New horizons in ablation therapy for hepatocellular carcinoma

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Hepatic Oncology

Practice points

- There is a clear trend of more active surgical treatment for hepatocellular cancer beyond the aging Barcelona Clinic Liver Cancer guidelines.
- Liver transplantation is a maximal invasive treatment that is the only option for removal of a carcinogenic cirrhotic liver with the tumors, thereby having a relative low risk of liver recurrences.
- Hepatic resections for hepatocellular cancer are possible and meaningful outside Barcelona Clinic Liver Cancer guidelines.
- Local resection seems to be equal to segmental resection in overall survival.
- Thermal ablation with radiofrequency ablation or microwave ablation gives results equal to resection in a subset of patients.
- New technologies for better targeting are evolving rapidly.
- It is not inconceivable that an ablative strategy for small (less than 30 mm) lesions will become the primary treatment of choice in the not-so-distant future.

Historically ablative treatment for hepatocellular cancer (HCC) has been regarded as inferior to transplantation and resection and has therefore been reserved for patients not suitable for surgical intervention in stage 0-A HCC according to the Barcelona Clinic Liver Cancer classification system. In the wake of surgical strategies challenging the current Barcelona Clinic Liver Cancer treatment guidelines and improvements in imaging, targeting and ablation technologies, ablation is likely to occupy a more central role in the management of patients with HCC, challenging its historically perceived inferiority to resection.

The aim of this paper is to give a short overview of ablation modalities used for treatment of hepatocellular carcinoma (HCC) and the indications for ablative treatment in common practice, and also to glimpse into the near future and how emerging technologies can help.

Hepatocellular carcinoma is the second most common cause of cancer death globally and affected 782,000 people and caused 746,000 deaths in 2012 [1], a figure that is probably underestimating the true incidence by as much as 120,000 cases due to underreporting in developing countries [2]. Most cancers are attributed to cirrhosis due to chronic hepatitis B and C infection, accounting for more than 90% of cases in the developing world and 40% in the developed world [3]. In the developed parts of the world other causes of cirrhosis include alcohol liver disease, the metabolic syndrome with nonalcohol fatty liver disease and nonalcohol steatohepatitis and metabolic and autoimmune liver

KEYWORDS

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diseases. Only 10% of HCC arise in a normal liver [4].

Treatment decisions for HCC are often based on the Barcelona Clinic Liver Cancer (BCLC) staging system (Figure 1) [5]. Typically, 20–30% of patients fall into stage 0, 50% into stage A–C and 20–30% into the palliative stage D [6]. In a recent survey on the HCC treatment in ten large tertiary referral centers worldwide, it was shown that 50% of resected patients were outside of the BCLC-based guidelines for liver resection with equal eventual outcome. This underscores the benefits of an active approach, extending the indications for curative-intended treatment with survival and complication rates similar to patients falling inside the criteria [6]. HCC is typically resected with an intended margin of 2 cm and in a segmental fashion because of concerns about satellite tumor deposits from portal seeding, causing early recurrences if not radically resected [7]. This view has been challenged and recent results contradict the segmental approach favoring a more limited local approach [8] thus setting the scene for local ablative procedures as a possibly equally effective

treatment option, even in patients where the BCLC guidelines would propose liver resection.

Ablation modalities

Within the BCLC guidelines, ablative treatment is allocated to patients with stage 0–A not suitable for surgical therapy. Tumors can be destroyed by chemical means (injection with alcohol or acetic acid), thermal means (freezing with cryotherapy or heating with radiofrequency ablation (RFA), microwave ablation, laser ablation or high-intensity focused ultrasound), electrical means (irreversible electroporation) or by radiation (stereotactic body radiation therapy). RFA has been the most widely used and reported hyperthermic method.

• Injection therapy

Percutaneous injection of alcohol into the center of the tumor is a simple technique that can be performed on sedated patients using ultrasound guidance. It is cheap and universally available. It has good results in lesions less than 20 mm in diameter with a response rate of approximately

Figure 1. Updated Barcelona Clinic Liver Cancer staging system and treatment strategy.

bil: Bilirubin; CIS: Carcinoma *in situ*; HCC: Hepatocellular cancer; PEI: Percutaneous ethanol injection; PS: Performance status; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization. Data taken from [5].

90% but with worse results in larger lesions [9] since the injected alcohol is unevenly distributed within and outside the tumor. Because of higher local recurrence rates compared with radiofrequency ablation, the technique has largely been abandoned in the west and is no longer recommended within the BCLC guidelines. However, good results with small lesions (<20 mm) have been shown in more recent studies with survival equal to RFA [10]. Besides alcohol, acetic acid has also been used for ablation with similar results having been reported although good quality data are lacking [11].

• Cryoablation

Freezing of the tumor is accomplished by using argon gas through a delivery needle inducing a temperature of -160°C and causing intracellular and extracellular damage by crystal formation and cell dehydration. The resulting ice ball is easy to visualize using ultrasound, computer tomography or MRI. The thawing results in release of cellular debris into the general circulation with the potential of causing cryoshock. The technique does not coagulate the needle tract, which might explain the higher risk for bleeding [12]. The freezing process is slow, usually taking up to 30 min, and the delivery system is expensive. Multiple ablations are usually needed to cover a lesion. Results have shown that cryoablation is inferior to radiofrequency ablation in the treatment of liver tumors [13].

• Radiofrequency ablation

This thermal ablation modality works by insertion of an electrode into the tumor and completing the circuit with a large skin electrode thereby concentrating the given energy at the tip of the ablation needle. Energy is delivered as a current with oscillations in the radiofrequency range causing polarized molecules, primarily water, to wobble and induce friction heat which is conducted from the electrode. A zone of necrosis dependent on tissue properties is produced. Ablations can also be done with bipolar or multiple electrodes. Too quick desiccation of the tissue inhibits propagation of the thermal ablation zone and slow heating is therefore preferred. With a slowly growing heated zone, the relative cooling effect of larger vessels becomes significant and counteracts the ablation effect, the so-called heat sink effect [14]. RFA, being the method most commonly used, is well-documented [15]. Main drawbacks are slow delivery of energy and the heat sink effect.

• Microwave ablation

Thermal ablation is caused by direct application of an electromagnetic field oscillating in the microwave frequency range, typically 0.915 or 2.45 GHz. This causes water molecules to oscillate and cause frictional heat. The electromagnetic field has a direct effect, independent of the tissue properties up to 2 cm from the antenna, from where heat is conducted further. The energy delivery is quick, typically achieving a complete ablation within 1–5 min. Larger ablation volumes can be achieved and the heat sink effect is less pronounced. The risk for damage to nearby structures is increased with the more potent energy delivery. The clinical results are comparable to RFA [16] as are complication rates [17]. The main benefits are quick ablations, allowing for multiple tumor ablations in one session, larger ablations and less heat sink effect. The technique is still evolving and the level of evidence has not reached that of RFA.

• High-intensity focused ultrasound

This is a truly noninvasive technique with energy being delivered with an ultrasound probe with multiple piezoelectric transducers focusing the energy in a 10–50 mm long and 1–5 mm wide point causing cavitation and heat in the tissue. The tumor must thus be covered in sweeps. The procedure is technically challenging and time consuming and very much in an experimental stage [18].

• LASER ablation

Thermal ablation can also be performed with LASER as energy source, transmitting the high energy photons by thin fiberglass filaments into the tumor. This is not a widely used technology but its use has been reported in HCC [19]. An advantage of this modality is that it is MRI-compatible. The main drawbacks are high cost, and the fact that it is time consuming. Compared to other ablative techniques data are scant.

• Irreversible electroporation

This novel nonthermal technique works by short bursts of 3000–5000 volts at 20–50 ampere being delivered between a lattice of electrodes surrounding the tumor, causing disruption of the cell-membranes, inducing apoptosis and cell death with minimal heat. Surrounding connective tissue is preserved keeping vessels, bile ducts and nerve sheaths intact [20]. Ablations can be

performed on tumors close to large vessels and sensitive structures like bile ducts, for example, in the liver hilum. Correct parallel and evenly spaced placement of the electrodes with a between-needle distance approximately 20 mm is crucial. A minimum of three electrodes are recommended making precise targeting challenging. Patients need to be in full anesthesia and deeply neuromuscularly blocked to prevent muscle activation by the strong currents. Furthermore, pulses have to be synchronized with the refractory period of the cardiac cycle to prevent arrhythmias. Irreversible electroporation is an evolving technique and is still recommended to be performed within clinical studies. Preliminary results have shown higher recurrence rates, compared with RFA, but technical feasibility with tumor locations near larger vessels where other ablation modalities are contraindicated [21].

• Stereotactic body radiation therapy

Radiation therapy is not included in the arsenal of curative ablative techniques for HCC but is sometimes applied in a palliative setting. The tumor site is often marked with gold fiducials placed near the tumor using ultrasound guidance. A radiation dose of 30–60 Gy is then administered in 3–6 sessions with the patient being awake and using a 3D radiation planning scheme [22]. Radiation-induced liver disease is a rare but potentially fatal complication.

• Complications

After liver resections, complications are seen in 30–40% depending on the size of the resected segment and the grade of cirrhosis. A quarter of these are serious complications requiring interventions or mortality [23]. Complications range from simple wound problems to deep infections, bile duct injuries, vascular injuries and remnant liver failure. Thirty day mortality is typically in the range of 2%.

Complications of coagulative ablative treatment is less common, with less than 10% having a Clavien-Dindo grade 2 or more, with a quarter having grade 3b or more requiring reintervention in anesthesia. Complications range from simple skin burns to hepatic abscesses, pleural effusions, pneumo- and hemo-thorax to biliary and vascular injury. There is also a small but real risk of tumor seeding in specific ablative scenarios [24].

With irreversible electroporation, there is a much quicker regrowth of the ablated volume and the risk for injuries to bile ducts or vessels seems

to be significantly less. Publications on the subject is lacking but the risk for missed ablations seems to be higher and the risk for tumor seeding could be higher because of nonablation of the needle track, which could potentially also increase the risk for bleeding.

Access & navigation

Regardless of the modality, accurate placement of the ablation device is crucial to outcome. The ablation device should be positioned in the most accurate and less invasive way in order to enable a safe and complete ablation of the target lesions. Options for detection are ultrasound, CT or MRI, visual inspection and bimanual palpation. Access can be percutaneous, laparoscopy assisted or laparotomy assisted. Ablation at laparotomy allows for additional staging and more options are available for directing the device, access only being limited by the incision. Furthermore mobilization of the liver can facilitate access and minimize movement artifacts. Damage to adjacent organs can be avoided by direct vision and displacement. The heat sink effect can be minimized by partial or total vascular exclusion. Performing ablations with an open abdomen is however somewhat counter-productive as the point with ablative therapy is to cure with minimal invasiveness. Laparoscopic ablation offers the same advantages except for the possibility to palpate the liver and directional possibilities are slightly more limited. It is particularly well-suited for tumors on the dome of the liver, close to the diaphragm or heart, tumors on the dorsal aspect of the left lateral sector in proximity to the stomach, tumors close to the gallbladder and superficial tumors close to the colon [27,28]. Percutaneous ablation, being the least invasive, is the most commonly used access. It does, however, carry a higher risk for collateral damage to nearby organs and some lesions may be inaccessible. Recurrence rates of 20–30% of have been reported for percutaneous ablation, compared with approximately 10% with open ablation [29,30].

Ultrasound is the most widely used modality for navigation [25]. It can be performed percutaneously, laparoscopically or laparotomy guided. It has the additional advantage that it is readily available, relatively cheap, has a high precision and one has the advantage of second generation contrast agents for tumor delineation. It is however operator-dependent and direct visualization is needed for targeting. CT-guided ablation is mostly performed percutaneous but can in theory

be laparoscopy or laparotomy assisted. It gives more sensitive targeting and allows for direct assessment of the ablation zone. It is however logistically more challenging, more expensive and there are radiation issues and the possibility of contrast allergies. MRI-navigated ablation offers

all the advantages of CT. Issues with access in the confined space and MRI compatibility of ablation devices makes it a less often used method. Recent development included double gantry circular and open systems have solved some of the access issues.

Figure 2. Use of virtual guidance system by CAScination AG (Bern, Switzerland) for multiple tumor ablations in a previously ablated liver. Blue and green dots correspond to matching of real liver and virtual model, computer with tracking cameras is inset as are laparoscopic images of previous ablated volume and laparoscopic needle insertions.

Tumor targeting can also be accomplished using 3D navigation where a computer reconstruction of the liver, based on preoperative imaging, can be overlaid on the real liver thus virtually directing ablation devices to tumors, even when not visible and even without ultrasound verification, and allowing for ablation device delivery from any angle (Figure 2) [24]. It may solve some of the problems of conventionally used access and targeting methods. With virtual segmentation of vascular and biliary structures these can be used both for matching with the virtual liver and for planning of an optimal needle trajectory [26]. With virtual targeting, there can be problems with accuracy since the form of the liver can change between imaging and intervention and respiratory movements of the diaphragm will displace the liver with up to 3 cm per breath. These

breathing problems can partially be bridged with temporary respiratory tube disconnection or with continuous high-frequency jet ventilation.

Using fusion with previous CT or MRI-images can increase targeting precision with ultrasound, an emerging technology with wide future applications in routine ultrasonography. At Danderyd Hospital the recurrence rate, that is, recurrent tumor within 1 cm of the ablation volume at 6 months follow-up, has dropped from 30 to 10% after the introduction of the fusion technology [UNPUBLISHED DATA]. CT guidance can be used applying a stepwise technique using fluoroscopy modes in the scanner or with virtual guidance techniques using optical tracking of the patient and ablation devices (Figure 3). In combining it with virtual guidance the radiation dose can be more than halved with very good precision with

Figure 3. CAS-One used for virtual needle guidance in the CT-laboratory demonstrating workflow, lesion targeting, multiple needle placements for irreversible electroporation and 3D reconstruction of lesion and electrodes. (A) Workflow in using CAS-One. (B) Image of targeting of tumor. (C) Placement of six needles for irreversible electroporation of liver tumor. (D) 3D reconstruction of CT image verifying needles around tumor.
CBCT: Cone beam computer tomography.

an error of typically around 4 mm [ENGSTRANDET AL., SUBMITTED] in any part of the liver. With the help of computer assisted systems, multiple needle placements for irreversible electroporation or lattice patterns for larger tumors can be simplified.

Prediction of ablation size

Even though charts are supplied from the manufacturers of ablation devices the actual ablation achieved is still a guessing game. This is an obvious weakness in ablation treatment. Charts are typically based on ablations on cadaveric bovine livers and do not take perfusion, liver consistency, chemotherapy, age or other possible clinical factors into account. Studies have shown that ablation zones are typically overestimated with the laboratory dry models, and more clinical data are needed to more precisely predict the ablation in order to reduce the risk for an incomplete ablation [31]. A factor counteracting this is the contraction of proteins that occurs with thermal ablations, where up to 45% of the tumor volume is lost, thereby actually increasing the safety margin of the ablative treatment [32].

Live monitoring of the ablation is another means to ascertain an adequate margin. This can be problematic. With ultrasound the heating effect can be evaluated by the gaseous cloud that develops in the ablated area. The vapor may, however, obscure the image making monitoring difficult and inexact, also complicating targeting of nearby lesions. Elastography is another possibility as the ablated area coagulates and becomes more firm and some promising results have been published [33]. Monitoring the ablation process in the CT scanner requires contrast medium, and as a good preablative contrast series is needed, further administration of contrast is limited by renal function. A way around this is placement of an angiography catheter in the hepatic artery and thereby greatly decrease of the amount of contrast needed for visualization of hepatic lesions and landmarks [34].

Clinical results of local ablations in hepatocellular carcinoma

For HCC, on the background of chronic liver disease, liver transplantation is widely regarded as the treatment of choice since it offers the best chance of long-term survival with complete removal of the carcinogenic cirrhotic liver. Surgical resection is second choice with ablation being the last alternative with a curative

intent. The Milan criteria and the revised San Francisco criteria limit the role for transplantation. The tumor burden must be limited and the patient should be in a condition to survive major surgery. Also there is a shortage of liver donors which further limits the role of transplantation. This has led to a situation where patients instead are treated with resection and there is mounting evidence that resection can be as effective as transplantation in a subset of patients [35,36], at least regarding 5-year survival but with the cost of a much higher liver recurrence rate. With resections, previous recommendations of segmental anatomical resection planes, to reduce the risk for recurrences within the same portal segment, have been challenged and recent data suggest that, as with resection of metastases, a margin of 5–10 mm is enough and nonanatomical resections have the same outcome but with better sparing of liver parenchyma [8]. The next leap of thought is then: does a complete destruction of the tumor with ablative techniques give an equal long-term survival?

This question has not been addressed in randomized trials but there is growing evidence from large eastern centers that this may be the case. A few recent registry-based studies and propensity score analyses are shown in **Figures 4 & 5**, and clearly the boundary between the indications for resection and ablation is getting fuzzy [37].

There is no question that ablations cause fewer complications than resections and a local destructive treatment also leaves antigens that can

Figure 4. Comparison between surgical resection and radiofrequency ablation in the treatment of hepatocellular carcinoma.

HR: Hepatic resection; RFA: Radiofrequency ablation.

Reproduced with permission from Korean Surgical Society [39].

Figure 5. Results of curative treatments for hepatocellular cancer.

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activate the patient's immune system and give a further benefit of ablation over resection [38].

Conclusion

Ablative therapies for HCC is getting more efficient with advances in energy delivery and targeting. It is now on the verge of becoming the first choice for treating tumor smaller than 30 mm in diameter with the benefit of sparing of liver parenchyma, shorter hospitalization, fewer complications and much shorter recovery times for patients.

Future perspective

With increasing precision in interventional technology and more exact control of energy delivery, minimally invasive ablative techniques are likely to become first line therapy for hepatocellular carcinomas up to a size of 30 mm. This will lower complication rates and intervention-related mortality and greatly enhance postoperative recovery and treatment-related hospital costs. Image fusion technologies are likely to develop further and images from operating room cameras, laparoscopic cameras, live ultrasound images and preoperative

functional and structural imaging in 3D will greatly enhance both surgical and ablative procedures. Surgeons will be more involved in ablative procedures and radiologists will have to move into a more surgeon-like capacity as interventionists, dealing more with treatment than diagnosis. It is likely that there will also be widening indications for adjuvant treatments with combinations of ablation, TACE and local and systemic treatment with cytotoxic agents and immunomodulatory agents to boost the immunological-activating effects of ablative procedures.

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