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Minimally Invasive Treatments for Liver Cancer

Nicolas Cardenas, Rahul Sheth and Joshua Kuban

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Abstract

While surgical resection and chemotherapy have remained mainstays in the treatment of both primary and metastatic liver cancers, various minimally invasive techniques have been developed to treat patients for whom traditional approaches either are not available or have failed. Percutaneous ablation techniques such as radiofrequency, microwave, cryoablation, and irreversible electroporation are considered as potentially curative treatments in patients with hepatocellular carcinoma with early-stage tumors. Transarterial chemoembolization (TACE) and radioembolization with yttrium-90 (Y-90) are palliative treatments that have improved survival in patients with unresectable disease. In this chapter, we discuss these minimally invasive techniques, the criteria for selecting appropriate candidates for treatment, and potential limitations to their use.

Keywords: chemoembolization, percutaneous ablation, radioembolization, minimally invasive therapies, liver cancer

1. Introduction

While surgical resection and chemotherapy have remained mainstays in the treatment of both primary and metastatic liver cancers, a variety of minimally invasive techniques have been developed to treat patients for whom traditional approaches are either not available or have failed. Percutaneous ablation techniques, such as radiofrequency, microwave, cryoablation, and irreversible electroporation, are considered potentially curative treatments in patients with hepatocellular carcinoma with early-stage tumors. Transarterial chemoembolization (TACE) and radioembolization with yttrium-90 (Y-90) are palliative treatments that have improved survival in patients with unresectable disease. In this chapter, we discuss these minimally

invasive techniques, the criteria for selecting appropriate candidates for treatment, and potential limitations to their use.

2. Transarterial chemoembolization

Transarterial chemoembolization (TACE) is a minimally invasive technique used to treat liver tumors, predominantly hepatocellular carcinoma (HCC). In the early 1970s, interventional radiologists (IRs) began utilizing embolization agents to effectively block the vascular supply of hepatic tumors, pioneering the technique known as trans-catheter arterial embolization (TAE) or bland embolization. TACE evolved from TAE 10 years later, when IRs began to perform intra-arterial injections of chemotherapeutic agents prior to the delivery of embolization agents [1].

TACE derives its therapeutic effects through two synergistic methods. Selective arterial occlusion induces ischemic tumor necrosis by limiting blood flow to the tumor. Concomitant administration of regional chemotherapy allows the drug to remain in the tumor for an extended period of time, enhancing its therapeutic effects and diminishing adverse systemic side effects [2].

The rationale for using arterial embolization as a treatment for hepatocellular carcinoma is based on the unique blood supply of both the liver and the tumor itself. Due to the liver's dual blood supply, IRs are able to embolize hepatic arteries without causing significant hepatic necrosis. Normal liver parenchyma receives two-thirds of its blood supply from the portal vein and the remaining one-third from the hepatic artery [2]. In contrast, Breedis and Young [3] found that hepatic neoplasms almost exclusively receive their blood supply from the hepatic artery. TACE takes advantage of these characteristics by selectively embolizing branches of the hepatic artery, successfully sparing normal hepatic tissue and targeting the neoplasm.

2.1. Components of TACE

Modern TACE can be segregated into two technical approaches: conventional TACE (cTACE) and drug-eluting bead TACE (DEB-TACE). cTACE bears the closest resemblance to the techniques used in the landmark trials that demonstrated a survival benefit with TACE [4, 5] and typically involves the administration of a mixture composed of a chemotherapeutic agent and ethiodized oil (Lipiodol, Guerbet, Paris, France). The chemotherapy component can be administered either as a mono-drug regimen or combination chemotherapy. The most commonly used single drug agents are doxorubicin and cisplatin. Some physicians prefer to use combination chemotherapy based on the notion that the mixture of agents leads to a synergistic effect and a better outcome. The most common drug combination includes cisplatin, doxorubicin, and mitomycin C. However, there is no established improvement in survival between any one mono-drug therapy vs. other drugs [6, 7] or mono-drug therapy vs. combination chemotherapy [8].

Lipiodol is an oily contrast media derived from poppy seeds that serves three important roles: drug delivery vehicle, microembolic material, and radio-opaque contrast agent [9]. Lipiodol's oily consistency allows for embolization of both arterial and portal vessels. This dual emboli‐ zation is clinically relevant because high-grade tumors may receive a portion of their blood supply from both the hepatic artery and portal vein [10]. Embolization of both vascular systems enhances the antitumor properties of the procedure in such cases [11].

The majority of cytotoxic molecules used in TACE are hydrophilic and are therefore emulsified in oil droplets when mixed with lipiodol. When injected into a tumor-supplying vessel, the emulsified lipiodol and drug mixture preferentially stays within the tumor vasculature for several weeks to over a year [2]. The reason for the selective and prolonged uptake of lipiodol by hepatocellular carcinoma continues to be debated. One possible explanation is the dense hypervascularity of HCC. Another explanation is the complete absence of a reticuloendothelial system in tumor vasculature, leading to the absence of Kupffer cells, which would normally phagocytize the oil [9].

A variety of embolic agents can be used for further embolization during cTACE, the most common being gelatin sponge, polyvinyl alcohol, and ethanol [12]. The literature has failed to reveal clear superiority of one agent over the other, leading to variability of use among providers [12].

In recent years, efforts have been directed at improving the drug delivery system used in TACE. Drug-eluting beads (DEB) are embolic microspheres loaded with chemotherapeutic agents, most commonly doxorubicin, which ensure slow drug release and decrease systemic spread. In theory, this "reservoir effect" permits deeper diffusion of the drug beyond the perivascular space and into the tumor. Moreover, by coupling chemotherapeutics with calibrated micro‐ spheres of reproducible size, the execution of TACE can be standardized to facilitate interpre‐ tation of outcomes across patients and institutions with less concern for biases based upon technical variability.

Several trials have investigated the efficacy of cTACE versus DEB-TACE. PRECISION V [13] was a phase II study that showed nonsignificantly higher complete response rates in the DEB-TACE arm; subset analyses, however, showed a significant improvement in response rates with DEB-TACE in patients with Childs-Pugh score B and in patients with bilobar disease. Addi‐ tionally, systemic toxicities of doxorubicin, including cardiovascular dysfunction and alopecia, as well as liver toxicity, were lower in the DEB-TACE arm.

2.2. Patient selection and indications for TACE

A multidisciplinary evaluation, including oncologists, hepatologists, and IRs, is essential for identifying appropriate candidates for TACE. TACE is considered the standard of care for patients with asymptomatic, unresectable HCC without macrovascular invasion, or extrahe‐ patic metastasis. Four studies, including two randomized trials by Lo et al. [5] and Llovet et al. [14] and two meta analyses by Cammà et al. [15] and Llovet and Bruix [4], established level I evidence showing improved 2-year survival with TACE when compared to symptomatic treatment alone.

The primary indication for TACE is a Barcelona Clinic Liver Cancer (BCLC) stage B HCC that is not amendable to resection. The BCLC is a staging system (**Table 1**) that integrates tumor characteristics and performance status with liver function (Child-Pugh Score) and links them to evidence-based therapeutic options. The BCLC is now established as the basis for American and European HCC management guidelines.

Stage	Performance status	Tumor stage, cancer symptoms	Hepatic function	Treatment
0 (very early)	0	Single nodule <5 cm	Child-Pugh A, normal portal pressure/bilirubin	Resection
A (early)	0	Single nodule <5 cm 3 nodules each <3 cm	Child-Pugh A, elevated portal pressure and/or bilirubin	Liver transplantation or ablation
B (intermediate)	0	Large, multinodular, no cancer symptoms	Child-Pugh A-B	TACE
C (advanced)	1–2	Portal invasion, extrahepatic disease, or cancer symptoms	Child-Pugh A-B	Systemic therapy
D (terminal)	>2	Any	Child-Pugh C	Symptomatic treatment

Table 1. Barcelona clinic liver cancer staging system.

Secondary indications for TACE include decreasing tumor size to facilitate resection or to meet transplantation size criteria [16]. TACE may also be used to extend patients' eligibility for a liver transplant by preventing them from exceeding the Milan liver transplantation criteria (one tumor less than 5 cm, or up to three tumors, each less than 3 cm).

2.3. Contraindications: absolute and relative

The primary indications for TACE encompass a large, heterogenous patient population. This population includes patients with varying tumor burden, underlying etiologies, and liver function. It is the physician's responsibility to select patients for whom TACE is likely to improve their quality of life. Furthermore, it is critical to identify patients at high risk for serious complications that outweigh the potential benefits of the procedure.

Absolute contraindications include poorly compensated advanced liver disease (Child Pugh C). This includes patients with refractory clinical encephalopathy, persistent ascites, jaundice, and hepatorenal syndrome [17]. Other absolute contraindications consist of extensive tumor burden involving both hepatic lobes, uncorrectable bleeding diathesis, renal insufficiency (creatinine ≥ 2 mg/dL or creatinine clearance ≤ 30 ml/min), anatomical issues involving untreated arteriovenous fistulas, and active infection [17, 18].

Relative contraindications include untreated esophageal varices at risk of bleeding, a tumor size greater than 10 cm, anaphylactic reactions to contrast (gadolinium or carbon dioxide can

be used as a substitute) or chemotherapeutic agents (bland embolization may be an alternative), hyperbilirubinemia, incompetent papilla with aerobilia, biliary dilatation, and impaired portal vein blood flow due to portal vein thrombosis (PVT) or hepatofugal blood flow [18]. Patients with PVT may still be eligible for TACE if selective or super selective chemoembolization is performed and the patient is Child-Pugh A [19].

2.4. Pre-procedure preparations

A consent form must be signed by the patient after an explanation of the procedure, risks, and benefits, and reasonable expectations are carefully explained, ideally in the outpatient IR clinic. Laboratory studies are ordered prior to the procedure and include complete blood count, metabolic panel with liver function tests, and coagulation profile. Obtaining abdominal triple-phase computed tomography (CT) or magnetic resonance imaging (MRI) is valuable prior to TACE to localize liver tumors, assess portal vein patency, observe for other conditions such as bile duct obstruction which would require decompression, and to assess arterial anatomy for treatment planning [20]. A patient is placed nil per os a minimum of 8 hours before the procedure, and intravenous fluids are started to maintain the patient well hydrated and avoid kidney damage due to contrast or tumor lysis syndrome. Medications to be administered prior to the procedure include antiemetics and anti-inflammatories to reduce the risk of post-embolization syndrome (discussed below) [20]. Prophylactic antibiotics are usually not given before or after the procedure unless the patient has risk factors for infection, such as a disrupted sphincter of Oddi [20].

2.5. Procedure

Most TACE procedures can be performed with moderate sedation and do not require a general anesthetic. Once appropriate sedation is achieved, the performing physician begins by gaining arterial access, typically from the common femoral artery or radial artery. An abdominal aortogram may be performed to visualize the visceral anatomy and identify any vessels supplying the tumor, such as the intercostal, phrenic, or lumbar arteries [20]. A superior mesenteric arteriogram is conducted to identify any variant anatomy and to assess portal vein patency. The celiac artery is then selected and an arteriogram is performed to study the arterial supply of the tumor and normal viscera. Particular attention is payed to identify vessels that should not be embolized, such as vessels feeding the stomach, intestines, and gallbladder.

Once the major vessels supplying the tumor are identified, a catheter—oftentimes a coaxial microcatheter—is advanced toward the tumor. The goal is to place the chemoembolizing solution as distal as possible to preserve normal liver parenchyma, but proximal enough to treat the entire tumor. With recent advances in imaging as well as catheter technology, "superselective" catheterization of the small subsegmental arteries supplying the tumor can be achieved, thus maximizing therapeutic efficacy while minimizing collateral parenchymal injury. The embolizing solution is then injected directly into the targeted vessel under continuous fluoroscopic visualization in order to prevent inadvertent embolization of vessels feeding normal parenchyma (**Figure 1**).
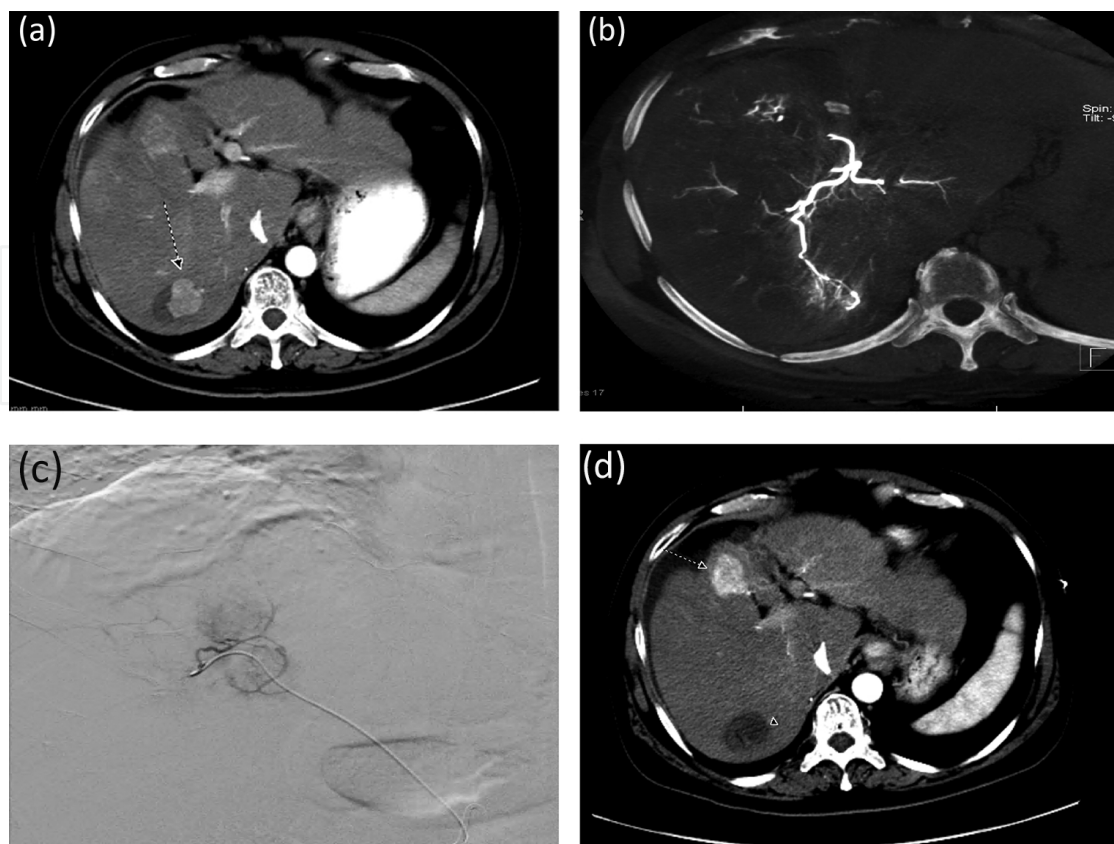
Figure 1. Chemoembolization of HCC. (a) Arterial phase contrast enhanced diagnostic CT of the abdomen showing hypervascular tumor in segment 7 consistent with HCC. (b) Intraoperative cone beam CT angiogram showing the vascular supply to the segment 7 HCC. (c) Digital subtraction angiogram from microcatheter in the feeding artery showing tumor "blush" and no collateral parenchymal supply. (d) Eight-week follow-up scan shows complete response with no arterial enhancement of the treated lesion in segment 7 (arrowhead). There is increased enhancement in a new segment 8 lesion seen anteriorly (arrow).

2.6. Post-procedure management and complications

Post-TACE patients are usually discharged from the hospital within 24 hours of the procedure. Patients are allowed to go home once their pain is controlled, they are tolerating PO intake, ambulating, and producing adequate amount of urine. A noncontrast CT of the abdomen is often performed the day after cTACE involving lipiodol embolization in order to visualize the distribution of the embolizing mixture.

A variety of complications may arise after transarterial chemoembolization, most of which are due to underlying causative factors present before the procedure. Post-embolization syndrome is the most common complication, occurring in 60–80% of patients [2]. The syndrome consists of transient abdominal pain, fever, and elevated liver enzymes. Many argue post-embolization syndrome is not a complication, but rather the body's reaction to necrosis, which was the objective of the procedure. If symptoms are severe enough, an extended hospital stay may be required. In the majority of patients, post-embolization syndrome is self-limiting and resolves in 3–4 days [2].

The most serious complications are fulminant hepatic failure, encephalopathy, and death. Pre-procedural risk factors include a Child-Pugh C, total bilirubin ≥ 4 mg/dL, albumin ≤ 2 mg/dL, major portal vein obstruction, refractory ascites, prolonged prothrombin time, and poor performance status. The incidence of TACE-induced hepatic failure varies widely, ranging from 0 to 49% with a median incidence of 8% [8]. Studies define TACE-induced hepatic failure using different criteria thus leading to the wide variation in incidence. The majority of patients return to pretreatment liver function before the next session of TACE, with only 3% of patients experiencing irreversible hepatic decompensation [8].

Additional TACE-related complications include hepatic abscess, biliary stricture, acute variceal bleed, pulmonary embolism, non-target embolization, and acute renal failure. Song et al. [21] reviewed over 6000 TACE patients and found a 0.2% incidence rate of liver abscess linked to previous intervention in the biliary system and with a compromised sphincter of Oddi.

2.7. Outcomes

The clinical significance of TACE was established following the publication of two pivotal trials in 2002. Llovet et al. [14] performed a randomized controlled trial to assess the survival benefit of frequently repeated chemoembolization (gelatin sponge plus doxorubicin) or arterial embolization (gelatin sponge) alone compared with conservative treatment. The trial was terminated early because chemoembolization provided a statistically significant survival benefit. One- and two-year survival for embolization was 75 and 50%, respectively. One- and two-year survival for chemoembolization was 82 and 63%, respectively, whereas the 1- and 2-year survival for conservative care was 63 and 27%, respectively.

Lo et al. [5] published a randomized trial in 2002 assessing the efficacy of transarterial chemo-embolization with a mixture of cisplatin, lipiodol, and gelatin sponge particles vs. symptomatic treatment. Chemoembolization resulted in significant tumor response and markedly improved survival (1 year, 57%; 2 years, 31%; 3 years, 26%) when compared to the control group (1 year, 32%; 2 years, 11%; 3 years, 3%).

A meta analysis conducted by Cammà et al. [15] concluded that TACE significantly reduced 2-year mortality in patients with unresectable HCC (odds ratio (OR), 0.54; 95% CI, 0.33–0.89; $P = 0.015$). Another meta-analysis performed by Llovet and Bruix [4] also showed decreased 2-year mortality in patients treated with TACE (odds ratio, 0.53; 95% CI, 0.32–0.89; $P = 0.017$).

3. Radioembolization

Radioembolization (Y90) is a form of intra-arterial brachytherapy conceptually similar to TACE in its application. However, rather than injecting chemotherapeutic agents, micro-spheres are embedded with a beta-emitting isotope known as yttrium-90. Highly localized internal radiation therapy is required rather than external beam radiotherapy because the liver is highly sensitive to radiation. The amount of radiation required to destroy tumor tissue is

estimated at ≥ 70 Gray (Gy), well above the 35 Gy tolerance dose of normal parenchyma [22]. The intra-arterial approach allows IRs to selectively deposit microspheres in tumor feeding vessels, focusing the radiation dose on tumor tissue while sparing normal parenchyma.

3.1. Components of Y-90

Yttrium-90 is a pure beta emitter with a half-life of 64.1 hours, an average energy emission of 0.9367 MeV, and mean tissue penetration of 2.5 mm with a maximum of 10 mm [23]. Y-90 is embedded in either glass or resin microspheres, facilitating delivery to the target tissue. Glass microspheres, also known as Theraspheres, are approved by the FDA for treatment of unresectable HCC under a "humanitarian device exemption." Resin microspheres, also known as SIR-Spheres, have received FDA premarket approval for treating hepatic metastases from colorectal cancer, coadministered with fluorodeoxyuridine (FUDR) [22]. The activity load of a single glass microsphere is 2500 Bq, whereas the activity load of resin microspheres is 50 Bq. The notable difference in activity load requires larger volumes of resin microspheres to be injected for a desired dose compared to glass microspheres [24].

3.2. Patient selection and indication for Y-90

Patients with HCC, if detected early, may be candidates for curative treatments such as resection and transplantation. Unfortunately, only 10–15% of HCC patients are eligible at the time of presentation [25]. The majority of patients are left with palliative treatment options, such as TACE, Y-90, or symptomatic treatment.

An interdisciplinary team consisting of IRs, surgical oncologists, nuclear medicine, hepatologists, and radiation safety personnel is required to properly evaluate patients for Y-90. Radioembolization is not currently included as a therapeutic option in any HCC treatment guidelines, but there is growing interest and experience in the use of this therapy for early, intermediate, and late-stage HCC [22]. Pretreatment evaluation includes serum chemistries, appropriate tumor markers (CEA, AFP), liver function tests, cross-sectional imaging with CT/MRI/PET scan, meticulous angiography, and ^{99m}Tc macro-aggregated albumin (MAA) scan. Patient characteristics are incorporated into staging systems; the most accepted being Barcelona Clinic Liver Cancer (BCLC) and Eastern Cooperative Oncology Group (ECOG) [26]. Usually, patients with an ECOG performance status between 0 and 2 are eligible for treatment.

### 3.3. Contraindications: absolute and relative

An absolute contraindication for radioembolization is substantial intratumoral arteriovenous shunting resulting in systemic or pulmonary delivery of the radioactive microspheres. For this reason, a pretreatment angiogram and nuclear medicine study involving the intra-arterial administration of technetium-99-labeled macroaggregated albumin (^{99m}Tc MAA) is performed. From the subsequent scintigraphic imaging, the degree of intratumoral shunting is estimated by quantifying the radioactivity trapped within the lungs. If there is a potential for greater than 30 Gy radiation exposure to the lungs, radioembolization is not performed due to the risk of radiation pneumonitis [19]. The MAA scan may also predict large amounts of radiation

exposure to the gastric circulation via reflux through visceral branches, including the gastro-duodenal and right gastric arteries. If the IR is unable to prophylactically embolize the appropriate arteries, the patient's visceral circulation may be exposed to large amounts of radiation, which can lead to severe ulceration, gastrointestinal bleeding, or pancreatitis [26]. Other absolute contraindications include severe renal insufficiency, uncorrectable coagulopathy, and a history of anaphylactoid reaction to iodinated contrast agents.

Relative contraindications include limited hepatic reserve, elevated total bilirubin level (>2 mg/dL) in the absence of a reversible cause, an ECOG score >2, prior radiation therapy involving the liver, and a main PVT with Child-Pugh B or C.

3.4. Pre-procedure preparations

A meticulous preliminary angiographic evaluation is essential in order to document visceral anatomy, localize anatomic variants, identify the hepatic circulation, and evaluate extrahepatic arteries that may require prophylactic embolization [19]. The importance of detailed angiography is augmented by HCC's high propensity to form aberrant vascular anatomy that, if present, requires identification prior to the procedure.
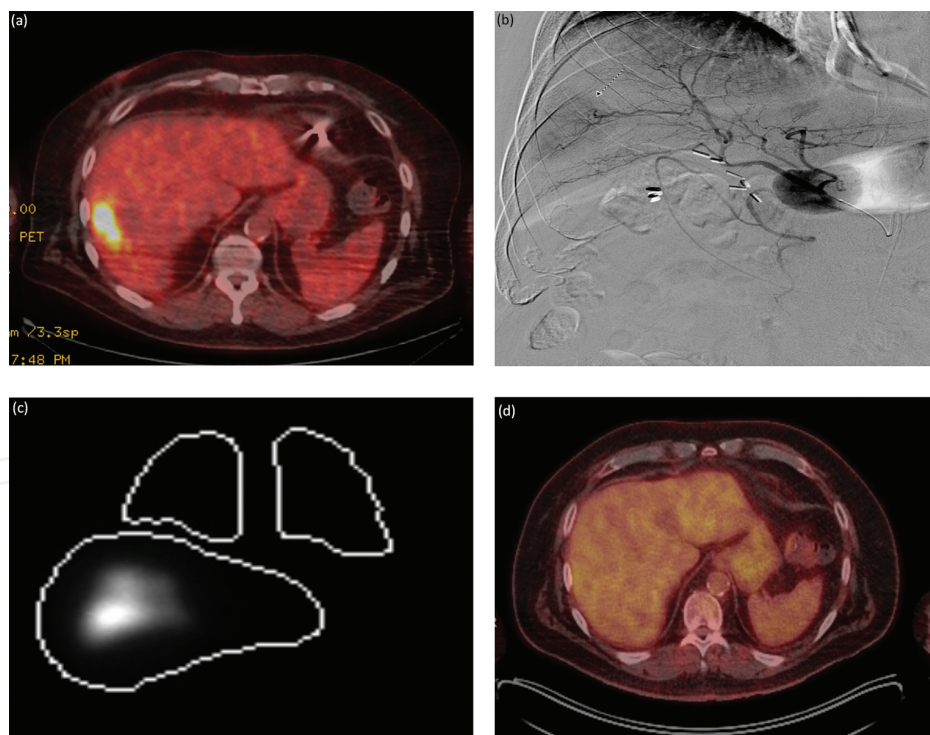
Figure 2. Radioembolization of liver metastasis. (a) 5 cm FDG avid metastatic colorectal lesion in the right liver. (b) Digital subtraction angiogram from a microcatheter in the common hepatic artery showing tumor hypervascularity (arrow) and visceral blood supply. (c) Scintigraphic scan obtained after injecting MAA into vessel supplying tumor with regions of interest (ROI) showing the liver and lungs. No significant counts are seen in the lung ROIs. The patient was therefore eligible for Y-90 treatment. (d) Eight-week follow-up PET/CT showing complete response after Y-90 treatment with no residual abnormal FDG activity.

Pretreatment arteriography involves evaluating the celiac, superior mesenteric, left gastric, gastroduodenal, proper hepatic, and right/left hepatic arteries. In the interest of redistributing blood flow away from the gastrointestinal tract, embolization of the gastroduodenal artery or any additional gastric artery may be required, most commonly the right gastric artery [19]. Other arteries that may necessitate embolization include the falciform, supraduodenal, retroduodenal, left inferior phrenic, accessory left gastric, and inferior esophageal. The objective is to prevent exposing the gastrointestinal tract to radiation, which can result in serious complications.

Selective arteriography is performed in the area where the yttrium-90 will be administered. This allows for dosimetry calculations to be based on the volume of the target vascular bed (liver segments) supplied by the artery to be catheterized [26].

Once the vascular anatomy has been established and prophylactic embolization of nontarget arteries complete, a ^{99m}Tc MAA scan is performed (**Figure 2**). Once injected, the distribution of the tagged albumin is visualized using planar or single photon emission CT (SPECT) γ cameras.

The lung shunt fraction (LSH) is used to assess the degree of shunting to the lungs and gastrointestinal tract. It describes the fraction of ^{99m}Tc MAA observed in the lungs or GI tract relative to the total ^{99m}Tc MAA activity observed. The lungs are able to tolerate 30 Gy per treatment session and a cumulative 50 Gy [27]. Patients are cleared for treatment if their cumulative pulmonary dose does not exceed 50 Gy and no pre-existing pulmonary pathology is present.

3.5. Post-procedure management

Radioembolization is a relatively safe procedure that can be typically performed on an outpatient basis. Patients are placed on a 7–10 day course of a proton pump inhibitor to prevent gastric ulceration. A 7–10 day course of a fluoroquinolone may also be prescribed if the entire right lobe is treated with the gallbladder present. Steroids may also be given after the procedure to decrease fatigue and systemic response to therapy.

A clinic appointment should be scheduled post procedure in order to evaluate the patient's tolerance of the treatment, ECOG performance status, and other adverse sequelae. The timing of the appointment is important because the majority of microsphere radioactivity decays by 12 days (4 half-lives) [26], allowing for an assessment of a patient when peak therapeutic response is achieved.

Cross-sectional imaging is performed 4–6 weeks after the procedure. It is important to note, however, that conventional imaging response criteria are poor predictors of response to radioembolization, particularly at early time points [26]. MRI diffusion-weighted imaging may provide a more accurate assessment of treatment efficacy. An FDG-PET scan may also be performed when appropriate.

In cases where bilobar disease is present, treatment of the second lobe is performed shortly after the assessment of response for the first treatment is complete. The process is repeated until all tumor foci have been treated.

3.6. Complications

Complications associated with radioembolization include post-radioembolization syndrome (PRS), hepatic dysfunction, biliary sequelae, GI ulcerations, radiation pneumonitis, vascular injury, and lymphopenia [28].

The incidence of PRS ranges from 20% to 55% [28]. Symptoms include fatigue, abdominal pain, nausea, vomiting, and fever. The duration of symptoms varies among patients, and hospitalization is usually not required. PRS is managed conservatively with hydration and over-the-counter analgesics. Post-embolization syndrome appears less frequently following Y-90 when compared to TACE because the radioembolization microspheres typically do not cause complete occlusion of the feeding artery [24].

Radiation-induced liver disease (RILD) occurs when normal liver parenchyma is exposed to high doses of radiation. The incidence reported in the literature ranges between 0% and 4% [28]. Hepatic dysfunction is characterized by elevated alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, and decreased albumin. Supportive care is recommended with close monitoring of patients with pre-existing poor hepatic reserve.

The incidence of biliary sequelae is less than 10% [28]. Damage to the biliary tree is induced by exposure to high doses of radiation or by the microembolic effects of microspheres. Patients are usually asymptomatic and recover with supportive care. Radiation cholecystitis requiring surgical intervention occurs in less than 1% of cases [29].

Radiation pneumonitis is caused by arteriovenous malformations shunting high doses of radiation to the lungs. With the use of standard dosimetry models and an accurate ^{99m}Tc MAA scan, the incidence of pneumonitis is well below 1% [30, 31]. The complication results in restrictive pulmonary dysfunction with a bat-wing appearance on chest CT [28].

Gastric ulceration may be caused when radioembolic microspheres enter the gastrointestinal circulation, becoming embedded in the lining of the GI tract. The incidence is less than 5% when accurate preliminary angiography and prophylactic embolization are performed [32–34]. Early management of severe epigastric pain is vital in preventing serious complications from developing.

3.7. Outcomes

A systematic review and meta-analysis was conducted by Facciorusso et al. [35] comparing the efficacy and safety of Y-90 radioembolization and TACE for treating unresectable HCC. Survival rates assessed at 1 year revealed no significant difference between the two treatment groups (OR = 1.01; 95% CI, 0.78–1.31; P= 0.93). The study revealed similar effects in terms of survival, response rate, and safety profile [35]. A study conducted by Salem et al. [36] concluded that Y-90 patients experienced a more desirable quality of life in terms of social and

functional well-being than those treated with TACE. The lower toxicity of radioembolization, its ability to be performed as an outpatient procedure, and the decreased incidence of post-embolization syndrome all contribute to improving the quality of life for patients. Patients with portal vein thrombosis, a relative contraindication for TACE, can be safely treated with Y-90, yielding median survival of 8–14 months [37].

4. Percutaneous tumor ablation

Image-guided percutaneous tumor ablation describes the utilization of needle-like devices to directly administer cytotoxic chemicals or energy to a target tissue. Chemical ablation is most commonly performed using ethanol or acetic acid, whereas energy ablation can be divided into thermal and nonthermal techniques. The most widely applied thermal ablation modalities include radiofrequency (RF), microwave (MW), cryoablation, laser, and high intensity focused ultrasonography (US). Irreversible electroporation (IRE) is considered as a form of nonthermal ablation, although high temperatures may be achieved.

4.1. Ablation types

Understanding the advantages, disadvantages, and mechanisms of action of each ablative technique, along with patient and tumor characteristics, is essential in choosing the modality with the greatest efficacy and safety.

Ethanol ablation is a type of chemical ablation that utilizes 95% ethanol to induce coagulative necrosis through cellular dehydration, protein denaturation, and blood vessel thrombosis. Chemical ablation has largely been replaced by thermal ablation due to the former's variable and unpredictable distribution to surrounding tissue, leading to a high rate of tumor recurrence. However, there are certain situations where chemical ablation remains a viable option. Patients with HCC are good candidates because the fibrosed cirrhotic liver around the tumor can act like a capsule that limits the diffusion of ethanol to the surrounding parenchyma [38]. Patients with metastatic liver disease are not considered good candidates due to the normal parenchyma surrounding the tumor. Chemical ablation may be preferred or used in conjunction with thermal ablation in situations where the tumor is in close proximity to delicate structures or in areas of high perfusion-mediated tissue cooling [38].

Radiofrequency ablation (RFA) is the most commonly used modality for treating HCC and metastatic colorectal carcinoma to the liver. This heat-based ablation technique involves the formation of a closed electrical circuit between an applicator that acts like a cathode and grounding pads applied to the patients' skin that act as the anode. An alternating current is conducted through the applicator causing surrounding ions to vibrate as they try to align with the current. The agitated ions generate heat leading to coagulative necrosis of surrounding tumor. RFA has proven effective in treating tumors less than 3 cm, with a significant drop-off in success noted in tumors greater than 3 cm. The reason for the decrease in effectiveness is likely due to RFA's poor conductive heating and limited ability to overcome perfusion-

mediated tissue cooling [38]. The flowing blood in highly vascularized tissue acts like a heat sink, not allowing the temperature to reach cytotoxic levels.

Microwave ablation (MWA) utilizes an antenna that emits electromagnetic waves producing an oscillating electrical field. Surrounding water molecules attempt to align with the changing field leading to the production of kinetic energy, which is converted to heat. Higher temperatures and larger ablations are possible with MWA when compared to RFA. The increase in power allows MWA to overcome perfusion-mediated tissue cooling and rely less on conduction heating. The increase in strength of MWA may lead to higher complications such as portal vein thrombosis, especially in cirrhotic patients where portal venous flow rate is reduced [39].

Cryoablation utilizes the Joule-Thompson principle of thermodynamics to effectively ablate a tumor through multiple freeze/thaw cycles. The process involves pumping high-pressure argon down an insulated narrow tube. A small opening at the end of the tube allows the argon to escape into an expansion chamber. The rapid expansion of the gas results in intense cooling leading to the formation of an ice ball. Similarly, high-pressure helium is forced down the hollow pipe, escaping through the opening, and into the expansion chamber. Rather than rapid cooling, helium causes rapid heating on expansion, effectively thawing the ice ball. The freeze/ thaw cycle is repeated multiple times leading to tumor cell death. The formation of intracellular ice crystals causes mechanical disruption of cell membranes, while extracellular crystals create osmotic shifts and local hypertonicity. The low temperatures also cause apoptosis through interruption of cellular metabolism and vascular thrombosis leading to ischemia. An advantage of cryoablation over other ablative techniques is the ability to visualize the ice ball with imaging during the procedure. This allows the physician to assess if an adequate ablation is achieved or if more cycles are needed. Cryoablation is associated with minimal pain, allowing patients who are not good candidates for general anesthesia to undergo the procedure.

Irreversible electroporation (IRE) is the only nonthermal ablative technique available at this time. The procedure involves delivering short bursts of high voltage electrical impulses between two parallel electrodes [40]. The impulses form large pores in cell membranes resulting in cell death. Cytotoxic temperatures may be achieved in certain IRE ablations depending on the parameters of the case. The non-thermal mechanism of IRE makes it a preferable option for tumors in close proximity to critical structures, such as the bile ducts.

4.2. Patient selection and indications for ablation

The American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) have adopted the Barcelona Clinic Liver Cancer (BCLC) staging system for the management of HCC. Tumor ablation, particularly radiofrequency ablation, is considered curative and the treatment of choice for patients with *very early* and *early stage* HCC not amendable to surgical resection or transplantation [41, 42]. *Very early stage* includes patients with a performance status of 0, Child-Pugh A, and a single HCC < 2 cm. An *early stage* HCC is a patient with a performance status of 0, Child-Pugh A-B, single HCC <5 cm or 3 nodules <3 cm each.

4.3. Contraindications: absolute and relative

Absolute contraindications for percutaneous tumor ablation include tumor located less than 1 cm from the main biliary duct, intrahepatic bile duct dilatation, anterior exophytic location of the tumor due to risk of tumor seeding, untreatable coagulopathy, and unmanageable liver failure [43].

The number of hepatic lesions, usually greater than 5, should be considered a relative contraindication if all tumor foci cannot be effectively treated. If the extent of liver metastasis is too great, percutaneous ablation is not indicated. The majority of treatment centers prefer to treat patients with five or fewer lesions. The highest rate of treatment success has been established in tumors 3 cm or less along their longest axis. Tumors larger than 3 cm are considered a relative contraindication. Tumors located superficially or near any high-risk structures, such as the gastrointestinal tract, gallbladder, or biliary tree, are considered relative contraindications.

4.4. Pre-procedure preparations

Once a patient has been thoroughly evaluated and considered a candidate for percutaneous ablation, the pre-procedure preparations begin. Laboratory studies, such as complete blood count, creatinine, prothrombin time/INR, liver function tests, and tumor markers (alpha-fetoprotein), are ordered prior to the procedure in order to establish baseline measurements. Pre-procedure calculations of the patient's ECOG performance status and tumor markers are especially important for monitoring hepatic complications and treatment success post procedure.

Multidetector spiral computed tomography (CT) or dynamic magnetic resonance (MR) imaging should be obtained in order to carefully define the location of each tumor and their respective surrounding anatomy. Accurate imaging is essential for selecting the most appropriate ablative modality with the highest efficacy and lowest risk of complications.

Tumors in close proximity to structures, such as the biliary system, gastrointestinal tract, and major blood vessels, require careful consideration. Although radiofrequency ablation is the gold standard modality, if the risk for thermal injury is too great, other techniques should be considered. Ethanol ablation in conjunction with radiofrequency may decrease the risk for thermal injury and effectively treat the tumor [44]. Other nonablative modalities such as TACE or radioembolization may be indicated if the risk of complications with ablation is too high.

Superficial tumors whose margins abut adjacent structures, such as bowel, gallbladder, pancreas, or abdominal wall, require careful pre-procedure planning in regard to patient position, needle leverage maneuvers, and the potential need for hydrodissection or pneumodissection [44]. Hydrodissection involves the creation of artificial ascites by injecting a solution of 5% dextrose and 2% contrast into the peritoneum. The fluid displaces the at-risk structures, allowing for thermal ablation to be performed. Analogously, displacement of anterior structures can be performed with pneumodissection using carbon dioxide gas (**Figure 3**).
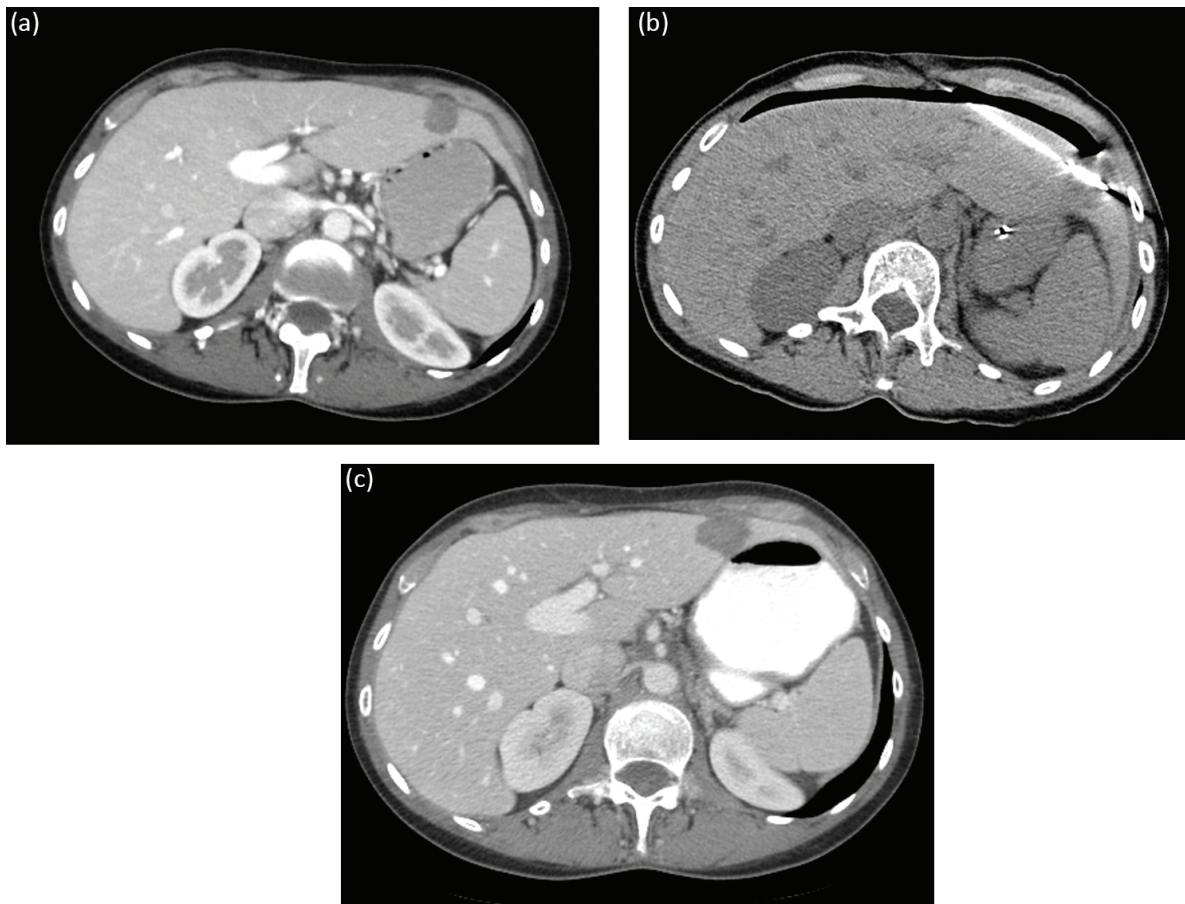
Figure 3. Thermal ablation of hepatic metastasis using pneumodissection. (a) A 59-year-old female with metastatic leiomyosarcoma to the left hepatic lobe. The tumor extends to the anterior liver border. (b) Microwave ablation of the metastasis was performed. To allow for the ablation margin to extend to the anterior liver border without injuring the peritoneal lining and abdominal wall, pneumodissection was performed by delivering carbon dioxide gas anterior to the liver, thus displacing the liver from the peritoneum. (c) Post-procedure CT demonstrates complete response of the metastasis.

4.5. Procedure

Tumor ablation may be performed under general anesthesia or conscious sedation with local anesthesia. Once appropriate sedation is achieved, the performing physician localizes the tumor under ultrasound or CT guidance. Ultrasound is most often used for initial needle placement due to the ability to visualize the needle in real time. Once the needle is in place, CT may be used to evaluate placement relative to surrounding critical structures.

Radiofrequency ablation utilizes thermal energy to cause cell death. The amount of tissue damage depends on the temperature achieved and duration of heating. Permanent cellular damage is attained when tissue temperature exceeds 50°C for 4–6 minutes. Temperatures above 100°C are not recommended due to tissue vaporization and carbonization leading to the production of gas which acts as an insulator. The gas production makes establishing a large enough ablation zone difficult. With this in mind, the objective is to maintain a temperature between 50°C and 100°C throughout the entire target tissue for at least 4–6 minutes. Depending

on the size of the lesion, multiple electrodes are usually required to achieve the target temperature.

In order to ensure low rates of local tumor recurrence, appropriate ablation margins need to be achieved. According to Crocetti et al., [43] the ablation must extend 1–2 cm beyond the tumor margin in order to treat possible microscopic satellite lesions. Repeat CT scans are performed throughout the procedure to assess achievement of adequate tumor margins and monitor potential surrounding tissue damage.

4.6. Post-procedure management

Post-ablation patients are usually admitted to the hospital for overnight observation. If vital signs and laboratory results remain within normal limits, patients are discharged home the day after the procedure.

A consensus has yet to be established on the optimal interval or frequency of post-ablation imaging. According to Crocetti et al., [45] imaging 4–8 weeks after the procedure is recommended. A successful ablation will appear as a nonenhancing area with or without a peripheral enhancing rim. Routine follow-up imaging along with tumor marker measurements is important to detect recurrence in the future.

4.7. Complications

The rate of major complications post ablation ranges between 2.2% and 3.1% and include intraperitoneal hemorrhage, liver abscess formation, bowel perforation, tumor seeding, bile duct stenosis, pneumothorax/hemothorax, and skin burns [46].

According to a multicenter study by Livraghi et al., [46] the incidence of intraperitoneal hemorrhage requiring therapy is 0.5%. An INR < 1.5 and a platelet count above 50,000 per μL are required to maintain a low risk of bleeding during or after the procedure. Tract cauterization when removing the needle also decreases the incidence of bleeding.

With the use of proper sterile technique, the incidence of intrahepatic abscess is maintained low at 0.3% [46]. Patients with risk factors such as biliary enteric anastomosis or altered bile ducts should be placed on a 10-day course of antibiotics post procedure.

The incidence of intestinal perforation and bile duct stenosis is 0.3% and 0.1%, respectively [46]. Accurate imaging, careful pre-procedural planning, and the use of hydrodissection if needed are important in avoiding thermal damage to these structures.

The incidence of tumor seeding is 0.5% [46]. Performing needle tract ablation and avoiding direct puncture of peripheral liver tumors help to keep the incidence of seeding low.

The incidence of minor complications ranges from 4.7% to 8.9% and include pain, fever, self-limiting intraperitoneal bleed, and minor skin burns. The mortality rate of patients undergoing ablation ranges from 0.1% to 0.5% and is most commonly caused by sepsis, hepatic failure, colon perforation, and portal vein thrombosis.

4.8. Outcomes

According to Livraghi et al. [47], the complete response rates of patients with *very early stage* HCC (<2 cm) treated with radiofrequency ablation approach 97%, with 5-year survival rates of 68%. A study conducted by Cho et al. [48] in 2010 concluded that radiofrequency ablation is just as effective in treating *very early stage* HCC when compared to surgical resection. Despite similar success rates, patient characteristics and tumor location may indicate the use of one treatment over the other. For example, lesions in a subcapsular location or adjacent to the gallbladder may be better treated with surgical resection instead of RF ablation.

A study conducted by Lencioni et al. [49] revealed that patients with *early stage* HCC (single tumor ≤ 5 cm, or fewer than three tumors each ≤ 3 cm) treated with radiofrequency ablation exhibited 5-year survival rates ranging between 51% and 64%. Surgical resection remains the most effective treatment in patients with *early stage* HCC.

A randomized controlled trial was conducted by Morimoto et al. [50] determining the efficacy of radiofrequency ablation combined with transcatheter arterial embolization. The study concluded that patients with intermediate sized (3.1–5 cm) HCC treated with combination TACE-RF ablation exhibited better outcomes and tumor control when compared to RF only. TACE-RF ablation patients had 6% local tumor progression compared to 39% in the RF only patients.

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References

[1] Guan Y-S, He Q, Wang M-Q, Guan Y-S, He Q, Wang M-Q. Transcatheter arterial chemoembolization: history for more than 30 years. Int Sch Res Not 2012, 2012:e480650.

[2] Shin SW. The current practice of transarterial chemoembolization for the treatment of hepatocellular carcinoma. Korean J Radiol 2009;10(5):425–434.

[3] Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol 1954;30(5): 969–985.

[4] Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 2003;37(2):429–442.

[5] Lo C-M, Ngan H, Tso W-K, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35(5):1164–1171.

[6] Kawai S, Tani M, Okamura J, et al. Prospective and randomized trial of lipiodol-transcatheter arterial chemoembolization for treatment of hepatocellular carcinoma: a comparison of epirubicin and doxorubicin (second cooperative study). The Cooperative Study Group for Liver Cancer Treatment of Japan. Semin Oncol 1997;24(2 Suppl 6):S6–38–S6–45.

[7] Watanabe S, Nishioka M, Ohta Y, Ogawa N, Ito S, Yamamoto Y. Prospective and randomized controlled study of chemoembolization therapy in patients with advanced hepatocellular carcinoma. Cooperative Study Group for Liver Cancer Treatment in Shikoku area. Cancer Chemother Pharmacol 1994;33 Suppl:S93–S96.

[8] Marelli L, Stigliano R, Triantos C, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. Cardiovasc Intervent Radiol 2006;30(1):6–25.

[9] Idée J-M, Guiu B. Use of Lipiodol as a drug-delivery system for transcatheter arterial chemoembolization of hepatocellular carcinoma: A review. Crit Rev Oncol Hematol 2013;88(3):530–549.

[10] Takayasu K, Shima Y, Muramatsu Y, et al. Hepatocellular carcinoma: treatment with intraarterial iodized oil with and without chemotherapeutic agents. Radiology 1987;163(2):345–351.

[11] Sasaki Y, Imaoka S, Kasugai H, et al. A new approach to chemoembolization therapy for hepatoma using ethiodized oil, cisplatin, and gelatin sponge. Cancer 1987;60(6):1194–1203.

[12] Coldwell DM, Stokes KR, Yakes WF. Embolotherapy: agents, clinical applications, and techniques. RadioGraphics 1994;14(3):623–643.

[13] Lammer J, Malagari K, Vogl T, 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(1):41–52.

[14] Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet Lond Engl 2002;359(9319):1734–1739.

[15] Cammà C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology 2002;224(1):47–54.

[16] Chapman WC, Majella Doyle MB, Stuart JE, et al. Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. Ann Surg 2008;248(4):617–625.

[17] Lencioni R, Petruzzi P, Crocetti L. Chemoembolization of hepatocellular carcinoma. Semin Interv Radiol 2013;30(1):3–11.

[18] Sieghart W, Hucke F, Peck-Radosavljevic M. Transarterial chemoembolization: modalities, indication, and patient selection. J Hepatol 2015;62(5):1187–1195.

[19] RMBD.pdf [Internet] [Cited 2016 July 9]. Available from: http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/RMBD.pdf

[20] Van Ha TG. Transarterial chemoembolization for hepatocellular carcinoma. Semin Interv Radiol 2009;26(3):270–275.

[21] Song SY, Chung JW, Han JK, et al. Liver abscess after transcatheter oily chemoembolization for hepatic tumors: incidence, predisposing factors, and clinical outcome. J Vasc Interv Radiol JVIR 2001;12(3):313–320.

[22] Kennedy A, Nag S, Salem R, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: A Consensus Panel Report from the Radioembolization Brachytherapy Oncology Consortium. Int J Radiat Oncol 2007;68(1):13–23.

[23] Salem R, Lewandowski RJ, Atassi B, et al. Treatment of unresectable hepatocellular carcinoma with use of 90Y microspheres (TheraSphere): safety, tumor response, and survival. J Vasc Interv Radiol 2005;16(12):1627–1639.

[24] Edeline J, Gilabert M, Garin E, Boucher E, Raoul J-L. Yttrium-90 microsphere radioembolization for hepatocellular carcinoma. Liver Cancer 2015;4(1):16–25.

[25] Llovet JM. Treatment of hepatocellular carcinoma. Curr Treat Options Gastroenterol 2004;7(6):431–441.

[26] Salem R, Thurston KG. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: technical and methodologic considerations. J Vasc Interv Radiol 2006;17(8):1251–1278.

[27] Ho S, Lau WY, Leung TW, Chan M, Johnson PJ, Li AK. Clinical evaluation of the partition model for estimating radiation doses from yttrium-90 microspheres in the treatment of hepatic cancer. Eur J Nucl Med 1997;24(3):293–298.

[28] Riaz A, Lewandowski RJ, Kulik LM, et al. Complications following radioembolization with yttrium-90 microspheres: a comprehensive literature review. J Vasc Interv Radiol 2009;20(9):1121–1130.

[29] Rhee TK, Naik NK, Deng J, et al. Tumor response after yttrium-90 radioembolization for hepatocellular carcinoma: comparison of diffusion-weighted functional MR imaging with anatomic MR imaging. J Vasc Interv Radiol JVIR 2008;19(8):1180–1186.

[30] Leung TW, Lau WY, Ho SK, et al. Radiation pneumonitis after selective internal radiation treatment with intraarterial 90yttrium-microspheres for inoperable hepatic tumors. Int J Radiat Oncol Biol Phys 1995;33(4):919–924.

[31] Salem R, Parikh P, Atassi B, et al. Incidence of radiation pneumonitis after hepatic intra-arterial radiotherapy with yttrium-90 microspheres assuming uniform lung distribution. Am J Clin Oncol 2008;31(5):431–438.

[32] Murthy R, Brown DB, Salem R, et al. Gastrointestinal complications associated with hepatic arterial Yttrium-90 microsphere therapy. J Vasc Interv Radiol JVIR 2007;18(4): 553–561; quiz 562.

[33] Mallach S, Ramp U, Erhardt A, Schmitt M, Häussinger D. An uncommon cause of gastro-duodenal ulceration. World J Gastroenterol 2008;14(16):2593–2595.

[34] Szyszko T, Al-Nahhas A, Tait P, et al. Management and prevention of adverse effects related to treatment of liver tumours with 90Y microspheres. Nucl Med Commun 2007;28(1):21–24.

[35] Facciorusso A, Serviddio G, Muscatiello N. Transarterial radioembolization vs chemo-embolization for hepatocarcinoma patients: a systematic review and meta-analysis. World J Hepatol 2016;8(18):770–778.

[36] Salem R, Gilbertsen M, Butt Z, et al. Increased quality of life among hepatocellular carcinoma patients treated with radioembolization, compared with chemoembolization. Clin Gastroenterol Hepatol 2013;11(10):1358–1365.e1.

[37] Kulik LM, Carr BI, Mulcahy MF, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatol Baltim Md 2008;47(1):71–81.

[38] Wells SA, Hinshaw JL, Lubner MG, Ziemlewicz TJ, Brace CL, Lee Jr. FT. Liver ablation: best practice. Radiol Clin North Am 2015;53(5):933–971.

[39] Livraghi T, Meloni F, Solbiati L, Zanus G, System F; CIG using AMICA system. Complications of microwave ablation for liver tumors: results of a multicenter study. Cardiovasc Intervent Radiol 2011;35(4):868–874.

[40] Golberg A, Yarmush ML. Nonthermal irreversible electroporation: fundamentals, applications, and challenges. IEEE Trans Biomed Eng 2013;60(3):707–714.

[41] Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatol Baltim Md 2011;53(3):1020–1022.

[42] European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL–EORTC Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56(4):908–943.

[43] Crocetti L, de Baere T, Lencioni R. Quality improvement guidelines for radiofrequency ablation of liver tumours. Cardiovasc Intervent Radiol 2010;33(1):11–17.

[44] Ziemlewicz TJ, Wells SA, Lubner MG, Brace CL, Lee FT, Hinshaw JL. Hepatic tumor ablation. Surg Clin North Am 2016;96(2):315–339.

[45] Crocetti L, Della Pina C, Cioni D, Lencioni R. Peri-intraprocedural imaging: US, CT, and MRI. Abdom Imaging 2011;36(6):648–660.

[46] Livraghi T, Solbiati L, Meloni MF, Gazelle GS, Halpern EF, Goldberg SN. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. Radiology 2003;226(2):441–451.

[47] Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? Hepatology 2008;47(1):82–89.

[48] Cho YK, Kim JK, Kim WT, Chung JW. Hepatic resection versus radiofrequency ablation for very early stage hepatocellular carcinoma: a Markov model analysis. Hepatol Baltim Md 2010;51(4):1284–1290.

[49] Lencioni R, Crocetti L. Local-regional treatment of hepatocellular carcinoma. Radiology 2012;262(1):43–58.

[50] Morimoto M, Numata K, Kondou M, Nozaki A, Morita S, Tanaka K. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. Cancer 2010;116(23):5452–5460.