Chapter 4

Liver Directed Therapies

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.75163

Abstract

Minimally invasive liver directed therapies have established their role in the treatment of hepatic neoplasms. The Barcelona Clinic staging systems is the most widely used staging system and combines staging and management. While surgical resection or liver transplantation are commonly performed for very early stage cancers, patient's typically present with advanced disease. For those with single or small lesions, percutaneous tumor ablation may be curative. Transarterial chemoembolization or radioembolization are palliative treatments reserved for those with unresectable tumors or as bridge to transplant. In this chapter, we discuss the role of liver directed therapies throughout various stages of liver cancer, the management of these procedures, and its impact on patient care.

Keywords: hepatocellular carcinoma, colorectal cancer, percutaneous liver ablation chemoembolization, radioembolization, liver directed therapies

1. Introduction

Hepatocellular carcinoma (HCC) is the 5th leading cause of cancer in the US and 2nd most common cause of cancer related death worldwide [1]. HCC has a dismal prognosis with a ratio of mortality to incidence of 0.95 [2]. The incidence of HCC is rising as its primary risk factors, hepatitis B and C, become more prevalent in the population, especially in developing countries where hepatitis B is endemic [3]. The majority of patients with HCC are often diagnosed in intermediate or advanced stage disease where curative therapeutic options are no longer available [4]. Moreover, HCC is associated with liver cirrhosis, which also limits therapeutic options. The management of HCC is generally based on the guideline of the Barcelona Clinic Liver Cancer (BCLC) staging system. If HCC is detected in its early stages (BCLC-0 or BCLC-A), the 5-year survival may be as high 70–80% with optimal therapies such as resection, orthotopic liver

transplantation, or percutaneous ablation [5]. In the intermediate stage (BCLC-B), patients are managed with image-guided catheter based therapies such as transarterial embolization or chemoembolization (TAE/TACE). However, intra-arterial locoregional therapies are palliative and most patients experience disease progression. In 2017, several new therapeutic options have become available for advanced HCC although this is beyond the scope of this chapter where locoregional therapies will be reviewed.

2. Percutaneous ablation

Percutaneous ablation is a curative intent procedure reserved for patients with early stage disease HCC. It involves accessing the tumor percutaneously under ultrasound or CT guidance with probes. Three broad categories of percutaneous ablation exist: chemical, thermal, and non-thermal.

Chemical ablation induces cellular dehydration, protein denaturation, and blood vessel thrombosis causing coagulation necrosis via ethanol administration into the tumor. The ethanol has an unpredictable distribution in the surrounding tissue, leading to a high rate of tumor recurrence. This technique has largely been replaced by thermal ablation though still finds its uses where thermal ablation is risky such as in tumors in close proximity to vital organs.

Thermal ablation can be classified into three modalities: radiofrequency, microwave ablation, and cryoablation.

Radiofrequency ablation (RFA) is the most commonly performed procedure for hepatic tumors. There is an alternating electrical current within the device that causes agitated ions to generate heat and induce coagulative necrosis. This technique is reserved for tumors less than 3 cm due to the techniques poor conductive heating over greater distances.

Microwave ablation (MWA) uses electromagnetic waves to induce an alternating electrical field that produces heat. This has the ability to reach higher temperatures to overcome perfusion-mediated tissue cooling when compared to RFA, making ablation of larger tumors possible along with faster ablation times. This technique is preferred for tumors near major vessels, such as the inferior vena cava or main hepatic veins, due to the attenuated heat sink effect [6].

Cryoablation consists of pumping high-pressure argon into a probe, which escapes at the very tip and causes rapid expansion of the gas leading to intense cooling and formation of an ice ball around the needle tip. This causes intracellular ice crystals and disrupts the cell membrane and cellular metabolism. The low temperature also causes vascular thrombosis. Multiple cycles of freezing and thawing are performed. The advantage of cryoablation is the ability to see the ice ball during the procedure on CT, which allows the physician to determine adequate ablation. The technique was historically not used because of reported cryoshock. Recent reports have demonstrated that hepatic cryoablation is feasible and safe.

Non-thermal ablation is performed through irreversible electroporation (IRE). This technique involves high voltage electrical impulses between parallel electrodes. The high voltage causes

large pores in the cellular membranes leading to apoptosis. The advantage of IRE is the ability to ablate tumors that are in close proximity to vital structures such as the portal veins or bile ducts. IRE is a technically difficult procedure, as it requires multiple devices to be inserted in a near-perfect parallel conformation.

2.1. Management

Based on the BCLC, percutaneous ablation is reserved for patients with very early disease or early stage HCC that are not amenable to surgical resection or transplantation. The criteria for very early stage include a single tumor less than 2 cm. The criteria for early stage include a single tumor less than 5 cm or 3 nodules less than 3 cm each.

Absolute contraindications include intrahepatic biliary ductal dilatation, uncorrectable bleeding diathesis, or decompensated liver failure. Relative contraindications include tumor burden to be greater than five lesions, tumors larger than 3 cm, or tumors in close proximity to vital structures such as the portal vein, biliary tree, or gastrointestinal tract.

Patients are usually monitored for a few hours post-procedure. If vital signs and lab values are not significantly changed, patients can be discharged the same day or the day after the procedure. Follow up imaging with CT or MRI is obtained 4–8 weeks post procedure.

2.2. Complications

Major complications include intraperitoneal bleeding, intestinal perforation, bile duct stenosis, pneumothorax or hemothorax, liver abscess formation, or skin burns. Skin burns occur in less than 1% [7]. Late complication would include tumor seeding along the needle track which was found to occur 0.5% of cases with HCC based on a multicenter survey [8]. Other complications include minor symptoms such as pain, fever, or self-limited bleeding. The procedural mortality rate is between 0.1 and 0.5% which are due to sepsis, liver failure, portal venous thrombosis, or gastrointestinal perforation.

2.3. Results

In patients with HCC, RFA was shown to have complete tumor necrosis in 83% for lesions less than 3 cm and 88% for lesions in non-perivascular locations [9]. RFA had higher efficacy compared to ethanol ablation. The complete response rate is close to 97% with 5-year survival rates of 68% [10]. A study conducted by Cho et al. showed that RFA was just as effective as surgical resection for very early stage HCC [11]. A study conducted by Lencioni et al. showed that surgical resection remains the most effective treatment for patients with early stage HCC when compared to RFA [12]. A meta-analysis of over 21,000 patients demonstrated that surgery has higher post-operative mortality but improved 5 year overall survival compared to ablation. Of note, this study combined chemical and thermal ablation even though chemical ablation is known to be less efficient [13].

The studies comparing MWA to RFA have varying results. A study by Abdelaziz reported local recurrence rates of MWA, 3.9%, to be superior to RFA, 13.5%. Another study reported

decreased recurrence rates with RFA, 9%, compared to MWA, 19% [14]. A review of multiple studies demonstrate overall comparable rates for MWA and RFA in terms of overall survival and local recurrence.

A study by Wang compared cryoablation to RFA in patients with HCC lesions less than or equal to 4 cm. Results demonstrated significantly lower local tumor progression rates with cryoablation, 5.6%, compared to RFA, 10% [15]. For lesions larger than 3 cm, the difference became more apparent with progression rates of 7.7% for cryoablation and 18.2% for RFA. The recurrence free survival and overall survival rates were not significantly different between cryoablation and RFA [15].

In patients with metastatic CRC, RFA was shown to have a complete response rate of 91–97% [16]. In patients with five or fewer lesions less than 5 cm, the 5-year survival rate was between 24 and 44% [17]. For patients who had complete tumor ablation, 98% did not require further surgical resection either due to remaining disease free or developing disease progression [18].

3. Transarterial chemoembolization

Transarterial chemoembolization (TACE) is the most commonly performed procedure by interventional radiologists for treatment of unresectable hepatic malignancies. Nearly half of all HCC patients receive TACE at some point in their disease course [19]. Multiple techniques have been used for TACE over the past few decades.

The theory behind TACE relies on the liver's dual blood supply as hepatic tumors derive their blood supply mainly from the hepatic artery while normal hepatic parenchyma is predominantly supplied by the portal vein. Percutaneous access to the arterial system is obtained via femoral or radial artery catheterization. Imaging is performed to assess for variant anatomy, portal vein patency, and tumoral blood supply. Angiograms were performed, however in recent years, Cone Beam Computed Tomography (CBCT) has played an important role during locoregional therapies and is recommended as standard of care during chemoembolization [20]. Once the feeding arteries to the tumor are identified, they are selectively catheterized and chemoembolization is performed. Chemoembolization can be achieved by bland embolization, conventional trans-arterial chemoembolization (cTACE) or with drug-eluting embolic trans-arterial chemoembolization (DEE-TACE).

cTACE consists of administering chemotherapeutic agent(s) combined with an ethiodized oil emulsion followed by an embolic agent i.e. Gelfoam, or microspheres. Historically, doxorubicin, cisplatin, and mitomycin C in combination were used for cTACE, however due to shortage of some of the drugs, the regimens changed. Neither drug alone or any combination of these agents have shown to be statistically superior [17, 18]. Currently in the United States and Europe, doxorubicin is used in the majority of cases while miriplatin and cisplatin are used in Japan [21].

Lipiodol is an ethiodized oil that is commonly used for cTACE and has been considered the standard of care. The thick consistency allows it act as an embolic agent, which travels further into the microvascular than microspheres. In addition, lipiodol is radio-opaque and it

emulsifies the chemotherapeutic agents in oil droplets, which helps with drug delivery. In a meta-analysis of multiple randomized control trials, lipiodol was shown to be a safe, effective agent in the treatment of HCC [22].

Embolic microspheres loaded with doxorubicin for HCC or irinotecan for CRC are injected in the tumor feeding artery in DEE-TACE. Studies have shown slower, more sustained drug release with decreased systemic concentrations.

Bland embolization is also performed for HCC and neuroendocrine tumors. It can be accomplished either by injecting a mixture of Lipiodol and Gelfoam or with bland beads.

3.1. Indications and contraindications

The main role for TACE is reserved for patients with stage B disease based on the Barcelona Clinic Liver Cancer (BCLC) staging system. Stage B disease is defined as patients with large, multinodular disease with good functional status and a Child-Pugh A-B score. Other indications would include downstaging patient's tumor burden to allow for transplantation.

Absolute contraindications would be reserved for patients with poorly compensated advanced liver disease since TACE may exacerbate patient's symptoms and increase risks of progression into liver failure. Other absolute contraindications include refractory bleeding diathesis, large metastatic disease burden outside the liver, active infection, main, right and left portal vein thrombosis as well as refractory encephalopathy.

3.2. Management

TACE is commonly performed under moderate sedation. Pre-procedural hydration may be performed to decrease risk of contrast/chemotherapy-induced nephropathy. Pre-operative antibiotics are only given for patients with high risk for infection such as disrupted biliary drainage pathways.

Patients are usually admitted overnight post-procedure to monitor for potential complications. Most often, patients develop minor symptoms that can be managed medically such as post-embolization syndrome. This self-limiting syndrome is comprised of abdominal pain, fever, and nausea and usually occurs within the first 72 h post-procedure. This can be seen in up to 80% of patients. Post-procedural transaminitis is more frequent with cTACE compared to DEE-TACE.

Patients are typically discharged the next day. The criteria for discharge include appropriate pain control, ambulation, adequate urine production, and tolerating PO intake. TACE may be repeated for tumor control. Multiple treatments are often required until either the MRI shows greater than 90% tumor necrosis, the patient is downstaged, there is a lack of tumor response after at least two treatments, or the development of disease progression or a contraindication to treatment.

3.3. Complications

There are varying criteria in determining patients who are at high risk for post-TACE liver failure. High-risk patients include a total bilirubin greater than 2 mg/dL, INR greater than 1.5,

MELD score greater than 15, Child C disease, portal venous thrombosis, thrombocytopenia, or the presence of ascites. While many of these criteria have excluded patients in the past, advancements in technology has led to selective and superselective chemoembolization allowing a number of these patients to be treated. Non-selective chemoembolization can damage surrounding healthy hepatic parenchyma leading patients to decompensated liver failure, especially those with poor hepatic reserve. With selective and superselective techniques, there is increased sparing of viable tissue. Many articles have exhibited TACE being safely performed in high-risk patients. One study demonstrated the rate of selective TACE-related irreversible liver failure to be 3% compared to 20% in nonselective cases [23]. Other studies showed TACE to be safe and effective in patients with portal venous thrombosis, especially in those with hepatic reserve and collateral circulation [24]. Kothary et al. analyzed 65 high-risk TACE procedures which showed a procedure-related morbidity rate of 10.8% and a 30-day mortality rate of 7.7% [25]. Yoon et al. observed a procedure-related morbidity rate of 2% and a 30-day mortality rate of 1% in 96 high-risk patients [26]. Overall, the general consensus seems to be on a case-to-case basis in which baseline hepatic function, hepatic reserve, and overall tumor burden are commonly taken into account.

Non-target embolization can occur due to reflux of chemoembolic agents or failure to recognize the arterial anatomy supplying non-hepatic structures. This can lead to gastrointestinal ulceration/perforation, pancreatitis, cholecystitis, pneumonitis, or skin burns.

Hepatic abscess formation is rare in patients with unaltered anatomy. However, patients with post-surgical or disrupted anatomy of the biliary tree are at increased risk due to colonization of the biliary tree from enteric flora. One study showed 6 out of 7 patients with a prior bilioenteric anastomosis formed hepatic abscesses even after receiving standard broad spectrum prophylactic antibiotics [27]. Another study showed no formation of hepatic abscess in four patients with prior bilioenteric anastomosis when adding an aggressive bowel preparation [28]. In addition, gas formation within embolized hepatic tumors may occur post-procedurally which may lead to the misdiagnosis of a hepatic abscess.

Vascular complications are uncommon but include access site hematomas, pseudoaneurysms, or arteriovenous fistulas.

Other rare complications include sepsis, biliary strictures, variceal bleeding, renal failure, or chemotherapy-related toxicities such as alopecia, anemia, or myelosuppression.

3.4. Results

Multiple studies have shown TACE to increase overall survival when compared to conservative management. A randomized control trial by Llovet et al. was terminated early as it demonstrated the one-year and two-year survival rates for chemoembolization to be 82 and 63% compared to 63 and 27% for supportive care [29]. Another randomized trial by Lo et al. showed the one-year and two-year survival rates for chemoembolization to be 57 and 31% compared to 32 and 11% for supportive care [30]. Two meta-analyses of randomized controlled trials by Camma et al. and Llovet et al. showed a significant decrease in 2 year mortality with

TACE in patients with unresectable HCC (odds ratio 0.54, 95% CI 0.33–89, P = 0.015 and odds ratio 0.53, 95% CI 0.32–0.89, P = 0.017) [31].

Several studies have compared DEE-TACE versus cTACE versus bland TACE. The PRECISION V study was a prospective randomized study analyzing cTACE versus DEE-TACE. The study did not meet its primary endpoint of superior response rate with DEE-TACE but did show DEE-TACE is better tolerated [32]. One major criticism is that the study used 300–500 μ beads, which are considered large for this application. However other randomized controlled trials also compared cTACE versus DEE-TACE including Golfieri et al. This study on 177 patients did not show any statistical difference in terms of local or overall tumor response with 2 year follow-up but demonstrated reduced post procedural pain with DEE-TACE [33]. Meta-analysis on the topic has had equivocal results.

Interestingly, a randomized trial of 101 patients treated with TAE using microspheres alone versus TACE using doxorubicin-eluting microspheres found no difference in the response to treatment (primary endpoint) and no difference in overall survival [34].

A recent meta-analysis of randomized controlled trials pertaining to 5700 patients concluded that none of the transcatheter chemoembolization options as stand-alone were superior to transarterial bland embolization. The authors added that the conclusions are based on large information size of moderate quality based on data from 3 randomized controlled trials (RCT) of TAE versus best supportive care, 4 RCT of TAE versus TACE and 2 TAE versus DEB-TACE [35].

The SPACE trial, a randomized, double-blinded, phase II trial, compared Sorafenib with DEB-TACE versus DEB-TACE alone (placebo) in the treatment of intermediate stage HCC. The study did not show improvement in time to progression nor overall survival between the two groups [36].

4. Radioembolization

Radioembolization, also known as selective internal radiation therapy (SIRT), consists of administering either glass or resin microspheres loaded with radioactive isotope, yttrium-90 (Y-90). Y-90 is a pure better emitter with a half-life of 64.1 h and a mean tissue penetration of 2–3 mm. Radioembolization is currently not part of the standard treatment guidelines. However, promising clinical research has driven its growing use in the management of hepatic malignancies. A multidisciplinary team consisting of surgeons, interventional radiologist, hepatologists, oncologists, and radiation oncologists determines if a patient is a candidate for Y-90 radioembolization. The Barcelona Clinic Liver Cancer (BCLC) and Eastern Cooperative Oncology Group (ECOG) scoring systems are taken into account in the decision process. The microspheres used today are either glass and resin microspheres. Glass microspheres, or TheraSpheres, is FDA approved for the treatment of unresectable HCC. Resin microspheres, or SIR-Spheres, is premarket approved by the FDA for the treatment of hepatic metastases from colorectal cancer in combination with floxuridine. Glass microspheres carry a higher activity load, thus requiring decreased volumes and number of spheres, compared to resin microspheres for the same dose [37]. Since resin

microspheres require a higher volume, it would in theory produce a greater ischemic/embolic effect that would decrease the efficacy of delivering the full radiation dose. That being said, technical differences between the microspheres have not resulted in differences for overall survival in HCC [38]. Moreover computational studies comparing the resin and glass microspheres have demonstrated that particle trajectory in vessels have very little dependence on particle size. Indeed the authors concluded that the carrier fluid provides enough momentum to overcome the range of microspheres characteristics [39].

4.1. Indications and contraindications

Aside from the multidisciplinary approach, patients should have a life expectancy greater than 3 months with an ECOG status less than 2. Radioembolization is often used an adjuvant therapy to chemotherapy and/or salvage therapy after failure of first-line chemotherapy. This technique is also preferred in patients with portal vein thrombosis.

Absolute contraindications would include poor liver function with an elevated total bilirubin or increasing bilirubin, previous radiation to the liver, or significant hepatopulmonary lung shunting as that would lead to radiation pneumonitis. TARE should not be used as first line therapy in CRC and should be avoided in patients with extensive extra-hepatic disease burden.

4.2. Management

Radioembolization is usually performed in an outpatient setting. Pre-procedural angiogram and nuclear medicine Technetium macro-aggregated albumin (Tc-MAA) scan are necessary prior to treatment.

The angiogram determines anatomy including replaced right or left hepatic arteries. The origin of the right gastric should be identified. Coil embolization of any gastro-intestinal vessels originating from the right or left hepatic artery must be performed. Tc-MAA is needed to assess lung shunt fraction and consequently lung dose as tumor vascularity often have arteriovenous shunts. The lungs dose cannot exceed 30 Gy in one treatment session or 50 Gy cumulative dose [40]. Several strategies have been employed with high lung shunt fraction including no treatment, reduction of SIRsphere dose, bland embolization of the shunt, and balloon occlusion of the hepatic vein during microspheres delivery.

A 7–10 day course of proton pump inhibitors may be given to prevent gastric ulceration.

Post-procedural MRI should be obtained no earlier than 2 months to assess tumor response. In addition, tumor markers and liver function tests are obtained 4–6 weeks post-procedure.

Post-radioembolization syndrome is a constellation of abdominal pain, fatigue, nausea, vomiting, and fever. This is usually managed conservatively with hydration and over the counter medications.

4.3. Complications

Radioembolization induced liver disease (REILD) presents as jaundice, ascites without tumor progression, biliary obstruction, or elevated alkaline phosphatase. Histopathology reveals

veno-occlusive disease, sinusoidal congestion, and necrosis. REILD is defined as liver failure within 90 days post-radioembolization or greater than 90 days without tumor progression. Patients with decreased baseline liver function, with whole liver treatments and poly-chemotherapy are at increased risk [41]. Low-dose steroids and ursodeoxycholic acid can reduce the risk of REILD.

Non-target embolization may also occur with the adverse effects similar to TACE. Gastrointestinal ulceration remains a risk though with careful administration technique and proper coil embolization during work-up, complications are decreased to less than 4% [42]. Radiation pneumonitis if very rare occurring less than 1% and is avoidable with proper work up.

Other rare complications include radiation pancreatitis, dermatitis, cholecystitis or cholangitis. In general, biliary complications occur in less than 10% of cases though patients with polychemotherapy or disrupted ampulla of Vater patients are at increased risk [43].

Vascular complications are also similar to TACE. Patients on bevacizumab (Avastin) and other biologic agents (i.e. cetuximab, aflibercept, etc.) are at increased risk of dissection and rupture so careful technique and use of microcatheters should be employed.

Rarely lymphopenia may occur after glass microsphere radioembolization with greater than 25% decrease in lymphocyte count [43]. Fortunately, no opportunistic infections have been described.

4.4. Results

For HCC, the average response rate is between 35 and 47% with median survival of 15–24 months [44–47].

SARAH, an open-label, multicenter phase III trial (France), compared patients treated with SIRT versus Sorafenib alone in patients with unresectable HCC. SIRveNIB was an open label randomized controlled trial (Asia Pacific) that compared SIRT versus Sorafenib in locally advanced HCC. Both trials had a superiority design with overall survival as the primary endpoint. Both trials did not meet endpoint as there was no statistical difference in overall survival or progression-free survival. Indeed, overall survival was 8.0 months versus 9.9 months in the SARAH trial and 8.8 months versus 10 months in the SIRveNIB trial for SIRT and Sorafenib respectively [48]. However, patients treated with SIRT showed higher tumoral response rates, and increased quality of life in the intent to treat population which increased over time [49]. Moreover major criticism of these trials include inexperienced sites, a high TACE failure rate among patients, and 26.8% of the SIRT cohort in SARAH and 28.8% of the SIRT cohort in SIRveNIB did not receive SIRT as intended.

For metastatic colorectal cancer (mCRC) disease to the liver, the average response rate was between 35 and 43% with a median survival of 5–14 months [50]. TARE has demonstrated its role in second line or salvage therapy.

Three multi-center, randomized controlled phase III trials (FOXFIRE, SIRFLOX, and FOXFIRE-Global) examined the role of TARE (Y-90 resin microspheres) in combination with chemotherapy as first line therapy versus chemotherapy alone (FOLFOX or OxMdG) for liver-only or liver-dominant mCRC. Although an improvement of liver progression free survival was seen,

overall progression free survival was not altered and the combination of the three studies did not demonstrate an improvement of overall survival but an increase in adverse events with the combination [51]. Careful patient selection is necessary for proper integration of SIRT in the management of mCRC and it should not be performed as first line therapy.

Conflict of interest

None.

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