Percutaneous Local Ablation Therapy for Hepatocellular Carcinoma

Dr. Victor Ai
MBChB, FRCR, FHKCR, FHKAM (Radiology)
Department of Radiology, Hong Kong Sanatorium & Hospital

Introduction
Hepatocellular carcinoma (HCC) is a prevalent disease in Asia and the second leading cause of cancer death in Hong Kong. Surgical resection is regarded as the curative treatment. However, only 20% to 30% of HCC patients are suitable surgical candidates. Over the years, various locoregional therapies have been employed for the treatment of unresectable HCC. These include the widely practised transarterial chemoembolisation (TACE), whose benefit on patient survival remains controversial in randomised controlled studies. Percutaneous image-guided ablation therapies also play an important role in the management of localised HCC in non-surgical patients. The most commonly used techniques are percutaneous ethanol injection (PEI), cryotherapy, microwave coagulation therapy (MCT) and radiofrequency ablation (RFA).

Percutaneous ethanol injection
PEI is a well-established ablation treatment for localised HCC. It involves percutaneous placement of one or more fine needle into the tumour under ultrasound guidance, and subsequent injection of 95%-99.5% ethanol to ablate the tumour. The ethanol diffuses into tumour cells, producing immediate coagulation necrosis due to effects of cellular dehydration and protein denaturation followed by small-vessel thrombosis.

PEI is only considered appropriate for small tumours of <3cm in size. Multiple treatment sessions are usually required. It is a relatively safe procedure. Minor complications include local pain, mild alcohol intoxication and elevated transaminase levels. Major complications such as portal thrombosis, intrahepatic or intrahepatic haemorrhage, and cholangitis are uncommon (1.3% to 2.4%).

The reported short-term efficacy of PEI for HCC in terms of percentage of tumour necrosis ranges between 36% and 90%. However, the recurrence rate at the treatment site is relatively high (up to 81% after 3 years follow up) due to inhomogeneous ethanol diffusion and difficulty in ensuring a complete ablation.

Cryotherapy
Cryotherapy was described in 1962 as the first local thermal ablative technique used for cancer treatment. The procedure is performed either with open laparotomy or, more recently, by laparoscopic and percutaneous approaches. A cryoprobe is placed centrally within the lesion under ultrasound guidance. Liquid nitrogen or argon gas is circulated through the probe to deliver subfreezing temperature (-20°C to -30°C), which causes irreversible cellular damage in the target lesion.

A rare (1%) but serious complication is the “cryoshock” phenomenon, which is possibly related to toxins released from necrotic liver tissues. This causes multi-organ failure and has a mortality rate of 18.2%. Other complications include intraoperative or postoperative haemorrhage due to liver cracking upon thawing or severe coagulopathy, bile leakage, abscess formation and acute tubular necrosis from myoglobinuria.

Microwave coagulation therapy
MCT for HCC can also be performed by percutaneous or laparoscopic approach. After insertion of an electrode into the tumour under ultrasound guidance, high-frequency electromagnetic radiation (2000-3000 MHz) is generated to heat the intracellular water molecules of the surrounding tissues. The resulting heat energy causes irreversible cellular damage.

The short-term efficacy of MCT appears encouraging, with a response rate of up to 70% for small HCC (≤3 cm). This falls to 55% for larger HCC (≥3 cm). In one series, local recurrence rate was 2% for small HCC, compared with 8% for large HCC after a 9-month follow-up period. Data on long-term survival is more limited. Itamoto et al. reported a 48.6% overall 5-year survival rate and a 50% overall 4-year survival rate for patients with primary and recurrent HCC, respectively.

Reported complication rate ranges between 11-14%. The complications include abscess formation, biloma, bleeding, hepatic failure and intraperitoneal dissemination of tumour cells.

Radiofrequency ablation
Among the various local ablative techniques, RFA has gained the most popularity in recent years owing to promising results reported in multiple series. It is now used for the treatment of unresectable HCC in many centres worldwide. The procedure again involves ultrasound-guided placement of an electrode into the tumour by percutaneous, laparoscopic or open approach. A connecting radiofrequency generator produces alternating current at 460-480 kHz, which causes oscillatory movement of ions and hence frictional heat in the tissues. The procedure can be closely monitored by ultrasound in real-time, as the ablated area is gradually covered by echogenic
tumours >6 cm in diameter. Concerning long-term survival RFA, with a median follow up of 22.6 months (range 3-66 result, Rossi et al. More than 80% of these local recurrences occurred in the same authors, however, subsequently reported a higher local recurrence rate was 33%. The local recurrence rate was higher for lesions close to or main bile duct and major blood vessels at the liver hilum. Tumour seeding along the needle track during RFA is rarely reported, except for one author who reported a track-seeding rate of 12.5% after percutaneous RFA. However, the result of this study may be related to biopsy prior to ablation. It was suggested that an increased risk of seeding, bleeding and local recurrence was associated with subcapsular location of tumour. This has not been supported by other studies.

The efficacy of RFA has been well documented. Curley et al. reported only three local recurrences among 123 patients (2.4%) in one of the largest series of clinical RFA study. The same authors, however, subsequently reported a higher local recurrence rate of 9% after treating more than 300 patients. More than 80% of these local recurrences occurred in tumours >6 cm in diameter. Concerning long-term survival result, Rossi et al. studied 39 HCC patients who underwent RFA, with a median follow up of 22.6 months (range 3-66 months). The cumulative median survival was 44 months, and the 1-year, 3-year and 5-year survival rates were 94%, 68% and 40%, respectively. Another study by Buscarini et al. compared the use of conventional and expandable RF electrodes in treating 80 HCC patients. The overall 5-year survival rate was 33%. The local recurrence rate was higher in patients treated by conventional electrode (29%) than in those treated by expandable electrode (14%).

Comparison between local ablation therapies
PEI is a safe and effective treatment for localised HCC, but is only suitable for small tumours (<3 cm). In recent years, it has been replaced in many centres by thermal ablative techniques, which in general produce more predictable tumour necrosis, and require fewer number of treatment sessions than PEI.

In one study comparing the efficacy of MCT and PEI in patients with small HCC (2 cm), the overall 5-year survival rate for MCT (78%) was significantly higher than that for PEI (35%). With a follow-up of 12-72 months, patients treated with MCT had a significantly lower recurrence rate (8%) than those treated with PEI (40%).

Cryotherapy has also been increasingly replaced by the hyperthermic local ablative therapies, because of its unacceptable complications. According to Pearson et al., the complication rates in patients treated with cryotherapy and RFA were 40.7% and 3.3% respectively. Operative mortality rates for cryotherapy and RFA were 2% and 0% respectively. Moreover, with a median follow-up of 15 months, the tumour recurrence rate for cryotherapy (13.6%) was significantly higher than that for RFA (2.2%).

In summary, RFA and MCT are more effective and capable of treating larger tumours compared with PEI and safer than cryotherapy. With the latest technology, RFA can produce larger ablation volume than MCT, and is considered by many to be the best technique.

Recently, increasing interest has been drawn towards combining different therapies in the treatment of HCC, instead of considering each therapy on its own merits. For example, it has been shown in vivo that combined RFA and PEI could increase the dimension of coagulation necrosis. Shankar et al. recently reported that by combining RFA and PEI, consistently larger lesions were obtained in fewer sessions without any increase of complications. Other data also suggested the synergistic effect of RFA and transcatheter embolisation. Therefore, the future trend for the treatment of HCC will likely be a multidisciplinary approach with a combination of therapies.

References
11. Hasegawa S, Yamazaki N, Hiwaki T, Factors that predict intrahepatic microbubbles. Compared with MCT, the ablation produced by RFA has a more predictable and reproducible shape and volume. Histologically, there is thermal coagulation necrosis and thrombosis of microvasculature. Two types of Food and Drug Administration-approved RF electrodes are currently available. The expandable electrode (RITA Medical Systems, and Radiotherapeutics, Mountain View, CA, USA) comprises a 14-gauge outer needle that houses 610 retractable electrodes to be deployed within the target lesion. The synergistic effect of the deployed electrodes increases the ablation volume up to 3.5 cm diameter. The second type, the cooled-tip electrode (Radionics, Burlington, MA, USA) uses an insulated 17-gauge needle with an exposed needle tip of variable length. The electrode has hollow internal channels for continuous circulation of chilled water during the procedure to cool the tissues around the needle tip. This reduces charring and impedance, increases energy deposition and thus maximises ablation volume (up to 3.1 cm diameter). For lesions larger than 3.5 cm, multiple electrodes may be used. Alternatively, a cluster electrode with three parallel cooled-tip electrodes placed in close proximity has been developed to further increase the ablation volume.

RFA is relatively safe, with a complication rate of 0-12% and an operative mortality rate of 0-3%. The complications include abscess formation, bleeding, pleural effusion, ascites, damage to hepatic vessels and bile duct, visceral damage, and liver failure. RFA is contraindicated for lesions close to important structures or organs, such as the gallbladder, bowel, or main bile duct and major blood vessels at the liver hilum. Thrombosis has also been reported in the liver venous system. PEI is a safe and effective treatment for localised HCC, but is only suitable for small tumours (<3 cm). In recent years, it has been replaced in many centres by thermal ablative techniques, which in general produce more predictable tumour necrosis, and require fewer number of treatment sessions than PEI. In a non-randomised prospective study comparing RFA and PEI in patients with small HCC (<3 cm), RFA has a higher complete tumour ablation rate (90%) than PEI (80%), and requires fewer treatment sessions (mean, 1.2) than PEI (4.8). The complication rate of RFA is however higher than that of PEI (12% versus 0%). Two randomised trials also show that RFA produces more complete tumour ablation with a shorter treatment time compared with PEI.


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