Tailoring of Interventional Procedures for HCC Patients-Review Article

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One of the most frequent primary malignant tumors in the world is hepatocellular carcinoma (HCC). Currently, the optimal treatment methods for HCC are hepatic resection and liver transplantation. Unfortunately, surgical therapies are suitable for 20% of patients and those who are not eligible for surgery should undergo interventional therapies. In the past decade, a variety of interventional procedures have been employed for local control of hepatocellular carcinoma (HCC) including transcatheter arterial chemoembolization (TACE) and many tumor ablation techniques, such as percutaneous ethanol injection (PEI), radio-frequency ablation (RFA), percutaneous microwave coagulation therapy (PMC), laser-induced interstitial thermotherapy (LITT), cryoablation, and acetic acid injection. By development of new technologies in imaging and drug delivery, it is likely that in the future patients with HCC will be treated by combination therapies to improve patient survival. Computed tomography (CT) and magnetic resonance imaging (MRI) have a crucial role in diagnosis and also follow-up of HCC patients treated by interventional procedures, by which the treatment efficacy, recurrence of disease and certain complications are evaluated.
In this review article, we discuss the imaging modalities and also tailoring of interventional procedures for HCC patients.

Keywords: Carcinoma, Hepatocellular, Trans-Arterial Chemoembolization

Introduction

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer and due to the poor prognosis and low response rate, it consists the fourth cause of death related to cancer worldwide.[1] The epidemiology and risk factors that contribute to the development of the disease govern the incidence and prevalence rate of HCC. The most prevalent risk factor of HCC development is chronic hepatitis B virus (HBV) infection regarding its endemic presence in the heavily crowded regions, for example in Sub-Saharan Africa and Southeast Asia.[1] Most cases are male and between 30 and 50 years of age.[2]

Hepatitis B virus (HBV) infection is the main cause of chronic liver disease in Iran.[3,4] "It was estimated that more than 35% of Iranians have been exposed to HBV and about 3% were chronic carriers".[5] National vaccination of infants and adolescents and intensified hepatitis B vaccination of high risk groups, surveillance of hepatitis B infected subjects and controlling the health status of our community has decreased the frequency of infection in Iran.[5-12] The infection is much lower in our neighbors such as Turkey and Pakistan.[13,14] The most common cause of HCC in Iran is HBV infection and at least 80% of HCC cases are positive for at least one of the markers of HBV.[15-18] Management of HCC is challenging due to its ever-changing epidemiology, the difficulties due to the underlying cirrhosis and the evolving therapeutic algorithms.[19] For management of patients we need collaboration between internists, gastroenterologists, oncologists, surgeons and interventional radiologists. This review provides an overview of the interventional procedures for HCC patients and methods for ablations.

Diagnosis by Imaging

Hepatocellular carcinoma is a hypervascular tumor which has a pseudo-capsule composed of collagenous fibers and a layer of compressed liver tissue. Typically HCCs have hepatic arterial enhancement. During the portal venous and equilibrium phases, HCC fades off and the pseudo-capsule enhances brightly.[20] In cases with two or more nodular components, the common boundary may form the internal septae that may show enhancement in the portal venous phase like the pseudocapsule. The internal septae and pseudocapsule are seen in 80% of these tumors[21] and are more commonly seen in larger lesions. Larger HCCs usually tend to be heterogeneous and to have central necrosis with abnormal internal vessels.[22] Depiction of focal masses within a cirrhotic liver is challenging. Besides, distinguishing HCC from other solid lesions such as regenerating nodules, dysplastic nodules and confluent hepatic fibrosis is an important issue.[23] Currently, ultrasonography, CT scan and MRI are frequently used in the diagnosis and follow-up studies for HCC (Fig. 1). Barcelona criteria for diagnosis of HCC are shown in Table 1.[24]

Bruix et al. presented an algorithm for the investigation of nodule depiction on sonography screening.[24] Based on this algorithm, in nodules less than 1 cm, we should repeat sonography at a 3-4 month interval and when the mass enlarges we must proceed based on the size of the lesion. In cases who have been stable for over 18-24 months we should return to the standard surveillance protocol (every 6-12 months).

In nodules between 1-2 cm, two dynamic imaging studies should be performed. In those who have a coincidental typical vascular pattern on dynamic imaging we must treat as HCC. Biopsy is indicated in cases who have a typical vascular pattern in one technique and patients who have atypical vascular pattern in both techniques.

In nodules over 2 cm, one dynamic imaging study should be performed. Biopsy is indicated in those who have an atypical vascular pattern and those with an atypical vascular pattern on dynamic imaging or AFP over 200 ng/ml should be treated as HCC.

Table 1: Criteria for HCC Diagnosis

Cytopathological Criteria
Non-invasive criteria (restricted to cirrhotic patients)
1) Radiological criteria:
-Two coincidental imaging techniques [a]
-Focal lesion>2 cm with arterial hypervascularization
2) Combined criteria: one imaging technique associated with AFP
-Focal lesion >2cm with arterial hypervascularization
-AFP levels>400 ng/ml

[a] Four techniques considered: US, spiral CT, MRI and angiography
AFP: Alpha Fetoprotein

Ultrasonography

Ultrasonography (US) is the first screening modality due to its safety, quick performance and cost-effectiveness. In addition, it may be performed as frequently as needed every 3-6 months. US is the recommended tool for screening of patients at risk of developing HCC.[25] On sonography, HCC has variable features, but most small lesions are hypo-echoic. HCC tends to invade the portal and hepatic veins and produces tumor thrombus. In rare cases, hepatocellular carcinoma may invade the biliary tree causing obstructive jaundice. However, in cases of cirrhosis, US screening for HCC does not have an optimal sensitivity and specificity.[26] In such patients with liver sonography depicting cirrhosis or a focal mass should often undergo a CT with contrast or MRI study.[26]

However, the differentiation of small malignant lesions in cirrhotic cases could be improved by contrast-enhanced sonography. This technique is especially useful for vascular volume assessment.[27] One disadvantage of contrast-enhanced sonography is that the images may be obtained when rupture of the microbubbles have not happened and imaging of this occurrence requires accurate planning of imaging time and image plane location.

Alfa-fetoprotein level measurement and sonography is useful for the early diagnosis of HCC. In one study performed by Sherman et al., the authors employed US and serum alpha fetoprotein (AFP) in 1069 non-cirrhotic hepatitis B carriers and found that US had a sensitivity of 78.8% and specificity of 93.8%.[28] Unfortunately the positive predictive value (PPV) of ultrasound is low (14%) and needs recall and work-up protocols.[29]

Computed Tomography (CT)

CT scan with a triphasic liver protocol is useful for characterization of focal lesions depicted on sonography and to evaluate patients with negative

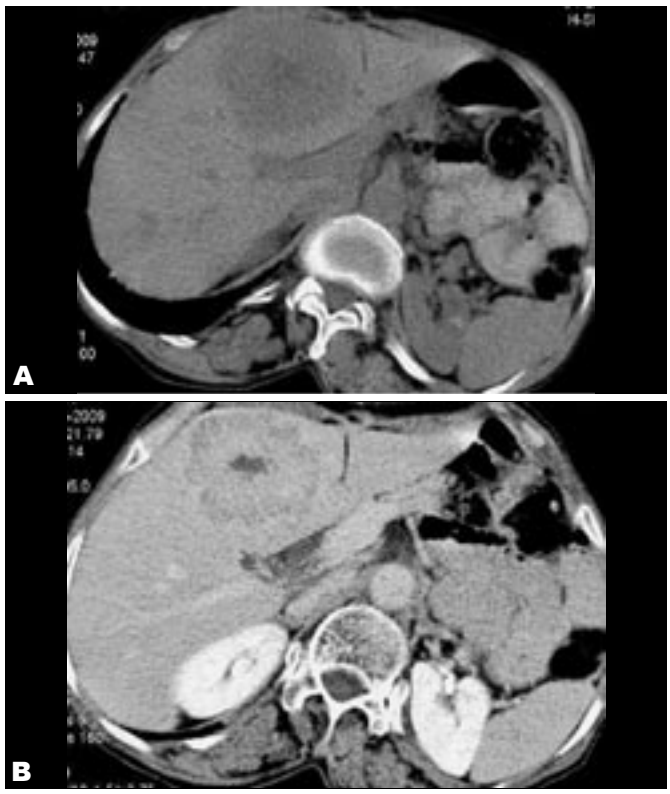


Fig. 1. Helical CT in hepatocellular carcinoma.
A. Hepatocellular carcinoma. Nonenhancing helical CT shows a low density structure (lesion) with ill defined border in the left hepatic lobe.
B. Hepatic parenchymal phase of helical CT shows a solid enhanced lesion with central scar.

findings on sonography and a significantly elevated α-fetoprotein value. CT-scan is used for the staging of HCC as well as follow-up of patients after surgical resection, radiofrequency ablation or percutaneous ethanol injection. In most cases with end-stage liver disease, changes in the liver, including hepatic nodularity and lobar redistribution are visible on imaging. In cirrhosis, the transformation of regenerative nodules to dysplastic nodules and subsequently to HCC is well assessed. Regenerative nodules correspond to regions of parenchymal enlargement surrounded by fibrous septae and occur in response to necrosis or altered circulation. In 25% of patients, regenerative nodules are visible on unenhanced CT and appear as hyper attenuating nodules.[30] On contrast-enhanced CT, these nodules are typically iso-intense and are not distinguishable from the surrounding liver parenchyma. On contrast-enhanced CT and MR imaging, arterial hypervascularity is the hallmark of hepatocellular carcinoma. The advantages of Multi Detector CT (MDCT) are shorter scan time, thinner sections and longer scan range. Therefore, better detection of hypervascular HCC with excellent function including double arterial phase images and isotropic volume imaging is practical with MDCT scanners. Using MDCT we could have early and late arterial phases of liver images. With late arterial phase images we can depict more hypervascular lesions in comparison with the early phase, and evaluation of both phases causes the best sensitivity.

Sensitivity of CT or MRI for early HCC detection is about 40–70% and both modalities arterial phase imaging is essential for early detection of HCC.[31]

Magnetic Resonance Imaging (MRI)

MR imaging is indicated primarily to depict liver lesions with indeterminate findings on CT and to evaluate patients with a contraindication to the use of iodinated contrast material.

As malignant lesions are typically T2 hyperintense, MRI is superior to CT in such cases.[26] The sensitivity of dynamic contrast-enhanced MRI is more than dynamic contrast-enhanced CT. MR is useful in the diagnosis of pseudo-lesions because the majority of these do not show signal changes on the unenhanced T1- and T2-weighted images.[32]

On MR imaging, hepatocellular carcinoma has variable signal intensities on T1-weighted images, whereas most hepatocellular carcinomas are mildly hyper-intense on T2- weighted images. Most HCCs are diagnosed by contrast enhancement in the arterial phase and well-timed arterial phase imaging is critical for detection and characterization of HCCs during dynamic MRI. Early-stage HCCs, which are usually small and well differentiated, tend to be hypovascular and they have been detected during the portal venous or delayed phase of serial imaging.[33] MR can also characterize regenerative nodules which are under 1 cm and T2 hypointense and dysplastic nodules which are typically greater than 1 cm and are T2 hypointense and T1 hyperintense.[23] On T1-weighted MR images, regenerative nodules have variable signal intensity but are usually iso-intense to the surrounding liver tissue. On T2-weighted MR images, regenerative nodules are of low signal intensity. Dysplastic nodules are regenerative nodules which have cellular atypia without malignant change. Super paramagnetic iron oxide particles and gadobenate dimeglumine are accurate diagnostic modalities in the detection of HCCs and are useful for characterization of HCC.[34]

Use of the liver-specific contrast agent gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) produces both dynamic and liver-specific hepatobiliary MR images.[35] Diffusion-weighted image (DWI) provides safe quantification of water diffusion and blood perfusion in micro capillaries. Using DWI, we can increase the detection rate of focal liver lesions for HCC with gadolinium-enhanced MR in cirrhotic patients.[36] Another application of DWI in liver tumors is treatment monitoring after chemotherapy or chemoembolization. Using DWI and ADC maps, we can evaluate the tumor viability at the cellular level and obtain information about the molecular water composition and tumor viability.[37]

Pathological Diagnosis of HCC

Cytological examination of a suspected lesion may be achieved by biopsy. Histopathological examination is the gold standard modality for the diagnosis of HCC.

Computed tomography (CT) has been used to guide interventional procedures. CT is the choice modality for guidance in many interventional procedures. Recently, fluoroscopic CT (FCT) has been introduced, which provides real time reconstruction. This modality causes faster image reconstruction, near continuous image update and convenient in-room table control and image viewing during CT-guided procedures.

In our experience the success rate of FCT (92%) was significantly (p=0.019) higher than CCT (65%) in taking biopsy of liver masses and we recommend this modality for image guided liver biopsies in suspected cases.[38]

Transjugular Liver Biopsy in Patients With Hemophilia

Most hemophilia patients who received exposure to clotting factor concentrates prior to the introduction of effective viral inactivation methods were exposed to blood-borne hepatitis viruses. Liver biopsy is necessary in the assessment of chronic liver disease especially in patients who are infected with HCV. For determination of the necessity of interferon therapy, liver biopsy is very important. All transjugular liver biopsies should be performed by an interventional radiologist.

In one study, we performed transjugular liver biopsy (TJLB) on 12 patients with congenital bleeding disorders (CBD) who suffered from chronic HCV infection and elevated liver enzymes. We applied the modified Ross needle with 100% transjugular access rate to the hepatic veins and 92% success rate in tissue obtaining. The specimen obtained was satisfactory but in 54.5% limited for histopathologic diagnosis. Mild hepatitis occurred in four patients (36.4%), moderate hepatitis in five (45.4%) and extended fibrosis or cirrhosis in two (18.2%) of our patients. There were two procedure-related complications (16.6%).[39]

Staging

The treatment plan and prognosis of HCC is related to the stage of the tumor. Now, the most accepted and practical staging system for HCC is Barcelona clinical classification (BCLC). In the BCLC system, prediction of prognosis is affected by different factors such as liver function or portal pressure level. In this system patients are categorized in five stages and advantages of this system in comparison with others is that the choice treatment of any group is defined. Very early HCC presents with an asymptomatic single mass smaller than 2 cm in diameter that does not have vascular invasion. Patients with a Child-Pugh class A may have a chance of cure with a good 5 year survival of at most 100%.[40] The early stage of HCC includes patients with Child-Pugh A and B and one or more up to three nodules smaller or equal to 3 cm in diameter. These patients can be treated effectively by liver transplantation, resection or percutaneous RF ablation. The 5-year survival is considered to be up to 75%.[41] The intermediate stage of HCC indicates large/multinodular lesions without tumoral symptoms or macro vascular invasion (patients with Child A and B). This group takes the highest benefit from chemoembolization.

In patients who have tumor-related symptoms, vascular invasion or extrahepatic spread of tumor are listed as advanced stage findings. This group may benefit from a new agent called "sorafenib".[42] Eventually, the patients with end stage HCC represent end stage liver disease and extensive tumor burden; unfortunately, their disease may be non-curable and symptomatic treatment only is preferred for them.

Treatment

Approach to management of HCC presented in Diagram 1.

Surgical Resection

Surgical resection is the treatment of choice in non-cirrhotic patients with HCC. These patients account for about 40% of patients in Asian countries and only 5% of cases in Western countries. Patient selection for this treatment depends on postsurgical hepatic compensation and is based on certain criteria consisting of absence of clinical portal hypertension or a portal vein pressure gradient less than 10 mmHg measured by catheterization and a platelet count higher than 100,000/cc.[41] In patients without decompensation after surgery, the 5-year survival may increase up to 70%.[40] After resection, the recurrence rate of 50% at 3 years and 70% at 5 years has been reported.[41] Intraoperative ultrasonography allows detection of small and numerous nodules and enables anatomic resection. The cause of the majority of recurrences is dissemination of the primary tumor. The risk of recurrence depends on several variables including microvascular invasion, multifocality, tumor size and incomplete resection of the involved margins. Treatment with alpha interferon has been introduced which may reduce post resection recurrence rate, especially in patients with previous HBV infection.[41]

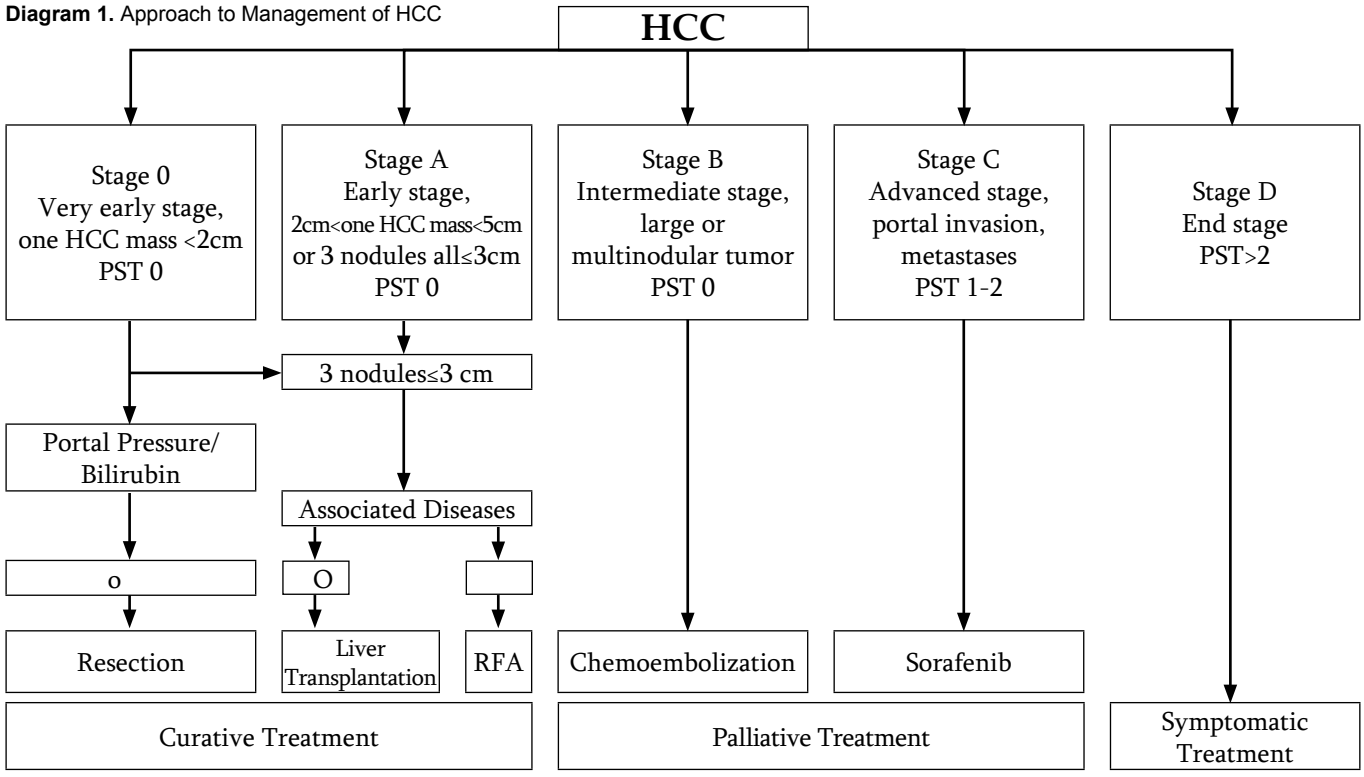
Liver Transplantation

Liver transplantation is a good option that has the best results in patients with early stage HCC corresponding to the "Milan Criteria" including 5 cm or less solitary tumors or up to three nodules each smaller or equal to 3 cm. In this group, the 5-year survival exceeds 70%. Liver transplantation offers cure in patients who have one or more associated underlying liver abnormality such as portal hypertension or an inadequate functional reserve of the liver.[43] The major problem of liver transplantation is lack of suitable liver donation. Another challenge is the waiting time between listing and transplantation that allows the tumor to grow and develop contraindications. For organ allocation, Milan Criteria state an model for end-stage liver disease (MELD) score of 22 and a probability of 15% of death within 3 months. Every 3 months causes a 10% increase in the mortality rate for patients in the waiting list.[41]

Systemic Treatment

HCC is a poor prognosis tumor when it is diagnosed in the advanced stage. Systemic chemotherapy does not have notable results and does not demonstrate survival improvement. However, recently molecular targeted therapies with the role of disruption of tumoral growth molecular pathways have been considered. These growth signalling pathways include numerous tyrosine pathways. Sorafenib is an oral multi kinase

Diagram 1. Approach to Management of HCC



PST: Performance Status; RFA: Radio Frequency Ablation; BCLC: Barcelona Clinical Classification

inhibitor which is expected to prevent tumoral growth and angiogenesis. Now, sorafenib has created a new method for management of patients with advanced stage HCC. In addition, it can be used in intermediate stage patients with a well-compensated liver but not appropriate for TACE.[41]

Therapy of HCC with the Assistance of Radiologists

Currently, the best non-surgical therapeutic procedure for HCC is image guided percutaneous ablation. Tumor ablation is performed using chemical substances (ethanol or acetic acid) or change in the tumor cells temperature (Table 2).

Table 2: Percutaneous Methods for Ablation of HCC

- Chemical ablation
1- Ethanol injection
2- Acetic acid injection
- Thermal ablation
1- Radiofrequency ablation (RFA)
2- Microwave ablation
3- Laser ablation
4- Cryoablation

Percutaneous Ethanol Injection

Percutaneous ethanol injection (PEI) has been considered as the first therapeutic modality for therapy of HCC. Ethanol diffusion causes dehydration of cytoplasmic proteins, coagulation necrosis, cell fibrosis, aggregation with thrombosis of small vessels and ischemia of neoplastic tissues.[44] PEI is administered by using 2-8 ml of 95% ethanol via a 21-gauge needle with ultrasound guidance under local anesthesia. This is very important to be aware of the pattern of tumor perfusion and to avoid ethanol leakage. Based on tumor size and pattern of tumor perfusion and also compliance of the patients, PEI should be performed in four to six sessions once or twice weekly. The advantages of PEI include no remarkable damage to remaining parenchyma, less complications, low cost, easy repetition in new lesions, easy operation and also good long-term results.[45,46] Contraindications of PEI are gross ascites, bleeding and obstructive jaundice.[2,45]

Complications of PEI include hepatic failure, abscess, intra peritoneal hemorrhage, biloma and cholangitis.[45] In one multi-center study performed on 1066 patients, one death and 34 complications (3.2%) were reported.[46] Tumor necrosis is correlated with tumor size. In HCCs smaller than 3 cm in size there is complete response in 90-100% of patients and in 3-5 cm and larger than 5 cm in diameter tumors, the complete response rate is 70% and 50%, respectively.[47]

Acetic Acid Injection

Acetic Acid is a chemical substance with a better tissue diffusion than ethanol and percutaneous acetic acid injection (PAI) firstly reported by Ohnishi et al. in 1994.[48] In addition, acetic acid has a higher necrotizing power compared with ethanol and also a better local control than PEI.[46,49] In one prospective randomized clinical trial study, which compared PEI and acetic acid ablation for HCC, the authors found that cancer-free survival rates and also overall survival rates were higher in the acetic acid group.[49] However, two other studies found similar outcomes for acetic acid and ethanol injection in the ablation of small HCC in mean follow-up times between 24 and 29 months.[49] PAI is minimally invasive and the side effects are not common. One of these complications is post treatment fever that may be due to tumor necrosis and decreased immunity in these cases. Bacteremia and significant infection complications could occur in a minority of patients and prophylaxis against infections may be necessary before treatment in high risk patients. In one study performed on 402 treatment episodes in 127 patients with HCC who underwent PAI, there were 37 (9.2%) episodes of fever in 29 patients.[50] In this study, the authors found that patients with a tumor size more than 3 cm and those who receive higher acid doses have a higher risk for post infection fever.

Radiofrequency Ablation

Radiofrequency ablation (RFA) is one of the most effective procedures for treatment of HCC with favorable tumor control and low rates of mortality.[51-53] RFA causes coagulative necrosis of the liver tumor by using electric heating around a probe generating electromagnetic radiation.[51-53] The mechanism of RFA is high-frequency current (100-500 kHz) which passes from an electrode tip into the surrounding tissues and causes ionic vibrations. This technique could be used percutaneously, laparoscopically or after laparotomy.[54] CT-scan or ultrasound is usually applied for probe guidance and MRI is another possible alternative. Contraindications

of RFA for HCC are a platelet count less than 50000, hemostasis disturbances, refractory ascites, jaundice and patients who have pacemakers. Lesions close to the gastrointestinal tract and billiary system and the heart are relative contraindications for RFA.[55]

In comparison with Ethanol injection, RFA can achieve tumor necrosis in fewer sessions with large necrosis in the tumor.[44] Efficiency of RFA mostly depends on tumor size and the location.[51] In lesions with 3-5 cm diameter, complete ablation is possible (Fig. 2). and for those larger than 5 cm, complete response is unlikely.[51,56,57] RFA for central lesions located near the hilum should be avoided due to the risk of vascular or biliary tract injury. For tumors which are located within 1 cm of the hepatic portal tract it is better to avoid RFA. The 1, 2, 3 and 5-year survival rates are 75-100%, 80-98%, 37-59% and 28%, respectively.[57]

Although RFA is a safe technique, adverse events have been reported in 4-5% of cases after this procedure.[58,59] The mortality of RFA is 1% which depends on the liver function and ablation volumes.[51] The major complications of RFA are liver failure, hemorrhage, infection, abscess, intercostal nerve injury, adjacent organs injury, tumor lysis syndrome and pneumothorax.[44,51] In one study which was performed by Kasugai et al.[60] the authors performed RFA for 3891 lesions in 2614 patients and nine patients (3%) died in their report due to acute aggravation sarcomatous change, liver failure, bile duct injury, ascites and GI hemorrhage. In their study, 207 patients (7.9%) were complicated

Microwave Ablation

Microwave ablation (MWA) is a thermal ablation therapy which has developed in the recent years.[61] The advantage of this modality is creating a coagulation area that provides reliable ablation for HCC.[61] MWA is used mainly for tumors smaller than 2 cm and for larger tumors, effectiveness of this modality is less promising. A multiple electrode insertion has been recommended to improve the ablation ability of MWA.[62] In a study, complete ablation in 48 HCC lesions smaller than 2 cm by MWA have been reported.

The common MWA which is 60w for 120 second, generates a coagulation area of about 1.6 cm in transverse diameter with a single energy application.[61] The region of coagulation may be extended with 300 second duration.[61] By using longer MWA about 300 second, 46 HCC nodules smaller than 2cm were treated with MWA and only one (2%) nodule developed local recurrence.[61]

Usually, two MWA sessions are performed in each nodule.[62] The second session is more efficient than the first because the first session destroys blood vessels in the tumor region and provides condition for better effectiveness of the second session. Dynamic contrast-enhanced CT is useful for evaluation of MWA. Hypo attenuating change without enhancement represents necrotic tissue.[64] CT is usually performed 7-14 days after MWA for evaluation of the technical success. Some studies advised CT performing one month after treatment because before this time a hyperemic

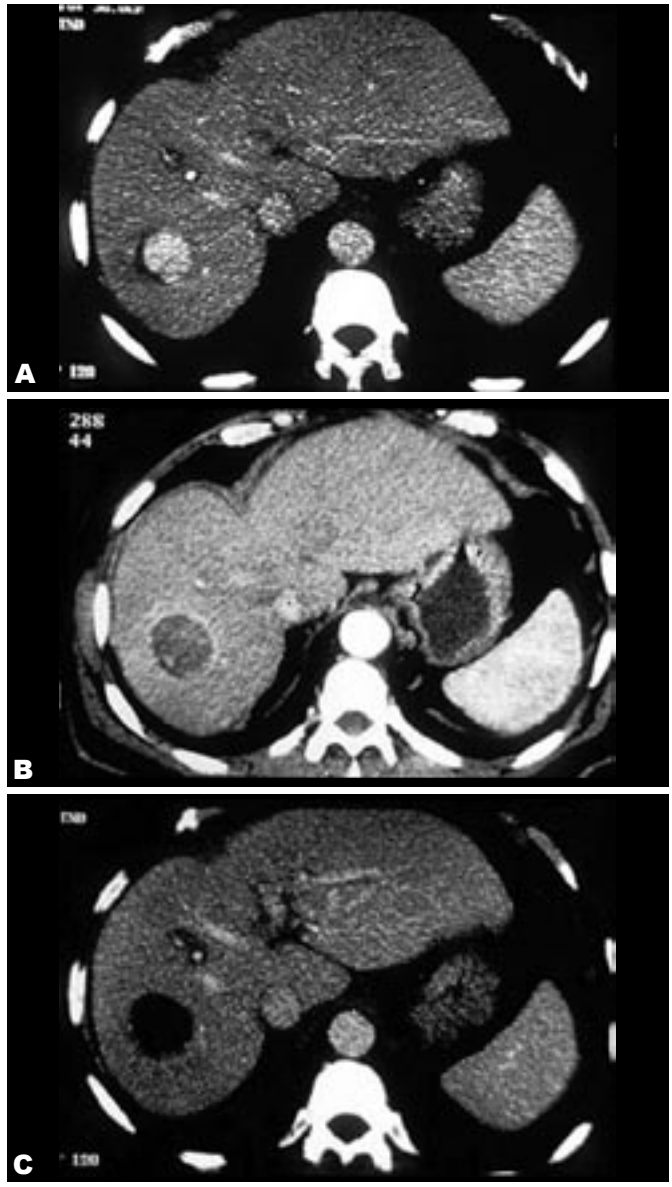


Fig. 2. A. A 3-cm HCC mass showed hyperdense enhancement after IV contrast injection post RF images.
B&C. Satisfactory necrosis due to heat therapy is visualized.

response shrouding the ablation sites may be confused with tumor re-growth at CT.[62]

As Solbiati et al.[65] reported, evaluation of therapeutic effectiveness at biopsy is unreliable due to the probable sampling error. Seki et al.[66] reported the long term results of PM CT for solitary HCCs smaller than 2 cm, the 5-year survival rate is higher than 70%.

Laser Ablation

Laser ablation (LA) of HCC is a safe and effective local therapy for patients with unresectable HCC. However, further data from randomized trials are required to establish long term survival rates after LA and its role in combination therapy, either with other interventions like TACE and RFA or surgery. The term laser ablation (LA) refers to the thermal tissue destruction of tissue by conversion of absorbed light (usually infrared) into heat which includes various technical variations on this theme including "laser coagulation therapy", "laser interstitial tumor therapy" and "laser interstitial photocoagulation.[67] It is shown that temperatures above 60°C cause coagulative necrosis and instant cell death, but irreversible cell death can also be achieved at lower temperatures (> 42°C) with longer durations (30-60 min).[68] Temperatures above 100°C will cause vaporization from evaporation of tissue water and above 300°C tissue carbonization occurs. In 1989, Steger et al. treated two patients who suffered hepatic metastasis using ultrasound-guided interstitial laser photocoagulation (ILP) percutaneously.[69] This treatment has been used predominantly in the treatment of unresectable liver metastases, although it has also been used in HCC. [70] The number and size of lesions that may be treated are similar to those indicated for RFA. Laser fibers are inserted using single or multiple microctheters or 19G needles for percutaneous LA. The procedure is performed under ultrasound, CT or MRI.

Percutaneous LA is indicated for patients with small unresectable HCCs, sized 5 cm or less, restricted in the liver, in cases who have limited liver reserve or altered liver function.[71] Repeated punctures are required for patients with multiple tumors (more than three). LA is believed to be contraindicated in patients with gross ascites, uncorrectable coagulopathy and obstructive jaundice due to the potential risk of bleeding and bile peritonitis. Increased risks of hemorrhage and peritoneal seeding should be considered when the tumors are located at or protrude from the liver surface. The procedure can be difficult and with higher complication rates when tumors are located under the diaphragm or too near to vital structures like the bile ducts, major blood vessels and the stomach.[71]

To date there is limited published data on long term outcome rates of LA in the treatment of HCC. In Eichler et al.'s[72] study, the mean survival time of 39 patients with 61 HCCs who were treated with laser was 4.4 years (95% CI: 3.6-5.2) and complete ablation was seen in 97.5% of their patients. In 2004, Ferrari et al. reported an improved ablation rate and survival in patients with large HCCs (>5cm) undergoing combination treatment of TACE and LA instead of LA alone. In 2005, Pacella et al. reported complete tumor ablation obtained in 90 lesions (90.9%) in 82 HCC cases between 50 and 72 years who underwent Laser Thermal Ablation. In this study, the tumor size treated by LA was no larger than 4.0 cm. In 2006, Pacella et al. published long term survival rates of 89%, 52% and 27% for 1, 3 and 5 years, respectively, in a series of 169 smaller than 40 mm lesions in 148 patients (144 biopsy proven HCCs) treated in 239 sessions. They state an overall 82% complete lesion ablation rate.[73]

Vogl et al.[74] reported 0.1% mortality and 1.8% major complication rate in 899 patients (including 2 HCCs) with 2520 lesions treated with 2132 episodes. They performed the procedure under local anesthesia and CT/MRI guidance. Recently Arienti et al.[75] reported 0.8% deaths and a 1.5% major complication rate. Major complications were hepatic failure, infarction, abscess/cholangitis, bile duct injury and hemorrhage. The common side effects were asymptomatic pleural effusion, post procedural fever and severe pain. Tumor seeding is a rare complication after laser ablation and none of the above groups reported this complication.

Percutaneous Cryoablation of Hepatocellular Carcinoma

The first cryotherapy reported in 1800s for freezing skin lesions. In 1963, Irving Cooper treated Parkinson's disease and some neuromuscular diseases using cryosurgery, and suggested extending the use of this procedure for liver cancers.[76] Cryoablation is according to the cyclic application of -196°C temperatures to the tumor using a probe, which is located in the tumor, cooled with either circulating liquid nitrogen or argon. Tumor destruction is due to crystal formation

after the repeated freezing and thawing process which cause cellular dehydration, protein denaturation and microcirculatory failure.[77]

"The heat sink effect" of flowing blood can protect the large vessels from damage,[78,79] but biliary tracts are more sensitive to cryogenic injury.

Cryotherapy is believed to be more effective in the second freeze thaw cycle and thereafter more destruction is observed at faster or slower cooling rates than 1-10°C/min. Besides, slow thawing of the treated tissue is more cytotoxic for the frozen tissue.[79]

Cryotherapy is indicated for both primary and metastatic liver masses in the cases with extrahepatic metastasis, surgically unresectable disease and/or tumor involving surgically resected margins.[77] Multiple lesions may be treated safely by this method due to the intact surrounding tissues. Tumors involving more than 50% of the liver are accompanied with higher morbidity, and those lesions which are larger than 6 cm in diameter are very difficult to treat, since ice balls larger than 8 cm in diameter can not be obtained.[80]

The percutaneous procedure is also indicated in high risk cases for surgery because of their comorbid diseases or local difficulties being expected after recurrence. Patients with unresectable hepatic tumors less than 5 cm in diameter and up to 3 nodules, or those with limited intrahepatic recurrence after previous liver resection are suitable for cryosurgery.[81] At present, there is still little data and published materials available of the results of percutaneous cryotherapy of HCC.

In Zhou and Tang's study,[81] the 5-year survival rate for 235 patients after cryotherapy was 39.8%, which was 55.4% for 80 patients with lesions less than 5 cm in diameter.

In a retrospective study, Rene Adam et al. compared the results of percutaneous cryosurgery (PCS) and percutaneous RFA for the treatment of hepatic malignancies. In their study, 64 cases were treated with either cryosurgery (n=31) or PRF (n=33) with at least a 6-month follow-up in living patients. Finally, they concluded that local recurrences occur more frequently after PCS, especially in metastases.[82]

Crews et al.[83] performed cryoablation in 40 patients with hepatic tumors and the estimated 18-month survival rates in their patients were 60% for HCC and 30% for colorectal metastasis.

Complications of cryotherapy include: generalized hypothermia, hemorrhage, bile fistula and collections, cryoshock, biliary leak or subsequent stenosis, liver capsular cracking, asymptomatic right-sided pleural effusions, liver abscess and transient thrombocytopenia.[71,77-79]

Transarterial Chemoembolization

Transarterial chemoembolization (TACE) has been approved as the gold standard treatment of unresectable HCC in the absence of documented extrahepatic tumor spread when the patient has preserved liver function.[84,85] As the HCCs greater than 2 cm take their blood supply mainly from arterial system, arterial flow blockage seems to be beneficial in destroying HCC neoplastic cells.[84,85] This point provides the rationale of the hepatic artery embolization and local chemotherapy via transarterial embolization (TAE) or transarterial chemoembolization (TACE). The embolization is done mainly by lipiodol; an oily contrast media that accumulates selectively in the tumor. This agent will be injected in the supplying artery to stagnate the blood circulation of the tumor.[85,86] The chemotherapeutic agent that is mainly doxorubicin or cisplatin accompanies the embolic agent.[84,86] In addition to producing ischemia, this mixture will increase local concentration of the chemotherapeutic drug that results in better destroying of the tumor.

Patient selection

According to the guidelines of the American Association for Study of Liver Diseases and the European Association for Study of the Liver, TACE is considered as a non-curative first line therapy for advanced-stage tumors in which surgery is not recommended and patients who have large or multifocal HCC without vascular invasion or extrahepatic spread.[87] Contraindications of TACE include severely impaired liver function (Child–Pugh C), serum bilirubin level higher than 2 mg/dl, clinically relevant refractory ascites, coagulopathy, significant thrombocytopenia, encephalopathy, active gastrointestinal bleeding, significant comorbidity (cardiac and/or renal failure), a tumor burden greater than 50% or end-stage tumorous disease (Okuda III), poor performance status (Karnofsky<70%) or WHO performance stages of 3 or 4, extrahepatic metastases, vascular invasion, portal vein occlusion due to thrombosis or liver tumor, hepatofugal blood flow in the portal vein or patients with a transjugular intrahepatic portosystemic shunt.

TACE could be considered in early-stage patients in whom surgery is contraindicated. In addition, TACE is an option in cirrhotic patient candidates for liver transplant to reduce the risk of tumor progression.[84,86,87]

Procedure

Preprocedure Workup: Before the procedure, the tumor will be assessed by contrast-enhanced MRI with perfusion and diffusion sequences; if this is not feasible, dual-phase MRI or CT will be performed. This imaging is potentially beneficial in more precise delineation of the tumor extent and necrosis at baseline and making more appropriate therapeutic decisions. Besides, it provides detailed information of the anatomy of the celiac trunk and its branches and portal vein invasion or thrombosis.[84]

Regarding post procedure bacterial colonization of the necrotic tumor resulting in liver abscess or sepsis, the use of prophylactic antibiotics before TACE is controversial. As the rate of liver abscess is very low, many reports show a prevalence lower than 1% [86,88,89] The major trend is not towards antibiotic use, but regarding the borderline conditions and critical situation of the patients, many prefer to use antibiotics.[88] Formation of abscess relates to the extent of necrosis and the organisms are enteric gram negative or exogenous gram positive bacterias which enter the liver during the procedure (60% of cases). Some baseline conditions such as poor liver function and especially previous biliary surgeries (specifically previous whipple surgery) due to the high probable exposure of the liver tissue to intestinal microorganisms, increase the risk of liver abscess and the routine use of prophylactic antibiotics has been recommended in these patients.[86,88,89]

Procedure: After local anesthesia in the right groin and percutaneous insertion of a 4F introducer sheath in the right common femoral artery, a diagnostic angiography of the celiac trunk and superior mesenteric artery with late-phase imaging of the portal venous system will be done in order to determine the vascular arterial and portal anatomy. The goals of this diagnostic study include determining the arterial supply to the tumor, detecting possible variations in the hepatic arterial supply, identifying the arteries that should be avoided during treatment delivery and determining the patency of the portal vein or the presence of hepatopetal flow through collaterals to the liver in case of portal vein tumor thrombosis. Assessing the vascular map helps to decide which branch or branches would be better to deliver the embolic agent and chemotherapeutic drugs.[84,87]

In comparison to catheterization of the tumor-feeding arteries with a 4 F catheter, it is better to perform the selective or superselective catheterization with the use of a large-hole microcatheter. These microcatheters have highly smooth distal ends that prevent potential arterial spasms; yet, delivering the chemotherapeutic drugs and the embolic agents through them is easy. After understanding the arterial anatomy, the catheter or microcatheter is guided superselectively into the right or left hepatic artery depending on the location of the greatest tumor volume. Using a 4 F hydrophilic cobra catheter with a hydrophilic guide-wire is enough in about half the cases. The catheter should not be less than twice the diameter of the vessel, as the catheter will cause a partial occlusion of the vessel lumen, resulting in pseudo-stasis. Withdrawal of such a catheter results in reflow to the tumor. In small vessels, the only route for access is using microcatheters designed for TACE. These microcatheters include Cragg wire, Turbo Tracker Infusion Catheter and the Renegade Hi-Flo. Wire choices include 0.018- or 0.025-in. glide wires, glide gold wire, Seeker 0.014 or Seeker 0.016 wire and Headliner wire. The only wire catheter that can accommodate a 0.025 in. guide wire is the Cragg. Microcatheters can be power-injected at 2.5-4.0 cm^3/s after lowering the pressure threshold on the injector to 300 psi.

It is recommended to perform coil-embolization of all distal ends of non-hepatic artery originations distal to the microcatheter tip. (e.g. right gastric artery, falciform artery). Performing an arteriogram before injecting any chemotherapy is recommended for exact confirmation of the anatomy. The final goal of the TACE procedure is complete blockage of the tumor-feeding branches. It is essential to check for extrahepatic collateral arteries feeding the HCC. Due to the close vicinity of the liver and the diaphragm, the diaphragm arteries may reach the liver by direct adherence. Hence, the right inferior phrenic artery is the most common collateral pathway. The findings in favor of external collateral artery (ExCA) feeding the tumor are an exophytic tumor growth or subcapsular

location or peripheral iodized oil retention defect within the tumor or a peripherally located portion of viable tumor on a follow-up CT scan (Fig. 3).

In patients with hepatic arteriovenous shunt (AV shunt), balloon occlusion of the hepatic vein draining the shunt should be performed during TACE.

At the end of injection, the right and left hepatic artery should still be patent in angiography with reduced flow in the second and third-order branches and absence of tumor blush. Once the catheters are removed, a plain abdominal film of the hepatic region is performed to assess the focal uptake of lipiodol into the HCC nodules. This could be done by a cone beam CT. Manual compression for 10 min is sufficient in most of the patients to decrease post-procedural groin bleeding; however, some authors prefer to use some closure device.

After the procedure, vigorous hydration and antiemetic therapy are administered. Optional antibiotics are continued. For pain control, nausea and fever, narcotics, chlorpromazine and acetominophen are prescribed. The patient will be discharged as soon as the oral intake is adequate; parenteral narcotics are not required. After 3-4 weeks, the second procedure focused at the other segment or lobe of the liver will be performed. Two to four TACE sessions are required depending on the arterial anatomy to treat the entire liver. The response will be evaluated by tumor markers and repeated imaging studies.[84,87]

It has been proposed that the sequential TACE is safe and feasible in many patients. This approach seems to increase the survival of the patients.[90]

Chemotherapeutic drugs and embolic agents as noted before, TACE procedure routinely includes the use of a chemotherapeutic drug emulsified in an oily medium as the carrier. Most of centers use doxorubicin (36%) or cisplatinum (31%). The other chemotherapeutic drugs used in TACE are epirubicin (12%), mitoxantrone (8%), mitomycin C (8%) and SMANCS (5%) (a synthetic copolymer of styrene maleic acid [SMA] and a proteinaceous anticancer agent neocarcinostatin [NCS]). Irinotecan has also been used in TACE.

Regarding embolic agents, most of the interventional radiologists use lipiodol (iodized oil; an oily contrast media) in mixture with the above mentioned drug(s) as the classic embolic agent. This agent represents a vehicle for these drugs and after injection into the hepatic artery, persists more selectively in tumor

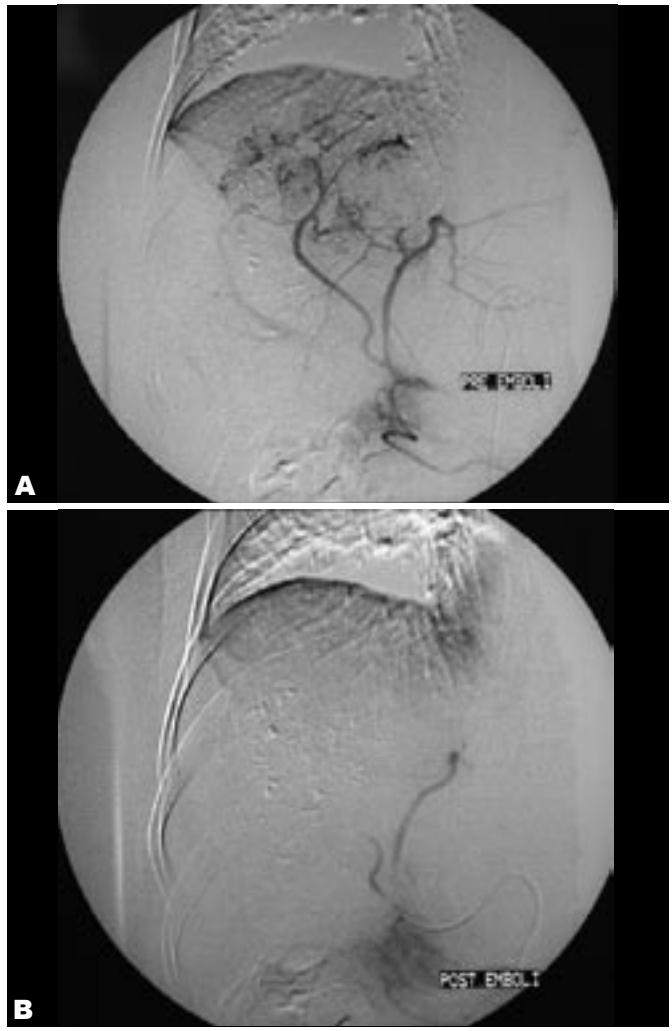


Fig. 3. A. Neovascularity and hypervascular lesion in segments 7 and 8 of the liver in favor of hypervascularity.
B. Complete obliteration of vascular structures within the tumor is seen. Lipiodol droplets are also visualized in the texture of the tumor.

nodules for some weeks up to some months. Most often, temporary hepatic artery obstruction is achieved by Gelfoam pledgets. (recanalization taking place within 2 weeks). Additionally, starch microspheres and permanent occluding agents like polyvinyl alcohol or trisacryl gelatin microparticles, metallic coils and autologous blood clots have been used. Polyvinyl alcohol particles, coils and microspheres are permanent embolic agents while the others are temporary agents. A new microsphere that can serve as a drug eluting agent has been introduced in the recent years named DC-Beads. This agent could provide a precisely controlled release of doxorubicin, irinotecan and some other chemotherapeutic drugs into the tumor bed. The microspheres composed of polyvinyl alcohol and a hydrophilic monomer named 2-acrylamido-2-methylpropane sulphonic acid; the particle sizes ranged between 100 and 900 micrometer. Regarding

the chemical structures of the agent and drugs, the drug can be loaded before procedure. Therefore, a one-step procedure would be possible means that the drug and the embolic agent will be delivered simultaneously into the tumor feeding arteries. This makes a local and sustained delivery of the drug. Diameter selection of beads will be according to the size and vascularity of the target tissue. Larger beads provide slower release of the drug; however, considering the possibility of small particle infusion into the adjacent normal tissues that may be harmful for their circulation, in practice, a combination of microspheres with different diameters are used.

It seems that the type of embolic agent does not influence the overall survival. Because of fast lysis, the probability of arterial thrombosis after using this technique is lower than the other methods.[84,86,91,92]

Follow-Up

Hepatic ischemia could occur due to microparticle injection. This can result in fever and abdominal pain. Administration of adequate pain medication during and after the procedure could fix the problem. An outpatient clinical visit should be performed one month after TACE to evaluate the patient's general condition and to decide if another TACE session should be considered. This decision is typically based on different conditions including clinical performance status, tolerance of TACE, biochemical profile and imaging analysis. Reviewing the images is really crucial. Volumetric changes happen late after TACE; thus, RECIST (Response Evaluation Criteria in Solid Tumors) criteria could be controversial. As the goal of TACE is also tumor stabilization and the induction of necrosis, the RECIST criteria that focuses on tumor size is not perfect. On the other hand, lipiodol deposits within the HCC could interfere in enhanced CT images to evaluate the residual perfusion/viability for determining tumor viability. Regarding these points, functional imaging techniques such as diffusion-weighted and perfusion-weighted MRI are the preferred follow-up imaging studies after TACE. These techniques make it possible to evaluate tumoral vascular and microstructural changes and to estimate treatment efficacy by the total amount of treatment-induced necrosis.[84]

Complications

The main complication of TACE is the postembolization syndrome (PES) that occurs in many of the patients and has variable manifestations. Typical symptoms include abdominal discomfort, pain, nausea, vomiting, fatigue and fever, which may last for a few hours up to 5 days. It seems the PES is due to tissue ischemia and an inflammatory response to chemoembolization. PES could be managed symptomatically but is the major cause of postprocedural hospitalization. Although adequate management is not a big challenge, it is important in the patient's compliance for future procedures. Two life-threatening complications are hepatic failure and hepatorenal syndrome that are more probable in patients with reduced liver function and/or reversed or occluded portal vein flow. High doses of cisplatin (9.5±5.9 mg) are another predisposing factor of liver failure. In the majority of patients, the liver function returned to pretreatment conditions before the next TACE. The minority of patients develop irreversible liver function. Other complications include liver abscess (in the necrotic liver tissue) and septicemia that should be recognized as soon as possible. If chemotherapeutic and embolizing agents are inadvertently injected into the organ, they can cause ischemic cholecystitis, pancreatitis, gastric erosions or ulcers. An uncommon complication is bile duct injury causing subcapsular biloma, focal strictures of the common hepatic duct or common bile duct and diffuse mild dilation of the intrahepatic ducts. Rare complication includes embolic events due to lipiopdol in the gastrointestinal tract, pulmonary or cerebral circulation.

According to some clinical and molecular studies, hematogenic dissemination of malignant cells may be facilitated. Of course, this topic remains debatable.[84,87]

Efficacy

Many systematic reviews have shown the efficacy of intra-arterial therapies including TACE in unresectable HCCs in terms of prolongation of survival. Important aspects of all such treatment modalities are their effective tumor responses, minimal toxicity and sparing of the normal liver tissue.[84,86,87,91,93,94] For example, Llado et al. reported the overall actuarial survival rates of 61%, 32% and 19% at 12 months, 24 months and 36 months, respectively.[95] O'Suilleabhain studied 320 patients who underwent TACE. In these patients, the median survival from the initial TACE treatment was 72.3 months (range, 60.7-138.8). They had three patients

diagnosed as disease-free at the end of the study. In addition, they found that unilobar tumor, an albumin concentration greater than 35 g/l and α-fetoprotein level below 1000 ng/ml were independent prognostic factors for survival in multivariate analysis.[96]

In conclusion, both diagnostic imaging and interventional therapy have an essential role in HCC diagnosis and management. Imaging is important for detection, staging and follow-up studies, and interventional therapy is an effective alternative for hepatic surgery in early HCC.

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