gonsalves, C.F.; Sato, T.; Eschelman, D.J.; Brown, D.B. Moxifloxacin prophylaxis for chemoembolization or embolization in patients with previous biliary interventions: A pilot study. *AJR Am. J. Roentgenol.* **2011**, *197*, W343–W345. [CrossRef]
28. Patel, S.; Tuite, C.M.; Mondschein, J.I.; Soulen, M.C. Effectiveness of an aggressive antibiotic regimen for chemoembolization in patients with previous biliary intervention. *J. Vasc. Interv. Radiol.* **2006**, *17*, 1931–1934. [CrossRef]
29. Castells, A.; Bruix, J.; Ayuso, C.; Bru, C.; Montayà, X.; Boix, L.; Rodés, J. Transarterial embolization for hepatocellular carcinoma. Antibiotic prophylaxis and clinical meaning of postembolization fever. *J. Hepatol.* **1995**, *22*, 410–415. [CrossRef]
30. Brown, D.B.; Geschwind, J.F.; Soulen, M.C.; Millward, S.F.; Sacks, D. Society of Interventional Radiology position statement on chemoembolization of hepatic malignancies. *J. Vasc. Interv. Radiol.* **2006**, *17*, 217–223. [CrossRef]
31. Pudusseri, A.; Spyropoulos, A.C. Management of anticoagulants in the periprocedural period for patients with cancer. *J. Natl. Compr. Cancer Netw.* **2014**, *12*, 1713–1720. [CrossRef]
32. Patel, I.J.; Davidson, J.C.; Nikolic, B.; Salazar, G.M.M.; Schwartzberg, M.S.; Walker, T.G.; Saad, W.A. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. *J. Vasc. Interv. Radiol.* **2012**, *23*, 727–736. [CrossRef]
33. Haste, P.; Johnson, M.S. Transarterial Chemoembolization. In *IR Playbook*; Keefe, N., Haskal, Z., Park, A., Angle, J., Eds.; Springer: Cham, Switzerland, 2018.
34. Johnson, P.J.; Berhane, S.; Kagebayashi, C.; Satomura, S.; Teng, M.; Reeves, H.L.; O'Beirne, J.; Fox, R.; Skowronska, A.; Palmer, D.; et al. Assessment of liver function in patients with hepatocellular carcinoma: A new evidence-based approach-the ALBI grade. *J. Clin. Oncol.* **2015**, *33*, 550–558. [CrossRef] [PubMed]
35. Levy, I.; Sherman, M. Staging of hepatocellular Carcinoma: Assessment of the CLIP, Okuda, and Child-Pugh staging systems in a cohort of 257 patients in Toronto. *Gut* **2002**, *50*, 881–885. [CrossRef] [PubMed]
36. Guerrini, G.P.; Pinelli, D.; Marini, E.; Corno, V.; Guizzetti, M.; Zambelli, M.; Aluffi, A.; Lincini, L.; Fagiuoli, S.; Lucianetti, A.; et al. Value of HCC-MELD Score in patients with Hepatocellular Carcinoma undergoing liver transplantation. *Prog. Transpl.* **2018**, *28*, 63–69. [CrossRef] [PubMed]
37. Sieghart, W.; Hucke, F.; Peck-Radosavljevic, M. Transarterial chemoembolization: Modalities, indication, and patient selection. *J. Hepatol.* **2015**, *62*, 1187–1195. [CrossRef]
38. Kishore, S.; Friedman, T.; Madoff, D.C. Update on embolization therapies for hepatocellular Carcinoma. *Curr. Oncol. Rep.* **2017**, *19*, 40. [CrossRef]
39. Hodavance, M.S.; Vikingstad, E.M.; Griffin, A.; Pabon-Ramos, W.M.; Berg, C.L.; Suhocki, P.V.; Kim, C.Y. Effectiveness of transarterial embolization of Hepatocellular Carcinoma as a bridge to transplantation. *J. Vasc. Interv. Radiol.* **2016**, *27*, 39–45. [CrossRef]
40. Raoul, J.-L.; Sangro, B.; Forner, A.; Mazzaferro, V.; Piscaglia, F.; Bolondi, L.; Lencioni, R. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: Available evidence and expert opinion on the use of transarterial chemoembolization. *Cancer Treat. Rev.* **2011**, *37*, 212–220. [CrossRef]
41. Grieco, A.; Pompili, M.; Caminiti, G.; Miele, L.; Covino, M.; Alfei, B.; Rapaccini, G.L.; Gasbarrini, G. Prognostic factors for survival in patients with early-intermediate hepatocellular carcinoma undergoing non-surgical therapy: Comparison of Okuda, CLIP, and BCLC staging systems in a single Italian centre. *Gut* **2005**, *54*, 411–418. [CrossRef]
42. Yau, T.; Tang, V.Y.; Yao, T.J.; Fan, S.T.; Lo, C.M.; Poon, R.T. Development of Hong Kong liver cancer staging system with treatment stratification for patients with hepatocellular carcinoma. *Gastroenterology* **2014**, *146*, 1691–1700.e3. [CrossRef]

43. Tsochatzis, E.A.; Fatourou, E.; O'beirne, J.; Meyer, T.; Burroughs, A.K. Transarterial chemoembolization and bland embolization for hepatocellular carcinoma. *World J. Gastroenterol.* **2014**, *20*, 3069–3077. [CrossRef] [PubMed]
44. Llovet, J.M.; Brú, C.; Bruix, J. Prognosis of hepatocellular carcinoma: The BCLC staging classification. *Semin Liver Dis* **1999**, *19*, 329–338. [CrossRef] [PubMed]
45. Ni, J.-Y.; Kong, J.; Sun, H.-L.; Chen, Y.-T.; Luo, J.-H.; Wang, W.-D.; Chen, N.; Jiang, X.-Y.; Xu, L. Prognostic factors for survival after transarterial chemoembolization combined with sorafenib in the treatment of BCLC Stage B and C hepatocellular Carcinomas. *Acad. Radiol.* **2018**, *25*, 423–429. [CrossRef] [PubMed]
46. Kim, M.N.; Kim, B.K.; Han, K.H.; Kim, S.U. Evolution from WHO to EASL and mRECIST for hepatocellular carcinoma: Considerations for tumor response assessment. *Expert Rev. Gastroenterol. Hepatol.* **2015**, *9*, 335–348. [CrossRef]
47. Llovet, J.M.; Real, M.I.; Montaña, X.; Planas, R.; Coll, S.; Aponte, J.; Ayuso, C.; Sala, M.; Muchart, J.; Sola, R.; et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial. *Lancet* **2002**, *359*, 1734–1739. [CrossRef]
48. Meyer, T.; Kirkwood, A.; Roughton, M.; Beare, S.; Tsochatzis, E.A.; Yu, D.; Davies, N.; Williams, E.; Pereira, S.P.; Hochhauser, D.; et al. A randomised phase II/III trial of 3-weekly cisplatin-based sequential transarterial chemoembolisation vs. embolisation alone for hepatocellular carcinoma. *Br. J. Cancer* **2013**, *108*, 1252–1259. [CrossRef]
49. Lee, E.W.; Khan, S. Recent advances in transarterial embolotherapies in the treatment of hepatocellular carcinoma. *Clin. Mol. Hepatol.* **2017**, *23*, 265–272. [CrossRef]
50. Kluger, M.D.; Halazun, K.J.; Barroso, R.T.; Fox, A.N.; Olsen, S.K.; Madoff, D.C.; Siegel, A.B.; Weintraub, J.L.; Sussman, J.; Jr, R.S.B.; et al. Bland embolization versus chemoembolization of hepatocellular carcinoma before transplantation. *Liver Transpl.* **2014**, *20*, 536–543. [CrossRef]
51. Massarweh, N.N.; Davila, J.A.; El-Serag, H.B.; Duan, Z.; Temple, S.; May, S.B.; Sada, Y.H.; Anaya, D.A. Transarterial bland versus chemoembolization for hepatocellular carcinoma: Rethinking a gold standard. *J. Surg. Res.* **2016**, *200*, 552–559. [CrossRef]
52. Brown, K.T.; Do, R.K.; Gonen, M.; Covey, A.M.; Getrajdman, G.I.; Sofocleous, C.T.; Jarnagin, W.R.; D'Angelica, M.I.; Allen, P.J.; Erinjeri, J.P.; et al. Randomized trial of hepatic artery embolization for hepatocellular Carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. *J. Clin. Oncol.* **2016**, *34*, 2046–2053. [CrossRef]
53. Malagari, K.; Pomoni, M.; Kelekis, A.; Pomoni, A.; Dourakis, S.; Spyridopoulos, T.; Moschouris, H.; Emmanouil, E.; Rizos, S.; Kelekis, D. Prospective randomized comparison of chemoembolization with doxorubicin-eluting beads and bland embolization with BeadBlock for hepatocellular carcinoma. *Cardiovasc. Intervent. Radiol.* **2010**, *33*, 541–551. [CrossRef]
54. Chuang, V.P.; Wallace, S. Hepatic artery embolization in the treatment of hepatic neoplasms. *Radiology* **1981**, *140*, 51–58. [CrossRef] [PubMed]
55. Tsochatzis, E.A.; Fatourou, E.M.; Triantos, C.K.; Burroughs, A.K. Transarterial therapies for hepatocellular carcinoma. *Recent Results Cancer Res.* **2013**, *190*, 195–206. [PubMed]
56. Varela, M.; Real, M.I.; Burrel, M.; Forner, A.; Sala, M.; Brunet, M.; Ayuso, C.; Castells, L.; Montaña, X.; Llovet, J.M.; et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: Efficacy and doxorubicin pharmacokinetics. *J. Hepatol.* **2007**, *46*, 474–481. [CrossRef] [PubMed]
57. Melchiorre, F.; Patella, F.; Pescatori, L.C.; Pesapane, F.; Fumarola, E.; Biondetti, P.; Brambillasca, P.; Monaco, C.; Carrafiello, G.; Franceschelli, G.; et al. DEB-TACE: A standard review. *Future Oncol.* **2018**, *14*, 2969–2984. [CrossRef] [PubMed]
58. Vogl, T.J.; Lammer, J.; Lencioni, R.; Malagari, K.; Watkinson, A.; Pilleul, F.; Denys, A.; Lee, C. Liver, gastrointestinal, and cardiac toxicity in intermediate hepatocellular carcinoma treated with PRECISION TACE with drug-eluting beads: Results from the PRECISION V randomized trial. *AJR Am. J. Roentgenol.* **2011**, *197*, W562–W570. [CrossRef]
59. Solomon, B.; Soulen, M.C.; Baum, R.A.; Haskal, Z.J.; Shlansky-goldberg, R.D.; Cope, C. Chemoembolization of hepatocellular carcinoma with cisplatin, doxorubicin, mitomycin-C, ethiodol, and polyvinyl alcohol: Prospective evaluation of response and survival in a U.S. population. *J. Vasc. Interv. Radiol.* **1999**, *10*, 793–798. [CrossRef]

60. Blackburn, H.; West, S. Management of postembolization syndrome following hepatic transarterial chemoembolization for primary or metastatic liver cancer. *Cancer Nurs.* **2016**, *39*, E1–E18. [CrossRef]
61. Jun, C.H.; Ki, H.S.; Lee, H.K.; Park, K.J.; Park, S.Y.; Cho, S.B.; Park, C.H.; Joo, Y.E.; Kim, H.S.; Choi, S.K.; et al. Clinical significance and risk factors of postembolization fever in patients with hepatocellular carcinoma. *World J Gastroenterol.* **2013**, *19*, 284–289. [CrossRef]
62. Hartnell, G.G.; Gates, J.; Stuart, K.; Underhill, J.; Brophy, D.P. Hepatic chemoembolization: Effect of intraarterial lidocaine on pain and postprocedure recovery. *Cardiovasc Intervent. Radiol.* **1999**, *22*, 293–297. [CrossRef]
63. Molgaard, C.P.; Teitelbaum, G.P.; Pentecost, M.J.; Finck, E.J.; Davis, S.H.; Dziubinski, J.E.; Daniels, J.R. Intraarterial administration of lidocaine for analgesia in hepatic chemoembolization. *J. Vasc. Interv. Radiol.* **1990**, *1*, 81–85. [CrossRef]
64. Benson, A.B.; Abrams, T.A.; Ben-Josef, E.; Bloomston, P.M.; Botha, J.F.; Clary, B.M.; Covey, A.; Curley, S.A.; D'Angelica, M.I.; Davila, R.; et al. Hepatobiliary Cancers. *J. Natl. Compr. Cancer Netw.* **2009**, *7*, 350–391. [CrossRef] [PubMed]
65. Villanueva, A.; Hernandez-gea, V.; Llovet, J.M. Medical therapies for hepatocellular carcinoma: A critical view of the evidence. *Nat. Rev. Gastroenterol. Hepatol.* **2013**, *10*, 34–42. [CrossRef] [PubMed]
66. Burrel, M.; Reig, M.; Forner, A.; Barrufet, M.; Rodriguez-Lope, C.; Tremosini, S.; Ayuso, C.; Llovet, J.M.; Real, M.I.; Bruix, J. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using drug eluting beads. Implications for clinical practice and trial design. *J. Hepatol.* **2012**, *56*, 1330–1335. [CrossRef] [PubMed]
67. May, B.J.; Madoff, D.C. Portal vein embolization: Rationale, technique, and current application. *Semin Intervent. Radiol.* **2012**, *29*, 81–89. [CrossRef]
68. Tazawa, J.; Maeda, M.; Sakai, Y.; Yamane, M.; Ohbayashi, H.; Kakinuma, S.; Miyasaka, Y.; Nagayama, K.; Enomoto, N.; Sato, C. Radiation therapy in combination with transcatheter arterial chemoembolization for hepatocellular carcinoma with extensive portal vein involvement. *J. Gastroenterol. Hepatol.* **2001**, *16*, 660–665. [CrossRef]
69. Yoon, S.M.; Lim, Y.-S.; Won, H.J.; Kim, J.H.; Kim, K.M.; Lee, H.C.; Chung, Y.; Lee, Y.S.; Lee, S.G.; Park, J.-H.; et al. Radiotherapy plus transarterial chemoembolization for hepatocellular carcinoma invading the portal vein: Long-term patient outcomes. *Int. J. Radiat. Oncol. Biol. Phys.* **2012**, *82*, 2004–2011. [CrossRef]
70. Lencioni, R.; Llovet, J.M.; Han, G.; Tak, W.Y.; Yang, J.; Guglielmi, A.; Paik, S.W.; Reig, M.; Kim, Y.; Chau, G.-Y.; et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. *J. Hepatol.* **2016**, *64*, 1090–1098. [CrossRef]
71. Hu, H.; Duan, Z.; Long, X.; Hertzanu, Y.; Shi, H.; Liu, S.; Yang, Z. Sorafenib combined with transarterial chemoembolization versus transarterial chemoembolization alone for advanced-stage hepatocellular carcinoma: A propensity score matching study. *PLoS ONE* **2014**, *9*, e96620. [CrossRef]
72. Golfieri, R.; Cappelli, A.; Cucchetti, A.; Piscaglia, F.; Carpenzano, M.; Peri, E.; Ravaioli, M.; D'Errico-Grigioni, A.; Pinna, A.D.; Bolondi, L. Efficacy of selective transarterial chemoembolization in inducing tumor necrosis in small (<5 cm) hepatocellular carcinomas. *Hepatology* **2011**, *53*, 1580–1589. [CrossRef]
73. Dorn, D.P.; Bryant, M.K.; Zarzour, J.; Smith, J.K.; Redden, D.T.; Saddekni, S.; Aal, A.K.A.; Gray, S.; White, J.; Eckhoff, D.E.; et al. Chemoembolization outcomes for hepatocellular carcinoma in cirrhotic patients with compromised liver function. *HPB* **2014**, *16*, 648–655. [CrossRef] [PubMed]
74. Marrero, J.A.; Kulik, L.M.; Sirlin, C.B.; Zhu, A.X.; Finn, R.S.; Abecassis, M.; Roberts, L.R.; Heimbach, J.K. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* **2018**, *68*, 723–750. [CrossRef]
75. Luo, J.; Guo, R.; Lai, E.C.H.; Zhang, Y.; Lau, W.Y.; Chen, M.-S.; Shi, M. Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: A prospective comparative study. *Ann. Surg. Oncol.* **2011**, *18*, 413–420. [CrossRef] [PubMed]
76. Georgiades, C.; Liapi, E.; Frangakis, C.; Park, J.-U.; Kim, H.W.; Hong, K.; Geschwind, J.-F. Prognostic accuracy of 12 liver staging systems in patients with unresectable hepatocellular carcinoma treated with transarterial chemoembolization. *J. Vasc. Interv. Radiol.* **2006**, *17*, 1619–1624. [CrossRef]

77. Hucke, F.; Sieghart, W.; Pinter, M.; Graziadei, I.W.; Vogel, W.; Müller, C.; Heinzl, H.; Waneck, F.; Trauner, M.; Peck-Radosavljevic, M. The ART-strategy: Sequential assessment of the ART score predicts outcome of patients with hepatocellular carcinoma re-treated with TACE. *J. Hepatol.* **2014**, *60*, 118–126. [CrossRef]
78. Lo, C.; Ngan, H.; Tso, W.; Liu, C.-L.; Lam, C.; Poon, R.T.P.; Fan, S.T.; Wong, J. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* **2002**, *35*, 1164–1171. [CrossRef]
79. Marelli, L.; Stigliano, R.; Triantos, C.; Senzolo, M.; Cholongitas, E.; Davies, N.; Tibballs, J.; Meyer, T.; Patch, D.W.; Burroughs, A.K. Transarterial therapy for hepatocellular carcinoma: Which technique is more effective? A systematic review of cohort and randomized studies. *Cardiovasc. Intervent. Radiol.* **2007**, *30*, 6–25. [CrossRef] [PubMed]
80. Llovet, J.M.; Bruix, J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology* **2003**, *37*, 429–442. [CrossRef] [PubMed]
81. Lammer, J.; Malagari, K.; Vogl, T.; Pilleul, F.; Denys, A.; Watkinson, A.; Pitton, M.; Sergent, G.; Pfammatter, T.; Terraz, S.; et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: Results of the PRECISION V study. *Cardiovasc. Intervent. Radiol.* **2010**, *33*, 41–52. [CrossRef]
82. Golfieri, R.; Giampalma, E.; Renzulli, M.; Cioni, R.; Bargellini, I.; Bartolozzi, C.; Breatta, A.D.; Gandini, G.; Nani, R.; Gasparini, D.; et al. Randomised controlled trial of doxorubicin-eluting beads vs. conventional chemoembolisation for hepatocellular carcinoma. *Br. J. Cancer* **2014**, *111*, 255–264. [CrossRef]
83. Facciorusso, A.; Mariani, L.; Sposito, C.; Spreafico, C.; Bongini, M.; Morosi, C.; Cascella, T.; Marchianò, A.; Camerini, T.; Bhoori, S.; et al. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma. *J. Gastroenterol. Hepatol.* **2016**, *31*, 645–653. [CrossRef] [PubMed]
84. Facciorusso, A.; Licinio, R.; Muscatiello, N.; Di leo, A.; Barone, M. Transarterial chemoembolization: Evidences from the literature and applications in hepatocellular carcinoma patients. *World J. Hepatol.* **2015**, *7*, 2009–2019. [CrossRef] [PubMed]
85. Llovet, J.M.; Ricci, S.; Mazzaferro, V.M.; Hilgard, P.; Gane, E.; Blanc, J.-F.; De Oliveira, A.C.; Santoro, A.; Raoul, J.-L.; Forner, A.; et al. Sorafenib in advanced hepatocellular carcinoma. *N. Engl. J. Med.* **2008**, *359*, 378–390. [CrossRef] [PubMed]
86. Cervello, M.; Bachvarov, D.; Lampiasi, N.; Cusimano, A.; Azzolina, A.; McCubrey, J.A.; Montalto, G. Molecular mechanisms of sorafenib action in liver cancer cells. *Cell Cycle* **2012**, *11*, 2843–2855. [CrossRef] [PubMed]
87. Sato, K.; Lewandowski, R.J.; Bui, J.T.; Omary, R.; Hunter, R.D.; Kulik, L.; Mulcahy, M.; Liu, D.; Chrisman, H.; Resnick, S.; et al. Treatment of unresectable primary and metastatic liver cancer with yttrium-90 microspheres (TheraSphere): Assessment of hepatic arterial embolization. *Cardiovasc. Intervent. Radiol.* **2006**, *29*, 522–529. [CrossRef]
88. Bhangoo, M.S.; Karnani, D.R.; Hein, P.N.; Giap, H.; Knowles, H.; Issa, C.; Steuterman, S.; Pockros, P.; Frenette, C. Radioembolization with Yttrium-90 microspheres for patients with unresectable hepatocellular carcinoma. *J. Gastrointest. Oncol.* **2015**, *6*, 469–478.
89. Lischalk, J.W.; Repka, M.C.; Unger, K. Radiation therapy for hepatobiliary malignancies. *J. Gastrointest. Oncol.* **2017**, *8*, 279–292. [CrossRef]
90. Murphy, J.D.; Lucas, D.R.; Somnay, Y.R.; Hamstra, D.A.; Ray, M.E. Gemcitabine-mediated radiosensitization of human soft tissue sarcoma. *Transl. Oncol.* **2008**, *1*, 50–56. [CrossRef]
91. Kennedy, A.S.; Brown, D.B.; Feilchenfeldt, J.; Marshall, J.; Wasan, H.; Fakih, M.; Gibbs, P.; Knuth, A.; Sangro, B.; Soulen, M.C.; et al. Safety of selective internal radiation therapy (SIRT) with yttrium-90 microspheres combined with systemic anticancer agents: Expert consensus. *J. Gastrointest. Oncol.* **2017**, *8*, 1079–1099. [CrossRef]
92. Hickey, R.; Lewandowski, R.J.; Salem, R. Transarterial Radioembolization (TARE). In *IR Playbook*; Keefe, N., Haskal, Z., Park, A., Angle, J., Eds.; Springer: Cham, Switzerland, 2018.
93. Makary, M.S.; Krishner, L.S.; Wuthrick, E.J.; Bloomston, M.P.; Dowell, J.D. Yttrium-90 microsphere selective internal radiation therapy for liver metastases following systemic chemotherapy and surgical resection for metastatic adrenocortical carcinoma. *World J. Clin. Oncol.* **2018**, *9*, 20–25. [CrossRef]

94. Salem, R.; Lewandowski, R.J.; Mulcahy, M.F.; Riaz, A.; Ryu, R.K.; Ibrahim, S.; Atassi, B.; Baker, T.; Gates, V.; Miller, F.H.; et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: A comprehensive report of long-term outcomes. *Gastroenterology* **2010**, *138*, 52–64. [CrossRef] [PubMed]
95. Kokabi, N.; Camacho, J.; Xing, M.; El-Rayes, B.F.; Spivey, J.R.; Knechtle, S.; Kim, H.S. Open-label prospective study of the safety and efficacy of glass-based yttrium 90 radioembolization for infiltrative hepatocellular carcinoma with portal vein thrombosis. *Cancer* **2015**, *121*, 2164–2174. [CrossRef] [PubMed]
96. Jia, Z.; Jiang, G.; Tian, F.; Zhu, C.; Qin, X. A systematic review on the safety and effectiveness of yttrium-90 radioembolization for hepatocellular carcinoma with portal vein tumor thrombosis. *Saudi J. Gastroenterol.* **2016**, *22*, 353–359. [PubMed]
97. Cho, Y.Y.; Lee, M.; Kim, H.-C.; Chung, J.W.; Kim, Y.H.; Gwak, G.-Y.; Bae, S.H.; Kim, Y.; Heo, J.; Kim, Y.J. Radioembolization Is a Safe and Effective Treatment for Hepatocellular Carcinoma with Portal Vein Thrombosis: A Propensity Score Analysis. *PLoS ONE* **2016**, *11*, e0154986. [CrossRef]
98. Heimbach, J.K.; Kulik, L.M.; Finn, R.S.; Sirlin, C.B.; Abecassis, M.M.; Roberts, L.R.; Zhu, A.X.; Murad, M.H.; Marrero, J.A. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* **2018**, *67*, 358–380. [CrossRef]
99. Benson, A.B.; D'Angelica, M.I.; Abbott, D.E.; Abrams, T.A.; Alberts, S.R.; Anaya, D.A.; Anders, R.; Are, C.; Brown, D.; Chang, D.T.; et al. Guidelines insights: Hepatobiliary cancers, version 2.2019. *J. Natl. Compr. Cancer Netw.* **2019**, *17*, 302–310. [CrossRef]
100. Riaz, A.; Gates, V.; Atassi, B.; Lewandowski, R.J.; Mulcahy, M.F.; Ryu, R.K.; Sato, K.T.; Baker, T.; Kulik, L.; Gupta, R.; et al. Radiation segmentectomy: A novel approach to increase safety and efficacy of radioembolization. *Int. J. Radiat. Oncol. Biol. Phys.* **2011**, *79*, 163–171. [CrossRef]
101. Vouche, M.; Habib, A.; Ward, T.J.; Kim, E.; Kulik, L.; Ganger, D.; Mulcahy, M.; Baker, T.; Abecassis, M.; Sato, K.T.; et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: Multicenter radiology-pathology correlation and survival of radiation segmentectomy. *Hepatology* **2014**, *60*, 192–201. [CrossRef]
102. Gabr, A.; Polineni, P.; Mouli, S.K.; Riaz, A.; Lewandowski, R.J.; Salem, R. Neoadjuvant radiation lobectomy as an alternative to portal vein embolization in hepatocellular Carcinoma. *Semin. Nucl. Med.* **2019**, *49*, 197–203. [CrossRef]
103. Gabr, A.; Abouchaleh, N.; Ali, R.; Baker, T.; Caicedo, J.; Katariya, N.; Abecassis, M.; Riaz, A.; Lewandowski, R.J.; Salem, R. Outcomes of Surgical Resection after Radioembolization for Hepatocellular Carcinoma. *J. Vasc. Interv. Radiol.* **2018**, *29*, 1502–1510.e1. [CrossRef]
104. Kulik, L.; Atassi, B.; Van Holsbeeck, L.; Souman, T.; Lewandowski, R.J.; Mulcahy, M.F.; Hunter, R.D.; Nemcek, A.A.; Abecassis, M.; Haines, K.G.; et al. Yttrium-90 microspheres (TheraSphere) treatment of unresectable hepatocellular carcinoma: Downstaging to resection, RFA and bridge to transplantation. *J. Surg. Oncol.* **2006**, *94*, 572–586. [CrossRef]
105. De La Torre, M.A.; Buades-Mateu, J.; De La Rosa, P.A.; Lue, A.; Bustamante, F.J.; Serrano, M.T.; Testillano, M.; Lorente, S.; Arenas, J.I.; Gil, C.; et al. A comparison of survival in patients with hepatocellular carcinoma and portal vein invasion treated by radioembolization or sorafenib. *Liver Int.* **2016**, *36*, 1206–1212. [CrossRef] [PubMed]
106. Lobo, L.; Yakoub, D.; Picado, O.; Ripat, C.; Pendola, F.; Sharma, R.; Eltawil, R.; Kwon, D.; Venkat, S.; Portelance, L.; et al. Unresectable Hepatocellular Carcinoma: Radioembolization Versus Chemoembolization: A Systematic Review and Meta-analysis. *Cardiovasc. Intervent. Radiol.* **2016**, *39*, 1580–1588. [CrossRef]
107. Salem, R.; Gordon, A.C.; Mouli, S.; Hickey, R.; Kallini, J.; Gabr, A.; Mulcahy, M.F.; Baker, T.; Abecassis, M.; Miller, F.H.; et al. Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. *Gastroenterology* **2016**, *151*, 1155–1163.e2. [CrossRef] [PubMed]
108. Salem, R.; Gilbertsen, M.; Butt, Z.; Memon, K.; Vouche, M.; Hickey, R.; Baker, T.; Abecassis, M.; Atassi, R.; Riaz, A.; et al. Increased quality of life among hepatocellular carcinoma patients treated with radioembolization, compared with chemoembolization. *Clin. Gastroenterol. Hepatol.* **2013**, *11*, 1358–1365.e1. [CrossRef] [PubMed]
109. Salem, R.; Gabr, A.; Riaz, A.; Mora, R.; Ali, R.; Abecassis, M.; Hickey, R.; Kulik, L.; Ganger, D.; Flamm, S.; et al. Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience. *Hepatology* **2018**, *68*, 1429–1440. [CrossRef] [PubMed]

110. Lewandowski, R.J.; Gabr, A.; Abouchaleh, N.; Ali, R.; Al Asadi, A.; Mora, R.; Kulik, L.; Ganger, D.; Desai, K.; Thornburg, B.; et al. Radiation segmentectomy: Potential curative therapy for early hepatocellular Carcinoma. *Radiology* **2018**, *287*, 1050–1058. [CrossRef]
111. Hilgard, P.; Hamami, M.; El Fouly, A.; Scherag, A.; Müller, S.; Ertle, J.; Heusner, T.; Cicinnati, V.R.; Paul, A.; Bockisch, A.; et al. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. *Hepatology* **2010**, *52*, 1741–1749. [CrossRef] [PubMed]
112. Chow, P.K.; Gandhi, M.; Tan, S.-B.; Khin, M.W.; Khasbazar, A.; Ong, J.; Choo, S.P.; Cheow, P.C.; Chotipanich, C.; Lim, K.; et al. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. *J. Clin. Oncol.* **2018**, *36*, 1913–1921. [CrossRef]
113. Vilgrain, V.; Pereira, H.; Assenat, E.; Guiu, B.; Ilonca, A.D.; Pageaux, G.-P.; Sibert, A.; Bouattour, M.; Lebtahi, R.; Allaham, W.; et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): An open-label randomised controlled phase 3 trial. *Lancet Oncol.* **2017**, *18*, 1624–1636. [CrossRef]
114. Poulou, L.S.; Botsa, E.; Thanou, I.; Ziakas, P.D.; Thanos, L. Percutaneous microwave ablation vs. radiofrequency ablation in the treatment of hepatocellular carcinoma. *World J. Hepatol.* **2015**, *7*, 1054–1063. [CrossRef] [PubMed]
115. Huang, Y.Z.; Zhou, S.C.; Zhou, H.; Tong, M. Radiofrequency ablation versus cryosurgery ablation for hepatocellular carcinoma: A meta-analysis. *Hepatogastroenterology* **2013**, *60*, 1131–1135. [PubMed]
116. Seifert, J.K.; Junginger, T.; Morris, D.L. A collective review of the world literature on hepatic cryotherapy. *J. R. Coll. Surg. Edinb.* **1998**, *43*, 141–154. [PubMed]
117. Mcgahan, J.P.; Brock, J.M.; Tesluk, H.; Gu, W.Z.; Schneider, P.; Browning, P.D. Hepatic ablation with use of radio-frequency electrocautery in the animal model. *J. Vasc. Interv. Radiol.* **1992**, *3*, 291–297. [CrossRef]
118. Sainani, N.I.; Gervais, D.A.; Mueller, P.R.; Arellano, R.S. Imaging after percutaneous radiofrequency ablation of hepatic tumors: Part 1, Normal findings. *AJR Am. J. Roentgenol.* **2013**, *200*, 184–193. [CrossRef] [PubMed]
119. Sainani, N.I.; Gervais, D.A.; Mueller, P.R.; Arellano, R.S. Imaging after percutaneous radiofrequency ablation of hepatic tumors: Part 2, Abnormal findings. *AJR Am. J. Roentgenol.* **2013**, *200*, 194–204. [CrossRef]
120. 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*, 339–344. [CrossRef]
121. Yi, Y.; Zhang, Y.; Wei, Q.; Zhao, L.; Han, J.; Song, Y.; Ding, Y.; Lu, G.; Liu, J.; Ding, H.; et al. Radiofrequency ablation or microwave ablation combined with transcatheter arterial chemoembolization in treatment of hepatocellular carcinoma by comparing with radiofrequency ablation alone. *Chin. J. Cancer Res.* **2014**, *26*, 112–118.
122. Yang, W.; Yan, K.; Wu, G.-X.; Wu, W.; Fu, Y.; Lee, J.-C.; Zhang, Z.-Y.; Wang, S.; Chen, M.-H. Radiofrequency ablation of hepatocellular carcinoma in difficult locations: Strategies and long-term outcomes. *World J. Gastroenterol.* **2015**, *21*, 1554–1566. [CrossRef]
123. Song, K.D.; Lee, M.W.; Rhim, H.; Cha, D.I.; Chong, Y.; Lim, H.K. Fusion imaging-guided radiofrequency ablation for hepatocellular carcinomas not visible on conventional ultrasound. *AJR Am. J. Roentgenol.* **2013**, *201*, 1141–1147. [CrossRef]
124. Lee, M.W.; Rhim, H.; Cha, D.I.; Kim, Y.J.; Choi, N.; Kim, Y.-S.; Lim, H.K. Percutaneous radiofrequency ablation of hepatocellular carcinoma: Fusion imaging guidance for management of lesions with poor conspicuity at conventional sonography. *AJR Am. J. Roentgenol.* **2012**, *198*, 1438–1444. [CrossRef] [PubMed]
125. Kasugai, H.; Osaki, Y.; Oka, H.; Kudo, M.; Seki, T. Severe complications of radiofrequency ablation therapy for hepatocellular carcinoma: An analysis of 3,891 ablations in 2,614 patients. *Oncology* **2007**, *72* (Suppl. 1), 72–75. [CrossRef] [PubMed]
126. Dodd, G.D.; Napier, D.; Schoolfield, J.D.; Hubbard, L. Percutaneous radiofrequency ablation of hepatic tumors: Postablation syndrome. *AJR Am. J. Roentgenol.* **2005**, *185*, 51–57. [CrossRef]
127. Balogh, J.; Victor, D.; Asham, E.H.; Burroughs, S.G.; Boktour, M.; Saharia, A.; Li, X.; Ghobrial, R.M.; Monsour, H.P. Hepatocellular carcinoma: A review. *J. Hepatocell. Carcinoma* **2016**, *3*, 41–53. [CrossRef]
128. Bruix, J.; Sherman, M. Management of hepatocellular carcinoma: An update. *Hepatology* **2011**, *53*, 1020–1022. [CrossRef] [PubMed]

129. Fang, Y.; Chen, W.; Liang, X.; Li, D.; Lou, H.; Chen, R.; Wang, K.; Pan, H. Comparison of long-term effectiveness and complications of radiofrequency ablation with hepatectomy for small hepatocellular carcinoma. *J. Gastroenterol. Hepatol.* **2014**, *29*, 193–200. [CrossRef]
130. Lü, M.-D.; Kuang, M.; Liang, L.-J.; Xie, X.-Y.; Peng, B.-G.; Liu, G.-J.; Li, D.-M.; Lai, J.-M.; Li, S.-Q. Surgical resection versus percutaneous thermal ablation for early-stage hepatocellular carcinoma: A randomized clinical trial. *Zhonghua Yi Xue Za Zhi* **2006**, *86*, 801–805.
131. Huang, J.; Yan, L.; Cheng, Z.; Wu, H.; Du, L.; Wang, J.; Xu, Y.; Zeng, Y. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann. Surg.* **2010**, *252*, 903–912. [CrossRef]
132. Xu, Z.; Xie, H.; Zhou, L.; Chen, X.; Zheng, S. The Combination strategy of transarterial Chemoembolization and radiofrequency ablation or microwave ablation against hepatocellular Carcinoma. *Anal Cell Pathol.* **2019**, *2019*. [CrossRef]
133. Sheta, E.; El-Kalla, F.; El-Gharib, M.; Kobtan, A.; Elhendawy, M.E.; Abd-Elsalam, S.; Mansour, L.; Amer, I. Comparison of single-session transarterial chemoembolization combined with microwave ablation or radiofrequency ablation in the treatment of hepatocellular carcinoma: A randomized-controlled study. *Eur. J. Gastroenterol. Hepatol.* **2016**, *28*, 1198–1203. [CrossRef]
134. Ginsburg, M.; Zivin, S.P.; Wroblewski, K.; Doshi, T.; Vasnani, R.J.; Van ha, T.G. Comparison of combination therapies in the management of hepatocellular carcinoma: Transarterial chemoembolization with radiofrequency ablation versus microwave ablation. *J. Vasc. Interv. Radiol.* **2015**, *26*, 330–341. [CrossRef] [PubMed]
135. Ni, J.-Y.; Sun, H.-L.; Chen, Y.-T.; Luo, J.-H.; Chen, N.; Jiang, X.-Y.; Xu, L.-F. Prognostic factors for survival after transarterial chemoembolization combined with microwave ablation for hepatocellular carcinoma. *World J. Gastroenterol.* **2014**, *20*, 17483–17490. [CrossRef]
136. 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*, 1277–1282. [CrossRef]
137. Ton, J.; Kuoy, E.; Abi-Jaoudeh, N. Liver Ablation. In *IR Playbook*; Keefe, N., Haskal, Z., Park, A., Angle, J., Eds.; Springer: Cham, Switzerland, 2018.
138. Yan, K.; Chen, M.-H.; Yang, W.; Bin Wang, Y.; Gao, W.; Hao, C.Y.; Xing, B.C.; Huang, X.F. Radiofrequency ablation of hepatocellular carcinoma: Long-term outcome and prognostic factors. *Eur. J. Radiol.* **2008**, *67*, 336–347. [CrossRef] [PubMed]
139. Shiina, S.; Tateishi, R.; Arano, T.; Uchino, K.; Enooku, K.; Nakagawa, H.; Asaoka, Y.; Sato, T.; Masuzaki, R.; Kondo, Y.; et al. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. *Am. J. Gastroenterol.* **2012**, *107*, 569–577. [CrossRef] [PubMed]
140. Brunello, F.; Cantamessa, A.; Gaia, S.; Carucci, P.; Rolle, E.; Castiglione, A.; Ciccone, G.; Rizzetto, M. Radiofrequency ablation: Technical and clinical long-term outcomes for single hepatocellular carcinoma up to 30 mm. *Eur. J. Gastroenterol. Hepatol.* **2013**, *25*, 842–849. [CrossRef] [PubMed]
141. Francica, G.; Saviano, A.; De Sio, I.; De Matthaeis, N.; Brunello, F.; Cantamessa, A.; Giorgio, A.; Scognamiglio, U.; Fornari, F.; Giangregorio, F.; et al. Long-term effectiveness of radiofrequency ablation for solitary small hepatocellular carcinoma: A retrospective analysis of 363 patients. *Dig. Liver Dis.* **2013**, *45*, 336–341. [CrossRef]
142. Liang, P.; Dong, B.; Yu, X.; Yu, D.; Wang, Y.; Feng, L.; Xiao, Q. Prognostic factors for survival in patients with hepatocellular carcinoma after percutaneous microwave ablation. *Radiology* **2005**, *235*, 299–307. [CrossRef]
143. Weis, S.; Franke, A.; Mössner, J.; Jakobsen, J.C.; Schoppmeyer, K. Radiofrequency (thermal) ablation versus no intervention or other interventions for hepatocellular carcinoma. *Cochrane Database Syst. Rev.* **2013**, *19*, CD003046. [CrossRef]
144. Pompili, M.; Saviano, A.; De Matthaeis, N.; Cucchetti, A.; Ardito, F.; Federico, B.; Brunello, F.; Pinna, A.D.; Giorgio, A.; Giulini, S.M.; 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*, 89–97. [CrossRef]
145. Ng, K.K.; Chok, K.S.-H.; Chan, A.C.Y.; Cheung, T.T.; Wong, T.C.L.; Fung, J.Y.Y.; Yuen, J.; Poon, R.T.P.; Fan, S.T.; Lo, C.M. Randomized clinical trial of hepatic resection versus radiofrequency ablation for early-stage hepatocellular carcinoma. *Br. J. Surg.* **2017**, *104*, 1775–1784. [CrossRef] [PubMed]

146. Ding, J.; Jing, X.; Liu, J.; Wang, F.; Wang, Y.; Du, Z. Complications of thermal ablation of hepatic tumours: Comparison of radiofrequency and microwave ablative techniques. *Clin. Radiol.* **2013**, *68*, 608–615. [CrossRef] [PubMed]
147. Wang, C.; Wang, H.; Yang, W.; Hu, K.; Xie, H.; Hu, K.-Q.; Bai, W.; Dong, Z.; Lu, Y.; Zeng, Z.; et al. Multicenter randomized controlled trial of percutaneous cryoablation versus radiofrequency ablation in hepatocellular carcinoma. *Hepatology* **2015**, *61*, 1579–1590. [CrossRef]
148. Kim, J.W.; Kim, J.-H.; Won, H.J.; Shin, Y.M.; Yoon, H.-K.; Sung, K.-B.; Kim, P.-N. Hepatocellular carcinomas 2–3 cm in diameter: Transarterial chemoembolization plus radiofrequency ablation vs. radiofrequency ablation alone. *Eur. J. Radiol.* **2012**, *81*, e189–e193. [CrossRef] [PubMed]
149. Iezzi, R.; Pompili, M.; Posa, A.; Coppola, G.; Gasbarrini, A.; Bonomo, L. Combined locoregional treatment of patients with hepatocellular carcinoma: State of the art. *World J. Gastroenterol.* **2016**, *22*, 1935–1942. [CrossRef]
150. Lu, Z.; Wen, F.; Guo, Q.; Liang, H.; Mao, X.; Sun, H. Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: A meta-analysis of randomized-controlled trials. *Eur. J. Gastroenterol. Hepatol.* **2013**, *25*, 187–194. [CrossRef]
151. Bruix, J.; Takayama, T.; Mazzaferro, V.M.; Chau, G.-Y.; Yang, J.; Kudo, M.; Cai, J.; Poon, R.T.; Han, K.-H.; Tak, W.Y.; 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*, 1344–1354. [CrossRef]
152. Fuchs, K.; Bize, P.-E.; Faes, O.D.S.; Denys, A.; Doelker, E.; Borchard, G.; Jordan, O. Drug-eluting beads loaded with antiangiogenic agents for chemoembolization: In vitro sunitinib loading and release and in vivo pharmacokinetics in an animal model. *J. Vasc. Interv. Radiol.* **2014**, *25*, 379–387.e3872. [CrossRef]
153. Bize, P.-E.; Duran, R.; Fuchs, K.; Faes, O.D.S.; Namur, J.; Decosterd, L.A.; Jordan, O.; Doelker, E.; Denys, A. Antitumoral Effect of Sunitinib-eluting beads in the rabbit VX2 tumor model. *Radiology* **2016**, *280*, 425–435. [CrossRef]
154. Hagan, A.; Phillips, G.J.; Macfarlane, W.M.; Lloyd, A.W.; Czuczman, P.; Lewis, A.L. Preparation and characterisation of vandetanib-eluting radiopaque beads for locoregional treatment of hepatic malignancies. *Eur. J. Pharm. Sci.* **2017**, *101*, 22–30. [CrossRef]
155. Sakr, O.S.; Berndt, S.; Carpentier, G.; Cuendet, M.; Jordan, O.; Borchard, G. Arming embolic beads with anti-VEGF antibodies and controlling their release using LbL technology. *J. Control. Release* **2016**, *224*, 199–207. [CrossRef] [PubMed]
156. Park, B.-H.; Hwang, T.; Liu, T.-C.; Sze, D.Y.; Kim, J.-S.; Kwon, H.-C.; Oh, S.Y.; Han, S.-Y.; Yoon, J.-H.; Hong, S.-H.; et al. Use of a targeted oncolytic poxvirus, JX-594, in patients with refractory primary or metastatic liver cancer: A phase I trial. *Lancet Oncol.* **2008**, *9*, 533–542. [CrossRef]
157. Obeid, J.M.; Kunk, P.R.; Zaydfudim, V.M.; Bullock, T.N.; Slingluff, C.L.; Rahma, O.E. Immunotherapy for hepatocellular carcinoma patients: Is it ready for prime time? *Cancer Immunol. Immunother.* **2018**, *67*, 161–174. [CrossRef] [PubMed]
158. El-Khoueiry, A.B.; Sangro, B.; Yau, T.C.C.; Crocenzi, T.S.; Kudo, M.; Hsu, C.; Kim, T.-Y.; Choo, S.-P.; Trojan, J.; Welling, T.H.; et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): An open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* **2017**, *389*, 2492–2502. [CrossRef]
159. Bteich, F.; Di bisceglie, A.M. Current and future systemic therapies for hepatocellular carcinoma. *Gastroenterol. Hepatol.* **2019**, *15*, 266–272.
160. Slovak, R.; Ludwig, J.M.; Gettinger, S.N.; Herbst, R.S.; Kim, H.S. Immuno-thermal ablations—Boosting the anticancer immune response. *J. Immunother. Cancer* **2017**, *5*, 78. [CrossRef]
161. Burkhart, R.A.; Ronnekleiv-kelly, S.M.; Pawlik, T.M. Personalized therapy in hepatocellular carcinoma: Molecular markers of prognosis and therapeutic response. *Surg. Oncol.* **2017**, *26*, 138–145. [CrossRef]
162. Couri, T.; Pillai, A. Goals and targets for personalized therapy for HCC. *Hepatol. Int.* **2019**, *13*, 125–137. [CrossRef]
163. Ma, L.; Chua, M.S.; Andrisani, O.; So, S. Epigenetics in hepatocellular carcinoma: An update and future therapy perspectives. *World J. Gastroenterol.* **2014**, *20*, 333–345. [CrossRef]
164. Kim, H.S.; Chapiro, J.; Geschwind, J.-F.H. Interventional oncology: The fourth pillar of oncology. *Cancer J.* **2016**, *22*, 363–364. [CrossRef]

165. Abajian, A.; Murali, N.; Savic, L.J.; Laage-Gaupp, F.M.; Nezami, N.; Duncan, J.S.; Schlachter, T.; Lin, M.; Geschwind, J.-F.; Chapiro, J. Predicting treatment response to intra-arterial therapies for hepatocellular carcinoma with the use of supervised machine learning-an artificial intelligence concept. *J. Vasc. Interven. Radiol.* **2018**, *29*, 850–857. [CrossRef] [PubMed]
166. Akateh, C.; Black, S.M.; Conteh, L.; Miller, E.D.; Noonan, A.; Elliott, E.; Pawlik, T.M.; Tsung, A.; Cloyd, J.M. Neoadjuvant and adjuvant treatment strategies for hepatocellular carcinoma. *World J. Gastroenterol.* **2019**, *25*, 3704–3721. [CrossRef] [PubMed]