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FIELD OF VISION

Advances in local ablation of malignant liver lesions

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Abstract

Local ablation of liver tumors matured during the recent years and is now proven to be an effective tool in the treatment of malignant liver lesions. Advances focus on the improvement of local tumor control by technical innovations, individual selection of imaging modalities, more accurate needle placement and the free choice of access to the liver. Considering data found in the current literature for conventional local ablative treatment strategies, virtually no single technology is able to demonstrate an unequivocal superiority. Hints at better performance of microwave compared to radiofrequency ablation regarding local tumor control, duration of the procedure and potentially achievable larger size of ablation areas favour the comparably more recent treatment modality; image fusion enables more patients to undergo ultrasound guided local ablation; magnetic resonance guidance may improve primary success rates in selected patients; navigation and robotics accelerate the needle placement and reduces deviation of needle positions; laparoscopic thermoablation results in larger ablation areas and therefore hypothetically better local tumor control under acceptable complication rates, but seems to be limited to patients with no, mild or moderate adhesions following earlier surgical procedures. Apart from that, most techniques appear technically feasible, albeit demanding. Which technology will in the long run become accepted, is subject to future work.

Key words: Local ablation; Liver; Microwave ablation; Hepatocellular carcinoma; Colorectal liver metastases; Navigation

Core tip: A wide variety of technical innovations enables us to use microwave as well as radiofrequency ablation, various image fusion technologies, magnetic resonance guidance for local ablation, navigation, robotics, and minimal invasive access to liver surgery in general in the 21st century. However, in comparison to data found in the current literature for conventional local ablative treatment strategies, virtually no single technology is able to demonstrate an unequivocal superiority. Most techniques appear technically feasible, albeit demanding. Which technology will in the long run become accepted, is subject to future work.

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COMMENTARY ON HOT TOPICS

Local ablation of liver tumors matured during the recent years and is now proven to be an effective tool in the treatment of malignant liver lesions. Advances focus on the improvement of local tumor control by technical innovations, individual selection of imaging modalities, more accurate needle placement and the free choice of access to the liver. Repeatedly, different elements of improving local ablation have been reported, including the use of microwaves instead of radiofrequency, magnetic resonance (MR) instead of computed tomography (CT) or ultrasound (US), navigation, robotics and minimal invasive surgical access routes instead of percutaneous or open surgical approaches. The following contribution is meant to illustrate some of the more recently envisioned developments with respect to the current literature.

TECHNICAL INNOVATIONS

The most important single step was certainly the spread of microwave coagulation therapy (MCT) largely replacing radiofrequency ablation (RFA) during the recent years. MCT is no real novelty, as first reports were available as early as 1994[1]. Microwaves emitted from a monopolar antenna lead to oscillation of water molecules in a dielectric surrounding such as liver tissue. Table 1 provides an overview displaying the cardinal characteristics of MCT in comparison to RFA, respectively. The renaissance of MCT is partly traced to better equipment with intelligent feedback controlled generators compared to the first devices[2], but as important seems to be, that MCT is meanwhile not considered yet another technique to generate heat in the same way like with RFA, but in contrast a completely distinct technology for thermal ablation with different and unique physical properties[3]. This leads eventually to an experimentally confirmed less susceptibility to heat sink phenomena[4,5], shorter treatment duration[6] and larger ablation areas[7]. So far, no clinical evidence supports the superiority of MCT to RFA; the only published randomized controlled trial revealed no statistically significant difference, and among 14 comparative cohort studies, only three found a significantly lower local recurrence rate (LR) following MCT[8-10]. The trend to shorter treatment times is however already clinically endorsed[11]. In general, RFA is believed to be most effective in tumors with a maximum diameter not larger than 3 cm. MCT promises to be successful also in the treatment of larger tumors[2], most probably when combined with transarterial chemoembolization (TACE)[12,13]. Sustained success may however also be achieved, if RFA is combined with TACE prior to or following the ablation[14]. At date, MCT - albeit promising - has not yet been convincingly confirmed to be superior to RFA.

Table 1 Differences comparing radiofrequency ablation to microwave coagulation therapy with regard to physical properties

	RFA	MCT
Electromagnetic waves	Radiowaves	Microwaves
Frequency	0.3-0.5 MHz	915-2450 MHz
Heating target	Ions	H_2O (approximately 50%)
Heat distribution	Convective	Direct heating (within field)
Alternating current	Closed circuit	Electromagnetic field
Applicator	Electrode	Antenna
Desiccation	Carbonization	Vaporization
Size of ablation area	Unaltered/slight increase	Marked shrinkage

RFA: Radiofrequency ablation; MCT: Microwave coagulation therapy.

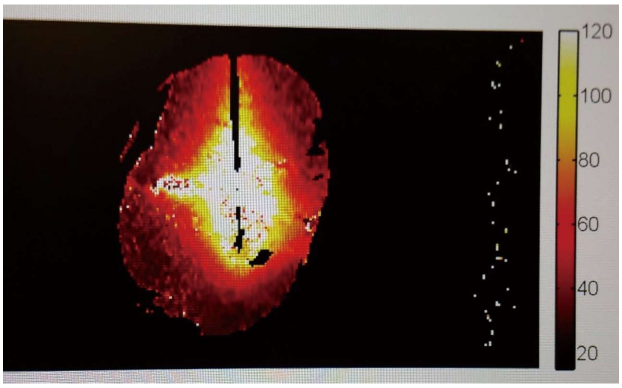

Figure 1 Thermal mapping using phase changes in magnetic resonance imaging, temperature code is depicted in the bar at the right margin of the image (values in degree Celsius). Courtesy of MedWaves Inc., San Diego, CA, United States.

IMAGING

US is presumably the most popular imaging modality in use for local ablation. Its value is undisputed; no differences to CT guidance are reported regarding success and time needed for needle placement. The widespread availability is considered a major advantage. In contrast, MR imaging is limited by shortcomings in organisation, number and cost of the required MR machines. MR offers in return several theoretical advantages in comparison to extant imaging modalities, including MR thermometry (Figure 1), absence of ionizing radiation and an impression of better imaging quality for soft tissues. The latter accounts for a significantly increased primary success rate following MR-guided RFA in comparison to CT-guided RFA (only 4% incomplete ablations *vs* 21%, *P*

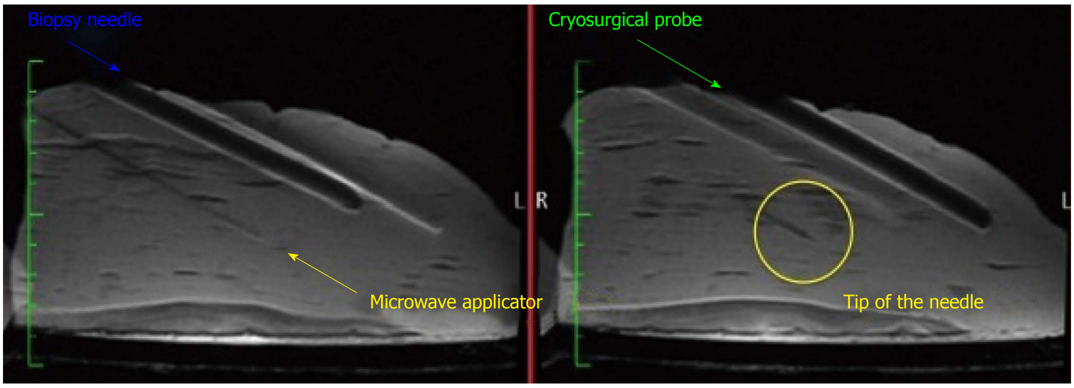

Figure 2 Magnetic resonance imaging of different devices for liver directed interventions. Of note is the inaccuracy in displaying the position of the needle shaft and tip with older devices and the complete absence of artifacts with the use of a novel microwave applicator. Courtesy of MedWaves Inc., San Diego, CA, United States.

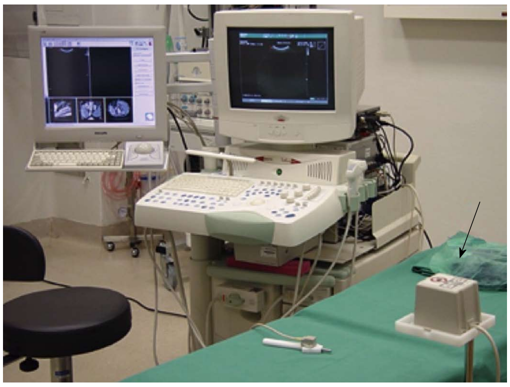

Figure 3 Clinical setup for ultrasound fusion imaging. The ultrasound machine is visible with an additional monitor for displaying the previously digitally acquired cross-sectional examination images. Meanwhile, there are also systems with a split screen. The arrow points at the electromagnetic reference point.

= 0.04), whereas the secondary success rate following a redo-ablation was not significantly different (4% *vs* 10%, *P* = 0.32)[15]. The former has been shown to be associated with an evolution of the interventional MR scanners from lower (*e.g.*, 0.2 T in 1997[16]) towards high field machines (*e.g.*, 1.5 T in 2008[17]). Nowadays, MR thermometry allows for an accurate prediction of size and geometry of an ablation area with a sensitivity of uniformly reported 87% using a threshold of 60 ℃[18,19]. The spatial resolution is however disappointing, and displaying the microwave applicator is cumbersome unless optimized hardware recently became available (Figure 2). In addition, no study exists comparing MR-guided interventions to US guidance except for an experimental evaluation of MR imaging by Chopra *et al*[20]. They found no differences in time to correct needle placement and number of required attempts. Dong *et al*[21] recently report on MR-guided MCT. Both experimental studies have in common the use of an open MR scanner instead of a closed or double doughnut system formerly used. An introduction into a clinically applicable surgical environment is not intended so far.

In contrast, intraoperative US is a clinical reality in most operation theaters, albeit some nodules are invisible in B-mode US. Additionally, mistargeting belongs to the crucial risk factors for local treatment failure[22]. A possible solution is registering the position of the US probe with a position tracking system and synchronizing the real-time US image with a previously recorded three-dimensional multiplanar imaging dataset derived from preoperatively obtained MR or CT scans (Figure 3), a method called Virtual Sonography or US Fusion Imaging (UFI). With UFI, technically successful RFA of hepatocellular carcinoma was achieved in 94.4%-100%, and local tumor progression occurred in 0%-8.3%[23]. In a recently published study from Japan[24], UFI was able to identify sonographically inconspicuous tumor nodules in 91.7% sufficiently for a successful RFA procedure, whereas by the application of US contrast media, the detection rate increased up to 96.7%. Local tumor control rate exceeded 90% after a follow-up of 3 years in nodules with a mean diameter of 14 mm (range 8 to 42 mm). The remaining tumors were treated by transarterial chemoembolization. The authors did not explain, why no other imaging modality was applied in order to perform a sufficient local ablation treatment.

So far, no evidence suggests superiority of one or the other imaging modality for guidance of local ablative therapies in the liver.

TARGETING Ⅰ: NAVIGATION

Registration and tracking are both technologies of image processing already mentioned above. Both are prerequisites for successful navigation. Three-dimensional visualization and navigation in deformable soft tissues like liver and lung is difficult to accomplish, if free movements of the patient’s body due to breathing, intervention during mild sedation or comorbidities are not prevented. Stereotaxy was first evaluated and eventually introduced in neurosurgery, initially using a frame in order to limit the degree of freedom for movements of the target area in the

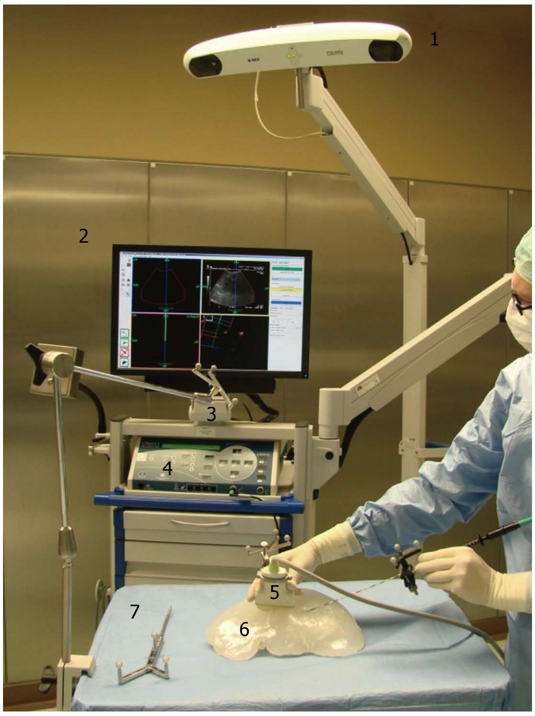

Figure 4 Example for a navigation device using optical tracking. The crucial elements are shown under intraoperative conditions with a phantom liver model. 1: Stereooptic camera; 2: Monitor with a horizontally and vertically split screen; 3: Reference point; 4: Radiofrequency generator; 5: Ultrasound probe; 6: Liver phantom; 7: Pointer.

central nervous system. Later, frameless navigation was available and evaluated in phantom experiments revealing deviations of 1.1 ± 0.4 mm for accurate needle placement with one commercially available system[25], ranging from 1.67 to 2.91 mm with two others under MR guidance[26]. Further research confirmed the high precision of yet another system with 1.1 ± 0.5 mm deviation[27]. Frameless stereotaxy opened the way for the application of navigation in the liver (Figure 4).

Navigation in liver directed surgery and interventions have been a subject of investigation for long. An overview is provided by Chopra *et al*[28] 2010. The authors describe a few single center experiences with optical and electromagnetic tracking, which after all reveal the disappointing result, that three-dimensional navigation seems to be feasible, but to date not yet superior to conventional two-dimensional biopsy US probes. Despite all obstacles, there are currently computer-assisted navigational systems commercially available. Similarities and differences among them are exhaustively discussed in an up-to-date paper[29] including a single center experience with one of the presented systems. The authors conclude, that working with the electromagnetic tracking system improved their performance compared to an ancient optical navigation device. Mean time to lesion acquisition was comparably short with only 3.5 min. Success rate with first-attempt passes was 93%. A direct comparison to conventional MCT procedures was not intended. The strategy for accurate liver intervention by an optical tracking system is outlined in a topical paper from Guangdong (China)[30]. The group suggests the use of fiducial markers to deal with the imminent inaccuracies of soft tissue navigation. So far, no vendor distributes such a technology.

TARGETING Ⅱ: ROBOTICS - A STEP FURTHER

If three-dimensional navigation increases the accuracy of the needle placement - at least under experimental *ex vivo* conditions, the complete elimination of the human component and probability for error by mechanical positioning will further improve the precision of an interventional treatment. Robotic surgery and ablation is emanating from this thesis. In phantom experiments, the use of a robot reduced Euklidic deviation from 2.2 to 1.9 mm and the mean standard distance from 1.8 to 1.6 mm[31]. The time for needle placement was however approximately 30 min. in comparison to approximately 18 min. without the roboter. A clinical study endorses the impression[32]: Robotic assistance required manual correction of the final needle position in more than 40% of all cases, resulting in a significantly decreased deviation of the active center of the microwave applicator from the tumor center (1.6 mm *vs* 3.3 mm). In addition, the exposure to radiation under fluoroscopy was significantly diminished in case of robotic needle placement. Methodological research with clinically applicable hard- and software was presented in 2010 by a group consisting in authors from the United States and China[33]. The data for accuracy of needle placement was within the previously mentioned range (positioning error between 1 and 2 mm), and the estimation of the created ablation area was except for a relative mean error of 5.6% correct. The projection of the ablation area is indeed the crucial point in robotic ablation, since it acts on the assumption of an ideal symmetric geometrical shape of the ablation area. Cai *et al*[34] describe nicely the mathematical functions and visualization backgrounds influencing the quality of predicting the ablation focus under conditions of unexpected soft tissue deformation, inhomogeneous heat conduction and undesired needle paths. The authors emphasize the demand for extensive training of the staff prior to the introduction of such techniques in a clinical environment. So far, no robotic application is set in clinical standard treatment protocols.

MINIMAL INVASIVE TREATMENT STRATEGIES

The goal of a local ablative treatment is complete tumor destruction with minimal side effects. In order to minimize adverse effects, miniaturization of the access to local ablation is intended. Occasionally, the

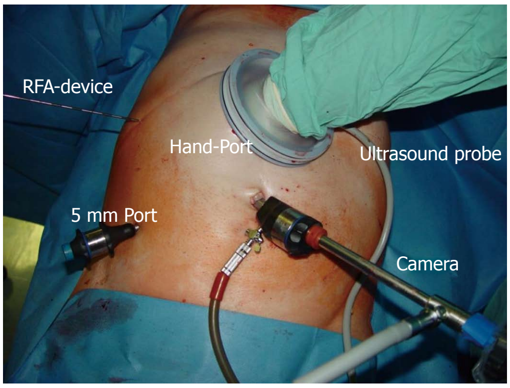

Figure 5 Clinical application of hand-assisted laparoscopic surgery. Intraoperative radiofrequency ablation using hand-assistance. The advantages of a minimal-invasive approach are preserved.

least invasive, percutaneous way is unsound or even dangerous[35]. In such cases, laparoscopic procedures are suggested[36]. Advantages of laparoscopy for thermoablation are related to the direct visualization of the abdominal cavity, which offers diagnostic features like better tumor staging using laparoscopic ultrasound (LUS) as well as the opportunity of detecting extra-hepatic intraabdominal tumor spread, and therapeutic implications in preventing thermal injury of abutting organs and structures, which are separated from the surface of the liver by the pneumoperitoneum itself or by distinct devices[36]. In addition, the combination of a thermoablation with laparoscopy results in specific additive effects. LUS works usually with higher frequencies and thus displays a higher resolution enabling a more accurate and precise needle placement besides the above mentioned diagnostic property. The pneumoperitoneum in turn decreases tissue perfusion and reduces convective heat sink phenomena, leading to larger ablation areas[37] and therefore preferably less local treatment failures. Clinical evidence for favourable outcome after laparoscopic RFA/MCT is scarce; a retrospective study recently presented a multivariate analysis of risk factors for local recurrence after US guided laparoscopic or percutaneous MCT[36]. Laparoscopic MCT was a statistically significant independent prognostic factor for better local tumor control. Since no randomized controlled trial is available, the conclusion of clinical superiority of laparoscopic compared to percutaneous MCT is drawn from this and other retrospective studies.

However, a large amount of indications to local ablation account for patients with recurrent disease following previous surgery. Adhesions frequently occurring after open surgery to a certain extent make laparoscopy difficult to accomplish if not impossible at all. Reluctance to offer open surgical access to local ablation in the liver is comprehensible. Hence, alternative approaches have been suggested including hand-assisted liver surgery (HALS, Figure 5)[38] and transthoracic local ablation[39]. Not a lot of experience is reported with both techniques worldwide. Besides technical remarks, no trial has ever been conducted showing superiority to more traditional procedures. Theoretic advantages encompass less risk of ascites and collateral injury to intraabdominal organs when comparing transthoracic ablation to open abdominal surgery, while local tumor control is reportedly superior to results obtained in percutaneous interventions, but no scientific evidence supports these postulations so far. With HALS, the advantages derived from the formation of pneumoperitoneum are preserved, albeit the open surgical part of the procedure imposes a similar risk to intraabdominal injury and consecutive morbidity upon the patient. In summary, except for proof of concepts, confirmation of improvements in local ablation using transthoracic approaches and/or HALS lacks.

Where are we now, and which prospects for the future may be drawn from the previous paragraphs? A wide variety of technical innovations enables us to use microwave as well as radiofrequency ablation, various image fusion technologies, MR guidance for local ablation, navigation, even robotics, and minimal invasive access to liver surgery in general in the 21st century. However, in comparison to data found in the current literature for conventional local ablative treatment strategies, virtually no single technology is able to demonstrate an unequivocal superiority. Hints at better performance of MCT compared to RFA regarding local tumor control, duration of the procedure and potentially achievable larger size of ablation areas favour the comparably more recent treatment modality; image fusion enables more patients to undergo ultrasound guided local ablation; MR guidance may improve primary success rates in selected patients; navigation and robotics accelerate the needle placement and reduces deviation of needle positions; laparoscopic thermoablation results in larger ablation areas and therefore hypothetically better local tumor control under acceptable complication rates, but seems to be limited to patients with no, mild or moderate adhesions following earlier surgical procedures. Apart from that, most techniques appear technically feasible, albeit demanding. It is a challenge to learn all novel treatment modalities and exhibit a satisfying command on it. So far, it remains an open question, which will eventually survive. In view of all mechanical and electronical support, there are some activities in our world, which are still best performed by humans, despite all highly sophisticated machines surrounding us.

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