Expert consensus on local ablation therapies for primary liver cancer

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Local ablation therapies are procedures that, guided by medical imaging technology, localize the targeted tumor and then kill tumor tissues through the local application of physical and/or chemical methods. The imaging technology includes ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), and the ablation can be performed through percataneous, laparoscopic, or open surgery. Local ablation has two advantages: First, it can act directly on tumor and thus is highly effective and efficient; second, the efficacy of this treatment is only confined on tumor and its neighboring tissues, with limited effect on human body, and therefore can be repeatedly applied. After the rapid development during the past two decades, local ablation therapy has became the third most promising local treatment (immediately after surgical resection and intervention) for primary liver cancer. Notably, radiofrequency ablation (RFA) is as effective as surgical resection but is simpler and safer in treating small hepatocellular carcinoma (SHCC). Therefore, RFA has been recognized as one of the radical treatment for SHCC and been widely applied in China.

To further standardize the local ablation therapies for primary liver cancer, Chinese Society of Liver Cancer (CSLC), Chinese Society of Clinical Oncology (CSCO), and Liver Cancer Group, Chinese Society of Hepatology jointly convened a multidisciplinary panel of experts in surgery, oncology, ultrasound medicine, and intervention to develop recommendations for the clinical utility. The current expert consensus document reflects these joint efforts and is intended to provide guidance and assistance to clinicians.

1. Rationales and categories of local ablation

Based on their treatment principles, local ablation therapies can be divided into two large categories: chemical and physical ablation. Chemical ablation refers the application of chemical method (i.e. instillation of chemical substance such as absolute ethanol and/or acetic acid into the tumor lesion) to make the local tissue cells dehydrate, decay, and disintegrate and thus inactivate the tumor lesion. Currently, chemical ablation for liver cancer mainly includes percutaneous ethanol injection (PEI) and percutaneous acetic acid injection (PAI). On the contrary, physical ablation uses physical approaches to destroy tumor lesions by heating or freezing local tissues. The main techniques of physical ablation include radiofrequency ablation (RFA), microwave coagulation therapy (MCT), cryoablation, high intensive focused ultrasound (HIFU), and laser ablation.

This consensus statement is focused on RFA; however,

its principles are also applicable for MCT and may also be informative for other techniques.

2. Principles of treatment

(I) Before the initiation of RFA, the patient's general condition, medical condition, and tumor biological behaviors should be thoroughly evaluated, with an attempt to predict the feasibility and effectiveness of RFA and decide the proper approaches and procedures of RFA and other combined therapies. Based on findings (including the size, involvement, and location of tumor) from adequate radiological examinations, treatment scheme and strategies should be carefully developed, with an priority to ensure the sufficient safety margin, so as to achieve a complete conformal tumor ablation after a single session of RFA. (II) Appropriate imaging pathway should be established and the treatment process should be monitored to guarantee the safety, accuracy, and effectiveness of treatment. (III) Proper integrated treatment scheme and follow-up plan should be developed.

3. Indications and contradictions

3.1. Indications

(I) Single tumor ≤5 cm in maximum diameter or multiple tumor (≤3 in number) ≤3 cm in maximum diameter. (II) Tumors without invasion into blood vessels, bile ducts, and/or surrounding organs and without distant metastasis. (III) Patients with liver function of Child-Pugh A or B (or downgraded after treatment with liver-protective drugs). (IV) For unresectable single tumor >5 cm in diameter or multiple tumor >3 cm in maximum diameter, local ablation can become an essential part of palliative treatment.

3.2. Contraindications

(I) Huge tumor or diffuse liver cancer; (II) Accompanied with intravascular cancer emboli, invasion into neighboring organs, or distant metastasis; (III) Patients with liver function of Child-Pugh C, which is not improved after treatment with liver-protective drugs; (IV) Acute bleeding of esophageal variceal episodes in the past one month; (V) untreatable coagulation disorder and abnormal haemogram, predictive of a hemorrhagic tendency; (VI) refractory massive ascites and cachexia; (VII) accompanied with active infection, especially inflammation of the bile ducts; (VIII) failures of major vital organs including liver, kidney, heart, lung, and brain; (IX) patients with consciousness disorders or those who are not able to cooperate during procedures. Tumors located at the first hepatic hilum are relatively contraindicated. Tumors near gallbladder, gastrointestinal tract, or diaphragma or those protrude outside liver capsule are relatively contraindicated. Lesions with extra-hepatic metastasis are not definitely contraindicated; rather, local ablation can still be considered for controlling lesions within the liver.

4. Pre-operative preparation

(I) A complete pre-operative check-up which includes routine blood tests, routine biochemical tests, hemorrhage/coagulation tests, determination of serum tumor markers (e.g., AFP), electrocardiography, chest X-ray, and ultrasound should be performed. Cardio-pulmonary function tests may also be required. (II) The tumor should be assessed with ultrasound (contrast-enhanced ultrasound if possible), triple-phase CT/MRI scanning of liver, and some other technology. Proper guidance method and ablation devices should be selected. (III) A definitive diagnosis should be made, and puncture biopsy may be performed when necessary. The diagnosis may be based on the diagnostic criteria developed by Chinese Society of Liver Cancer in 2001 or on the diagnostic criteria in the Expert Consensus on the Standardized Diagnosis and Treatment of Primary Liver Cancer jointly issued by CSLC, CSCO, and Liver Cancer Group, Chinese Society of Hepatology in 2009. (IV) Skin preparation at the operation field and puncture site. (V) Preparation of ablation devices: Before the treatment, inspect the ablation devices/equipment to make sure that they are in good working status, can function normally, and have well prepared electrodes and/or lines. (VI) Signing of the informed consent: All patients must sign an informed consent form acknowledging their thorough understanding of the procedures, risks, and possible outcomes of the surgery.

5. Treatment procedures

Local ablation for liver cancer can be performed through percataneous, laparoscopic, or open surgery.

5.1. Percutaneous local ablation for liver cancer (guided by ultrasound or CT)

(I) The patient fasts for 8 hours before the procedure. The liver lesions should be identified after careful interpretation of ultrasound and CT, and then reasonable needle insertion pathway and electrode placement protocol should be developed. (II) Anesthesia planning: The anesthesia and analgesia modalities including local anesthesia at the puncture site, intravenous analgesia, intravenous anesthesia, epidural anesthesia, and endotracheal anesthesia should be carefully selected based on the specific conditions. (III) Disinfection and draping should be routinely performed in the surgical field. (IV) A second complete ultrasound or CT shall be performed to decide the needle position, needle angle, and electrode placement protocol. (V) With ultrasound or CT guidance, needle should be introduced between ribs; preferably, the needle should go though some normal liver tissues first and then enter the tumor. The puncture site should be accurately located. Multiple punctures should be avoided to minimize the risks of tumor seeding, damage to neighboring tissues, and rupture and bleeding of the liver tumor. If the needle is inserted too deeply, the electrode needle should not be withdrawn directly; rather, it should remain at the original site until ablation is completed, and then it can be withdrawn for re-location. By doing so, it may avoid the risk of tumor seeding. Generally, multisegmental ablation is performed from the deep to shallow. (VI) Ablation therapy is performed, one lesion after another, in accordance with the manufacturer's instructions for use of each specific ablation treatment device. An ablative safety margin of at least 0.5 cm should be established to guarantee the effectiveness of ablation therapy. Overlapping ablation using the technique of "multifocal ablation with a single needle" can guarantee the ablation extent and lower the incidence of leakage. After the ablation is completed, prophylactic ablation of the needle track should be performed whenever possible, so as to prevent post-operative bleeding or needle tract seeding. (VII) Liver ultrasound or CT should be performed again prior to the completion of treatment to ensure that the tumor is fully covered by ablation spheres and there is an ablative safety margin of 0.5-1.0 cm; risk factors that may cause complications such as tumor rupture, bleeding, and hemopneumothorax have been ruled out.

5.2. Laparoscopic local ablation therapy (suitable for tumors under liver capsule or near gallbladder and gastrointestinal tract, and for tumors that can not be clearly shown by ultrasound or CT and therefore are difficult to enter by percutaneous puncture)

During a routine laparoscopic procedure, ligaments and tissues around the liver may be dissociated, when necessary, to expose liver and liver tumor. When necessary, laparoscopic sonogpraghy may be performed to toidentify the number and location of tumor foci. The surrounding normal organs and tissues should be protected and packed away. The radio-frequency ablation needle is percutaneously inserted into abdomen, and then the electrode needle is inserted into tumor under direct laparoscopic visualization or with laparoscopic ultrasound guidance. Electrode placement and ablation treatment can then be performed in accordance with the established scheme. During the ablation, intermittent and repeated occlusion of hepatic blood inflow can be conducted with devices such as hemostatic clamp, so as to increase ablation efficiency and expand ablation scope. The surgical site should be carefully examined after the ablation to make sure that there is no active bleeding or damage to neighboring organs.

5.3. Open surgical approach for local ablation (Suitable for conditions that can not be managed with the above two methods, or for tumors confirmed to be unresectable after surgical exploration)

Open abdominal surgery is routinely performed. The ligament around the liver is dissociated to expose liver tumors. The surrounding normal tissues/organs are protected. The electrode needle is inserted into tumor with ultrasound guidance. Electrode placement and ablation treatment can then be performed in accordance with the established scheme. During the ablation, intermittent and repeated occlusion of hepatic blood inflow can be conducted to increase ablation efficiency and expand ablation scope. The surgical site should be carefully examined after the ablation to make sure that there is no active bleeding or damage to neighboring organs. Close the abdomen.

5.4. Post-operative management

Surgical patients routinely fast postoperatively, with their

vital signs closely monitored for 4 hours. Patients should be bedridden for at least 6 hours, during which they should undergo examinations including routine blood tests and hepatic/renal function tests and treatment including drug-protective medications, infection prevention, analgesia, and management of bleeding. Complications should be prevented; once a complication occurs, it should be actively managed.

6. Prevention and management of complications

Complications are normally classified as minor or major. Minor complications: Grade A: usually needs no treatment and will not result in poor outcome; Grade B: needs a little treatment (e.g., a medical observation no more than 12 hours) but will not result in poor outcome. Major complications: Grade C: needs treatment and requires less than a forty-eight hour period of hospitalization; Grade D: needs intensive treatment and increased health care level, and the period of hospitalization usually is longer than 48 hours; Grade E: will result in longer-term sequelae; and Grade F: death.

RFA has shown to be with high safety: the incidence of complications ranged 0-12% and the case-fatality rate was 0-1%. With an incidence of about 4.7%, the minor complications mainly include fever, pain, shallow second-degree burn wounds, small pleural effusions, and small pneumothorax. With an incidence of about 2.2%, the major complications mainly include infections, gastrointestinal hemorrhage, intra-abdominal hemorrhage, tumor seeding, liver failure, and intestinal perforation. Adequate preoperative preparation, strict operational procedures, accurate positioning, and fewer ablation sessions are essential for lowering the incidence of complications.

Classification of complications: (I) Post-ablation syndrome: the main symptoms include fever and pain. Hematuria and chills/rigor may occur in some patients. The specific causes are unclear. The management measures mainly include intensified monitoring, fluid infusion, pain relief, symptomatic treatment, and regular hepatic/renal function evaluations. (II) Infections: the common infections are liver abscess and puncture site infection. They may be prevented by strict aseptic operation and by use of postoperative prophylactic antibiotics. (III) Gastrointestinal hemorrhage: Gastrointestinal hemorrhage are often caused by esophagus-gastric fundus variceal bleeding or stress ulcer. Prevention and treatment: For patients accompanied with severe portal hypertension, the portal hypertension should be managed pre-operatively; in addition, antiacid agents may be routinely administered post-operatively to prevent bleeding resulted from stress ulcer. Management measures for gastrointestinal hemorrhage include: monitoring of vital signs; fasting; active application of measures for fluid expansion, fluid infusion, hemostasis, blood transfusion, antiacid, and elevation of blood pressure; and, if necessary, endoscopic hemostasis. (IV) Intra-abdominal hemorrhage: the clinical manifestations of intra-abdominal hemorrhage mainly depend on the bleeding volume. While a small volume of bleeding normally does not incur notable symptoms, massive bleeding can cause abdominal distension and pain, and may be associated with cold sweat, decreased blood pressure and shock symptoms in severer cases. The occurrence of intra-abdominal hemorrhage can be explained by two possibilities: the location of the liver tumor is relatively superficial and will become ruptured after puncture; or, in patients with poor coagulation function, the hepatic puncture site can bleed easily. Preventive measures: the indication of local ablation should be strictly followed. For cirrhotic patients with poor coagulation function, the condition should be improved before initiating local ablation. For superficial foci, the ablation should preferably be performed under laparoscopy or under direct visualization during open surgery. The puncture sessions should be minimized during percutaneous RFA. After completion of an ablation, a second ultrasound or CT should be performed to rule out the possibilities of tumor rupture or bleeding. The management measures include: monitoring of vital signs; active application of measures for fluid expansion, fluid infusion, hemostasis, blood transfusion, and elevation of blood pressure; and, if necessary, hemostasis by surgical exploration. (V) Tumor seeding: tumor seeding is often resulted from multiple punctures. Preventive measures: puncture should be precisely positioned to avoid multiple punctures. If the needle is inserted too deeply, the electrode needle should not be withdrawn directly; rather, it should remain at the original site until ablation is completed, and then it can be withdrawn for re-location. (VI) Liver failure: liver failure is often resulted from pre-operative poor liver function due to severe cirrhosis or from major complications such as infections or hemorrhage. Prevention and management: the

indications of local ablation should be strictly followed. The surgery is contraindicated in patients with liver function of Child-Pugh C, massive ascites, and/or severe jaundice. After the surgery, it is important to prevent other complications, avoid infections, and actively carry out liver-protective treatment. (VII) Damage to neighboring organs: percutaneous RFA may easily cause thermal injury to the neighboring organs or vessels when: (I) the tumor is near gallbladder, gastrointestinal tract, bile ducts, or diaphragma; and (II) the tumor is located at the first hepatic hilum or under liver capsule. For these tumors, RFA should preferably be performed under laparoscopy or under direct visualization during open surgery. Meanwhile, the neighboring organs should be protected using no-touch isolation technique.

7. Assessment of treatment efficacy

Patients should be re-examined one month later with triple-phase CT/MRI scanning of liver or ultrasound to assess the treatment efficacy of ablation. The therapeutic effectiveness is divided into: (I) complete response (CR): follow-up with triple-phase CT/MRI scanning of liver or ultrasound shows hypodense area at the site of an ablated lesion (and hyperechogenic under ultrasound), with no enhancement on arterial phase images. (II) incomplete response (ICR): Follow-up with triple-phase CT/MRI scanning of liver or ultrasound shows enhancement on arterial phase images at some parts of tumor lesions, indicating the existence of residual tumor.

For patients with residual tumor, a second session of ablation may be applied. If residual tumor still exists after two ablation sessions, ablation is regarded as failure, and other treatment should be considered.

8. Follow-up

Patients should be routinely followed up after surgery. Patients should be re-examined monthly during the first two months after surgery with triple-phase CT/MRI scanning of liver (or ultrasound) and tests for liver function and tumor markers to observe the necrosis of foci and changes in tumor markers. In the following months, patients should undergo tumor markers tests, ultrasound or triple-phase CT/MRI scanning of liver every 2 or 3 months, during which ultrasound and CT/MRI should be applied in an alternating manner. Two years after surgery, patients should undergo tumor markers tests, ultrasound or triple-phase CT/MRI scanning of liver every 3 or 6 months, during which ultrasound and CT/MRI should be applied in an alternating manner. The possible tumor recurrence or progression can be judged based on follow-up results. They include: (I) local tumor progression: local tumor progression is defined as the presence of new lesions around the margin of the ablated lesion after the achievement of CR, and the new lesions are connected with the ablated lesion; (II) new lesion: lesions newly occur at the other sites within the liver; and (III) distant recurrence: metastatic lesions occur outside the liver.

9. Other considerations

9.1. RFA for tumors in high-risk locations

If a tumor is near gallbladder, gastrointestinal tract, bile ducts, or diaphragma, or if a tumor is located at the first hepatic hilum or under liver capsule, these locations are regarded as at high-risk. RFA for these tumors are associated with high risks including the thermal injury to the neighboring organs or vessels and the rupture and bleeding of tumors. Special attention should be paid to these risks. For these tumors, RFA should preferably be performed under laparoscopy or under direct visualization during open surgery, so as to protect the neighboring organs using no-touch isolation technique. Literatures also have reported that RFA may be performed with the assistance of artificial pleural effusion, artificial ascites, or some special maneuvers (e.g., liver hanging maneuver). However, the treatment efficacy of RFA shows no sifgnificant difference between tumors in high-risk locations and those in other locations.

9.2. RFA for large liver cancer

The extent of ablation of currently available RFA system ranged 3-5 cm in a single session; therefore, for tumors with diameters longer than 5 cm, monopolar FRA often can not achieve CR. It has also been reported that, by adopting some new electrode placement protocols using polyhedral model-based multi-needle and multi-polar techniques, multiple ablations can provide spheres of ablation up to >7 cm in diameter.

9.3. RFA combined with other treatment

The combination of RFA with transcatheter hepatic arterial

chemoembolization (TACE) or percutaneous ethanol injection therapy (PEI) has shown higher treatment efficacy, especially for single tumor >3 cm in diameter or multiple nodules. However, for patients respond poorly to RFA, other treatment modalities including surgical resection, TACE, molecular targeted drugs (e.g., sorafenib), and systemic chemotherapy may be applied. Effective systemic drug therapy may be provided to patients with distant recurrence.

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