Microwave Ablation Treatment of Solid Tumors

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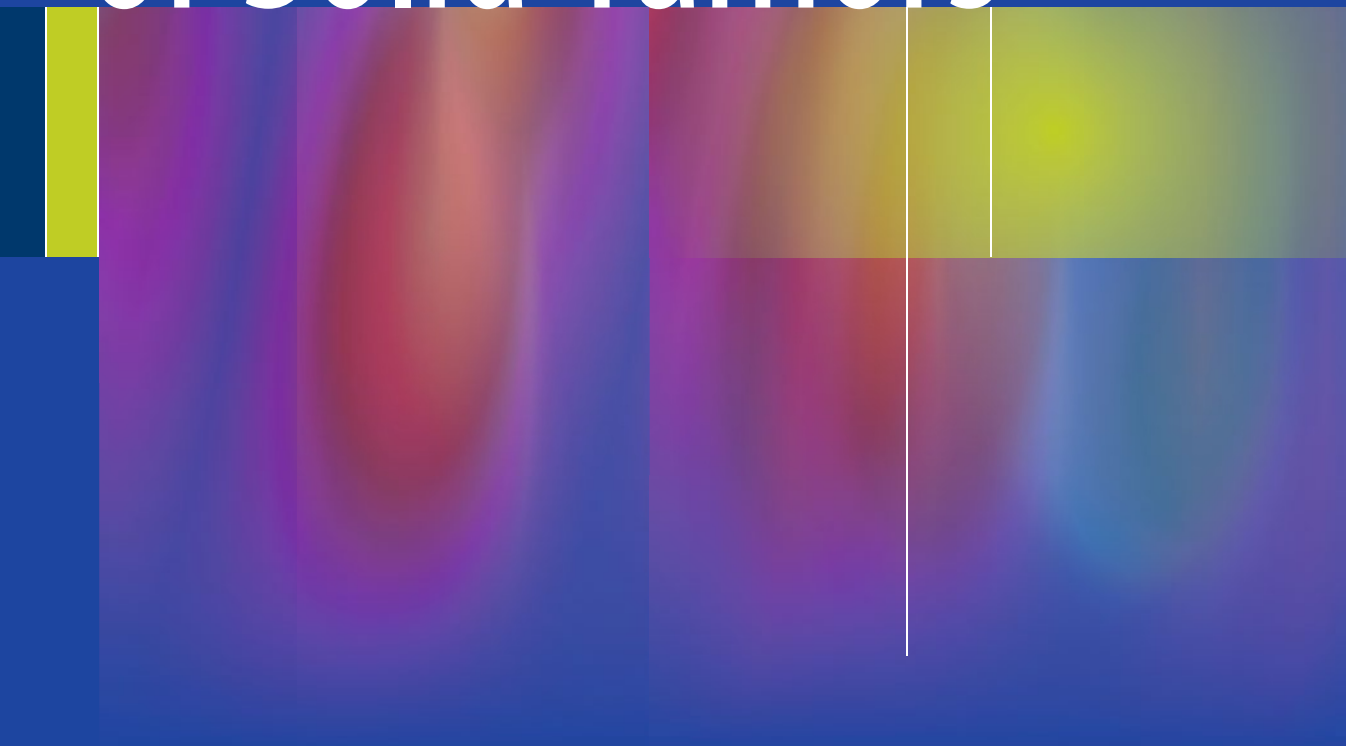

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Preface

Tumor ablation refers to the direct application of chemical or thermal therapies to a tumor to achieve eradication or substantial tumor destruction. The principle of tumor ablation has been known for more than 100 years. Microwave ablation (MWA) is the term used for all electromagnetic methods of inducing tumor destruction by using devices with frequencies greater than or equal to 900 kHz. Microwave coagulation was initially developed in the early 1980s to achieve hemostasis along the plane of transection during hepatic resection; however, microwave coagulation of tissue surfaces was slower than electrocautery units and produced deeper areas of tissue necrosis. Although microwave coagulation has not been useful during hepatic resection, the extended area of tissue necrosis led to investigation of the use of MWA to treat unresectable hepatic malignancies since the 1990s.

Among the various therapeutic options available for the treatment of solid tumors, surgery is the leading form of treatment because it offers the chance of long-term cure. However, a majority of patients suffering from solid tumors are not candidates for surgery because of unresectable tumors, recurrent tumors, tumors at difficult anatomical locations, or patients too severely debilitated to tolerate resection. Therefore, minimally invasive techniques have become available for local destruction of solid tumors in multiple organs. The past decade has witnessed a widespread expansion into the clinical setting of image-guided minimally invasive ablation techniques using various thermal energy sources such as radiofrequency, microwave, high-intensity focused ultrasound, and laser to destroy focal tumors in multiple organ sites. Owing to advancements in both imaging modalities used for visualization and percutaneous devices used for delivery of energy into tumor tissue, these techniques have established themselves as viable treatment options for the eradication of solid tumors.

Just as radiofrequency ablation, MWA is based on biological response to tissue hyperthermia for solid tumor treatment with a relatively low-risk procedure. However, because the two thermal ablation techniques share the different heating principles, MWA has several theoretical advantages compared with radiofrequency ablation for the treatment of solid tumors.

Though as a relatively new technique compared with radiofrequency ablation, MWA has become popularized in many institutions in Far East countries and is obtaining great interest from parts of western countries. In recent years, with the advance of technique and equipment, MWA has been successfully

applied in focal solid tumors in locations such as the liver, kidney, adrenal, and lung and with ever-expanding utility to additional locations including the spleen, uterus, head, and neck and subcutaneous superficial tissue with favorable therapeutic efficacy.

The book itself is divided into five parts. Part I deals with the MWA in the aspects of its history, mechanism, principles, equipment development and application procedure. In Part II the clinical aspects of MWA in treatment of benign and malignant liver tumors are widely described. Meanwhile the section describes the complications after MWA of liver. Part III discusses the clinical effect of MWA of liver tumor at different locations including adjacent to large vessels, gallbladder, hilum, gastrointestinal tract and diaphragm. Assisted techniques (including ethanol alation, artificial effusion and radioactive particles implantation) with MWA are also introduced. Part IV describes the technique combination of MWA with systemic treatment including cellular immunotherapy and traditional Chinese medicine therapy in liver cancer. Comparison effect of MWA, RFA and surgery in hepatocellular carcinoma is also provided. Part V discusses the clinical application of MWA in treatment of benign and malignant renal tumors, and covers the expanded application of MWA in other solid tumors including adrenal, thyroid, spleen, uterus, subcutaneous superficial tissue, lung, bone and breast. The final part involves the application value of contrast enhanced ultrasound, virtual navigation and three-dimensional visualization techniques in the whole procedure of ultrasound guided percutaneous MWA including pre-ablation location, intra-ablation guidance and post-ablation assessment.

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Contents

Part I

Microwave Ablation Principles and Techniques

Microwave Ablation: Principles and Techniques

1

Baowei Dong, Jie Yu, and Ping Liang

Abstract

Tumor ablation is defined as the direct application of chemical or thermal therapies to a tumor to achieve eradication or substantial tumor destruction. Currently, minimally invasive ablation techniques have become available for local destruction of focal tumors in multiple organ sites. Microwave ablation is based on biological response to tissue hyperthermia for solid tumor treatment with relatively low-risk procedure. Because of several advantages including higher thermal efficiency, higher capability of coagulating blood vessels, faster ablation time, and simultaneous application of multiple antennas, microwave ablation could be a promising minimally invasive ablation technique for the treatment of solid tumors. The aim of this chapter is to review the basic principles and the state of the art of different device technologies, approaches, treatment strategies, current therapeutic status, and future trends of microwave ablation for solid tumors.

Keywords

Microwave ablation • Minimally invasive therapy • Solid tumor

Abbreviations and Acronyms

CT	Computed tomography
MRI	Magnetic resonance imaging
MWA	Microwave ablation
RFA	Radiofrequency ablation
TACE	Transcatheter arterial chemoembolization
US	Ultrasound

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Tumor ablation is defined as the direct application of chemical or thermal therapies to a tumor to achieve eradication or substantial tumor destruction. The principle of tumor ablation has been known for more than 100 years [1]. The past decade has witnessed a widespread expansion into the clinical setting of image-guided minimally invasive ablation techniques using various thermal energy sources, such as radiofrequency, microwave, high-intensity focused ultrasound, and laser to destroy focal tumors in multiple organ sites. Owing to advancements in both imaging modalities used for visualization

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and percutaneous devices used for delivery of energy into tumor tissue, these techniques have established themselves as viable treatment options for eradication of solid tumors in locations such as the liver [2–4], kidney [5–7], adrenals [8–10], and lung [11–13], with ever expanding utility to additional locations including the bone [14, 15], head and neck [16, 17], spleen, and others [18–21].

Microwave coagulation was initially developed in the early 1980s to achieve hemostasis along the plane of transection during hepatic resection [22]. Microwave coagulation of tissue surfaces was slower than electrocautery units and produced deeper areas of tissue necrosis. Although microwave coagulation has not been useful during hepatic resection, the extended area of tissue necrosis led to investigation of the use of microwave ablation (MWA) to treat unresectable hepatic malignancies. Radiofrequency electrical current remains the most widely used heat generation source for thermal ablation. Compared with radiofrequency ablation (RFA), MWA is a relatively new thermal ablation technique for different types of tumors, providing all the benefits of radiofrequency and substantial advantages. In recent years with the advance of technique and equipment, MWA has become popularized in many institutions in the Far East countries and part of Western countries because of its favorable therapeutic efficacy. Preliminary works show that MWA may be a viable alternative to other ablation techniques in selected patients.

1.1 Mechanism and Principles

Microwave radiation as high-frequency electromagnetic wave exerts its function by inducing frictional heating from its interaction with polar molecules [23, 24]. Water molecules are polar molecules with the hydrogen side of the molecule carrying a positive charge and the oxygen side of the molecule carrying a negative charge. When microwave radiation hits the water molecules, they oscillate between two and five billion times to align themselves with the fluctuating microwave. This rapid molecular rotation generates and uniformly distributes heat leading to cell death through coagulation necrosis, which is instantaneous and continuous until the radiation is stopped. Another mechanism of heat generation is ionic polarization which occurs when ions move in response to the applied microwave electric field. The ionic polarization causes collision with other ions, converting kinetic energy into heat. However, it is a rather less important mechanism than dipole rotation in living tissue. Heating of tissue at 50–55 °C for 4–6 min produces irreversible cellular damage. At temperatures between 60 and 100 °C nearly immediate coagulation of tissue is induced, with irreversible damage to mitochondrial and cytosolic enzymes of the cells. At more than 100–110 °C, tissue vaporizes and carbonizes [25]. During these procedures, very intense thermal doses are usually applied upon the tissue, with the observed temperature profiles being markedly higher than those seen in traditional hyperthermia applications, often reaching (and in some cases exceeding) the boiling point of the tissue. This enables the energy to be applied for much shorter periods of time than for hyperthermia (usually less than 15–30 min). Furthermore, while in hyperthermia applications, once a thermal steady state is achieved (typically within 10–15 min), temperatures do not change appreciably throughout the volume of the tissue for the rest of the several hours of treatment [26]. The high temperature produced by microwave irradiation creates an ablation area around the needle in a column or round shape, depending on the type of needle used and the generating power [27].

Theoretically, MWA shows the several technique advantages over RFA: (1) The tissue heating of RFA is passive and limited to a few millimeters surrounding the active electrode, with the circumjacent ablation zone relying on the conduction of electricity into the tissue [28]. Microwave delivers electromagnetic energy with the much broader field of power density (up to 2 cm surrounding the antenna) to rapidly rotate adjacent polar water molecules to produce primarily active heating, which can achieve a much broader heating zone [29]. (2) RFA is a self-limiting process since ablative temperatures lead

to water vaporization and dehydration, which in turn increase impedance to electrical current flow [28]. Microwave energy, on the other hand, propagates through all types of nonmetallic material, including the dehydrated, charred, and desiccated tissues associated with thermal ablation zones. As a result, continuous powers can be applied during MWA. Therefore, temperatures greater than 100 °C are readily achieved for MWA [27]. (3) While RF currents flow only in high-conductivity paths and heating is limited to areas of high current density located very close to the electrode. Such limited heating also makes RFA susceptible to the "heat-sink" effect of nearby blood vessels. Large vascular heat sinks cause suboptimal perivascular heating and increased risk for tumor recurrence in patients undergoing RFA. Microwaves are capable of propagating through tissues with low conductivity, such as charred tissues. Owing to the active heating ability, MWA can produce higher intratumoral temperatures and larger ablation volumes with shorter ablation time [27, 30–32]. Because the cooling effect of blood flow (the heat-sink effect) is most significant within the zone of conductive rather than active heating, MWA is less affected by the heat-sink effect. These advantages have the potential to allow for a more uniform tumor kill in the ablation zone, both within the targeted zone and perivascular tissue [32, 33]. (4) The ablation of large tumors can be time consuming to ensure total overlapping coverage of ablation zones; thus, the use of multiple electrodes to achieve large coagulation volumes has been proposed. Microwave should be more amenable than radiowave to synchronous ablations using multiple probes to obtain larger coagulation volumes in shorter time [27–29]. (5) MWA does not need the placement of grounding pads and the electrical energy takes effect in the target tissue only, which avoids applied energy losing and skin burns. Moreover, MWA is not contraindicated by the metallic materials like surgical clips or pacemaker.

In comparison among energy sources including microwave, radiofrequency, and laser, for a given ablation diameter, there are significant differences in required thermal dose [34]. Laser requires about 10^1–10^2 times more energy than microwave; microwave has at least an order of magnitude greater requirement than radiofrequency. The range of end temperatures recorded at the margin of coagulation is lowest for radiofrequency (33–58 °C), higher for laser (52–72 °C), and the widest range of coverage for microwave (42–95 °C). And unlike radiofrequency and cryoablation, microwave induces microscopically well-demarcated lesions, with no intralesional hepatocyte survival. Intralesional cell survival in radiofrequency and cryoablation may be due to the relatively prolonged treatment times needed, allowing thermal energy to dissipate via blood flow [35].

However, as one of the most recent advances in the field of thermoablative technology, MWA has a few limitations: (1) Although blood flow of surrounding large vessels has less influence in withdrawing thermal power to result in heat decline, the higher thermal efficiency of MWA may become a double-edged sword that easily injures the adjacent critical tissues because of the tissue surrounding the antenna being rapidly ablated. (2) Simultaneously multiple probe deployment of microwave antennas can significantly increase the diameter of ablation zone, whereas the recess of the coagulation zone for the over great inter-antenna distance may not entirely cover the large tumor and result in incomplete ablation [36].

1.2 Equipment Development

The goal of MWA is to destroy the entire tumor as well as a 5–10 mm sufficient margin of surrounding healthy tissue along the entire boundary of the tumor. All MWA systems contain three basic elements—microwave generator, low-loss flexible coaxial cable, and microwave antenna [37]. Microwave is generated by magnetron. The magnetron has a space called resonant cavities which act as tuned circuits and generate electric fields. The output frequency of microwave is also determined by the resonant cavities. Antenna is connected via a low-loss coaxial cable to the microwave equipment and delivers microwave

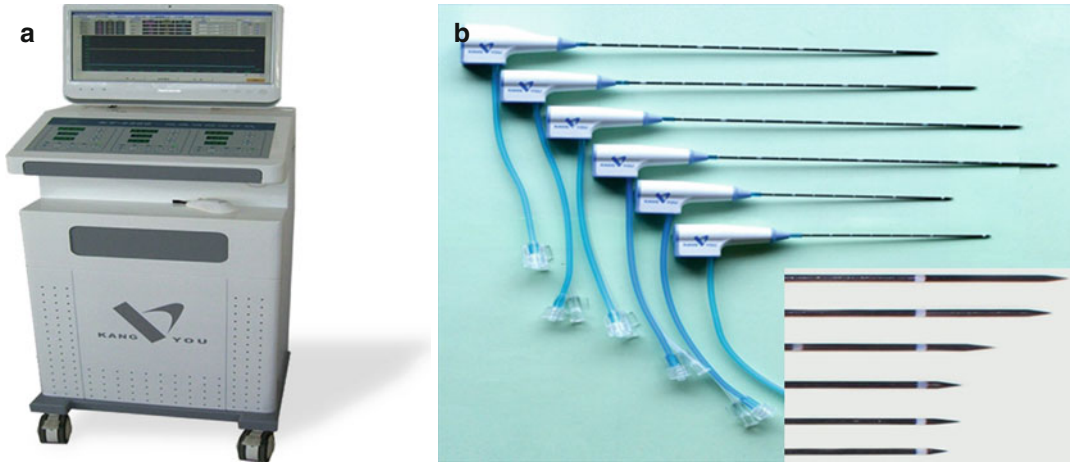

Fig. 1.1 Photographs of microwave equipment. (**a**) Intelligent microwave generator. (**b**) Prototype internally cooled microwave antenna with different shaft length (10–18 cm) and active tip (3–22 mm). The diameters of the applicators vary from 1.6 to 1.8 mm

energy from the magnetron into the tissue. Design of the antenna is most important to the therapeutic efficacy. Microwave antenna can be classified into three types (dipole, slot, or monopole) based on their physical features and radiative properties [38]. Shape of antenna includes straight, loop shaped, and triaxial. The coaxial choke is a conductor surrounding the outer conductor of the coaxial antenna feed line separated by a dielectric and electrically shorted at the proximal end. Its length is commonly a quarter wavelength, which constrains wave propagation along the outside of the outer conductor and leads to more spherical ablation zones [39, 40]. Electromagnetic microwave is emitted from the exposed, noninsulated portion of the antenna. Currently there are nine commercially available microwave ablation devices. The design has focused largely on needlelike, thin, internally cooled, coaxial-based interstitial antenna [38–41], for the purpose of achieving larger ablation zone and being appropriate for percutaneous use. The diameter of antenna is from 1.5 to 2.8 mm (12–17 gauge), while the antenna with the diameter of 14–16 gauge is clinically commonly used. The results of microwave ablation of tumors in multiple organs in this book are from the use of Kangyou equipment (Kangyou Institute, Nanjing, China), with the frequency of 915 and 2,450 MHz and multiple sizes of antennas (Fig. 1.1a, b).

Over the years, there have been continued efforts focusing on increasing the coagulation diameters by refinement of the antenna and generator. The first-generation system including Microtaze (Heiwa Denshi Kogyo, Osaka, Japan), UMC-I, and FORSEA system (both produced in China) with the needle antenna of 1.4–2.0 mm in diameter can create a coagulation zone of (3.7–5.8) × (2.6–2.8) cm in diameter when operated at 2,450 MHz. However, it is plagued by higher-power feedback; temperature of the antenna shaft rises quickly which can cause elongation of coagulation zone along the shaft due to thermal conduction and result in skin burn. Consequently, protective cooling of the skin is routinely used during ablation and the application of microwave emission is largely limited. Charring along the needle shaft may decrease energy deposited in the direction perpendicular to the shaft and reduce the short-axis diameter of coagulation. In order to keep off overheating of the shaft, to avoid skin injury, and to permit further deposition of energy into tissue with low impedance during ablation, cooled-shaft antennas have been developed in recent years. Inside the shaft lumen, there are dual

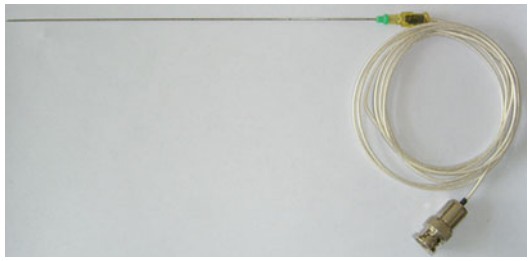

Fig. 1.2 Thermal monitoring needle with the size of 0.8 mm (21 G), which can be connected to the microwave equipment

channels through which chilled distilled water is circulated by a peristaltic pump continuously cooling the shaft. As shaft temperature can be effectively kept low, higher-power output and longer treatment duration are allowed which can deliver more energy into the tissue without causing skin burn. The cooled-shaft antenna has facilitated remarkable progress in obtaining larger ablation zone [27, 42].

With further improvement, currently, two kinds of frequencies—915 and 2,450 MHz—are used for MWA. The equipment with 915 MHz frequency is a newly developed instrument which can penetrate more deeply than that with 2,450 MHz and may yield larger ablation zone with the size of (5.2–5.8)×(3.0–3.8) cm [43]. Though MWA is mainly clinically used in eastern Asian countries, Western countries have attached great importance to it and begin to develop their own MWA systems [44]. And some other types of antennas such as loop-shaped antennas and triaxial antenna are also proposed but have not acquired wide use clinically [45, 46].

Some radiofrequency equipments contain a thermocouple in the nickel-titanium lateral tine of expandable electrode tip to allow temperature recording and monitoring during the ablation procedure, with the aim of ensuring that the maximum energy be applied by using the standard algorithm with the system [47]. Some MW machines are also equipped with a thermal monitoring system which can continuously measure temperature in real time during ablation. Thermal monitoring needle (Fig. 1.2) can be classified into thermocouple and thermistor type with the diameter of 0.7–0.9 mm (20–22 gauge), which is introduced into the liver parenchyma through a nonconducting needle trocar. Thermal monitoring needle is inserted into the target area to monitor temperature in real time during ablation under ultrasound (US) guidance. The aims of temperature monitoring include (1) therapeutic, the temperature monitoring needle is inserted about 5–10 mm away from the tumor margin. The complete tumor necrosis is considered achieved when the temperature remains at 54 °C for at least 3 min or reaches 60 °C; (2) protective, for high-risk localized tumors (less than 5 mm from the bile duct, gastrointestinal tract, gallbladder, pelvis, and so on), the real-time temperature of tumor margin is recorded to ensure that temperature does not reach damaging levels. The temperature cutoff of ablation is set at 54 °C in the patients without a history of prior laparotomy or 50 °C in the patients with laparotomy history. (We controlled the monitoring of temperature in patients with laparotomy history lower than those in patients without laparotomy history. That is because bowel peristalsis in patients without laparotomy history would help to avoid persistent heating of the same area. Adhesion may occur and decrease bowel peristalsis, thus increasing the risk of thermal injury of the bowel loop in patients with laparotomy history.) Then the emission of microwave is restarted after the temperature decreases to 45 °C and just so in cycles until the entire tumor is completely encompassed by hot bulb [37].

1.3 Procedure

1.3.1 Indications (Taking Liver Cancer as Example)

Given the complexity of the hepatic malignancy, multidisciplinary assessment of tumor stage, liver function, and physical status is required for proper therapeutic planning. In general, the indications for MWA are broad. One important application is to treat patients who are not considered surgical candidates. Included in this category are patients with inadequate liver remnant to tolerate resection, tumor multinodularity, and unresectable

lesions at difficult anatomical locations or patients who decline resection. Previous MWA was limited to treat small liver tumors, with the improvement of antenna and treatment strategy; lesions greater than 5 cm (5.0–8.0 cm) can also be effectively ablated [10, 39, 42].

For patients with early-stage primary liver cancer and limited metastases, MWA should be considered as curative therapy. The inclusion criteria are (1) a single nodule with a diameter smaller than 5 cm or a maximum of three nodules with a diameter smaller than 3 cm; (2) absence of portal vein cancerous thrombus; and (3) no extrahepatic spread to the surrounding lymph nodes, lungs, abdominal organs, or bone.

Palliative treatment criteria for MWA include patients (1) with lesion larger than 5 cm in diameter or multiple lesions, (2) suffering from a small extrahepatic tumor burden, and (3) unsuitable for other modalities and capable of tolerating the MWA procedure.

1.3.2 Contraindications (Taking Liver Cancer as Example)

Contraindications include patients who have (1) clinical evident liver function failure, such as massive ascites or hepatic encephalopathy or with a trancelike state; (2) severe blood coagulation dysfunction (prothrombin time >30 s, prothrombin activity <40 %, and platelet count <30 cells $\times 10^9$/L); (3) high intrahepatic tumor burden (tumor volume >70 % of the target liver volume or multiple tumor nodules) or high extrahepatic tumor burden; (4) acute or active inflammatory lesions at any organ; (5) acute or severe chronic multiple organ dysfunction, including renal failure, pulmonary insufficiency, or heart dysfunction; and (6) relative contraindication that concerns medical risk for the tumor proximity to the diaphragm, gastrointestinal tract, gallbladder, pancreas, hepatic hilum, and major bile duct or vessels, which may require adjunctive techniques to prevent off-target heating of adjacent structures during the ablation procedure.

1.3.3 Patient Preparation and Data Required

Patients should be accurately evaluated through clinical history, physical examination, laboratory test, and performance status before MWA. Pretherapy test of serum liver and renal function, respiratory and circulation function, cholinesterase, blood cell count, tumor markers, and coagulation should be known before the procedure. The impaired function needs to be corrected to withstand the ablation procedures. A full imaging work-up (a combination of contrast-enhanced imaging including US, computed tomography (CT), or magnetic resonance imaging (MRI)) should be performed to accurately stage and locate the lesions and exclude venous thrombosis and metastases before ablation.

Patients should receive both written and verbal information about the ablation procedure prior to therapy. Informed written consent must be obtained from each patient. Patients should be informed that MWA is not likely to cure their disease and is a palliative treatment directed to their liver lesions. Patients must be informed of the potential side effects of MWA as well.

1.3.4 Techniques

Similar to RFA, MWA can be performed percutaneously, laparoscopically, and thoracoscopically or at laparotomy as well. Whenever possible, MWA should be performed percutaneously for its least invasion, relatively low cost, and repeatability. General anesthesia with mechanical ventilation is required for laparoscopic or laparotomy approach. However, intravenous anesthesia combined with local anesthesia is usually sufficient for percutaneous approach. Detailed techniques have been described in the guideline of MWA in liver malignancy [37] and as follows: Patients are laid in the interventional US suite. US is performed to choose the safest needle access. Local anesthesia or plus intravenous conscious analgesia-sedation is usually sufficient for percutaneous MWA approach. After local anesthesia,

the skin is pricked with a small lancet, and the antenna is placed into the chosen area of the tumor. In multiple needle procedure, two or three prefixed puncture lines are done. Two or three active needle antennas directly connected to the microwave generator are inserted into the tumor in parallel 1.0–2.5 cm apart. Thermal dosimetry of a single MWA applicator is dependent not only on tissue type but also on the amount of energy delivered to the tissue and the distance of the critical ablation margin from the applicator. For the patients' breathing, cooperation to complete the insertion is needed; intravenous conscious analgesia-sedation is induced associated with standard hemodynamic monitoring after placing all the antennas. At each insertion, the tip of the needle is placed in the deepest part of the tumor. Multiple thermal lesions are produced along the needle antenna's major axis by simply withdrawing the needle from the preceding thermal lesion and reactivating the microwave generator. If necessary, based on tumor size, multiple overlapping ablations are usually needed to envelope the entire tumor with a safety margin. Generally, the microwave energy is set at 50–80 W for 5–10 min in a session.

Size of the ablation zone can be roughly judged by an expanding hyperechoic area during the procedure. To have accurate assessment of the treatment efficacy, the thermal monitoring system attached to the microwave system can be used during MWA. One to three thermal monitor needles are placed at different sites 5–10 mm outside the tumor. The thermal monitor needle can be introduced into the parenchyma through 18 gauge, 70 mm length, nonconducting needle trocars (Hakko Co., Ltd, Japan). If the measured temperature does not reach 60 °C by the end of treatment or not remain at 54 °C for at least 3 min, the ablation is prolonged until the desired temperature is reached. When withdrawing the antenna, the needle track needs to be coagulated with the circulated distilled water in the shaft channel stopped to prevent bleeding and tumor cell seeding.

This ablation therapy includes a 5–10 mm ablative margin of apparently healthy tissue adjacent to the lesion to avoid local tumor progression for microscopic foci of disease and the uncertainty that often exists regarding the precise location of actual tumor margins. For patients with severe liver cirrhosis or the lesion adjacent to critical organ, an ablation margin of 5 mm or conformal ablation fitting tumor shape and contour is recommended to ensure a safe and radical treatment, and otherwise, a 10 mm enough margin is preferred. Reducing the tumor bulk is the strategy for patients who underwent palliative ablation treatment.

1.3.5 Care After MWA

After the MWA procedure, the punctured site is covered with a sterile dressing under pressure. The patient then needs to undergo a recovery for 4–6 h of bed rest. If necessary, the patients are observed for two to three additional days and discharged from the hospital when they feel no severe pain or when their body temperature does not exceed 38 °C.

1.3.6 Therapeutic Efficacy Assessment and Follow-Up

In recent years, contrast-enhanced US has been employed for immediate assessment of technical success which can be performed 10–15 min after MWA [48]. If the foci of nodular enhancement in or around the treated tumor are observed, a next MWA session with an identical device is performed as part of another course of treatment. Contrast-enhanced imaging needs to be performed at 1 month after the last course of a defined ablation protocol. If irregular peripheral enhancement occurred, which represents residual unablated tumor, this sign indicates incomplete ablation, and further treatment should be considered as soon as possible if the patient still meets the criteria for MWA. On the contrary, if complete ablation is achieved, then routine contrast-enhanced US, CT, or MRI and serum tumor marker are repeated at 3 months after MWA and then at 6-month intervals.

1.4 Clinical Applications

Though RFA remains the most widely used thermoablative technique worldwide, MWA as another effective local thermal ablation technique has undergone tremendous progress due to technical advances. Initially MWA was limited to treat small liver cancer, with the improvement of antenna and treatment strategy; large liver cancer greater than 5 cm can also be effectively ablated [49, 50]. In addition, MWA has expanded its clinical application field to multiple solid tumors including the kidney, adrenal, spleen, thyroid, lung, abdominal wall, and uterus [5, 8, 13, 17, 19, 21, 51].

The therapeutic efficacy of MWA can be augmented by other therapies. Similar to other thermal ablation techniques, the coagulation diameters for MWA are also influenced by perfusion-mediated cooling. Interruption of hepatic blood flow can significantly increase the coagulation diameters [52, 53]. Transcatheter arterial chemoembolization (TACE) is an effective method for reducing the blood flow of tumors and controlling the large tumors because of blocking artery effect. MWA combined with TACE may yield increased ablation volume and can destroy the peripheral part of the tumor remaining viable after TACE, whereas TACE may possibly control microscopic intrahepatic metastasis that cannot be treated by MWA [54]. Combination therapy with MWA and percutaneous ethanol injection can also increase the treatment efficacy, especially for tumors adjacent to vital organs [55]. For patients with high-risk localized tumors (tumor adjacent to important organs and tissues including the diaphragm, gastrointestinal tract, hilum, and major bile duct or vessels), combination of additional multiple techniques (artificial ascites, artificial pleural effusion, intraductal saline perfusion, and radioactive particle implantation) with MWA can also ensure favorable effect and low complications [56–58], which make MWA in the treatment of dangerous site tumors become feasible without sacrificing the therapeutic efficacy.

US as guidance tool has several limitations including the occasional poor lesion visualization as a result of a lack of innate tissue conspicuity or overlying bone- or gas-containing structures. MWA assisted by a real-time virtual navigation system is a feasible and efficient treatment of patients with lesions undetectable by conventional US [59].

In general, the indications for MWA are broad. One important application is to treat patients who are not considered surgical candidates. Included in this category are patients with unresectable tumor, patients with tumor at difficult anatomical locations, and patients who are too severely debilitated to tolerate resection. Similar to indications for RFA, MWA is also applicable to achieve curative therapy for small and early-stage liver or renal cancers with minimal invasion. MWA has achieved similar effect compared with surgery, RFA, and percutaneous ethanol injection treatment for hepatocellular carcinoma [60–62]. Long-term survival data and large-scale prospectively randomized controlled trials comparing it with other modalities, especially with RFA for ultimately determining its effectiveness, are earnestly anticipated.

Conclusions

MWA is a promising minimally invasive technique with many thermal characteristic advantages for the treatment of solid tumors. It can be performed safely using percutaneous, laparoscopic, or open surgical techniques. Advances in antenna design, treatment strategy, and combined therapies are anticipated to improve the therapeutic outcome of MWA in the future, making it a clinically important treatment option.

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Part II

Microwave Ablation of Liver Tumor

Microwave Ablation of Hepatocellular Carcinoma

2

Jie Yu and Ping Liang

Abstract

Hepatocellular carcinoma (HCC) is the sixth most common neoplasm and the third most frequent cause of cancer death. Percutaneous ablation has been recommended as the conventional treatment option for patients with early-stage HCC by multiple guidelines. Radiofrequency ablation has obtained wide use worldwide and been deemed as the first-line technique for small HCC. As one of the most recent and exciting advances in the field of thermoablative technology, microwave ablation (MWA) also achieves favorable local tumor control and survival effect with low complications in HCC therapy. The purpose of this chapter is to present the application status of MWA in HCC treatment and to present the results of several multicenter studies of microwave ablation for HCC treatment with relatively large-scale sample and long-term follow-up and newly developed internally cooled electrode.

Keywords

Microwave • Ablation • Hepatocellular carcinoma

Abbreviations and Acronyms

AFP	Alpha-fetoprotein
HCC	Hepatocellular carcinoma
LTP	Local tumor progression
MWA	Microwave ablation
RFA	Radiofrequency ablation

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Hepatocellular carcinoma (HCC) is the sixth most common neoplasm and the third most frequent cause of cancer death. More than 700,000 cases of this malignant disease were diagnosed in 2008, with an age-adjusted worldwide incidence of 16 cases per 100,000 inhabitants [1]. HCC is the leading cause of death among patients with cirrhosis [2]. For treatment to be most effective, patients should be selected carefully and the treatment applied skillfully. In view of the complexity of HCC and the many potentially useful treatments, patients diagnosed with this malignant disease should be referred to multidisciplinary

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teams that include hepatologists, radiologists, surgeons, pathologists, and oncologists. Percutaneous ablation has been recommended as the conventional treatment option for patients with early-stage HCC by multiple guidelines [3–5]. Microwave ablation (MWA) and radiofrequency ablation (RFA) are two main thermal ablation techniques used for HCC treatment currently. They induce tumor necrosis in situ by temperature modification. Although tumor ablation can be undertaken at laparoscopy or surgery, percutaneous method is the most minimally invasive and commonly used procedure. RFA has obtained wide use worldwide and been deemed as the first-line technique for small HCC [6]. MWA is one of the most recent and exciting advances in the field of thermoablative technology, because of its multiple theoretical advantages compared with RFA.

The purpose of this chapter is to present the application status of MWA in HCC treatment and to present the results of several multicenter studies of microwave ablation for HCC treatment with relatively large-scale sample and long-term follow-up and newly developed internally cooled electrode.

2.1 Application Status of MWA in HCC Treatment

MWA of HCC was first adopted in Japan by Seki et al. in 1994 [7], and follow-up computed tomography (CT) scans showed complete ablation in all the 18 patients. Then MWA has been widely applied for HCC therapy in China over the past two decades [8–10] and is increasingly utilized worldwide. Compared with the traditional Microtaze microwave system used by the Japanese, the newly internally cooled system can yield larger ablation diameters [11, 12]; thus, more patients can meet the inclusion criteria and more reliable assessment of the therapeutic efficacy of MWA becomes possible. The largest series of MWA for HCC in a single institution was reported by Liang et al. which comprised 288 patients with 477 tumors [9]. The 1-, 2-, 3-, 4-, and 5-year cumulative survival rates were 93, 82, 72, 63, and 51 %, respectively. Local tumor progression (LTP) was observed in 8 % of the patients. Jiao et al. evaluated effects of MWA with a 2,450-MHz internally cooled-shaft antenna in treating 60 HCC lesions with the size of 1–8 cm [13]. During a mean follow-up period of 17.17 ± 6.52 months, complete ablation rates in small (≤3.0 cm), intermediate (3.1–5.0 cm), and large (5.1–8.0 cm) liver cancers were 97.06, 93.34, and 81.82 %, respectively. LTP occurred in 6.67 % of treated cancers. Martin et al. [14] performed a long-term investigation for MWA of hepatic malignancies by using 915-MHz generation. One hundred patients underwent combination resection and MWA or ablation alone with median tumor size of 3.0 (range, 0.6–6.0) cm. After a median follow-up of 36 months, 5 % of patients had incomplete ablation, 2 % had LTP, and median overall survival was 41 months for HCC patients. Though promising single-center reports have demonstrated MWA's safety and efficacy [7–10, 12–16], it is necessary to evaluate this modality in the prospective, multicenter study (Table 2.1). A recent multicenter study from China documented that 1,007 patients with primary liver cancer treated by MWA achieved 1-, 3-, and 5-year survival rates of 91.2, 72.5, and 59.8 %, respectively [17]. According to the report of the 12th–15th nationwide follow-up survey of the Liver Cancer Study Group of Japan (including 791 institutions), the 1-, 2-, 3-, 4-, and 5-year survival rates of 1,751 patients treated by MWA were 94.2, 84.0, 72.9, 57.6, and 44.1 %, respectively [18]. Lloyd et al. organized a study with 18 international centers involved in 2011. The result showed that the major morbidity was 8.3 % and in-hospital mortality was 1.9 % in treating 299 tumors with the median size of 2.5 cm [19]. In addition, by combining with artificial ascites, artificial pleural effusion, intermittent emission of microwave antenna, and temperature monitoring assisted with small dose of ethanol infusion technique, it becomes feasible for MWA of dangerous site tumors without sacrificing the therapeutic efficacy [20–22]. In brief, MWA of HCC, especially small HCC, can achieve favorable local tumor control and survival effect with low complications. MWA is a promising minimally invasive treatment option with improved antenna design, refined treatment strategy, and reasonable

Table 2.1 Major researches of MWA in HCC treatment

Author	Patients	System	Tumor size (cm)	Follow-up (months)	CA (%)	LTP (%)	Five-year survival (%)	Major complication (%)
Seki et al. [7]	18	Microtaze	<2	11–33	100	0	N/A	0
Qian et al. [8]	22	FORSEA	2.1 ± 0.4	5.1	95.5	18.2	N/A	N/A
Liang et al. [9]	288	UMC-I	3.75 ± 1.58	31.41	NA	8	51	N/A
Lu et al. [10]	50	UMC-I	2.7 ± 1.5	18.1	94.4	≤2 cm:2 >2 cm, 8	3-year, 73 %	0
Kuang et al. [12]	74	FORSEA	0.8–8.0	17.4	93.2	5	N/A	12
Jiao et al. [13]	60	ECO-100A	1.0–8.0	17.17	92.71	5.21	N/A	0
Kawamoto et al. [15]	69	Microtaze OT-110M	≤4.0	54	93	28.6	63.9	NA
Itoh et al. [16]	60	Microtaze OT-110M	1.95	19	95	11.6	43.1	18.3
Liang et al. [17]	1,007	KY-2000	2.9 ± 1.8	17.3	97.1	5.9	59.8	2.2
Ikai et al. [18]	1,751	N/A	N/A	N/A	75.1	N/A	44.1	N/A

Note: *MWA* microwave ablation, *CA* complete ablation, *LTP* local tumor progression, *N/A* not available

combination therapies. However, long-term follow-up and reasonable designed controlled clinical trials will be required to determine the efficacy of MWA relative to other forms of ablative therapy, especially the widely used RFA.

2.2 MWA Technique in HCC

The general technique principles of MWA in HCC have been described in the previous chapter. According to the preliminary experimental study [11], in MWA of HCC, one antenna is inserted for tumors less than 2.0 cm and two for tumors measuring 2.0 cm or greater with an interantenna distance of no more than 2.5 cm. After one to three sessions of ablation, 1–3 days after the last course of a defined ablation protocol, contrast-enhanced imaging needs to be performed to evaluate the treatment efficacy. Technique effectiveness, namely, complete ablation, is defined as the absence of enhancement of any areas of the mass on a follow-up enhanced imaging performed 1 month after MWA, which represented the treatment that obtains initial success (Figs. 2.1 and 2.2). On the contrary, if residual unablated tumor exists, further ablation should be considered as soon as possible if the patient still met the criteria for MWA (Fig. 2.3).

2.3 Results of Multicenter Studies for MWA of HCC

MWA of HCC was first adopted in Japan over two decades ago using a 2.45-GHz system (Microtaze; Heiwa Electronic Industrial Co., Ltd, Osaka, Japan) [7]; then this frequency has been in use in Europe and Asia since the 1990s. Microwave technology was first used in the USA in 2003 and involved a 915-MHz system (Vivant Medical, Inc., Mountain View, CA, USA) [23]. Now both 915-MHz and 2.45-GHz systems are employed in the clinical treatment of HCC worldwide. Despite its apparent advantages, MWA is still a relatively new ablative modality and current clinical trials mainly consist of single institution case series, albeit with promising results. Moreover, new MWA technology is rapidly becoming available for clinical use, and each new combination of generator and ablation antenna cannot be presumed to provide equivalent results. Therefore, it is increasingly important that clinical validation models are in place as technological innovation in this field progresses. Therefore, the multicenter study with prospective database is expected to provide a platform from which to critically evaluate a new modality. Currently, there are four such multi-institutional studies that have been reported. Lloyd et al. reported the

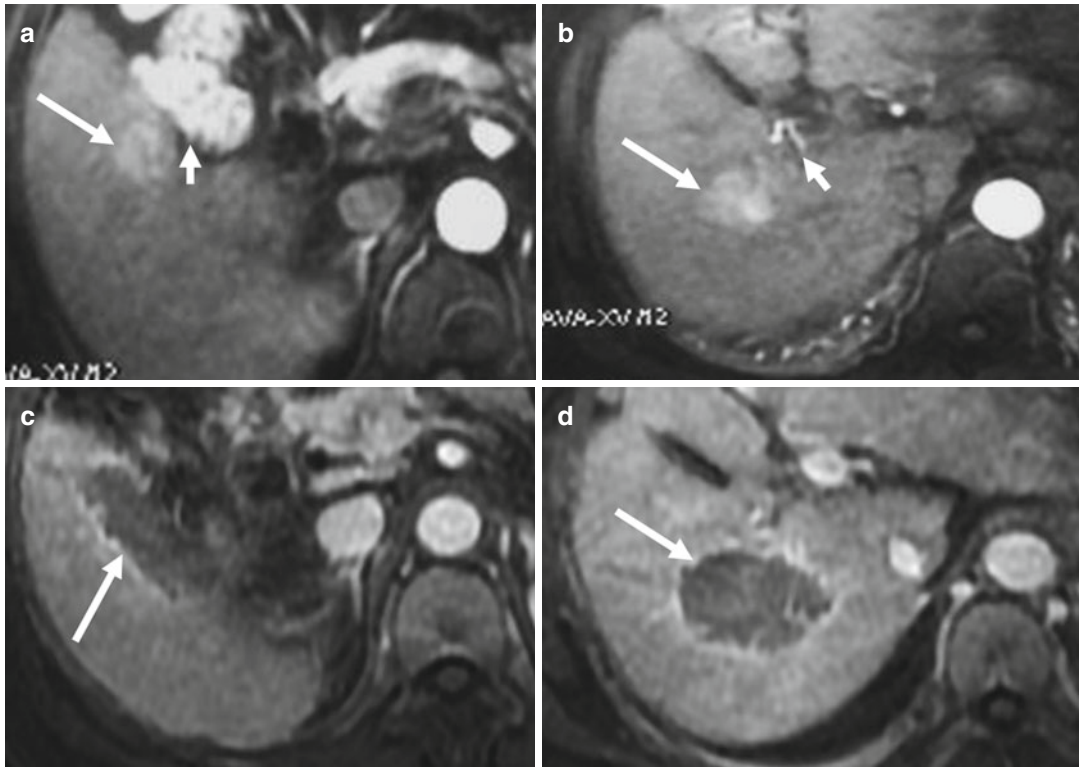


Fig. 2.1 Transverse images in a 64-year-old woman with two hepatocellular carcinoma (HCC) lesions treated by microwave ablation (MWA). (**a**) Contrast-enhanced magnetic resonance imaging (MRI) before ablation shows a 2.7×2.5 cm hyperintense nodule (*long arrow*) adjacent to intestinal tract (*short arrow*) at arterial phase. (**b**) Contrast-enhanced MRI before ablation shows a 3.3×2.9 cm hyperintense nodule (*long arrow*) adjacent to hilum (*short arrow*) at arterial phase. (**c**) Contrast-enhanced MRI scan obtained 1 month after ablation shows nonenhanced ablation zone (*arrow*) adjacent to intestinal tract. (**d**) Contrast-enhanced MRI scan obtained 1 month after ablation shows the nonenhanced ablation zone (*arrow*) adjacent to hilum

preliminary results of international multicenter prospective study on microwave ablation of liver tumors [19]. One hundred and forty patients with 299 tumors from 18 international centers underwent MWA using a 2.45-GHz generator with a 5-mm antenna. Among all the 140 patients, 114 (81.4 %) were treated with MWA alone and 26 (18.6 %) were treated with MWA combined with resection. The median size of ablated lesions was 2.5 cm (range, 0.5–9.5 cm). Tumors were treated with a median of one application (range, 1–6 applications) for a median of 4 min (range, 0.5–30.0 min). A power setting of 100 W was used in 78.9 % of cases. They only showed that the results of the major morbidity were 8.3 % and in-hospital mortality was 1.9 %. Groeschl et al. reported a multi-institutional analysis of MWA for hepatic malignancies [24]. Four hundred and fifty patients with a total of 875 tumors (139 HCCs, 198 colorectal liver metastases, 61 neuroendocrine liver metastases, and 75 others) from 4 high-volume institutions were treated by MWA with 473 procedures. During a median follow-up of 18 months, complete ablation was confirmed for 97.0 % of tumors. A surgical approach (open, laparoscopic, or percutaneous) had no significant impact on complication rates and survival. The local recurrence rate was 6.0 % overall and was highest for HCC (10.1 %, $P=0.045$) and percutaneously treated lesions (14.1 %, $P=0.014$). In this large data set, tumor size of 3 cm or more predicted poorer recurrence-free survival (hazard

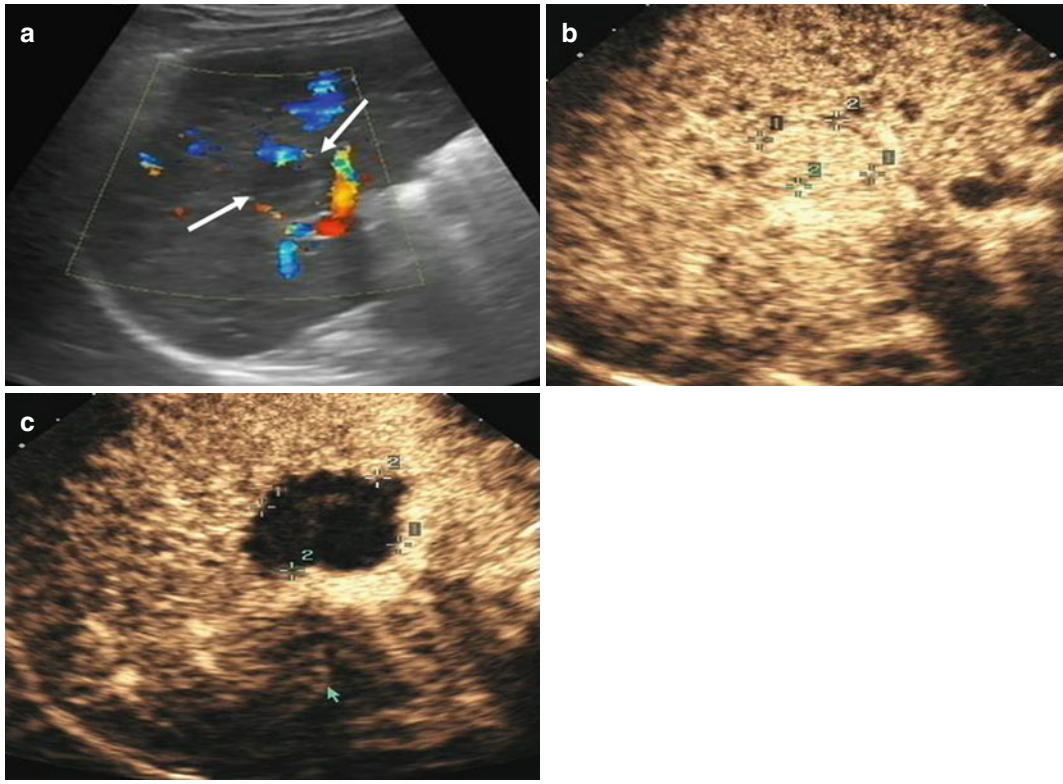


Fig. 2.2 Transverse images in a 41-year-old man with a single focus of HCC (2.5×2.0 cm) and accompanying cirrhosis. (**a**) Conventional ultrasound before ablation shows a hypoechoic nodule surrounded by several large vessels at liver hilum (*arrows*). (**b**) Contrast-enhanced ultrasound scan obtained before ablation shows a well-demarcated tumor (*marks*) with hyperenhancement at arterial phase. (**c**) Contrast-enhanced ultrasound scan obtained 24 months after ablation shows the nonenhanced ablation zone (*marks*)

ratio, 1.60, 95 %; CI, 1.02–2.50; $P=0.039$), regardless of histology. Livraghi et al. reported a multicenter study focusing on the complications of MWA for liver tumors [25]. Seven hundred and thirty-six patients with 1.037 lesions (522 HCCs and 187 metastases) of 14 Italian centers were ablated by using a 2.45-GMHz generator delivering energy through a cooled miniature-choke MW antenna. Tumor size ranged from 0.5 to 10 cm. In 13 centers, the approach used was percutaneous, in 4 video laparoscopy and in 3 laparotomy. Results of this multicenter study confirmed no deaths occurred. Major complications occurred in 22 cases (2.9 %) and minor complications in 54 patients (7.3 %), which did not differ from those after RFA. The three multicenter studies all demonstrate the low morbidity rate of MWA for liver tumors, but they cannot provide the long-term survival and recurrence efficacy of MWA.

To assess the long-term efficacy of MWA for treatment-naive primary liver cancer with internally cooled probe and to examine additional factors that affect survival after MWA of liver cancer, between January 2005 and July 2010, a large database was generated by the recruitment and management of 1,007 patients with 1,363 lesions in seven Chinese centers with different levels of experience. The median follow-up period for all the patients after MWA was 17.3 months (range, 3–68.9 months). There were 819 men and 188 women with a mean age of 56.3 ± 11.1 years (range, 21–90 years). The lesion mean diameter was 2.9 ± 1.8 cm (range, 0.4–18.5 cm). Cancer types treated among patients with pathological diagnosis included 778 HCCs

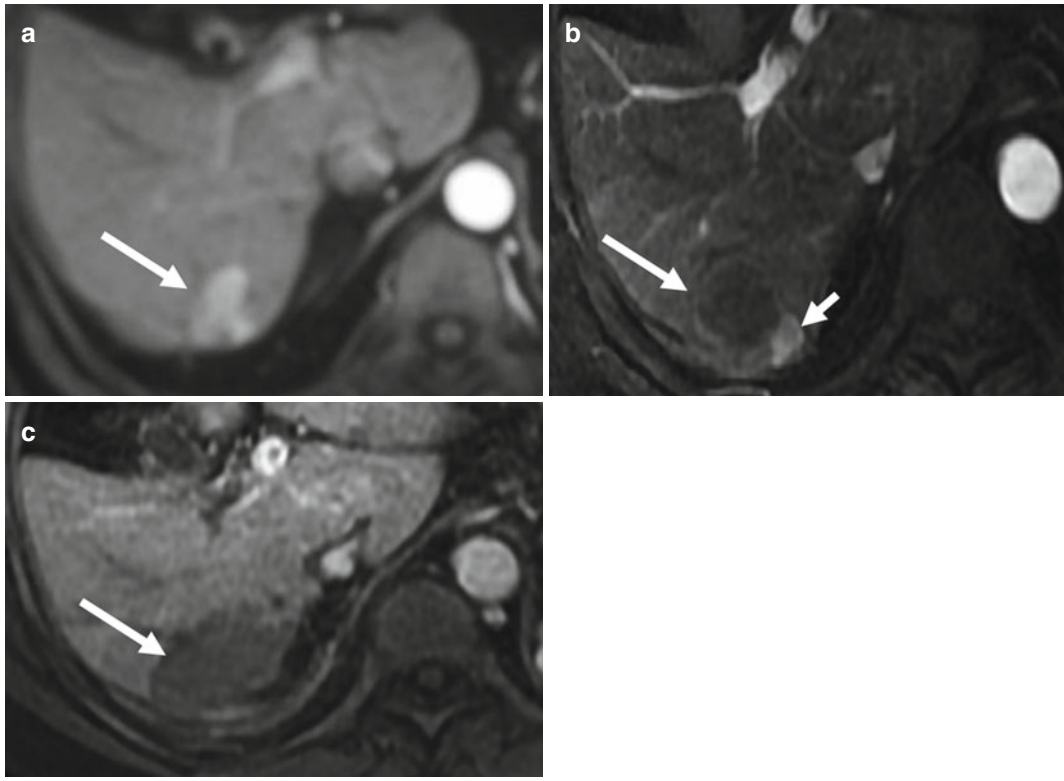


Fig. 2.3 Transverse images in a 54-year-old man with a single focus of HCC (3.7×3.6 cm) and accompanying cirrhosis. (**a**) Contrast-enhanced MRI before ablation shows a hyperintense nodule adjacent to the diaphragm at arterial phase (*arrow*). (**b**) Contrast-enhanced MRI scan obtained 1 month after ablation shows a 1.2×1.1 cm hyperintense nodule (*short arrow*) with hyperenhancement adjacent to ablation zone (*long arrow*) at arterial phase. (**c**) Contrast-enhanced MRI scan obtained 5 months after second ablation shows the nonenhanced ablation zone (*arrow*)

(96.4 %), 28 intrahepatic cholangiocarcinomas (3.5 %), and 1 cholangiohepatocellular carcinoma (0.1 %). Among the 1,363 lesions, 198 (14.5 %) are adjacent to gastrointestinal tract, 77 (5.6 %) to hepatic hilum, 364 (26.7 %) to the diaphragm or liver capsule, 167 (12.3 %) to large (≥3 mm) vessel, and 71 (5.2 %) to the gallbladder.

Nine hundred and seventy patients with 1,314 nodules underwent radical MWA treatment and 37 patients with 49 nodules received palliative treatment. The median ablation time was 450 S (range, 120–3,654 S) and the mean treatment session of patients was 1.2±0.4 (range, 1–4). The results showed that technique effectiveness was achieved in 936 (96.5 %) patients and 1,276 (97.1 %) tumors for radical treatment, and LTP was observed in 75 (7.7 %) patients and 78 (5.9 %) tumors for radical treatment. HCC patients had 1-, 3-, and 5-year cumulative survival rates of 92.3, 73.1, and 60.8 %, respectively. The rate of major complication was 2.2 %. The multivariate analysis (Table 2.2, Fig. 2.2) showed that survival rates were related to sex, tumor number, tumor size, tumor pathology type, Child-Pugh classification, preablation alpha-fetoprotein level, liver cirrhosis, and presence of postablation extrahepatic metastasis. The hazard ratio of death was 2.67 times higher for ICC patients than that for HCC nodules, 1.59 times higher for patients with multiple nodules, and 2.39 times higher for patients with worse liver function (Fig. 2.4).

Table 2.2 Multivariate analysis of prognostic factors with Cox proportional hazards model

Variable	Hazard ratio	Standard error	*u* value	*P* value	95 % confidence interval
Sex	2.30	0.35	2.41	0.016	1.17 ~ 4.54
No. of tumors	1.59	0.11	4.22	<0.001	1.28 ~ 1.97
Tumor diameter	1.91	0.15	4.25	<0.001	1.42 ~ 2.57
Tumor type	2.67	0.48	2.07	0.039	1.05 ~ 6.78
Child-Pugh classification	2.39	0.19	4.67	<0.001	1.66 ~ 3.44
Liver cirrhosis	2.24	0.35	2.34	0.019	0.23 ~ 0.88
AFP	1.91	0.22	2.89	0.004	1.23 ~ 2.96
Extrahepatic metastasis	2.22	0.22	3.59	<0.001	1.44 ~ 3.43
Tumor location	0.98	0.07	0.30	0.766	0.85 ~ 1.13
TE	1.01	0.36	0.04	0.969	0.50 ~ 2.06
LTP	0.73	0.29	1.05	0.292	0.77 ~ 2.42
Major complications	0.93	0.39	0.19	0.848	0.50 ~ 2.31
Intrahepatic metastasis	0.64	0.23	1.90	0.058	0.99 ~ 2.45

2.4 Discussion

According to the four multicenter studies of MWA of the liver, results demonstrated that use of MWA could produce TE in more than 97.0 % of HCC tumors and that the LTP was controlled at 5.9–10.1 % for HCC tumors with radical treatment aim. The 5-year survival rate with MWA of PLCs could attain to more than 60 % and the major complication was 2.2–8.3 %. According to several studies with long-term results in large series, RFA of HCC could achieve a 1-, 3-, and 5-year survival rate of 82.9–95.2 %, 57.9–77.7 %, and 42.9–58 %, respectively [26–28]. For PEI treatment of small HCC, the 1-, 3-, and 5-year survival rates of 95.7, 73.5, and 49.3 % were reported [29], whereas our results of MWA for HCC have a slight advantage over the RFA and PEI therapy reports, all with comparable tumor sizes. However, the latest outcome in several multicenter studies of liver transplantation showed slightly more optimistic results with a 5-year survival of 61–67.8 % [30–32].

In Liang et al.'s study, four factors (Child-Pugh classification, number of tumors, tumor size, and presence of extrahepatic metastasis after MWA) were the most important prognostic factors in determining survival rates ($P < 0.001$). They were also confirmed by the studies from other nonsurgical treatment modalities including RFA, transcatheter arterial chemoembolization, and PEI and surgical treatment modalities including hepatectomy and liver transplantation [26, 28, 33, 34]; however, several important clinical factors, such as tumor in different risky location, technique effectiveness, LTP, intrahepatic metastasis, and major complications after ablation, did not show significance for patients' overall survival, which may indicate that combination of precise MWA and other modalities including PEI, temperature monitoring, artificial ascites, and artificial pleural effusion technique used for riskily located tumors can achieve favorable effectiveness. Meanwhile, for patients with LTP and intrahepatic metastases after procedures, repeated MWA as major treatment method lays an ideal foundation for prolonging the survival of patients. Furthermore, the major complications, though as severe traumas for patients, do not show distinct passive impact on patient's overall survival for the low incidence.

The favorable efficacy of MWA in HCC may be attributed to the following reasons: Firstly, MWA heating is primarily active, which has a much broader zone of active heating for not relying on the conduction of electricity into the tissue

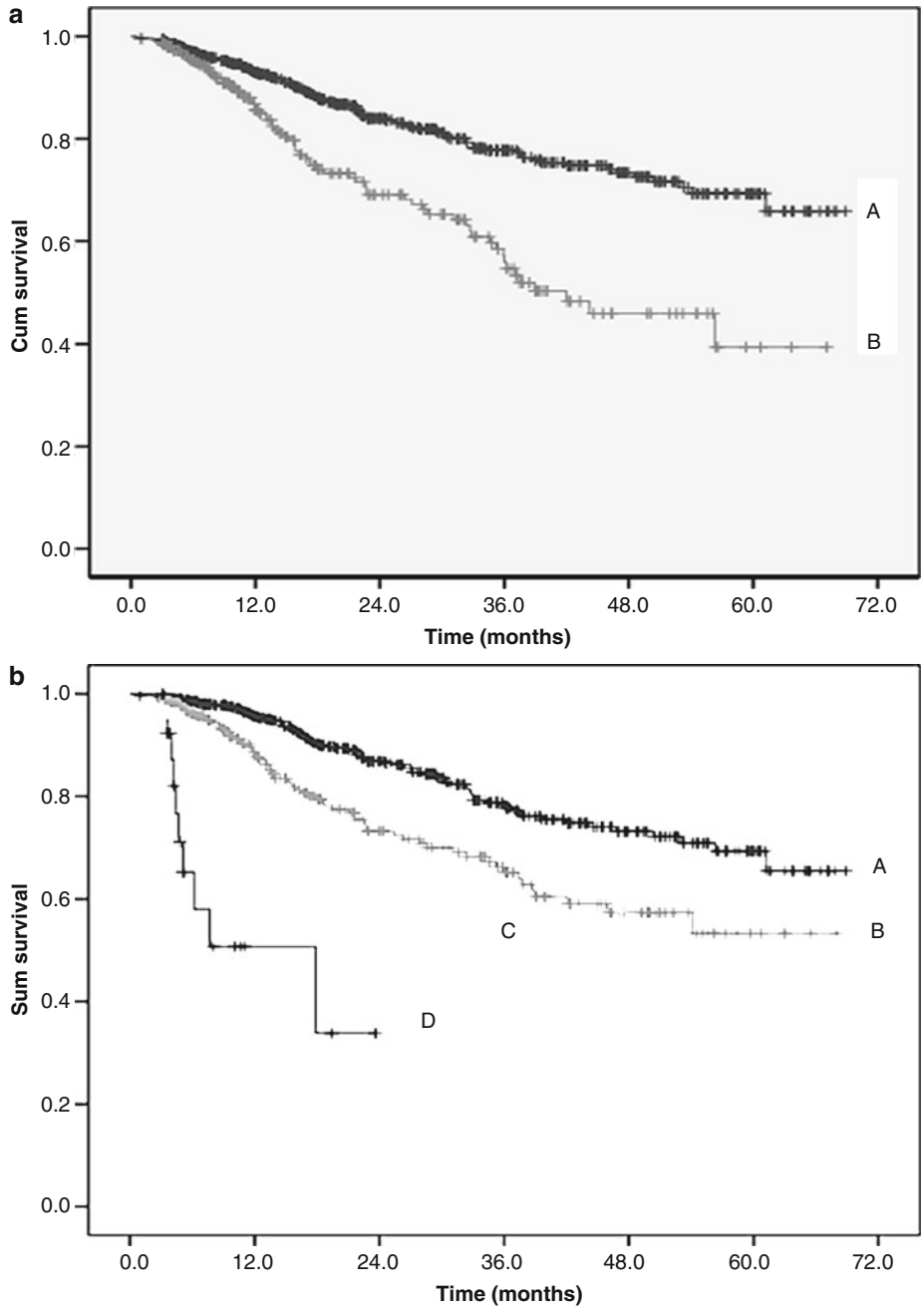


Fig. 2.4 Graphs show 5-year cumulative survival rate of 1,007 patients with primary liver cancer after percutaneous MWA based on multivariate analysis results. (**a**) Comparing between patients with a single nodule (*A*) and those with multiple nodules (*B*), the survival rate of patients with a single nodule is significantly higher than that of patients with multiple nodules ($P=0.001$). (**b**) Data are stratified according to the maximum diameter of the tumor: (*A*) smaller than 3 cm, (*B*) 3.1–5.0 cm, (*C*) 5.1–8 cm, (*D*) larger than 8.1 cm ($P<0.001$). (**c**) Comparing between patients with HCC (*A*) and those with ICC (*B*), the survival rate of HCC patients is significantly higher than that of ICC patients ($P<0.001$). (**d**) Data are stratified according to Child-Pugh classification of preablation liver dysfunction: (*A*) class A disease, (*B*) class B disease, (*C*) class C disease ($P=0.01$). (**e**) Comparing between patients with preablation alpha-fetoprotein (*AFP*) ≤ 20 μg/L (*A*) and those with AFP >20 μg/L (*B*), the survival rate of patients with normal AFP is significantly higher than that of patients with elevated AFP ($P=0.03$). (**f**) Comparing between patients without extrahepatic metastasis (*A*) and those with extrahepatic metastasis (*B*), the survival rate of patients without extrahepatic metastasis is significantly higher than that of patients with extrahepatic metastasis ($P<0.001$)

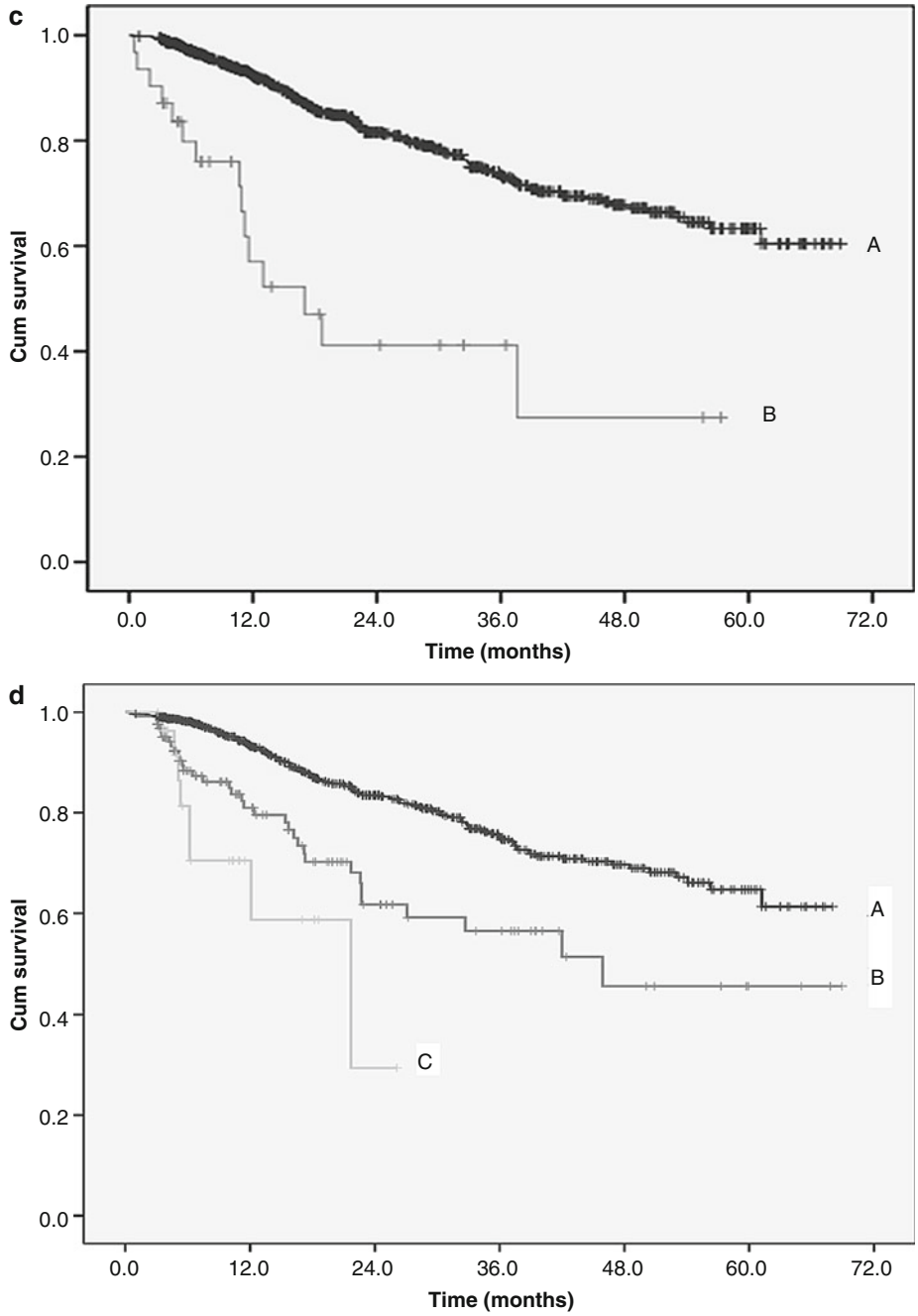
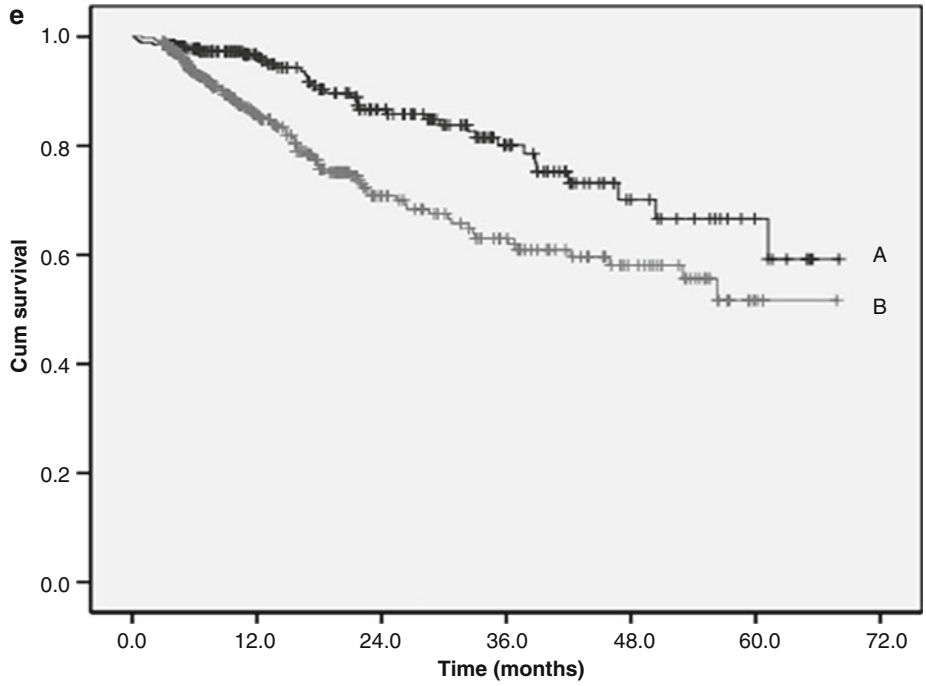


Fig. 2.4 (continued)



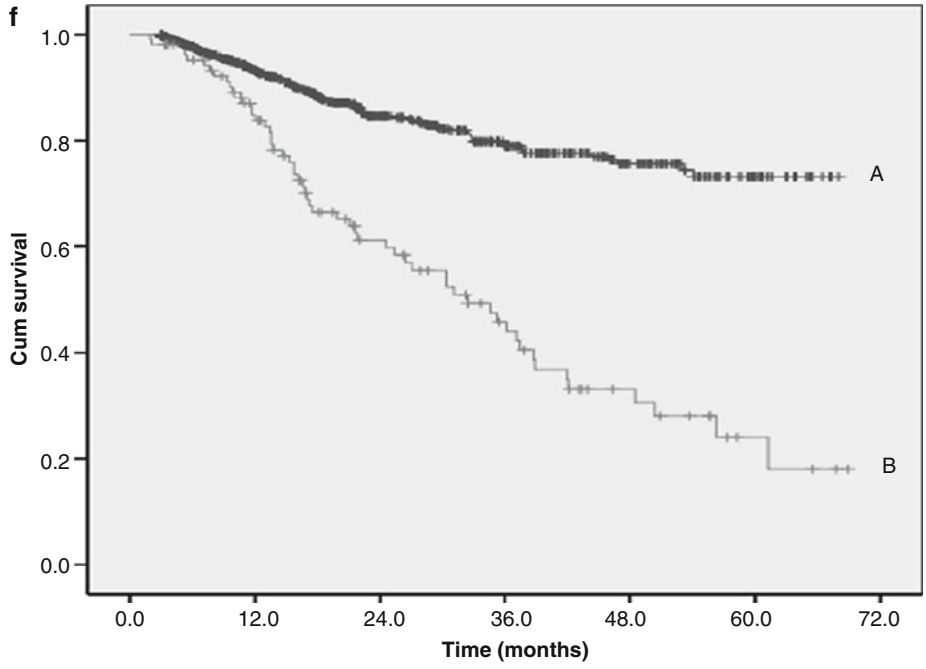


Fig. 2.4 (continued)

[11, 35]. Secondly, cooled-shaft coaxial-based interstitial microwave antennae can effectively keep a low temperature and thus higher-power output, and longer treatment duration is allowed which can deliver more energy into the tissue and produce larger and more spherical ablation zones than noncooled-shaft antenna. Thirdly, consistently higher intratumoral temperatures can lead to a larger zone of ablation and be less prone to convective heat loss from blood flow with ablation zone remaining uniform [11], which may be attributable to low LTP, especially for tumors adjacent to large vessels (only 6.6 % per tumor according to Liang). Finally, the simultaneous treatment of multiple tumors is feasible with multiple microwave antennae, which shortens the treatment time and leads to synergistically larger elliptical-shaped ablation zone for round and large tumors.

These large-scale studies, which were based on a multi-institutional database, provide a strong explanation on the actual effectiveness of MWA treatment for HCC. The further study with internationally representative database with long-term follow-up needs to be carried out to quantitatively assess the contribution of this technique for HCC treatment.

Conclusion

In conclusion, present studies on MWA in HCC confirmed it is an effective therapy modality for HCC with minimal invasion, and the studies provide useful information in guiding clinical practice of MWA technique. The elucidation of independent adverse prognostic factors for survival may provide some selection criteria for better stratification of patients for MWA and also help in the future to select patients with a less favorable prognosis for adjuvant therapy after MWA.

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Percutaneous Ultrasound-Guided Microwave Ablation of Liver Metastasis

3

Yan Lin and Ping Liang

Abstract

Metastatic disease of the liver carries a significant mortality in many kinds of malignant solid tumours. Systemic chemotherapy is still considered the mainstay in the treatment of patients with liver metastases, but the therapeutic efficacy is limited. Besides, aggressive treatments including surgical resection, thermal ablation and transcatheter arterial chemoembolisation improve prognosis in suitable patients with hepatic metastases. Surgical resection remains the standard recommended local therapy for some selected patients. However, for the patients with poor general condition who cannot tolerate the operation, minimally invasive therapy is badly in demand. In recent years, transcatheter arterial chemoembolisation and local thermal ablation therapy including radiofrequency ablation, microwave ablation, cryoablation, laser ablation and high-intensity focused ultrasound have been developed widely and rapidly. As an innovative technique for the management of hepatic metastases, microwave ablation can be performed effectively and has an acceptably low complication rate. Microwave ablation adds another potential treatment modality to the hepatic surgeon armament. The aim of this chapter is to review the current concepts and evolving practices for the application of microwave ablation technology in the treatment of metastatic disease to the liver.

Keywords

Liver metastases • Surgery • Transcatheter arterial chemoembolisation • Radiofrequency ablation • Microwave ablation

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Abbreviations and Acronyms

BCLM	Breast cancer liver metastases
CLM	Colorectal liver metastases
MWA	Microwave ablation
RFA	Radiofrequency ablation
TACE	Transcatheter arterial chemoembolisation

3.1 Epidemiology of Liver Metastasis

The liver is a preferred site of distant metastases for many kinds of malignant tumours, and many patients eventually die with liver metastasis. Of hepatic metastatic disease, there is a high prevalence of gastrointestinal and breast primary malignancies, which is likely related to the high blood volume and dual blood supply of the liver. Colorectal cancer is by far the most common, with up to 55 % of patients with primary colorectal cancer having liver metastases [1, 2]. Besides, nearly half of women diagnosed with metastatic breast cancer will eventually develop liver metastases [3]. Other primary malignancies that commonly metastasise to the liver include the pancreas, stomach and ovary. Metastatic cancer to the liver is considered as a systemic disease, and it is associated with a dismal prognosis. Liver metastases may occur either synchronously as a sign of advanced primary tumour growth or metachronously as an event related to tumour recurrence. If left untreated, survival beyond 5 years is extremely rare. To manage hepatic metastases various treatment modalities have been introduced, such as systemic chemotherapy and local treatments. Although systemic chemotherapy with the new molecular targeting agents is the standard treatment modality, the outcomes remain disappointing and the management of hepatic metastasis remains challenging [4–7]. Local treatments including surgical resection and minimally invasive therapies have received much attention for their advantages in eliminating tumour burden than systemic chemotherapy with little systemic side effects.

3.2 Current Local Treatment Approach

Patients with synchronous disease, multiple diffuse metastases, metastases larger than 5 cm and disease-free interval of less than 1 year from the diagnosis of primary disease were previously considered unresectable and suitable only for palliative treatment [8]. However, the concept of local management of liver metastases has changed considerably over the last decade. The highly selected group of patients with liver metastases may benefit from an aggressive treatment such as surgical resection [9], transcatheter arterial chemoembolisation (TACE) [10] and local thermal ablation [11, 12].

3.2.1 Surgical Resection

Recent advances in surgical technique and systemic chemotherapy have enabled resection after downsizing of lesions which were deemed unresectable due to size or location. Current studies suggest that resection of hepatic metastases from colorectal cancer increases the 5-year survival rate from 0–1 % to 31–58 % [13–15]. Surgical resection of isolated liver metastases from breast cancer may also improve survival for these patients. Single-institutional series have reported 5-year surgery-related survival rates of 18–51 % [7, 9, 16–18] in treating liver metastases from breast cancer. Clinical outcomes of surgical resection of hepatic metastases are summarised in Table 3.1. Traditionally, patients with a maximum of three colorectal cancer liver metastases, located peripherally at one side of the liver with an anticipated resection margin greater than 10 mm and without signs of extrahepatic disease, were considered eligible for a partial liver resection [24–26]. Recent studies have shown that liver resection in patients with multiple and/or bilateral colorectal liver metastases (CLM) results in overall 5-year survival rates between 23 and 51 % [25, 27]. Moreover, centrally located liver metastases are no longer a contraindication for liver surgery. In

Table 3.1 Surgical resection of liver metastases studies including at least 40 patients

Author	Patient number	Primary cancer	R0 resection	MST (months)	Survival (%)		
					1-year	3-year	5-year
Choti et al. [14]	226	Colorectal	N/A	46	N/A	N/A	40
Sarmiento et al. [19]	170	Neuroendocrine	N/A	N/A	N/A	N/A	61
Takemura et al. [20]	145	Non-colorectal Non-neuroendocrine	N/A	41.8	83.9	55.4	41.0
Amano R et al. [15]	117	Colorectal	N/A	58	92.3	60.0	46.1
Takemura et al. [21]	64	Gastric	55	34	84	50	37
Niu et al. [22]	60	Ovarian	54	39	N/A	N/A	30
Kostov et al. [18]	42	Breast	35	60	84.61	64.11	38.45
Cheon et al. [23]	41	Gastric	N/A	17	75.3	31.7	20.8

Note: *R0* a negative hepatic margin, *MST* median survival time, *N/A* not available

patients with a normal functioning liver, extended hemihepatectomies can be performed safely, and mesohepatectomy or a central liver resection is an alternative for an extended hemihepatectomy when parenchymal loss needs to be minimised [28]. If resectable extrahepatic metastases are present, a resection can be offered with 5-year overall survival rates up to 28 % [28, 29]. Thus, liver resection criteria for colorectal cancer liver metastases are at present only limited by an anticipated R0 (a negative hepatic margin) status and an adequate functional liver remnant [30]. Patients in good general health, with technically resectable metastatic disease limited to the liver, regional lymph nodes and/or lungs, are considered for resection regardless of associated clinical predictive factors [31–33]. Yet, the surgical indications for liver metastases from other malignant tumours such as gastric cancer and pancreatic cancer must be carefully determined because of the more severe biologic nature of this disease [34], and the survival rate after hepatectomy is rather unsatisfactory because of the frequent intrahepatic recurrence [5]. This high recurrence rate within 2 years of surgery might suggest the presence of occult intrahepatic metastases even at the time of the hepatectomy. Repeated hepatectomy of recurrent colorectal cancer metastases was also reported to be safe and feasible, and the patients undergoing a second liver resection due to CLM have 5-year survival rates comparable to those of patients who have only undergone one hepatic resection due to CLM [35, 36]; however, repeated hepatectomy requires better functional future liver remnant and general body condition.

3.2.2 Minimally Invasive Treatment

A small percentage of patients are surgical candidates, and patients will live longer with cancer; for these reasons, comorbid conditions become a major factor in selecting patients for surgical resection. This is particularly important in those patients with multiple comorbidities, or more advanced disease. Besides, the high rate of recurrence of liver metastases, affecting 53–68 % of patients, would require repeated resection, which can be tolerated by only a minority of patients with adequate functional future liver remnant and good liver function. For the above reasons, other alternatives that are effective and minimally invasive and repeatable techniques for the treatment of liver metastases are badly in demand. Clinical outcomes of minimally invasive treatment of hepatic metastases are summarised in Table 3.2.

3.2.2.1 TACE

TACE is a local, catheter-based, minimally invasive therapeutic option for unresectable liver

Table 3.2 Minimally invasive treatment of liver metastases studies since 2001

Author	Technique	Patient number	Primary cancer	Mean size (cm)	CA (%)	LTP (%)	MST (m)	Survival (%)		
								1-year	3-year	5-year
Vogl et al. [37]	TACE	208	Breast	N/A	N/A	N/A	18.5	69	33	N/A
Albert et al. [38]	TACE	121	Colorectal	N/A	N/A	N/A	27	N/A	N/A	N/A
Ruers et al. [39]	Cryoablation	30	Colorectal	N/A	N/A	9	32	76	N/A	N/A
Mala et al. [40]	Cryoablation	19	Colorectal	N/A	N/A	44	N/A	N/A	N/A	N/A
Gillams et al. [41]	RFA	309	Colorectal	3.7	N/A	N/A	N/A	N/A	N/A	34
Solbiati et al. [42]	RFA	117	Colorectal	3.2	98	39	36	93	69	46
Machi et al. [43]	RFA	100	Colorectal	N/A	N/A	N/A	28	90	42	30.5
Liang et al. [44]	MWA	74	Colorectal (28)	3.12	N/A	14	N/A	91.4	46.4	29
Lorentzen et al. [45]	MWA	39	Colorectal (31)	N/A	100	9.6	N/A	N/A	N/A	N/A

Note: *TACE* transcatheter arterial chemoembolization, *RFA* radiofrequency ablation, *MWA* microwave ablation, *CA* complete ablation, *LTP* local tumour progression

tumours and is defined as a selective administration of chemotherapy usually combined with embolisation of the vascular supply of the tumour [46]. As a combination of local arterial application of chemotherapeutic drugs with additional usage of embolisation particles, TACE is an effective and recommended treatment [47]. TACE was successfully applied in patients with liver metastases from colorectal carcinoma [38, 47]. Duan et al. reported that the combined treatment of TACE and systemic chemotherapy may prolong survival for liver metastases in breast cancer after mastectomy. Albert et al. also suggested that chemoembolisation with cisplatin, doxorubicin, mitomycin C, Ethiodol and polyvinyl alcohol provides local control of metastatic colorectal carcinoma to the liver during or after standard systemic therapy [38]. In selected patients with liver metastases from ovarian cancer, TACE is an effective palliative treatment in achieving local control, and from the start of TACE, the 1-, 2- and 3-year survival rates were 58, 19 and 13 %, respectively [10]. For the unresectable hepatic metastases of breast cancer, the 1-, 2- and 3-year survival rates after TACE with mitomycin C and gemcitabine were 69, 40 and 33 % [37]. Although considered to be relatively safe, TACE has been associated with several disadvantages including drug resistance, recurrence of marginal tumour and bad therapeutic effect in tumour absence of blood supply as well as relatively high complication rate. Some risk factors have been associated with an increase in complications after TACE treatment, the most known being a poor hepatic reserve with increased serum bilirubin levels. Around 75 % of patients had postembolisation syndrome (fever, pain, nausea) and the total complication rate per procedure was about 9.1 % [48]. For these reasons, TACE combined with local physical therapy including radiofrequency ablation (RFA), microwave ablation (MWA), ethanol ablation, cryoablation and laser ablation will achieve better tumour control than monotherapy.

3.2.2.2 Cryoablation

Several local tumour ablative techniques may offer an alternative therapeutic option in case of liver metastases. Cryoablation, the use of low temperatures to induce local tissue necrosis, was among the first line of the thermal ablative techniques widely used [49]. In the past, cryosurgery has proven to be a relatively safe and effective ablative technique [39, 50]. A median survival of 13–32 months has been reported following cryoablation of CLM [39, 51, 52]. However, a large study of cryoablation of colorectal metastases

reported a local recurrence rate of 33 % after a median follow-up of 22 months [53]. Intra-arterial chemotherapy was given to 91 % of the patients. Mala and colleagues reported that 44 % of the patients developed local tumour recurrence during follow-up [40]. New intra- or extra-hepatic recurrences of CLM are found in 20–67 % and 40–46 % of the patients, respectively [53]. Local tumour recurrences are more frequent following freezing of large metastases (>3 cm) and metastases located close to large vessels [52, 53]. The complications of hepatic cryoablation seem to be related to the extent. Myoglobinaemia is a special complication correlated to the amount of tissue frozen [54]. Serum myoglobin returns to normal within three days, but may cause renal failure if adequate urinary output is not maintained. Cryoshock is a potentially lethal complication following freezing of large liver volumes [55]. The syndrome is characterised by multiorgan failure and resembles a condition of septic shock without evidence of systemic sepsis.

3.2.2.3 RFA

In recent years, with the additional refinements to the design and power of the equipments, RFA has emerged as the most popular tool for the destruction of hepatic and other malignancies. Current RFA uses a high-energy alternating current applied via an exposed electrode placed directly into a target lesion. Initially, RFA has been applied to treat patients with tumour limited to the liver who did not meet the criteria for surgical resectability [56–58]. Currently, RFA is offered to those who cannot undergo resection because of inadequate liver reserve, coexisting morbidity or patient choice and is performed with a curative intent as in surgical resection. There are increasing reports evaluating the use of RFA in the treatment of liver metastases of colorectal cancer patients with the 5-year survival rate from 34 to 46 % [41–43]. There are a small number of retrospective reports on RFA for breast cancer liver metastases (BCLM). In 2001, Livraghi et al. reported on 24 patients with 64 hepatic breast metastatic foci treated with RFA [59]. Complete necrosis by imaging was found in 92 %, and 58 % went on to develop new sites of metastases during follow-up. Metastatic breast cancer is a systemic disease, and most of the patients are receiving concurrent systemic chemotherapy. For this reason, both ablation and resection for BCLM should be considered an adjuvant therapy rather than a substitute for systemic therapy. Based on this theory, RFA may ultimately prove to be as effective as surgical resection for debulking of BCLM. The complication rates for percutaneous RFA of hepatic tumours in 3,670 patients are 7.2 % [60]. Overall, the frequency of major complications of percutaneous RFA ranges from 0.6 to 8.9 % [61]. RFA has a potential to achieve the same overall and disease-free survival rate as surgical resection for patients with liver metastases, whilst causing fewer side effects.

3.2.2.4 MWA

MWA therapy is a relatively new technique that can be applied to different types of tumour. In the early 1980s, a microwave device similar to the “Bovie knife” was firstly used to coagulate the tissue during hepatic resection [62, 63]. Over the next 20 years, this technique evolved rapidly and was used in many of the clinical applications, such as the treatment of primary hepatic malignancies and secondary hepatic malignancies, kidney tumours as well as benign thyroid nodule. One of the main benefits of MWA is that microwaves can propagate through desiccated and charred tissue formed during ablation to form a large ablation zone. For this reason, compared with RFA the size and shape of the MWA zone may be more consistent and less dependent on the heat-sink effect from vascular structures or large bile in proximity of the lesion [64, 65]. Iannitti et al. [66] treated 11 patients with BCLM and showed that after the 19-month follow-up, 36.4 % of the patients were alive with no disease, 9.1 % were alive with disease and 54.5 % had died of disease [66]. Abe et al. [67] used magnetic resonance imaging-guided MWA on 11 nodules in 8 patients with BCLM. No mortality or major complications occurred as a result

of the procedure [67]. Lorentzen et al. [45] and our team (2003) have reported the prognostic factors that can affect survival after MWA therapies [45, 68]. Stättner et al. compared the efficacy of surgical MWA with or without resection for CLM [69]. Twenty-eight underwent combined MWA and resection, whilst 15 underwent MWA as the sole treatment modality. At a median follow-up of 15 months, local treatment failure was observed in 4 % of ablated lesions. Three-year OS was 36 % for MWA group, compared to 45 % for the combined ablate/resect group with 3-year DFS of 32 and 8 %, respectively.

Since 1998, our team has gained rich experience in managing many kinds of solid malignancies including primary liver cancer [70] and hepatic metastasis [68]. In 2003, our study showed that the cumulative survival rate of all 74 patients with liver metastases (11 patients had breast cancer) was 29 % at 5 years. Patient age, sex and site of primary malignancies were not related to prognosis, whereas tumour grade, number of metastases and local recurrence or new metastasis affected survival as single independent factors. Multivariate analysis revealed that tumour grades, number of metastases and local recurrence or new metastasis had a significant effect on survival. In the past few years with the additional refinements to the power and design of the MW system including water-cooled-shaft antenna, thermal monitoring system and other assistive technologies, more and more patients with primary and secondary hepatic malignancies benefit from this thermal technique.

3.2.3 Indications

For the patients with metastatic tumours (single lesion of 5 cm or smaller, five or fewer multiple lesions with a maximum diameter of 3 cm or less and absence of apparent vascular or biliary invasion) and for the patients that do not come up to the above requirements, standard chemotherapy or targeted molecular medicine was suggested to use and a second evaluation should be performed before MWA. There is no severe dysfunction of the liver, kidney, heart and central nervous system; blood coagulate function is normal or close to normal; refusal of surgery or unresectable central type or deep-seated lesions. For the large lesions with rich blood supply, TACE treatment should be performed firstly, and the residual tumour could be destroyed with the guidance of contrast-enhanced ultrasound. For those with too much or too large tumour lesion, both surgery and systemic chemotherapy may have no apparent effect; MWA can reduce the tumour load to slow down the tumour progress for pain relief and life extension.

3.2.4 Contraindications

In diffuse liver metastasis with apparent vascular or biliary invasion, oversized tumour lesion and the ablation zone should reach to about one third of the whole liver or larger. There is severe dysfunction of major organs, irremediable coagulation disorders (platelet count is less than 30×10^9/L, prothrombin time is 30 s or more and prothrombin activity is less than 40 %) and haematologic diseases with severely abnormal blood routine index.

3.2.5 Equipments

The same as stated in the above chapters.

3.2.6 Techniques

Most of the techniques of MWA are the same with liver metastases as with primary liver cancer. However, there are many differences in pathological characteristic between liver metastases and primary liver cancer; accordingly, during MWA of liver metastases, special technical skills

are applied according to the types of the tumour lesion and the source of primary tumour. In order to destroy the tumour in treating primary liver cancer, one to three thermal couples are placed at different sites 0.5 cm outside the tumour. However, for liver metastases, the safe boundary should be enlarged to 1 cm outside of the tumour. Specially, for the cystic or cystic-solid mixed liver metastases from ovarian cancer and nasopharyngeal cancer, before MWA hydatid fluid should be aspirated and appropriate amount of dehydrated alcohol be injected into the cyst for at least 3 min, and then MWA is performed to destroy the solid part of the tumour lesion (Fig. 3.1).

3.2.7 Results

From 2005 to 2012, in our department 206 patients with 511 hepatic metastases were treated with percutaneous cooled-shaft MWA under sonographic guidance. The study group was composed of 121 men and 84 women who ranged in age from 27 to 87 years (average age, 58.1 years). The largest metastasis in each patient ranged from 0.7 to 9.5 cm (mean, 2.72 cm; SD, 1.50 cm).

Primary tumours included colorectal adenocarcinoma in 106 patients, gastric adenocarcinoma in 22 patients, breast carcinoma in 22 patients, lung cancer in 14 patients, small

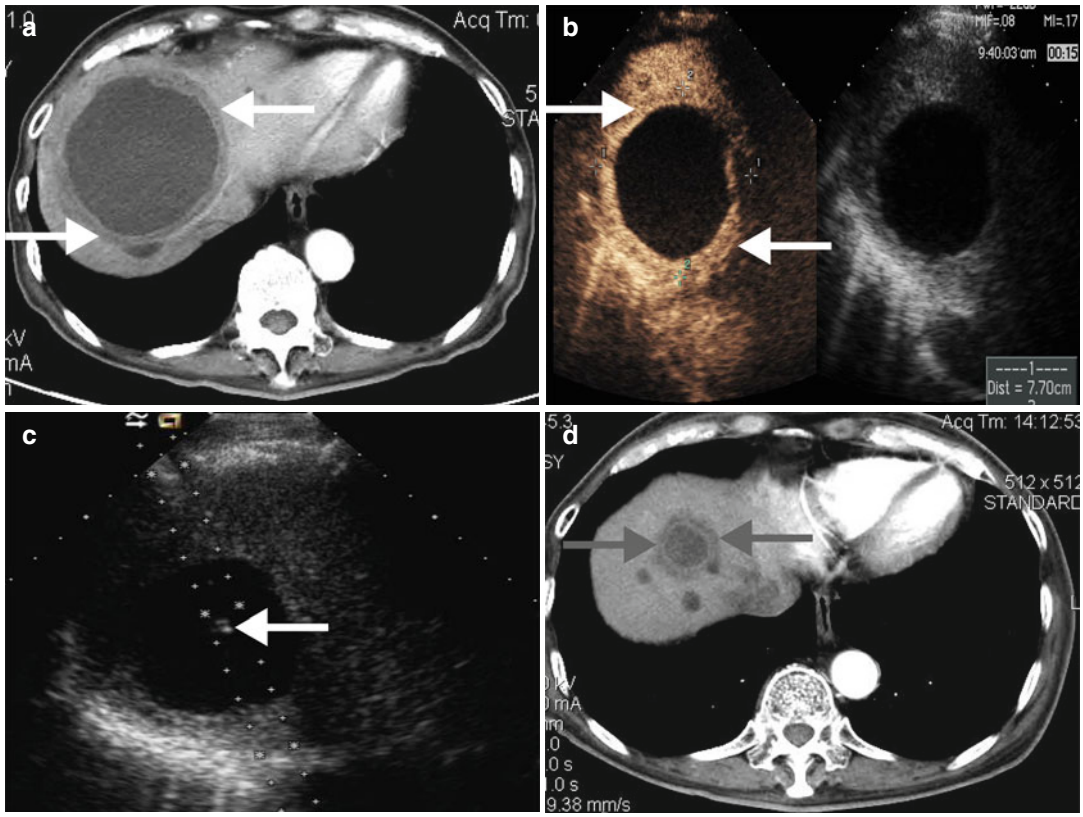

Fig. 3.1 An 81-year-old man with cystic-solid mixed liver metastases from duodenum stromal tumour treated with MWA. (**a**) Preablation-enhanced CT image shows a cystic-solid mixed lesion (*white arrows*); (**b**) contrast-enhanced ultrasound shows rim-like hyperenhancement in the solid part of the lesion (*white arrows*); (**c**) before MWA, with the guidance of ultrasound, the hydatid fluid was aspirated and dehydrated alcohol was injected into the cyst through PTC needle (*white arrow*); (**d**) 3 months after treatment, enhanced CT image shows the ablation zone without recurrence (*grey arrows*)

intestinal stromal tumour in 12 patients (Fig. 3.2), pancreatic adenocarcinoma in 10 patients, ovarian cancer in 10 patients, oesophageal cancer in 9 patients and retroperitoneal leiomyosarcoma in 1 patient (Fig. 3.3). All patients had undergone resection of the primary tumours 3–120 months before undergoing MWA.

All 206 patients underwent systemic chemotherapy before and after MWA. Five hundred eleven hepatic metastases underwent 607 MWA sessions, and complete ablation was achieved in 511 of 511 lesions (100 %). Four hundred nineteen lesions necrosed after the first ablation; the 88 incompletely destroyed tumours were ablated successfully in a second MWA session; four lesions received the third MWA session for the large tumour size (more than 5 cm).

The mean follow-up period for the 206 patients after percutaneous MWA was 22.3 ± 17.5 months (mean ± SD; range, 1.0–90.6 months). Local tumour progression was detected in 67 of 511 tumours (13.1 %) and the 1-, 3- and 5-year local tumour progression rates were 10.3, 15.2 and 17.3 %. Survival times ranged from 0.5 to 90.6 months (median, 46.7 months). The 1-, 3- and 5-year cumulative survival rates were 92.3, 63.2 and 45.3 %, respectively.

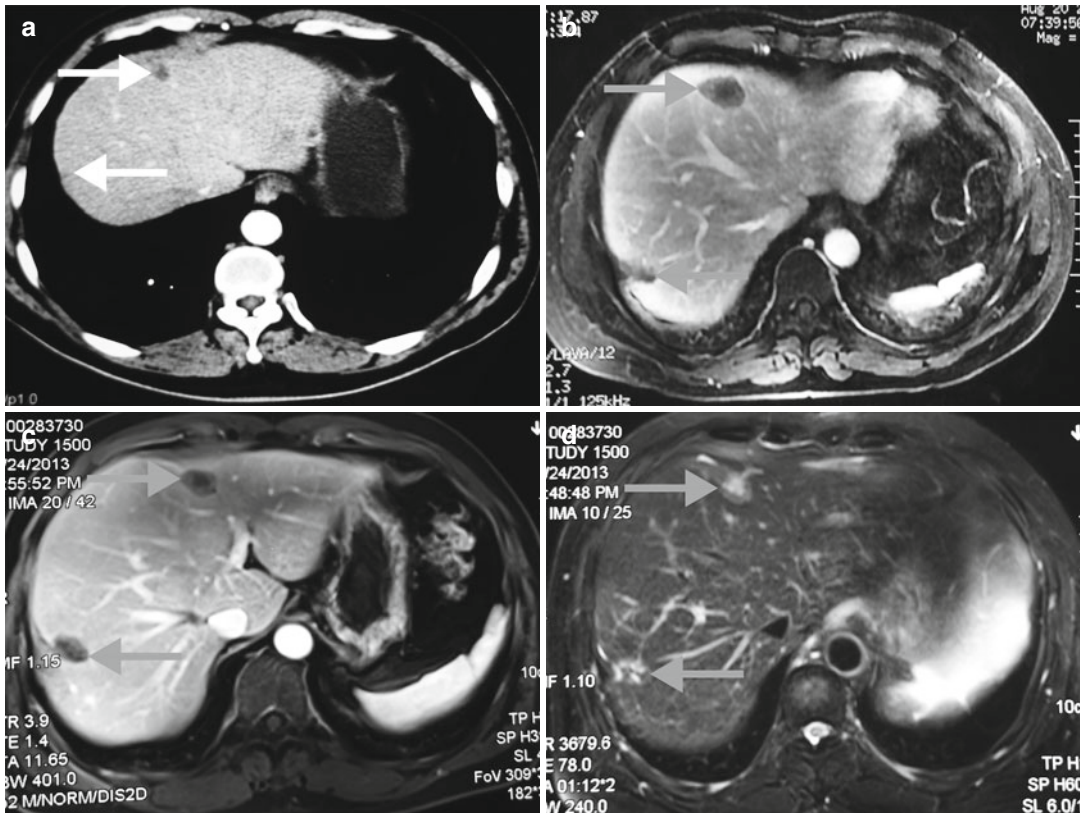

Fig. 3.2 A 47-year-old man with liver metastasis from small intestinal stromal tumour treated with MWA. (**a**) Preablation-enhanced computed tomography (*CT*) image shows two hepatic lesions (2.0 cm × 1.7 cm, 0.9 cm × 0.7 cm) (*white arrow*); (**b**) 6 months after MWA, enhanced MRI shows no residual tumour in the ablation zone (*grey arrow*); (**c**, **d**) 15 months after MWA, enhanced MRI shows the ablation zone without recurrence (*grey arrows*)

3.2.8 Complications and Side Effects

Complications associated with ablation therapy have been generally related to the electrode application and include abscesses, bleeding, bile duct injury, burns, thoracic complications and bowel injury. Reported complications of MWA are similar to those reported for RFA, both being based on the heat damage. In the previous literatures, the major complication rates of MWA were 2.9–3.1 %, and the minor complication rates were 5.7–7.3 % [71, 72].

3.3 Conclusion and Prospect

MWA is a feasible and effective treatment modality in the management of liver metastases to supplement hepatectomy as an additional therapy. It is especially applicable for those patients with multiple metastases and bilobar disease or those with multiple comorbidities who are not fit for surgical intervention. Further investigations of MWA in a greater number of patients with more numerous metastases are needed to confirm these encouraging findings, and a randomised controlled trial is mandatory to compare other

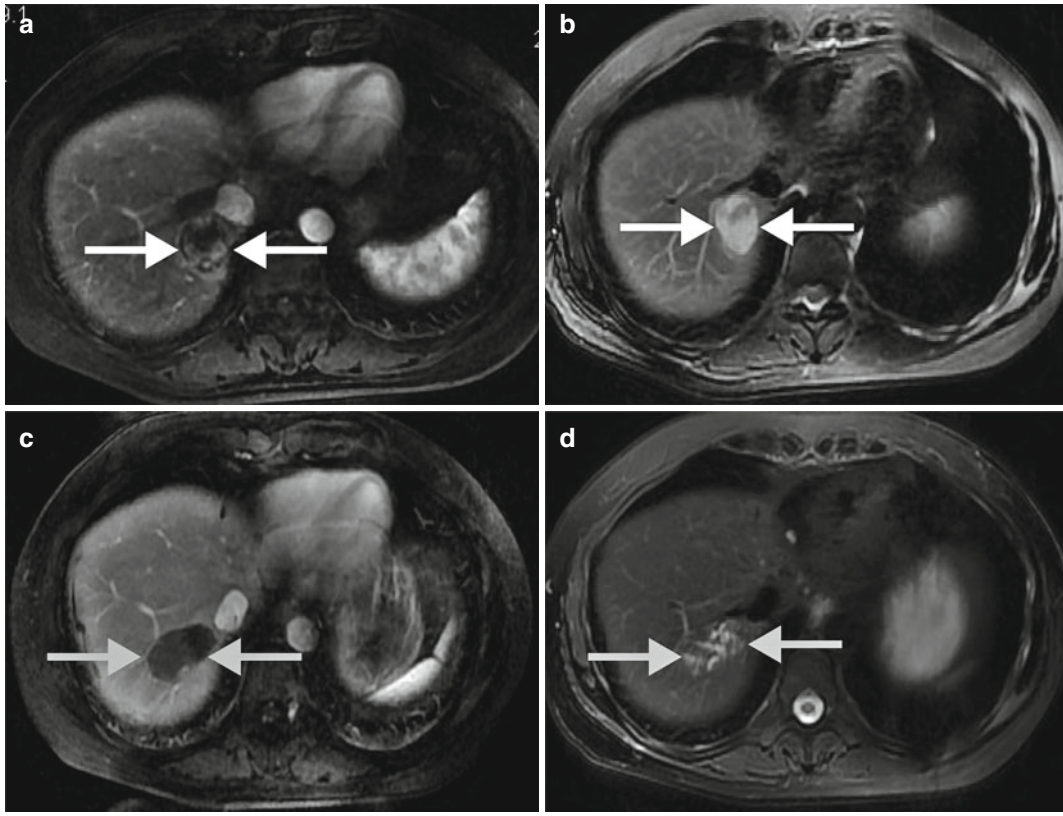

Fig. 3.3 A 51-year-old woman with liver metastasis from retroperitoneal leiomyosarcoma treated with microwave ablation (*MWA*). (**a**, **b**) Preablation-enhanced magnetic resonance imaging (*MRI*) shows the lesion (3.3 cm × 3.2 cm) adjacent to the inferior vena cava (*white arrow*); (**c**, **d**) 6 months after MWA, enhanced MRI shows no residual tumour in the ablation zone (*grey arrow*); (**e**, **f**) 8 months after MWA, enhanced MRI displays a new lesion (1.3 cm × 1.1 cm) in the left lobe of the liver (*white arrow*); (**g**) 3 days after MWA, enhanced MRI shows the ablation zone without residual tumour (*grey arrow*); (**h**) 6 months after second MWA, enhanced MRI shows the ablation zone with a decreased size (*grey arrow*)

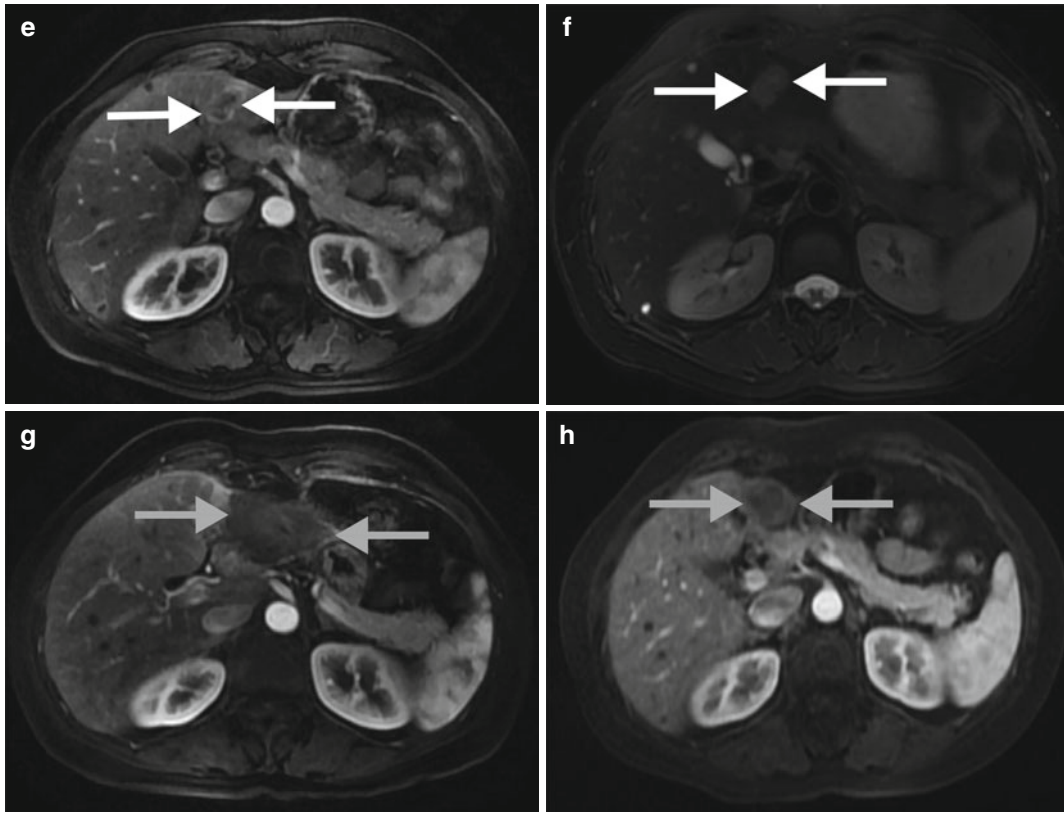

Fig. 3.3 (continued)

minimally invasive modalities to MWA in the treatment of liver metastases.

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Microwave Ablation of Large (≥5.0 cm) Hepatocellular Carcinoma

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Ying Wei and Xiao-ling Yu

Abstract

In contrast with the promising effectiveness of thermal ablation for hepatocellular carcinoma (HCC) smaller than 3 cm, the management of large HCC (>5 cm) in patients who are not candidates for surgical resection remains a major challenge. At present, with further refinement in the devices and techniques, thermal ablation has exhibited prospective capability in treating larger HCC measuring up to 5 cm. Compared with radiofrequency ablation, microwave ablation can achieve higher intratumoral temperatures, larger ablation volumes and shorter ablation times. Additionally, energy transmission is not limited by tissue desiccation and charring. Hence, it may become a more effective treatment and can potentially be adopted in treating larger HCC. In this chapter, we review the indications, equipment, procedures, therapeutic efficacy, assessment and complications of microwave ablation on large HCC, in comparison to transcatheter arterial chemoembolization and radiofrequency ablation.

Keywords

Hepatocellular carcinoma • Microwave • Radiofrequency • Ablation • Ultrasound • Transcatheter arterial chemoembolization

Abbreviations and Acronyms

HCC	Hepatocellular carcinoma
MWA	Microwave ablation
RFA	Radiofrequency ablation
TACE	Transcatheter arterial chemoembolization
US	Ultrasound

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4.1 Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide and is estimated to cause more than 500,000 deaths worldwide annually [1]. In most cases, hepatic resection is considered to be the reference

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standard in the treatment of HCC; however, a large number of patients with HCC are not amenable to surgical therapy because of tumour size, unfavourable anatomy location, the presence of multiple tumours or inadequate hepatic function related to coexistent cirrhosis [2, 3]. Thermal ablation, including radiofrequency ablation (RFA) and microwave ablation (MWA), has achieved encouraging results for small HCC less than 3 cm in diameter and offered favourable outcomes similar to surgical resection [4–6]. With the development of devices and techniques, thermal ablation has displayed the potential for treating HCC larger than 3 cm in diameter [7–10]. Especially of MWA, it uses high-frequency electromagnetic radiation, results in primarily active heating of surrounding tissues and more efficient energy deposition. Owing to the active heating ability, MWA can achieve higher intratumoral temperature, larger ablation volume and shorter ablation time. Additionally, energy transmission is not limited by tissue desiccation and charring [11–14]. Hence, MWA may become a more effective treatment and can potentially be adopted in treating larger HCC. According to the studies, neither 915 MHz cooled-shaft MWA nor 2,450 MHz cooled-shaft MWA has successfully been used in larger hepatic lesions by multiple sequential overlapping ablations to ensure adequate coverage [10, 15, 17]. For HCCs with diameter of 3–5 cm, the results were encouraging [11, 15, 16]. Regarding to tumours measuring 5–8 cm, few studies had reported favourable local effect [11, 17]. This chapter describes the technique, discusses the results and evaluates the feasibility of ultrasound-guided percutaneous MWA for the treatment of hepatocellular carcinomas 5.0 cm in diameter or lager.

4.2 Indications

MWA can be used as the first therapy method for large HCC or the supplementary treatment of transcatheter arterial chemoembolization and comprehensive therapy. For the patients with HCCs (single or no more than three lesions with at least one tumour diameter of ≥5.0 cm) and absence of apparent vascular or biliary invasion. Others are the same as the general indications for liver cancer ablation.

4.3 Preablation Imaging Work-Up

All patients need to undergo US, contrast-enhanced US and contrast-enhanced computed tomography or gadolinium-enhanced magnetic resonance imaging to delineate the target tumour before MWA. And the maximum diameters of the index tumours can be measured on contrast-enhanced US image.

4.4 Equipment

Large HCC is recommended to be ablated by 915-MHz microwave unit if possible. The 915-MHz MWA unit (KY-2100, Kangyou Medical, Nanjing China) consists of two independent microwave generators, two flexible coaxial cables and two water-pumping machines which can drive two 15-gauge cooled-shaft antennas (2.2-cm antenna tip) simultaneously. Certainly, if the tumour is not suitable for 915-MHz MWA for the reason of tumour location, 2,450-MHz MWA can be used. The equipment is the same as in the description in the previous chapter.

4.5 Microwave Ablation Procedures

The general ablation procedures are similar to the ablation of small HCC (≤3 cm) (Fig. 4.1). An overlapping ablative technique with multiple electrode insertions is applied to treat tumours to ensure adequate coagulation necrosis in large HCC, specifically. The penetration depth of microwave in liver tissue is about 3 cm at 915 MHz and 1.7 cm at 2,450 MHz. MWA performs at 60 W using two to three cooled-shaft antennas simultaneously, the distance between

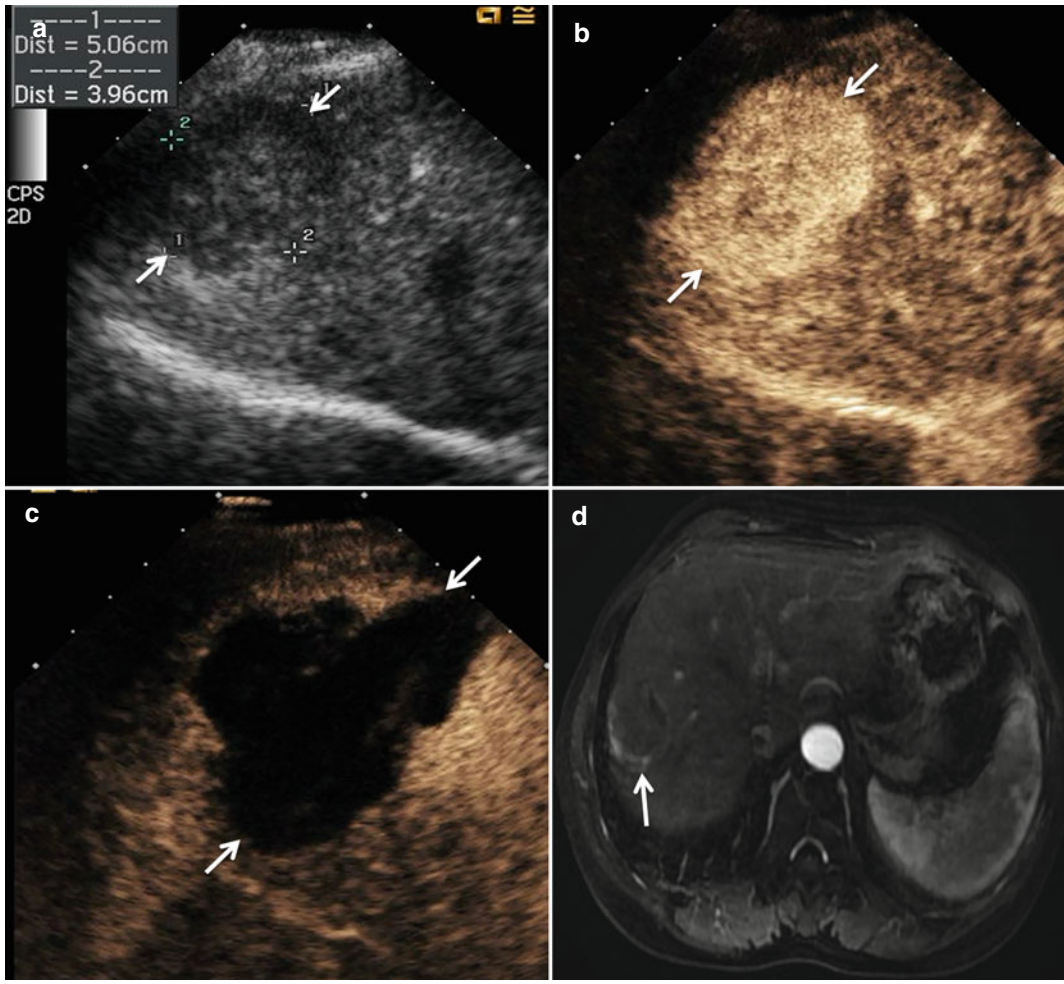

Fig. 4.1 Microwave ablation (MWA) in a 55-year-old woman with HCC on right lobe of the liver (S8), who refuses to undergo hepatic resection. (**a**) Preablation conventional ultrasound (US) scan shows a hypoechoic lesion with poor blood supply (*arrows*). (**b**) Contrast-enhanced US before MWA shows tumor enhancement in arterial phase with the size of 5.1×4.0×3.8 cm (*arrows*). (**c**) Contrast-enhanced US shows no enhancement of the ablation zone at 7 days after treatment. (**d**) Arterial phase magnetic resonance imaging (MRI) scan obtained 2 months after ablation shows hypoattenuating ablation zone (*arrow*) without enhancement

which is no more than 3 cm for 915-MHz MWA and no more than 2.5 cm for 2,450-MHz MWA (Fig. 4.2). Our previous study [10] showed that percutaneous 915-MHz MWA could achieve a high technique effectiveness rate with fewer insertion numbers than 2,450-MHz MWA in the treatment of large lesion. If MWA is performed at 50 W within the same 600 s, the maximum ablation range is 5.7×3.4 cm in 915-MHz MWA. By contrast, in 2,450-MHz WMA, the maximum ablation range is 3.2×2.6 cm only; 2,450-MHz WMA is more suitable for HCCs that are with less residual tumour after transcatheter arterial chemoembolization (TACE) or lesions which cannot be treated by 915-MHz MWA because of inappropriate location. The thermal efficiency between antennas is higher because of mutually complementary affect, and the safety ablative margin of the whole lesion should be noticed no less than 0.5 cm. The key

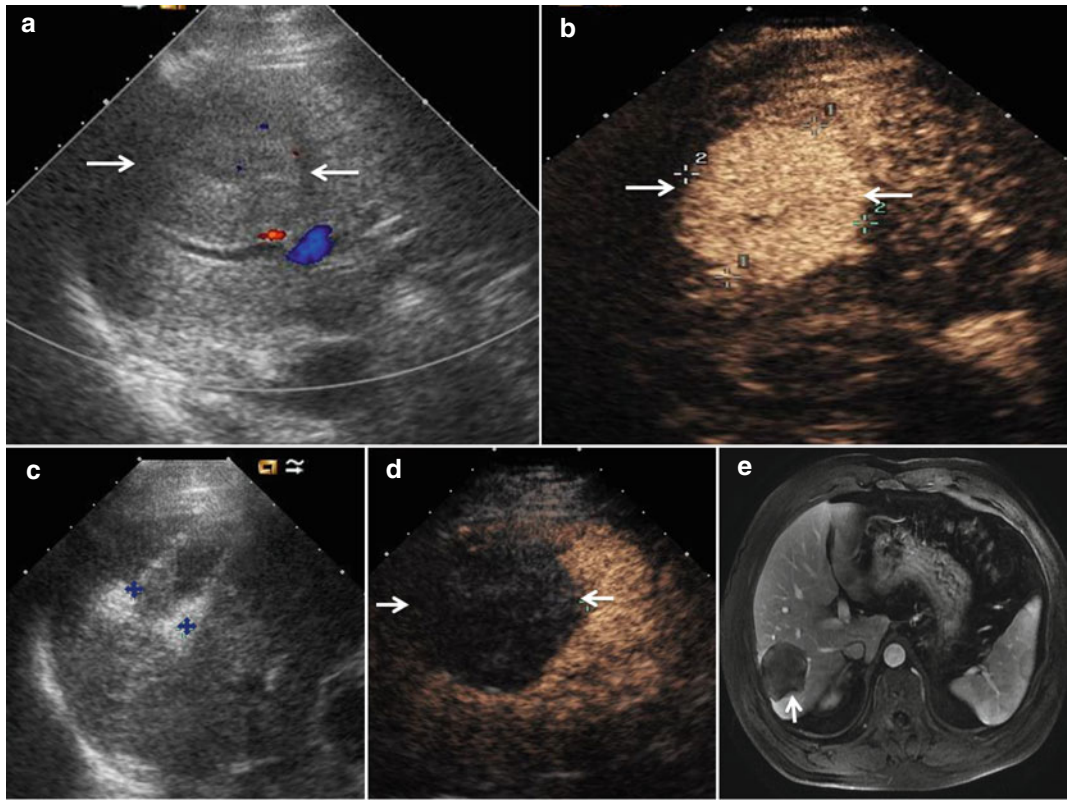

Fig. 4.2 MWA in a 45-year-old woman with HCC on right lobe of the liver. (**a**) Preablation conventional ultrasound (US) scan shows a hypoechoic lesion with blood supply (*arrows*). (**b**) Contrast-enhanced US before MWA shows tumor enhancement in arterial phase with the size of 5.5×4.7 cm (*arrows*). (**c**) Conventional US shows two microwave antennas (*mark*) are placed in the tumor. (**d**) Contrast-enhanced US shows no enhancement of the ablation zone at 12 month after treatment (*arrows*). (**e**) MRI scan obtained 21 month after ablation shows hypoattenuating ablation zone (*arrow*) without enhancement

technological point in the ablation of large HCC is to avoid the recess between two antennas, and overlapping ablation is very important. The distance between the antennas should be less than 2.5 cm in 2,450-MHz WMA. Additionally, dehydrated alcohol (2–10 ml) can be injected with 5 mm beside some important organs (gall bladder, stomach, intestine and bile duct) for protection or next to (less than 5 mm) adjacent vessels to lead to vasospasm which helps to raise thermal efficiency. Lastly, for those lesions with large feeding vessels as shown on US or with blood flow rate higher than 100 cm/s, preablation TACE is helpful. It not only reduces the blood supply but also stimulates the formation of false capsule which can improve thermal efficiency. During MWA, one or two 21-G MW thermal monitoring needles are inserted in the margin of targeted tumour (proximity to the tumour periphery about 5 mm) under US guidance to monitor target temperature of the thermal needles (over 60 °C for lesions in safe location and keeping 54–60 °C for more than 3 min for lesions adjacent to the gastrointestinal tract, diaphragm, gallbladder, etc.). The treatment session would be ended if the transient hyperechoic zone between antennas on grey-scale US merges and covers the target region; meanwhile, the temperature of the thermal needles achieved target temperature.

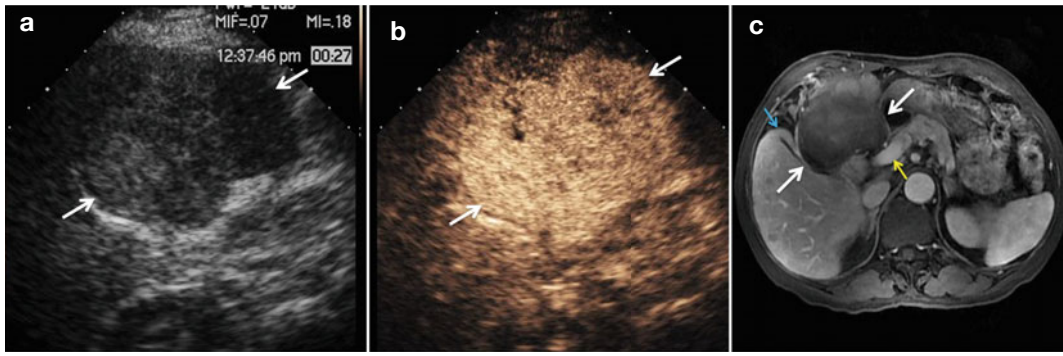

Fig. 4.3 MWA in a 75-year-old man with HCC that is adjacent to portal vein (*yellow arrow*) and gallbladder (*blue arrow*). (**a**) Preablation conventional US scan shows a hypoechoic lesion (*arrows*). (**b**) Contrast-enhanced US shows one hyperenhancement neoplasm with the size of 8.6×6.6×8.0 cm (*arrows*). (**c**) MRI scan obtained 25 months after ablation shows hypoattenuating ablation zone (*white arrows*) without enhancement

4.6 Therapeutic Efficacy, Assessment and Follow-Up

Every patient receives contrast-enhanced US 10–15 min after ablation to evaluate treatment response. Possible residual tumour is doubted if any abnormal nodular hypervascular region exists at the peripheral region of ablation. In addition, for large HCCs, the assessment of the possible residual tumour region between antennas is particularly critical. Complete ablation is considered as the entire tumour shows no enhancement on contrast-enhanced US. The follow-up period was calculated starting from the beginning of MWA. All patients were monitored with contrast-enhanced ultrasound, contrast-enhanced computed tomography or gadolinium-enhanced magnetic resonance imaging every 3–6 months (Fig. 4.3). A new lesion that appeared in or adjacent to the successfully treated nodule or an enlargement of the treated nodule is considered to be local recurrence. The presence of intrahepatic or extrahepatic new tumour nodules was defined as distant recurrence.

4.7 Clinical Efficacy of MWA in HCC (≥5 cm)

The research on MWA of large HCCs is few (Table 4.1). In 2001, Chen J. W. et al. [26] had proven that MWA could completely ablate 14 liver cancer nodules about 6 cm in diameter by suitably prolonging the irradiation duration and using rational multiple insertion schemes through ex vivo model. Kuang M. et al. [11] presented a complete ablation rate of 92 % (12 of 13 tumours) in large HCCs (5.1–8.0 cm), and Yu Z. et al. [17] reported a complete ablation rate of 100 % in four HCC lesions measuring >6 cm. Lately, Liu Y. et al. [8] treated 28 patients with HCC tumours measuring 5.1–8 cm using MWA and achieved a complete rate of 75 % and median survival month of 19. All these studies achieved favourable local effect. However, the samples are limited.

In our latest study, 107 patients with HCCs larger than 5 cm underwent percutaneous MWA with US guidance. Of these patients, 31 had initial HCC (mean diameter of 5.8 ± 0.9 cm) and 76 had recurrent HCC (mean diameter of 6.1 ± 1.4 cm). Ninety-one of 107 (85 %) patients achieved complete ablation (initial HCCs 90.3 %, recurrent HCCs 82.9 %). Incomplete ablation was gotten on the remaining 16 patients because the danger of tumours near important organs including inferior vena cava, port of liver, gallbladder, the ultrasound-guided blind regions, etc. The remains were treated by local injection of ethanol and/or comprehensive treatment. One to seven antenna insertions per patient were performed. The ablation session was no more than three per patient. The mean procedure time was 2,044 s. At a follow-up period ranged from 5 to

Table 4.1 Prognosis of patients with large-size HCC treated by MWA

Author	No. of patient	Diameter (cm)	CA (%)	LR (%)	DR (%)	Overall survival		
						1-	3-	5-year
Yin et al. [7]	68	≥3.1	78.1	24.6	56.7	62.3	29.6	21.6
Liu et al. [8]	80	3–8	87.5	22.2	N/A	81.1	56.5	34.6
Yin et al. [7]	49	N/A	95.9	17.0	N/A	N/A	N/A	N/A
Kuang et al. [11]	90	3–8	92.0	5.0	N/A	N/A	N/A	N/A
Chen et al. [27]	99	>4	94.0	18.7	15.2	89.9	53.1	28.6
Liu et al. [10]	39	>4	73.7–85.7	14.3–26.3	N/A	N/A	N/A	N/A

Note: *HCC* hepatocellular carcinoma, *MWA* microwave ablation, *CA* complete ablation, *LR* local recurrence, *DR* distant recurrence, *N/A* not available

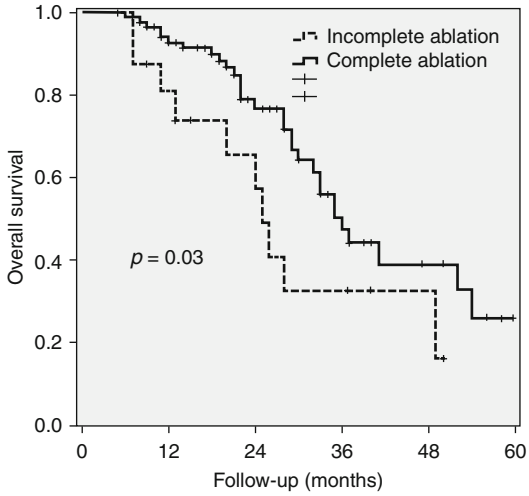

Fig. 4.4 Univariate analysis indicated that patients with initial hepatocellular carcinoma (HCC) had better long-term survival

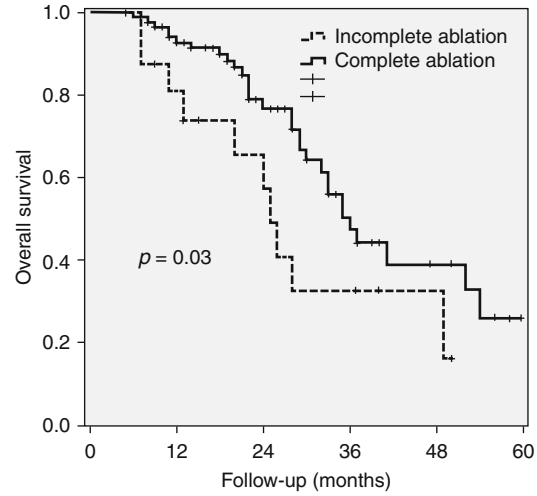

Fig. 4.5 Complete destruction of tumour was a prognostic factor that affected long-term survival

60 months, local recurrence was observed in 24 out of the 91 (26.4 %). In a univariate analysis, incomplete destruction of tumour was the risk factor of local recurrence. During the follow-up, distant recurrences developed in 57.9 % of patients after ablation, including new intrahepatic lesions in 45 patients, kidney metastases in 1 patient, lung metastases in 3 patients, retroperitoneal lymph metastases in 3 patient and multiple metastases in 11 patients. New intrahepatic tumours were observed in 13 of 31 (41.2 %) patients with initial HCC and in 49 of 76 (63.5 %) patients with recurrent HCC ($p=0.032$). The 1-, 3- and 5-year overall survival rates were 80.3, 54.0 and 48.0 %, respectively, with a median survival of 23.8 ± 13.4 months. Of the initial HCCs, the 1, 3 and 5 overall survival rates were 87.0, 70.0 and 38.6 %, respectively. Of the recurrent HCCs, the probabilities of 1, 3 and 5 overall survival rates, respectively, were 77.6, 43.0 and 17.7 %. Univariate analysis indicated that patients with initial HCCs had better long-term survival ($p=0.001$; Fig. 4.4). For patients with initial HCCs, the 1-, 3- and 5-year overall survival rates after the complete ablation were 87.0, 70.0 and 57 %, with mean survival of 31.7 ± 15.4 months. As the results for patients with recurrent HCCs were 77.6, 43.0 and 14.3 %, with mean survival 20.6 ± 11.1 months. Complete destruction of tumour was another significant prognostic factor that affected long-term survival (Fig. 4.5). Complete ablation had better long-term survival than incomplete ones (26.6 vs. 17.5 months, $p=0.033$). Cox regression analysis confirmed

that incomplete tumour ablation and recurrent tumours were independent unfavourable prognostic factors ($p=0.018$).

4.8 Complications

Side effects and minor complications of MWA for large HCC include slight to moderate postprocedural pain, a noninfective slight fever (≤37.5 °C), increase in liver transaminase levels (usually reverted to normal levels within 7 days), nausea, hydrothorax and skin burn [8, 10]. Liu Y. et al. reported a rate of 14.3 % (4/28) major complications in 5–8-cm HCC MWA [8]. In their study, one patient developed hepatic subcapsular hematoma, and acute renal dysfunction occurred in two patients. All were treated with conservative treatment. Long-time complications such as needle track tumour seeding had not been reported.

4.9 Other Local Techniques

4.9.1 TACE

According to current treatment guidelines, TACE has been established as the standard therapy for patients who are not eligible for curative therapies, especially for large, multiple and rich blood supply HCC [27, 28]. The survival benefit of TACE treatment has been proved in two randomised clinical trials [28, 29]. TACE can slow tumour progression and improve survival by combining the effect of targeted chemotherapy with ischemic necrosis by arterial embolization [31, 32]. It can also control or eliminate micrometastasis, which cannot always be detected by ultrasound, CT or MRI. It was found to improve survival, with 1, 2 and 3 year overall survival rates of 82, 63 and 29 % [19]. However, the long-term outcome for patients with unresectable HCC treated with TACE was unsatisfactorily due to the inability to achieve complete tumour necrosis (<50 %) [20, 21, 30]. Repeated TACE was often needed to completely eradicate the residual tumours, but its efficiency was limited and the rate of tumour recurrence or relapse after initial remission or stable disease was very high. Additionally, repetitive TACE treatments might damage liver function reserve and decrease survival time. Studies have also proven that the effect of TACE was influenced by tumour size which decreases inactivation ability, especially for HCCs which are larger than 5 cm [33, 34]. Therefore, it is challenging and dissatisfactory for TACE alone to treat large HCC.

4.9.2 Radiofrequency Ablation (RFA)

Livraghi T. et al. [24] firstly evaluated the feasibility and effects of RFA in 46 tumours (5.1–9.1 cm). Complete necrosis was attained in 11 lesions (23.9 %), and nearly complete (90–99 %) necrosis was attained in 30 lesions (65.2 %). Medium tumours (3–5 cm) were treated successfully significantly more often than the large ones (5.1–9.1 cm). According to the study of Seror O.N. et al. [9], RFA performed on 28 HCC patients with a tumour dimension between 5 and 9 cm, the complete ablation rate was 81 % and the 2-year survival rate was 56 % in all patients. They reported that the complete ablation of tumours up to 8 cm was feasible and safe in patients with HCC and cirrhosis. Seror's latest study used multiple sequential overlapping ablations to ensure adequate coverage and had indicated that multipolar RFA may overcome the main limitation of the percutaneous technique – namely, the size of the tumour. They showed that the complete ablation of tumours up to 8 cm was feasible and safe in patients with HCC and cirrhosis [10].

RFA has been a well-researched and widely used technique [18]. Compared with RFA, MWA uses high-frequency electromagnetic radiation, resulting primarily in active heating of surrounding tissues and more efficient energy deposition [11–14]. Our previous studies had showed that 915-MHz MW produced significantly larger ablation zone than all the RF ablations ($P<0.05$) and 2,450-MHz MW ablation; meanwhile, the 2,450-MHz MW ablation zone was significantly larger than RF ablations ($P<0.05$) in the same time. Owing to the above superiorities of MW, MW might be much suitable for large HCC

ablation: (1) strong thermal efficiency would be achieved with same condition; (2) complete ablation could be attained in short time; and (3) fewer antenna insertions mean less invasions, less expenditure, easier technical procedure and, furthermore, lower complication rates.

4.9.3 Combined Therapy

Compared with small-/middle-sized HCC, the treatment of large HCC is challenging. Recently, comprehensive therapy showed more favourable clinical efficacy rather than TACE or thermal ablation alone (Table 4.2). Either TACE or thermal ablation has its own limitations. In particular, neither can result in the adequate control of medium or large HCC [27, 28, 34–36]. Blood flow will lead to heat loss which may reduce the effectiveness of ablation. One possible way to increase the ablation zone might be to reduce or eliminate the heat loss which is mediated by tissue perfusion [37]. Blood flow to HCC lesions can be substantially reduced by the arterial embolization effect of TACE. Moreover, TACE has a strong antitumour effect on HCC lesions. The synergy between TACE and thermal ablation has been well described [25, 31–34, 37–41]. Occlusion of hepatic arterial flow by embolization reduces the heat-sink effects of hepatic blood flow on thermal coagulation and increases the necrotic area induced by ablation [22]. In addition, the effect of anticancer agents on cancer cells may be enhanced by hyperthermia. Furthermore, iodised oil and gelatin sponge particles used in TACE fill the peripheral portal vein around the tumour by going through multiple arterioportal communications [38], thus reducing the portal venous flow and targeting undetected satellite lesions outside of the ablative area [23]. Moreover, ablation can disrupt intratumoral septa, which usually happens after TACE, and facilitates heat distribution within the tumour. At present, the combination of TACE with immediate synchronous RFA for unresectable and large HCC was recommended. Wang Z. J. et al. [25]

Table 4.2 Minimally invasive treatment results of patients with large-size HCC

Author	Treatment type	No. of patient	Diameter (cm)	CA (%)	LR (%)	DR (%)	Overall survival			Mean survival time (month)
							1-	3-	5-year	
Peng et al. [40]	TACE + RFA	94	3–7	NA	NA	NA	92.6	66.6	34.6	N/A
Liapi et al. [32]	TACE + RFA	96	3–7.5	NA	NA	NA	83.0	55.0	31.0	NA
Fan et al. [33]	TACE + MWA	20	5–10	94	66.7	71.1	80.0	6.7	N/A	N/A
	TACE + RFA	25								
Liu et al. [41]	TACE + MWA	16	>5	N/A	N/A	N/A	N/A	N/A	N/A	11.61 ± 1.59
Seror et al. [9]	RFA	26	≥5	81.1	14	24	68	N/A	N/A	N/A
Livraghi et al. [24]	RFA	46	≥5	65.2	N/A	N/A	NA	N/A	N/A	N/A
Tateishi et al. [18]	RFA	77	5.2–17.6	75.3	N/A	N/A	67.4	N/A	N/A	N/A
Llovet et al. [29]	TACE	21	≥5	N/A	N/A	N/A	82.0	N/A	N/A	N/A
Lo et al. [28]	TACE	80	>5	N/A	N/A	N/A	57.0	N/A	26.0	N/A
Takayasu et al. [36]	TACE	8,510	>4	N/A	N/A	N/A	82.0	47.0	26.0	34

Note: *RFA* radiofrequency ablation, *TACE* transcatheter arterial chemoembolization

reported that compared with conventional sequential therapy, immediate combination therapy could be fully synergistic: (1) lipiodol precipitation in the lesion wraps around and inactivates the surrounding tissue of the tumour, thereby preventing recurrence from residual tumours, and (2) lipiodol cannot be released and chemotherapeutics in lipiodol can inhibit tumours due to their high accumulative concentration.

Recently, Liu C. et al. [41] studied 34 consecutive patients with large unresectable HCC (>5 cm) and reported that the combination of MWA and TACE possessed longer survival time than TACE alone (11.61 months ± 1.59 vs. 6.13 months ± 0.83). Recently, some authors have used meta-analysis to verify the role of TACE combined with RFA in the treatment of HCC. For the treatment of large HCC, the decision as to whether combined therapy with TACE, intermittent treatment or sequential therapy is adopted should be based on the patient's general condition, liver function, local tumour size and number, tumour infiltration, tumour vascularization and reaction of tumour to local treatment. Therefore, the principle of individual treatment must be advocated (Fig. 4.6).

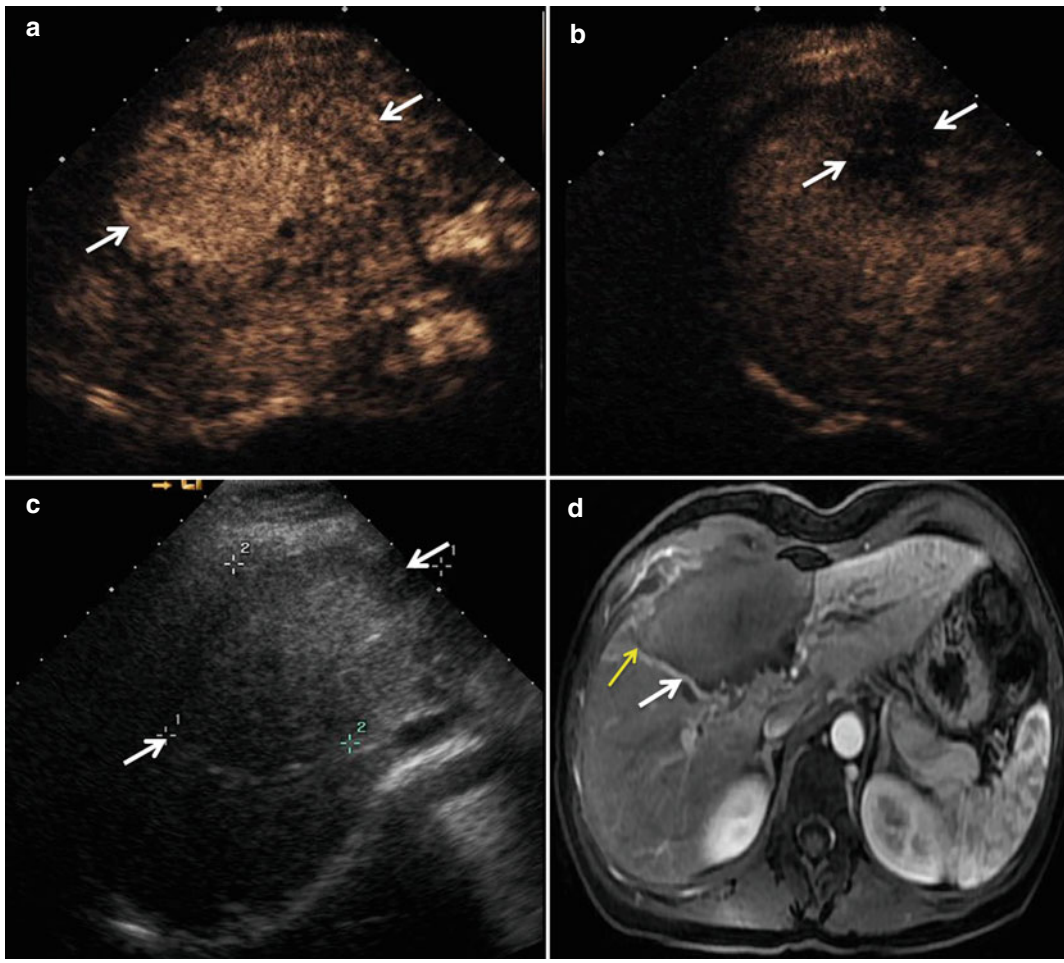

Fig. 4.6 MWA in a 42-year-old woman with HCC that is adjacent to gallbladder (*yellow arrow*). The patient has received transcatheter arterial chemoembolization (TACE) 3 month before. (**a**) Preablation Contrast-enhanced US shows one inhomogeneous hyperenhancement neoplasm (*arrows*) with the size of 9.8×6.5×6.8 cm. (**b**) Contrast-enhanced US displays a little amount necrosis zone (*arrows*) in the tumour after TACE. (**c**) Conventional US shows hyperechoic ball (*arrows*) formed by microwave emitting covered the tumor in the procedure. (**d**) MRI scan obtained 19 months after ablation shows hypoattenuating ablation zone (*arrow*) without enhancement

Conclusions

MW generates satisfactory ablation zones which makes it promising in the thermal ablation for large HCCs that are not amenable to surgical therapy. For large initial HCC, percutaneous 915-MHz MW ablation could achieve a high technique effectiveness rate with fewer insertion numbers in the treatment than 2,450-MHz MW. Preablation TACE first interrupted hepatic blood flow, and MWA then could cure small remaining lesions. Therefore, for patients with HCC lesions with a maximum diameter of ≥5 cm, combination of multiple techniques would ensure more favourable effects. The prospective randomised studies with large sample and long-term follow-up period are necessary to determine efficacy, safety and survival rate.

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Percutaneous Microwave Ablation for Benign Focal Liver Lesions

5

Zhigang Cheng and Ping Liang

Abstract

With the widespread use of imaging modalities and routine medical checkups, more liver lesions are found in the general population. The essential issue is to ensure the proper diagnoses of these lesions, and modern imaging technologies, such as ultrasound, computed tomography, and magnetic resonance imaging, play important roles in the differentiation between benign and malignant hepatic lesions. With the continuous improvement and development of imagings, most liver lesions can be diagnosed, so that clear management recommendations can be provided. For benign focal liver lesions, a regular follow-up strategy is commonly recommended. The indications for treatment of benign focal liver lesions must be very strict, such as with tumor-specific symptoms and complications. The management of these lesions has evolved following improvement in surgical techniques (including laparoscopy) and development in nonsurgical modalities, including transcatheter arterial embolization, radiofrequency ablation, and microwave ablation.

Keywords

Benign focal liver lesion • Resection • Laparoscopic surgery • Transcatheter arterial embolization • Radiofrequency ablation • Microwave ablation

Abbreviations and Acronyms

BFLL	Benign focal liver lesion
FNH	Focal nodular hyperplasia
HA	Hepatic adenoma
HCH	Hepatic cavernous hemangioma
MWA	Microwave ablation
RFA	Radiofrequency ablation
TAE	Transcatheter arterial embolization
US	Ultrasound

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It is generally appreciated that benign focal liver lesions (BFLLs) are common diseases in the liver. Benign hepatic tumors, such as hepatic cavernous hemangiomas (HCHs), angiomyolipomas, hepatic adenomas (HAs), and hepatic epithelioid hemangioendothelioma, and benign tumorlike lesions including focal nodular hyperplasias (FNHs), inflammatory pseudotumors of the liver, and solitary necrotic nodules belong to BFLLs [1, 2]. The high prevalence of BFLLs is up to 52 % in autopsy studies in the general population [3].

With technological advancements of high-sensitive clinical imaging including ultrasound (US), computed tomography, and magnetic resonance imaging, more and more hepatic lesions are incidentally detected during imaging for nonspecific abdominal symptoms [4]. It is crucial that the lesions are essential to be diagnosed differentially between benignity and malignancy on imaging. It is fortunate that most hepatic lesions can be clearly diagnosed by modern imaging because of their increasing accuracy [5–11]. In most cases of BFLLs such as an asymptomatic HCH or FNH, a "watch and wait" strategy is commonly recommended. The indications for clinical treatment must be very strict such as tumor-specific symptoms and complications [12–16].

It is absolutely no doubt that surgical resection is one of the most important methods in treating BFLLs [13, 17–25], with the improvement and advancement of surgical techniques, especially the comprehensive application of laparoscopic surgery. According to a world review of laparoscopic liver resection for treatment of 2,804 patients [26], the results were exciting that overall mortality and morbidity were 0.3 % (9/2,804) and 10.5 %, respectively. However, an important caution is that a surgical procedure without morbidity and mortality does not exist and indications for surgery must be evaluated carefully, especially in treating benign lesions [27, 28].

Though it is necessary for further evaluations depending on the reports of a large series of patients, it was encouraging that a few of nonoperative and minimally invasive modalities, such as transcatheter arterial embolization (TAE) [29–35] and radiofrequency ablation (RFA) [36–42], were documented in recent years. Initially, clinical researches demonstrated that there may be equally effective and less risky alternatives related to surgery in specific cases with BFLLs [43].

Besides application in ablating hepatic malignancies, RFA has been used to treat some BFLLs, such as HCHs [36–40] and HAs [41, 42]. Microwave ablation (MWA) and RFA belong to thermal ablation therapies and have become increasingly attractive in treating liver tumors [44]. It is generally acknowledged that MWA has similarities in complete ablation rates, local tumor control, complications related to treatment, and long-term survival rates with RFA in treating liver malignancies [45–47]. With techniques and equipments' remarkable progress, some advantages of MWA including fewer limitations by tissue charring and desiccation, higher temperature in ablative zone, and less influence of heat-sink have emerged [48]. In addition, 915 MHz MWA with cooled-shaft antenna was successfully applied in clinical therapy for large hepatocellular carcinoma [49] and made it possible to treat large hepatic tumors, such as symptomatic large BFLLs. To provide an additional choice of minimal intervention and explore indications, ablation principles, curative effects, side effects, and complications for some patients who are inoperable or unwilling surgical volunteers, initially clinical treatments of percutaneous MWA under US guidance are started for exploration.

5.1 Indications and Contraindications

It is conceivable that strict controls of indications and contraindications play an important role in clinical treatments, especially in the therapies of benign diseases. Indications and contraindications for the treatments of BFLLs using surgical resection, TAE, and RFA were clearly mentioned in the published documents, such as the complaint of symptoms, the development of complications, or the need to draw a definite diagnosis when radiological and histological studies were not conclusive. The indications and contraindications of MWA in treating BFLLs are coincided with those and summarized as follows.

5.1.1 Indications

I. The presentations of BFLLs on enhanced imaging are uncertain between benignancy and malignancy or doubtful malignancy, especially in patients with positive history, such as infection of hepatitis B or C virus, liver cirrhosis, and a history of malignancy except in the liver.
II. BFLLs enlarged obviously with the increment of the maximum diameter more than 1 cm, found in a half-year follow-up period.
III. The lesions had malignant tendency, such as HAs.
IV. The symptoms patients complained are lesion-specific ones, such as local pain, discomfort, or compression.
V. Evidently, psychological pressure and mental nervousness arose because of hepatic lesions detected incidentally, especially in patients with positive history.

5.1.2 Contraindications

I. Clinical evidences of severe dysfunction in important organs, such as the heart, lung, liver, etc.
II. Severe blood coagulation dysfunction (prothrombin time > 30 s, prothrombin activity < 40 %, and platelet count < 30×10^9/L cells).
III. Acute or active inflammatory and infectious lesions in any organ.
IV. Target lesions could not be clearly shown in grayscale or contrast-enhanced US imaging.

5.2 MWA Recommendations

In general, the technique and procedure of MWA on BFLLs are in accord with those of liver malignancy, which has been described in the previous chapter. However, some special key points for BFLLs treatment are needed to be paid attention to.

1. Unless refused by patients, biopsy is routinely done to obtain the pathological diagnosis before ablation during the same procedure, which can decrease the risk of bleeding or potential seeding, especially for the patients with the malignancy possibility.
2. For benign lesions with propensity to malignancy or the doubtful malignant nodule on imaging before ablation, the ablated area needed to include the tumor and adjacent 5–10 mm normal liver tissue.
3. For the possible benignancy or certain benign lesions without propensity to malignancy on imaging before treatment, the area of MWA is commonly recommended conformably covering the entire lesion to decrease the damage of normal liver tissue.
4. One important therapeutic purpose of BFLLs is to decrease the rupture risk of tumors, especially for the large ones. In addition, if nodules are proximate to some vital organs such as the gastrointestinal tract, bile duct, and gallbladder, severe complications could possibly be caused once damaged by high temperature during ablation. Partial ablation, the ablation area overlapping most of the lesion but reserving the part of lesion adjacent to vulnerable organs, can effectively shrink the tumor volume to decrease the risk of rupture and avoid major complications. If necessary, one or two thermocouple needles equipped by the MWA system can be inserted to monitor temperature to avoid injuring peripheral organs by overheat.
5. The application of 915 MHz MWA can significantly reduce the insertion numbers compared with 2,450 MHz MWA [49]. When the maximum diameter of lesion is less than and equal to 5 cm, 2,450 MHz MWA with output of 50 W is recommended, and 915 MHz MWA with output of 60 W is selected in the nodule with a maximum diameter more than 5 cm.

5.3 Clinical MWA Treatment

According to our knowledge, there is no study yet that reports the results of MWA for BFLLs. Here we will share our treatment experience in BFLLs with readers.

5.3.1 Patients' Data

Between May 2005 and March 2013, 60 consecutive patients with 68 BFLLs were referred to our department for MWA therapy, one nodule in 53 cases, two nodules in 6 cases, and three nodules in 1 case (Table 5.1). The maximum diameters of 44 lesions were 8–98 mm (mean 36.0 ± 21.3 mm). Enrolling ones included 26 men and 34 women aged 23–70 years (mean age, 46.0 ± 10.9 years). The patients were followed up for 2–60 months (mean 32.7 ± 20.6 months).

The pathological diagnosis was proven in 95.0 % (57/60) of patients with US-guided needle biopsy before ablation, including 23 hepatic cavernous hemangiomas (HCHs), 9 focal nodular hyperplasias (FNHs), 9 inflammatory pseudotumors of the liver, 8 solitary necrotic nodules, 4 hepatic adenomas (HAs), 3 angiomyolipomas, and 1 hepatic epithelioid hemangioendothelioma.

Table 5.1 The clinical features of patients with BFLLs treated by MWA

Characteristics	
Number of patients	
Male	26 (37.8 %)
Female	34 (62.2 %)
With 1 mass ablated	53 (88.3 %)
With 2 masses ablated	6 (10.0 %)
With 3 masses ablated	1 (1.7 %)
Mean age ± (SD)	46.0 ± 10.9 years
Number of tumors	68
Mean tumor diameter ± (SD)	36.0 ± 21.3 mm
Diagnosis	
Hemangioma	26 (43.3 %)
Focal nodular hyperplasias	9 (15.0 %)
Inflammatory pseudotumor	9 (15.0 %)
Solitary necrotic nodules	8 (13.3 %)
Adenoma	4 (6.7 %)
Angiomyolipoma	3 (5.0 %)
Epithelioid hemangioendothelioma	1 (1.7 %)
Ablation time ± (SD)	1136.8 ± 837.9 s
Ablation energy ± (SD)	60.8 ± 50.3 kJ
Mean ablation session ± (SD)	1.3 ± 0.5
Mean ablation insertion ± (SD)	2.4 ± 1.4
Mean follow-up month ± (SD)	32.7 ± 20.6 months

Note: *MWA* microwave ablation; *SD* standard deviation; *BFLLs* benign focal liver lesions

The other three cases refused biopsy and were confirmed to have HCHs by imaging. Two or three nodules in one person were determined with the same pathological diagnosis because they had similar presentations on contrast-enhanced imaging.

All cases matched at least one of the five indications mentioned above. The liver lesions of 17 patients were uncertain of benignancy and malignancy or doubtful malignancy on imaging. One of the possible reasons for an uncertain diagnosis was atypical imaging features of small lesions. Another one was imaging diagnosis confused by the positive history. Twenty-four nodules enlarged in a follow-up and four had malignant tendency, and 13 patients had symptoms related to occupation of lesions. Sixteen patients complained evidently psychological pressure and mental nervousness because of hepatic lesions detected incidentally, especially in those with positive history.

5.3.2 Ablation Parameters and Curative Effects

Sixty-eight lesions were successfully treated. Average ablated sessions and needle insertions were 1.3 ± 0.5 (one to two sessions) and 2.4 ± 1.4 (one to six insertions) for each lesion, respectively. Average microwave energy and emission time were 60.8 ± 50.3 kJ (range 9–230.4 kJ) and 1136.8 ± 837.9 s (range 180–3,840 s) for every nodule, respectively.

Fifty-five (55/68, 80.9 %) lesions with a maximum diameter of less than and equal to 5 cm and two lesions (2.9 %) with a maximum diameter of more than 5 cm were completely ablated, and no evidence of recurrence was found in the peripheral ablated area (Fig. 5.1).

The ten large HCHs ablated partially showed good results during the follow-up period, and the residual parts had no obvious progress (Fig. 5.2). However, the residual part of the large FNH with a maximal diameter of 56 mm ablated partially continued to grow after 4 months of follow-up because of a new tortuous arterial vessel and was retreated by TAE 18 months after ablation.

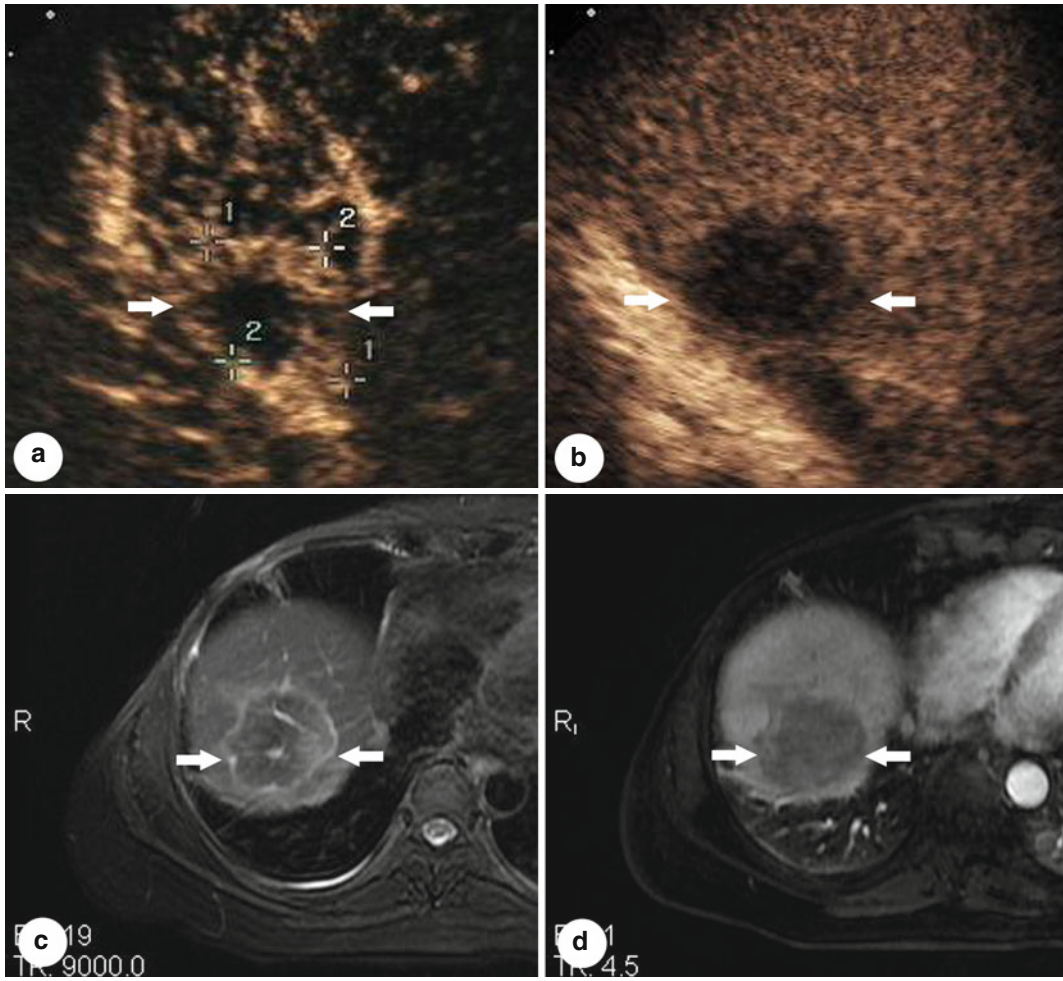

Fig. 5.1 Presentations of a hepatic epithelioid hemangioendothelioma in hepatic segment VIII of a 47-year-old female patient on ultrasound (US) and magnetic resonance imaging before and after microwave ablation (MWA). The patient had a history of radical resection of the breast 1 year ago, and the diagnosis of the lesion was doubtfully malignant on enhanced imaging before ablation. The diagnosis was pathologically proven by biopsy under US guidance. (**a**) Contrast-enhanced US showed the lesion with a maximum diameter of 24 mm slightly peripheral hyper-enhancement and central non-enhancement (*arrows*) in arterial phase before treatment. (**b**) Contrast-enhanced US showed the whole lesion non-enhancement (*arrows*) in portal phase before treatment. (**c**) Magnetic resonance imaging T2-weighted image showed the ablated lesion mixed signal presentation (*arrows*) 3 months after treatment. (**d**) Contrast-enhanced magnetic resonance imaging showed the ablated lesion non-enhancement (*arrows*) in arterial phase 3 months after treatment

The lesion-specific symptoms of the 13 patients (100 %) disappeared or relieved in different degree after ablation. One thing to be mentioned was that the 16 patients (100 %) with evident psychological pressure due to the finding of the hepatic lesion preoperation were relieved of the heavy burden and resumed to normal life.

5.3.3 Side Effects and Complications

According to the definitions of complications and side effects which are consistent with the standardization of terminology and reporting criteria for image-guided tumor ablation [50], side effects

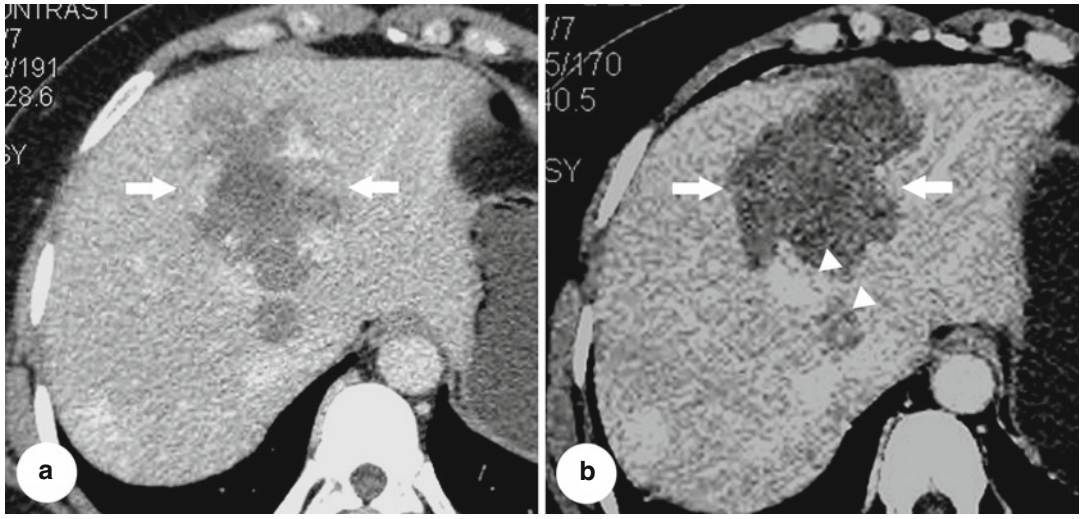

Fig. 5.2 Presentations of a hepatic cavernous hemangioma (HCH) in hepatic segment IV of a 39-year-old female patient on contrast-enhanced computed tomography before and after MWA. (**a**) Contrast-enhanced computed tomography showed the HCH peripheral hyper-enhancement (*arrows*) in delay phase with a maximum diameter of 72 mm before treatment. (**b**) Contrast-enhanced computed tomography showed the ablated HCH non-enhancement (*arrows*) in delay phase 3 months after treatment. Partially unablated areas (*arrow heads*) close to the middle hepatic vein and inferior vena cava showed no changes compared with those before ablation

are expected undesired consequences of the procedure that, although occurring frequently, rarely, if ever, result in substantial morbidity. These include pain, the postablation syndrome, asymptomatic pleural effusions, minor liver dysfunction in blood serum test, and minimal asymptomatic perihepatic fluid or blood collections seen at imaging. These are not true complications because they do not lead to an unexpected increased level of care.

After MWA of patients with BFLLs, the incidence rates of side effects were similar to the presentations of hepatic malignancy ablation [51]. The body temperature of 44 cases (73.3 %) undulated between 37.2 and 38.5 °C lasting 1–2 days. It was unnecessary to manage it in most patients. Five patients were brought down a fever admitted with the remedy because the body temperature was more than 38.5 °C. According to the common toxicity criteria for reporting pain of the National Cancer Institute, local pain with grade 1 was complained in 55 % (33/60) of all cases, lasting 1–3 days without the drug to relieve. Seven patients complained local pain with grade 2 after ablation as the ablated areas adjacent to the surface of the liver require oral analgesics (oxycodone) and the symptoms gradually disappeared within 1 week. The liver function study showed that serum aspartate aminotransferase and alanine aminotransferase levels were increased in 86.7 % (52/60) of all cases. The incremental levels were various, but the highest one was less than three times above the baseline values. Both of these enzymes were normalized in 7 days postoperation. No obvious changes were observed in other serum element levels.

A major complication is defined as an event that led to substantial morbidity and disability, increasing the level of care, or that resulted in a hospital admission or substantially lengthened hospital stay. All other complications were considered minor.

After ablation of BFLLs, the complications of all patients belong to the minor ones. Severe complications such as abscess, bile duct injury, perforation of the gastrointestinal tracts, and hemorrhage requiring embolization did not occur in the perioperative and follow-up periods. Transient hemoglobinuria was found one time in the first urination after therapy in five cases with

large HCHs and then resume normal without additional remedy or management. The reason of the occurrence of hemoglobinuria might be a mass of blood cells that were ruined during the ablation of hemangioma in one session.

5.4 Other Nonsurgical Techniques

The clinical reports of nonoperative methods including TAE and RFA were far less than those of surgery, and the number of cases documented was not very large. However, when surgical resection is being considered for BFLLs, the risk of the treatment must be carefully balanced against the benefit of the operation. For those patients in whom resection is impossible or contraindicated because of the location or size of the lesion or other patient factors, nonoperative methods should be considered. Due to minimal invasion, minor morbidity, and satisfying outcomes, the clinical applications of TAE and RFA for successfully treating BFLLs such as HCHs, FNHs, and HAs have been shown as an inspiring prospect.

5.4.1 TAE

In 1991, a clinical literature review summarized that TAE prior to elective hepatic resection should be a good choice to high-risk patients once the HCHs had ruptured [29]. In 2001, a prospective study that evaluated the clinical and radiologic results of TAE for treating symptomatic HCHs was published by Srivastava D. N. et al. [30]. Eight patients (five males and three females) with symptomatic HCHs were treated by TAE with polyvinyl alcohol particles or Gelfoam and steel coils in single session. The largest diameter of the HCHs was 6–18 cm (9.28 ± 5.13 cm). Indications for TAE were abdominal pain (eight patients), rapid tumor enlargement (four of eight), and recurrent jaundice (one of eight). The results showed that the mean size of the tumor did not change significantly; however, symptomatic improvement was documented in all patients after TAE. It was concluded that TAE was a useful procedure in the therapy of symptomatic HCHs. In 2013, a retrospective study to evaluate the effectiveness of small-sized trisacryl gelatin microsphere embolization as a minimally invasive treatment method for patients with symptomatic FNH was reported by Birn J. et al. [34]. Twelve patients (ten women and two men; age range, 18–61 years) with a total of 17 lesions presenting with symptoms of pain were intervened with superselective embolization with 100–300 μm trisacryl gelatin microspheres during the period of 2006–2011. FNH was pathologically proven in 11 lesions from ten patients, and the other lesions exhibited the classic presentation on enhancement imaging for FNH. After TAE, seven patients showed complete relief and five patients showed partial relief of symptoms. Compared with lesion size before the procedure, mean reduction was 61 % (range, 26–90 %) on imaging after TAE 4–10 weeks. Contrast enhancement of lesions was universally decreased after TAE, with 5 of 17 lesions showing no enhancement. Due to the potentiality to malignant change or spontaneous hemorrhage, it was more active to treat HAs clinically. In 2013, a comparative study about resection, embolization, or observation for managing HA was documented by Karkar A. M. et al. [35]. Demographic and outcomes data were retrospectively collected on patients diagnosed with HA from 1992 to 2011. In total, 52 patients (45 females and 7 males) with 100 HAs were divided into single HA ($n = 27$), multiple HAs ($n = 18$), and adenomatosis ($n = 7$) groups. Median sizes of resected, embolized, and observed adenomas were 3.6 cm, 2.6 cm, and 1.2 cm, respectively. Forty-eight HAs were resected as a result of suspicion of malignancy (39 %) or large size (39 %); 61 % of these were solitary. Thirty-seven were embolized for suspicion of malignancy (56 %) or hemorrhage (20 %); 92 % of these were multifocal. Two out of three resected adenomas with malignancy were ≥10 cm and recurred locally (4 %, CI 1–14 %). Ninety-two percent of the embolized adenomas were effectively treated, three persisted (8.1 %, CI 2–22 %). Most observed lesions did not change over time. To draw a conclusion,

solitary adenomas were often resected and the multifocal ones were frequently embolized and small ones can safely be observed routinely. Given low recurrence rates, select HAs can be considered for TAE.

5.4.2 RFA

Park S. Y. et al. [38] reported a clinical research about percutaneous US-guided RFA for the management of symptomatic enlarging HCHs to evaluate its feasibility, efficacy, and safety in 2011. Twenty-four patients (5 males and 19 females, with mean age of 49.5 ± 2.2 years old) with 25 HCHs with a diameter of more than 4 cm were treated by percutaneous RFA due to either the presence of symptoms or the enlargement of size compared with the previous imaging studies. The mean diameter of hemangioma was 7.2 ± 0.7 cm (4.0–15.0 cm) with 16 HCHs in the right and nine in the left lobe. Twenty-three HCHs (92.0 %) were successfully treated by RFA. The mean diameter of HCHs was decreased to 4.5 ± 2.4 cm ($p < 0.001$) in a serial follow-up computed tomography over a mean follow-up period of 23 ± 3.8 months (23–114 months). Symptoms related to HCH disappeared in all successfully treated patients. There were 14 side effects in ten patients including abdominal pain, indirect hyperbilirubinemia (>3.0 mg/dl), fever (38.3 °C), anemia (<10 g/dl), and ascites, which were successfully managed by conservative treatment. It is concluded that percutaneous US-guided RFA is an effective, minimally invasive, and safe procedure for the management of symptomatic enlarging HCH. An exploration to treat HAs using percutaneous RFA was reported by Rhim H. and his colleagues to assess the therapeutic efficacy and safety in 2008 [42]. Ten patients with HA proven pathologically were treated with an internally cooled RF electrode system under US guidance. Eight patients were asymptomatic and two patients had a recurrent tumor after surgical resection. The maximal diameter of the tumors was 2.25 ± 0.76 cm (range: 1.5–4.5 cm). All patients tolerated well the percutaneous RFA procedure without any incident. Contrast-enhanced computed tomography ($n = 7$) or US ($n = 3$) obtained immediately (<24 h) after the procedure revealed complete ablation of the tumor in all cases. There was no case of local tumor progression or new recurrence during the 2–35 months' (mean, 17.5 months) follow-up period. Neither procedure-related mortality nor major complication requiring specific treatment was observed. It is concluded that percutaneous RFA can be a new potential alternative therapy for HA without overt complication.

Some published documents about TAE and RFA treating BFLLs and the present study about MWA treating BFLLs were listed in Table 5.2. According to the table, the technique effectiveness of MWA was coincident with the ones of RFA. However, it is encouraging that MWA has more potential than RFA to treat lesions with rich blood flow due to less influence in tissue charring and heat-sink [52], which is one of the most important factors to influence the curative effect of thermal ablation including RFA and

Table 5.2 Nonsurgical techniques for treating BFLLs

Author	Technique	Diagnosis	Lesion numbers	Lesion sizes (cm)	Technique effectiveness (%)
Srivastava et al. [30]	TAE	HCHs	8	9.28 ± 5.13	87.5
Birn et al. [34]	TAE	FNHs	17	N/A	100
Karkar et al. [35]	TAE	HAs	37	2.6 (median sizes)	92
Park et al. [38]	RFA	HCHs	25	7.2 ± 0.7	100
Gao et al. [41]	RFA	HCHs	41	10 ± 4	93
Rhim et al. [42]	RFA	HAs	10	2.25 ± 0.76	100
Present study	MWA	BFLLs	68	3.6 ± 2.1	98.5

Note: *TAE* transcatheter arterial embolization; *RFA* radiofrequency ablation; *HCHs* hepatic cavernous hemangiomas; *FNHs* focal nodular hyperplasias; *HAs* hepatic adenomas; *N/A* not available

MWA in clinical treatment. It is not very easy to make the whole lesion necrosis but TAE can occlude most of arterial vessels inside lesion, which are the most significant influences to donate heat-sink effect. Therefore, effective combination of TAE with ablation treatment would be a reasonable choice for treating BFLLs in order to satisfy both minimal invasion and good curative effect.

Conclusion

To draw a conclusion, percutaneous MWA is a safe, effective therapy and is a minimally interventional method for patients with BFLLs. The complications are minor. But the indications have to be strictly administered to enroll the patients. Moreover, for nonoperative and minimally invasive treatments of BFLLs, further study with a large series of patients and long-term follow-up is necessary to evaluate safety, effectiveness, and curative effect.

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Complications of Microwave Ablation for Liver Tumors

6

Shi-Rong Liu and Ping Liang

Abstract

In recent two decades, microwave ablation has been accepted as an effective method in the treatment of primary liver tumors, with a 5-year survival rate comparable to that of hepatic resection for small hepatocellular carcinoma. However, the risks of various complications and benefits of the procedure should be carefully weighed. A systematic review reported acceptable mortality and morbidity rates for microwave ablation technique. The mortality rate was 0.23 % (95 % CI: 0.0–0.58), and the major complication rate was 4.6 % (95 % CI: 2.6–3.1). Death always follows major complications after ablation procedure. Major complications are rare, but it may lead to serious consequences or even death if not appropriately managed. Minor complications and side effects are more common, but most of them are transient and self-limiting. Careful selection of the patient and needle path, real-time monitoring of the entire procedure, combined use of assisted techniques, and early detection and management of any major complications will be helpful in reducing the harmful impact of major complications. This chapter will provide an overview of the types and possible causes of complications, relevant preventive measures and treatment methods, and standard operation techniques to reduce the incidence of complications that occur during or after microwave ablation procedures.

Keywords

Microwave ablation • Complication • Liver tumors • Image guided

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Abbreviations and Acronyms

CT	Computed tomography
GB	Gallbladder
GIT	Gastrointestinal tract
IR	Interventional radiologist
MWA	Microwave ablation
MW	Microwave
PVT	Portal vein thrombosis
RFA	Radiofrequency ablation
US	Ultrasound

Microwave ablation (MWA) technique has been rapidly developed as a branch of interventional oncology that uses heat to coagulate and destroy tumor tissues. In recent years, it has been successfully applied to liver cancer treatment and recognized as a relatively well-tolerated procedure [1]. However, with the wide range of applications and increased cases of treatment, complications of MWA have been increasingly reported [2–6], which may lead to serious consequences or even death if not managed appropriately. Although there have been many investigations addressing complications of radiofrequency ablation (RFA) for liver cancers, complications of MWA have not been fully reported. Large-scale studies reporting complications of MWA comparing to other modalities are still needed to understand this technique and avoid complications. An interventional radiologist (IR) should accurately assess the risks and benefits for each procedure. The whole spectrum of complications and their possible causes and relevant measures should be fully grasped, which will facilitate a better choice of indications and significantly reduce the incidences of serious complications. This chapter aims to review the whole spectrum of complications and to present relevant measures and standard operation techniques of MWA in patients with liver tumors.

6.1 Current Status of Complications After MWA of Liver Tumors

Few studies focusing on complications of MWA of liver malignancies have been published, and the major clinical data are summarized in Table 6.1. The mortality and morbidity rates for MWA technique were 0–1.9 % and 1.9–7.9 %, respectively. However, reports from literature are heterogeneous due to the different sample sizes, technical approaches, nonuniform terms, and different parameters to calculate the complication rates. Our lasted statistics has the characteristics of the largest population-based analysis, the lasted water-cooled equipment, the only one comparative analysis focus on differences in complications between primary and metastatic liver cancers, and the standardized parameters to calculate the mortality and morbidity rates. From January 2005 to December 2012, ultrasound (US)-guided percutaneous MWA with cooled-shaft antenna was performed on 1,313 patients at

Table 6.1 Clinical studies including at least 500 patients reporting complications following MWA in malignant liver tumors

Author	No. of patients	Approach	No. of tumors		Tumor size (cm)	Mortality (%)	Major complications (%) (per patient/per session)
			PHC	Mets			
Liang et al. [2]	1,136	PC	1,412	516	3.4 (0.7–8)	0.2	2.6/N/A
Livraghi et al. [4]	736	PC(554) LS(137) OS (45)	Total 1,037		0.5–10	0	2.9/N/A
Ding et al. [5]	556	PC	Total 1,090		2.3(0.5–6.0)	0.4	3.6/N/A
Wang et al. [6]	693	PC	898		2.5	0.4	3.9/N/A

Note: *PC* percutaneous, *LS* laparoscopy, *OS* open surgery, *N/A* not applicable, *PHC* primary hepatic carcinoma, *Mets* metastasis, *MWA* microwave ablation

our center. One thousand one hundred and eight patients with 1,969 tumors had primary liver cancers and 205 patients with 509 tumors had metastatic ones were enrolled. There were 1,037 men and 276 women. The maximum diameter ranged from 0.4 to 10.0 cm (mean 2.5 ± 1.2 cm) for the primary group versus 0.6–9.5 cm (mean 2.7 ± 1.5 cm) for the metastatic ones. A total of 2,879 sessions were performed (1,969 with primary group and 605 with metastasis). Five perioperative deaths (0.4 %) not directly attributable to MWA procedure were recorded, including one case of pulmonary embolism caused by detachment of inferior vena cava thrombus 14 days after ablation, one multiple organ failure 5 days after ablation, one hepatorenal syndrome 12 days after ablation, and two upper gastrointestinal hemorrhage due to server portal hypertension 12 and 16 days, respectively, after ablation. Major complications occurred in 53 patients (1.8 % per session). For the primary group, complications included 1.0 % pleural effusion requiring drainage ($n = 20$), 0.1 % liver abscess ($n = 3$), 0.7 % tumor seeding ($n = 15$), 0.05 % intraperitoneal hemorrhage ($n = 1$), 0.05 % bile duct injury ($n = 1$), and 0.05 % portal vein thrombosis (PVT) ($n = 1$). For the metastatic ones, complications were 0.7 % pleural effusion requiring drainage ($n = 4$), 0.7 % liver abscess ($n = 4$), 0.5 % tumor seeding ($n = 3$), and 0.2 % biloma ($n = 1$). Compared to primary liver cancers, ablation for the metastatic ones had no difference in the incidences of major complications ($P = 0.87$).

6.2 The Spectrum of Complications

6.2.1 Major Complications

According to the recent proposal of the International Working Group of Image-Guided Tumor Ablation in 2009, the definition of death is self-explanatory and should be reported on a per-patient basis. Any patient death within 30 days after ablation should be addressed. The definition of major complication is an event that leads to substantial morbidity, increasing the level of care, or results in hospital admission or substantially lengthened hospital stay. This includes any case in which a blood transfusion or interventional drainage procedure is required. All other complications are considered minor [7].

6.2.1.1 Patient Mortality

Death within 30 days always follows major complications after ablation. The mortality rates ranged from 0.2 to 0.4 %. Our latest results showed five cases (0.4 %) of death. The possible causes are massive arterial bleeding, liver failure, cardiopulmonary complications, multiple organ failure, hepatorenal syndrome, ischemic bowel due to poor physical status, pulmonary embolism caused by detachment of inferior vena cava thrombus, upper gastrointestinal hemorrhage due to severe portal hypertension, or other existing basic illnesses [2, 8, 9]. Careful selection of patients should be highlighted before any procedure. To avoid the possible risks of death, ablation should be carefully weighted on those with severe liver dysfunction, poor physical status, advanced stage diseases, cardiopulmonary diseases, and other serious underlying diseases. An IR should grasp the whole spectrum of major complications, detect complications, and give appropriate treatment as early as possible.

6.2.1.2 Intraperitoneal Hemorrhage

Bleeding is a frequent complication of MWA for liver tumors due to the coagulopathy associated with the underlying liver cirrhosis. However, intraperitoneal hemorrhage is rare, with an incidence rate ranging from 0.1 to 0.4 %. The possible causes are as follows: direct injury to the intrahepatic vessel due to electrode placement, coagulation dysfunction due to cirrhosis, needle-tract bleeding or tumor rupture, delayed hemorrhage of ruptured pseudoaneurysm, etc. [5, 10, 11]. Bleeding is more likely due to direct mechanical damage to the vessel than thermal injury. Our latest results showed only one case of hepatic artery injury hemorrhage due to noncooperation of the patient. Every effort should be made to prevent such serious complication, particularly in cases of superficial and large liver tumors [12]. Our tips are as follows: (1) coagulation dysfunction

should be corrected in an acceptable level before any interventional procedure; (2) it is important to select an appropriate needle path that avoids vital structures and traverses sufficient normal hepatic parenchyma; (3) real-time monitoring of the entire procedure, including microwave (MW) electrode placement, is crucial for avoiding such complications; and (4) sufficient ablation of needle track, minimum needle puncture into tumor issues, and cooperative breath from patients or even sedation anesthesia will be necessary.

Bleeding usually occurs during the procedure or within 6 h after therapy. Peripheral hepatic effusion and its amount should be checked during or immediately after the procedure. Patients' vital signs and laboratory tests after the ablation should be closely monitored for early detection of this life-threatening complication, especially for those with severe cirrhosis and bleeding tendency. Conservative treatment such as thrombin for injection or blood transfusion will be helpful to most cases of venous hemorrhage. But for intractable arterial hemorrhage, transarterial embolization or open surgery will be necessary.

6.2.1.3 Hepatic Abscess

Hepatic abscess is a rather serious complication after thermal ablation, if not appropriately managed, which may cause sepsis, septic shock, multiorgan failure, or even death. The incidence rate was 0.1–0.4 %. Bilioenteric anastomosis was reported as an independent risk factor in the formation of liver abscess [13] (Fig. 6.1). Other abnormalities include cholangitis, diabetes mellitus, retained iodized oil in the ablation region, an internally cooled electrode with great power (200 W), and absorption of massive necrotic material after one-time ablation of large lesions [14–16]. Yu et al. concluded that intrahepatic cholangiocarcinoma and possible MWA also contributed to the high incidence of liver abscess [17]. In our latest study, although the metastatic group has a higher incidence of cholangiojejunostomy history, there was no significant difference in abscess rates between the two groups ($P = 0.08$). This is probably because of the wide use of intestinal preparation and prophylactic administration of high-efficiency antibiotic in the case with history of bilioenteric anastomosis or pathologic diagnosis of intrahepatic cholangiocarcinoma. An IR should differentiate fever secondary to hepatic abscess from postablation syndrome. High fever lasting longer than 2 weeks should be alerted. For patients with diabetes, the fasting blood glucose should be controlled under 8.0 mmol/L. For larger lesions, two or more sessions are recommended to prevent the formation of liver abscess. Once abscess occurs, adequate broad-spectrum antibiotic should be used as soon as possible. Then, appropriate medication should be selected according to drug resistance and blood culture. US-guided catheter drainage should be performed if necessary (Fig. 6.1–6.4).

6.2.1.4 Hepatic Failure

Liver failure after ablation is not common but often fatal. It mainly occurs in patients with multiple tumors or a Child-Pugh score of B or above. Increased ablation sessions or large volume of liver coagulative necrosis may add such risks in patients with liver cirrhosis [5]. In our latest study, no hepatic failure was recorded. Strict control of indications and cautious management of large or multiple lesions in patients with limited hepatic reserve capacity will be helpful to decrease such risks. Any sign of prolonged hepatic decompensation after ablation should be carefully followed and early aggressively treated.

6.2.1.5 Biliary Complications

Bile Duct Injury

Bile duct injury, including biliary stenosis, cholangitis, biloma, biliary fistula, etc., mainly occurs in patient with tumor adjacent to the hepatic hilum (Fig. 6.2). Excessive heating or mechanical injury secondary to electrode placement may cause damage to the major bile ducts. However, severe bile duct injury is not common. The incidence rate was 0.1–0.7 %. Cooling of the main bile duct with chilled isotonic saline solution and implantation of prophylactic stent have been documented [10, 11], but these techniques are difficult to perform for percutaneous procedure, thus seldomly used. Our latest results showed only one case of biliary stenosis in the primary group and one case of biloma in the metastatic group

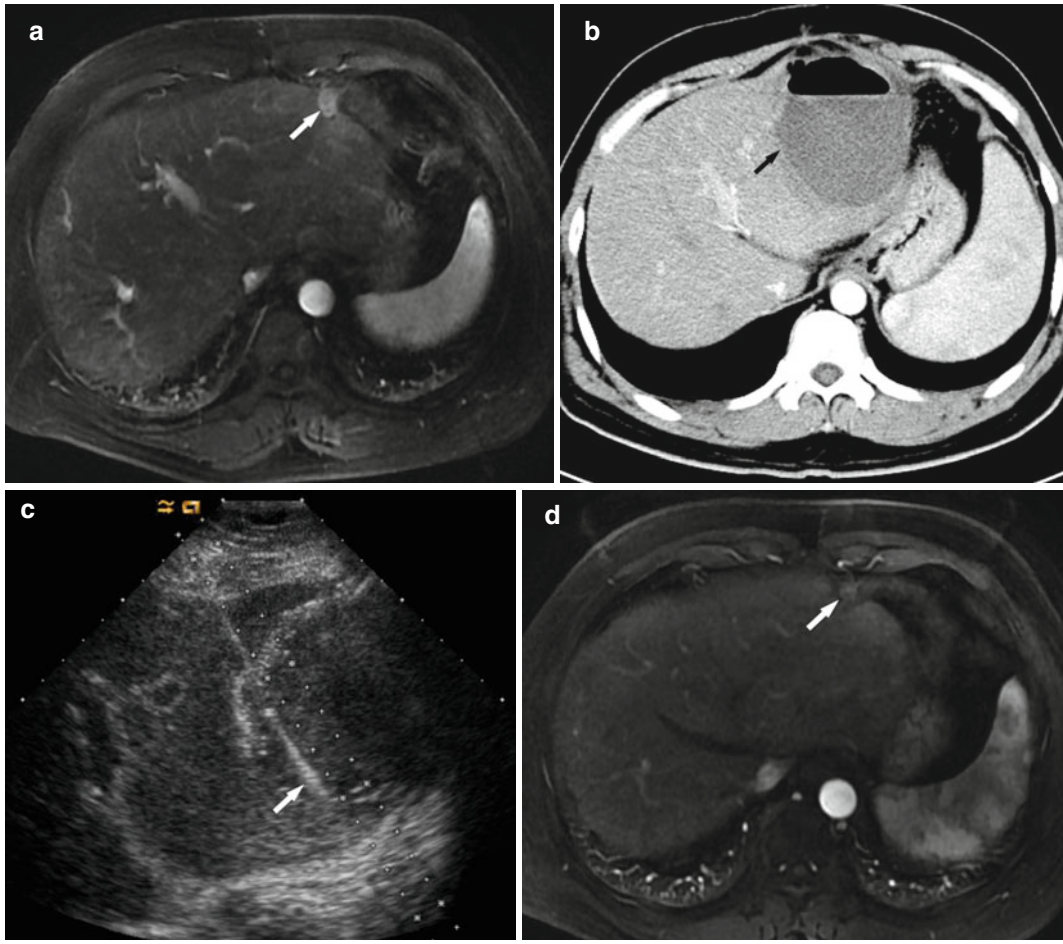

Fig. 6.1 Hepatic abscess in a 42-year-old man with liver metastasis from rectal cancer. (**a**) Contrast magnetic resonance imaging obtained before ablation showed a moderate enhancement of the nodule in the left lateral segment with the size of 1.6 × 1.2 cm (*white arrow*). (**b**) Follow-up competed tomography (*CT*) showed air-containing abscess in the ablated area (*black arrow*). (**c**) Ultrasound (*US*)-guided percutaneous drainage (*white arrow*). (**d**) Magnetic resonance imaging obtained 3 months after drainage showed obvious absorption (*white arrow*)

due to the hepatic helium location and increased number of ablation session. Several tips in our center are as follows: long-duration and low-power microwave emission (45–50 W), real-time temperature monitoring at the periphery of the tumor, and combined ethanol injection will be helpful for minimizing major bile duct injuries. Injury of second branches or above may cause bile duct stricture or even severe obstructive jaundice, which requires percutaneous transhepatic cholangial drainage. For serious bile duct stenosis of the left and right branches, a stent implantation will be necessary (Fig. 6.2).

Gallbladder Injury

The risk of gallbladder (GB) injury increases when there is ablation of a mass adjacent to the GB bed. Inflammatory changes in the GB wall that manifest as minimal wall thickening are common, but GB perforation is very rare due to liquid flow within it that dissipates the heat [18]. Adhesion of GB and its surrounding organs caused by previous surgery is a risk factor for potential GB injury. Cholecystokinin-assisted hydrodissection of the GB fossa has been reported to decrease the risk of such complication [19]. To avoid mechanical damage to the GB, real-time

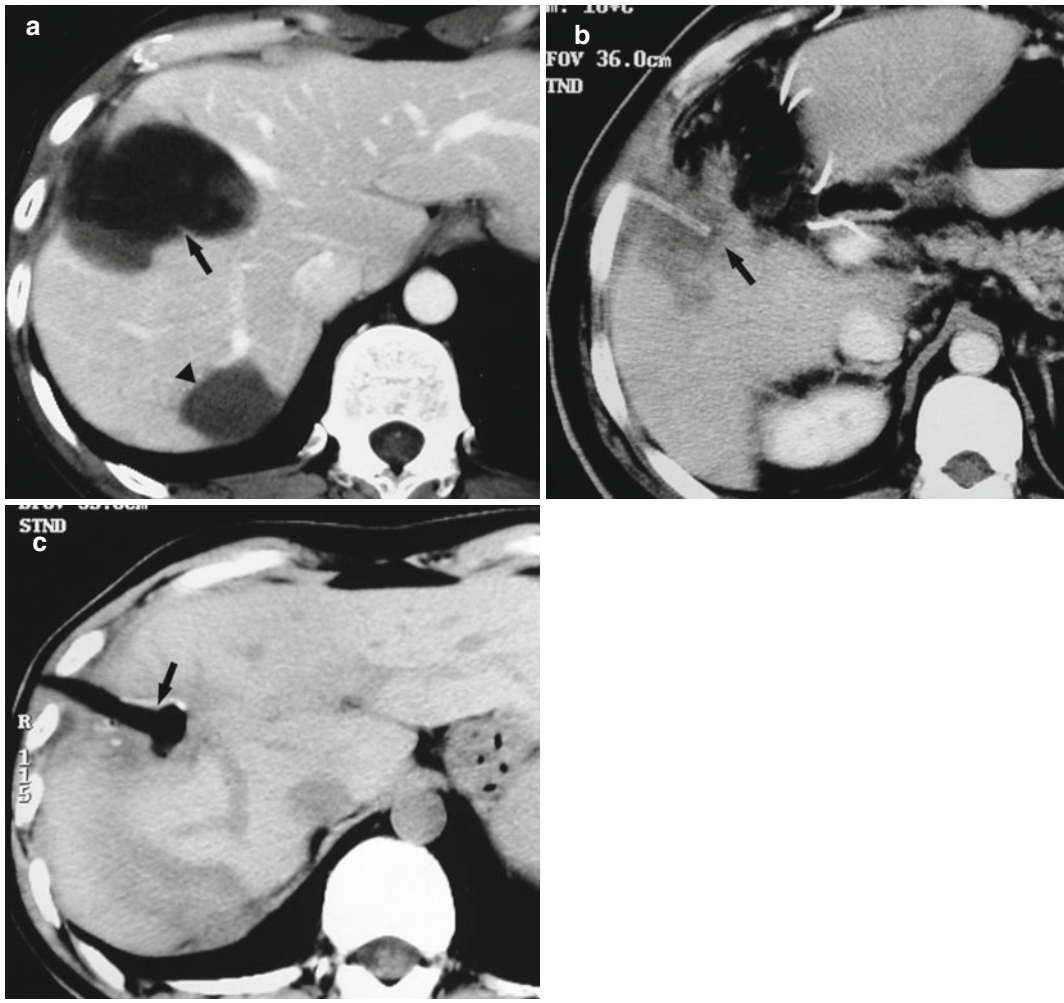

Fig. 6.2 Biloma in a 62-year-old man with liver metastatic nasopharyngeal carcinoma (3.9×4.1 cm in size) (Picture Credits: Liang et al. [2]. Copyright holder: 2009 Radiological Society of North America). (**a**) Contrast CT obtained 1 month after microwave ablation (MWA) showed biloma represented by an area of fluid-filled cavity (*black arrow*) and another complete ablated tumor represented by low-density lesion in the right posterior lobe (*arrowhead*). (**b**) After subsequent percutaneous drainage (*black arrow*). (**c**) CT scan showed resolution of biloma after 3 months of drainage (*black arrow*)

US should be performed to monitor the position of MW electrode. Our experiences [20] showed that real-time temperature monitoring during MWA (<54 °C), with a small amount of assisted ethanol injection, is a key point to minimize the thermal-mediated GB injury. Anti-infection treatment, if necessary, percutaneous US-guided drainage, or cholecystectomy should be performed to these patients with acute cholecystitis or severe edema of the GB after ablation.

6.2.1.6 Gastrointestinal Tract Perforation

Gastrointestinal tract (GIT) perforation mainly occurred in patients with tumors adjacent to the GIT, which is life-threatening, if not properly managed, and may cause septic shock or even death. The incidence rate was 0.1–0.2 %. Fibrotic adhesion between the bowel and the liver due to history of abdominal surgery is the most common cause of such complication. In our experience,

colon involvement is relatively more common, because it is relatively fixed with a thin wall and poor blood supply compared with the small intestine or stomach wall [21]. No GIT perforation was observed in our latest study due to the selected puncture path and ablation-assisted techniques. Strict preoperative bowel preparation is one of the important measures of prevent such complications. Artificial ascites is a key point to separate the target tumor from the GIT [22]. Real-time monitoring of the temperature of the marginal tissue proximal to the GIT and adjuvant therapy with small dose of ethanol injection in the vicinity of the marginal tissue of tumor may prevent the GIT from thermal damage and achieve complete necrosis of tumor margin [23]. An IR should carefully perform the ablation procedure and closely follow the clinical symptoms and should carefully assess whether there is a thickening bowel wall adjacent to the target lesions. When perforation does occur, surgical repair should be performed immediately.

6.2.1.7 Portal Vein Thrombosis

PVT mainly occurs in patient with a centrally located tumor in the immediate vicinity of a compressed portal vein. Thrombosis of vessels larger than 4 mm in diameter is uncommon because of the heat-sink effects of blood flow. Extensive heat, slow portal flow caused by liver cirrhosis, or interrupted real-time scan due to gas bubbles after MW irradiation may be responsible for PVT [5, 24]. In our latest study, PVT was founded in only one patient with tumor adjacent to hilar portal vein. Our tips to decrease such complication are as follows: long-duration and low-power (45–50 W) ablation, real-time peritumoral temperature monitoring, additional ablation sessions, and small dose of ethanol injection [25]. Although often asymptomatic, PVT requires great attention as it is occasionally associated with aggravated portal hypertension, worsened liver function or even liver failure, mesenteric vein thrombosis, or small bowel infarction. Once acute PVT happens, fibrinolytic therapy using high dose of urokinase is a reasonable treatment method [26].

6.2.1.8 Thoracic-Diaphragm Complications

Thoracic-diaphragm complications, including pleural effusion, pneumothorax, hemothorax, emphysema, and diaphragmatic hernia, often occur in patients with tumors located close to the diaphragm [2, 4, 5, 11, 22, 26–31] (Fig. 6.3). Pleural effusion requiring drainage was most common, with the occurrence rate ranging from 0.4 to 1.7 %. The main cause is thermal damage to the diaphragm due to the tumor location adjacent to the diaphragmatic dome. Serious injury may lead to diaphragmatic hernia or perforation. Hemothorax or pneumothorax is infrequent [4, 5]; the possible causes are injuries to the intercostal or diaphragmatic blood vessels secondary to electrode placement. Artificial hydrothorax or ascites may effectively lower the incidence of diaphragm injury, due to both thermal buffering and better visualization [14, 32]. Close observation of the changes of patients' clinical symptoms is recommended. When chest pain and dyspnea happen, computed tomography (CT) or US will be necessary to determine the absence and amount of liquid. Small to moderate amount of pleural effusion does not require treatment, while the large ones with symptoms of dyspnea should be treated with aspiration or drainage. An IR should actively look for the causes of hemothorax. For progressive bleeding not responsive to conservative treatment, arterial embolization or thoracotomy will be recommended (Fig. 6.3).

6.2.1.9 Tumor Seeding

The possibility of tumor seeding increases if the tumor is closed to the liver surface. The incidence rate of tumor seeding was 0.1–1.4 %. Several reasons may be responsible for this complication: incomplete ablation of tumor cells, repeated biopsy or needle puncture, fast speed of electrode withdrawal or not enough intratumoral temperature, superficial tumor location, low degree of differentiation, tumor size, or immunodepression [33] (Fig. 6.4). Great attention should be paid to avoid tumor seeding complications. Our experiences are as follows: (1) puncturing through some normal liver parenchyma if possible; (2) ensuring optimal positioning on the

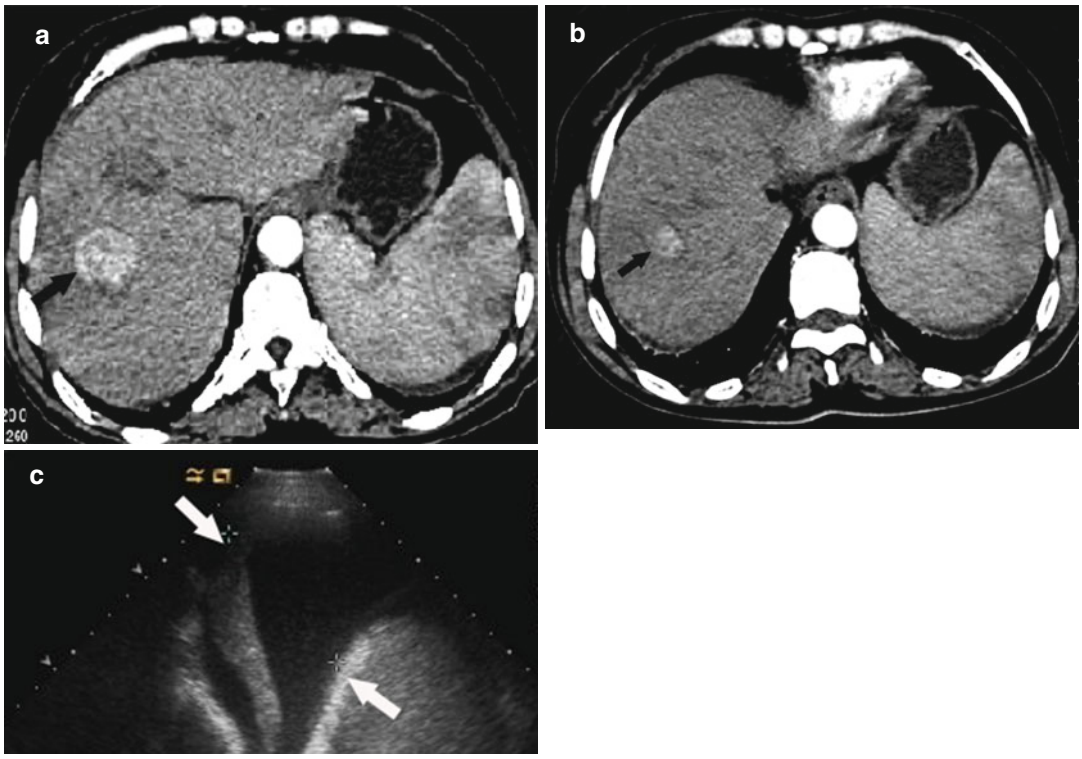

Fig. 6.3 Pleural effusion in a 61-year-old female patient with primary hepatocellular carcinoma with the size of 3.1×3.0 cm. (**a**) Preoperative CT showed a marked enhancement of mass in segment 7 close to the diaphragm (*black arrow*). (**b**) The superior border of this lesion was closed to the diaphragm (*black arrow*). (**c**) US obtained within 4 h after ablation showed right thoracic cavity effusion with maximum depth of 6.5 cm (*white arrows*)

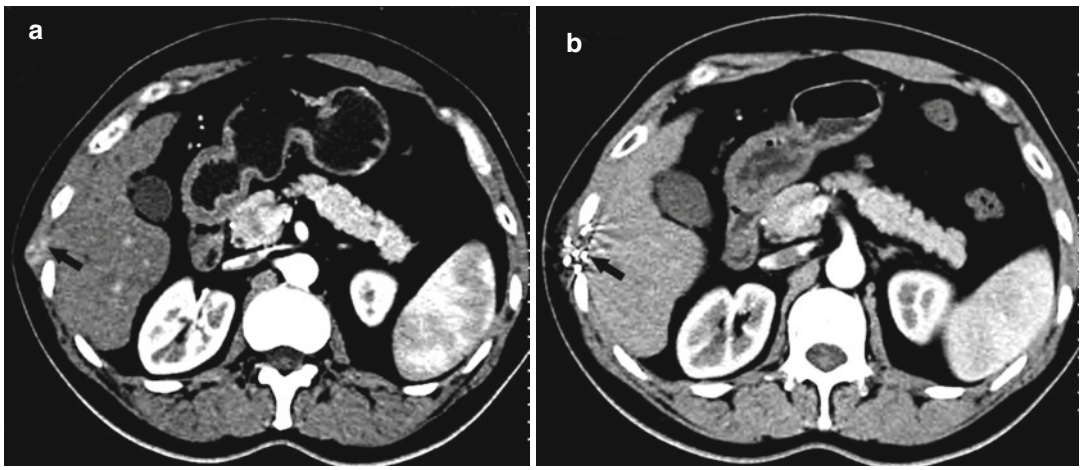

Fig. 6.4 Needle-tract seeding in a 50-year-old man who was previously performed with biopsy for three insertions with primary liver cancer in the deep site. (**a**) Contrast CT showed heterogeneous high-density seeding nodule (*black arrow*) in the muscle of the abdominal wall with the size of 2.0×1.4 cm. (**b**) CT obtained 3 months after radioactive seed interstitial implanting showed reduced tumor (*black arrow*)

first pass to minimize the number of insertions; (3) decreasing biopsy before ablation as much as possible if noninvasive method can get definite diagnosis; if necessary, simultaneous biopsy and ablation would be recommended; (4) maintaining sufficient MW energy by stopping the water-cooling system to coagulate the needle tract; and (5) lasting MW energy emitting for a few seconds when the antenna was withdrawn to the liver capsule. If such complication occurs, additional ablation, interstitial implanting of radioactive seeds, or surgical resection will be recommended (Fig. 6.4).

6.2.1.10 Skin Burn

Skin burn is more common in patient with tumor located near the surface of the liver, with an incidence rate ranging from 0.1 to 0.3 %. The risk of burn is associated with the use non-water-cooled electrode, not incorrect use of skin protection sleeve, not enough backward distance of MW electrode, and higher output power. In our latest study, no skin burn was observed due to the wide application of water-cooled antenna. Several strategies are summarized to decrease the incidence of such complication. An IR should fully incise the skin and subcutaneous tissue and place the skin protection sleeve correctly. Ice bag at the puncture site will be helpful to drop the temperature. For those superficial lesions, low power with 40–45 W is recommended. If necessary, temperature monitoring will be considered. When skin burn happens, surgical resection and adequate drainage will be necessary. The wound usually heals within 3–8 weeks.

6.2.1.11 Others

Other major complications include hepatic infarction, hemoglobinuria or myoglobinemia, cardiac complications, and vasovagal reflex [4, 5, 32].

6.2.2 Minor Complications

The spectrum of minor complications is the same as the major ones but does not lead to hospital admission, lengthened hospital stay, and any associated substantial morbidity and disability [7]. Other minor complications include subcapsular hematoma not requiring transfusion, small discharge from the puncture wound, abdominal wall bleeding, subcutaneous emphysema, subcutaneous effusion, transient hematuria, arterioportal shunting, bradycardia, asymptomatic hepatic infarction, etc.

6.2.3 Side Effects

Side effects are undesired consequences of the procedure that, although occurring frequently, rarely result in substantial morbidity. These include pain, the postablation syndrome, asymptomatic pleural effusions, slight asymptomatic perihepatic fluid or blood, and asymptomatic imaging evidence of minimal collateral damage [7].

6.2.3.1 Pain

Even treated under sedation, about 60–80 % of patients may experience pain during or after ablation procedures. The pain is mostly mild to moderate, generally do not need treatment, and will alleviate by itself in about 1 week. Painkillers will be necessary in 10–20 % of patients, especially when the tumor is adjacent to the diaphragm, liver capsule, GB, or main branches of the portal vein. The pain is usually located at the puncture site. Tumors near the diaphragmatic surface often cause pain in the right shoulder. When tumors are adjacent to the GB, some patients may develop symptoms of cholecystitis, manifested as right upper quadrant pain and localized tenderness. These symptoms are usually mild, which do not need medical attention and tend to heal in 2–3 weeks.

6.2.3.2 Postablation Syndrome

This syndrome is a transient self-limiting symptom or a complex of low-grade fever and overall feeling of discomfort. The duration depends on the volume of the necrosis produced, the overall condition, and the integrity of the immune

Table 6.2 Major studies on complications between the comparison of MWA and RFA for liver malignancies

Author	No. of patient	Treatment (MWA/RFA)	Approach	Tumor size (cm) (MWA/RFA)	Major complications (%) (MWA/RFA)	*P*-value
Ding et al. [5]	879	556/323	PC	2.3(0.5–6.0)/ 2.3(0.5–6.0)	3.1/3.5	NS
Lu et al. [35]	102	49/53	PC	2.5(0.9–7.2)/ 2.6(1.0–6.1)	8.2/5.7	NS
Shibata et al. [36]	72	36/36	PC	2.2(0.9–3.4)/ 2.3(1.0–3.7)	11/3	NS

Note: *NS* not significant, *RFA* radiofrequency ablation

system of the patient. The majority of patients will be relieved within 2–7 days. If very large areas are ablated, the syndrome may persist for 2–3 weeks [7].

6.3 MWA Compared to RFA

Only a few clinical studies focused on complications comparing MWA for liver malignancies to other ablation modalities. Data summarized in Table 6.2 showed the complications comparing MWA to RFA. In terms of complications, most studies failed to detect superiority of one modality over another. A systematic review of percutaneous ablative techniques for liver tumors did not show significant difference in mortality and complication rates of the two ablative modalities. The reported mortality rate for RFA was 0.15 % versus 0.23 % for MWA, and the major complication rate was 4.1 % versus 4.6 %, respectively [34]. A large sample comparative study [5] showed that there was no significant difference between the types and incidences of complications caused by RFA and MWA. The lack of adequate comparative studies between MWA and other modalities, such as cryoablation and TACE, provide much room for investigation.

6.4 MWA Compared to Hepatic Resection

Despite technical advances of hepatectomy, it is still burdened by relatively high rates of postoperative mortality (0.24–9.7 %) and morbidity (4.09–47.7 %) [37–39]. Complications of hepatic resection include venous catheter-related infection, pleural effusion, incisional infection, pulmonary atelectasis or infection, ascites, subphrenic infection, urinary tract infection, intraperitoneal hemorrhage, bile leakage, gastrointestinal tract bleeding, biliary tract hemorrhage, coagulation disorders, and hepatic failure [40]. Bleeding is the most feared technical complication and may be grounds for urgent reoperation. Liver failure poses a significant hazard to patients with underlying liver cirrhosis. Complications after MW ablation are less common than those of hepatectomy [41, 42]. The amount of intraoperative blood loss was smaller and the length of hospital stay was shorter. These may demonstrate low invasiveness of MWA.

Conclusion

MWA has been accepted as an effective method in the treatment of liver tumors, with excellent local control and acceptable morbidity and mortality rates. An IR should fully grasp the whole spectrum of complications. Careful patient selection, appropriate approach, followed by early detection and appropriate management will help to minimize the incidence and morbidity rate from any complications.

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Part III

Microwave Ablation of Liver Tumor at Different Locations

Percutaneous Microwave Ablation for Liver Tumors Adjacent to Large Vessels

7

Shi-jia Huang, Jie Yu, and Ping Liang

Abstract

Traditionally, hepatic resection is the first-line treatment option for liver tumors, and the 5-year survival rate is up to 60–80 %. However, because of only partial patients being suitable for surgery and the high recurrence rate, minimally invasive treatment including transcatheter arterial chemoembolization and local thermal ablation techniques develops rapidly these years. Among the measures, radiofrequency ablation and microwave ablation have already been recommended as alternatives for the treatment of liver tumors. However, some researchers hold the view that central tumors close to the hepatic hilum or large vessels are unsuitable for percutaneous thermal ablation because of the risk of injuring adjacent bile ducts, and an important inherent effect of heat-sink from large vessels on thermal ablation may influence the treatment result for these tumors. At present, some researchers have already tried to put radiofrequency ablation into practice for treating liver tumors adjacent to large vessels with satisfying results. As another kind of thermal ablation techniques, microwave ablation has its special features, such as higher intratumoral temperatures, larger ablation zones, less ablation time, and less dependence on the electrical conductivities of tissue. These advantages may make microwave ablation treatment less affected by heat-sink. In this chapter, we will discuss the effectiveness and safety of percutaneous microwave ablation for liver tumors adjacent to large vessels.

Keywords

Liver tumor • Microwave ablation • Large vessels • Ultrasound

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Abbreviations

CEUS	Contrast-enhanced ultrasound
HCC	Hepatocellular carcinoma
MWA	Microwave ablation
RFA	Radiofrequency ablation
TACE	Transcatheter arterial chemoembolization

7.1 Introduction

7.1.1 Multiple Modalities for Liver Tumors Adjacent to Large Vessels

7.1.1.1 Hepatic Resection

Traditionally, in terms of patients with solitary tumors and well-preserved liver function, hepatic resection is the first-line treatment option [1–3]. It becomes one of the most effective treatments for early hepatocellular carcinoma (HCC). Patients treated with hepatic resection turned out to be satisfying in therapeutic effect. However, many factors make surgical resection inapplicable to most patients with liver cancer, such as associated severe liver cirrhosis, multiple lesions in different hepatic segments, or extrahepatic metastasis. And another limitation for resection is tumors located in unfavorable sites.

Resections turned out to be practicable for malignant zones near main hepatic veins or vena cava. Yamamoto et al. performed surgical treatment on seven patients with colorectal liver metastases involving the paracaval portion of the caudate lobe. Liver metastases involving the S1r were resected radically with en bloc resection of the major hepatic veins and/or the inferior vena cava. Four of the seven patients survived more than 5 years. And the median survival time of the seven patients was 60 months [4]. Nakamura et al. who recommended direct hepatic vein anastomosis reported that metastatic liver tumors with special reference to the hepatic venous system of eight patients were treated in resection. Three of the eight patients died of recurrent carcinoma at 6, 30, and 48 months after operation, respectively. And five have remained alive and disease-free for 18, 30, 46, 67, and 79 months, respectively [5]. In the study of nine patients with colorectal liver metastases infiltrating the inferior vena cava or hepatic venous confluence treated by hepatectomy combined with inferior vena cava or hepatic venous confluence reconstruction as reported by Aoki et al. compared with the comparison group, patients in the inferior vena cava/hepatic venous confluence group had a shorter survival time [6]. In general, though long duration is needed, hepatic resection is credible for this kind of patients. However, as report goes, the operation tends to be followed by increased risks [7], such as sepsis, postoperative liver failure, and perioperative deaths. As a result, for the liver tumor patients, minimally invasive effective therapeutic options are indispensable for the improvement of prognosis [8].

7.1.1.2 Transcatheter Arterial Chemoembolization

Transcatheter arterial chemoembolization (TACE), a local and catheter-based minimally invasive therapeutic option, is effective for unresectable liver tumors. Through the selective administration of chemotherapy which usually combines with embolization of the vascular supply of the tumor, it will confine the growth of partial tumors efficiently and enlarge the lifetime of patients. Therefore, it is the first choice for liver cancer patients treated with palliative therapy and would be used in follow-up treatment for postoperative recurrence [8]. As a rather safe method, TACE is still accompanied by several complications, the most widely occurred one is a poor hepatic reserve with increased serum bilirubin levels. The total complication rate was about 9.1 %, and near 75 % of the patients had postembolization syndrome, such as fever, pain, or nausea [9]. If the indications were chosen inappropriately, the result of anticancer would be offset by chemotherapeutics and embolism. For patients whose liver function leveled as Child-C and with poor blood supply, the therapeutic effect of TACE was not satisfactory [8, 10]. In recent years, the application of TACE ablation in treating liver cancer becomes wider. Researches show that combina-

tion therapy with TACE and radiofrequency ablation is feasible and safe and increases the lifetime of patients validly [11]. Comparing with TACE treatment of liver tumors in safe site, there is no special technique of TACE in treating liver tumors adjacent to large vessels but no injury of endangium. Then, no researches were reported on liver tumors adjacent to large vessels treated by TACE so far.

7.1.1.3 Local Ablation Techniques

For patients with tumors adjacent to large vessels, local thermal ablation provides a feasible choice [12–16]. Radiofrequency ablation (RFA) and microwave ablation (MWA), as minimally invasive percutaneous local ablation techniques, have already been recommended as best choices for small HCC treatment [1, 12–14]. It is proved by an RFA cohort study that complete ablation of lesions smaller than 2 cm is curable in over 90 % of cases and the local recurrence rate is less than 1 % [17]. But some researches show that central tumors close to the hepatic hilum are unsuitable for percutaneous RFA as a result of possibly injuring adjacent bile ducts [18]. And for tumors adjacent to large vessels (≥3 mm), an essential inherent effect of heat-sink on thermal ablation would have a negative effect on the treatment result [19]. Laser ablation and cryoablation are also applied to treat liver tumor extensively [20, 21]. However, as yet, no researches were reported on liver tumors adjacent to large vessels treated by these two kinds of techniques.

7.2 Advantages of MWA

MWA, another kind of thermal ablation technique, also has its irreplaceable characteristics. MWA has its special features, such as higher intratumoral temperatures, larger ablation zones, less ablation time, and less dependence on the electrical conductivities of tissue. Hence, MWA treatment may be less influenced by heat-sink [22]. He Ren believes that MWA seems to be practicable and effective in treating liver tumors adjacent to the hepatic hilum. It is worth noting that although MWA has been widely used in liver cancer therapy [13], there are rarely authoritative clinical achievements on treating tumors adjacent to large vessels [23].

7.3 Indications

Liver tumor adjacent to large vessels is defined as tumors located less than 5 mm from large vessels (large vessels are defined as the first or second branch of the portal vein, the base of hepatic veins, or the inferior vena cava of which diameters being equal or bigger than 3 mm). All patients have to meet the following criteria: vessel injury can be avoided; the size of single nodular hepatic lesion is less than or equal to 5 cm; three or fewer multiple lesions, with a maximum dimension of 3 cm or less; to minish burthen of tumor, palliative ablation could be implemented as one part of systemic comprehensive treatment when the lesion size is more than 5 cm or the lesion number is more than three; there is no injury of endangium. Others are the same as for the general indications of liver cancer ablation.

7.4 MWA Procedure

The procedure is similar as previously reported. It is worth noting that appropriate overtime could reduce the effect of heat-sink and insure the ablation zone. And bile ducts should be protected and prevented from injury when the antenna is inserted in the tumors.

7.4.1 Thermal Monitoring During the Procedure

To continuously measure temperature in real time and make sure to reach the required temperature of the margin during the ablation of liver tumor, the microwave machine is also equipped with a thermal monitoring system. At the site of 5 mm away from the tumor margin adjacent to

large vessels, a 20-gauge thermocouple is inserted. Tumors are regarded as necrotic thoroughly if the measured temperature reached 60 or 54 °C lasting for over 3 min. The situation would not change except when the entire tumor is completely covered by the hyperechoic microbubbles under grayscale ultrasound. What is more, the temperature in the sites of bile ducts should be controlled below 50 °C, which can avoid bile duct injury.

7.5 Adjuvant Therapy with Small Dose of Ethanol Ablation

For the lesions adjacent to both large vessels and bile ducts, one to two 21-G PTC needles should be placed into the marginal tissue of the tumor proximal to the large vessels with ultrasound guidance. At the time of microwave emission, dehydrated sterile 99.5 % ethanol could be slowly injected into the margin of tumors (about 1 ml/min). And the quotas of ethanol injected are in accordance with the size and location of the tumor empirically. No more than 5 ml ethanol is injected for tumors less than 3 cm; 5–10 ml ethanol is injected for tumors larger than 3 cm. All ethanol ablations are planned before the ablation procedure.

7.6 Therapeutic Efficacy Assessment

Except for the routine examinations after MWA, these patients with liver tumor adjacent to large vessels could be examined more frequently than those with tumors in safe sites (more than 5 mm from the hepatic surface, large vessels, gallbladder, and gastrointestinal tract). Contrast-enhanced imaging such as contrast-enhanced ultrasound (CEUS) and computed tomography or magnetic resonance imaging should be performed in 1–3 days after the last ablation and the later at 3 months and then repeated every 6 months. And simultaneously, two kinds of imaging examinations should be suggested.

7.7 Clinical Efficacy of MWA

According to our latest study data, we evaluated the effectiveness and safety of MWA in 139 patients with 163 liver tumors adjacent to large vessels (diameter, 1.0–7.0 cm; mean, 2.5 ± 1.1 cm, Group L), as compared with 313 patients with 442 lesions (diameter, 1.0–8.0 cm; mean, 2.5 ± 1.2 cm, Group C) located more than 5 mm away from the hepatic surface and large vessels. The median follow-up time was 24.5 months (range 2.1–87.7 months) in Group L and 25.7 months (range 1.6–93.9 months) in Group C. Technical effectiveness was achieved in 157 of 163 (96.3 %) tumors in Group L and 429 of 442 (97.1 %) tumors in Group C, respectively ($p > 0.05$). The 1-, 3-, and 5-year local tumor progression rates and the 1-, 3-, and 5-year accumulative survival rates in the two groups have no significant statistical differences.

The treatment effectiveness of MWA in liver tumors adjacent to large vessels in our study was very encouraging. No significant differences were found between the large vessel group and control group in ablation sessions, local tumor, and survival aspects. These results show that MWA treatment of liver tumors adjacent to large vessels is not influenced markedly by heat-sink effect. And, compared with the results in other researches on RFA for liver tumors (Table 7.1), the technical effectiveness rate is higher and the local tumor progression rate is lower [24–26].

Technical points are as follows: (1) Theoretical merits of MWA make it produce higher intratumoral temperatures, larger ablation zones, less ablation time, and less dependence on the electrical conductivities of tissue consistently. Also, the energy delivery is less controlled by the exponentially rising electrical impedance of tumor tissue. (2) According to our experience, long-duration ablation (about 1 min more than the ablation time of tumors in safe sites) may cause gradual ablation of the tumors adjacent to large vessels and compensate the defect from heat-sink effect in the large vessels. (3) After the first procedure, contrast-enhanced imaging (CEUS, computed tomography, or magnetic resonance imaging) should be performed in time in the fol-

Table 7.1 Treatment results of patients with liver tumors adjacent to large vessels

Author	No. of patients/ nodules	Tumor size (cm)	Treatment	Median operating times (mins)	Technical effectiveness (%)	Total/local recurrence (%)	Median survival time (mons)	Survival rate (%)			Complications (%)	Follow-up (months)
								1-	3-	5-year		
Yamamoto et al. [4]	7/7	N/A	Hepatic resection	890	N/A	85.7/N/A	39	N/A	N/A	57.1	42.9	118
Aoki et al. [6]	9/9	3.2	Hepatic resection	600	N/A	88.9/N/A	25.8	N/A	N/A	N/A	66.7	N/A
Hemming et al. [7]	16/16	N/A	Hepatic resection	N/A	N/A	N/A	N/A	88	50	N/A	36	22
Teratani et al. [28]	81/81	2.7	RFA	34	N/A	N/A/3.1	N/A	N/A	N/A	N/A	4.8	N/A
Lu et al. [29]	N/A/31	2.4	RFA	N/A	52	N/A/14.3	N/A	N/A	N/A	N/A	6.4	11.3
Ren et al. [32]	18/18	2.8	MWA	N/A	94.4	N/A/5.6	N/A	100	N/A	N/A	5.6	15
Huang Shijia [33]	139/163	2.5	MWA	10.4	96.3	N/A/13.5	N/A	94	72	64	14.4	24.5

RFA radiofrequency ablation, *MWA* microwave ablation, *N/A* not available

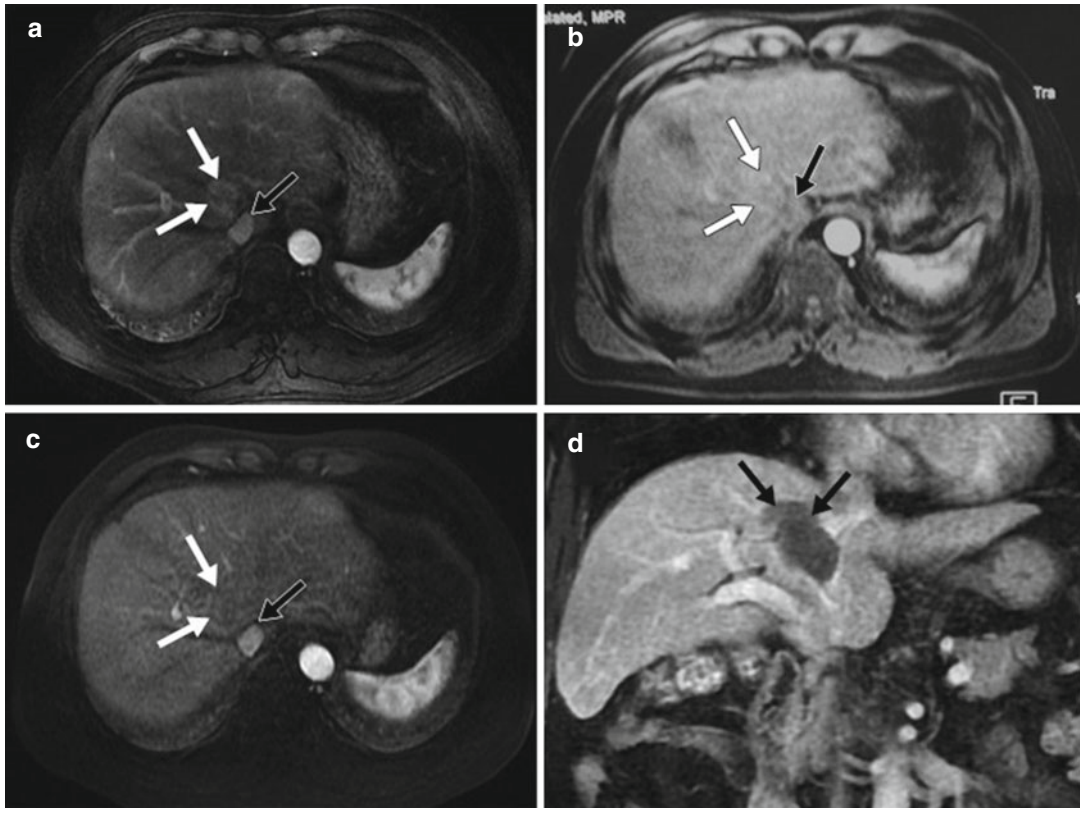

Fig. 7.1 Contrast-enhanced magnetic resonance imaging (*MRI*) of a 48-year-old man shows a 4.1 × 3.4 cm nodule of hepatocellular carcinoma (*HCC*) adjacent to the inferior vena cava (*black arrows* in **b** and **c**) treated by microwave ablation (*MWA*). (**a**) Preablation image shows one neoplasm (*white arrows*) adjacent to the inferior vena cava (*black arrow*). (**b**) On the arterial phase image obtained in the 12th month after treatment, no enhancement is seen in the ablation zone (*white arrows*). (**c**) Transverse and (**d**) coronal images show that there remains no enhancement of the ablation zone (*white arrows* in **c** and *black arrows* in **d**) in the 36 months after treatment

lowing 3 days to examine whether any residual cancer still have not been eliminated. Consequently, a second session will be determined to achieve complete ablation. (4) With MWA emission, ethanol ablation should be performed at the same time for tumors adjacent to both large vessels and bile ducts. The purpose of the procedures is to wipe out the tumor tissue adjacent to the biliary duct and blood vessel and to avoid the overheating injury to those vital tissues by means of increasing thermal conduction and diffusivity [27]. (5) Real-time peritumoral temperature monitoring should be used as an indicator for complete MWA. (6) Rich experience in detailed treatment protocol, accurate image guiding, and proper placement of antennas contribute a lot for the success of the treatment (Figs. 7.1 and 7.2) [33].

7.8 Complications

Side effects of MWA for liver tumors include slight pain, mild bleeding, and slight fever after ablation. According to our research, no immediate or periprocedural major complications and no delayed complication of vessel or bile duct injury were found in both groups. One patient in Group L (0.7 %) was diagnosed with thrombosis by CEUS in the right portal vein and the central part of the left portal vein (lengths of thrombosis: 3 mm, 2.5 mm) in the second month after

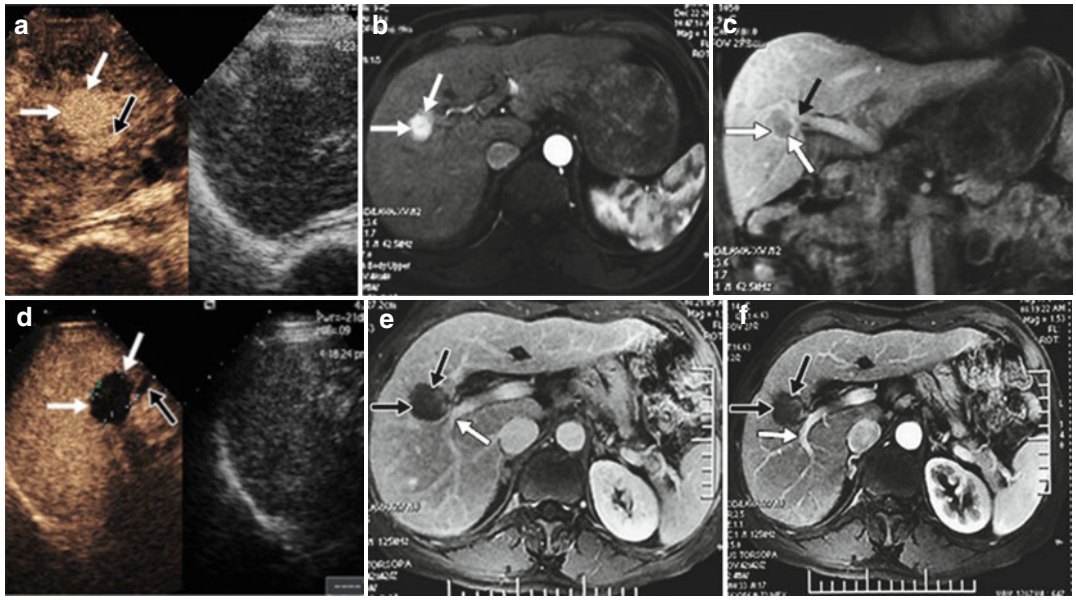

Fig. 7.2 Contrast-enhanced images show a 3.3×2.3 cm HCC nodule adjacent to the right portal vein (*white arrows* in **e** and **f**) in the liver of a 63-year-old man treated with MWA. (**a**) Preoperative contrast-enhanced ultrasound (*CEUS*) and (**b**) transverse and (**c**) coronal preoperative MRI show that there is one HCC nodule (*white arrows*) with hyperenhancement during the arterial phase of CEUS, with high signal during the arterial phase of MRI and with low signal during the portal phase of MRI. The lesion is in front of the right portal vein (*black arrow*). (**d**) After one session, the nodule (*white arrows*) which is close to the blood vessel (*black arrow*) was completely ablated. (**e**) On the arterial phase image obtained in 12 months after treatment, no enhancement is seen in the ablation zone (*black arrows*). And (**f**) the arterial phase image shows that there remains no enhancement of the ablation zone (*black arrows*) in 24 months after treatment

treatment, which disappeared 3 months later without any management. And blood coagulation effected by heat may be the main cause. Two cases of tumor seeding were found in Group L (2/139, 1.4 %, at 9 and 12 months) and Group C (2/313, 0.6 %, at 7 and 13 months), respectively. Teratani et al. performed RFA for liver tumors adjacent to large vessels, and bile duct injury was observed in 6 (7.6 %) of 79 cases [28]. And Lu et al. put RFA into the practice of that kind of tumors as well. Abscess and perihepatic hematoma, the two major complications, were discovered in 2 of 31 patients [29]. Meloni et al. performed MWA in an in vivo porcine model, and diffuse endothelial damage of the portal vein was found in 3 of 21 (14 %) cases [30]. Yu et al. reported that seven Yorkshire pigs underwent percutaneous or open microwave liver ablation, and in 103 sections – 29 of 37 (78 %) small, 27 of 48 (56 %) medium, and 7 of 18 (39 %) large veins – the thermal injury of the vein wall and two thrombosed veins were observed [31].

Because of the tumor sites adjacent to the large vessels and some close to the bile ducts, protecting against thrombosis and vessel and bile duct injury is necessary.

7.9 Conclusion and Prospect

Percutaneous image-guided thermal ablation has been recognized as an effective technique in the treatment of liver tumors adjacent to large vessels. According to the reports, the potential risk of vessel and bile duct injury may be lower because of the lower thermal efficiency of RFA. However, MWA could provide larger ablation zones and higher intratumoral temperatures, and the protection of the vessels and bile ducts

should be noticed. The percutaneous MWA approach with exciting therapeutic effects is practicable to nodules adjacent to large vessels. And protecting against thrombosis, bile duct injury, and other complications is necessary.

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Microwave Ablation Therapy of Malignant Liver Tumors Adjacent to the Gallbladder

8

Hui Huang, Jie Yu, and Ping Liang

Abstract

Local ablation has been an important therapy for malignant liver tumors for satisfactory therapeutic effects. The malignant liver tumors adjacent to the gallbladder are considered to be one of the most dangerous and special position tumors. This chapter's objective is to evaluate the current situation and progress of MWA and other kinds of local ablation therapy in terms of its principles, indications, therapeutic effects, complications, contraindications, and pros and cons of various ablation therapies for malignant liver tumors adjacent to the gallbladder.

Keywords

Microwave • Radiofrequency • Ablation • Hepatocellular carcinoma

Abbreviations and Acronyms

CT	Computed tomography
HCC	Hepatocellular carcinoma
LC	Laparoscopic cholecystectomy
LUS	Laparoscopic ultrasound
MRI	Magnetic resonance imaging
MWA	Microwave ablation
PTC	Percutaneous transhepatic cholangiography
RFA	Radiofrequency ablation
TACE	Transcatheter arterial chemoembolization
US	Ultrasound

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8.1 Introduction

Local thermal ablation as a minimally invasive technique has been widely used for the treatment of primary and metastatic liver cancer in the past decade. Thermal ablation methods such as microwave ablation (MWA) and radiofrequency ablation (RFA) have good efficacy and low complication rates in the liver [1–7]. However, collateral thermal damage of adjacent extrahepatic organs can occur when treating subcapsular tumors. The gallbladder is at risk for potential thermal damage which would lead to perforation or acute cholecystitis after ablation [8, 9].

Ethanol ablation therapy, which once was widely used as an effective and less invasive treatment for small hepatocellular carcinoma HCC [10, 11], is now substituted by other thermal

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ablations with the use of different energy sources in large liver cancers, such as radiofrequency and microwave [8, 9, 11–14]. However, MWA therapy combined with ethanol ablation could coagulate significantly larger volumes of liver tumor and improve the rate of complete necrosis [15].

There are two minimally invasive ablation approaches for malignant liver tumors adjacent to the gallbladder. Percutaneous approach and laparoscopic approach. But there are only few reports of tumors adjacent to the gallbladder. This chapter's objective is to evaluate the current situation and progress of MWA in terms of its principles, indications, therapeutic effects, complications, contraindications, and pros and cons of various ablation therapies for malignant liver tumors adjacent to the gallbladder.

8.2 MWA

8.2.1 The Criteria for MWA

The criteria for MWA are as follows: tumor accessible via a safely route if percutaneous approach, nodular HCC lesions is of 5 cm in diameter or smaller, tumors are adjacent to the gallbladder even oppressed to gallbladder but not involved to the mucosa of gallbladder. Other criteria are the same as those depicted in previous chapters.

8.2.2 Technique

The MWA system is the same with that described in previous chapters.

In general, for tumors less than 2 cm in diameter, a single antenna is used; for tumors 2 cm or larger, multiple antennas are required. The tip of the antenna is at least 3 mm away from the gallbladder, and the body of the antenna is at least 5 mm away from the gallbladder according to the antenna's thermal field effect. One or two 21-gauge ethanol needles are inserted and placed at the tumor periphery close to the gallbladder. A 20-gauge thermocouple is inserted proximal to the gallbladder, allowing real-time temperature monitoring during MWA and prevention of thermal-mediated gallbladder injury.

Power was applied from 40 W and is increased to the maximum level 50–60 W if the patient could tolerate the procedure with stable vital signs. To avoid thermal injury to the gallbladder during tumor ablation, the temperature proximal to the gallbladder is monitored by one or two 21-G thermal monitoring needles (Kangyou Medical, China) throughout the procedure. If the temperature measured by the thermocouple reached 56 °C, MW emission stops immediately and restarts when the temperature becomes lower than 45 °C. The total time of ablation is estimated to be about 300 s, and this is continued until the entire tumor is completely covered by the hyperechoic microbubbles on grayscale US. For tumors larger than 30 mm, antennas were first inserted into the deeper region of the lesions. If the hyperechoic region covered the deeper region of the lesion on US after a series of microwave emission, antennas were withdrawn 5–10 mm and microwave emission was restarted and stopped until the hyperechoic region covered the lesion along the axis of antennas, and/or antennas were reinserted to the non-ablation tumor zone for another ablation (Fig. 8.1). Other technique details are the same as those in safely located liver tumors.

Dehydrated, sterile, 99.5 % ethanol is injected into the tumor very slowly (approximately 1 mL per min) by assistants through one to two 21-G PTC needles at exactly the same time as microwave emission to enlarge the coagulation zone proximal to the gallbladder by diffusion of ethanol. The amount of absolute ethanol injected is determined according to the size and location of the tumor empirically with a gross dose of 5–10 ml. The diffusion of ethanol is also monitored on grayscale US to avoid injecting ethanol into vessels or the gallbladder. All ethanol injections are planned beforehand.

Percutaneous MWA combined with ethanol ablation is performed at the same treatment time. Ethanol is injected slowly during the ablation when microwave emitting. This will enlarge the coagulation zone by the diffusion of hot ethanol.

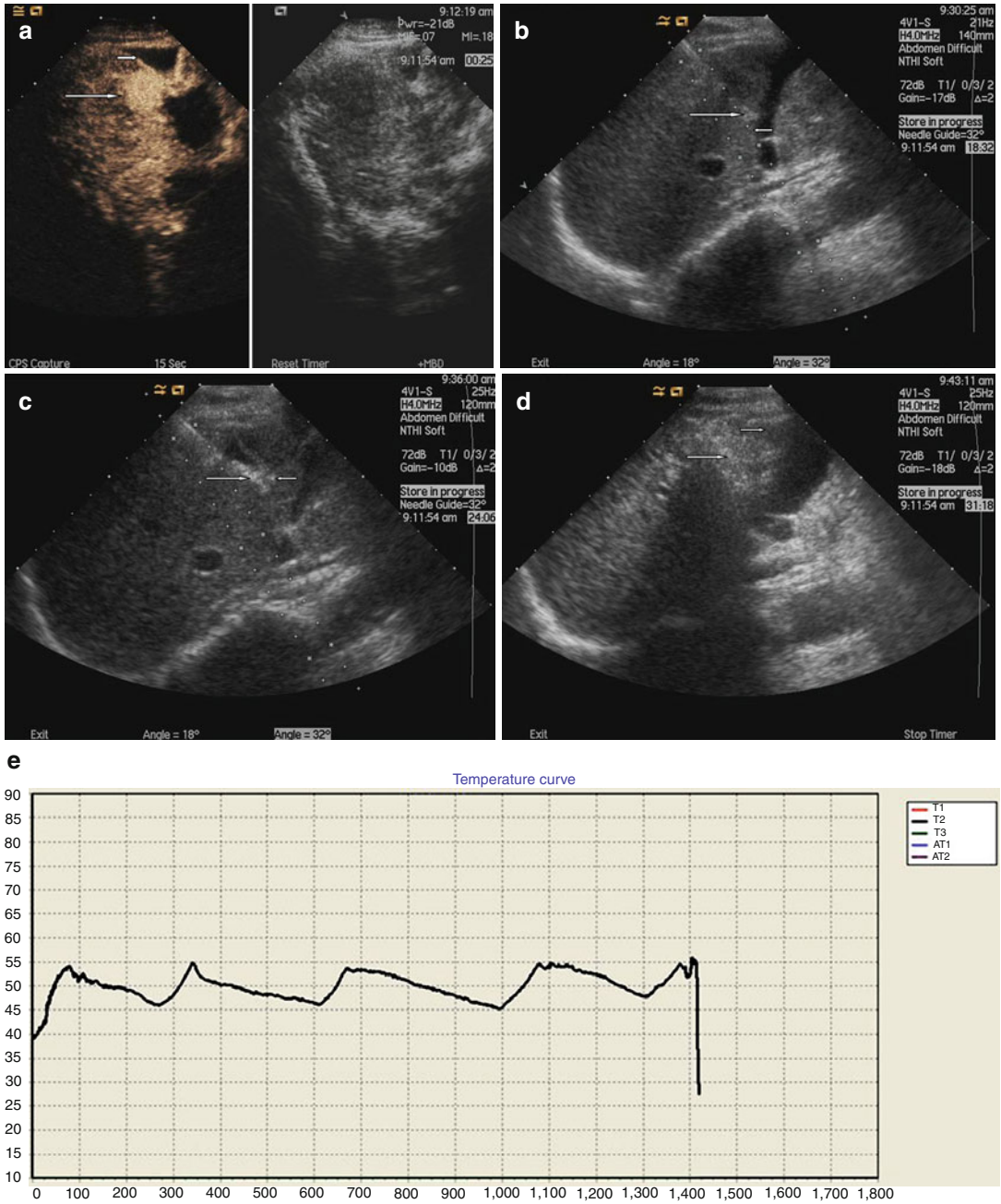

Fig. 8.1 Microwave ablation (MWA) in a 64-year-old man with hepatocellular carcinoma (HCC) adjacent to the gallbladder. The tumor size is 2.4 × 2.1 × 1.9 cm. The distance between the gallbladder and tumor is about 1 mm. (**a**) Preablation contrast-enhanced ultrasound scan (CEUS) shows an HCC lesion (*long arrow*) located adjacent to the gallbladder (*short arrow*). (**b**) A 21-G thermal monitoring needle (*long arrow*) is inserted to the wall of the gallbladder; the tumor (*short arrow*) is adjacent to the gallbladder. (**c**) A 15-G microwave antenna (*long arrow*) gives out emission, while thermal monitoring needle (*short arrow*) is used throughout the ablation procedure. (**d**) A hyperechoic region (*long arrow*) covers the lesion along the axis of antennas, gallbladder (*short arrow*). (**e**) The temperature is measured by the thermocouple. If the temperature reaches 56 °C, microwave emission stops immediately and restarts when the temperature becomes lower than 45 °C. (**f**) CEUS shows that the tumor adjacent to the gallbladder is still incompletely ablated (*long arrow*) 3 days after the first session, and then the second MWA session is performed under CEUS guidance. (**g**) Magnetic resonance imaging (artery phase) shows that the tumor area (*long arrow*) is totally ablated by microwave (at 1 day after the second session), without injury of the gallbladder (*short arrow*)

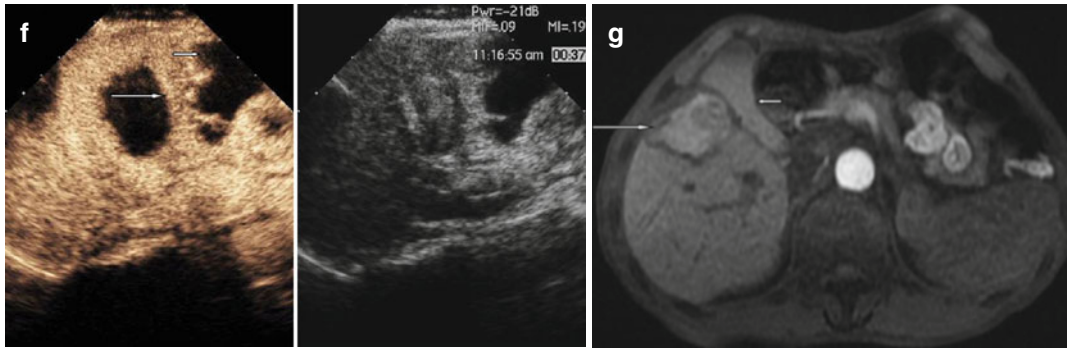

Fig. 8.1 (continued)

8.2.3 Clinical Effect

From January 2005 to December 2012, 160 patients with 162 malignant liver tumors adjacent to the gallbladder underwent percutaneous MWA in our hospital. The patient population included 121 men and 39 women (age range, 30–86 years; mean age, 59.6 years). The maximum diameter of the tumors ranged 2.88 ± 1.39 cm × 241±1.31 cm. Eighty-four tumors were located <0.5 cm from the gallbladder and 78 tumors were located 0.6–1.0 cm from the gallbladder. There are 150 patients with primary liver cancer and 10 with metastatic tumors. All patients were successfully treated. There were no treatment-related deaths and no major complications such as cholecystitis or gallbladder perforation in the patients. Complete ablation was achieved in 96.9 % (157/162). During a median follow up of 15 months (range 4 to 27 months), 29(17.9%, 29/162) patients died of progression of primary disease. Among them, four patients grew liver metastases and lost effective treatment. The tumor recurred in local site in five patients; two patients were treated by ethanol ablation and the other three patients by partial hepatectomy, transcatheter arterial chemoembolization, and liver transplantation therapy. Among the five patients, three patients died of tumor progression and two patients died of cardiopulmonary diseases.

The ablation zone was well defined on contrast-enhanced CT/MRI and contrast-enhanced US and shrank gradually over time (Figs. 8.2 and 8.3).

Fang et al. reported 27 hepatic tumors were treated with laparoscopic cholecystectomy (LC) and 16 patients were treated with laparoscopy-assisted MWA [16]. Eighteen lesions were identified to be close to the gallbladder. Laparoscopic cholecystectomy (LC) was first performed. MWA was guided by LC and LUS. The power was 60 W and the time of the therapy was 6–7 min. Complete ablation was achieved in 25 lesions and incomplete ablation in two lesions. There was no mortality in this group. Fang argued that laparoscopic ultrasound (LUS) made a more complete scan to detect the tumors than ultrasound did, and the bleeding in needle ways was easy to control under laparoscopy.

The above reports presented two different kinds of approaches with relatively large cases.

However, the gallbladder wall is incrassate and more collateral circulation can be found in severe liver cirrhosis. Although the thick gallbladder wall can provide more ablation area, collateral circulation would result to massive hemorrhage and would not be helpful in the isolation or resection [17].

8.2.4 Complication

Major complications of thermal ablation to malignant liver tumors adjacent to the gallbladder may include acute cholecystitis or gallbladder perforation, which is different to those in

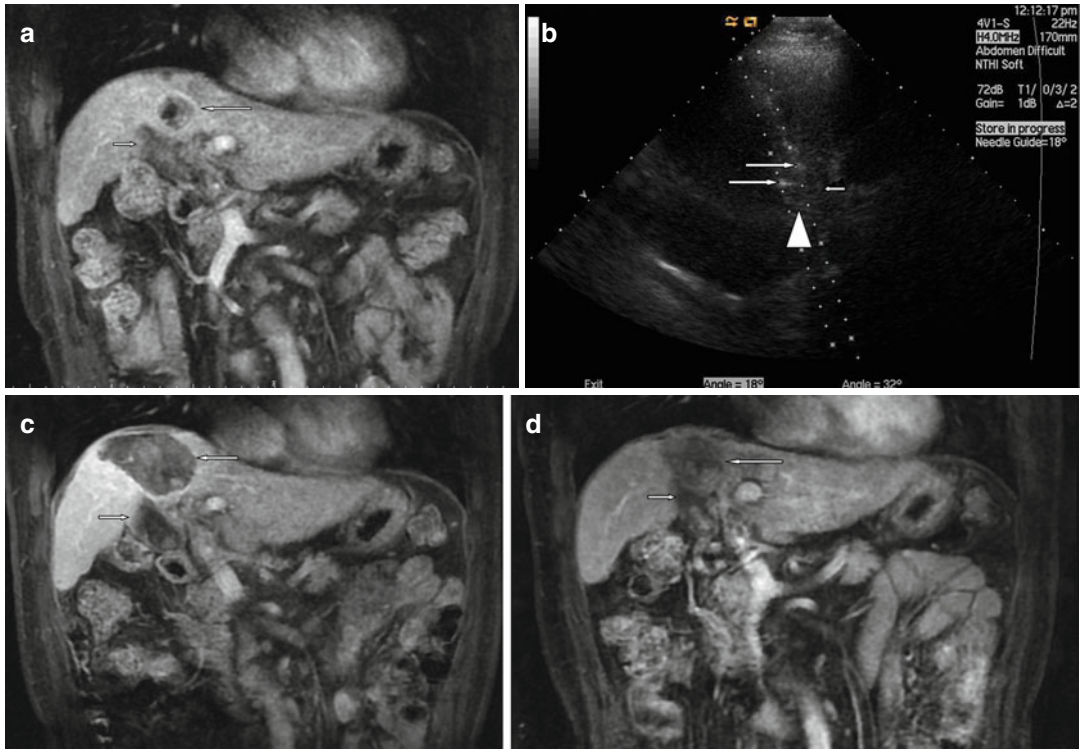

Fig. 8.2 MWA in a 77-year-old man with HCC adjacent to the gallbladder. The tumor size is 3.1×3.0×3.0 cm. The distance between the gallbladder and tumor is 3 mm. (**a**) Preablation MRI scan shows an HCC lesion (*long arrow*) located adjacent to the gallbladder (*short arrow*). (**b**) Conventional ultrasound shows that two microwave antennas (*long arrow*) are placed in the tumor (*triangle arrow*) and one temperature monitor (*short arrow*) is placed at the tumor margin during the WMA procedure. (**c**) MRI (coronal section) shows the tumor area (*long arrow*) totally ablated by microwave (at 1 month after treatment), without injury to the gallbladder (*short arrow*). (**d**) MRI (coronal section) shows the tumor area totally ablated by microwave (at 1 year after treatment). The ablation area (*long arrow*) shrinks obviously, without injury of the gallbladder (*short arrow*)

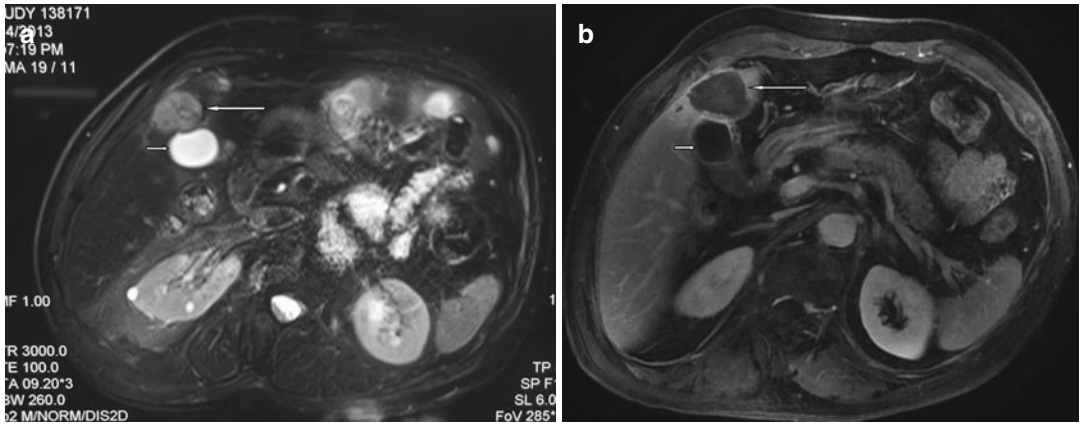

Fig. 8.3 MWA in another 73-year-old man with HCC adjacent to the gallbladder. (**a**) The tumor size is 4.3×3.8×3.4 cm. The distance between the gallbladder and tumor is 2 mm. Preablation MRI (T2 phase) scan shows an HCC lesion (*long arrow*) located adjacent to the gallbladder (*short arrow*). (**b**) MRI (portal phase) shows tumor area totally ablated by microwave (at 3 months after ablation). The margin of the ablated area (*long arrow*) is the wall of the gallbladder (*short arrow*)

other area [14]. But there are no acute cholecystitis and perforation that appeared in our hospital and in Fang's report. Thickening of the gallbladder wall, which is not accompanied with acute cholecystitis, was noted 1–3 days after MWA in 51 (31.5 %) patients. The thickness of the gallbladder wall ranged from 3 to 8 mm. There are 39 cases of thickening of the gallbladder wall in the group of tumors located within 0.5 cm of the gallbladder and 12 in the group of tumors located within 0.6–1.0 cm of the gallbladder.

Minor complications are fever, pain, right-side pleural effusion, and nausea like other MWA treatments. After treatment in our hospital, 24 patients experienced grade 1–3 pain at the puncture site according to the standardization of terms and reporting criteria for image-guided tumor ablation [18]. Severe abdominal pain that required the administration of analgesics was noted in ten patients. Thirty-two patients had a fever of 37.5–39.8 °C which persisted for 1–5 days, and nausea occurred in 76 patients. Right-side pleural effusion occurred in seven patients. In Fang's report, six patients had right upper abdominal pain or precordial region pain, and nine patients had fever. One patient had 480 ml of bloody fluid in the first day, and two patients had mild to moderate dose of ascitic fluid.

8.3 Other Kinds of Ablation and Approach

The most ablation treatments are performed by ultrasound imaging guidance approach. The mainly ablation techniques are focus on MWA, RFA and ethanol ablation, while there are a few reports in laser ablation, high intensity focus ultrasound (HIFU) and cryoablation.

Other imaging-guided approaches include CT, MR, or ultrasound guidance. However, because of the specificity of the gallbladder, which makes the organ easier to detect and observe under ultrasound, and because the gallbladder is a cavity visceral organ, which easily leads to inflammation and perforation, most ablations to malignant liver tumors adjacent to the gallbladder are performed under an ultrasound guide which could be a real-time monitor and make the puncture procedure accurate to avoid gallbladder damage.

The venture of this approach needs more reports. The venture of this approach needed more reports. The cost is higher than the imaging-guided percutaneous approach and the patients are under carbon dioxide pneumoperitoneum.

8.3.1 RFA

Local RFA of liver tumors adjacent to the gallbladder is a feasible and safe procedure, which is first reported by Chopra et al. [19]. More investigators come to the same conclusion regarding with the feasibility and safety of RFA in liver tumors adjacent to gallbladder [20–22].

Sang et al. reports 45 patients with 46 HCC (mean size, 2.2 cm) adjacent to the gallbladder (1.0 cm) treated with RFA using an internally cooled electrode system [20]. The article is the major report of RFA for tumors adjacent to the gallbladder. An electrode was inserted into the tumor either parallel ($n=38$) or perpendicular ($n=8$) to the gallbladder wall. All procedures were performed under real-time sonographic guidance. The mean time for application of RFA was 12 min (range, 6–15 min). There were no major complications such as cholecystitis or gallbladder perforation in the patient population. Three minor complications were noted: one case of vasovagal syncope and two cases of bilomas. Eight patients complained of severe pain, and pain was controlled with analgesic. Eight patients presented with low-grade fever. Nausea occurred in three patients. Right-side pleural effusion occurred in one patient. Focal wall thickening of the gallbladder adjacent to the RFA zone was noted in 14 cases. Four cases had residual tumors noted which abutted the gallbladder. Two residual unablated tumors were treated again with a second session of RFA, and no residual unablated tumor was seen on 1-month follow-up. Six tumors showed local tumor progression as seen on late follow-up. They drew a conclusion that

the direction of electrode insertion (perpendicular), tumor size (>3 cm), and tumor location (a tumor that abutted the gallbladder) were associated with an increased risk of early incomplete treatment, and RFA of an HCC adjacent to the gallbladder can be performed safely and effectively with proper selection of patients and electrode direction.

Jiang et al. reported five cases of HCC adjacent to gallbladder in different location were performed by Laparoscopy-assisted RFA without isolation or resection of gallbladder [23]. The tumor diameter ranged from 2.5 to 4.2 cm. The power of RFA began with 90 W for 10 min and a maximum of up to 200 w. If the air bubble flows to the gallbladder, the aspirator represses the vessel to decrease the river-flow effect. Ultrasound examination showed that the gallbladder wall close to the ablated area was increased by 0.3–0.4 cm, and the CT images showed that the density of the gallbladder wall was increased 3 days after the operation. The gallbladder was intact and no high-density area was observed in all patients 6 months after the operation. All cases were treated under general anesthesia. Jiang made a conclusion that laparoscopy-assisted one-stage RFA for HCC adjoining the gallbladder with maintenance of the anatomical integrity of the gallbladder was technically safe and feasible. Even if the wall of gallbladder was completely necrosis under ablation, bile would not inflow into enterocoelia, if the gallbladder wall kept intact.

There are only a few reports about CT or MR guidance. Ishizaka et al. reported the use of a two-step coaxial system with a fine guide needle wire unit in liver tumor ablation in high-risk location under CT-guided radiofrequency [24]: the two-step approach involves a 21-gauge pencil-tip guide needle wire (GNW) unit comprising a 150-mm-long needle segment and a 250-mm-long wire segment, and a 140-mm-long outer cannula with its stylet, which accepts a 17-gauge RF electrode needle. The GNW was inserted until the route of the GNW was confirmed to be positioned correctly. The cannula with the stylet was then advanced along the GNW. Lesions were successfully accessed using the GNW, and manipulation was feasible within the limited space of the CT gantry. The light GNW also facilitated step-by-step CT-guided angular manipulations. Therefore, this system enabled sequential ablations of large tumors by ensuring three different routes in advance by using the GNW. The insertion of the cannula along the GNW was simple. The two-step coaxial system enabled the CT-guided RF tumor ablation to be performed in cases conventionally contraindicated owing to a high risk of serious complications. CT- or MR- guided ablation needs two or more examinations and is not the real-time surveillance.

8.3.2 Ethanol Ablation

Ethanol ablation has been widely used since the late twentieth century [25–27]. Because it is dangerous to apply MWA or RFA to tumors located near bile ducts, the gallbladder, and the diaphragm, ethanol ablation is relatively feasible, efficacious, and very safe for these dangerously located tumors.

Soo et al. reported three cases of well-differentiated HCC smaller than 15 mm in diameter totally eradicated with pure ethanol ablation instead of RFA in special position [28]. One nodule was in segment 2 (near bile ducts, 10 mm in size), one in segment 5 (near the gallbladder, 15 mm in size), and one in segment 7 (near the diaphragm, 15 mm in size). Ethanol ablation was administered by injections of 99 % sterile ethyl alcohol (total 10.4 ml, 15.5 ml, and 48 ml for each nodule, respectively) to the nodule with a multiple side-hole 21-gauge needle. After that, contrast-enhanced CT revealed complete necrosis of the nodule during an 18-month follow-up.

8.4 Discussion

In the past two decades, local thermal ablation has become more widely accepted in the therapy of liver tumors. However, tumors near special areas such as the hepatic hilum, large vessels,

gastrointestinal tract, bile duct, gallbladder, and diaphragm are difficult to treat completely [11, 14, 19, 21, 22]. Thermal ablation for these tumors may result in incomplete necrosis or collateral thermal damage to adjacent organs. Therefore, special precautions and strategies are needed to treat tumors in these dangerous locations.

Firstly, thermal ablation combines with chemical ablation. The combination of RFA or MWA and ethanol ablation in the management of HCC in high-risk locations was more effective than RFA or MWA alone in some reports [15, 29]. MWA therapy combined with ethanol ablation could coagulate significantly larger volumes of liver tumor and improve the rate of complete necrosis, and ethanol is injected adjacent to the gallbladder to reduce gallbladder thermal damage and supply an extra chemical ablation in order to expand the ablation area. Secondly, temperature monitoring is controlled in the whole thermal ablation procedure. Ablation to the tumors adjacent to the gallbladder is always accompanied with the risk of gallbladder perforation or acute cholecystitis. The main reason for thermal damage is temperature over the threshold of coagulation. Temperature can be used as a reliable indicator to reflect the pathologic changes of MWA in liver cancers. A real-time peritumoral temperature monitoring can be used as an indicator for avoiding thermal injury. The protected temperature monitoring technique avoids injury brought by the high temperature of MWA to reduce acute cholecystitis or gallbladder perforation. Thirdly, radiotherapy or radioactive seed implantation is combined with thermal ablation for the unablated area. They are the additional therapy measurements for those with uncompleted ablation lesions or residue tumors. Lastly, saline is injected into the wall of the gallbladder or directly to the gallbladder cavity in order to reduce thermal injury in the gallbladder wall. Saline injection can thicken the wall of the gallbladder in order to reduce the damage of thermal ablation.

Conclusion

In conclusion, MWA combined with ethanol injection and temperature monitoring is a safe and effective treatment option for malignant liver tumors adjacent to the gallbladder.

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Microwave Ablation for Malignant Liver Tumors Adjacent to the Hepatic Hilum

9

He Ren, Wenjia Cai, and Ping Liang

Abstract

Thermal ablation, such as radiofrequency ablation, microwave ablation, high-intensity focused ultrasound, and laser ablation, has been widely applied for the management of malignant liver tumors, owing to its advantages of minimal invasion, favorable efficacy, and reproducibility. However, thermal ablation has been generally considered to be unsuitable for tumors adjacent to the hepatic hilum for fear of the thermal-mediated biliary injury such as bile duct stricture and fistula formation. In recent years, with the improvement of equipment device and technique development, more investigators have begun to investigate the feasibility, safety, and efficacy of local thermal ablation of liver tumors adjacent to the hepatic hilum. In this chapter, we focus on the microwave ablation technique, including the equipment, indications, patient preparation, procedures, clinical results, and complications in the treatment of malignant liver tumors adjacent to the hepatic hilum, and other thermal ablation techniques (radiofrequency ablation, high-intensity focused ultrasound, and laser ablation) are also introduced.

Keywords

Malignant liver tumors • Hepatic hilum • Microwave ablation • Radiofrequency ablation • High-intensity focused ultrasound • Laser ablation

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9.1 Introduction

The treatment for patients with tumors adjacent to the hepatic hilum is difficult. Conventional surgical resection can be challenging or technically impossible. In the past decade, local thermal ablation, such as radiofrequency, microwave ablation, high-intensity focused ultrasound, and laser ablation, has gained great popularity in the treatment of malignant liver tumors as a minimally invasive, safe, and effective treatment option [1–4]. However, thermal ablation has been generally considered to be unsuitable for tumors adjacent to the hepatic hilum for fear of thermal-mediated biliary injury such as bile duct stricture and fistula formation [5–15]. In recent years, more efforts have been made to gain complete necrosis and decrease the bile duct complications by adjusting the technical parameters and ablation time, using the thermal monitoring system, and combining multiple techniques.

9.2 Microwave Ablation Equipment

The microwave ablation equipment is the same as that of previous chapters.

9.3 Preprocedure Evaluation

All patients have to meet the following criteria: the percutaneous approach is accessible to the tumors adjacent to the hepatic hilum; the size of a single nodular lesion is less than or equal to 5 cm; each multiple nodular hepatic lesion, each of, is with a maximum dimension of 4 cm lesion; and no portal vein embolus and invasion to the bile ducts. Others are the same as the general indications of malignant liver tumor ablation.

Before operation, the location of tumors and the absence of portal vein and bile duct thrombosis are evaluated by contrast-enhanced ultrasound (CEUS), computed tomography (CT), or magnetic resonance imaging (MRI). The maximum diameter of nodules is measured by CEUS. The absence of extrahepatic metastases was determined by means of a thorough clinical assessment, chest radiography, abdominal ultrasound, and abdominal CT or MRI or position-emission tomography (PET).

9.4 Microwave Ablation Procedures

Patients are laid in the supine or oblique position in the interventional ultrasound suite. The safest needle route is chosen by color Doppler and grayscale ultrasound. Before inserting the antennae, local anesthesia is induced first with 1 % lidocaine from the insertion point on the skin to the peritoneum along the ultrasound-guided puncture line. Then, the skin is pricked with a small lancet, and the antenna is introduced into the designated area of the tumor. In the multiple-needle procedure, two or three active needle antennae are inserted into the tumor in parallel 1–2.5 cm apart under ultrasound guidance. The antenna is inserted to the part adjacent to the hepatic hilum first with a distance of at least 0.5 cm away from the hepatic hilum, the tip of the antenna is placed in the deepest part of the tumor, and then multiple thermal lesions can be created along the major axis of the needle antenna by simply withdrawing the needle from the preceding thermal lesion. One or two 21-gauge percutaneous transhepatic cholangiography (PTC) needles are inserted and placed at the tumor periphery close to the hepatic hilum. One or two thermocouples are introduced adjacent to the hilar bile duct closest to the tumor through an 18-G, 70-mm-long, nonconducting needle trocar, allowing real-time temperature monitoring during MWA and prevention of thermal-mediated bile duct injury. To complete the insertion, breathing cooperation from the patient is required. After all the insertions, venous conscious analgesia–sedation is induced with propofol and ketamine associated with standard hemodynamic monitoring. The microwave generator is then reactivated. A power output of 45–50 W for 200–700 s is used during MWA to gain conformal ablation of the tumor. Temperatures measured by the thermocouple are

kept at less than 54 °C for no more than 3 min, with intermittent emission of microwaves. If the temperature reaches 54 °C, microwave emission is stopped immediately and is restarted when the temperature becomes lower than 45 °C. This continues until the entire tumor is completely covered by the expanding hyperechoic area on grayscale ultrasound. Dehydrated sterile 99.5 % ethanol is injected into the tumor very slowly (approximate 1 ml per min) by assistants at the same time as microwave emission to enlarge the coagulation zone by diffusion of hot ethanol. The amount of ethanol injected is determined according to the size of the tumor empirically. For tumors less than 3 cm, no more than 5 ml ethanol is injected; for tumors larger than 3 cm, 5–10 ml ethanol is injected. All ethanol injections are planned before the ablation procedure. After MWA of the tumor, the antennae are gradually withdrawn, and microwave emission is continued until the antennae are pulled to just below the skin entrance site. This method allows needle track cauterization to prevent bleeding and tumor-cell seeding and helps prevent potential skin burn [15–17]. CEUS is performed for immediate assessment of technical success 10–15 min after MWA. If the foci of nodular enhancement in the treated tumor are observed, a new session with an identical device is performed as part of another course of treatment [18].

9.5 Follow-Up Protocol

The follow-up protocol is the same as that of the previous chapter.

9.6 Clinical Efficacy

MWA of malignant liver tumors adjacent to the hepatic hilum is included in some studies as a part of the treatment protocol, and there are no special result analyses for the tumor at this location, so the ablation efficacy could not be determined accurately.

To our knowledge, the study of Dr. Ren et al. is the only MWA report that has been focused exclusively on malignant liver tumors adjacent to the hepatic hilum [16]. According to this study, MWA was performed on 18 malignant liver tumors adjacent to the hepatic hilum, including 15 HCCs and three liver metastases (two from the colon, one from the ovary). Complete ablation was achieved in 94.4 % (17/18) (Figs. 9.1 and 9.2). During a median follow-up of 15 months (range 4–27 months, mean 13.5 months), there was no mortality. Residual tumor was detected in CEUS and MRI 1 month after treatment in one patient. Local tumor progression was noted in one patient 12 months after treatment and partial hepatectomy was performed. On the basis of previous study, we continued to gather more experience; 32 consecutive patients with 32 pathologically proven or clinically diagnosed malignant liver tumors adjacent to the hepatic hilum received ultrasound-guided percutaneous MWA combined with PEI, and the tumor size in maximum diameter ranged from 1.6 to 4.7 cm (mean size, 2.7 ± 0.8 cm). Complete ablation was achieved in 93.7 % (30/32). During a median follow-up of 23 months (range 4–83 months, median 29.5 months), there was no mortality. Residual tumor was detected in the CEUS and MRI 1 month after treatment in one patient. Local tumor progression was noted in five (15 %) patients at 4, 6, 42, 45, and 51 months, respectively, after treatment, and another MWA was performed in three patients and partial hepatectomy was performed in two patients (Figs. 9.1 and 9.2).

9.7 Complications

Heat injury to adjacent bile ducts remains a problem because bile flow is slow and has little cooling effect in contrast to blood flow, and MWA may ablate surrounding tissue of antenna rapidly because of higher thermal efficiency [15, 19]. Excessive heating to overcome the “heat sink effect” of hilar large vessels can cause significant damage to the major bile ducts. Bile duct stricture may develop weeks to months after thermal ablation due to heat damage to the bile duct [14, 20]. Strictures of the peripheral bile ducts

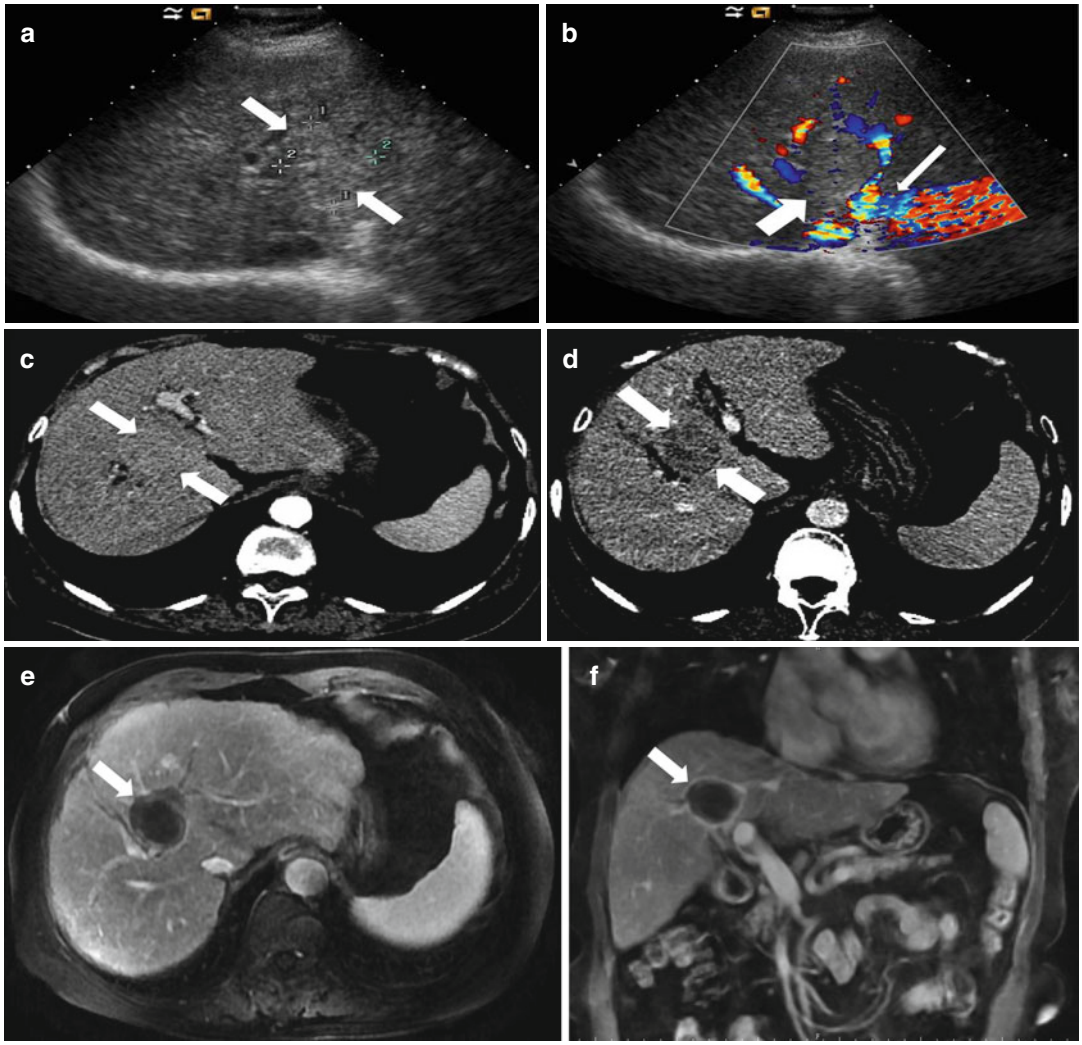

Fig. 9.1 Microwave ablation (*MWA*) in a 75-year-old woman with liver tumor (3.3×3.1 cm) adjacent to the hepatic hilum. (**a**) Grayscale ultrasonography before MWA showed an isoechoic tumor adjacent to the hepatic hilum (*arrow*). (**b**) Color Doppler showed tumor (*arrow*) adjacent to portal vein (*narrow arrow*). (**c**) Contrast-enhanced computed tomography (*CT*) before MWA showed mild enhancement of the tumor in arterial phase (*arrows*). (**d**) Contrast-enhanced CT before MWA showed low enhancement in portal venous phase (*arrows*). (**e**) Contrast-enhanced axial magnetic resonance imaging (*MRI*) 4 months after treatment showed no enhancement of the tumor in arterial phase (*arrow*). (**f**) Coronal MRI 4 months after treatment showed no enhancement of the tumor in portal venous phase (*arrow*)

Complications related to bile duct injury were reported to occur in between 0 and 25.6 % with an average of 11.7 % [21]. In Liang's study [17], 1,136 patients with 1928 malignant liver tumors underwent ultrasonographically guided percutaneous MWA; the incidence of bile duct injury was 0.2 % (2/1,136). One patient with an HCC 10 mm away from the hepatic hilum underwent three sessions of MWA. CT depicted dilatation of other patient with a metastasis 7 mm away from the hepatic hilum underwent two sessions of MWA. A biloma was detected 38 days after MWA, and it was cured after 3 months of drainage. In Ren's study [16], MWA was performed together with percutaneous ethanol injection on 18 malignant liver tumors adjacent to the hepatic hilum, and thrombosis was found in the right portal vein and the umbilical part of the left

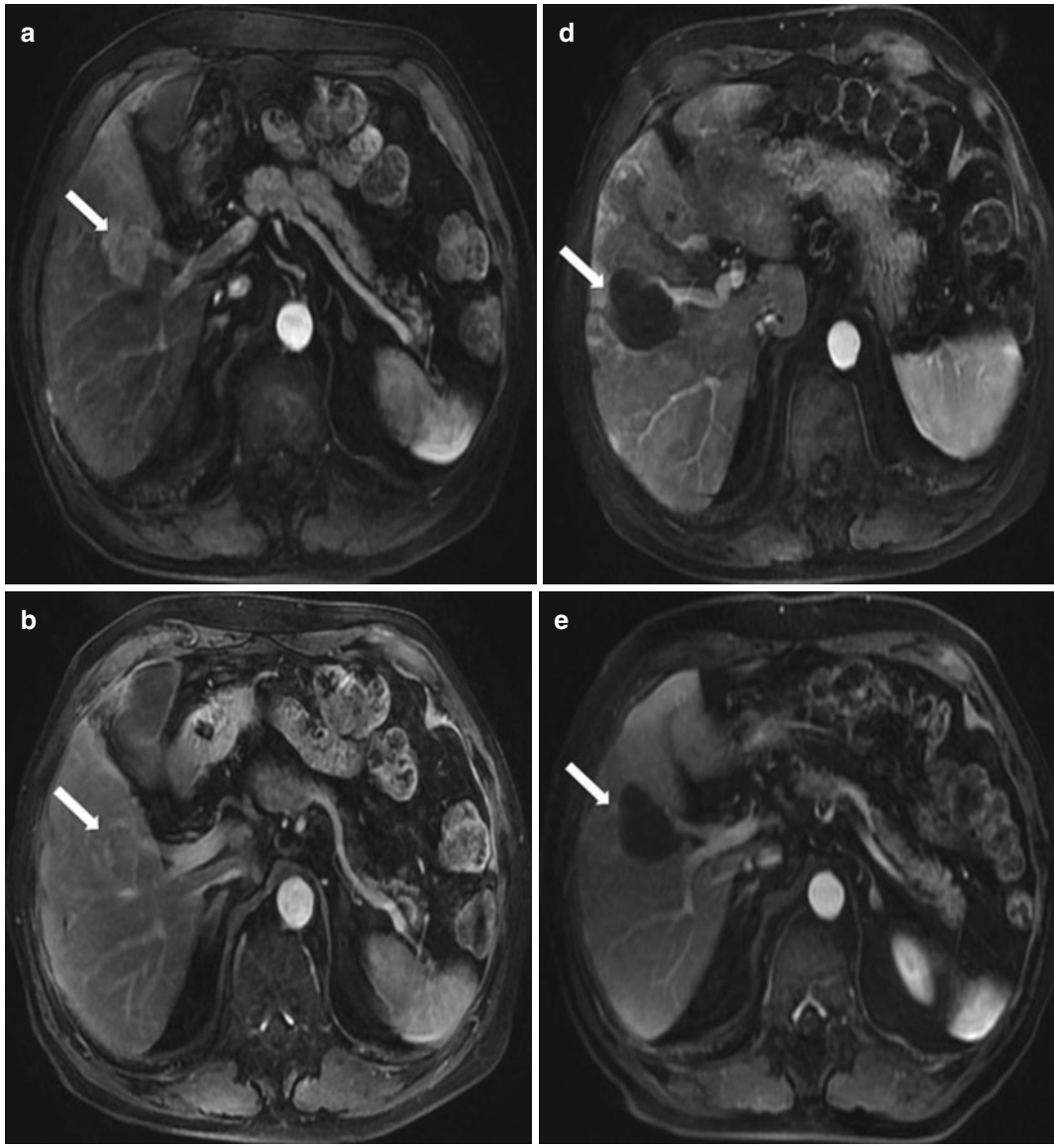

Fig. 9.2 Microwave ablation (*MWA*) in an 85-year-old man with liver tumor (3.2 × 3.0 cm) adjacent to the hepatic hilum. (**a**) Contrast-enhanced magnetic resonance imaging (*MRI*) before MWA showed the tumor with high enhancement in arterial phase (*arrow*). (**b**) Contrast-enhanced MRI before MWA showed the tumor with low enhancement in portal venous phase (*arrow*). (**c**) Coronal MRI showed the lesion adjacent to the hepatic hilum (*small arrow*); besides, there were multiple cysts in the liver (*thick arrow*). (**d**) Contrast-enhanced axial MRI 1 month after treatment showed no enhancement of the lesion in arterial phase (*small arrow*). (**e**) Axial MRI 4 months after treatment showed no enhancement of the tumor in arterial phase (*arrow*). (**f**) Coronal MRI 4 months after treatment showed no enhancement of the tumor in portal venous phase (*arrows*)

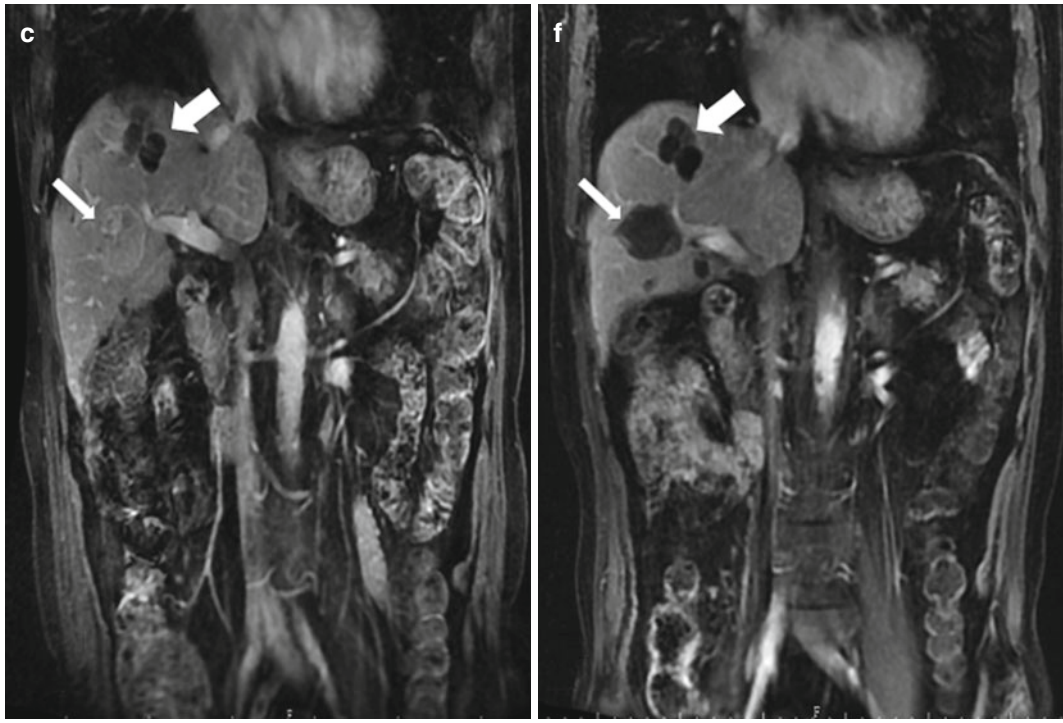

Fig. 9.2 (continued)

portal vein by CEUS in one patient 1 month after treatment, which disappeared 3 months later without any management, but no injury to the bile duct occurred.

9.8 Technique Key Points of MWA

In order to gain complete ablation of the tumor and avoid relative complications, there are some key points: (1) carefully consider the route of antenna insertion and the anatomical relationship between the tumor and the portal vein and main bile duct on ultrasound scrutiny; (2) to gain complete ablation of the tumor periphery adjacent to the hilum, percutaneous ethanol injection is performed simultaneously with microwave emission to augment the effect of MWA; (3) to avoid bile duct injury during ablation, long-duration, low-power (45–50 W) ablation and intermittent microwave emission should be performed, and real-time temperature monitoring during MWA may help to prevent thermal-mediated bile duct injury; and (4) MWA can be used in combination with other techniques to augment the ablation effect, such as transarterial chemoembolization (TACE), intraductal chilled saline perfusion (ICSP), and estimation of spatial location of the tumor by 3-D visual software.

9.9 Other Local Techniques

Other thermal ablation techniques include radiofrequency ablation, high-intensity focused ultrasound, laser ablation, and percutaneous ethanol injection, among which radiofrequency ablation gets the most popularity in the treatment of malignant liver tumors. However, no special study is reported on the ablation effect of tumors adjacent to the hepatic hilum, so the clinical efficacy could not be determined accurately. Here, clinical efficacy and complications of ablation of

malignant liver tumors in high-risk locations by these ablation techniques are summarized.

9.9.1 Radiofrequency Ablation (RFA)

Tang et al. [22] evaluated the feasibility and safety of ultrasound-guided RFA of hepatic tumors in high-risk areas (163 patients, including 20 tumors close to the hilum, 11 in the caudate, 79 adjacent to the capsule, 24 near the gallbladder, and 29 cases against the diaphragm) in comparison with those in low-risk areas; there was no mortality or major complications in either group, and they concluded that RFA using cool-tip electrodes for liver tumors in high-risk areas is comparable to those in low-risk areas in the aspects of complete ablation, complications, and mortality.

In a study of three patients with tumors within 3–5 mm to the central bile ducts, Elias et al. [23] performed an open intraoperative choledochotomy, inserted a catheter, and continuously perfused the intrahepatic bile ducts with chilled Ringer solution during radiofrequency ablation. No signs or symptoms of biliary stricture showed up in the 3-month follow-up period after radiofrequency ablation, and no imaging performance of biliary stricture was found on the follow-up CT or MRI at 3 months. In another study of Elias [8], radiofrequency ablation was performed for 13 patients with liver tumors less than 6 mm away from the central bile duct. Thermal-mediated injury of bile ducts was avoided by cooling the main bile ducts (right, left, or both) with a 4 °C saline solution quickly infused by a catheter introduced inside the bile duct through an intraoperative choledochotomy.

Takaya et al. placed a nasobiliary tube endoscopically before radiofrequency ablation and performed intraductal chilled saline perfusion (ICSP) during RFA. Of the 40 enrolled patients, only one had biliary injury, whereas the remaining 39 patients were able to avoid it. Moreover, the liver function 6 months after RFA was also better preserved according to Child–Pugh grading, thus resulting in a better clinical outcome [24].

The combination of radiofrequency ablation and percutaneous ethanol injection in the management of HCC in high-risk locations has a slightly higher primary effectiveness rate than radiofrequency ablation alone. Wong et al. [25] compared the outcome of the management of high-risk tumors with PEI and radiofrequency ablation ($n=50$) or radiofrequency ablation alone ($n=114$) with the outcome of radiofrequency ablation of non-high-risk tumors ($n=44$). The results showed that the primary effectiveness rate of high-risk radiofrequency ablation and PEI (92 %) was similar to that of non-high-risk radiofrequency ablation (96 %). The primary effectiveness rate of high-risk radiofrequency ablation and PEI was slightly higher ($p=0.1$) than that of high-risk radiofrequency ablation (85 %). The local tumor progression rates (21 % vs. 33 % vs. 24 % at 18 months) were not statistically different ($p=0.91$). Patients with and those without high-risk tumors had equal survival rates ($p=0.42$) after 12 (87 % vs. 100 %) and 24 (77 % vs. 80 %) months of follow-up.

9.9.2 High-Intensity Focused Ultrasound (HIFU)

Franco et al. [26] performed ultrasound-guided high-intensity focused ultrasound on tumors in difficult locations (including four tumors no more than 1 cm to the main bile duct); in a median follow-up period of 12 months, no bile duct injury were detected. They drew the conclusion that ultrasound-guided high-intensity focused ultrasound ablation could be considered a safe and feasible approach to the management of solid tumors in difficult locations.

9.9.3 Laser Ablation (LA)

Francica et al. [27] treated 116 HCC nodules in high-risk sites (high-risk group, including 16 nodules adjacent to the hepatic hilum) and 66 nodules located elsewhere (standard-risk group) in 164 cirrhotic patients by laser ablation; the results during an overall median follow-up of 81 months (range, 6–144 months) showed that the initial complete ablation rate per nodule

(92.2 % vs. 95.5 %, respectively; $p=0.2711$), rates of major complications (1.9 % vs. 0 %), and minor complications (5.6 % vs. 1.0 %) were not statistically different between the two groups. There was no significant difference in either the cumulative incidence of local tumor progression ($p=0.499$) or local tumor progression-free survival ($p=0.499$, log rank test) between the two groups. They concluded that tumor location did not have a significant negative impact on the technique's primary effectiveness or safety or on its ability to achieve local control of disease during laser ablation.

In a study of Caspani et al. published in 2010 [28], 140 patients with HCC nodules were treated by laser ablation. The lesions were localized in "critical sites" in 49 patients (the accurate number of lesions adjacent to the hepatic hilum was not known for certain). No substantial differences were observed upon comparing the percentage of minor and major complications. This study drew a conclusion that the use of laser ablation of HCCs localized in difficult lesions can be accepted and considered a safe treatment without significant differences in comparison with non-critical nodules.

9.9.4 Percutaneous Ethanol Injection (PEI)

To our knowledge, there are no reports of treatment of malignant liver tumors adjacent to the hepatic hilum by percutaneous ethanol injection alone. The combined use of percutaneous ethanol injection with other thermal ablation techniques is demonstrated in the former part of this chapter.

9.9.5 Radioactive Seed Implantation Treatment

Radioactive seed implantation treatment may be a potential adjuvant therapy for malignant liver tumors adjacent to the hepatic hilum. As Lin et al. report [29], RFA combined with I-125 radioactive seed implantation was a safe and effective technology, which was used to treat HCC adjacent to large blood vessels. In our department, the study that MWA combined with radioactive seed implantation was used to treat liver tumors adjacent to the hepatic hilum in progress also shows promising results. However, more researches containing sufficient samples are still needed.

Conclusions

Thermal ablation has been performed on liver tumors adjacent to the hepatic hilum by some researchers; the initial results of different thermal techniques are all satisfying, and some experience has been gathered. However, the treatment effect of different thermal ablation techniques cannot be compared for the reason that there are just a small number of reports.

MWA has some theoretical advantages; it would produce consistently higher intratumoral temperatures, larger ablation zones, less ablation time, and less dependence on the electrical conductivities of tissue. In addition, energy delivery is less limited by the exponentially rising electrical impedance of tumor tissue. MWA has been used widely in the treatment of malignant liver tumors, but the study of MWA of malignant liver tumors adjacent to the hepatic hilum has been few, and prospective randomized studies with a large sample and long-term follow-up period are necessary to determine accurately its efficacy and safety.

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10 Percutaneous Microwave Ablation with Temperature Monitor Combined with Ethanol Ablation for Hepatocellular Carcinoma Abutting the Gastrointestinal Tract

Pei Zhou, Yue Kong, and Ping Liang

Abstract

Percutaneous thermal ablation of hepatocellular carcinoma abutting the gastrointestinal tract is generally acknowledged to be high risk of gastrointestinal perforation. Percutaneous microwave ablation with temperature monitor assisted with a small dose of percutaneous ethanol infusion for hepatic lesions abutting the gastrointestinal tract has been proved to be safe and effective. In this chapter, this method is introduced from a technique procedure and clinical result viewpoint.

Keywords

Hepatocellular carcinoma • Microwave • Radiofrequency • Ethanol • Ablation

Abbreviations and Acronyms

EA	Ethanol ablation
GIT	Gastrointestinal tract
HCC	Hepatocellular carcinoma
MWA	Microwave ablation
RFA	Radiofrequency ablation
US	Ultrasound

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Percutaneous thermal ablation of hepatocellular carcinoma (HCC) tumors abutting the gastrointestinal tract (GIT) is generally acknowledged to be high risk of collateral thermal injury. Perforation of the GIT has been reported as a serious complication of thermal ablations with an overall incidence of 0.1–0.3 % [1, 2]. Radiofrequency ablation (RFA) with laparoscopic guidance for hepatic tumors is highly recommended for patients with lesions adjacent to the GIT to avoid the complication of perforation. The local recurrence rate of laparoscopic RFA varies from 0 to 12 % with 2.2–8 % postoperative complications although without gastrointestinal perforation [3–5]. However, previous abdominal surgery history is a contraindication specific to laparoscopic RFA. Percutaneous thermal ablations

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are the common applied treatment methods for hepatic lesions abutting GIT. Many efforts during percutaneous thermal ablations have been made to avoid thermal damage to GIT such as a balloon interposed between the index tumor and the GIT, an artificial ascites to separate the GIT or ethanol ablation (EA) for the marginal tissue neighboring the GIT of the index tumor combining with thermal ablation [6–14]. In this chapter, percutaneous microwave ablation (MWA) with temperature monitor assisted with EA of small dose for hepatic tumors abutting the GIT is introduced from technique procedure and clinical result viewpoint.

10.1 Indications and Imaging Evaluation

Hepatic tumors abutting the GIT is defined according to the location of hepatic tumors at a distance less than 5 mm from the GIT. The distance between the edge of the tumor and the GIT was measured on computed tomography or magnetic resonance imaging images and on contrast-enhanced ultrasound (US). Inclusion criteria for MWA are unresectable cancer or patient's refusal to undergo surgery; tumor accessibility via a percutaneous approach; single nodular HCC lesions of 5 cm or smaller; three or fewer multiple nodular hepatic lesions with a maximum dimension of 4 cm or less in each nodule; absence of portal vein thrombosis or extrahepatic metastases; and prothrombin time of less than 25 s, prothrombin activity higher than 40 %, and platelet count higher than 40 cells $\times 10^9$/L. Pretreatment investigation includes US, contrast-enhanced US, contrast-enhanced computed tomography and/or contrast-enhanced magnetic resonance imaging, and tumor marker assay in all subjects. Histological diagnosis was obtained by ultrasound-guided tumor biopsy using an 18-gauge needle in patients without postoperative pathologic diagnosis or conforming diagnosis of at least two contrast-enhanced imagings. In patients with multiple nodules, at least one biopsy was performed. Therapeutic effectiveness is assessed on the basis of the results of contrast-enhanced imaging and serum tumor marker levels. Contrast-enhanced computed tomography or magnetic resonance imaging and contrast-enhanced US are repeated at 1-month and at 3-month intervals within 1 year after microwave ablation treatment and then at 6-month intervals after treatment.

10.2 Microwave Ablation Technique and Equipment

The MWA instrument (KY-2000, Kangyou Medical, Nanjing, China) is capable of producing 1–100 W of power at 2,450 MHz. The needle antenna has a diameter of 1.9 mm and a 15 cm shaft coated with polytetrafluoroethylene to prevent tissue adhesion. A narrow radiating segment of 3 mm is embedded on the shaft, 5 or 11 mm away from the tip of antenna. The microwave system is equipped with three independent 21 G thermocouple needles which can be inserted into the designated places with the guidance of ultrasound to monitor real-time temperature during MWA.

A detailed protocol should be worked out for each patient on an individual basis before treatment which included the placement of the antennas, power output setting, emission time, and appropriate approach. For tumors less than 1.7 cm in diameter, a single antenna is used; for tumors 1.7 cm or larger, multiple antennas are required. Forty- to sixty-watt output was used during ablations.

10.3 Temperature Monitor Procedure

To avoid thermal injury to the GIT during ablation, the temperature of the marginal tissue of the tumor or liver proximal to the GIT is monitored throughout the ablation procedure with one or two 21G thermocouple needles inserted under US guidance. The threshold of coagulation necrosis for thermal ablation is 60 or 54 °C for 3 min. According to our clinical experience and intraoperative observation of the hyperechoic ablative area and neigh-

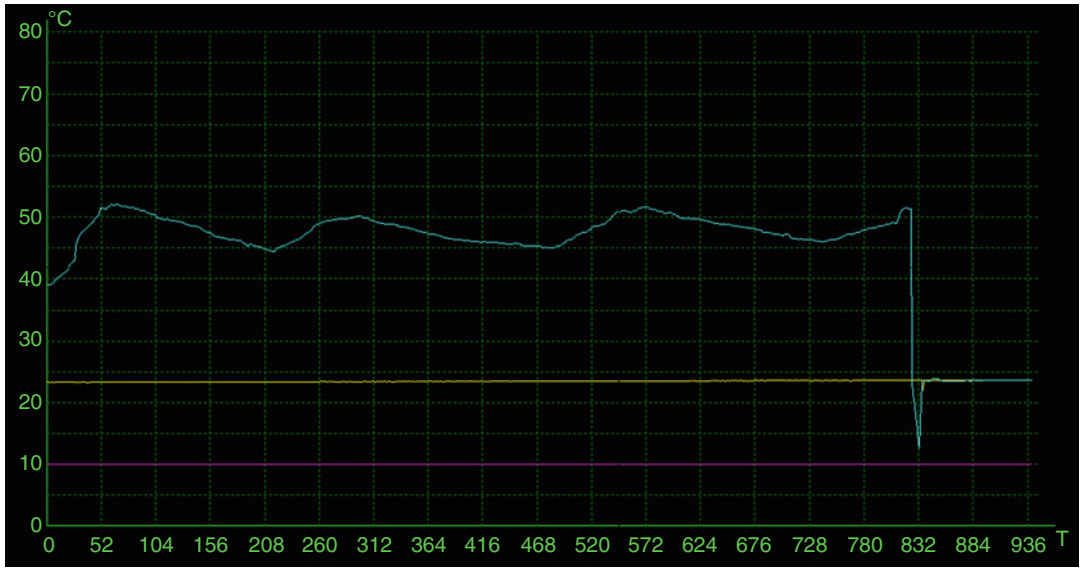


Fig. 10.1 The curve of the temperature monitor during microwave ablation (MWA) for a metastatic hepatic tumor abutting the small intestine. The temperature of the marginal tissue of the tumor neighboring the gastrointestinal tract is monitored and controlled to fluctuate between 45 and 52 °C during the whole treatment procedure according to the abdominal operation history of the patient

boring gastrointestinal movement, the temperature cutoff of ablation therapy is set at 54–60 °C in the patients without surgical resection history or 50–54 °C in the patients with abdominal surgical resection history for the reason of possible adhesion between GIT and liver capsule. If the measured temperature almost reaches the cutoff temperature, emission of microwave should be stopped immediately, which could be reactivated after the temperature decreases to 45 °C (Fig. 10.1). By the end of treatment session, the measured temperature fluctuates between 45 °C and the cutoff temperature for more than 5 min and should not exceed 54 °C for more than 3 min in the patients without surgical resection history or exceed 50 °C for more than 3 min in the patients with abdominal surgical resection history.

10.4 Adjuvant Therapy with EA of Small Dose

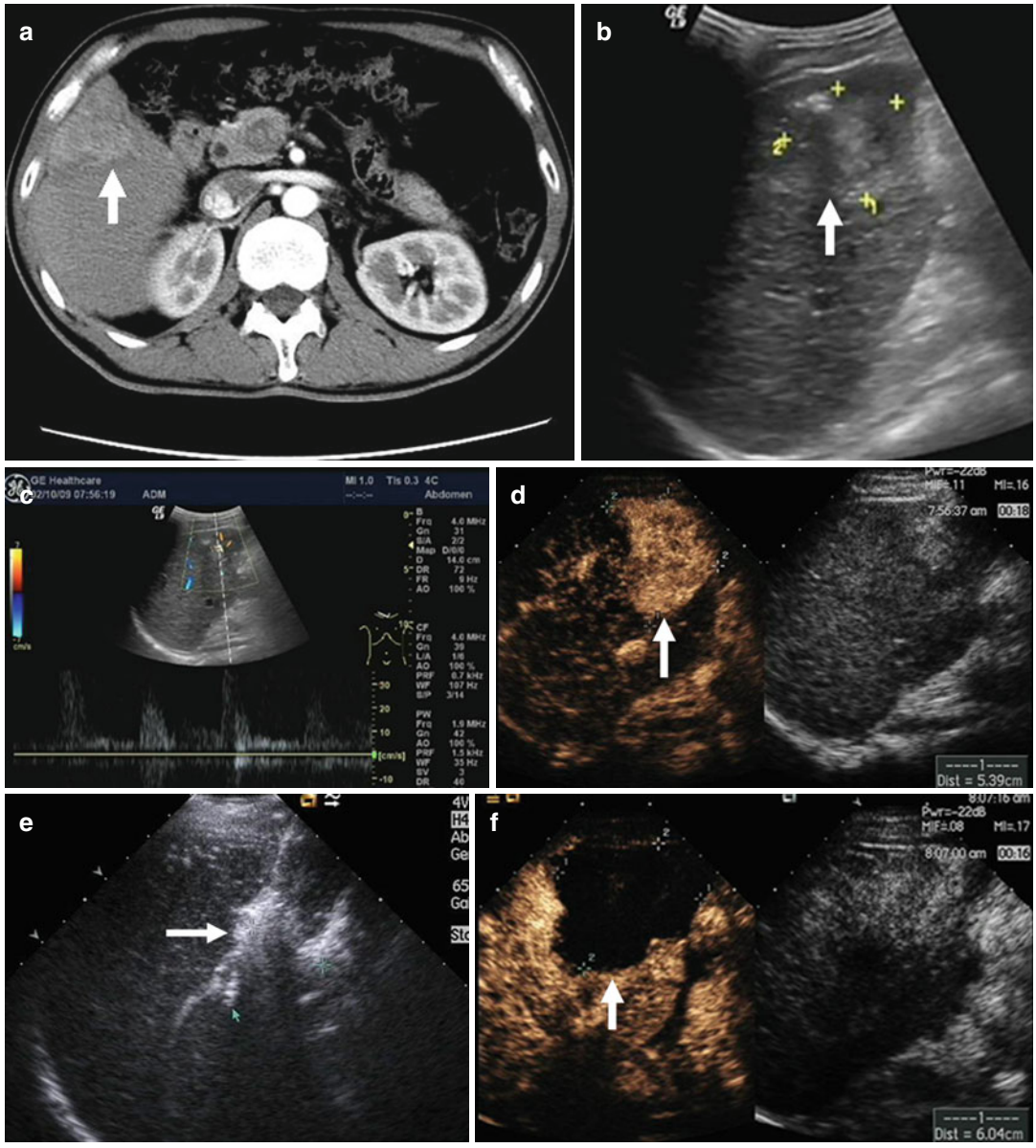
For tumors protruding or in contact with the GIT, one to two 21G PTC needles could be placed into marginal tissue of the tumor proximal to the GIT under US guidance. A small dose (<20 ml for per session) of dehydrated, sterile, 99.5 % ethanol could be slowly injected into the marginal tissue of the tumor during the process of ablation treatment until the marginal tissue of the tumor proximal to the GIT is completely overlapped with hyperechogenicity.

10.5 Clinical Effect

Our latest data of MWA for 175 hepatic tumors abutting the GIT show that the complete ablation rate is 96.5 % (169/175) and local tumor progression is 10.1 % (17/169) (Figs. 10.2, 10.3, 10.4, and 10.5) which is similar with the results of our previous published paper [15, 16].

RFA for hepatic tumors abutting GIT is reported by several authors using different protective methods (Table 10.1). Artificial ascites is usually used as a protective method in percutaneous RFA through which the GIT was satisfactorily separated from 78 to 91.7 % lesions with 3.1–17.5 % local tumor progression rate and low

rate of major complications [6–9]. Although the separating rate between the GIT and liver could not reach 100 %, artificial ascites is an easy and feasible method in majority of patients with hepatic tumor abutting the GIT. Temperature monitor during thermal ablation is another method to protect extrahepatic organs. The thermocouple needle should be inserted accurately into the site of tumor margin abutting the GIT and should be monitored continuously during ablation to timely discover the possible movement of thermocouple needle. Moreover, abdominal adhesion after abdominal operation may cause separation between the liver and GIT to be difficult; artificial ascites technique is suitable for patients without abdominal operation history. Different from it, Temperature monitor do not get restricted by abdominal operation history. The complete



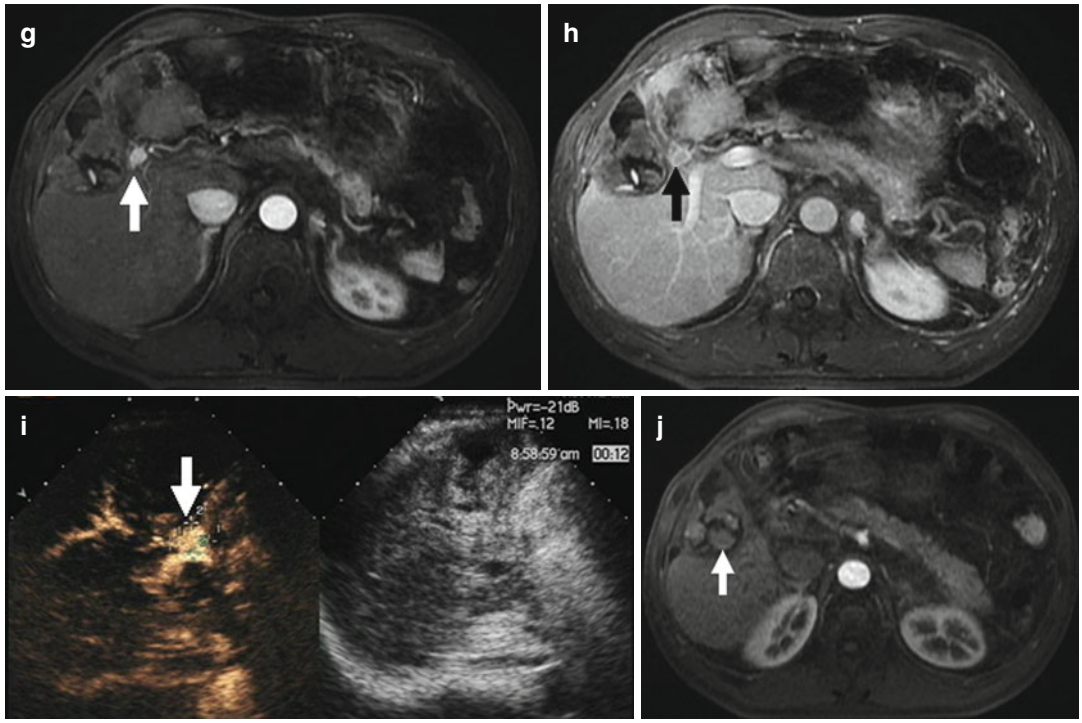
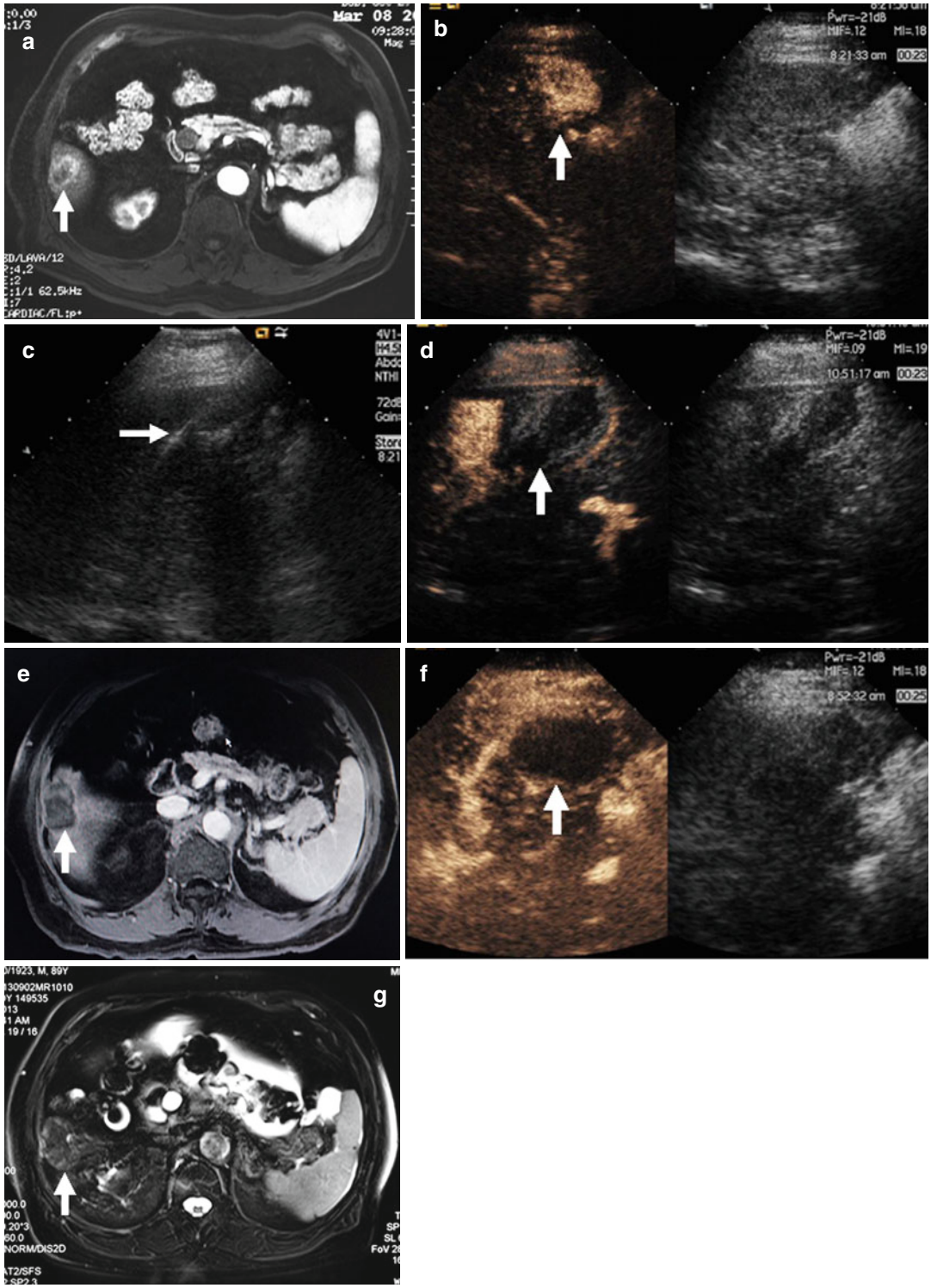


Fig. 10.2 (continued)

Fig. 10.2 A 44-year-old man with a history of chronic hepatitis B, cirrhosis, and splenectomy is found to have a hepatic lesion (6.0×5.4×5.4 cm) located in the right anterior lobe and abutting the small intestine. The lesion is diagnosed to be hepatocellular carcinoma (HCC) and treated with MWA and ethanol ablation (*EA*). (**a**) The hepatic lesion located in the right anterior lobe (*arrow*) is hypervascular and adjacent to the small intestine on contrast-enhanced computed tomography before treatment. (**b**) The hepatic lesion abutting the small intestine (*arrow*) is slight hyperechoic with obscure margin on B-mode ultrasound (US) before treatment. (**c**) Color and pulsed Doppler flow image before treatment shows arterial blood flow signals appearing within and around the lesion. (**d**) The lesion (*arrow*) highly enhances in the early arterial phase with irregular and multiple nodules fusion shape slightly protruded from liver capsule on contrast-enhanced US before treatment. (**e**) The lesion (*arrow*) is treated with MWA with two antennas and three insertions of antenna under powers of 60 W. One 21G thermocouple needle is inserted under US guidance into the edge of the lesion abutting the intestine to survey the temperature of the marginal tissue of the tumor and control MW emission. The temperature cutoff of ablation therapy is set at 50 °C. (**f**) Four days after MWA, contrast-enhanced US shows a no-enhancement area of 6.0×6.0×5.8 cm in the treatment region (*arrow*). (**g**) Magnetic resonance imaging (*MRI*) obtained 23 months after MWA finds a new lesion adjacent to ablation zone which shows high enhancement in arterial phase on contrast-enhanced T1-WI (*arrow*). (**h**) The new lesion adjacent ablation zone is central low enhancement in portal venous phase on contrast-enhanced T1-WI MRI (*arrow*). (**i**) Contrast-enhanced US performed 23 months after MWA shows two hypervascular lesions with size of 1.6×1.3 cm and 1.3×1.0 cm near the marginal site of the no enhanced ablation zone abutting the intestine in the arterial phase (*arrow*). The two lesions are treated with EA. (**j**) On MRI obtained 50 months after MWA, local tumor progression is not found (*arrow*)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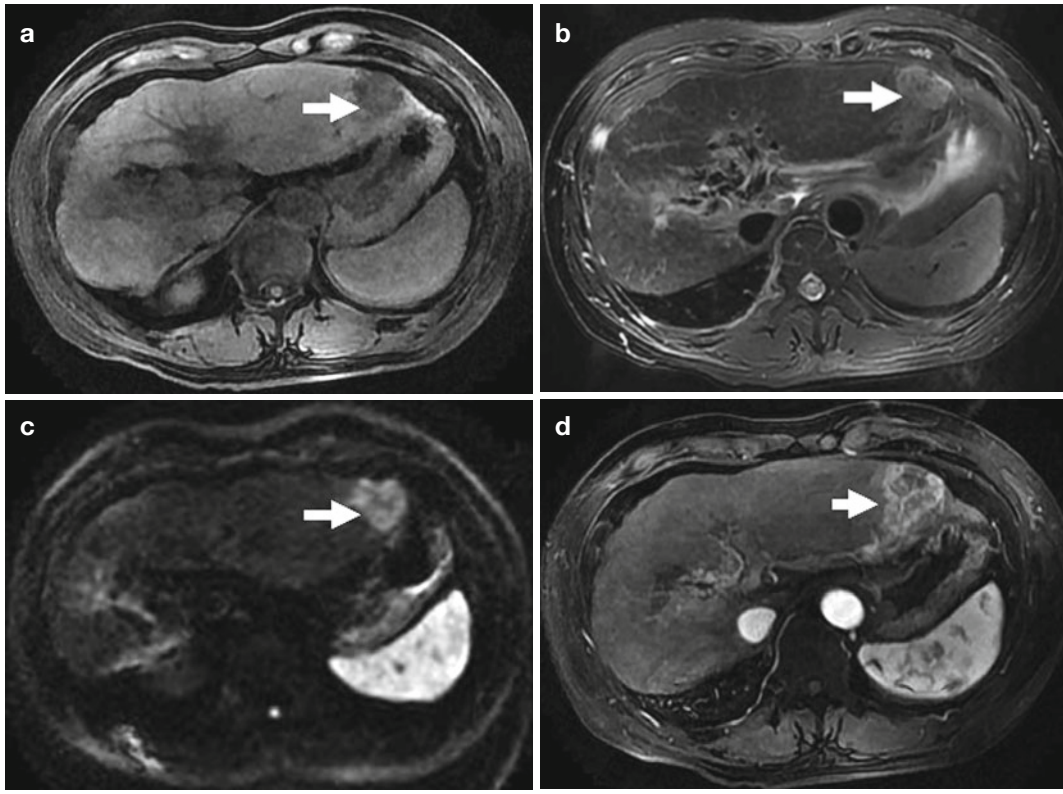

Fig. 10.4 A 55-year-old man with a history of chronic hepatitis B, cirrhosis, and transcatheter arterial chemoembolization for HCC is found with a hepatic lesion (5 cm) located in the left lateral lobe and adjacent to stomach. The lesion is diagnosed to be HCC combined with history and contrast-enhanced images and treated with MWA and EA. (**a**) The hepatic lesion located in the left lateral lobe (*arrow*) is hypointense and adjacent to stomach on T1-WI MRI before treatment. (**b**) The hepatic lesion is hyperintense (*arrow*) on T2-WI MRI before treatment. (**c**) The hepatic lesion is hyperintense (*arrow*) on DWI MRI before treatment. (**d**) The hepatic lesion is highly enhanced in the arterial phase (*arrow*) of contrast-enhanced MRI before treatment. (**e**) The hepatic lesion located in the left lateral lobe has no enhancement in the arterial phase (*arrow*) of contrast-enhanced MRI obtained 19 months after MWA and EA. (**f**) The ablated area is larger than and has completely covered the treated HCC lesion on the delayed phase (*arrow*) of MRI obtained 19 months after MWA and EA

Fig. 10.3 An 88-year-old man without a history of chronic hepatitis is found with a hepatic lesion (3.5×2.8×2.6 cm) located in the right posterior lobe and abutting the small intestine. The lesion is diagnosed to be HCC with contrast-enhanced images and treated with MWA and EA. (**a**) The hepatic lesion located in the right posterior lobe is heterogeneously hypervascular and adjacent to the small intestine (*arrow*) on contrast-enhanced MRI before treatment. (**b**) The lesion is highly enhanced (*arrow*) on contrast-enhanced US before treatment. (**c**) The lesion is treated with MWA (*arrow*) with two antennas under powers of 50 W and EA (total dose 7.5 ml) with three 21G PTC needles. One 21G thermocouple needle is inserted under US guidance near the capsule of liver abutting the intestine. The temperature cutoff of ablation therapy is set at 50 °C. (**d**) Seven days after MWA, contrast-enhanced US shows a no-enhancement area of 3.7×3.2×2.7 cm in the treatment region without residual focus (*arrow*). (**e**) On MRI obtained 12 months after MWA and EA, the treated lesion abutting the intestine has no enhancement in arterial phase on contrast-enhanced T1-WI and local tumor progression is not found (*arrow*). (**f**) Contrast-enhanced US performed 12 months after MWA and EA; the treated lesion has totally no enhancement (*arrow*). (**g**) Local tumor progression is not found (*arrow*) on MRI obtained 18 months after MWA and EA

ablation rate of our result is similar with that of MWA and RFA for hepatic tumors reported in large clinical series [17, 18] and that of RFA combined with artificial ascites for hepatic tumors abutting the GIT [6–9]. Local tumor progression is similar with other reports of percutaneous thermal ablation for hepatic lesions adjacent to the GIT (Table 10.1) [6–13].

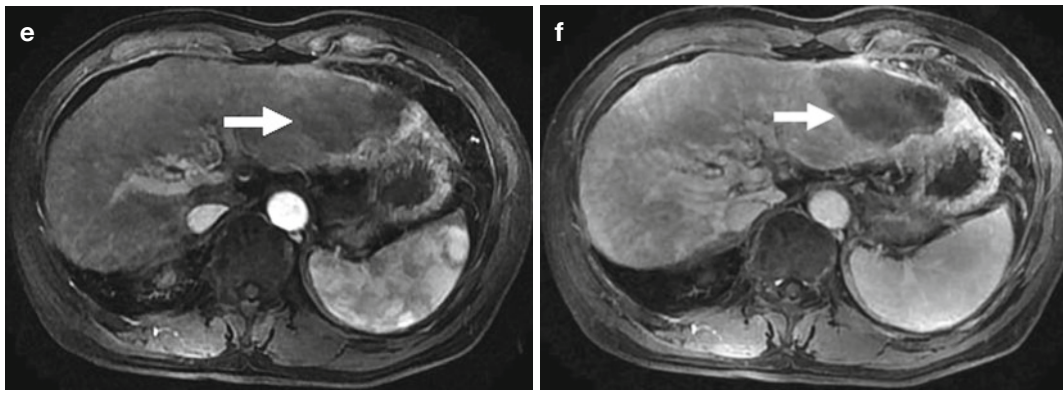

Fig. 10.4 (continued)

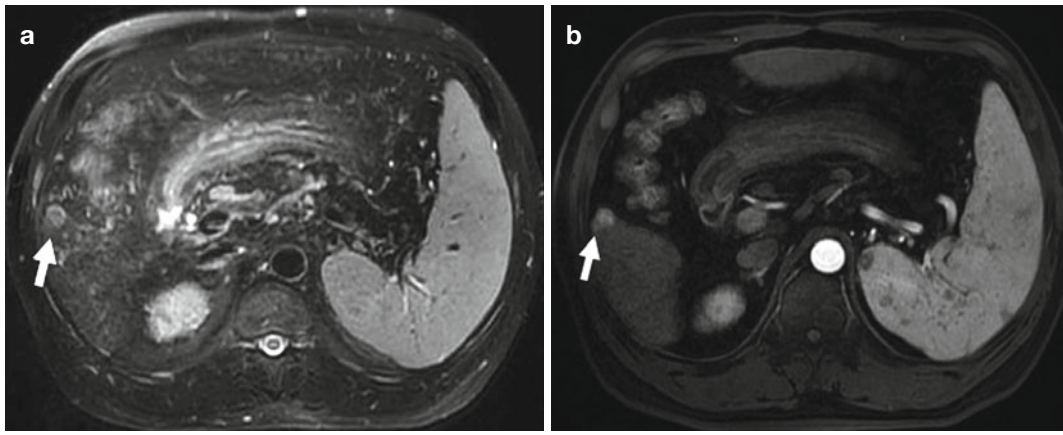

Fig. 10.5 A 53-year-old man with a history of chronic hepatitis B, cirrhosis, and transcatheter arterial chemoembolization for HCC is found with a hepatic lesion (2.1 × 1.8 cm) located in the right anterior lobe and adjacent to intestine. The lesion is diagnosed to be HCC combined with history and contrast-enhanced images and treated with MWA and EA. (**a**) The hepatic lesion located in the right anterior lobe has high intensity and is adjacent to the intestine (*arrow*) on T2-WI MRI before treatment. (**b**) The hepatic lesion adjacent to intestine is highly enhanced (*arrow*) on contrast-enhanced T1-WI MRI before treatment. (**c**) On contrast-enhanced US before treatment, the hepatic lesion of the right anterior lobe adjacent to the intestine is hypervascular (*arrow*). (**d**) On T1-WI MRI obtained 17 months after MWA and EA treatment, the hepatic lesion of the right anterior lobe adjacent to the intestine (*arrow*) is heterogeneous. (**e**) On contrast-enhanced T1-WI MRI obtained 17 months after treatment, the hepatic lesion of the right anterior lobe adjacent to the intestine had no enhancement and local tumor progression is not found (*arrow*)

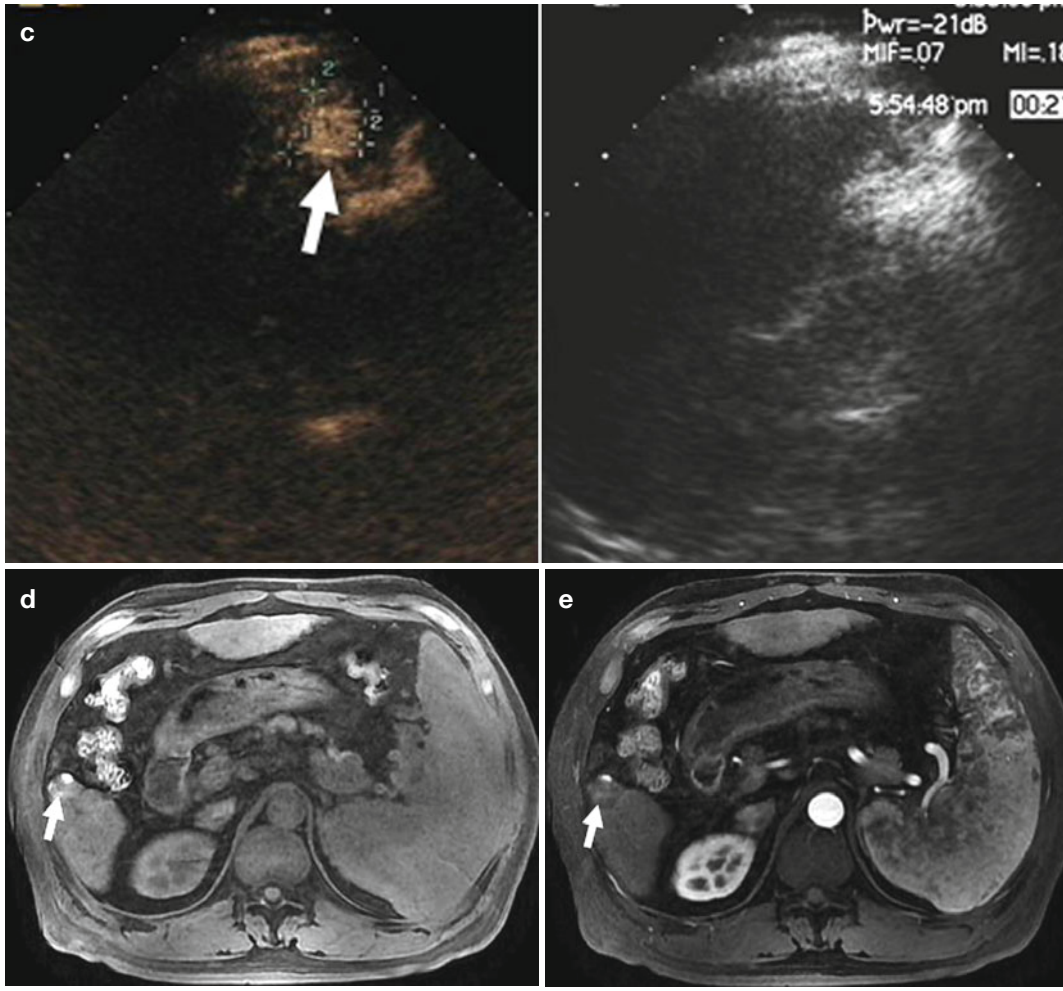

Fig. 10.5 (continued)

10.6 Complications

Side effects and minor complications of MWA for hepatic tumors abutting the GIT include pain, fever, bleeding, pleural effusion, portal vein thrombosis, biliary tract dilation, and skin burn. Pain is the most common side effect after MWA and may occur during percutaneous approach under local anesthesia after the ablation. The severity of pain tends to be worse in patients with more superficial lesion. Fever is the second most common side effect and generally subsides after 1–2 days.

The possible major complications of MWA for hepatic tumors abutting the GIT include abscess, rupture, seeding, complicated pleural effusion, cholecystitis, GIT tract injury, and liver failure. The results of our previous published paper [15, 16] and latest data show that no gastrointestinal perforation happened after MWA and that the major and minor complication rates were less than 2 %. The result was similar to other reports of percutaneous thermal ablations [6–13].

10.7 Technical Key Points Summary

Many factors can influence the size of ablation, such as the condition of blood flow and the background of cirrhotic or non-cirrhotic liver which

Table 10.1 Clinical studies reporting outcomes of thermal ablation for hepatic lesions abutting the gastrointestinal tract

Authors	Number of patients	Number of lesions	Therapy methods	Protective methods	Guide	Lesion size in cm	Number of sessions	CA rate	Local recurrence	Major complications
					Method	(mean, range)				
Kelogrigoris et al. [12]	12	12	PRFA	NO	CT	1.5–6.0	N/A	91.7 %	9.2 %	NO
Liu et al. [8]	36	36	PMWA or PRFA	Artificial ascites	US	3.1 (1.0–6.7)	1–2	95.7 %(D<3 cm) 86.2 %(D≥3 cm)	5.8 %	NO
Zhou et al. [15]	51	53	PMWA or PMWA + EA	Temperature monitor	US	2.7 (1.0–6.0)	1.2±0.4	N/A	11.3 %	NO
Hirooka et al. [9]	37	42	TAE + LRFA	NO	Laparoscope	2.6 (2.0–4.1)	1	100 %	0 (2 years)	NO
Hirooka et al. [9]	37	44	TAE + PRFA	Artificial ascites	US	2.5 (2.0–4.1)	2.1±1.0	100 %	17.5 %(2 years)	NO
Chen et al. [11]	N/A	54	PRFA + EA	NO	US	3.5±1.2 (Mean±SD)	N/A	90.7 %	9.3 %	1 GIT perforation
Teratani et al. [6]	N/A	21	PRFA	Artificial ascites	US	2.5±1.4 (Mean±SD)	N/A	99.1 %	3.1 % (3 years)	1 GIT perforation
Kondo et al. [7]	52	58	PRFA	Artificial ascites	US	2.3	1.4 (1–4)	98.3 %	4 %	1 GIT perforation
Choi et al. [10]	41	41	PRFA	NO	US	2.5 (1.2–4.3)	1.3 (1–4)	93 %	11 %	1 small perihepatic abscess
Yamakado et al. [13]	2	2	PRFA	Balloon catheter interposition	CT fluoroscopic guidance	2.5, 3.0	N/A	N/A	0	NO

PRFA percutaneous radiofrequency ablation, *PMWA* percutaneous microwave ablation, *TAE* transhepatic arterial embolization, *EA* ethanol ablation, *US* ultrasound, *CT* computed tomography, *GIT* gastrointestinal tract, *N/A* not available

influence the conductivity of heat to surrounding tissues. However, the main factor of thermal damage in tissue is temperature over the threshold of coagulation, namely, 60 °C. Temperature can be used as a reliable indicator to reflect the pathologic changes during ablation for liver tumors. Thus, we monitor the temperature of the marginal tissue of the tumor or liver proximal to the GIT to obtain two goals: the first is to avoid thermal damage of adjacent bowel loop, and the second is to ensure treatment efficacy of the marginal tissue of the tumor. We intend to control the temperature of the marginal tissue of the tumor lower than 60 °C to avoid thermal damage of adjacent bowel loop but higher than 45 °C to ensure microwave thermal field covering the marginal field of the tumor. We deliberately control the monitored temperature in patients with laparotomy history lower than those in patients without laparotomy history. That is because bowel peristalsis in patients without laparotomy history would help to avoid persistent heating of the same area. Adhesion may occur and decrease bowel peristalsis and thus increase the risk of thermal damage of bowel loop in patients with laparotomy history. Our results show our modality is safe for the treatment of hepatic tumors abutting the GIT.

Although controlled temperature of the marginal tissue of tumors protruding to or in contact with the GIT is lower than the threshold temperature of coagulation, we add adjuvant therapy with small dose of ethanol injection in the vicinity of the adjacent bowel loop to achieve complete necrosis of the marginal tissue of tumors. Ethanol injection has two effects: one, implementing chemical ablation for marginal cells of tumor and, two, obtaining synergistic necrotizing effect under combining use of ethanol and microwave ablation. Experimental and clinical reports show that the combined use of ethanol and radiofrequency or microwave ablation causes a synergistic necrotizing effect, with coagulation volumes clearly larger than those usually obtained with EA or RFA and MWA alone [19–21].

Although the size of tumors abutting the GIT meets the indication of ablation, tumors abutting the GIT require longer duration of ablation than those in the low-risk locations; however, they did not require larger number of treatment sessions [15]. That result is similar with a previous report of radiofrequency ablation for tumors abutting the GIT with other adjuvant techniques, such as artificial ascites and a balloon interposed between the tumor and GIT.

Conclusion

In conclusion, under strict temperature monitor, microwave ablation assisted with a small dose of ethanol injection for hepatic tumors adjacent to the GIT is safe and can achieve a high complete ablation rate and low local tumor progression rate.

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11 Artificial Ascites in Assisting Percutaneous Microwave Ablation for Hepatic Tumors Adjacent to the Gastrointestinal Tract

Min Zhang and Ping Liang

Abstract

When a hepatic tumor is adjacent to the gastrointestinal tract (GT), the thermal ablation therapy could probably damage the GT to induce serious complications. Gastrointestinal perforation is the most important extrahepatic complication due to thermal damage, especially in patients with a history of celiac operation or transcatheter hepatic arterial chemoembolization. Therefore, it is challengeable to use percutaneous thermal ablation to treat hepatic tumors adjacent to the GT safely and effectively. Several experimental and clinical researches verified that artificial ascites is a safe and effective strategy in using radiofrequency ablation to treat hepatic tumors adjacent to the GT. Few clinical researches concerning microwave ablation (MWA) with artificial ascites for the treatment of such tumors have been reported. The result of our clinical study verifies that ultrasound-guided percutaneous microwave ablation assisted with artificial ascites is a safe and effective method for the treatment of primary and metastatic hepatic tumors adjacent to the GT and can achieve good local control of such tumors. In this chapter, we will introduce artificial ascites technique in assisting percutaneous microwave ablation for hepatic tumors adjacent to the GT: overview, technique, efficacy, and safety.

Keywords

Artificial ascites • Catheter ablation • Microwaves • Liver neoplasms

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Abbreviations and Acronyms

GT	Gastrointestinal tract
RFA	Radiofrequency ablation
MWA	Microwave ablation

11.1 Introduction

When using microwave ablation (MWA) to treat hepatic tumors abutting the gastrointestinal tract (GT), the gas in the GT could cause incomplete visualization of the tumors. Moreover, the thermal energy could probably damage the GT to induce serious complications such as gastrointestinal perforation, especially for the patients with the history of abdominal operation or transcatheter hepatic arterial chemoembolization which can cause intra-abdominal adhesions [1, 2]. The incidence of the gastrointestinal perforation associated with thermal ablation for hepatic tumors has been reported to range from 0.06 to 0.7 % [1, 3–6]. Gastrointestinal perforation may be fatal to some weak patients; therefore, it is challengeable to use percutaneous MWA to treat hepatic tumors adjacent to the GT safely and effectively. Strategies for such cases include laparoscopic thermal ablation [7], artificial ascites, balloon catheter interposition [8], and sodium hyaluronate solution [9] between the hepatic tumor and the GT.

Several experimental and clinical researches verified the safety and effectiveness of the treatment of hepatic tumors adjacent to the GT by using radiofrequency ablation (RFA) assisted with artificial ascites [2, 10–12]. However, few clinical researches concerning MWA with artificial ascites for the treatment of such cases have been reported. We have made a primary clinical research that verifies the efficacy and safety of artificial ascites in assisting percutaneous MWA for hepatic tumors adjacent to the GT. In this chapter, we will discuss artificial ascites technique in assisting percutaneous MWA for hepatic tumors adjacent to the GT: overview, technique, efficacy, and safety.

11.2 Rationale of Artificial Ascites

Hepatic tumors that are located <5 mm from the GT can be treated safely by percutaneous MWA assisted by the artificial ascites technique. MWA does not apply to the cases wherein hepatic tumor has invaded the GT, showed by ultrasound, computed tomography, or magnetic resonance imaging. The rationale of the use of artificial ascites is that artificial ascites can create a space between the liver surface and the adjacent organs. The fluid between the hepatic tumor and the GT plays a role in insulating thermal energy transmission and lowering the temperature around the GT, thus protecting the GT from thermal injury. In addition, the instillation of artificial ascites increases the conspicuity of hepatic tumor on ultrasound by replacing surrounding air in the GT and lessens pain by avoiding the damage of the abdominal wall.

The fluid space of 5–10 mm thick is sufficient to prevent thermal damage of the GT. Animal experience concerning RFA suggested that small amounts of artificial ascites between the liver and surrounding organs (2.7 mm thick) had a protective effect [13]. Our primary clinical study concerning MWA for treating liver cancer suggested a separation of at least 5 mm between the target tumor and adjacent the GT should be obtained while performing treatment. Therefore, artificial ascites is usually introduced until the sufficient separation or sonic window is archived. But the amount of artificial ascites is inconclusive (Table 11.1). Artificial ascites can be introduced in volumes up to 3,000 mL without significant complications in a previous report [14]. In our study, the mean volume of artificial ascites is 633 ± 359 mL (range 100–1,500 mL). During the treatment, the drip infusion should continue to maintain the distance of at least 5 mm between the ablation zone and adjacent organs due to peritoneal absorbing fluid (Fig. 11.4c).

Table 11.1 Artificial ascites in assisting thermal ablation for liver cancer adjacent to the GT

Author	Therapy	No. of tumors	Diameter (cm)	Volume of ascites (ml)	TER (%)	LTP (%)	Follow-up (months)	Complication (%)
Nishimura et al. [12]	RFA	46	2.0	500–2,000	100	4.5–5.7	12	0
Song et al. [2]	RFA	148	2.2	436 ± 273	85.3	12	20.4	2.1
Hirooka et al. [7]	RFA	44	2.5	N/A	100	0	12	0
						17.5	24	
Kondo et al. [14]	RFA	58	2.3	681 (mean) (250–3,000)	96	4	11.2	1.9
Liu et al. [26]	MWA and RFA	34	3.1	150–1,000	90.4	5.8	N/A	7.3
Our research	MWA	36	2.8	633 ± 359 (100–1,500)	96.9	16.1	12.1	2.8

TER technique effective rate, *LTP* local tumor progression, *N/A* not available

11.3 Introduction of Artificial Ascites

The introduction of artificial ascites can be achieved by various techniques with the use of different equipment such as angiosheath, spinal needle, and intravenous catheter. Although the successful induction rate and the puncture time among the use of these techniques are not significantly different, we prefer the technique using the angiosheath or intravenous catheter because of their soft sheathes or catheters which can sustain saline infusion during MWA without real-time monitoring of the tip of the sheathes or catheters on ultrasound. Normal saline (0.9 %) and 5 % dextrose solution can be utilized as a protective fluid [2, 15]. Infusion of 0.9 % saline solution into the abdomen is safe and effective during MWA procedure in our study.

Puncture of a catheter is performed under local anesthesia. Following the administration of local anesthesia with 1 % lidocaine to the skin, abdominal wall, and peritoneum, an intravenous catheter is inserted into peritoneal cavity under ultrasound guidance. When ultrasound shows that the catheter is inserted into the correct site along the edge of the liver, the outer catheter is advanced further to position the tip near the hepatic tumor whenever possible, and the inner stylet is removed (Fig. 11.1a, b). Once the catheter is in place, a sufficient amount of 0.9 % saline solution is injected until a separation of at least 5 mm between the index tumor and the adjacent GT is achieved (Fig. 11.1c). After the successful induction of artificial ascites, the MWA procedure is performed (Figs. 11.1d and 11.3a, b). Sometimes it is very difficult to insert the catheter directly into the correct site due to the GT's interference. The method of puncture step by step is useful (Fig. 11.2). The intravenous catheter is inserted into the shallow site firstly, and then a small amount of saline is injected to separate the GT or omentum from the liver surface. Meanwhile, the tip of the catheter could be well revealed. Next, the catheter is inserted deeper, and the process is repeated until the tip of the catheter is positioned near the index tumor.

Contrast-enhanced ultrasound can be performed to aid the good revelation of the catheter position if conventional ultrasound failed to visualize it clearly. During the insertion of catheter, a minute amount (0.1 mL contrast agent dissolved in 10 mL 0.9 % saline) of ultrasound contrast agent (SonoVue, Bracco, Milan, Italy) is injected into the catheter, and the position of catheter could be revealed clearly by observing the contrast agent's diffusion (Fig. 11.3c, d).

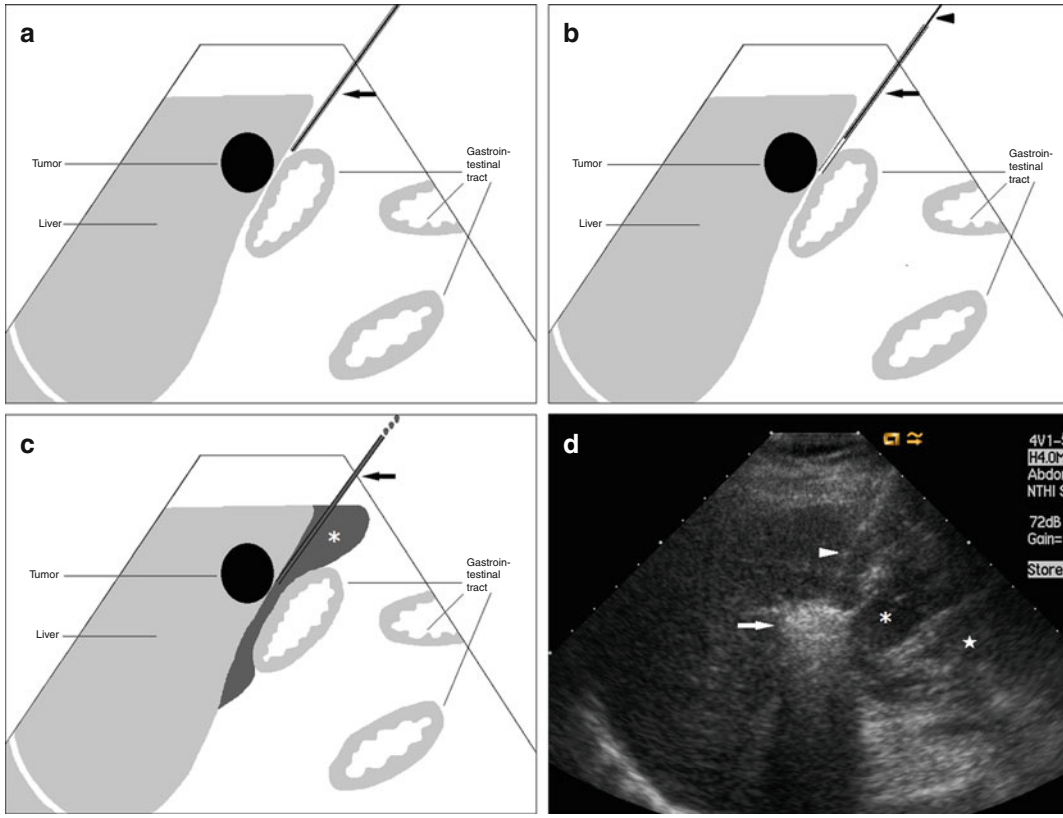

Fig. 11.1 Artificial ascites technique in assisting microwave ablation (MWA) of hepatic tumors adjacent to the gastrointestinal tract (GT). (**a**) An intravenous catheter (*arrow*) is inserted into the space between the surface of the liver and the GT along the edge of the liver under ultrasound (US) guidance. (**b**) The outer catheter (*arrow*) is advanced further to close to the index tumor whenever possible; next, the inner stylet (*arrowhead*) is removed. (**c**) The saline solution (*) is injected via the catheter (*arrow*) until the GT is separated successfully from the index tumor. (**d**) After the successful introduction of artificial ascites (*), the MWA procedure (*arrow*) is performed safely, avoiding the thermal injuries of the GT (☆). Note the microwave antenna (*arrowhead*)

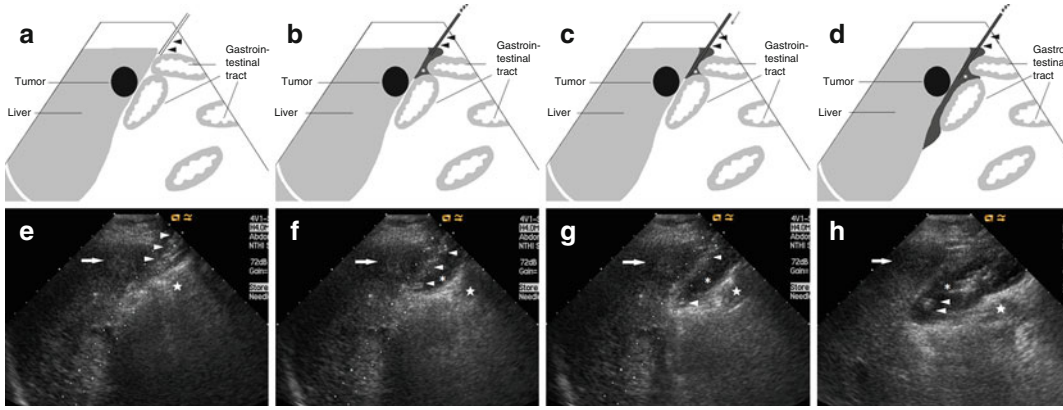

Fig. 11.2 The method of puncture step by step. (**a**–**e**) An intravenous catheter (*arrowheads*) is inserted into the shallow site firstly. (**b**, **f**) A small amount of saline (*) is injected to separate the shallow GT (☆) from the index tumor (*arrow*). (**c**, **g**) The catheter (*arrowheads*) is inserted deeper and the saline is injected sequentially. (**d**, **h**) The process is repeated until the deep GT (☆) is separated successfully from the index tumor (*arrow*)

11.4 Efficacy of Artificial Ascites in Assisting MWA for Hepatic Tumors Adjacent to the GT

Kondo et al. [14] firstly reported that the method of artificial ascites made RFA safe and effective for hepatic tumors abutting the GT. Later, several experimental and clinical researches have been reported, which verified the safety and effectiveness of the treatment of hepatic tumors abutting the GT using RFA assisted by artificial ascites. An in vivo experiment suggested that artificial ascites during RFA did not cause heat-sink effect that could affect the volume of ablation zone [16]. A clinical study reported by Song et al. [2] included 143 patients with 148 hepatocellular carcinoma nodules abutting the diaphragm and the GT treated by RFA procedure with artificial ascites. The study showed that artificial ascites was a simple and effective method to avoid thermal injury and improve tumor visibility, with an artificial ascites induction success rate of 90.9 %, primary technique effectiveness of 85.3 %, and local tumor progression of 12 %.

MWA has gained increasing attention due to its higher intratumorous temperature, larger ablation volume, shorter ablation time, and lesser heat-sink effect compared with RFA [17–20]. And multicenter studies have validated that the effectiveness and safety of MWA in the treatment of hepatic tumors [6, 21]. However, few studies which access safety and effectiveness of MWA assisted by artificial ascites for the treatment of hepatic tumors abutting the GT have been reported. Liu et al. reported the value of thermal ablation (including RFA and MWA) with the use of artificial pleural effusion or ascites for treating 56 hepatic tumors close to the diaphragm or the GT. The separation success rate of artificial ascites for 34 tumors close to the GT was 91.2 % (31/34), and the first-time complete ablation rate in 52 cases with successful artificial pleural effusion and ascites use was 90.4 % (47/52), but there were no detailed data about the two thermal ablation modalities in the report.

In our latest study, a total of 36 patients with 36 hepatic malignancies that were located <5 mm from the GT underwent the introduction of artificial ascites before ultrasound-guided percutaneous MWA. These patients included 25 cases with hepatocellular carcinoma and 11 cases with metastatic liver cancer. The mean tumor size was 2.8 ± 1.0 cm. The separation success rate of artificial ascites was 88.9 % (32/36), and the technical effectiveness of MWA in 32 cases with successful separation was 96.9 % (31/32) with a short ablation time (423 ± 124 s) (Figs. 11.4 and 11.5). A thermal monitoring system attached to the microwave unit was used to continuously measure temperature in real time during the MWA procedure. One or two thermocouples (Kangyou Medical, Nanjing, China) were placed into the hepatic tissue around the tumor margin proximal to the GT or the artificial ascites between the index tumor and the GT under ultrasound guidance (Fig. 11.3a, b). Once the measured temperature reached 54 °C, the emission of MWs was stopped immediately and then reactivated after the temperature decreased to 45 °C. The study data showed the temperature of artificial ascites was significantly lower than that of tumor margin (39.1 ± 4.6 °C vs. 52.3 ± 4.5 °C, $P < 0.001$). The temperature data verifies that artificial ascites play a role of cooling and preventing thermal injury to the adjacent GT, even with higher temperature and faster temperature rising during MWA process. The cooling effect did not cause heat-sink effect to reduce the efficacy of MWA, as shown by the high technical effectiveness of MWA in our study.

In our study, local tumor progression was 16.1 % (5/31) during a mean follow-up of 12.1 months. The value is similar to the results (5.9–17 %) of previous reports of MWA for liver cancer [21–23]. But it is relatively higher than the results (4–12 %) of previous reports of RFA with artificial ascites for liver cancer [2, 12, 14]. Although there could be several risk factors for local tumor progression, an ablative margin of 0.5 cm or greater has been suggested as the most important factor for the local control of liver cancer [24, 25]. The fluid space of 5–10 mm thick between the targeted hepatic tumor and important organs after the introduction of artificial ascites is helpful to achieve an adequate ablative margin owing to keep adjacent important organs from

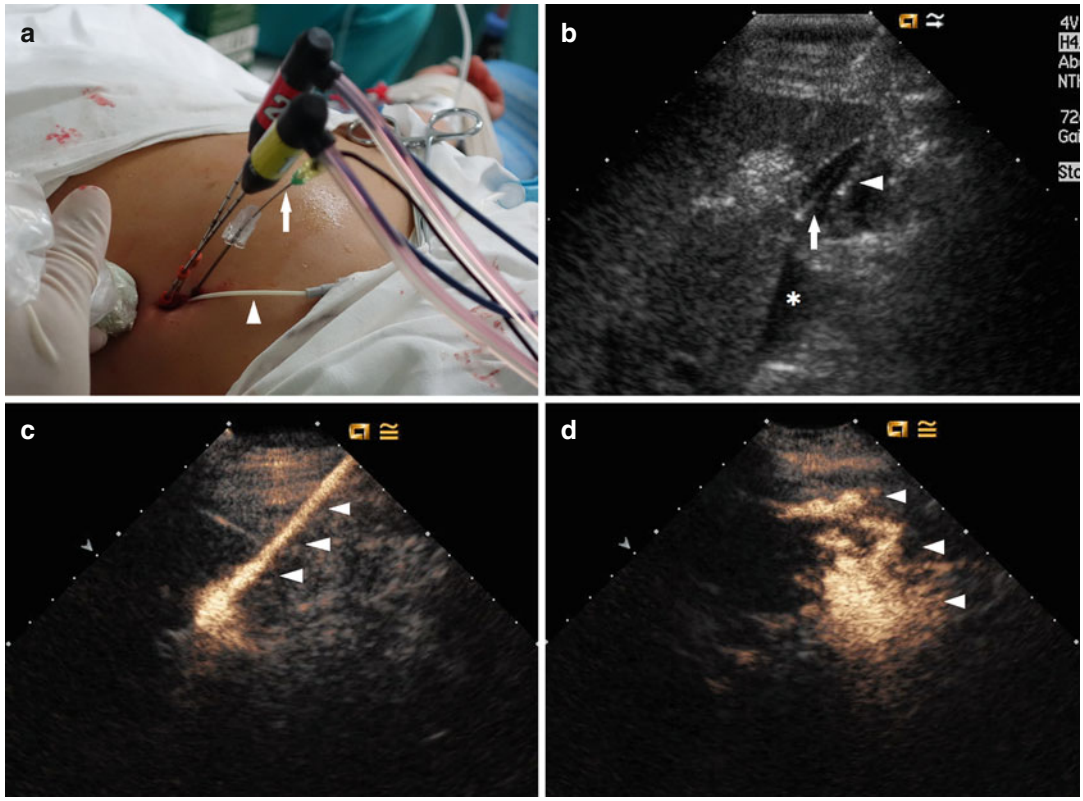

Fig. 11.3 The use of thermal monitoring system and contrast-enhanced US during MWA assisted by artificial ascites. (**a**, **b**) The thermocouple (*arrow*) is placed into the artificial ascites (*). Note the catheter (*arrowhead*). (**c**, **d**) Contrast-enhanced US is helpful to well display the position of the catheter by observing the contrast agent's diffusion (*arrowheads*)

thermal injury. However, the ablative margin was difficult to assess accurately in our study because we mainly performed contrast-enhanced ultrasound after MWA for the early evaluation of the treatment response instead of contrast-enhanced computed tomography or magnetic resonance imaging (Fig. 11.4d, e). In addition, the ablation treatment for metastatic liver cancer generally needs to achieve greater ablative margin than the treatment for hepatocellular carcinoma that was the major study object of previous reports of RFA therapy assisted by artificial ascites.

Postoperative adhesion between abdominal organs following abdominal surgery appears to increase the risk of injury to organs adjacent to index tumor of thermal ablation therapy [1] and prevent the separation of the organs by artificial ascites [2, 26]. Song et al. [2] suggested a prior history of hepatic resection or transcatheter hepatic arterial chemoembolization was the main cause of unsuccessful introduction of artificial ascites. However, Kondo et al. [14] showed the relationship between separability and history of laparotomy was uncertain, and they argued that it was possible that some of the patients with previous history of laparotomy had no adhesions near the index tumor. During introduction of artificial ascites, if distinct adhesion between liver surface and the GT is observed, successful separation would not be achieved. Otherwise, artificial ascites may fail to separate the tumor and adjacent organs due to liquid flowability and influence of body position. On these occasions, it is unsafe to perform thermal ablation even though under strict temperature monitoring; therefore, it is difficult to achieve complete ablation.

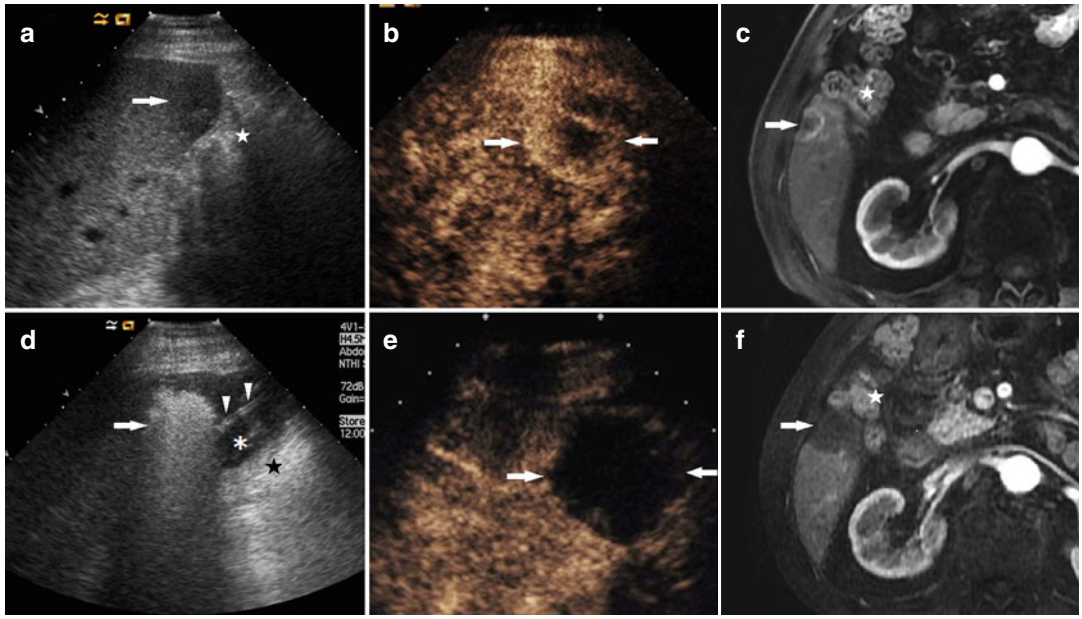

Fig. 11.4 A 74-year-old man with metastatic liver cancer in the right lobe of liver. (**a**) Conventional US shows a 2.5-cm tumor (*arrow*) located at the edge of hepatic segment V adjacent to the intestine (☆). (**b**) Contrast-enhanced US before MWA shows tumor enhancement (*arrows*) in arterial phase. (**c**) Transverse contrast-enhanced magnetic resonance imaging before MWA shows a tumor (*arrow*) with ring enhancement located at the edge of segment V close to the intestine (☆). (**d**) The drip infusion is continued via the catheter (*arrowheads*) to maintain the sufficient fluid space (*) between the ablation zone (*arrow*) and the intestine (☆). (**e**) Contrast-enhanced US shows no enhancement of the ablation zone (*arrows*) at 3 days after MWA treatment. (**f**) Six-month follow-up shows the tumor is completely ablated (*arrow*)

11.5 Safety of Artificial Ascites in Assisting MWA for Hepatic Tumors Adjacent to the GT

Introducing artificial ascites is a simple, safe, and quick technique. Nishimura et al. [12] suggested the artificial ascites could be safely performed in Child-Pugh B cirrhosis patients and did not result in the deterioration of liver function. According most previous studies, residual ascites disappeared spontaneously without additional diuretics and paracentesis [2, 11, 14]. But Nishimura et al. [12] reported that post-procedural diuretics were required in few cases (7.5 %) with a large volume (>1,000 ml) of artificial ascites. Hemorrhage and tumor seeding are potential complications related to artificial ascites, because ascites could wash away coagulation substances at the puncture site, decrease the compression of the opposing abdominal wall against the liver, and also facilitate the dissemination of tumor cells at the same time. However, no intraperitoneal hemorrhage and tumor seeding after RFA and MWA were observed during follow-up in previous investigations. According to our experience, cauterizing the needle track during MW antenna withdrawal may effectively prevent hemorrhage and tumor seeding. In our clinical study, one patient experienced a major complication involving infection of the hepatic ablation zone after MWA who was cured by antibiotic therapy. The incidence rate of complication in our study (2.8 %) was similar to the results in most previous studies of RFA or MWA with artificial ascites for liver cancer (Table 11.1).

11.6 Other Techniques of Treatment for Hepatic Tumors Adjacent to the GT

Our previous research showed MWA assisted with small dose of ethanol injection for hepatic tumors abutting the GT could achieve high complete ablation rate under strict temperature monitoring

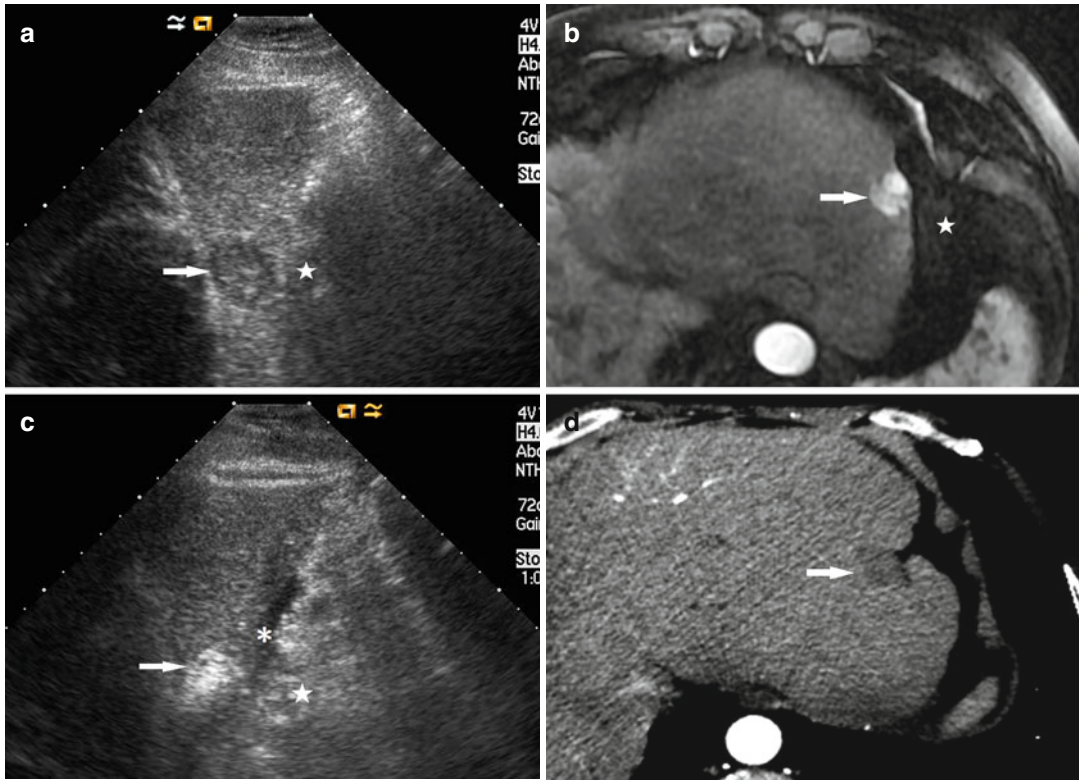

Fig. 11.5 A 51-year-old man with hepatocellular carcinoma in the left lobe of liver. (**a**) Conventional US shows a 2.7-cm hypoechoic nodule (*arrow*) located at the edge of hepatic segment II adjacent to the stomach (☆). (**b**) Contrast-enhanced magnetic resonance imaging before MWA shows a tumor (*arrow*) located at the edge of segment II adjacent to the stomach (☆). (**c**) After the introduction of artificial ascites (*), the stomach (☆) is successfully separated from the ablated zone (*arrow*). (**d**) Contrast-enhanced computed tomography 12 months after MWA shows nonenhancing ablation zone (*arrow*)

[27]. But this strategy mostly depends on the operator's experiences and techniques. Though artificial ascites is a minimally invasive method and is easily carried out without general anesthesia, successful separation cannot always be achieved especially for patients with a history of abdominal surgery or transcatheter hepatic arterial chemoembolization. In such circumstances, laparoscopic thermal ablation may offer a better therapeutic choice. Hirooka et al. suggested that laparoscopic thermal ablation should be carried out in cases with tumor >2 cm or adhesions near the tumor [7]. Image-guided brachytherapy technique may be applied in tumors located near risk structures such as liver hilum, gallbladder, and GT, due to its efficiency and its minimal invasiveness [28]. We performed iodine-125 brachytherapy as a supplement therapy after MWA for such cases that had not achieved separation between the hepatic tumor and the GT (Fig. 11.6). The interposition of a balloon catheter [8] and placement of sodium hyaluronate solution [9] are other methods that can avoid damage to the adjacent GT by separating the ablation area and adjacent organs. The interposition of a balloon catheter is used infrequently and no research of the relatively large size has been reported. A preliminary report showed that sodium hyaluronate created a continuous separation between the liver surface and the adjacent organs due to its high viscosity; therefore, it could effectively prevent thermal injuries to adjacent organs [9].

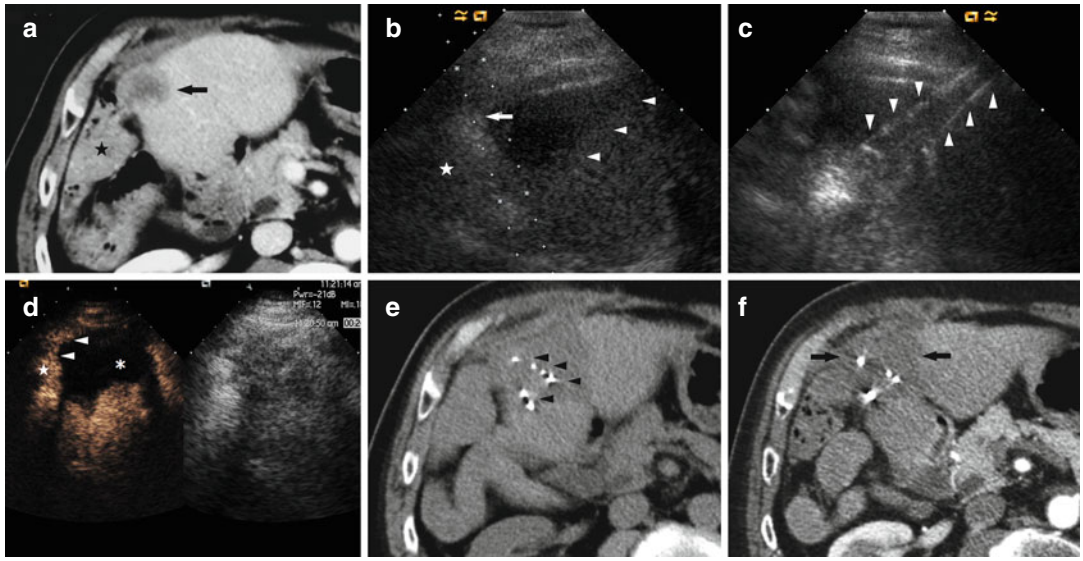

Fig. 11.6 A 75-year-old man with a history of partial hepatectomy suffering from metastatic liver cancer in the right lobe of liver. (**a**) Contrast-enhanced computed tomography before MWA shows a tumor (*arrow*) with ring enhancement located at the edge of segment V adjacent to the intestine (☆). (**b**) Conventional US shows a 4.2-cm hypoechoic nodule (*arrowheads*) located at the edge of hepatic segment V adjacent to the intestine (☆). After 350 mL saline is injected via the catheter (*arrow*), the separation between the index tumor (*arrowheads*) and the intestine (☆) is unsuccessful. (**c**) Microwave antennas (*arrowheads*) are placed in the relatively safe area in the nodule. (**d**) Contrast-enhanced US shows irregular enhancement (*arrowheads*) representing residual unablated tumor at the edge of ablation zone (*) adjacent to the intestine (☆). (**e**) Computed tomography shows that iodine-125 particles (*arrowheads*) are implanted in the edge of the index tumor. (**f**) Six-month follow-up shows nonenhancing treatment zone (*arrows*)

Conclusion

Ultrasound-guided percutaneous MWA assisted by artificial ascites is a safe and effective method for the treatment of primary and metastatic hepatic tumors adjacent to the GT. This strategy can achieve good local control of such tumors without serious complications. The use of artificial ascites can extend the indications of MWA therapy and can reduce the complications after MWA treatment.

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Microwave Ablation in the Treatment of Hepatocellular Carcinoma Near Diaphragm

12

Ying Jia, Xiao-ling Yu, and Ping Liang

Abstract

Hepatocellular carcinoma near the diaphragm is known as refractory tumor due to its special position. Surgery is regarded as the "golden standard," but over 70 % of the patients would experience intrahepatic recurrence within 5 years and most of them have been considered unsuitable for operation any more. Also, there are some limits of surgery, such as large surgical trauma, severe cerebrovascular diseases of patients who cannot undergo the surgery, and advanced age of the patients. Retrospective study shows that long-term prognosis of percutaneous ethanol ablation for small tumors (diameter <3 cm) is similar to those reported with the surgery, but it is easier to result in incomplete necrosis for those diameter between 3 and 5 cm or diaphragm damage because of the unclear reflection of tumor nearby the diaphragm sometimes. Some studies have reported that the percutaneous radiofrequency ablation is easier to cause thermal damage in treating the liver tumors near important organs and tissues (including near the diaphragm) and results in tumor recurrence because of the insufficiency of the safe range. In this chapter, microwave ablation for hepatic tumors near the diaphragm is introduced from a clinical result viewpoint.

Keywords

Microwave • Radiofrequency • Ablation • Hepatocellular carcinoma

Abbreviations and Acronyms

HCC	Hepatocellular carcinoma
MWA	Microwave ablation
RFA	Radiofrequency ablation
US	Ultrasound

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12.1 Introduction

Hepatocellular carcinoma (HCC) near the diaphragm is known as refractory tumor due to its special position. Sometimes it is hard to display because of the gases from the lung, and it could result in diaphragm damage. Appropriate and effective treatment is the target that doctors are trying to achieve. The most commonly used treatment methods are surgery, transcatheter arterial chemoembolization, percutaneous ethanol ablation, radiofrequency ablation (RFA), microwave ablation (MWA), and so on. This chapter describes the technique, discusses the results, and evaluates the feasibility of ultrasound (US)-guided percutaneous MWA for HCC near the diaphragm.

12.2 Equipment

The MWA and US instruments are the same as before.

12.3 Indications

MWA can be used to treat the patients with HCC near the diaphragm when they meet the following conditions: (1) the size of single nodular hepatic lesion is less than or equal to 3 cm; three or fewer multiple lesions, with a maximum dimension of 3 cm or less; (2) the percutaneous approach is accessible to the tumors; (3) the nodules can be displayed clearly under US; (4) to diminish burden of tumor, palliative care could be implemented as one part of systemic comprehensive treatment when the size of single nodular hepatic lesion is more than 5 cm or the number of lesions is more than three; and (5) others are the same as with the general indications of liver cancer ablation.

12.4 Technical Essential

Under the circumstance of no artificial pleural effusion, we summarize some technique skills based on experience, in order to better display the diaphragmatic top tumor to reach better treatment [1]:

1. Use the left recumbent position or the right anterior oblique when the tumor under the diaphragm is in the right lobe of the liver. While the tumor under the diaphragm is in the left lobe, using right side or left anterior oblique can make the tumor separate from the diaphragm.
2. Ablate tumor area adjacent to the diaphragm first; the direction is to enter the needle tip from the foot side to the diaphragm.
3. Attach great importance to the real-time monitoring. Scan the treatment area from the right costal margin and xiphoid process to the diaphragmatic top. Or scan it from the right axillary midline and axillary line between the ribs in a horizontal position. These scan methods can improve the display of the diaphragm part. The above scanning plane is also used in displaying the small tumors near the diaphragm of the atrophic right hepatic lobe.
4. The direction of the needle should be vertical with the diaphragm. And the reasonable distance between the needlepoint and the diaphragm should be more than 3 mm. We also can use the temperature measurement techniques when necessary to keep the temperature at 50–60 °C.
5. The numbers of needles are according to the size of the tumor. Generally speaking, we use two needles when the size of the tumor is bigger than 2 cm.
6. The treatment of tumors adjacent to the heart margin should be careful. Ten to fifteen milliliters of dehydrated sterile 99.5 % ethanol can be injected into the tumor in the dangerous area neighboring the heart margin.

12.5 Clinical Efficacy of MWA

MWA is one of the effective localized thermal ablation methods, which has been widely used in East Asia. Microwave energy does not appear to be limited by charring and tissue

desiccation compared with RFA. So, lesion temperature may become considerably higher with microwave systems than it does with radiofrequency systems [2]. It has been reported that MWA in tumor near the diaphragm is safe and effective [3, 4]. In 2002, Shibata reported 36 cases with tumors near the diaphragm received MWA. The result showed that the technique effectiveness rate was 89 %. And in 2012, Meng Li et al. [5] reported 96 cases with tumors adjacent to the diaphragm acquired a satisfactory result. The technique effectiveness rate was 94.8 % and the locoregional recurrence rate was 18.8 %. Like that in the RFA treatment, artificial pleural effusion in the therapy of MWA is also effective. The tumor near the diaphragm is more likely to be affected by lung air and thus reveals bad condition or cannot be shown completely. Injecting pleural effusion under the diaphragm can not only protect the diaphragm but also improve the display of tumor on top of the lung. In 2013, Dezhi Zhang et al. [6] reported 112 cases with tumors near the diaphragm received MWA after artificial pleural effusion. The result showed that the technique effectiveness rate was 98.2 % and the locoregional recurrence rate was only 8 %. From the above data, we can see that the artificial pleural effusion in the therapy of microwave ablation can improve the technique effectiveness rate and reduce the locoregional recurrence rate. But not all the tumors adjacent to the diaphragm need artificial pleural effusion. Artificial pleural effusion is needed when the tumor cannot be displayed clearly under US. Also, using artificial pleural effusion will lengthen the time of therapy and increase the trauma. So, if the lesions can be displayed clearly under US, the artificial pleural effusion is not indispensible in MWA.

According to our latest study data (between December 2007 and December 2012), we evaluated the feasibility and effects of MWA in 227 patients (M:F = 179:48; mean age, 59 ± 10 years, range 32–82 years) with 329 lesions (average diameter, 2.4 ± 1.2 cm) adjacent to the diaphragm. Meanwhile, we compared the curative effect with another 104 lesions (average diameter, 2.5 ± 1.6 cm) not near the diaphragm as control group. The technique effectiveness rates of the study group and the control group are 93.3 and 97.1 %, respectively ($p = 0.78$). The follow-up time are 1–60 months (median, 15 months) 35 lesions (10.6 %) of study group occurred local recurrence in 1–30 months after ablation; seven lesions (6.9 %) of control group occurred local recurrence in 4–24 months. No significant statistical difference in the local recurrence rate was found between two groups ($p = 0.67$). In a study group, new lesions were observed in 83 of 227 (36.6 %) in 1–35 months after ablation, and 80 cases (35.2 %) received treatment again due to tumor local recurrence or new lesions. The 1-, 3-, and 5-year survival rates in the study group were 87.7, 61.2, and 41.0 %, respectively and the 1-, 3-, and 5-year survival rates in the control group were 88.1, 57.5, and 36.0 %, respectively. There was no significant difference in the survival rates between two groups ($p = 0.88$) (Figs. 12.1, 12.2, and 12.3).

This study shows that the technique effectiveness rate of MWA of tumor adjacent to the diaphragm is similar with the control group with the tumor not near the diaphragm. No obvious difference of the recurrence rate and survival rate was found between the two groups. And this research result is consistent with other reports using RFA [7, 8]. The rate of complications is low in our study. One reason is the application of the cooled-shaft antennas which could easily avoid skin burn. Another reason of low incidence rate of complications is that we performed percutaneous MWA assisted with temperature monitoring, which could avoid damage to adjacent organs.

Meanwhile, US has its limits. Some nodule adjacent to the diaphragm still cannot be displayed clearly even using artificial pleural effusion. In this situation, other MWA techniques are feasible, such as MRI-/CT-guided MWA, laparotomy MWA and laparoscope-guided MWA. But there were no reports of the application of these technologies in tumors near the diaphragm so far (Figs. 12.1, 12.2, and 12.3).

12.6 Complications

Side effects and complications of thermal ablation for lesions adjacent to the diaphragm include pleural effusion, pneumothorax, diaphragmatic muscle injury, mild bleeding, skin burn, pain, slight fever, nausea, and vomiting [9, 10]. Li et al. [5] reported nine cases (10.1 %) suffered from mild or moderate right shoulder pain which ranged in duration from 2 to 13 days, with a mean duration of 6.5 days; two cases (2.2 %) suffered from severe right shoulder pain which needed analgesics for control and ranged in 10 days' duration, followed by mild pain for 2 months; and 21 cases (23.6 %) developed pleural effusion. Of these 21 cases, 18 cases had a small amount of pleural effusion and had the symptoms self-relieved in 1 week, and three cases had a moderate or great amount of pleural effusion and were treated by placement of a tube drain. Nausea and vomiting developed in eight cases (9.0 %) and disappeared within 1–2 days after ablation.

In our study, 227 patients had no immediate serious complications. Only seven cases (3.1 %) had a small amount of pleural effusion without special treatment. One case had a

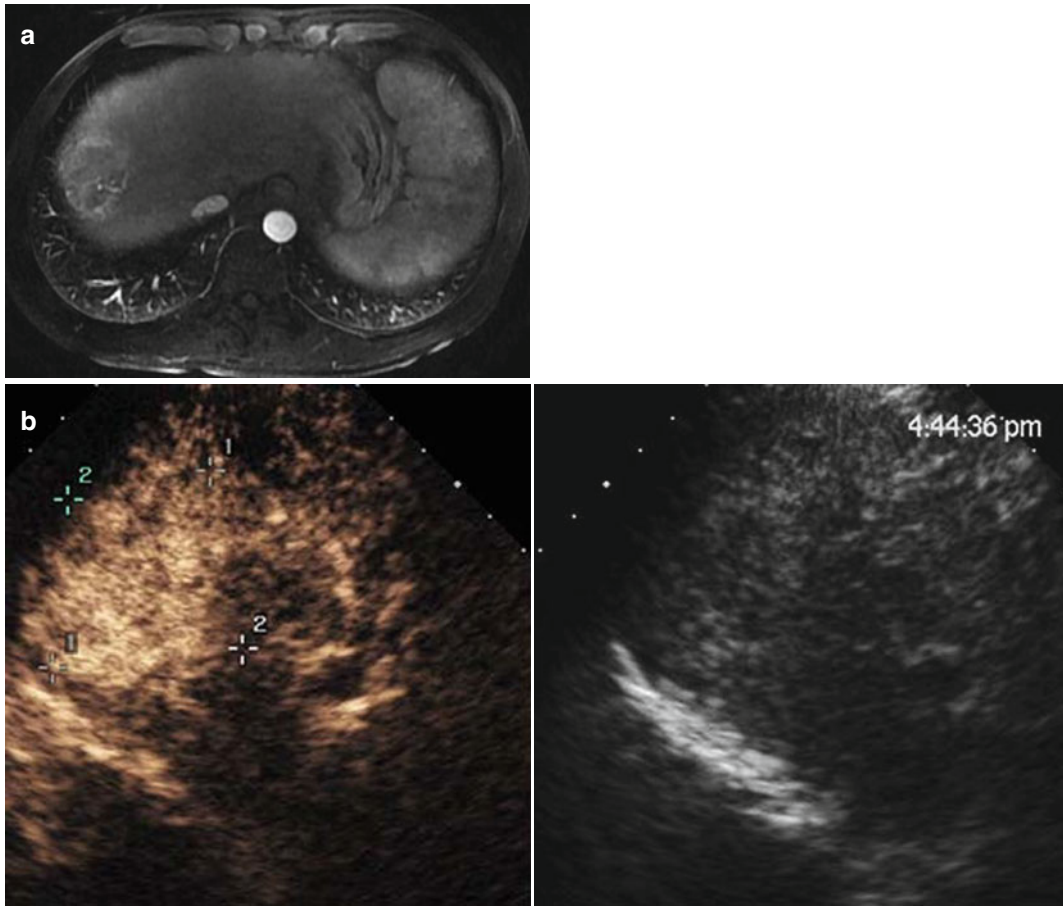

Fig. 12.1 Magnetic resonance imaging (MRI) findings in a 45-year-old woman with hepatocellular carcinoma (HCC). (**a**) Contrast-enhanced MRI scan shows a lesion with hyperenhancement images near diaphragm (*arrow*); (**b**) arterial phase in contrast-enhanced ultrasound (CEUS) shows one hyperenhancement lesions (*arrow*) with the size of 5.4×4.9 cm; (**c**) MRI scan obtained 3 months after MWA shows a signal area with no enhancement, suggestive of complete necrosis (*arrow*); (**d**) CEUS scan obtained 3 months after MWA shows a hypoechoic area with no enhancement, suggestive of complete necrosis (*arrow*)

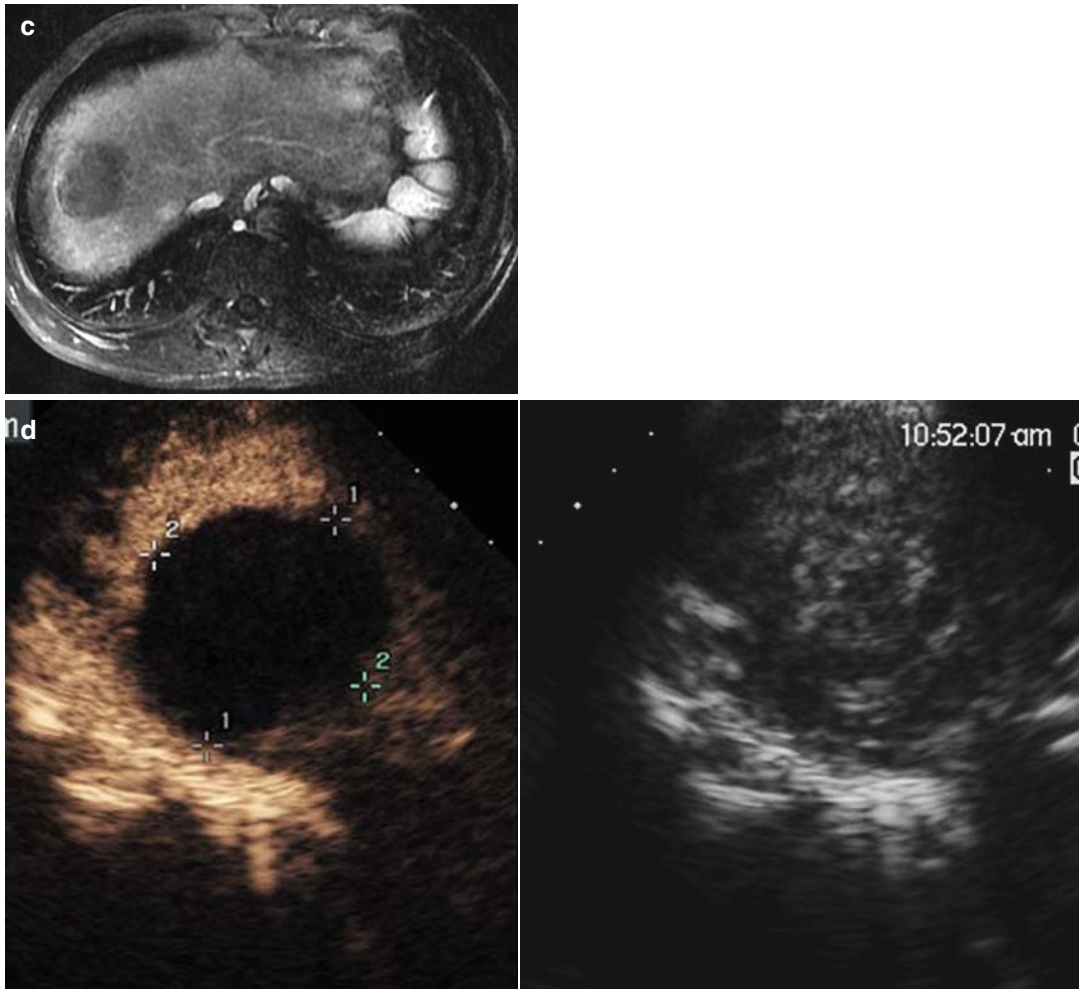

Fig. 12.1 (continued)

moderate amount of pleural effusion with the treatment of a tube drain, and the symptom was relieved in 1 week. Fifty cases had a low-grade fever (not more than 38.1 °C), and the temperature reduced to normal within 1–7 days without special treatments. Also, there were some patients who had moderate pain. The pain disappeared spontaneously without any special treatment within 2 weeks.

12.7 Other Local Techniques

Other local therapies have been employed to treat HCC near the diaphragm (Table 12.1).

12.7.1 Surgery

Surgery is regarded as the "golden standard" to treat HCC, as well as those tumors near the diaphragm. However, there is no report about resection for the tumors adjacent to the diaphragm.

12.7.2 Percutaneous Ethanol Ablation

The lesion texture of HCC is softer than the dense cirrhosis group around, so the ethanol is more likely to disperse within the tumor to make 70 % of the small tumors completely necrotized

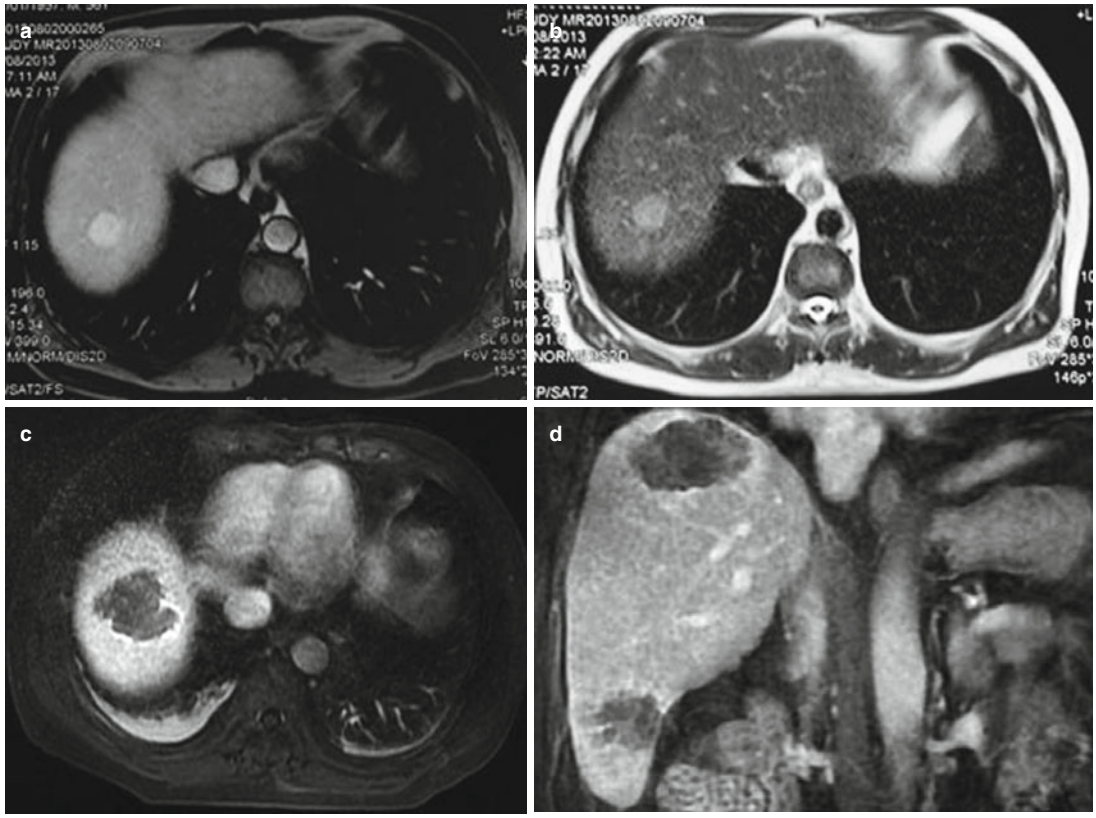

Fig. 12.2 Contrast-enhanced MRI in a 56-year-old man who underwent MWA of HCC. (**a**) Hepatic delay phase preablation image shows an HCC (*arrow*); (**b**) hepatic T2 preablation image shows an HCC (*arrow*) with the size of 2.0 × 1.8 cm; (**c**) hepatic transverse image after 6 months of postablation shows a nonenhancing zone of hypointensity enveloping the tumor (*arrow*); (**d**) hepatic coronal plane image after 6 months of postablation shows a nonenhancing zone of hypointensity enveloping the tumor (*arrow*)

[11–14]. Retrospective study shows that ethanol ablation's long-term prognosis for small tumors is similar to those reported with the surgery, but is with higher local recurrence, and 43 % of the tumors are over 3 cm long [15]. Because goals of skilled puncture technique and uniform distribution of the ethanol within the lesion are difficult to reach, it is easy to result in incomplete necrosis. Nonrandomized study shows that RFA and MWA curative effect (including the survival rate and local control rate) of HCC is better than that of anhydrous alcohol injection. But in recent years, some reports about the anhydrous alcohol injection in the treatment of tumor near the diaphragm also can be found. And the results are as follows. In 2003, Lencioni reported 50 cases with tumors (diameter <3 cm) near the diaphragm received percutaneous ethanol ablation. The result showed that the technique effectiveness rate was 82.6 %, while the locoregional recurrence rate was 38 %. In 2004 and 2005, Lin reported 52 cases and 62 cases, respectively, with tumors (diameter ≤3 cm) adjacent to the diaphragm, acquired a satisfactory technique

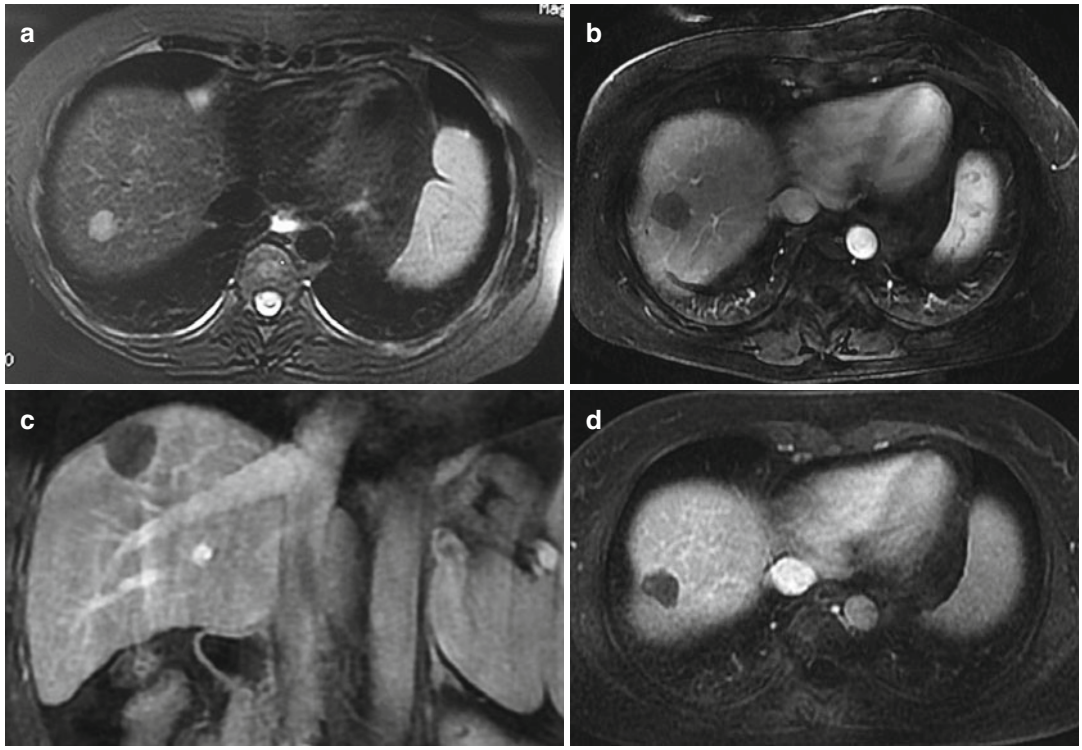

Fig. 12.3 Contrast-enhanced MRI in a 42-year-old man who underwent MWA of HCC. (**a**) Hepatic T2 preablation image shows an HCC (*arrow*) with the size of 1.6×1.4 cm; (**b**) MRI scan obtained 3 months after MWA shows a signal area with no enhancement, suggestive of complete necrosis (*arrow*); (**c**) hepatic coronal plane image after 12 months of postablation shows a nonenhancing zone of hypointensity enveloping the tumor (*arrow*); (**d**) hepatic transverse image postablation 12 months shows a nonenhancing zone of hypointensity enveloping the tumor (*arrow*)

effectiveness rate of 88 %. But the locoregional recurrence rate was only as much as 45 and 34 %, respectively.

12.7.3 RFA

RFA in small HCC has received a wide clinical application. Some earlier studies have reported that the RFA was easier to cause thermal ablation damage in treating the liver tumors near the diaphragm [16]. So the liver tumors near the diaphragm once were considered to be the refractory cases with RFA. Some studies even thought these tumors were not the indications of the RFA [17]. But some recent studies reported that the RFA in HCC near the diaphragm had achieved satisfactory results. In 2005, Lin reported a total of 78 patients with HCCs of 3 cm or less received RFA. The rate of complete tumor necrosis was 96.1 % (75/78 HCC tumors). After a median of 35 months (mean, 26.3 ± 12.7 months; range, 4–44 months) of follow-up, some patients were lost to follow-up. The local recurrence rate was 13.3 % (8/60). And the overall survival rates at 1, 2, and 3 years were 93, 81, and 74 %, respectively.

Table 12.1 The curative effect of a variety of minimally invasive techniques in HCC near the diaphragm

Author	Method	No. of patients	Size (cm)	Technique effectiveness rate (%)	1-year survival rate (%)	2-year survival rate (%)	3-year survival rate (%)	4-year survival rate (%)	Follow-up (month)	Locoregional recurrence rate (%)
Shiina et al. [18]	RFA	118	N/A	100	97	91	N/A	74	N/A	2
Lin et al. [19]	RFA	52	≤4	96	90	82	N/A	N/A	24.5 ± 11.3	18
Lin et al. [19]	PEI	62	N/A	88	88	66	51	N/A	36	34
Lencioni et al. [20]	PEI	50	N/A	82.6	96	N/A	N/A	N/A	22.4 ± 8.6	38
Li et al. [5]	MW	96	≤4	94.8	N/A	N/A	N/A	N/A	15–17.5	18.8
Zhang et al. [6]	MW	112	2.5	98.2	65.8	53.6	53.6	N/A	1.2–35.4	8
Our study	MW	329	2.4	93.3	87.7	N/A	61.2	N/A	15	10.6

RFA radiofrequency ablation, *PEI* percutaneous ethanol injection, *N/A* not available

Conclusion

In conclusion, MWA with cooled-shaft antennas is safe and can achieve a satisfactory effect in the treatment without artificial pleural effusion of HCC near the diaphragm percutaneously.

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13 Application of Artificial Pleural Effusion in Microwave Ablation of Liver Tumor

Dezhi Zhang and Ping Liang

Abstract

Image-guided percutaneous thermal ablation therapy, such as radiofrequency or microwave, has been widely used for liver tumors. However, when the tumors are located in the hepatic dome, it is difficult to perform ablation because of poor visualization due to the presence of pulmonary air, which can obstruct the transmission of ultrasound or make it impossible to identify a safe puncture path. In order to perform therapy on liver tumors located in the hepatic dome, the artificial pleural effusion technique has been applied. This chapter introduces indications for artificial pleural effusion, procedure for artificial pleural effusion, the category of solution injected, and our study concerning the efficacy of artificial pleural effusion.

Keyword

Microwave • Ablation • Hepatocellular carcinoma • Artificial pleural effusion

Abbreviations and Acronyms

MWA Microwave ablation

13.1 Introduction

Image-guided percutaneous thermal ablation therapy, such as radiofrequency or microwave, has been widely used for liver tumors, especially for small hepatocellular carcinoma [1–10]. For imaging guidance, ultrasound has many advantages such as easy availability and real-time monitoring capability, which make make it the most common imaging guidance approach [11–15]. However, when the tumors are located in the hepatic dome, it is difficult to perform ablation because of poor visualization

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owing to the presence of pulmonary air, which can obstruct the transmission of ultrasound or make it impossible to identify a safe puncture path [16–20].

In order to perform therapy on liver tumors located in the hepatic dome, the artificial pleural effusion technique has been applied. Shinya Shimada et al. in 2001 first reported the application of an artificial hydrothorax in microwave coagulation therapy of liver tumors, and concluded that the technique is a simple, inexpensive, and accurate therapy for the treatment of liver tumors in the hepatic dome [21]. After that, a series of articles about the application of artificial pleural effusion in microwave or radiofrequency ablation of liver tumor were published, which proved that artificial pleural effusion with percutaneous MWA or radiofrequency ablation could be used to perform therapy on liver tumors in the hepatic dome [18–20, 22–25].

13.2 Indication of Artificial Pleural Effusion

So far, the purpose of artificial pleural effusion in all papers was to extend the indications of percutaneous thermal ablation for liver tumors in the hepatic dome. Therefore, the indications for artificial pleural effusion is as follows: firstly, liver tumors in the hepatic dome can not be revealed by ultrasound, or liver tumors can only be showed partially which would cause an incomplete ablation necrosis zone, and secondly, no proper puncture path can be identified because of restriction in the lungs. Other indications are the same as the general indications of liver cancer ablation. Contraindications include all kinds of acute or severe chronic respiratory insufficiency and cardiac insufficiency, chest infection, and empyema.

13.3 Procedure for Artificial Pleural Effusion

The basic instruments for artificial pleural effusion are an ultrasonic instrument with puncture needle holder, a 16G trocar, and infusion apparatus. The position of patients is semi-erect and left lateral. The region of the pleural cavity can be identified on ultrasound between the right anterior axillary line and the right posterior axillary line in patients. After local anesthesia, the 16G trocar is inserted through the costophrenic angle. Interventional radiologists can monitor the process of puncture by ultrasound and tell patient to hold their breath. When the sudden reduction of resistance is felt, 10 ml of 0.9 % saline solution is injected from the trocar to identify whether the tip of the needle has entered into the pleural cavity. If the tip of the needle is in the pleural cavity, the outer soft sheath is pushed into the pleural cavity to avoid injuring the lung, and the stylet of the needle is extracted. Then, the outer sheath is connected with the infusion set, and the fluctuation of the infusion in relation to the rhythm of breath can be observed. A sufficient amount of 0.9 % saline solution is injected until the tumor can be well-revealed or a safe path for puncture is fully identified. The volume of solution injected is about 500–1,500 ml. At the same time, the vital signs and oxygen saturation of the blood must be checked. After the therapy, the pleural effusion will be drawn out.

Different methods or instruments for artificial pleural effusion have been reported. Shinya Shimada et al., who first reported artificial pleural effusion, used the 14-F trocar to carry out thoracocentesis under general anesthesia using one-lung ventilation. Considering safety and avoiding injuring the lung, artificial pleural effusion as an innovative technology was performed under general anesthesia using one-lung ventilation at the beginning. Nowadays, artificial pleural effusion can be performed under local anesthesia. Akimichi Kume et al. reported two kinds of method for inducing artificial pleural effusion, which were called the two-step method and the one-step method [22]. The two-step method was performed as follows. First, a 23-gauge needle was inserted into the pleural space. After 200 ml of saline was injected into the pleural space, the 23-gauge needle was withdrawn and a central venous access kit was catheterized to instill more saline. Although a little complicated and time-consuming, this was a relatively safe method. Takahide Uehara et al. also reported a similar method to induce artificial pleural effusion [19]. The one-step method was performed as follows. Akimichi Kume et al. used

an18-gauge Tuohy needle which was connected to a drip infusion set with 500 ml saline to puncture the thorax. The needle tip was inserted into the thorax under ultrasound monitoring, which can also be confirmed by the drip of saline. In addition, Yasunori Minami et al. [20] and Masahiko Koda et al. [23] reported the use of a Veress needle (Olympus Optical, Tokyo, Japan). The Veress needle consists of a blunt-tipped inner stylet and a sharp outer needle. Once the needle entered the pleural cavity, the blunt-tipped inner stylet extended to push the lung away to prevent injury. In a short, any of the methods mentioned above can acquire a satisfactory result.

13.4 Category of Solution Injected

Considering the kinds of fluid instilled into thorax, Paul F. Laeseke et al. reported their research with regard to the relative effectiveness of 0.9 % saline and 5 % dextrose in water for protecting the diaphragm and lung during radiofrequency [26, 27]. They draw a conclusion that "Instillation of 5 % dextrose in water into the peritoneal cavity before hepatic radiofrequency ablation decreases the risk and severity of diaphragm and lung injuries compared with 0.9 % saline in an animal model." Because the heating effect of radiofrequency ablation is caused by the friction of ions, 5 % dextrose in water which is isotonic and nonionic could be an ideal buffer to infuse into the pleural cavity. However, when the method of ablation is microwave, 0.9 % saline solution as an artificial fluid is recommended, firstly because the heating theory of microwave ablation is the vibration of dipolar molecules rather than the friction of ions, and secondly because the use of 5 % dextrose in water is not suitable for diabetes patients, which restricts the use of 5 % dextrose in water.

13.5 Safety of Artificial Pleural Effusion

With regard to the safety of artificial pleural effusion, potential complications related to the procedure are bleeding, tumor seeding, and pleuritis. No major complications or deaths related to the artificial pleural effusion procedure have been identified in the published literature. Minor complications such as moderate pain, cough, mild dyspnea, low-grade fever, temporary elevation of liver transaminase, few subcutaneous hydrops, etc. disappeared spontaneously without any special treatment. Tae Wook Kang et al. [25] reported thermal injury to the diaphragm, and used computed tomography to observe the thickness of the diaphragm. Some papers reported that only a few patients had moderate pain, which aggravated when deeply breathing or changing position, and the pain disappeared spontaneously without any special treatment within 2 weeks. To avoid tumor seeding in the pleural cavity, puncture biopsy through artificial pleural effusion is forbidden. If it is necessary to insert a microwave antenna into tumor through artificial pleural effusion because there was no other safe path, repeated punctures are forbidden, and the applicator track must be heated with sufficient microwave energy by stopping the cooling-shaft water dump. No tumor seeding in pleural cavity has occurred in the existing literature.

13.6 Efficacy of Artificial Pleural Effusion

In reviewing the efficacy of artificial pleural effusion, our department summarized the data of 112 sessions of MWA with artificial pleural effusion which were performed on 102 consecutive patients with 119 liver tumors (17 of the patients had two tumors). Induction of artificial pleural effusion was achieved successfully in 110 of 112 sessions (98.2 %). Two sessions of artificial pleural effusion failed. One session had to stop inducing saline solution at the beginning of the procedure because of dyspnea. The other one was a recurring case, and artificial pleural effusion had been induced previously. The saline solution could not be induced into the thorax, and some liquid effused into the chest wall.

Among 110 successful artificial pleural effusion sessions, 82/83 sessions (98.8 %) made tumors clearly visible by gray-scale ultrasound ($n=74$) and contrast-enhanced ultrasound ($n=8$);

26/27 sessions (96.3 %) acquired a safe puncture path for percutaneous MWA. Two sessions failed to achieve the preoperative objective. One patient's tumor was located at segment VII. The size of the tumor was about 0.9×0.7×0.7 cm. Even after about 800 ml 0.9 % saline solution had been injected, the tumor could not be revealed clearly. The other patient's tumor was located at segment II. After about 1,500 ml 0.9 % saline solution had been injected, there was still no safe puncture path to avoid injuring the lung (Figs. 13.1 and 13.2).

13.7 Efficacy of Percutaneous MWA with Artificial Pleural Effusion

To examine the efficacy of percutaneous MWA with artificial pleural effusion, we designed a case-control study, and compared the primary technique effectiveness rate, local tumor progression rate, and tumor-free survival rate between an artificial pleural effusion group and a control group which was matched in terms of tumor differentiation, tumor size, and tumor

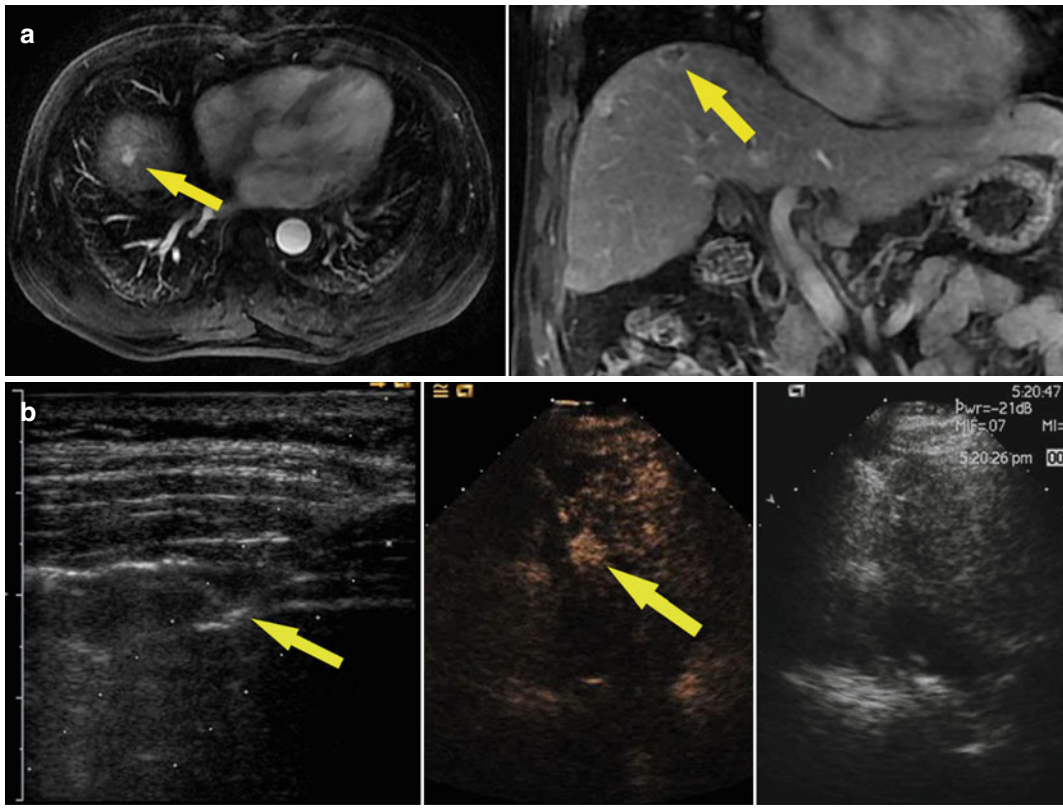

Fig. 13.1 Images in a 58-year-old man with 1.8 cm hepatocellular carcinoma treated by percutaneous microwave ablation (MWA) with artificial pleural effusion. (**a**) Contrast-enhanced magnetic resonance imaging (MRI) before MWA shows the neoplasm appearing in hyper-enhancement (*small arrow*) on arterial phrase and hypo-enhancement (*large arrow*) on venous phrase. (**b**) *Left* sonogram shows the puncture of the pleural cavity with a 16-gauge BD angiocath needle (*small arrow*). The *middle* sonogram shows the hyper-enhanced nodule on contrast-enhanced ultrasound, which is unclear on grey scale (*large arrow*). (**c**) Sonogram shows the procedure of MWA. The ablating area appears as a hyper-echoic region (*large arrows*) with artificial pleural effusion surrounded on grey-scale (*small arrows*). (**d**) Contrast-enhanced MRI 1 month after MWA shows the ablation zone appearing unenhanced in the arterial phrase (*small arrow*) and the venous phrase (*large arrow*)

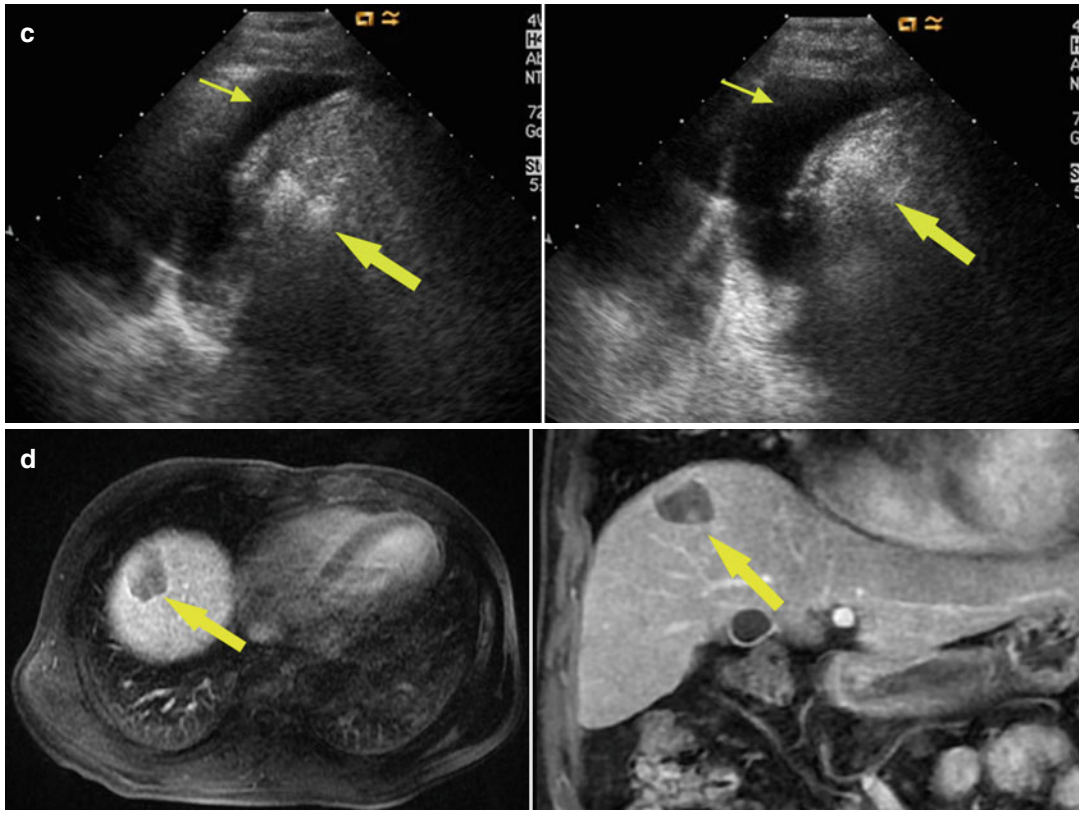

Fig. 13.1 (continued)

location. In previous studies [1, 3], tumor differentiation and tumor size were chosen as the independent prognostic factors affecting recurrence of hepatocellular carcinoma after microwave ablation treatment. Therefore, tumor differentiation and tumor size were selected as a matching standard to make sure that the two groups were balanced as far as possible. In addition, we matched tumor location between the two groups to compare complications after treatment. The results of our study showed that the primary technique effectiveness rate, the 1-, 2-, and 3-year local tumor progression rates, and the 1-, 2-, and 3-year tumor-free survival rates in the two groups had no significant difference. Therefore, percutaneous MWA with artificial pleural effusion for liver tumors located in the hepatic dome has a similar therapeutic effect to that of percutaneous MWA for liver tumors with good ultrasonic visibility.

Conclusion

Artificial pleural effusion could be a feasible, safe, and effective assistive technique for the expansion of indications of microwave or radiofrequency ablation for liver tumors located in the hepatic dome.

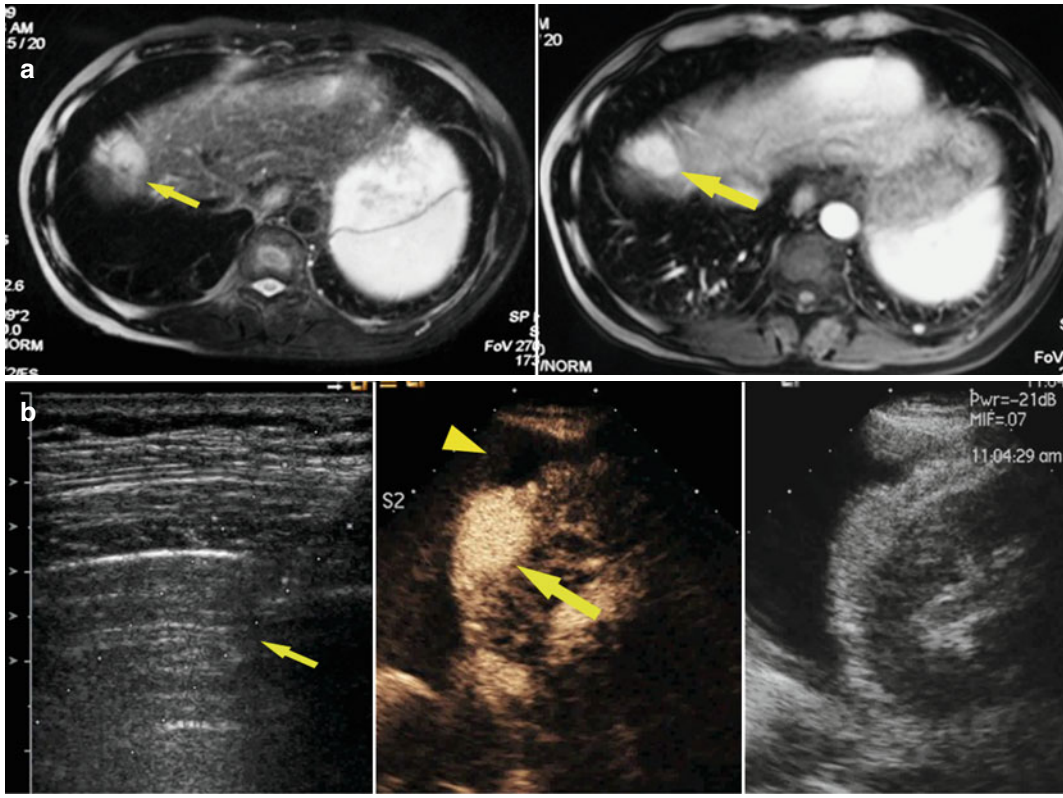

Fig. 13.2 Images in a 58-year-old man with 2.6 cm hepatocellular carcinoma treated by percutaneous MWA with artificial pleural effusion. (**a**) Contrast-enhanced MRI before MWA shows the neoplasm appearing as a high signal on T2WI (*small arrow*) and in hyper-enhancement (*large arrow*) on arterial phrase. (**b**) *Left* sonogram shows the puncture of the pleural cavity with a 16-gauge BD angiocath needle (*small arrow*). The *middle* sonogram shows the hyper-enhanced nodule on contrast-enhanced ultrasound (*large arrow*) with the artificial pleural effusion surrounded (*triangle*). (**c**) Sonogram shows the procedure of MWA. The ablating area appears as a disturbed blood flow on color-Doppler (*small arrow*) for microwave emitting, and as a hyper-echoic region on grey-scale (*large arrow*). (**d**) Contrast-enhanced MRI 1 month after MWA shows the ablation zone appearing as a low signal on T2WI (*small arrow*) and unenhanced in the arterial phrase (*large arrow*)

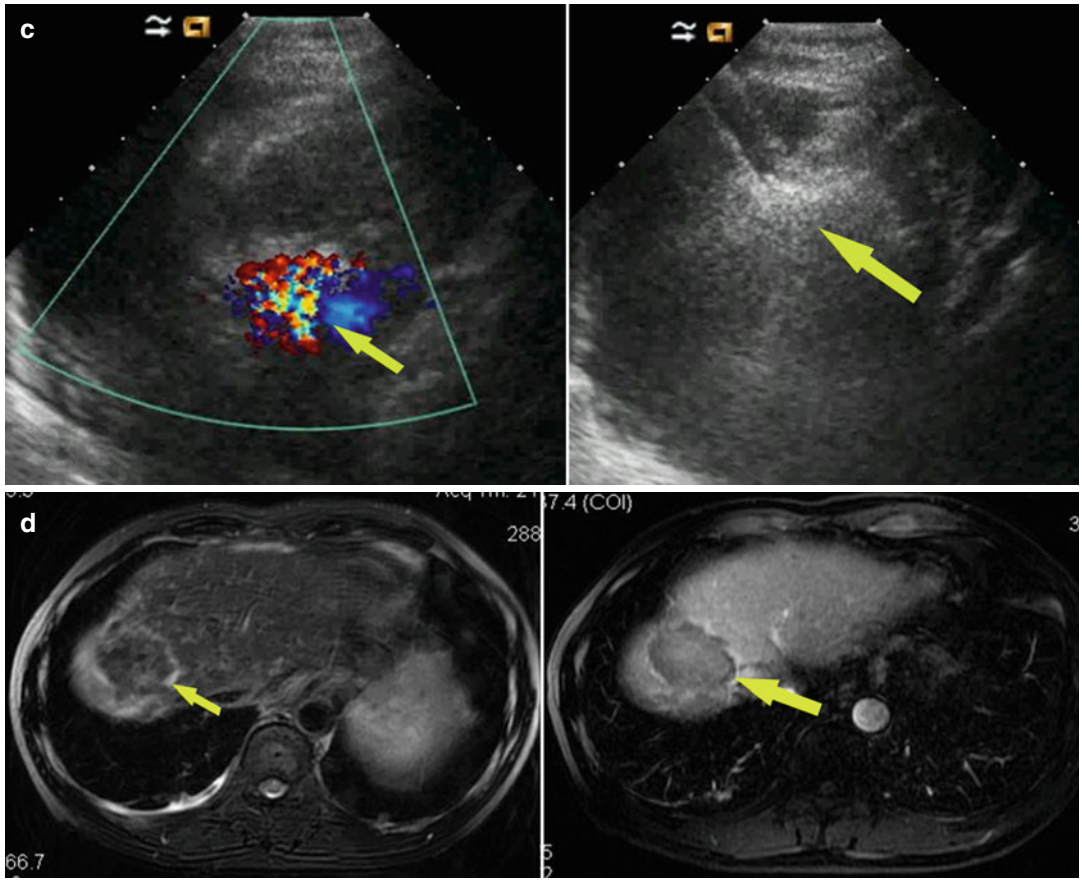

Fig. 13.2 (continued)

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Part IV

Combination and Comparison of Microwave Ablation and Other Treatment for Liver Tumor

Microwave Ablation Combined with Cellular Immunotherapy for Hepatocellular Carcinoma

14

Ming-an Yu and Ping Liang

Abstract

Hepatocellular carcinoma (HCC) is the most common liver malignancy with a rising incidence. The treatment options for HCC are limited and disappointing mainly due to the high recurrence rate even after radical treatment. The immune system plays a pivotal role in the development of HCC. It usually can protect against the HCC occurrence and development to some extent, as well as against recurrence after surgical resection or thermal ablation treatment. Therefore, many strategies are employed to modulate HCC patients' immune system for improvement of clinical outcome. Immunotherapy is a relatively new approach for tumor therapy. The aim of immunotherapy is to enhance the natural antitumor immunity of HCC patients, to act against hepatitis or destroy malignantly transformed cells, and to break the immunosuppressive barriers established by HCC. For the management of HCC, thermal ablation techniques including microwave ablation, radiofrequency ablation, and high-intensity focused ultrasound have become increasingly popular. In this chapter, a systematic review is presented, which mainly emphasizes on the efficacy of microwave ablation, combined with immunotherapy for HCC management, including the relationship between the immune system and HCC occurrence, as well as immunoreaction following thermal ablation.

Keywords

Hepatocellular carcinoma • Microwave ablation • Radiofrequency ablation • Immunotherapy • Recurrence

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Abbreviations and Acronyms

CEA	Carcinoembryonic antigen
CIK	Cytokine-induced killer
CTL	Cytotoxic T lymphocyte
DC	Dendritic cell
HCC	Hepatocellular carcinoma
HSP	Heat shock protein
MWA	Microwave ablation
NK	Natural killer cells
RFA	Radiofrequency ablation
RFS	Recurrence-free survival
SEC	Staphylococcal enterotoxin C
TACE	Transcatheter arterial chemoembolization

Hepatocellular carcinoma (HCC) is the most common liver malignancy with a rising incidence. HCC patients often have a dim clinical outcome mostly due to the high recurrence rate even after radical treatment. The immune system plays a pivotal role in the occurrence, development, as well as post-treatment recurrence of HCC. As a relatively new approach against the progression or recurrence of HCC, immunotherapy is often employed to enhance the natural antitumor immunity of HCC patients, to directly destroy malignantly transformed cells, and to break the immunosuppressive barriers established by HCC [1, 2].

14.1 Relationship Between the Immune System and HCC Occurrence

14.1.1 Natural Role of the Immune System in the Development of HCC

The accumulating mutations of hepatocyte could develop into HCC because these mutations alter the expression and function of genes responsible for cellular proliferation. Moreover, the signaling pathways such as Hedgehog and Wnt/β-catenin pathways are altered during hepatocarcinogenesis [3, 4]. Some of these changes can also be induced by chronic viral hepatitis, the leading cause of HCC [5]. Interestingly, the rate of double-strand DNA breaks is increased in a mouse model of chronic hepatitis [6], which directly contributes to mutagenesis and thus carcinogenesis.

Apart from these direct changes, chronic viral hepatitis also induces a chronic inflammation of the liver. Indeed, in the HBV transgenic mouse model, it could be shown that this chronic inflammation alone was sufficient to induce hepatocarcinogenesis even in the absence of a viral infection [7].

Different cytokines and growth factors induced by inflammation lead to permanently increasing cellular turnover and finally the development of HCC [8]. Lymphotoxins are produced by a variety of lymphocytes such as T cells or natural killer (NK) cells, which demonstrates that the adoptive and the innate immune response are involved in the development of HCC [9]. These data support a model in which the immune system creates an environment of increasing cellular turnover, which is prone to mutagenesis and thus ultimately to the development of HCC. These data also support the concept that tumors of a certain size gain the ability to manipulate immune cells for their own benefit [10].

14.1.2 Control Effect of the Immune System on HCC

In HCC, the immune system certainly can help to induce hepatocarcinogenesis from normal hepatocyte. However, several evidences also suggest a protective role to control tumor growth [11–13]. In fact, there are many results of clinical studies attributing to this assumption. First, HCC patients with an intratumoral accumulation of lymphocytes mainly containing cytotoxic CD8+ T cells have a superior 5-year survival rate and a prolonged recurrence-free survival (RFS) after resection [11, 12], which indicate a protective role of tumor-infiltrating lymphocytes in HCC. In addition, a strong CD8+ T cell response against relative tumor-associated antigens was found to coincide with improved recurrence-free survival after liver resection [13]. Moreover, the

prior studies have disclosed that the NK cells and natural killer T lymphocyte cells play an important role in antitumor immune responses by direct lysis of malignant cells and clearance of hepatoma cells [14, 15].

14.1.3 Causes of Immune System Failing to Control Tumor Development or Growth

For most patients, HCC-specific immune responses fail to control the tumor. Generally, HCC cells have two main strategies to escape from the immune response – defense and attack. Defense enables the tumor cell to pass unnoticed by the immune response, and attack is designed to attack the immune cells, hence avoiding their antitumor action [16, 17]. Concretely, HCC cells are often found to have no expression of Fas (CD95) and the IFN-γ receptor, and both Fas and IFN-γ receptor are important factors for antitumor immune response engaged by cytotoxic cells [18, 19]. On the other hand, the dysfunction of tumor-specific CD8+ T cells in HCC patients has also been reported. These cells are found to express inhibitory receptors such as programmed death-1 (PD-1). Additionally, they downregulate costimulatory molecules such as CD28 or components of the T cell receptor complex (e.g., CD3ζ) [20–22]. As a result, the CD8+ T cells are functionally impaired and apt to apoptosis. According to the results of clinical study an impaired CD8+ T cell phenotype usually predicts an earlier recurrence of HCC after liver resection [23], which further illustrates that the failure of the immune response to HCC is mainly a failure of tumor-specific CD8+ T cells.

14.2 Immunoreaction Following Thermal Ablation

14.2.1 Tumor Antigen Release Following Ablation of HCC

Hyperthermia may modulate immunity by cell killing, altering heat shock protein (HSP) release from tumor cells and/or activating antigen-presenting cells such as dendritic cell (DC), and altering cytokine release from tumor cells [24–27].

During ablation of tumor, the tumor cell dies directly from membrane fusion, protein coagulation, and coagulative necrosis in the central zone around the antenna where the temperature is between 60 and 100 °C [24]. According to our study, after MWA of orthotopic HCC in Kunming mice, a carbonization zone with sheet distribution could be observed around needle track; the distribution of cell is sparse, with only the cell contours visible and the internal structure and mesenchyme disappearing (Fig. 14.1). In the margin of the tumor where the temperature is about 60 °C, the apoptotic cells show a loss of enzymatic activity, impaired membrane function, and structural changes in mitochondria.

In situ tumor ablation (destruction) can involve tumor antigen release. Our in vitro experiment study has demonstrated that most of H22 cells underwent apoptosis (Fig. 14.2) and expressed HSP70 on the surface of cells after MWA of cell suspension with a temperature condition of 60 °C, but few cells expressed HSP70 before ablation (Fig. 14.3). It could be predicted that hyperthermia with temperature control of 60 °C might be immunogenic due to release of abundant levels of HSPs that accumulate during heating [28]. Hsp70 released during heating might contain tumor antigens and thus act like a molecular chaperone vaccine, by transporting tumor antigens to antigen-presenting cells and triggering activation of tumor-specific cytotoxic T lymphocyte (CTL) [29, 30]. In conventional surgical resection of colorectal liver metastases, it is known that values of carcinoembryonic antigen (CEA) fall rapidly, which reflects the elimination of the tumor load. While following RFA, patients show an initial rise and then a slow drop to background levels of CEA value, suggesting a slow release of immune reactive antigens from the tumor debris [31].

Systemically releasing antigens becomes available for professional antigen-presenting cells after ablation. As a kind of antigen-presenting cells, the DCs residing in the tumor-draining lymph node readily internalize antigens

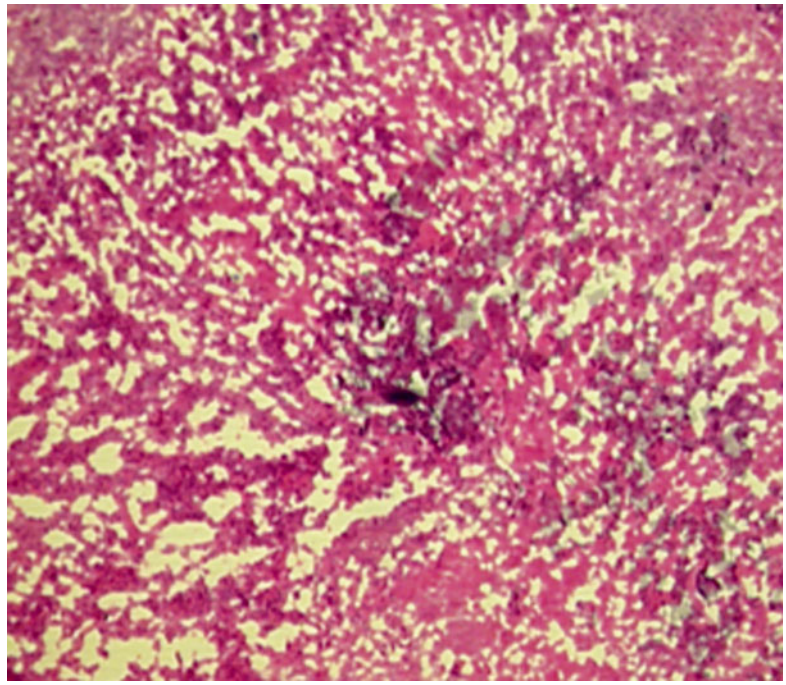

Fig. 14.1 The H&E staining slide of mice hepatocellular carcinoma (HCC) in situ after microwave ablation (MWA) (40×)

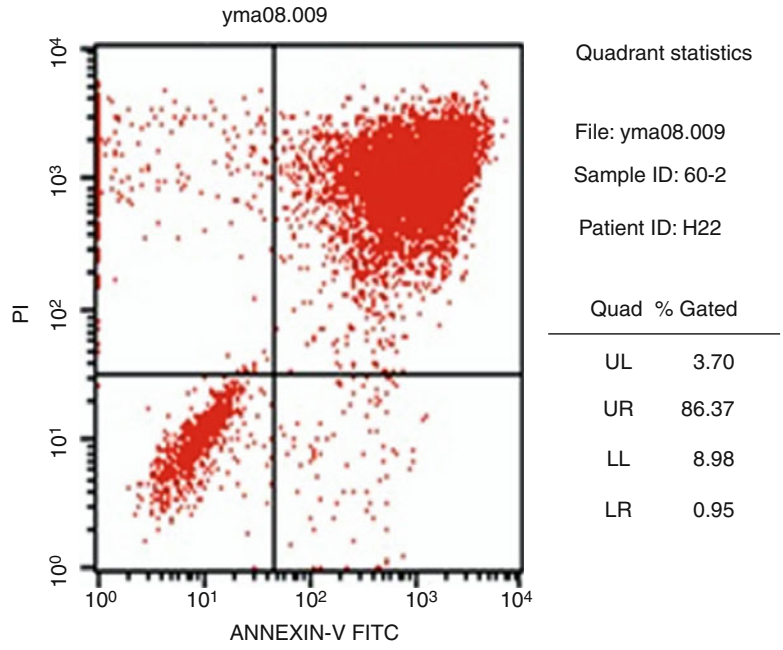

Fig. 14.2 The flow test result for H22 cells suspension after MWA with temperature control of 60 °C. Most cells have already undergone apoptosis in the upper right quadrant 2 h after MWA

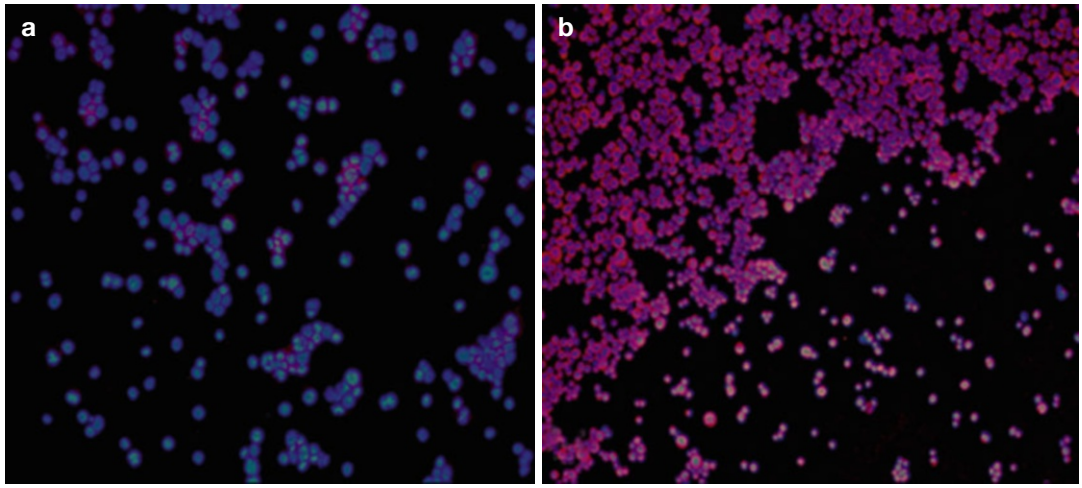

Fig. 14.3 The HSP70 expression on H22 cells before and after MWA by immunofluorescence (40×). (**a**) There are few H22 cells expressing HSP70 on the cytomembrane before MWA. (**b**) HSP70 expression both on cytomembrane and cytoplasm by most H22 cells 2 h after MWA

from the tumor microenvironment during the first 2 days after RFA [32]. And then the mature DCs can mediate antigen-specific cellular immunity via presentation of processed tumor antigens to T cells. Hence, the tumor antigen release after ablation could stimulate the tumor-specific immune response through the pinocytosis and presence of DCs.

14.2.2 Specific and Nonspecific Immune Response to Tumor After Ablation

The specific and nonspecific immune response belong to adaptive and innate immune response, respectively. The tumor-specific immunity often employs T lymphocyte to exclusively act against tumor cells, while the nonspecific immunity often employs NK cells and macrophagocyte to act against all pathogens including germ, virus, and tumor cells.

Zerbini et al. [33] showed increased IFN-γ production and cytotoxic activity of NK cells 4 weeks after RFA of HCC. By classifying the patients into high and low responders, these parameters gained predictive value on the efficacy of the ablative treatment. The result suggested the NK cells had the effect of inhibiting tumor development after RFA [34]. In patients with HCC and colorectal liver metastases, IFN-γ production (directed against autologous tumor tissue) was observed in both CD8+ and CD4+ T cells after RFA [33, 35] The CTLs possessed highly elevated cytotoxic activity as indicated by adenylate cyclase release [35]. Interestingly, cross-recognition between ablated and non-ablated tissue was observed, but responses to autologous non-tumor tissue were absent or weak [33]. These results suggest specificity for tumor antigens that are absent in normal tissue, thereby limiting autoimmune reactivity.

In cancer patients, only few studies have described the induction of specific immune responses after RFA. Napoletano et al. [36] reported that naïve and memory CD62L + T cells translocate to the tissues and that T cells produced IFN-γ in response, in cancer patients, to the tumor-associated MUC1 antigen, while humoral immune responses were unaffected by RFA treatment. The latter is in contrast to a study by Widenmeyer et al. [37] who concluded that tumor-associated antigen-specific antibodies increased within weeks to months after ablation in 6 out of 49 treated patients. Univariate analyses of parameters in 20 patients identified the number of tumor-associated antigen-specific CD8+ T cells as a significant prognostic factor

for recurrence-free survival after RFA [13]. However, RFA induces weak immune responses that are only occasionally strong enough to lead to spontaneous regression [38]. Clinical data additionally shows that it does poorly protect against secondary growth, local recurrence, or intrahepatic metastasis and thus encompasses a high rate of intra-hepatic metastases and recurrent disease [39]. Similarly, Zerbini et al. [33] reported the absence of a correlation between enhancement of antitumor T cell responses and disease progression, which may be due to tumor escape mechanisms.

There have been few that reported about tumor-specific and nonspecific immune response following MWA of HCC mostly due to the tardy prevalence. However, MWA and RFA should have similar immune responses for HCC patients because of the similar mechanism and thermal efficiency between RFA and MWA.

Although the specific and nonspecific immune response following RFA of HCC have been reported, the high recurrence rate of HCC after ablation is still troublesome. It may be due to the weakness and transience of immune reaction. Hence, immunotherapy should be employed to overcome the hypoimmunity of HCC patients.

14.3 Efficacy of MWA Combined with Immunotherapy for HCC Management

14.3.1 Superantigen Administration After MWA

Cancer immunotherapy can be defined as a set of techniques aimed to eliminate malignant tumors through mechanisms involving immune system responses [40, 41].

Ablation provides a feasible strategy to administer immunomodulatory compounds in close proximity to the released antigens. Immunotherapy is currently one of the most studied novel cancer treatments. Therefore, combination therapies of ablation with other debulking strategies or immune stimulatory approaches are therefore of great interest.

In clinical, different strategies are employed to enhance the immune response to recurrence after MWA/RFA. Our group performed a clinical study to prospectively evaluate safety and effectiveness of injection of superantigen staphylococcal enterotoxin C (SEC) to peripheral area of ablated tumor on days 24 and 28, and 2, 5, and 7 months after MWA. The results displayed an extremely low concentration of SEC could induce strong nonspecific immune response by stimulation of T lymphocyte [42]. The overall survival rates for 1, 3, and 5 years were 93.3, 72.9, and 60.8 % in the SEC group and 94, 66, and 44.4 % in the control group. For patients with tumor of maximum diameter more than 30 mm, the disease-free survival rates at 1 and 3 years were 62 % versus 56.6 % and 37 % versus 9.4 % in the SEC and control group, respectively ($p = 0.032$). Adverse event related to SEC injection was associated with minimal systemic toxicity which included fever, general malaise, and muscular soreness. These results demonstrated that the local superantigen injection into ablated HCC early after MWA is safe and achieves longer overall survival as well as disease-free survival of larger tumors.

14.3.2 MWA or RFA Associated with Adoptive Immunotherapy to HCC

Immunotherapeutic strategies to overcome suppression and further stimulate DC and T cell activation are therefore of great interest. The application of these strategies as a monotherapy has so far resulted in meager responses in clinical trials. This may be because the patients enrolled did not respond to standard therapy and thus had a lower chance on clinical responses. Moreover, the stimulation of the immune system may particularly be of value in combination with standard therapies, like RFA, to reduce the tumor mass and inhibit the immunosuppressive tumor microenvironment. In fact, multiple studies were designed to evaluate the safety and effect of immunotherapy for patients with HCC after curative treatment including RFA or RFA

combined with transcatheter arterial chemoembolization (TACE). Many results are inspiring. Cui et al. [43] have applied immune cells including NK cells, γδT cells, and cytokine-induced killer (CIK) cells to be infused intravenously to HCC patients for three or six courses after radical RFA. Compared to the patients in RFA alone group, the patients in combination strategy group get higher progression-free survival; furthermore, viral load of hepatitis C was decreased in two of three patients without antiviral therapy in RFA/CIT group, but was increased in RFA group. Huang et al. [44] have evaluated the clinical efficacy of autologous CIK cell transfusion in combination with TACE and RFA, compared to sequential therapy with TACE and RFA. The results showed that the patients in the TACE+RFA+CIK group had significantly longer overall survival (56 vs. 31 mo, $p=0.001$) and progression-free survival (17 vs. 10 mo, $p=0.001$) than those in the TACE+RFA group and no severe side effects occurred in the CIK cell transfusion patients, so they made a conclusion that the CIK cell immunotherapy may be a valuable therapeutic strategy to prevent recurrence and metastasis in HCC patients after TACE and RFA.

A meta-analysis of adjuvant therapy after potentially curative treatment for HCC has shown that adjuvant adoptive immunotherapy conferred significant benefit for RFS but not for overall survival, while adjuvant IFN therapy can improve both RFS and overall survival, but with accompanying severe side effects [45].

In addition to the application of singleness of combination of various immune cells like DC, CIK, and CTL and relative complexity operation was employed to enhance the immune response to reduce post-ablation recurrence of HCC. In our group, a phase I clinical study of combination therapy with MWA and cellular immunotherapy in HCC was carried out. Ten HCC ($D \leq 5$ cm, fewer than three tumors) patients were treated with radical MWA and three courses of immunotherapy, which were started on the day of ablation, 2 weeks and 3 months after MWA. Immature DCs, CIK, and CTL were cultivated from peripheral blood of patients. Immature DCs were injected into the marginal area of ablated tumors under contrast-enhanced sonographic guidance 2 h after ablation. Tumor lysate-pulsed DC was injected into groin lymph nodes 11 and 100 days after ablation, while DC-CIK and CTL were injected into the abdominal cavity 5 days after ablation. CIK was infused intravenously 5 and 102 days after ablation. The infusion time of different immune cells was determined by the maximization of cell count and viability reflected in cell growth curve. The results displayed that no adverse effects of grade III/IV were observed and the viral load was decreased in 57.14 % (four of seven) of patients and was undetectable in two (28.6 %) patients without antiviral therapy. The percentage of CD4+CD25 high regulatory T lymphocytes decreased significantly and the percentage of CD8+CD28+ effector cells increased significantly 1 month after therapy. However, 6 months later, there was no significant difference [46].

In a following study, the immune response and clinical outcome of HCC patients attributed to immunotherapy after MWA were further investigated. The immunotherapy group includes 14 HCC patients who received 3–7 (mean 4.6) courses of immunotherapy after MWA, and the control group includes 42 HCC patients who have not received immunotherapy or other adjuvant therapy after radical MWA. All patients enrolled met the criteria of prior study. The results showed the absolute lymphocyte count, the proliferation rate of T lymphocyte, and the ratios of effector T lymphocyte subsets in immunotherapy group were significantly increased than those in the control group ($p=0.038$, 0.011, 0.036). The values of albumin and cholinesterase in immunotherapy group were obviously increased after immunotherapy ($p=0.004$, 0.037). The RFS and overall survival between two groups had no statistical difference possibly due to the limited sample in both groups and relatively short-term follow-up. However, the encouraging results in immune system responding to immunotherapy may help to against to HCC recurrence after MWA in a long run. Definite and positive results in disease-free survival rate and overall survival rate need further

randomized controlled trial study with a long follow-up period.

The persistent confrontation between immune system and HCC cells lies on the whole process of occurrence, development, and deterioration of HCC. The dim clinical results of HCC mostly due to the high recurrence rate after radical treatment often imply the weakness of immune system against HCC. Multiple experimental and clinical studies involving immunotherapy for HCC patients following various treatments have given encouraging results in promoting tumor-specific immunity, directly killing tumor cells, or preventing post-treatment recurrence. However, the immunotherapy is far from perfect to applying in clinical, which even needs a further more abundant data to contribute to a mature strategy that HCC patients can benefit from.

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15 Traditional Chinese Medicine Combined with Microwave Ablation Against Hepatocellular Carcinoma

Jianbin Wang and Ping Liang

Abstract

Traditional Chinese medicine (TCM) has been widely used for hepatocellular carcinoma (HCC) in China. It is reported that TCM such as herbal medicine is more effective in HCC. TCM is used for HCC alone or combined with other treatment, such as trans-catheter arterial chemo-embolization (TACE) and chemotherapy. But TCM combined with microwave ablation has not been reported. The purpose of this chapter is to present the application status of TCM in HCC treatment, and to present a cohort study of TCM combined with microwave ablation against HCC. In this study, 305 patients treated by percutaneous microwave ablation were enrolled. Traditional Chinese herbs were orally received according to patients' preference. Recurrence, metastasis, and survival were observed. The median follow-up period was 38 months (range 24–55 months). The study indicated that the treatment of TCM might reduce the recurrence and metastasis of HCC after percutaneous microwave ablation, and improve the general well-being and survival rate without obvious adverse reactions.

Keywords

Traditional Chinese medicine • Microwave ablation • Hepatocellular carcinoma

Abbreviations and Acronyms

CAM	Complementary and alternative medicine
HCC	Hepatocellular carcinoma
OS	Overall survival
PMWA	Percutaneous microwave ablation
TACE	Trans-catheter arterial chemo-embolization
TCM	Traditional Chinese medicine

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15.1 Introduction

15.1.1 Using of Traditional Chinese Medicine Widely

Traditional Chinese medicine (TCM) has been widely used in cancer in China [1], particularly in hepatocellular carcinoma (HCC). The use of TCM for cancer treatment dates back more than 2,000 years in China [2] and is still prevalent. TCM is also one of the most popular complementary and alternative medicine (CAM) forms worldwide. The motives for the use of CAM include perceived failure of standard health care, the patient's need for autonomy, and preference for holistic or natural therapy in western populations [3–5]. According to an interview survey, the prevalence of CAM use is about 38 % in American adults [6]. CAM is commonly used together with conventional medicine, and has entered mainstream society and culture [7, 8]. TCM has been used for cultural belief reasons to manage illness symptoms, maximize conventional treatment effect, and prevent recurrence in Chinese populations. In Chinese and East Asian societies, TCM plays an active role in the modern health care system [9–12]. Unlike other forms of CAM, TCM consists mostly of syndrome differentiation and prescription of herbal formulae.

15.1.2 TCM Treatment for HCC

It is widely acknowledged that HCC is one of the leading causes of cancer-related mortality worldwide. The survival rate is still unsatisfactory due to the high recurrence and metastasis rate after conventional treatment [13]. Most patients suffer both physically and mentally from multiple symptoms, either due to the cancer disease itself or caused by allopathic treatments, resulting in a decrease in quality of life [14]. Patients with HCC often turn to TCM treatment; it is believed that TCM can be helpful in improving general well-being, relief of symptoms, and possibly even curing the disease. TCM practitioners view the human body as a working organism, and the treatment protocol is based on pattern differentiation of symptoms of individual patients. The main principles for treating primary liver cancer include replenishing qi to invigorate the spleen, using sparse liver data to regulate the flow of vital energy, clearing heat and promoting diuresis, promoting blood circulation for removing blood stasis, nourishing yin, and detoxification. Finally, TCM may offer a cost-effective protective alternative to individuals known to have a high risk of developing HCC through maintaining cell integrity, reversing oxidative stress, and modulating different molecular pathways in preventing carcinogenesis. As a result, TCM is considered appropriate in managing cancer. The treatment of TCM such as herbal medicine is more effective in HCC [15, 16].

15.1.3 Therapeutic Effect of TCM on HCC in Previous Studies

Herbal composite formula is a commonly used Chinese herbal medicine. In general, the herbs used in herbal medicine often result from a combination of herbs with multiple ingredients, called "herbal composite formula". Many studies on the prevention and treatment of HCC using herbal medicine have been accumulated during the past decades. Shi-Quan-Da-Bu-Tang (SQDBT, Juzen-taiho-to in Japanese) is a classic herbal composite formula, which consists of ten kinds of herbs and has been used for HCC patients after surgical treatment. A significantly longer intrahepatic recurrence-free survival was observed in the Shi-Quan-Da-Bu-Tang group, even though most of the patients experienced recurrence of HCC [17]. Xiao-Chai-Hu-Tang (XCHT, Shosaiko-to in Japanese), another classic herbal composite formula, is commonly administered to patients with chronic viral liver disease in order to prevent the development of liver cancer. A prospective, randomized, non-blind controlled study showed that the 5-year survival curve for the trial group was significantly higher than that of the control group. They concluded that Xiao-Chai-Hu-Tang may prevent or delay the emergence of latent HCC in patients with cirrhosis [18]. Another study showed that long-term oral Ruanjianhugan (RJHG) tablets, a Chinese herbal medicine compound, comprised of ten herbal materials, was

more advantageous than interventional therapy in improving the overall survival (OS) for small HCC after resection [19].

15.1.4 TCM Combined with Other Treatment on HCC

TCM is also used for HCC combined with other treatment, such as trans-catheter arterial chemoembolization (TACE) and chemotherapy, with a large amount of reports. TCM combined with thermal ablation has not been reported. A meta-analysis has been reported concerning TCM in the treatment of HCC, included 45 randomized clinical trials involving 3,236 patients (1,682 in the treatment groups and 1,554 in the control groups). The majority of trials included patients with stage II or more advanced cancers. All studies employed TACE as adjunct therapy [16]. Another meta-analysis of 37 randomized controlled trials involving 2,653 patients revealed that TCM plus TACE improve patient survival, quality of life, and tumor response alleviation of symptoms [20]. In another meta-analysis, TCM plus TACE significantly increases the survival, complete or partial response, non-deterioration performance, T cells, natural killer cells, and white blood cell count, significantly decreases the level of blood alpha–fetoprotein concentration, and significantly lowers the risk for nausea and vomiting [21]. A recent meta-analysis has also demonstrated that TCM plus TACE increases the proportions of cluster differentiation (CD) 3^+ T cells, $CD4^+$ T cells, and natural killer cells, as well as the ratio of $CD4^+/CD8^+$ before and after treatment [22]. A meta-analysis of randomized controlled trials for TCM combined with chemotherapy has reported promising evidence that the combination treatment may benefit patients with HCC [23].

15.1.5 TCM Combined with Microwave Ablation for HCC Patients

Although TCM is generally accepted as a complementary approach in addition to conventional treatment of HCC patients, high-level evidence of its efficacy is still lacking [16]. Our previous studies showed that percutaneous microwave ablation (PMWA) as a procedure involving less injury, strong recovery, and repeatable treatment had shown survival benefits for HCC patients in the last two decades [24, 25]. However, TCM use among patients with HCC after microwave ablation has not yet been reported. The following study is to assess the effect of different courses of TCM on recurrence and metastasis of HCC patients after PMWA in cohort study.

15.2 Methods

From January 2008 to July 2010, 305 patients with HCC (253 male, 52 female) aged from 29 to 80 years (56.24 ± 11.19) were treated with PMWA by the guidance of ultrasound or contrast-enhanced sonography and TCM treatment. The study was approved by the local research ethics committee of Chinese PLA General Hospital. Written informed consent was obtained from all patients before their enrollment into the study. All of the procedures were carried out in accordance with the Declaration of Helsinki and relevant policies in China.

Inclusion criteria included the following: (1) a diameter of single nodule ≤ 5 cm; a diameter ≤ 3 cm when the number of nodules is two or three, (2) neither the invasion of blood vessels, bile duct, and adjacent organs nor a distant metastasis, (3) Child–Pugh classification A or B, and (4) tumor accessible via a percutaneous approach.

Exclusion criteria included the following: (1) the PMWA led to serious complications or comorbidities (gastrointestinal bleeding, active infection, massive ascites, etc.), (2) serious dysfunction in some main organ (liver, kidney, heart), (3) patients with other kinds of tumor, and (4) allergy to Chinese herbal medicine.

15.2.1 PMWA Treatment

According to the practice guidelines for ultrasound-guided PMWA for hepatic malignancy, all the patients were treated by a cooled-shaft microwave system (KY-2000, Kangyou Medical, Nanjing, China) [26, 27].

15.2.2 TCM Treatment

Traditional Chinese herbs were orally received according to patients' preference. Popular classical prescriptions such as Sijunzi Tang, Xiaochaihu Tang, YiguanJian, Xiangsha Liujunzi Tang, Xiaoyao Wan and Gexia Zhuyu Tang, Liuwei Dihuang Tang and Yinchenhao Tang, etc. are often selected. *Gallic Gigerii Endothelium Corneum* and *Ophiopogonis Radix* are the most common drugs for poor appetite. *Astragali Radix* is the most common drug for fatigue. *Corydalis Rhizoma*, *Toosendan Fructus* are most common for liver pain; *Pericarpium Arecae*, *Polyporus*, *Poria* are the most common herbs for ascites, *Artemisiae Scopariae Herba* is a common drug for jaundice. One dose is made into a decoction by an automatic herb-boiling machine, about 200 ml, twice a day. One course of treatment lasts 3 months. Smoking, alcohol, spicy and greasy food are forbidden during the courses.

15.2.3 Cohort Definition

We defined the exposure of TCM as the variable factor. The high-exposure group was treated by herbs for at least 3 months after PMWA. The low-exposure group was treated for less than 3 months or only treated by anti-tumor Chinese patent medicine without any herbs of syndrome differentiation. The non-exposure group was treated neither by herbs of syndrome differentiation nor by anti-tumor Chinese patent medicine.

15.2.4 Follow-Up

Enhanced computed tomography or magnetic resonance imaging and ultrasound imaging were implemented in the first month and every 3 months subsequently after PMWA. The examination of peripheral blood, urine routine, and liver and kidney function were also reviewed synchronously.

15.3 Results

All 305 patients were followed up until July 2012. The median follow-up period was 38 months (range 24–55 months). The patients in the high, low, and non-exposure groups were 105, 93, and 107 respectively.

There was no significant difference in gender, age, number of lesions, lesion size, the types of liver disease, and Child–Pugh classification of patients among the three groups (Table 15.1).

Table 15.1 Comparison of three groups of baseline data

Parameter	Non-exposure ($n=107$)	Low exposure ($n=93$)	High exposure ($n=105$)	p
Gender				
Male	90	78	85	0.797
Female	17	15	20	
Age (year)	57.1 ± 12.0	56.7 ± 10.8	56.4 ± 11.3	0.996
Number of lesions				
1	89	72	84	0.546
2	15	19	16	
3	3	2	5	
Maximum diameter (cm)	2.6 ± 1.1	2.7 ± 1.3	2.8 ± 1.3	0.802
Liver diseases				
HBV	90	83	88	0.052
HCV	13	8	12	
Other	4	2	5	
Child–Pugh classification				
A	97	83	93	0.485
B	10	10	12	

15.3.1 Recurrence and Metastasis

The recurrence and metastasis rate in the high, low and non-exposure groups were 61.9 % (65/105), 50.5 % (47/93), and 69.2 % (74/107) respectively. The 1- and 2-year recurrence and metastasis rates are shown in Table 15.2. In the low-exposure group, the rates were significantly lower than in the non-exposure group ($p=0.014$ and 0.009). In the high-exposure group, the 1-year recurrence and metastasis rates were significantly lower than in the non-exposure group ($p=0.025$), while there was no significant difference in the 2-year recurrence and metastasis rates, though a decrease trend was detected ($p=0.131$). There was no significant difference between the high- and low-exposure groups in 1- and 2-year recurrence and metastasis rates ($p=0.880$ and 0.306).

15.3.2 Survival

The 1-, 2- and 3-year cumulative survival rates of each group are shown in Table 15.3. There was no significant difference in the 1-year OS rate among the three groups (all OS > 90 %, $p>0.05$). It was detected that the 2- and 3-year OS rates of the high-exposure group were significant higher than in the non-exposure group ($p=0.000$, $p=0.043$). Different survival curves of exposure factors are shown in Fig. 15.1.

Table 15.2 The 1-, 2-year recurrence and metastasis rate of different cohort

Cohort	1-year	2-year
Non-exposure	50.5 % (54/107)	63.6 % (68/107)
Low-exposure	32.3 % (30/93)[a]	44.1 % (41/93)[c]
High-exposure	34.3 % (36/105)[b]	52.4 % (55/105)

[a]Compared with non-exposure group, $p=0.014$
[b]Compared with non-exposure group, $p=0.009$
[c]Compared with non-exposure group, $p=0.025$

Table 15.3 The 1-, 2- and 3-year cumulative survival rate of different cohort

Cohort	1-year	2-year	3-year
Non-exposure (%)	90.7	70.1	64.4
Low-exposure (%)	90.5	81.7	72.0
High-exposure (%)	93.3	84.8[a]	77.1[b]

[a]Compared with non-exposure group, $p=0.000$
[b]Compared with non-exposure group, $p=0.043$

15.3.3 Cox Multivariate Regression Analysis of Disease-Free Survival

The data of gender, age, number of lesions, lesion size, the maximum diameter, the type of liver disease, Child–Pugh classification, exposure factors, and disease-free survival time were analyzed by Cox multivariate regression analysis, and are listed in Table 15.4.

As shown in Table 15.4, the regression coefficient B = −0.434, and the relative risk of the exposure group is 0.648 ($p=0.024$). The results showed that the TCM treatment was a protective factor.

15.3.4 Major Adverse Reactions

One case of hematuria occurred in both the high- and low-exposure groups, when they were given orally both traditional Chinese herbs and Jinlong Capsule (a kind of Chinese patent medicine for improving the immunity of primary liver cancer). Seven days after withdrawal of the Jinlong Capsule, the hematuria disappeared. There were no adverse reactions in other patients during TCM treatment.

15.4 Discussion

The morbidity and mortality of HCC is increasing yearly worldwide [28]. Several retrospective studies of treating HCC show that when the tumor size is less than 5 cm, there is no significant difference between surgery, microwave and radiofrequency ablation treatment [29, 30]. Nowadays, with the increasing development of imageology, minimally invasive ablation treatment has become the principal way to treat HCC [31]. Although progress in therapeutic modalities has significantly improved in the last few decades, the survival rate is still unsatisfactory. The main reason is the high recurrence rate after treatment. The limited effect of single therapy suggested that combination therapy would enhance the overall treatment efficiency.

TCM has been widely applied for cancer treatment in China. Further progress has been made in

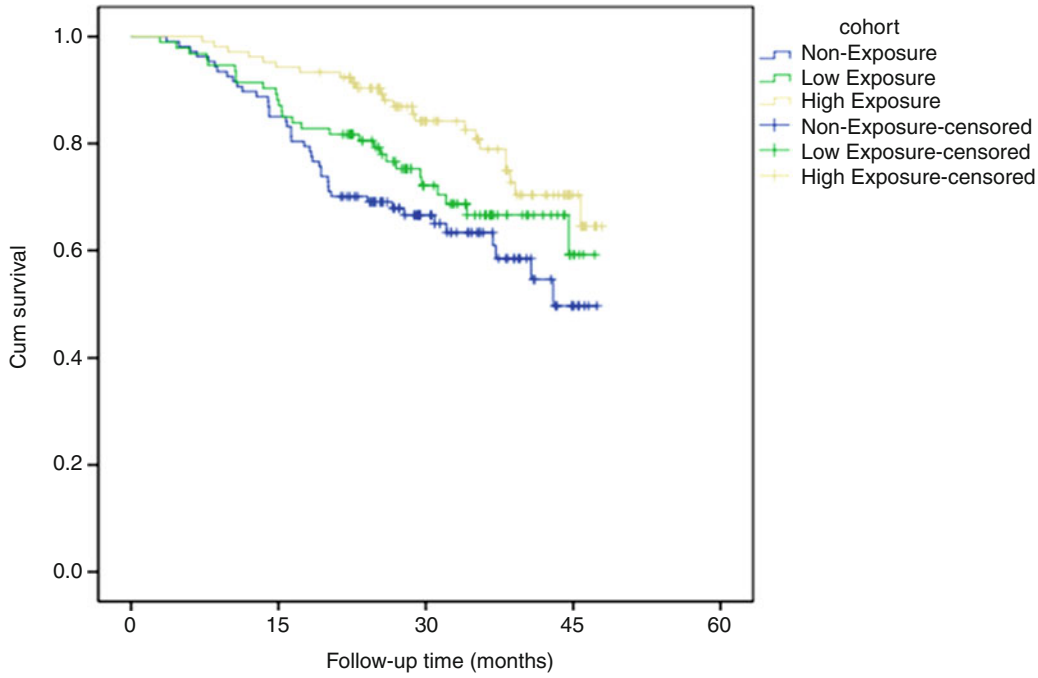

Fig. 15.1 The OS rate of the high exposure group was significant higher than the non-exposure group ($p=0.002$). There was no significant difference between the high- and low-exposure groups ($p=0.080$), and there was also no significant difference between the low- and non-exposure groups ($p=0.208$)

Table 15.4 Multi-factor Cox multivariate regression analysis with disease-free survival time

						95.0 % CI for Exp(B)	
Factor	B	SE	Wald	Sig.	Exp(B)	Lower	Upper
Exposure factor	–0.434	0.193	5.076	0.024	0.648	0.444	0.945
Age	0.007	0.007	1.033	0.309	1.007	0.994	1.020
Gender	0.070	0.205	0.115	0.734	1.072	0.717	1.603
Liver diseases	0.383	0.277	1.910	0.167	1.467	0.852	2.524
Number of lesions	0.139	0.123	1.276	0.259	1.150	0.903	1.464
Maximum diameter	0.075	0.087	0.746	0.388	1.078	0.909	1.278
Child–Pugh classification	0.084	0.203	0.173	0.678	1.088	0.730	1.621

TCM for primary liver cancer over the past few years, especially in research on the TCM treatment principle, improvement of therapeutic results, and prolonging the survival [1, 10, 32].

No matter which modality of treatment is used, recurrence and metastasis are the main factors affecting the survival of patients with HCC. Unlike radiofrequency ablation, PMWA is not influenced by charred and desiccated tissue at the tip of the probe, leading to more uniform and reliable tissue ablation zones, which may achieve more optimistic long-term survival rates [33, 34]; the recurrence rates in the high- and low-exposure groups were lower than in the non-exposure group, which indicated that TCM could reduce the recurrence and metastasis of HCC patients. Moreover, the recurrence rate of the high-exposure group is higher than the low-exposure group. This may be due to the fact that patients with recurrence or metastasis will persist for a longer time with TCM treatment. However, the 3-year OS rate of the high-exposure group was

significant higher than that in the non-exposure group ($p=0.043$). It was detected that PMWA combined with TCM treatment can promote sustained survival time.

The effect of HCC therapies depends on killing the tumor and protecting the normal liver tissues [35]. TCM, to some extent, can reduce the clinical symptoms of advanced patients, improve general well-being and promote quality of life [15, 16]. Normal liver function is the key for HCC patients to defend against cancer. So promoting liver function can prolong the survival period. In this study, the survival rates of the high- and low-exposure groups were higher than in the non-exposure group. This may be attributed to the treatment with TCM; however, this initial result needs confirmation via further studies.

As TCM treatment is always a syndrome differentiation treatment, Chinese herbal medicine compounds including variety of ingredients will be given to patients according to different symptoms. This study can merely prove the efficiency of TCM but not of the exact components. So we need to do further randomized double-blind controlled studies.

In conclusion, this study indicated that the treatment of TCM might reduce the recurrence and metastasis of HCC after PMWA, and improve the general well-being and survival rate without obvious adverse reactions.

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16 Comparison of Microwave Ablation with Resection and with Radiofrequency Ablation Treatment in Hepatocellular Carcinoma

Jie Yu, Ping Liang, and Chao-nan Chen

Abstract

According to the Barcelona Clinic Liver Cancer classification and Milan criteria, the early-stage (≤5 cm, ≤3 nodules) hepatocellular carcinoma (HCC) patients are candidates for radical hepatic resection and ablation therapy. Radiofrequency ablation has obtained wide use worldwide and been deemed as the first-line technique for small HCC. As one of the most recent and exciting advances in the field of thermoablative technology, microwave ablation also achieves favorable local tumor control and survival effect with low complications in HCC therapy. However, the comparison studies of microwave ablation with resection and microwave ablation with radiofrequency ablation for HCC are relatively limited with very inconsistent results and majority of them didn't use the newly cool-tip ablation equipment. The purpose of this chapter is to present a prospective comparative study with a large-scale sample, long-term follow-up, and newly developed ablation electrode to evaluate the clinical efficacy between resection and ablation for early-stage HCC treatment. Multiple parameters including liver function, operation time, hospitalization, cost, recurrence, survival, and complication are summarized. The therapy effect of controversial 3–5 cm tumor will also be discussed.

Keywords

Microwave • Radiofrequency • Ablation • Resection • Hepatocellular carcinoma

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Abbreviations and Acronyms

AASLD	American Association for the Study of the Liver
BCLC	Barcelona Clinic Liver Cancer
EASL	European Association for the Study of the Liver
HCC	Hepatocellular carcinoma
HR	Hepatic resection
LTP	Local tumor progression
MWA	Microwave ablation
RFA	Radiofrequency ablation
TE	Technique effectiveness

Hepatocellular carcinoma (HCC) is a major health problem worldwide, with an estimated incidence ranging between 500,000 and 1,000,000 new cases annually, and it is currently the third cause of cancer-related death globally, behind only lung and colon cancers [1]. Chronic hepatitis B virus infection is the main risk factor in Asia and Africa, and hepatitis C virus infection is the main risk factor in Western countries and Japan. The Barcelona Clinic Liver Cancer (BCLC) classification has emerged as the standard classification for trial design and clinical management of HCC [2]. This classification is endorsed by the European Association for the Study of the Liver (EASL) and the American Association for the Study of the Liver (AASLD) guidelines [3, 4]. Patients at stage 0 with very early HCC (tumors <2 cm in diameter, Child-Pugh class A) and patients at stage A with early HCC (single or three nodules <3 cm, Child-Pugh class A–B) are candidates for radical therapies (resection, liver transplantation, or percutaneous treatments) according to a well-established schedule. Some researchers have expanded radical hepatic resection (HR) and ablation therapy to <5 cm HCC (Milan criteria) with favorable survival effect [5–9]. HR remains the best hope for a cure but is suitable for only 9–27 % of patients [10, 11]. The presence of significant background liver cirrhosis often precludes HR in patients with HCC. Recurrence in the liver remnant is also common in patients who have undergone radical hepatic resection. Currently, local ablative therapy competes with HR as primary treatment for small HCC. Various locoregional therapies are used to treat patients who are with small HCC or not candidates for surgery because of the severity of the underlying liver disease. Percutaneous radiofrequency ablation (RFA) and microwave ablation (MWA), two recently developed local ablative techniques, have attracted great interest and popularity because of its efficacy and safety [12–15].

The purpose of this chapter is to compare the therapeutic efficacy and safety of MWA/RFA with HR and MWA with RFA) for the treatment of HCC measuring ≤5 cm in diameter.

16.1 Comparative of MWA/RFA Versus HR

16.1.1 Studies Status

For the comparison of thermal ablation with HR in HCC, there are a large reports on clinical effect comparison between RFA and HR treatment of HCC measuring ≤5 cm in diameter [9, 16–21]. However, many of them are retrospective studies and RFA didn't use cooled-tip electrode which can achieve larger ablation zone. There are only two randomized controlled trial to evaluate the difference of RAF versus HR for early-stage HCC [9, 19]. We summarized the results of published meta-analysis and randomized controlled trial on RFA versus HR for HCC (Table 16.1). Majority of studies showed RFA could achieve similar survival and local tumor control effect for HCC <2 cm. However, for 3–5 cm HCC, the research conclusions were not very consistent. Some showed two modalities had similar therapeutic results, while some showed HR had the advantages in long-term survival and local complete necrosis. As far as comparative study between MWA and HR, there is no prospective report to our knowledge. The only research was a retrospective observation with non-cooled-tip MWA versus HR in 2008 [22]. There are only limited reports on thermal ablation (RFA and

Table 16.1 Clinical comparative studies for ablation and HR

Author	Design	Patients (HR vs ablation)	Tumor size (cm)	Recurrence	Survival	Complication
Xu et al. [16]	Meta-analysis	1233 vs 1302	≤5	Lower for HR	Higher for HR	Higher for HR
Zhou et al. [17]	Meta-analysis	667 vs 744	≤5	Lower for HR	Higher for HR (similar when diameter ≤3 cm)	Higher for HR
Li et al. [18]	Meta-analysis	436 vs 441	≤5	Lower for HR	Higher for HR	N/A
Liu et al. [20]	Meta-analysis	534 vs 654	≤5	Lower for HR	Similar	Similar
Cho et al. [7]	Meta-analysis	550 vs 550	≤5	Lower for HR	Similar	N/A
Chen et al. [21]	Meta-analysis	339 vs 358	≤5	Lower for HR	Similar	Higher for HR
Tombesi et al. [22]	Meta-analysis	74 vs 71	≤2	Similar	Lower for HR	Higher for HR
Feng et al. [19]	RCT	84 vs 84	≤4	N/A	Similar	N/A
Huang et al. [9]	RCT	115 vs 115	≤5	Lower for HR	Higher for HR	N/A
Lü et al. [23]	RCT	54 vs 51	≤5	Similar	Similar	Similar
Wang et al. [22]	Case-control study	80 vs 114	≤5	Similar	Similar	Lower for HR

HR hepatic resection, *N/A* not available

MWA) compared with HR as well [23, 24]. The main cause may be MWA (especially cooled-tip MWA) is a relatively new thermal ablation compared with RFA and MWA's clinical appliance is not as wide as RFA.

16.1.2 Prospective Cohort Study for HR and MWA/RAF

Our group is performing a prospective cohort study to compare the intermediate-term therapeutic effectiveness of HR with ultrasound-guided percutaneous cooled-tip MWA and RFA in the treatment of early-stage HCC within Milan criteria. From August 2008 to January 2013, 290 cases of biopsy-proved HCC patients with 364 nodules were treated by MWA or RFA treatment. Three hundred six patients with 339 nodules were treated by HR. The tumor size and tumor number of both groups were similar. The average age was 58.2 years old for ablation group and 53.7 years old for HR group ($P<0.001$). Average operation times were significantly shorter in the ablation group ($P<0.001$). The average intraoperative bleeding amounts were 20–3,100 ml (median 200 ml) for HR, while ablation with the bleeding amount less than 10 ml. Hospitalization costs were being significantly fewer in the ablation group ($P<0.001$) as well.

The follow-up period was 2–54.8 months (median 21.6 months). The technique effectiveness (TE) rate was 99.2 % (361/364) in the tumors treated with ablation and 99.3 % (304/306) in those treated with HR, with no significant difference between the two groups ($P=0.85$). Local tumor progression (LTP) was observed in 4.9 % (18/364) tumors at 1–38.5 months after the first ablation therapy and in 2.0 % (6/306) tumors at 1–17.5 months after the first HR ($P=0.04$), respectively. There were no significant difference of LTP between the two groups in ≤3 cm tumors ($P=0.94$). But for 3–5 cm tumors, ablation showed significant higher LTP compared with HR ($P=0.004$). The 1-, 2-, and 3-year intrahepatic metastatic rates were 20.9, 31.9, and 45.1 % for ablation versus 14.5, 18.6, and 35.6 % for HR, respectively ($P=0.11$) (Fig. 16.1). The 1-year, 2-year, and 3-year cumulative survival rates after ablation were 95.8, 89.4, and 83.9 %, and the 1-year, 2-year, and 3-year disease-free survival rates after ablation were 83.3, 71.4, and 64.4 %. The 1-year, 2-year, and 3-year cumulative survival rates after HR were 97.5, 91.2, and

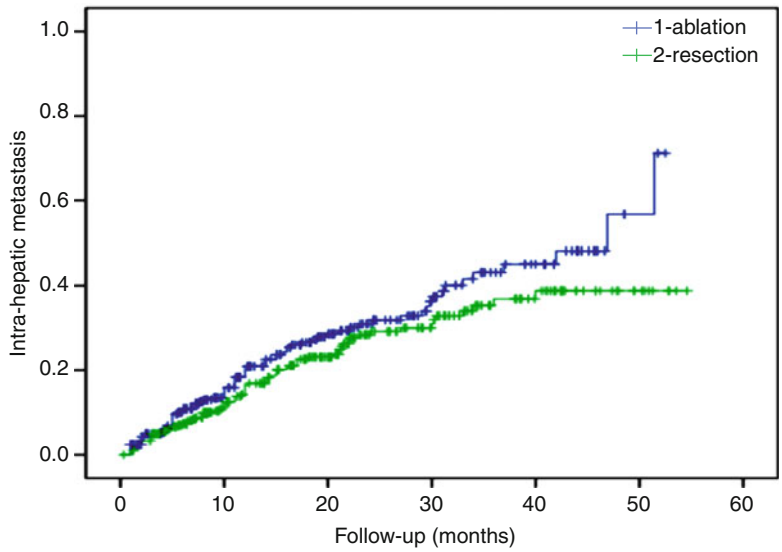

Fig. 16.1 Intrahepatic metastasis curves after thermal ablation and HR treatment of HCC. There is no significant difference between two groups ($P=0.11$)

84.1 %, and the 1-year, 2-year, and 3-year disease-free survival rates after HR were 81.6, 66.9, and 56.3 %. There were no significant differences of cumulative survival rates ($P=0.31$) and disease-free survival rates ($P=0.71$) between the two groups (Fig. 16.2) by using log-rank test analysis.

The major complication rates were 3.8 % (11/290) for ablation and 6.9 % (21/306) for HR ($P=0.10$), respectively. Five needle seedings (1.4 %, 5/364) occurred at 6–42 months after ablation and one incision seeding (0.3 %, 1/306) occurred at 20 months after operation, respectively. There were four pleural effusion cases (1.4 %, 4/290) after ablation and ten cases (3.3 %, 10/306) after HR who needed drainage intervention. There was two gastrointestinal bleeding (0.7 %, 2/290) after ablation and none for HR. In addition, major complications occurred each after HR treatment, which were subphrenic abscess, abdominal cavity bacterial infection, gallbladder perforation, heart failure, bile leakage, adhesive intestinal obstruction, operative incision split, and intraoperative tumor rupture, respectively. There were no statistical differences for all the major complications between the two groups ($P>0.05$).

16.1.3 Conclusion

The present prospective cohort study provides many valuable information to evaluate minimally invasive percutaneous MWA/RFA with traditional HR for <5 cm HCC therapy with relatively large series, long follow-up, and prospective data collection. The study performed the comparison in multiple parameters including liver function, operation time, hospitalization, cost, recurrence, survival, and complication. Furthermore, all the ablation procedures used cooled-tip applicators with larger ablation zone, which may increase the possibility of successfully ablation for 3–5 cm HCC.

In conclusion, for the early-stage (≤5 cm, ≤3 nodules) HCC treatment, ultrasound-guided percutaneous cooled-probe MWA/RFA and HR achieved similar intermediate-term effectiveness. Though hepatectomy showed better local tumor control for 3–5 cm tumor, ablation showed the advantages of lower expense, minimal invasion, and repeatability. Further study with long-term follow-up and more patients is expected to provide more reliable efficacy evaluation and survival analysis.

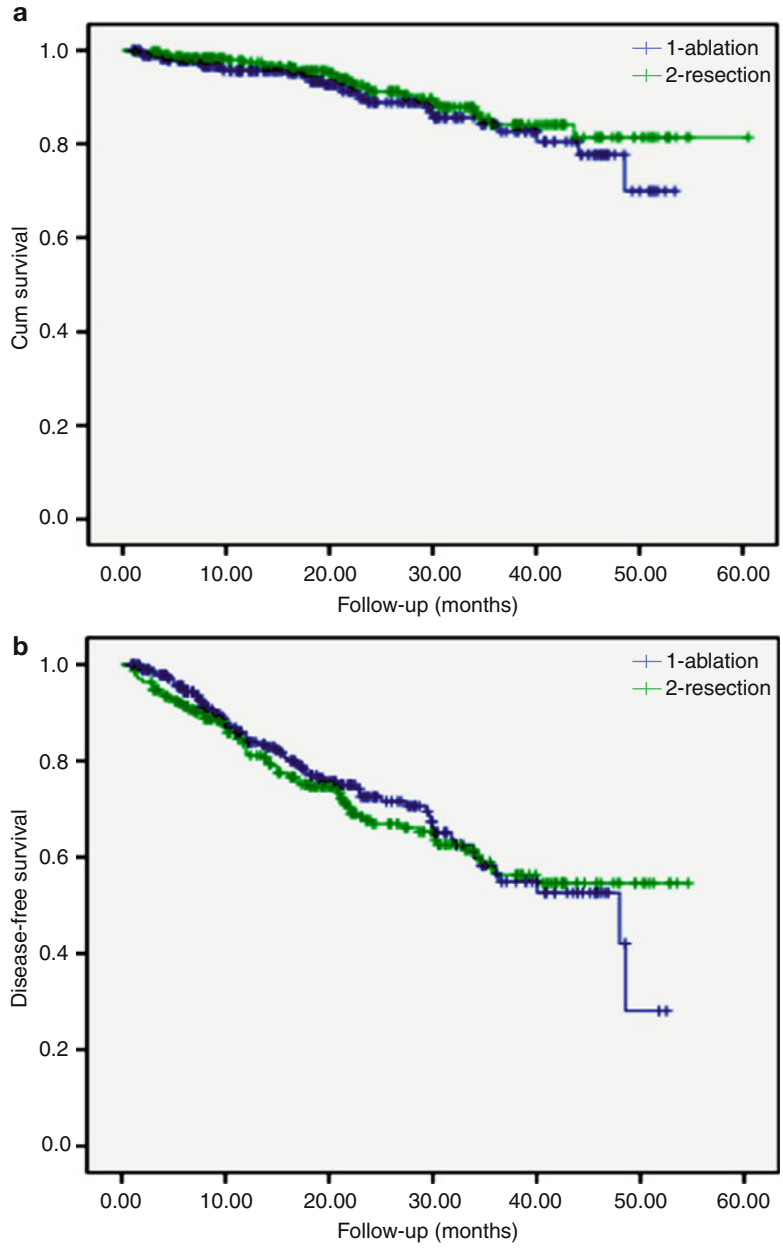

Fig. 16.2 (**a**) Overall survival curve comparison between thermal ablation and HR treatment of HCC. There is no significant difference between two groups ($P=0.31$). (**b**) Disease-free survival curve comparison between thermal ablation and HR treatment of HCC. There is no significant difference between two groups ($P=0.71$)

16.2 Comparative of MWA Versus RAF

16.2.1 Difference of Thermal Field Characteristics Between MWA and RFA

In RFA, a high-frequency alternating electrical current (375–500 kHz) is used to create ionic agitation, which produces frictional heat and heat conduction to achieve subsequent tissue necrosis [25, 26]. MWA uses electromagnetic energy to rapidly rotate adjacent polar water molecules in the surrounding tissue, which flip back and forth 2–5 billion times a second depending on the frequency of the microwave energy. The rapid friction produces heat, thus inducing cellular death via coagulation necrosis. Ionic polarization as another mechanism responsible for heat generation is a far less important mechanism in living tissue.

The difference between MWA and RFA characteristics are summarized as follows (Table 16.2): (1) the active tissue heating of RFA is limited to a few millimeters surrounding the active electrode, with the remainder of ablation zone relying on the conduction of electricity into the tissue [26]. Microwave uses electromagnetic energy with the much broader field of power density (up to 2 cm surrounding the antenna) to rapidly rotate adjacent polar water molecules to achieve primarily active heating, which can get a much broader zone of active heating [27]. (2) RFA is limited by the increase in impedance with tissue boiling and charring [26], because water vapor and char act as electrical insulators. MWA does not seem to be subject to this limitation. Therefore, temperature greater than 100 °C is readily achieved [28]. (3) Owing to the active heating ability, MWA can achieve higher intratumoral temperatures, larger ablation volumes, and shorter ablation time [28–31]. Because the cooling effect of blood flow is most pronounced within the zone of conductive rather than active heating, MWA is less affected by blood vessel-mediated cooling (the heat-sink effect). These benefits have the potential to allow for a more uniform tumor kill in the ablation zone, both within the targeted zone and perivascular tissue [31, 32]. (4) MWA allows for simultaneously multiple probes deployment to reduce the duration of therapy and increase the diameter of ablation zone [26–28]. (5) MWA does not require the placement of grounding pads, and the electrical energy is deployed in the target tissue only, which avoids applied energy losing and skin burns. Moreover, MWA is not contraindicated by the metallic materials like surgical clips or pacemaker.

Table 16.2 Different thermal characteristics between MWA and RFA

	MWA	RAF
Frequency	915, 2,450 MHz	400–600 KHz
Mechanism	Oscillation of polar molecule and ion	Oscillation of ion
Temperature rise	High efficiency	Low efficiency
Coagulation zone	Regular, narrow congestion zone	Irregular, wide congestion zone
Ablation time	Shorter (3 cm with 10 min)	Longer (3 cm with 20–30 min)
Ability of vessel coagulation	Strong	Weak
Time to highest temperature	Faster (20–30 s)	Slower
Highest temperature	Higher (15–25 °C)	Lower
Ablated zone of in vivo	(3.9 × 2.4) cm	(3.2 × 1.6) cm

MWA microwave ablation, *RFA* radiofrequency ablation

16.2.2 Studies Status

For the comparison of two techniques in HCC, only a limited number of studies have been performed, most of which are retrospective studies and all with a relatively small samples and short-term follow-up (Table 16.3). The only reported randomized controlled trial was performed by Japanese researches in 2002 [33]. Most of the researches showed MWA and RFA achieved similar tumor necrosis effect and survival [34–37]. But Japanese researchers thought RFA had tumor

Table 16.3 The clinical comparative studies for MWA and RFA

Author	Design	Tumor size (cm)[a]	Patients[a]	System	Follow-up (months)	CA	LTP	Survival	Complication
Shibata et al. [33]	RCT	2.2 vs 2.3	36 vs 36	Non-cool tip	18	Similar	Similar	N/A	Similar
Qian et al. [34]	Prospective	2.1 vs 2.0	22 vs 20	Cool tip	5.1	Similar	Similar	N/A	N/A
Simo et al. [36]	Retrospective	2.3 vs 2.5	13 vs 27	N/A	7	N/A	N/A	Similar	N/A
Iida et al. [37]	Retrospective		40 vs 18	N/A	N/A	N/A	Similar	Similar	N/A
Lu et al. [35]	Retrospective	2.5 vs 2.6	49 vs 53	Non-cool tip	25	Similar	Similar	Similar	Similar
Ohmoto et al. [38]	Retrospective	1.7 vs 1.6 (<3 cm)	70 vs 48	Non-cool tip	N/A	Better for RFA	Better for RFA	Better for RFA	Better for RFA
Ohmoto et al. [39]	Retrospective	1.6 vs 1.5 (<2 cm)	39 vs 24	Non-cool tip	N/A	Less for RFA	Better for RFA	Better for RFA	Better for RFA

[a]Data based on MWA vs RFA; *RCT* randomized controlled trial, *N/A*, not available

Table 16.4 Patients' treatment parameter between MWA and RFA groups

Category	MWA	RFA	*t* value	*P* value
Power (W)	49.8 ± 1.6	58.3 ± 11.7	−9.97	<0.001
Time (min)	8.7 ± 4.8	23.5 ± 11.1	−16.81	<0.001
Energy (KJ)	26.0 ± 14.4	45.6 ± 25.8	−9.07	<0.001
Ablation needle	1.8 ± 0.4	2.0 ± 0.3	−5.35	<0.001
Ablation session	1.3 ± 0.5	1.5 ± 0.5	−3.81	0.0002
Puncture time (times)	2.5 ± 1.3	3.0 ± 1.3	−3.66	0.0003
Applicator distance (cm)	1.5 ± 0.6	1.4 ± 0.4	1.85	0.07

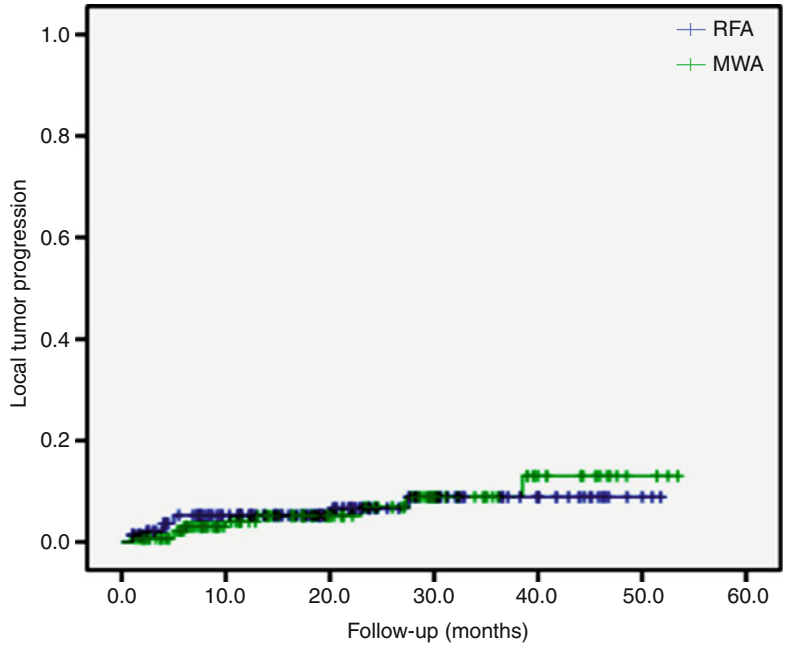

Fig. 16.3 Comparison curves of LTP after MWA and RFA of HCC. There is no significant difference between two treatments ($P = 0.96$)

control advantage in small liver lesions [38, 39]. However, randomized controlled trial with large sample and long-term follow-up is lacking and strongly recommended to provide evidence of evidence-based medicine.

16.2.3 Randomized Controlled Trial for MWA and RFA

Our group is performing a randomized controlled trial to compare intermediate-term therapeutic effectiveness of the ultrasound-guided percutaneous cooled-probe MWA and RFA in early-stage HCC treatment.

From October 2008 to January 2013, 290 cases of biopsy-proved HCC patients were involved in a randomized controlled study. One hundred forty-six (192 nodules) cases were treated with percutaneous MWA, and 144 (172 nodules) cases were treated with percutaneous RFA. The patients were treated by the cool-tip microwave unit (KY-2000, Kangyou Medical, China) and cool-tip multipolar radiofrequency generator (CelonLab Power, with firmware version 1v12; Celon, Berlin, Germany).

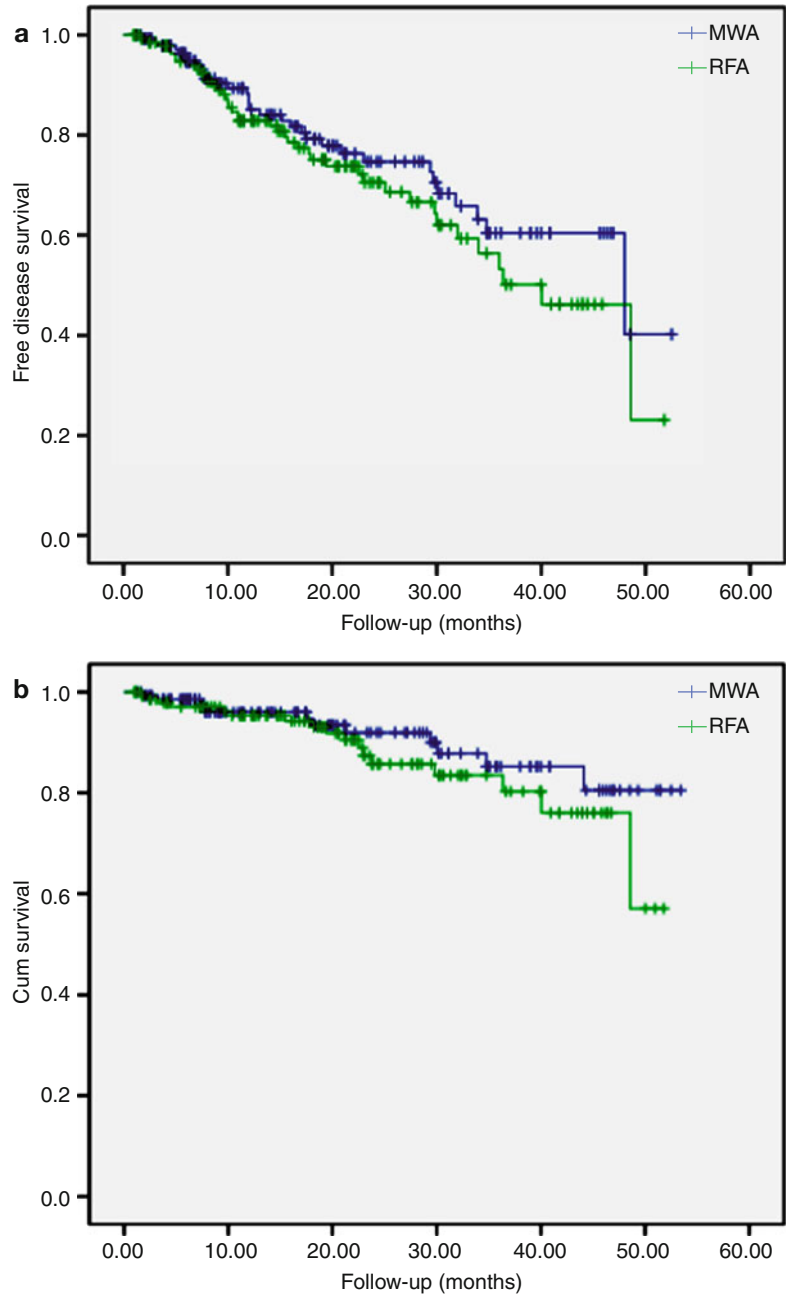

Fig. 16.4 Survival comparison between MWA and RFA of early-stage HCC. (**a**) Free disease survival curves after MWA and RFA of HCC. There is no significant difference between two treatments ($P=0.30$). (**b**) Overall survival curves after MWA and RFA of HCC. There is no significant difference between two treatments ($P=0.31$)

The demographics and pre-ablation liver function tests of both groups were similar.

The average numbers of treatment sessions were 1.3 ± 0.5 for MWA and 1.5 ± 0.5 for RFA, respectively, being significantly fewer in the MWA group ($P<0.001$) (Table 16.4). Average ablation times were 8.7 ± 4.8 min for MWA and 23.5 ± 11.1 min for RFA, being significantly

fewer in the MWA group ($P<0.001$). The average puncture numbers were 2.5±1.3 for MWA and 3.0±1.3 for RFA, respectively, being significantly fewer in the MWA group ($P<0.001$) as well.

The follow-up period was 2–51.8 months (median 19.8 months). The TE rate was 99.5 % (191/192) in the tumors treated with MWA and 98.8 % (170/172) in those treated with RFA, with no significant difference between the two groups ($P=0.92$). The 1-year, 2-year, and 3-year LTP were 3.7, 5.8, and 9.6 % for MWA versus 5.3, 6.7, and 8.9 % for RFA, respectively ($P=0.96$) (Fig. 16.3). The 1-year, 2-year, and 3-year intrahepatic metastatic rates were 19.1, 30.0, and 39.4 % for MWA versus 22.9, 34.0, and 50.9 % for RFA, respectively ($P=0.39$). The 1-year, 2-year, and 3-year cumulative survival rates after MWA were 96.2, 91.4, and 85.7 %, and the 1-year, 2-year, and 3-year disease-free survival rates after MWA were 87.6, 75.8, and 62.7 %. The 1-year, 2-year, and 3-year cumulative survival rates after RFA were 95.5, 86.8, and 82.9 %, and the 1-year, 2-year, and 3-year disease-free survival rates after RFA were 83.2, 71.6, and 52.8 %. There were no significant differences of cumulative survival rates ($P=0.31$) and disease-free survival rates ($P=0.30$) between the two groups (Fig. 16.4). No treatment-related death was observed in both groups. The major complication rates were 4.8 % (7/146) for MWA and 2.8 % (4/144) for RFA ($P>0.05$), respectively.

Conclusion

The present randomized controlled trial provides many valuable information for HCC ablation modalities assess and selection, such as relatively large series, long follow-up, and prospective data collection for exact ablation time, session, puncture number, cost, recurrence, survival, and complication.

In conclusion, for the early-stage (≤5 cm, ≤3 nodules) HCC treatment, US-guided percutaneous cooled-probe MWA and RFA achieved similar intermediate-term effectiveness. However, MWA showed slight advantage in local tumor control for tumors adjacent to important structures and larger tumors, and MWA needed less ablation time, session, and hospital expense, which reduced the invasion and saved the medical resources. Further study with long-term follow-up and more patients is expected to provide more reliable efficacy evaluation and survival analysis.

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Part V

Microwave Ablation of Other Solid Tumor

Microwave Ablation in Renal Cell Carcinoma

17

Jie Yu and Ping Liang

Abstract

Cancer of the kidney is the third most common cancer of the urinary tract and renal cell carcinoma (RCC) is the most lethal of all genitourinary tumors. Recently, minimally invasive ablation technologies have emerged as potential treatment options for clinically localized RCC to reduce procedural morbidity further and maintain equivalent oncologic control effectiveness with surgery. Microwave ablation (MWA) has achieved mature development in liver cancer therapy. As a newer nephron-sparing technique, it appears promising for the treatment of RCC in selected patients, especially for small RCC patients with acceptable major complications. The purpose of this chapter is to present the application status of MWA and to introduce the technique principle of MWA in RCC treatment. The limited comparative results between MWA and radical nephrectomy and partial nephrectomy will be discussed as well.

Keywords

Microwave • Ablation • Renal cell carcinoma • Nephrectomy

Abbreviations and Acronyms

CT	Computed tomography
LRN	Laparoscopic radial nephrectomy
LTP	Local tumor progression
MRI	Magnetic resonance imaging
MWA	Microwave ablation
ORN	Open radical nephrectomy
RCC	Renal cell carcinoma
RFA	Radiofrequency ablation
TE	Technique effectiveness
US	Ultrasound

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17.1 Introduction

About 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred in 2008 worldwide [1]. Cancer of the

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kidney accounts for approximately 3.5 % of all malignancies and it is the third most common cancer of the urinary tract. Renal cell carcinoma (RCC) is the most lethal of all genitourinary tumors [1]. The clinical diagnosis of RCC is radiographic, and effective imaging of the kidney can be achieved by ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI). With the advent of cross-sectional imaging, more incidental renal masses are being detected. Although larger tumors are occasionally detected, most masses detected incidentally are small renal masses of <4 cm in diameter and are classified as T1a on the tumor, node, metastasis classification system. Small renal masses incidentally discovered account for 48–66 % of RCC diagnoses [2]. The standard of care for clinically localized RCC remains surgical resection due to the favorable prognosis associated with surgery and the relative ineffectiveness of systemic therapy. Patients undergoing radical or partial nephrectomy for small RCC achieved similar 5-year cumulative survival in excess of 95 % [3, 4], but partial nephrectomy for small renal tumors provides superior intermediate- to long-term preservation of renal function compared with radical nephrectomy [5]. Because of the increased detection for small RCC, more treatment choices are being provided for the tumor control. Recently minimally invasive ablation technologies have emerged as potential treatment options for clinically localized RCC to reduce procedural morbidity further and maintain equivalent oncologic control effectiveness with surgery. Effective renal cryoablation and radiofrequency ablation (RFA) have been achieved by open and laparoscopic approaches as well as by percutaneous image-guided techniques [6–8]. Percutaneous thermal ablation has also been successfully performed under US, CT, or MRI guidance [9–11]. As one of the most recent and exciting advances in the field of thermal ablation techniques, microwave ablation (MWA) has achieved mature development in liver cancer therapy. The clinical application of MWA in RCC is anticipated as well.

17.2 MWA Procedure

17.2.1 Indications

Inclusion criteria of MWA for RCC are as follows: (1) a peripherally located single lesion 4 cm or smaller, (2) no tumor invasion to the renal pelvis/calix, (3) tumors not abutting the bowel or ureter, (4) absent renal vein tumor thrombus or extrarenal metastasis, (5) an appropriate puncture route noted on imaging if ablation guided by imaging, (6) poor surgical candidates for advanced age and significant comorbidities, (7) poor renal function or single kidney after nephrectomy, (8) patient preference, and (9) a general patient condition permitting MWA. However, with the technique and equipment advancement, MWA can also be expanded to treat small RCC adjacent to the renal pelvis and bowel with the help of temperature monitoring and artificial abdominal and ureteral perfusion. And for tumors larger than 4 cm, MWA can be as an effective modality by combination with radiotherapy or transcatheter arterial chemoembolization for selected patients with poor surgical candidates.

17.2.2 Contraindications

Contraindications are as follows: (1) advanced renal dysfunction; (2) severe coagulation disorders; (3) enhanced fibrinolysis; (4) cardiac ischemia and severe disorders of the electric conduction of the myocardium; (5) severe lung function insufficiency; (6) severe infection; (7) renal vascular malformation (such as arterial aneurysm); (8) clinically evident heart failure and liver failure, such as massive ascites or hepatic encephalopathy or with a trancelike state; (9) unlimited extrarenal metastatic disease; and (10) life expectancy ≤6–12 months.

17.2.3 Patient Preparation and Data Required

Patients considered for MWA should be accurately evaluated through clinical history, physical

examination, laboratory values, and performance status. Pre-therapy evaluation of electrocardiogram, serum liver enzymes, blood cell count, routine urine test, serum creatinine and urea nitrogen level, and coagulation should be monitored and known before the procedure. Imaging studies including chest radiography, abdominal contrast-enhanced US, dynamic CT, or MRI examination should be performed to accurately stage and locate the lesions and exclude renal venous thrombosis and extrarenal metastases. The growth patterns of the renal nodules can be classified into three types: exophytic, parenchymal, and endophytic. Exophytic nodules are defined when they projected out of the renal contour with no component extending into the renal sinus. Parenchymal nodules are defined when they are confined within the parenchyma without contour bulging or sinus extension. Endophytic nodules are defined when they extended into the renal sinus with no exophytic component.

17.2.4 US-Guided Microwave Ablation

The microwave unit (KY-2000, Kangyou Medical, Nanjing, China) is capable of producing 100 W of power at 2,450 MHz. The needle antenna has a diameter of 1.9 mm (15 gauge) and a length of 18 cm. Inside the antenna shaft, there are dual channels through which distilled water under room temperature is pumped by a peristaltic pump. After local anesthesia with 1 % lidocaine, US-guided biopsy can be performed first by an automatic biopsy gun with an 18 gauge cutting needle; two to three separate punctures are performed to obtain the pathological diagnosis. Subsequently, the antenna is percutaneously inserted into the tumor through the abdomen or retroperitoneum and placed at the desired location under US guidance. For tumors less than 2.0 cm, one antenna is inserted, and for tumors measuring 2.0 cm or greater, two antennas are inserted with an inter-antenna distance of no more than 1.8 cm. A power output of 50 W for 10 min is routinely used during MWA. If the heat-generated hyperechoic water vapor does not completely encompass the entire tumor, prolonged MW emission is applied until the desired temperature is reached. After all insertions, intravenous anesthesia is administered by a combination of propofol and ketamine via the peripheral vein during standard hemodynamic monitoring. When withdrawing the antenna, applicator track is heated ablated with sufficient MW energy by stopping the cooling-shaft water dump.

17.2.5 Thermal Monitoring During the Procedure

The microwave machine is also equipped with a thermal monitoring system which can continuously measure temperature in real time during ablation. For safely located tumors, if the measured temperature at the site of 5–10 mm away from the tumor margin reaches 60 °C or remains above 54 °C for at least 3 min, complete tumor necrosis is considered achieved. For high-risk localized tumors, the real-time temperature of tumor margins or the kidney proximal to the collecting structures or intestinal tract is monitored. The temperature cutoff of ablation therapy is set at 54 °C in the patients without a history of prior laparotomy or 50 °C in the patients with laparotomy history for the reason of intestinal adhesion. Then the emission of microwave was reactivated after the temperature decreased to 45 °C.

17.3 Complication

All complications of the ablation procedure should be reported, including those that do not appear related to the procedure. According to the classification system used by the Society of Interventional Radiology for grading complications and reporting standards for percutaneous thermal ablation of RCC [12, 13], minor complications refer to side effect with no therapy and no consequence, nominal therapy and no consequence, or overnight admission for observation only. Major complications include requiring minor therapy with hospitalization <48 h,

requiring major therapy and unplanned increase in level of care with prolonged hospitalization >48 h, permanent adverse sequelae, and death. Abscess, hematoma, hematuria, lumbar radiculopathy, myocardial infarction, pleural effusion, renal failure, pneumothorax, skin burn, collecting system or ureteral stricture, urinary fistula, unintended perforation of hollow viscus, and vagal reaction are major complications that may occur after the ablation procedure.

17.4 Follow-Up

The follow-up includes routine physical examination, laboratory tests (blood count, routine urine test, serum creatinine and urea nitrogen level), and three-phase contrast-enhanced US and dynamic CT/MRI at 1 and 3 months after treatment and then at 6-month intervals. Technique effectiveness is defined as the absence of enhancement of any areas of the mass on a follow-up enhanced imaging performed 1 month after treatment [12]. Local tumor progression (LTP) is defined as the appearance of irregular peripheral enhancement in scattered, nodular, or eccentric pattern on contrast-enhanced imaging scans around the ablation zone during the follow-up period. Complication is defined according to reporting standards [12, 13]. Follow-up is closed at the time of death or the last visit of the patient.

17.5 Application Status of MWA in RCC

MWA acts by destroying tumor through application of high temperature produced by electromagnetic energy to rapidly rotate adjacent polar water molecules within the targeted pathological tissue leading to protein denaturation, cell membrane disruption, and finally coagulation necrosis with cellular death. Though RFA achieves more widely clinical appliance, MWA shares several theoretical advantages over RFA in consistently higher intratumoral temperatures, larger ablation volumes, faster ablation time, less dependency on the electrical conductivities of tissue, and energy delivery less limited by the exponential rising electrical impedances of tumor tissue [14–17]. MWA is also less affected by the perfusion-mediated "heat-sink" effect, which may be helpful for treating tumors in the kidney with rich blood supply. In addition, multiple antennas can be used simultaneously to achieve larger ablation zone.

Compared with development in the liver, MWA only performs preliminary researches with small volumes in treating small RCC. There have been several recent studies assessing the safety and efficacy of emerging ablation techniques for treatment of small renal tumors (Table 17.1). Liang et al. and Carrafielloa et al. reported their MWA application in small RCCs with the mean size less than 3 cm. They observed no residual tumor or recurrence at median follow-up of

Table 17.1 Clinical application of MWA in the kidney

Authors	Tumor number	Tumor size (cm)	Antenna type	Frequency (MHz)	Complete reaction (%)	Local recurrence (%)	Complication (%)	Median follow-up (months)
Liang et al. [18]	12	2.5	Cooled tip	2,450	100	0	0	11
Carrafiello et al. [19]	12	2.0	Cooled tip	915	100	0	0	6
Muto et al. [21]	10	2.75	Cooled tip	915	100	0	0	13
Bai et al. [22]	23	2.8	Cooled tip	2,450	94.4	0	0	20
Yu et al. [23]	46	3.0	Cooled tip	2,450	98	0	0	20.1
Castle et al. [24]	10	3.65	Cooled tip	915	NA	38	40	18

MWA microwave ablation

6–11 months [18, 19]. Clark et al. performed a study to identify the presence of skip lesions (areas of solid tumor) within the ablation zone by performing MWA before nephrectomy [20]. The result showed that there were no skip areas within the ablation zone in all ten patients with RCC, and MWA could safely and quickly generate large ablation zones with uniform tissue necrosis. Muto et al. performed unclamped laparoscopic MWA followed by partial nephrectomy in a series of ten patients with RCC without complications. The ablation lesions were then analyzed and found to have extensive coagulation necrosis without skip lesions [21]. Bai et al. performed retroperitoneal laparoscopic MWA on 23 RCC tumors with the size less than 4 cm and reported successful initial ablation in 94.4 % of patients; no recurrences at a median follow-up of 20 months and no major complication occurred, while minor complications occurred with an incidence of 18.2 %, consisting of fever and flank numbness [22]. Yu et al. reported their US-guided MWA of RCC experience with the largest volume and longest follow-up according to our knowledge [23]. Their technical effectiveness was 98.0 % and no metastasis or recurrence occurred. The 3-year local tumor progression rate was 7.7 % and 3-year overall survival rate was 97.8 %, respectively. No major complications occurred. Multivariate analysis showed that the tumor number, growth patterns of tumors, and ablation time were independent unfavorable prognostic factors. Castle et al. reviewed their laparoscopic or percutaneous experience in ten patients using a 915 MHz microwave ablation device [24]. However, the results of this study were disappointing and substantially worse than would be expected for cryoablation or RFA or other MWA studies. The study reported a high recurrence rate of 38 % at median follow-up of 18 months with the mean tumor size of 3.65 cm, and the intraoperative complication rate was 20 % and up to 40 % postoperatively. The major reason of this unfavorable result may attribute to 50 % of the tumors involved of the renal collecting system and the unsuitable antenna (relatively long tip of 3.7 cm and the frequency of 915 MHz) in their study. In summary, MWA appears to be a safe and effective technique for the management of RCC especially small RCC in selected patients.

Except the short-term and intermediate-term studies of MWA in RCC which were reported by our group previously, now we are collecting the patient volume and prolonging the follow-up to provide further clinical effect results of MWA for small RCC. The results showed that US-guided MWA was performed for 102 renal tumors (size range, 0.6–4.0 cm; mean size, 2.7 ± 0.9 cm) in 97 patients (70 men and 27 women; age range, 22–87 years; mean age, 65.0 ± 14.4 years) between April 2006 and December 2013. There were 92 patients with one nodule and five patients with two nodules. Among all the 102 lesions, 32 (31.4 %) lesions were located adjacent to the bowel or renal pelvis (distance between tumor margin and bowel/renal pelvis less than 5 mm). Ninety-seven patients received a total of 119 session (mean 1.2 ± 0.4, from 1 to 2) treatments with MWA for all the tumors. Eighty-five nodules were successfully treated by one MWA session, and 17 nodules were offered two sessions. Desired temperatures were attained in no more than 1,080 s (range, 150–1,080; mean, 448.8 ± 168.1 s). Median follow-up was 23.7 months (range, 3–89.4 months). Based on follow-up imaging, TE was achieved in all the tumors and metastasis-free and LTP-free rates were 94.8 % (92/97) and 98.0 % (100/102), respectively. Two LTPs were discovered at 5 and 32 months after MWA with an initial nodule size of 2.7 and 3.7 cm, respectively. Therapeutic options offered to patients with LTP included radiotherapy for one patient and radical nephrectomy for one patient. Eight of the 97 patients died during follow-up as a result of non-RCC causes in six patients (one stomach bleeding, one heart failure, one hepatocellular carcinoma, one liver failure, and two coronary heart disease, respectively) and RCC progression cause in two patients after MWA. The 1-, 3-, and 5-year overall survival rates were 98.4, 96.7, and 96.7 %, respectively. The 1-, 3-, and 5-year disease-free survival rates were 96.0, 88.3, and 84.3 %, respectively. The ablation zone was well defined on contrast-enhanced MRI/CT and contrast-enhanced US, and it gradually shrank with time (Figs. 17.1, 17.2, and 17.3). Six major

complications (5.0 %, 6/119) occurred after 119 MWA sessions including one hepatic encephalopathy with liver dysfunction, one urinary fistula that had diabetes and high-risk tumor location adjacent to the renal collecting system, one bowel perforation with tumor adjacent to the colon, one arteriovenous fistula, one pleural effusion, and one ascites needing drainage. The hepatic encephalopathy patient was successfully treated by intravenous hepatoprotective medicine for 1 week, and

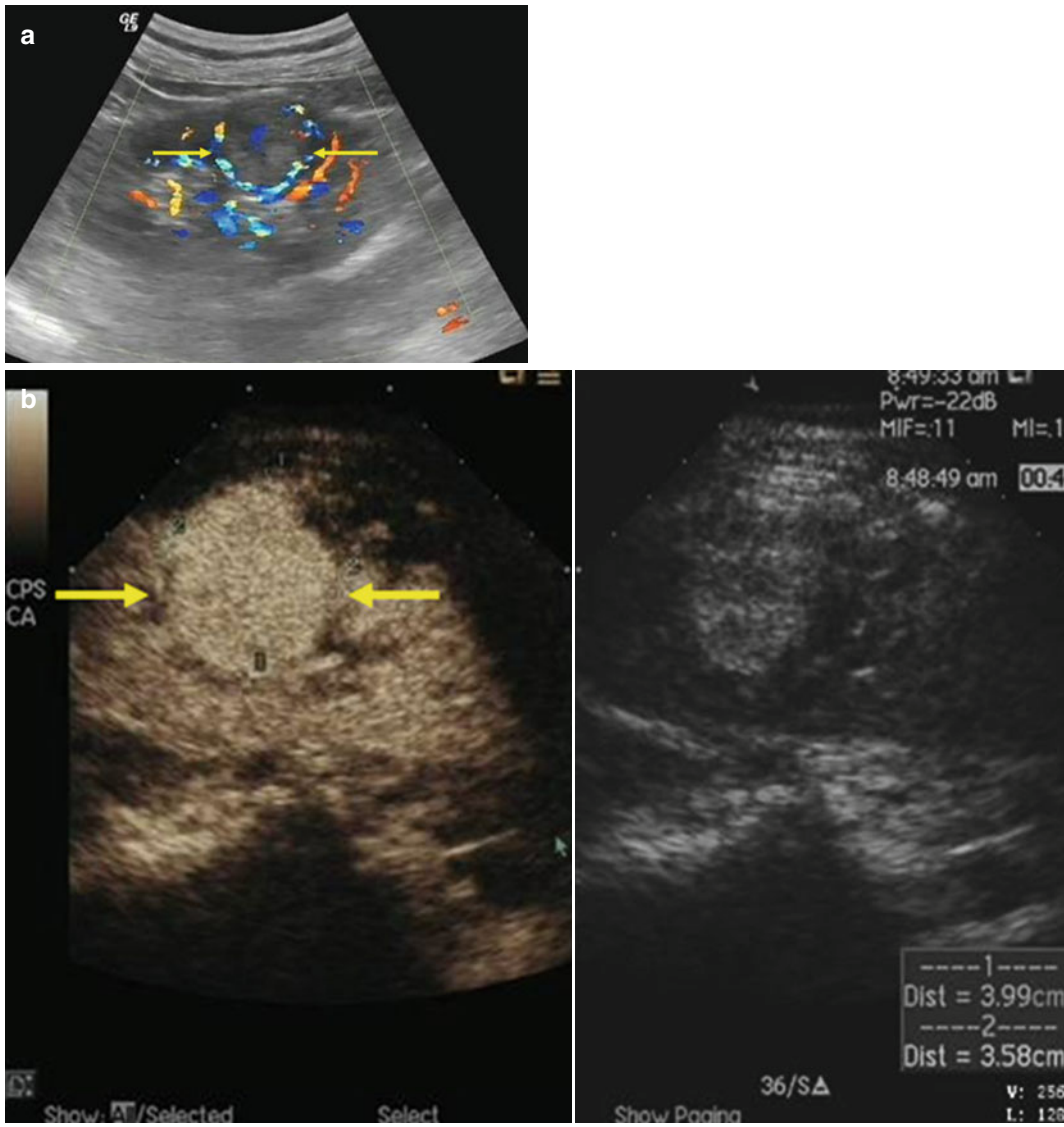

Fig. 17.1 Microwave ablation (MWA) in an 87-year-old man with right renal cell carcinoma (RCC), who was unable to undergo nephrectomy because of coronary heart disease. (**a**) Preablation conventional ultrasound (US) scan shows a hypoechoic lesion with rich blood supply (*arrows*). (**b**) Contrast-enhanced US before MWA shows tumor enhancement in arterial phase with the size of 4.0×3.6 cm (*mark*). (**c**) Conventional US shows two microwave antennas (*long arrow*) are placed in the tumor and one temperature monitor (*short arrow*) is placed at the tumor margin during the MWA procedure. (**d**) Conventional US shows hyperechoic ball formed by microwave emitting covers the tumor. (**e**) Contrast-enhanced US shows no enhancement of the ablation zone at 3 days after treatment (*mark*)

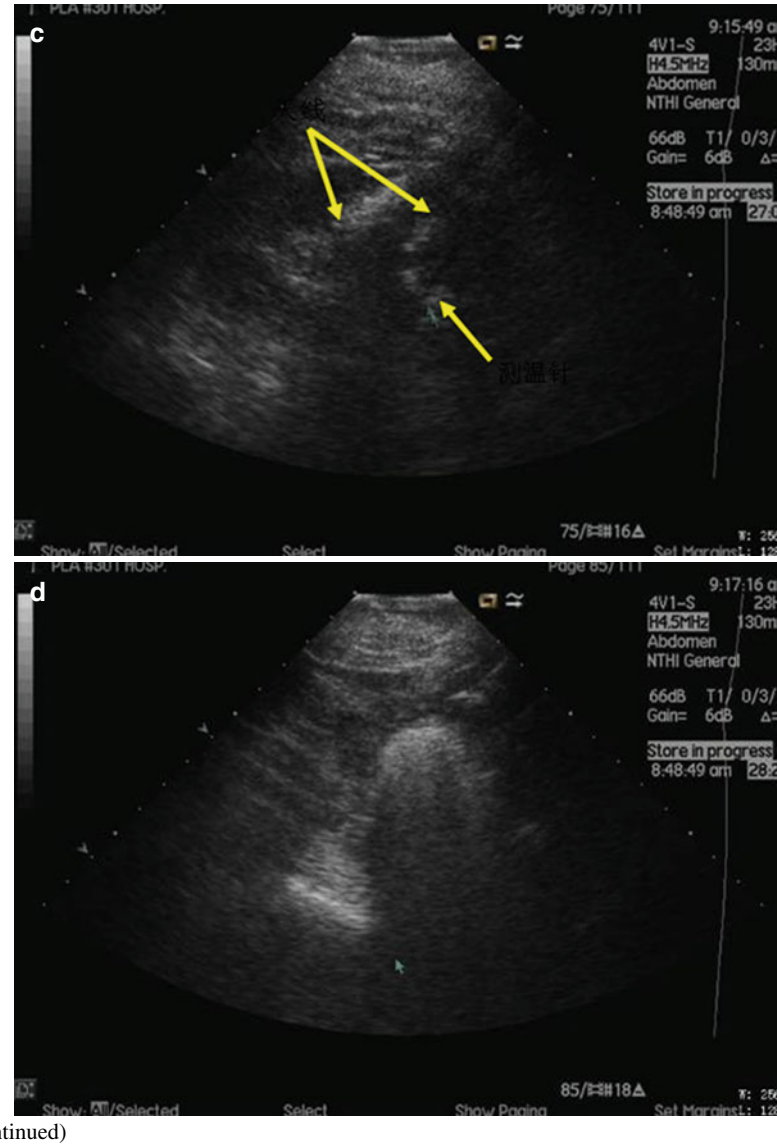

Fig. 17.1 (continued)

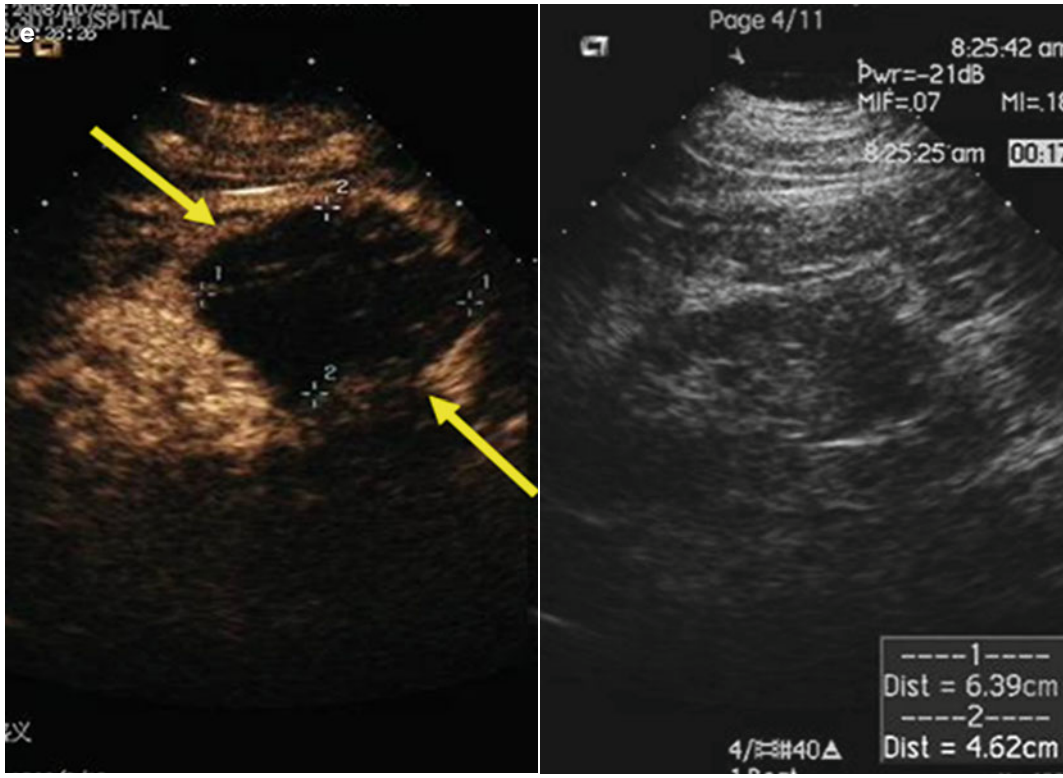

Fig. 17.1 (continued)

the urinary fistula patient was cured by intravenous anti-infective and antidiabetic medicine for 10 days. Bowel perforation was cured by enterostomy and intravenous anti-infective for 40 days. Arteriovenous fistula was successfully treated by percutaneous injection of thrombin at fistula with a 21 gauge needle and the patient discharged 3 days later. Two effusion patients were treated by drainage and recovered 2–3 days later. Another minor complication case of perinephric hematoma occurred which was controlled by medicine therapy. MWA showed no significant side effect on patient's serum urea nitrogen and creatinine level. And renal function in patients with preablation renal insufficiency did not worsen enough to necessitate dialysis.

To present the clinical outcomes after MWA of RCC in patients with renal dysfunction, we analyzed the results of 15 tumors of 14 RCC patients with renal dysfunction who underwent percutaneous ultrasound-guided MWA treatment. The tumor diameters ranged from 1.9 to 5.0 cm. Complete ablation was achieved in 15/15 (100 %) lesions after 1 or 2 MWA sessions. During a median follow-up time of 11.3 months (range, 2.9–70.0 months), two patients died of non-RCC disease and other patients survived with no tumor recurrence. Before MWA all 14 patients had abnormal initial serum creatinine values, with the mean level of 261.2 mmol/L (normal range). It was 279.9 mmol/L 1 day after MWA and 345.1 mmol/L at the last follow-up. The mean serum urea nitrogen level was 10.9 mmol/L before the initial procedure, 11.6 mmol/L 1 day after MWA, and 12.2 mmol/L of the last follow-up. There was no statistical difference between the pre-MWA and post-MWA serum creatinine and urea nitrogen levels. Renal function in nine patients did not worsen enough to necessitate dialysis until the last follow-up, and five patients who have received dialysis before MWA survived and depended on long-term

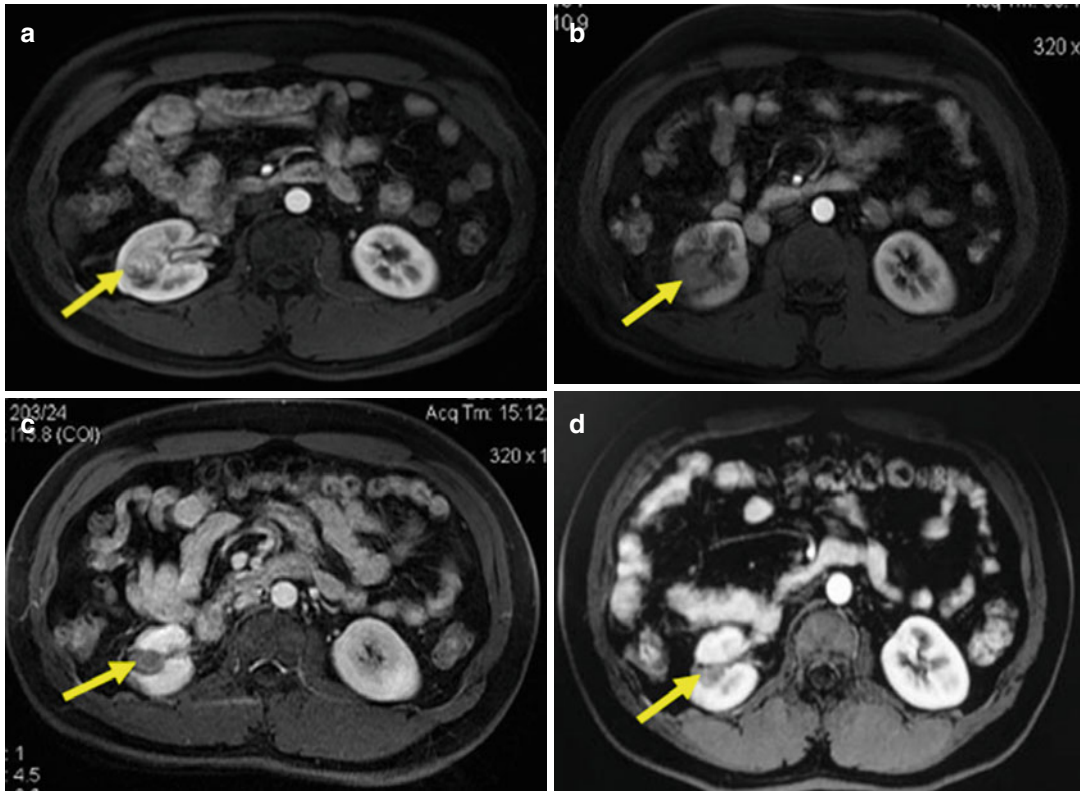

Fig. 17.2 MWA in a 45-year-old man with right RCC adjacent to the renal pelvis. (**a**) Preablation arterial phase magnetic resonance imaging (*MRI*) scan shows one heterogeneous enhancement of neoplasm (*arrow*) near the renal pelvis with the size of 2.4×1.9 cm. (**b**) Arterial phase MRI scan obtained 2 months after ablation shows hypoattenuating ablation zone (*arrow*) without enhancement. (**c**) Scan obtained 12 months after ablation shows hypoattenuating ablation zone (*arrow*) without enhancement corresponding to treated region. (**d**) Scan obtained 24 months after ablation shows diminishing hypoattenuating ablation zone (*arrow*) without enhancement

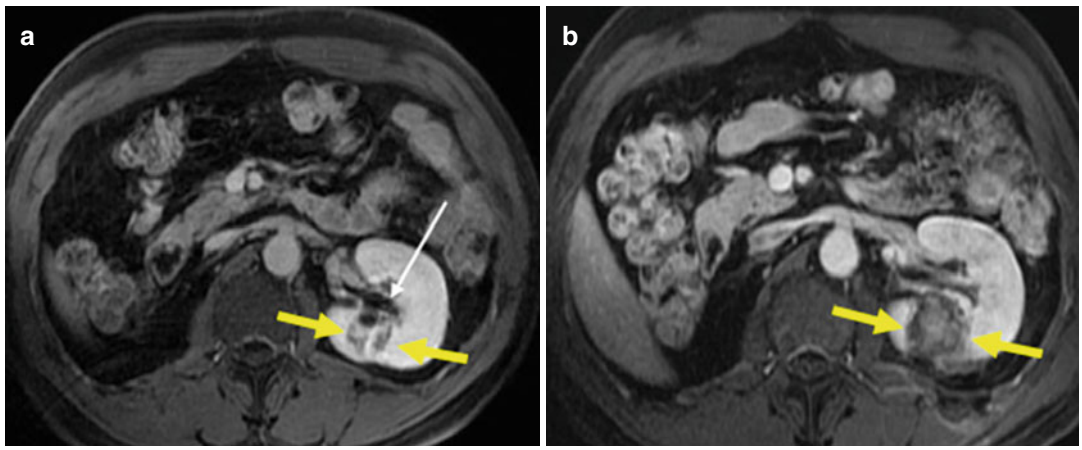

Fig. 17.3 MWA in a 51-year-old man with left RCC, who has a solitary kidney for nephrectomy for right RCC 1 year ago. (**a**) Preablation MRI scan shows one hypoattenuating neoplasm (*short arrow*) near the renal pelvis (*long arrows*) with the size of 3.0×2.6 cm. (**b**) Arterial phase MRI scan obtained 64 months after ablation shows hypoattenuating ablation zone (*arrows*) without enhancement and there is no renal pelvis injury

dialysis. This showed that MWA is an effective and relatively safe treatment option for RCC patients suffering from renal dysfunction.

17.6 Comparative Study of MWA with Other Modalities in RCC

Guan et al. performed a prospective randomized trial comparing MWA (laparoscopic or percutaneous) to partial nephrectomy (open or laparoscopic) in a cohort of 102 patients, finding estimated blood loss, complications, and postoperative decline of renal function to be significantly better in the MWA group than the partial nephrectomy group. They reported 3-year recurrence-free survival in patients with RCC of 90.4 % for MWA and 96.6 % for partial nephrectomy, which were not statistically significantly different [25]. Yu et al. reported their experience of retrospective comparative study between MWA and open radical nephrectomy (ORN) in small RCC [26]. They concluded that the RCC-related survival (97.1 % at 5 years) was comparable to those following ORN (97.8 % at 5 years). The major complication rates were comparable between the two techniques (2.5 % in MWA vs 3.1 % in ORN). The MWA group needed less operative time, estimated blood loss, and postoperative hospitalization. The group is performing another retrospective comparative study between MWA and retroperitoneal laparoscopic radial nephrectomy (LRN) in small RCC. The RCC-related survival (97 % at 5 years) after MWA was also comparable to those following LRN (98 % at 5 years). And the major complication rates were comparable between the two techniques (1.7 % in MWA vs 1.5 % in LRN), but MWA showed less renal function damage than LRN. The multivariate analysis showed that age, tumor type, postoperative urea nitrogen, and comorbid disease may become predictors related to the survival rate. There is no other comparative study to report the effective difference between MWA and other modalities including nephrectomy, RFA, cryoablation, and so on in RCC by now. As one of new ablation techniques, MWA of small RCC can achieve comparable results with radical and partial nephrectomy in oncologic outcomes. MWA appears to be a safe and effective technique for the management of small RCC patients with little loss of renal function.

Conclusion

In summary, MWA as a newer nephron-sparing technique appears promising. It yields effective tumor kill in RCC patients. It is a safe and effective technique for the treatment of RCC in selected patients, especially for small RCC patients with acceptable major complications. The technique provides another optional minimally invasive modality for renal tumor patients including some patients who lose the chance of nephrectomy. While the data on their long-term effectiveness are still lacking. Therefore, further studies with longer follow-up period are needed to include more larger RCCs and evaluate the efficacy for treating tumors at unfavorable locations, such as near the hilum or adjacent to the bowel. And randomized controlled trials with other modalities such as radical nephrectomy, partial nephrectomy, RFA, and cryoablation should be conducted for better assessment of safety and efficacy of MWA treatment.

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Microwave Ablation of Renal Angiomyolipoma

18

Zhi-yu Han and Ping Liang

Abstract

Tissue perfusion and vascular-mediated cooling have less impact on microwave ablation when compared with radiofrequency ablation. Microwave ablation could create larger and more lethal ablation zones with shorter treatment times. The minimally invasive microwave ablation of renal angiomyolipoma could directly reduce the lesion size, which could reduce the risk of hemorrhage, avoid a surgical procedure, and alleviate symptoms such as pain. The procedures were tolerated well. Microwave ablation may be an alternative minimally invasive technique for the management of angiomyolipoma that can preserve renal function with acceptable complication rates.

Keywords

Microwave ablation • Benign tumor • Renal angiomyolipoma • Ultrasound

Abbreviations and Acronyms

AML	Angiomyolipoma
MWA	Microwave ablation
RFA	Radiofrequency ablation
US	Ultrasound

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18.1 Introduction

Benign renal tumors constitute a heterogeneous group of tumors with characteristic histology and variable clinical profiles. The 2004 World Health Organization classification schemata categorize benign renal tumors on the basis of histogenesis (cell of origin) and histopathology [1, 2]. Benign renal tumors are thus classified into renal cell, metanephric, mesenchymal, and mixed epithelial and mesenchymal tumors. The most common types of benign kidney tumors are adenoma, oncocytoma, and angiomyolipoma (AML).

AML is the most common benign mesenchymal tumor of the kidney and is most commonly found in middle-aged women. The tumor is

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composed of blood vessels, smooth muscle cells, and fat cells [3]. It can occur sporadically (approximately 70 %) or appear to be a part of the tuberous sclerosis complex. AML is strongly associated with the genetic disease tuberous sclerosis. Most of these patients will have several AMLs in both kidneys [4–6]. Large renal AML (the diameter is more than 3.5 cm) may cause symptoms such as flank pain, hematuria, and retroperitoneal hemorrhage. It is generally agreed that asymptomatic AML larger than 4 cm and symptomatic lesions of any size should be treated [4–6].

As a benign renal tumor, AML is considered non-cancerous and not life-threatening; no treatment is offered but active surveillance [3, 7]. However, for the tumors causing symptoms or tumors that grow after being watched with imaging tests, an appropriate clinical management is required. Because of benign renal tumors, the renal function preservation is especially a priority. The traditional treatment is surgical excision of the lesion or the whole kidney. With advancements in minimally invasive medicine, several other modalities have now emerged as nephron-sparing surgical approaches. These include pure or robot-assisted laparoscopic partial nephrectomy, selective angioembolization, and laparoscopic and percutaneous ablative therapies such as cryoablation, radiofrequency ablation (RFA), or microwave ablation (MWA) [8–14].

The hemostatic effect of RFA allows AML to be treated without bleeding complications while preserving renal function. Moreover, compared with partial nephrectomy, the potential benefits of ablative therapy included minimal invasiveness, a high percentage of complete tumor necrosis, easy treatment for multiple lesions, lower costs than surgical resection, and improved quality of life [8, 14]. MWA was an additional ablation technology, which may be applied for the same indications as RFA ablation but had several advantages in energy delivery. Most importantly, microwave propagation is not limited by charred tissue, so intratumoral temperatures could be elevated consistently to very high level (>150 °C) without impairing energy deposition [15, 16]. So, high temperatures are more likely to overcome vascular-mediated cooling and create larger and more lethal ablation zones with shorter treatment times [17, 18].

Most cases of AML are asymptomatic, discovered incidentally on a computer tomography or ultrasound scan of the abdomen. Symptoms may appear when the tumor grows into surrounding tissues and organs. Some of the possible symptoms are hematuria, flank pain, abdominal mass, hemorrhage, etc. [3, 4]. Most benign renal tumors appear as solid enhancing masses and are thus indistinguishable from the more common malignant renal neoplasms, such as renal cell carcinoma. Biopsy of the renal mass may help establish the definitive diagnosis and may obviate aggressive treatment [3].

18.2 Treatment Protocol of MWA

18.2.1 Indications

It is generally agreed that asymptomatic AML larger than 4 cm and symptomatic (hematuria, flank pain, abdominal mass, hemorrhage, etc.) lesions of any size should be treated [4–6]. However, percutaneous ablative therapies guided with imaging techniques have the advantage of minimal invasion and accurate location. The indication of ablative therapies on AML can be expanded to solitary or multiple lesions less than 4 cm with safe and effective outcomes, because some patients very worry about the risk of haemorrhage or surgery and have huge psychological pressure.

18.2.2 Contraindications

If the lesions of AML distinctly bulge into the collecting system or cannot be separated with adjacent organs (such as the colon or small intestine), those patients are not the appropriate candidates of MWA. The other contraindications are the patients who have the high anesthetic risks, severe blood coagulation dysfunction (prothrombin time >30 s, prothrombin activity <40 %, and platelet count $<30\times10^9$/L cells), or serious comorbidities (such as heart failure, renal failure, etc.).

18.2.3 Procedures

Although those tumors are benign, complete ablation is considered to be an optimal result. The complete ablation of the lesion is considered to be achieved if the non-enhancing area of contrast imageology just is covered the lesion borders.

The treatment protocol should be designed according to the size and location of the lesions. In general, for lesions less than 1.7 cm in diameter, single antenna is used to insert in the center of the lesion, and for lesions ranging from 1.7 to 3.0 cm, two antennas are required to insert in the maximum plane of the lesion and kept at a distance no more than 1.5 cm. As for lesions larger than 3.0 cm, two antennas are required to insert in the upper plane of the lesion and another in the lower plane. Moreover, two antennas should be firstly inserted into the deeper region and withdrawn if the hyperechoic region covered the deeper region on ultrasound (US) after microwave emission. A thermal monitoring system attached to the microwave unit is used during ablation when the temperatures of some special point (such as the lowest lethal temperature of the margin of the lesion and the highest tolerant temperature of the important normal structures (renal collecting system, colon, etc.) need to acquire. The retroperitoneal route is the best choose of the puncture because the way of not through the peritoneal cavity can reduce the injury of the intestinal tract. One or two 21G thermal monitoring needles are inserted into the margin of targeted tumor or the important normal structures under US guidance [19, 20]. Heating of tissue at 50–55 °C markedly shortens the duration necessary to irreversibly damage cells to 4–6 min [21]. According to our previous study [19, 20], temperatures near the important structures such as the colon and renal pelvis are kept at 50–54 °C for no more than 3 min, with intermittent emission of microwave. During ablation, the region of ablation is monitored by US. The treatment session is finished if the hyperechoic region on gray-scale US covers the entire target region. When withdrawing the antennas, the needle tracks are routinely cauterized to avoid bleeding. Complete ablation of the lesion is considered to be achieved if contrast-enhanced US revealed absence of enhancement in the lesion. The complete ablation of the lesion is considered to be achieved if the non-enhancing area of contrast imageology just is covered the lesion borders.

18.3 Outcomes

From May 2006 to May 2011, 19 AML lesions (0.8cm-6.1cm) in 14 patients were confirmed by ultrasound-guided biopsy and underwent the treatment of MWA. Although all lesions were finished the treatment sessions, 15 lesions achieved complete ablation in postoperative evaluation with contrast enhanced US. The rest were not the complete ablation. The incompletely ablated area ranged from 0.5 to 1.9 cm (mean 1.1±0.6 cm) by long diameter and ranged from 0.3 to 1.1 cm (mean 0.6±0.3 cm) by short diameter. The reasons of the incomplete ablation were as follows: firstly, the size of those lesions was bigger (the mean long diameter was 5.4±0.6 cm and ranged from 4.8 to 6.1 cm). Secondly, 3 lesions located in the anterior kidney and were close to the colon. Consideration of the benign tumor, the safe reason and the residual size, the supplementary treatment session was not taken.

The follow-up period was 6–36 months (median, 10 months). No AML-related symptoms were detected in all the patients. The size of all lesions reduced distinctly, especially in the smaller lesions. No AML recurrence was observed during the follow-up in the 15 lesions of complete ablation. The imaging of the four incompletely ablated lesions displayed persistent AML.

18.4 Complications

Pain and fever are the common minor postoperative complications in most patients. According to the reporting criteria for image-guided tumor ablation [22], the pain level range from mildly to moderately, and the drug is not necessary. Fever which is always lower than 38.5 °C occurs usually on the day of MWA and lasts for 3 days. Even mild subcapsular hemorrhage is rare.

The other major complications are local infection around ablation zone and colon or urinary fistula. As for the possible reasons, firstly, the colon is fixed in narrow retroperitoneal space and the lesion location of the kidney is close to the colon. Moreover, the permeability of the colon wall and the bacteria in colon exudation increases after heat irritation. Secondly, there are large amounts of fat in AML which could easily reach high temperatures. The heat could not disperse easily in the fatty renal capsule and the narrow retroperitoneal space. Therefore, operators should be aware of intestinal tract injury if the lesions were close to the colon.

18.5 Other Minimally Invasive Methods

RFA is the most widely used thermal ablation technique for local solid tumors. RFA is an elective procedure, which can be used in the treatment of renal AML in a safe and effective manner. Sooriakumaran et al. [23] and Gregory et al. [24] reported that RFA is technically feasible in AML with the median (range) tumor size of 9.5 (9–19) cm and 11.0 (6.1–32.4) cm. Pervoo et al. [25] and Castle et al. [26] reported that RFA is safe and effective in smaller than 4.5 cm AML. According to Castle's report, there were no intraoperative complications, while four postoperative complications occurred. Two complications were procedure related including transient hematuria and intercostal nerve transection, while two were related to surgery (myocardial infarction and pneumonia). No patients had radiographic evidence of persistent AML (enhancement in computed tomography) at a mean (range) follow-up of 21.1 (1.5–72) months [26].

Byrd et al. [27] reported on the first series of patients with AMLs (2.5–7.0 cm) treated with laparoscopic cryoablation. The procedures were tolerated well. Follow-up imaging using MRI showed reduction in lesion size, lack of blood flow, and no subsequent regrowth in all patients. Johnson et al. [28] reported three patients with AMLs (1.2–2.5 cm) involving a solitary kidney who underwent percutaneous cryoablation. The patients experienced minimal to no pain during percutaneous cryoablation, and all were discharged the same day. No procedural or postoperative complications were noted. The percutaneous cryoablation was proved to be a safe and effective method for treating AMLs.

Selective angioembolization and nephron-sparing surgery were the common treatment methods of AML, which could preserve normal renal unit. In a larger cohort of 58 patients, nephron-sparing surgery was successfully performed in all patients with 12 % of the overall complication rate and 3.4 % of the local recurrence rate [29]. Although selective angioembolization had also been used in the treatment for AML, the outcomes after embolization required critical review because re-embolization or subsequent surgical intervention had frequently been required in patients for recurrent bleeding, persistent symptoms, or lack of regression of the lesion [30]. Long-term follow-up of renal angioembolization in AML shows recurrence rates up to 30 % [13, 31]. Bisser [32] et al. reported post-embolization syndrome (abscess formation, nonfunctioning kidney, and refractory hypertension secondary to segmental renal infarct) occurring in 89 % of patients in a review of 13 case series, which can be reduced to 30 % with a regimen of tapered steroids and prophylactic antibiotics. Excluding post-embolization syndrome, complication rates are about 10 % [33]. Berglund et al. [34] reported 38 patients of partial nephrectomy for AML with a 23 % complication rate, 14 % loss of a renal unit, and six (16 %) patients with new-onset chronic kidney disease.

Selective angioembolization has been used frequently in the treatment of renal AML. It has been shown to have technical success rates of 90–100 % [12]. But the long-term results have shown recurrence rates of nearly one third [13, 31]. From the results of three ablation methods, it showed similar availability and curative efficacy with low recurrence rates. However, the current literatures have limitations and the cases are too small (Fig. 18.1 and Table 18.1).

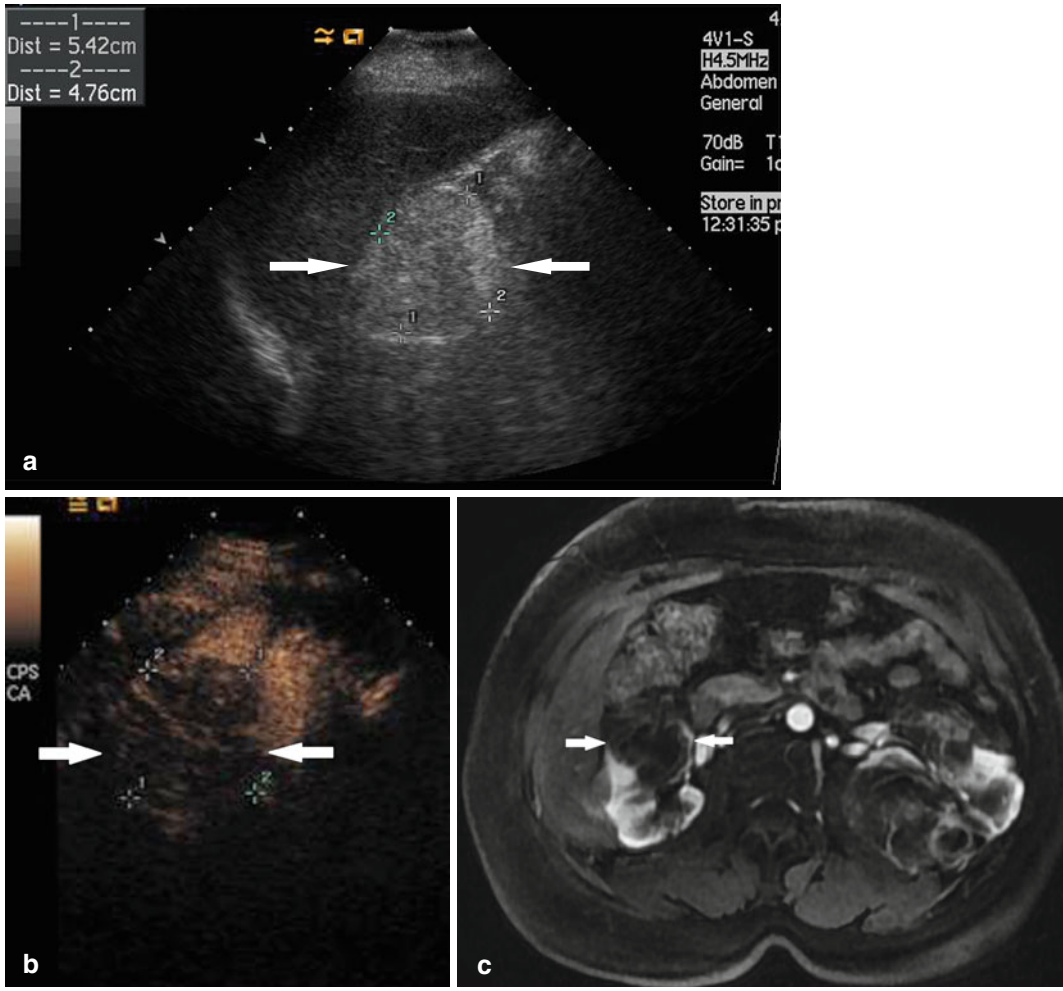

Fig. 18.1 Ultrasound-guided percutaneous microwave ablation (MWA) in a 55-year-old female patient with angiomyolipoma in the upper pole of the right kidney. (**a**) The lesion is hyperechoic and with well-defined borders in ultrasound (*arrow*). (**b**) The lesion showed heterogeneous hypo-enhancement in the arterial phase of contrast-enhanced ultrasound and the dimension is 5.7×5.4 cm (*arrows*). (**c**) After ablation, the lesion showed no enhancement in the arterial phase with contrast-enhanced MRI in transversal scan (*arrows*). (**d**) After ablation, the lesion showed no enhancement in the delayed phase with contrast-enhanced MRI in coronal scan (*arrows*). The significance of 1 and 2 in the Fig. 18.1 (**a**) and (**b**) is the two perpendicular diameters

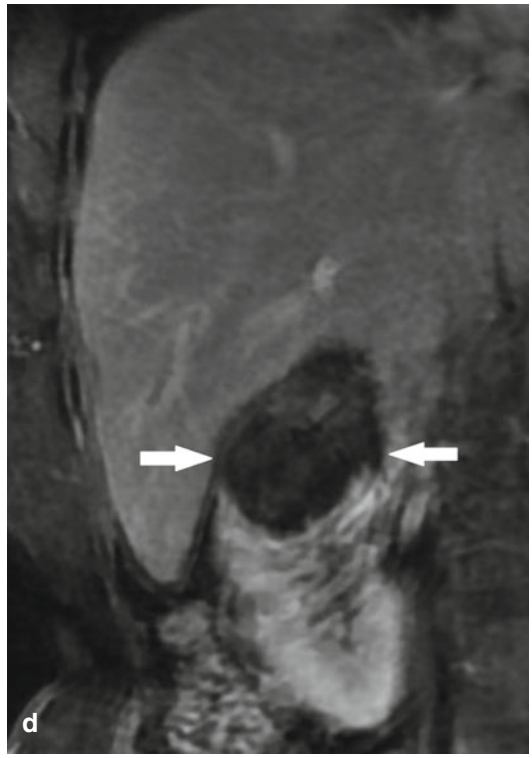

Fig. 18.1 (continued)

Table 18.1 Basic characteristics and clinical results of patients with renal AMLs treated with ablation

Author	No. of Pts (nodules)	Size (cm)	Treatment type	Guided methods	Follow-up (months)	Results (no. of recurrence/ persistence)	Major complications (patients)
Sooriakumaran et al. [26]	4 (4)	9.5 (9–19)	RFA	N/A	9 (2–13)	0/4	0
Gregory et al. [27]	4 (4)	15.1 (6.1–32.4)	RFA	CT	48	0/4	0
Prevoo et al. [28]	1 (1)	4.5	RFA	CT	12	1/0	0
Castle et al. [29]	15 (15)	2.6 (1.0–3.7)	RFA	Laparoscopic (5) or CT (10)	21.1 (1.5–72)	15/0	2
Byrd et al. [30]	6 (12)	4.2 (2.5–7.0)	Cryoablation	Laparoscopic	N/A	7/0	0
Johnson et al. [13]	3 (3)	(1.2–2.5)	Cryoablation	CT	5–36	2/1	0
Han et al. [35]	14 (19)	3.4 (0.8–6.1)	MWA	US	10 (6–36)	15/4	2

AML Angiomyolipoma, *Pts* patients, *MWA* microwave ablation, *RFA* radiofrequency ablation, *US* ultrasound, *N/A* not available, *CT* computed tomography; "no recurrence" was evaluated in the completely ablated lesions and "persistent" was evaluated in the incompletely ablated lesions

Conclusion

Because of the nonaggressive biologic behavior of these benign renal tumors, there is increasing interest in minimally invasive treatment modalities, particularly for the elderly, the infirm, and patients with comorbid conditions. MWA may be an alternative minimally invasive technique for the treatment of renal AML. However, the studies of large sample and long-term follow-up period are necessary to determine efficacy, and safety.

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Microwave Ablation of Benign Thyroid Nodules

19

Bing Feng and Ping Liang

Abstract

Image-guided microwave ablation is being considered as an optional minimally invasive treatment for benign thyroid nodules because of its relative low cost, its ability to provide large regions of coagulative necrosis, and its relatively short treatment period. Microwave ablation can reduce volume of benign thyroid nodules and solve nodule-related clinical problems. In the following chapter, we review the equipment, indications, patient preparation, procedures, clinical results, and complications of microwave ablation on benign thyroid nodules, in comparison to percutaneous ethanol ablation, radiofrequency ablation, and laser ablation.

Keyword

Thyroid nodule • Microwave ablation • Radiofrequency ablation • Laser ablation • Percutaneous ethanol injection

Abbreviations and Acronyms

EA	Ethanol ablation
fT4	Free thyroxine
LA	Laser ablation
MWA	Microwave ablation
RFA	Radiofrequency ablation
T3	Triiodothyronine
TSH	Thyroid-stimulating hormone
US	Ultrasound

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19.1 Introduction

Thyroid nodules are found in 3–7 % of general population by means of palpation and in 20–76 % by means of ultrasound (US) scan, with prevalence similar to that reported from autopsy data [1]. Although most thyroid nodules are benign and do not require treatment, some benign nodules may require treatment for associated symptoms and/or cosmetic problems [2]. Curative surgery has several drawbacks such as long hospitalization, scar formation, iatrogenic hypothyroidism, and difficulty in reoperation [1]. The efficacy of thyroid hormone-suppressive therapy has not yet been determined [3]. Therefore, minimally invasive surgical

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alternatives, such as ethanol ablation (EA), laser ablation (LA), radiofrequency ablation (RFA), and microwave ablation (MWA), are becoming more attractive for the treatment of thyroid nodules due to improvements in technology, reduced morbidity and mortality, and the ability to reduce scar formation. MWA has become a desirable image-guided ablative method because of its relative low cost, its ability to provide large regions of coagulative necrosis, and its relatively short treatment period. Although MWA has been investigated in the liver, kidney, adrenal gland, spleen, and lung [4–8], there has been minimal experience with this technique in the head and neck region. Therefore, we applied MWA to patients with benign thyroid nodules for cosmetic reasons, subjective symptoms, or anxiety about a malignant change. This chapter describes the technique, discusses the results, and evaluates the feasibility of ultrasound-guided percutaneous MWA for benign thyroid nodules.

19.2 Equipment

An MWA instrument (KY-2000, Kangyou Medical, Nanjing, China) is capable of producing 1–100 W of power at 2,450 MHz. The needle antenna has a diameter of 1.6 mm [1] or 1.9 mm [9] and a 10 or 15 cm shaft coated with polytetrafluoroethylene to prevent tissue adhesion. A narrow radiating segment of 3 mm is embedded on the shaft, 3 or 5 mm away from the tip for 2,450 MHz applicator. The microwave system is equipped with 21 G thermocouple needles which can be inserted into the designated places with the guidance of ultrasound to monitor real-time temperature during MWA.

US examinations are performed on Sequoia 512 unit (Siemens Ultrasound, Mountain View, CA) and GE LOGIQ E9 in terms of 2D color Doppler US and ultrasonic contrast before and after ablation. The sonographic contrast agent was sulfur hexafluoride (SonoVue, Bracco, Milan, Italy).

19.3 Inclusion Criteria and Exclusion Criteria

Inclusion criteria for MWA of benign thyroid nodules are as follows: (1) Nodules are pathologically benign and are solid or predominantly solid; (2) patients have significant nodule-related symptoms (such as foreign body sensation, neck discomfort, or pain) or symptoms related to hyperthyroidism caused by autonomously functioning nodules; (3) nodules have obviously an outer convex which affects the appearance and require treatment; (4) nodules increased significantly (volume increases more than 50 % within 1 year or at least two diameters increase over 20 % and more than 2 mm); (5) patients want to stop clinical observation because of the huge psychological pressure which affects daily life; and (6) patients have refused operative resection or are deemed to be nonsurgical candidates due to advanced staging and/or medical comorbidities.

Exclusion criteria are as follows: (1) abnormal contralateral vocal cord, (2) severe coagulation disorders, and (3) severe cardiac or pulmonary disease.

19.4 Patient Preparation

Written informed consent should be obtained from each patient. According to the 2012 consensus statement and recommendations of the Korean Society of Thyroid Radiology [10], informed consent forms should include number of expected treatment sessions, possibility of various degrees of pain during or after ablation, need of several months for ablated thyroid nodules to decrease slowly in size, possibility of regrowth of the treated nodules, possible complications of MWA, and requirement of further observation or admission after MWA.

US examination is important for characterizing a nodule and to evaluate the surrounding anatomical structures [11]. The diameters, shape, margin, composition, calcification, internal vascularity, and enhancement modality of nodules should be observed and evaluated before and

after MWA. The composition of the nodules, assessed by US examiner subjectively, could be classified as mainly solid (solid portion >80 %), mainly cystic (cystic portion >80 %), or mixed type. Nodule internal vascularity could be classified with a five- point scale: 0 (no color signal in nodule), (1) (a few spotty color signals in nodule), (2) (color signals in <25 % of the nodule), (3) (color signals in 25–50 % of the nodule), and (4) (color signals in >50 % of the nodule) [12]. Three orthogonal diameters of thyroid nodules (the largest diameter and the two other perpendicular ones) should be measured, and the nodule volume could be calculated by the following equation: $V = \pi abc/6$ (V is the volume, a is the largest diameter, b and c are the other two perpendicular diameters). US-guided fine-needle aspirations or core needle biopsies are necessary before MWA to confirm the pathological results of the nodules.

Laboratory tests usually include thyroid function [thyroid-stimulating hormone (TSH), triiodothyronine (T3), free thyroxine (fT4)], complete blood count, and blood coagulation test (prothrombin time, activated partial thromboplastin time). Fiber laryngoscopy is performed on all patients before MWA and on patients who complain of hoarseness or other symptoms related to nerve injury after MWA [1]. Clinical symptoms are evaluated using symptom grading score (visual analog scale, grades 0–10) [1, 10, 13] and cosmetic grading score (grade 1, no palpable mass; grade 2, invisible but palpable mass; grade 3, visible mass only by experienced clinician's eyes; grade 4, easily visible mass) [1, 12].

19.5 MWA Procedures

The patient is placed in the supine position with hyperextended neck, and a venous catheter is inserted in a forearm vein. A multiparametric monitor is connected to the patient monitoring blood pressure, pO2, and electrocardiogram. Local anesthesia with 1 % lidocaine is performed subcutaneously on the puncture site, and then a small incision less than 2 mm in length is made. The internally cooled microwave antenna is placed into the thyroid nodule along its longest axis under ultrasound guidance. After the antenna is placed at designated site, unconscious intravenous anesthesia (propofol, 6–12 mg/kg/h; ketamine, 1–2 mg/kg) is administered via the forearm vein by an anesthesiologist, and then microwave procedure is started. A power output of 20–30 W is used during MWA.

The trans-isthmic approach method for RFA on thyroid nodules is recommended by the Korean Society of Thyroid Radiology [10]. The technique is suitable for MWA. The antenna is inserted from the isthmus to the lateral aspect of a targeted nodule. The method has several advantages [14]. First, the entire length of the antenna can be visualized on a transverse US view. Second, the antenna passes through a sufficient amount of thyroid parenchyma, which prevents a change in the position of the antenna tip. Third, there is minimal heat exposure to critical structures including the recurrent laryngeal nerve and esophagus.

The fixed antenna in position during ablation may result in a round ablation zone. As thyroid nodules are usually ellipsoid in shape, prolonged fixation of the antenna is dangerous to surrounding critical structures; Baek et al. [14] have proposed a moving shot technique for thyroid nodules. Baek et al. [14] suggest to divide thyroid nodules into multiple small conceptual ablation units and perform ablation unit by unit, by moving the applicator. The technique is also suitable for MWA. The units are small at the periphery and large in the center of the nodule or in regions remote from critical structures. The extent of ablation area is presumed by the echogenic change around the antenna. To prevent visual disturbance caused by echogenic bubbles, the antenna tip is initially positioned in the deepest portion of the nodule [2]. When a transient echogenic area appears at the targeted unit, microwave power is decreased, and the antenna tip is moved to an untreated area. The MWA is terminated when all conceptual units of the targeted nodule have become transient hyperechoic zones.

If the nodules are close to the anterior muscle, carotid artery, recurrent laryngeal nerve, or esophagus, liquid isolation composed of 1 % lidocaine would be injected in the thyroid capsule to separate the above structure from thyroid nodules and avoid thermal injury.

For safely located tumors, complete tumor necrosis would be considered if the measured temperature at the site 5–10 mm away from tumor margin reaches 60 °C or remains above 54 °C for at least 3 min [15]. In an ex vivo study, the mean temperature at 5 mm site from the antenna tip is driven rapidly high to 60 °C [1]. Temperature is monitored continuously during microwave emission when the thyroid nodule is close to the recurrent laryngeal nerve. The thermocouple is inserted into the nodule site at least 10 mm away from nerve area, and the temperature cutoff of ablation is set at 54 °C. In cases of mainly cystic nodules, percutaneous puncture needle (18 G, Hakko Co, Chikuma-shi, Japan) is inserted to the cystic portion and contained fluid is aspirated. When the cystic portion has completely collapsed, microwave ablation is performed on the solid portion.

Application of an ice bag during ablation may prevent skin burns at the electrode puncture site. At the end of procedure, all patients remain under observation for 30 min by compressing an ice bag on the neck for 2 h to prevent bleeding or hematoma formation.

19.6 Therapeutic Efficacy Assessment

Efficacy of MWA for benign thyroid nodules can be evaluated by volume reduction ratio (VRR = (initial volume – final volume) × 100/initial volume), nodule internal vascularity grade, enhancement modality, symptom grading score, and cosmetic grading score. Color Doppler ultrasound is useful for the evaluation of the presence of vascularity within the ablated nodule, which suggests a possible untreated area of the nodule [10, 16]. Tumor necrosis is considered if complete non-enhancement is shown at the site of treated nodule on contrast-enhanced US examination.

Ultrasound examination, laboratory data, and clinical symptoms are evaluated at 1 day and 1, 3, 6, 9, and 12 months after the procedure. The ultrasound examination is acquired to assess the changes of MW-induced lesions, including the size, vascularity, echogenicity, and enhancement modality. The laboratory data such as T3, fT4, and TSH and the symptom grading score and cosmetic grading score are also evaluated and recorded at each follow-up. Side effects and complications of MWA are evaluated at the end of ablation as well as at 24 h and 1 month after the procedure.

19.7 Clinical Efficacy of MWA

According to the study of Feng et al. [1] on MWA performed on 11 patients with benign thyroid nodules, the volume decreased statistically from 5.30 ± 4.88 to 2.40 ± 2.06 ml, and cosmetic grading score was reduced from 3.20 ± 0.79 to 2.30 ± 0.95 ($p < 0.05$). Yue et al. [9] presented a series of 477 benign thyroid nodules in 222 patients treated with MWA. A period of 6-month follow-up was achieved in 254 of 477 nodules, and the mean volume decrease was from 2.13 ± 4.42 ml to 0.45 ± 0.90 ml, with a mean percent decrease of 0.65 ± 0.65. A volume reduction ratio greater than 50 % was observed in 82.3 % of the nodules (209/254) and 30.7 % of the nodules (78/254) disappeared.

According to our latest study data, we evaluated the feasibility and effects of MWA in 41 patients (M:F = 7:34; mean age, 49 ± 11 years; range, 19–73 years) with 44 benign thyroid nodules (diameter range, 1.20–6.80 cm; volume range, 0.37–81.65 ml). The composition of the nodules was mainly solid ($n = 23$), mixed ($n = 18$), and mainly cystic ($n = 3$). A single antenna was used in 39 patients and two antennas were used in two patients. The total treatment time was 8.5 ± 4.9 (range, 2.3–27.7) min. For some patients with mainly cystic or mixed thyroid nodule, the obsolete bloody fluid was aspirated and ethanol was injected, and then MWA was performed on the solid portion. After ablation, color Doppler ultrasound showed significant reduction of vascular signals (before vs. after ablation, 2.84 ± 1.18 vs.

0.57 ± 0.85, $p<0.05$). At a follow-up period that ranged from 1 to 12 months, mean nodule diameter fell from 3.06 ± 1.10 cm to 2.30 ± 0.94 cm ($p=0.0007$), nodule volume decreased from 9.89 ± 13.84 ml to 4.80 ± 6.45 ml ($p=0.03$), and the mean VRR was 39.69 ± 43.03 % (Figs. 19.1 and 19.2). Symptom score changed from 1.19 ± 1.68 to 0.60 ± 0.88 ($p<0.05$) and cosmetic grading score changed from 3.10 ± 0.88 to 2.36 ± 0.81 ($p<0.01$). Initial mean T3, fT4, and TSH were 1.60 ± 0.26 nmol/l, 14.54 ± 2.98 pmol/l, and 2.34 ± 1.58 mU/l, respectively. A significant change of mean T3, fT4, and TSH was observed at 1 day after ablation (T3, 1.84 ± 0.51 nmol/l, $p=0.0007$; fT4, 17.14 ± 2.37 pmol/l, $p=0.0001$; TSH, 1.51 ± 1.36 mU/l, $p=0.01$).

19.8 Complication

Side effects and minor complications of MWA for thyroid nodules include a mild sensation of heat in the neck or slight pain, vasovagal reaction, choking and coughing, slight fever not more than 37.5 °C, mild bleeding or hematoma, vomiting, and skin burn [1, 17]. Yue et al. [9] reported

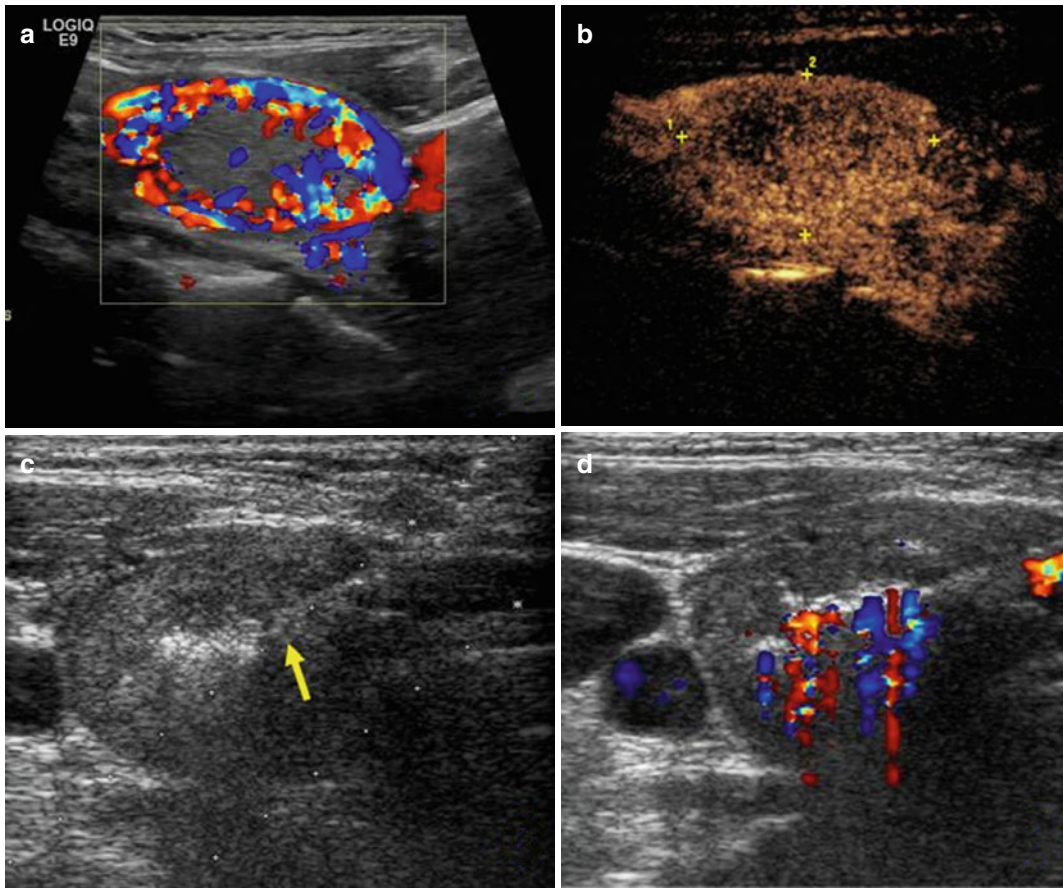

Fig. 19.1 Ultrasound-guided percutaneous microwave ablation (*MWA*) in a 47-year-old female patient with thyroid oxyphilic adenoma with a volume of 3.3 ml. The nodule is on the right thyroid lobe. (**a**) Before MWA, nodule internal vascularity is grade 4 (color signals in >50 % of the nodule). (**b**) The nodule shows heterogeneous enhancement on contrast-enhanced ultrasound before MWA. (**c**) Microwave antenna (*arrow*) is percutaneously placed into the nodule, and multiple echogenic microbubbles started to appear around the antenna tip. (**d**) Multiple echogenic microbubbles are seen on color ultrasound. (**e**) Nodule internal vascularity is grade 1 (a few spotty color signals in nodule) after MWA. (**f**) The ablated nodule shows no enhancement after MWA. (**g**) Two months after ablation, the ablated nodule volume decreases from 3.3 to 0.6 ml. (**h**) Two months after MWA, the ablated nodule volume decreases

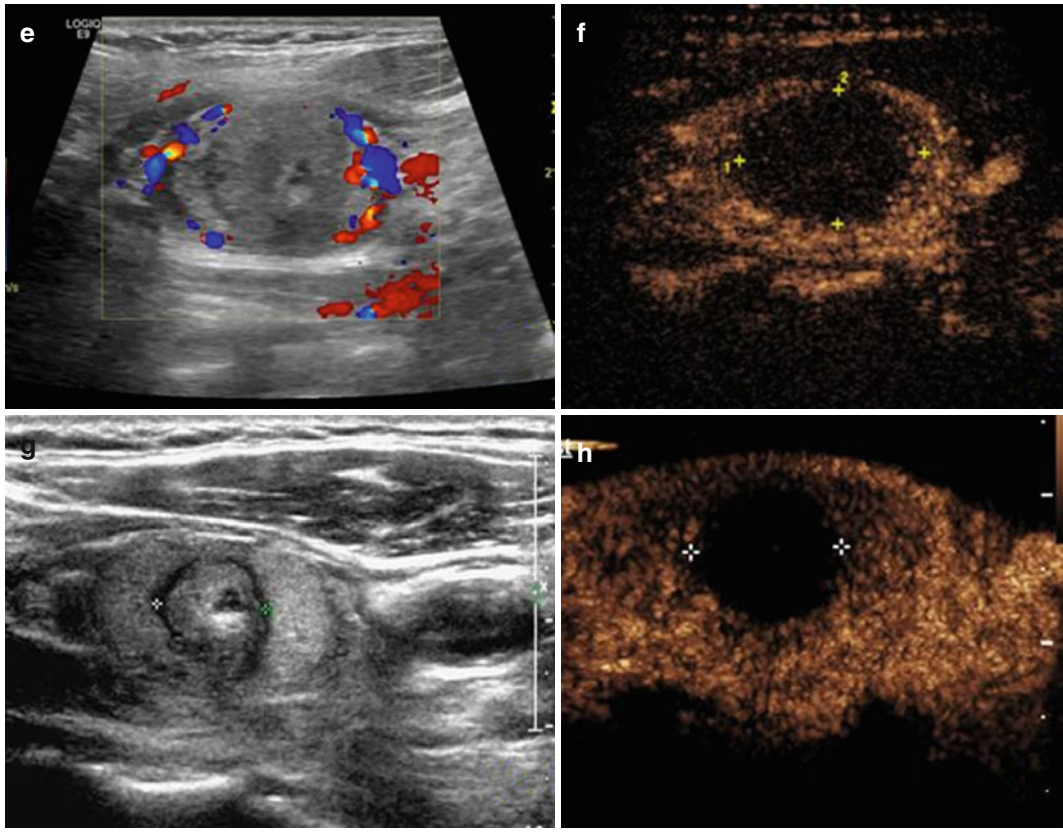

Fig. 19.1 (continued)

12 patients (5.4 %) complained of choking and coughing at the end of MWA which disappeared without any treatment (eight patients within 24 h, four patients in a week); besides, a mild sensation of heat in the neck was experienced by most patients, but no one needed the procedure to stop.

The possible major complications of MWA for thyroid nodules include voice change, nodule rupture, abscess formation, hypothyroidism, and brachial plexus injury [17]. In the article of Feng et al., one patient experienced temporary nerve palsy and recovered within 2 months after MWA treatment [1]. Yue et al. [9] reported 3.6 % patients (8/222) complained of voice changes and all patients recovered within 3 months spontaneously. Various technical tips for avoiding complications during ablation of thyroid nodules can be adopted. For example, thermal injury to the recurrent laryngeal nerve may be prevented by using the moving shot technique and by undertreating the conceptual units adjacent to the nerve. Hematoma can usually be controlled by mild compression of the neck for several minutes. Intranodular hemorrhage can usually be well controlled by means of direct ablation of the hemorrhagic focus. In addition, modified small-bore antenna may decrease the risk of hemorrhage.

19.9 Other Local Techniques

Other local therapies have been employed to treat thyroid nodules (Table 19.1).

19.9.1 Ethanol Ablation

Since Livraghi et al. [26] used US-guided EA for the treatment of hyperfunctioning thyroid nodules, many published studies have reported

appreciable efficacy of EA in treatment of benign thyroid nodules [25, 27]. Advantages of EA include low cost, low risk, practicability in the outpatient clinic, and ease of performance [25], but EA has side effects related to the leakage of ethanol outside the capsule of nodule and the need for multiple ethanol injections. The side effects include extraglandular fibrosis, vocal cord paresis, hematoma, and mild to severe pain [23, 28]. Compared with MWA, EA is very effective when used to treat cystic thyroid nodules, but EA is less effective in solid nodules.

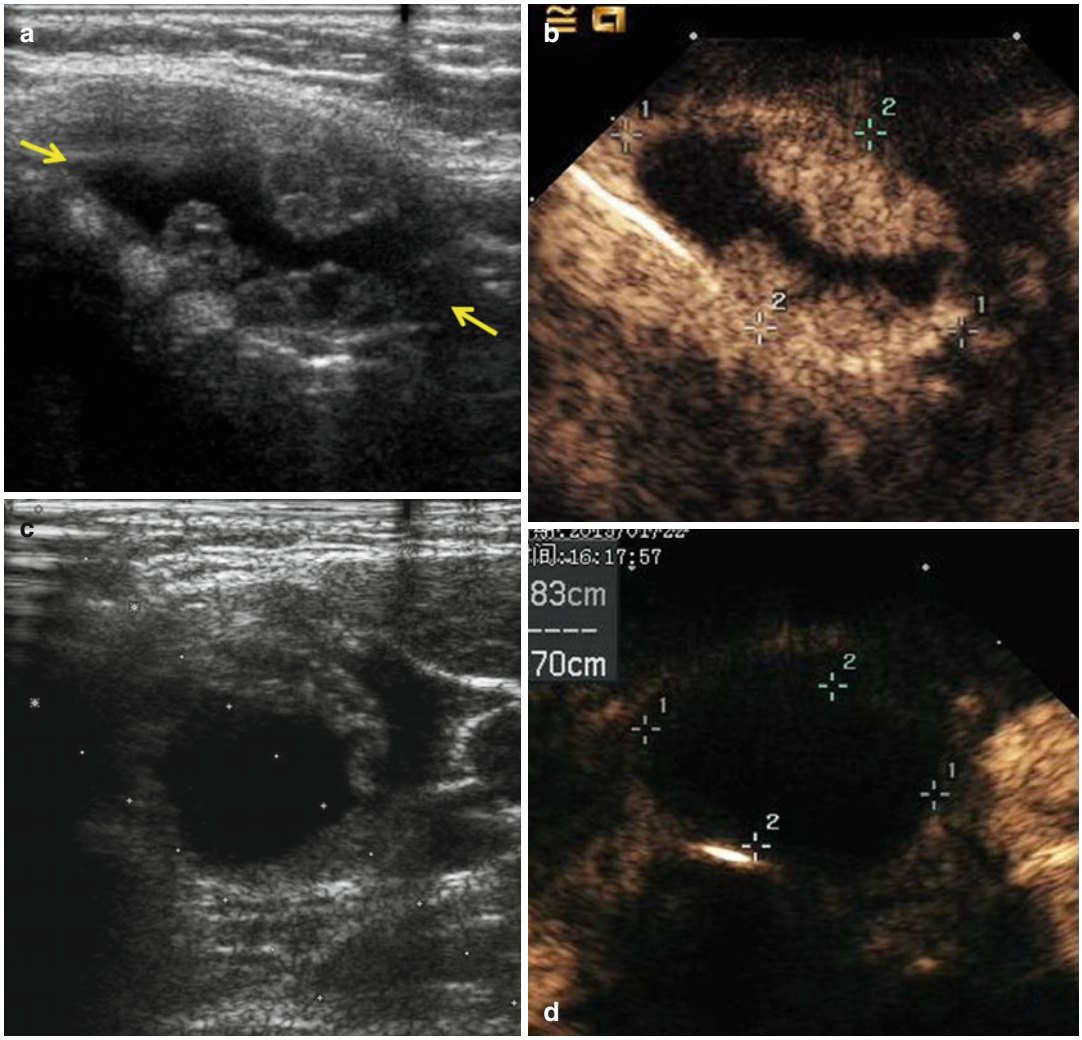

Fig. 19.2 Ultrasound-guided percutaneous MWA in a 63-year-old female patient with nodular goiter. The nodule is on the left thyroid lobe. (**a**) Preablation conventional ultrasound scan shows a mixed thyroid nodule (*arrow*) with the size of 3.1×2.0×2.3 cm (volume, 7.4 ml). (**b**) Contrast-enhanced ultrasound before MWA shows enhancement on solid portion of the nodule and no enhancement on cystic portion. (**c**) Percutaneous puncture needle (18 G, Hakko Co, Chikuma-shi, Japan) is inserted to the cystic portion and contained fluid is aspirated. When the cystic portion has completely collapsed, MWA is performed on the solid portion. (**d**) The ablated nodule shows no enhancement 1 day after MWA. (**e**) The ablated nodule shows no enhancement with the size of 2.1×1.2×1.8 cm (volume, 2.4 ml) 6 months after MWA. (**f**) Before MWA, a walnut-sized nodule can be seen outside the skin of the neck (*arrow*). (**g**) Six months after MWA, the thyroid nodule completely disappears and no scars are *left* on the neck (*arrow*)

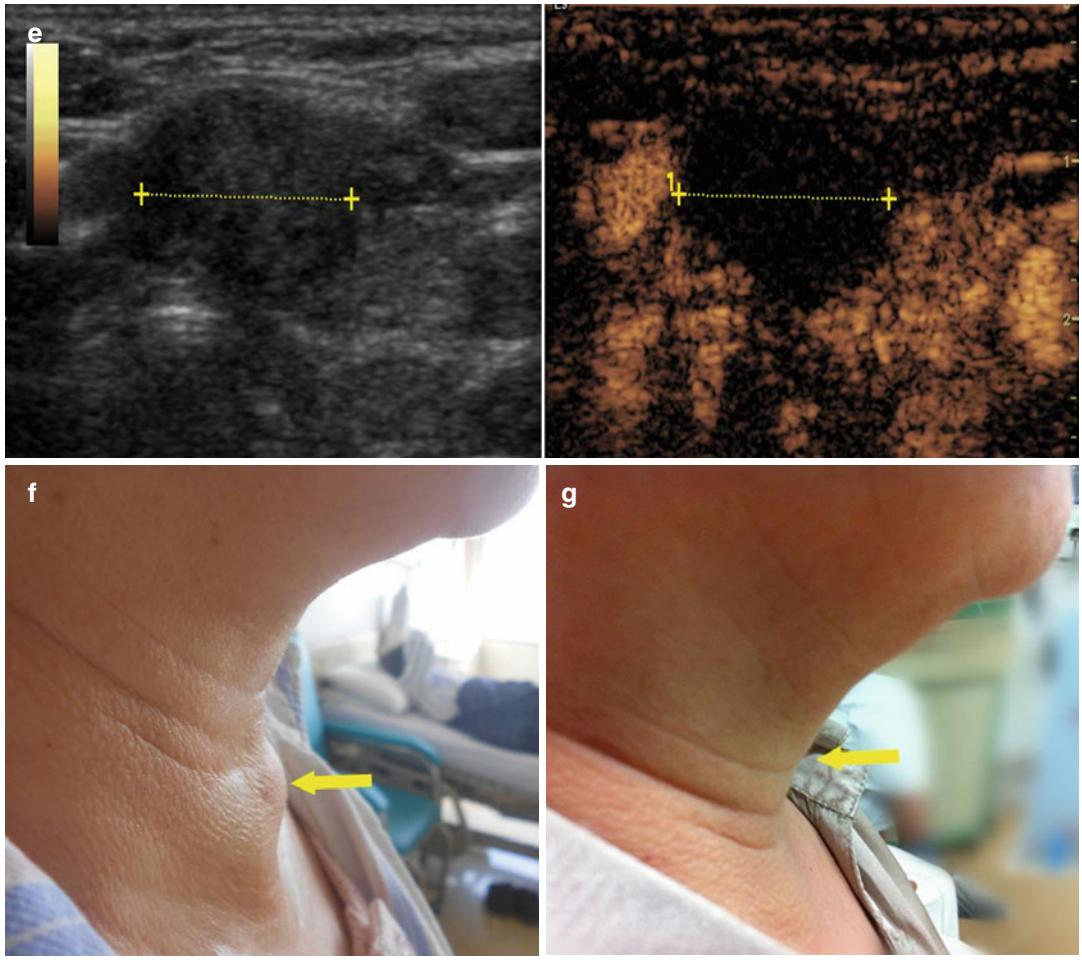

Fig. 19.2 (continued)

Regarding cystic thyroid nodules, Verges et al. performed EA on nine patients with recurrent large thyroid cysts following aspiration; mean volume was significantly reduced from 31.3 to 9.9 ml, the mean percentage volume reduction was 72.7 %, and a size reduction of the thyroid lesion more than 50 % was achieved in 89 % of patients [29]. In the study of 110 patients with thyroid cyst or pseudocysts treated with EA reported by Raggiunti et al., volume was reduced by 82.6 % after 12 months and 93.03 % after 84 months [24]. There are some factors relating to the efficacy of EA on cystic or predominantly cystic thyroid nodules. Kim et al. [30] found that vascularity and initial volume were independent factors of efficacy in predominantly cystic nodules [30]. From a study of 64 benign cystic nodules treated with EA, In et al. found that the degree of aspiration and color of aspirates correlated significantly with the success of EA [27].

Because of the efficacy of EA on benign cystic thyroid nodules, predominantly cystic nodules are often treated with both EA and RFA to enhance the efficacy [31]. Kim et al. treated 8 of 18 post-RFA nodules with EA because of incomplete ablation, two of which showed marked hypoechogenicity and no vascularity of the remaining solid components, while three nodules showed considerably decreased echogenicity and vascularity of remaining solid components and three showed no significant decrease or mild decrease in the echogenicity and vascularity [32].

Table 19.1 Clinical results of patients with benign thyroid nodules treated by ablation

Author	No. of Pts (nodule)	Treatment type	Solid component (%)	Session	Follow-up (months)	Initial volume (ml)	1 month VR (%)	6 months VR (%)	Last VR (%)
Feng et al. [1]	11	MWA	20–100	1–2 (1.1)	1–9	5.3	N/A	N/A	46
Yue et al. [9]	222 (477)	MWA	0–100	N/A	6	2.1	−0.1	65	38
Jeong et al. [18]	236 (302)	RFA	0–100	1–6 (1.4)	1–41	6.1	58	85	84
Spiezia et al. [19]	94	RFA	>30	1–3 (1.4)	12–24	24.5	54	N/A	79
Lim et al. [20]	111 (126)	RFA	0–100	1–7 (2.2)	49	9.8	N/A	70	94
Valcavi et al. [21]	122	Laser	>80	1–4 (2.4)	36	23.1	6.2	47.5	47.8
Dossing et al. [22]	78	Laser	100	N/A	12–114 (67)	8.2	N/A	N/A	51
Tarantino et al. [23]	125 (127)	EA	0–100	1–11 (3.9)	9–144	10.3	N/A	N/A	66
Raggiunti et al. [24]	110	EA	0	N/A	12–84	15	N/A	N/A	93
Kim et al. [25]	27 (30)	EA	>50	1–2 (1.2)	6–30	8.4	N/A	N/A	64.3

Pts patients, *VR* volume reduction, *AFTN* autonomously functioning thyroid nodule, *EA* ethanol ablation, *N/A* not available

Besides, studies about the efficacy of EA for solid or predominantly solid thyroid nodules have also been published, but the results have been variable and less effective than EA for cystic nodules [25, 27, 31]. Kim et al. performed EA on 30 predominantly solid thyroid nodules in 27 patients and found that the effective rate of EA was 60 % [25]. Thus, EA is rarely selected for the treatment of solid thyroid nodules compared with RFA and MWA, owning to controversy over its efficacy and clinical indications [25].

19.9.2 Radiofrequency Ablation

For benign thyroid nodules, RFA has been used earlier and more widely than MWA, and articles about RFA are more available than MWA. The RFA needle (17 G) was thinner than MWA antenna (16 G) [1], so the small-bore antenna of RFA may decrease the risk of hemorrhage. Since RFA of benign thyroid nodules was introduced in 2006 [33], it has been reported to be safe and effective by many studies. The efficacy of RFA for reducing thyroid nodule volume and improving pressure symptoms was established by the comparative study reported by Faggiano et al. [34]. Lim et al. [20] evaluated 126 benign nonfunctioning thyroid nodules of 111 patients treated with RFA; at the mean follow-up duration of 49.4 months, mean volume decreased significantly from 9.8 to 0.9 ml (mean volume reduction was 93.4 %). In the study of 236 patients with 302 cold benign thyroid nodules treated with RFA, VRR was 58 % at 1 month and 85 % at 6 months [18]. The greatest decrease in the volume was observed after 1 month, and it decreased gradually during the follow-up.

RFA showed efficacy not only in cold thyroid nodules but also in autonomously functioning thyroid nodule. Spiezia et al. performed RFA on 94 patients (66 had nontoxic goiter, and 28 had toxic or pretoxic goiter); the mean VRR was 78.6 % at 1 year and 79.4 % at 2 years. In the study, all patients who were euthyroid before RFA had normal serum thyroid function after RFA, and 79 % of patients with autonomously functioning thyroid nodule showed completely withdrawn of hyperthyroidism allowing methimazole [19]. RFA was also useful to treat patients who showed incompletely resolved clinical symptoms after EA [13, 35]. The study showed that EA was less effective in nodules when solid component is >20 %, and additional RFA was performed effectively on 20/94 patients with predominantly cystic thyroid nodules who underwent EA [13].

Regarding the factors related to nodule volume reduction, Lim et al. found that solidity was an independent factor related to efficacy; the VRR was greater for nodules of ≤50 % solidity than those of >50 % solidity [20]. Baek et al. suggest that cystic nodules primarily showed a greater decrease in size at 1 and 3 months, but there were no significant differences in VRR at 6 months [14]. Initial volume of thyroid nodules was also a factor related to volume reduction [19, 20]; Spiezia et al. reported that VRR was significant for nodules that were initially small [19].

19.9.3 Laser Ablation

LA is a thermal ablative method which is considered as an optimal therapeutic option for treatment of benign thyroid nodules. Several articles on LA in cold nodules, cystic nodules, and autonomously functioning thyroid nodule have been published, including controlled trials, suggesting effectiveness and safety of this technique [3, 21, 36–39]. The advantage includes well-defined area of complete tissue ablation with a regular, homogeneous, and reproducible pattern [39]. However, near-spherical lesions with the largest diameter ranging from 1.2 to 1.6 cm can be produced using a single laser fiber; lesion volume can be increased by using multiple fibers simultaneously in an array within the nodules [14]. LA requires up to three sessions or the insertion of multiple fibers for treating large nodules, which increases the risk of local adverse events [22].

LA has been reported to cause shrinkage of benign thyroid nodules with various volume reduction rates. Valcavi et al. performed thermal Nd:YAG LA on 122 patients with benign cold thyroid solitary nodules; mean nodule volume decreased from 23.1 to 12.5 ml (VRR, 47.8 %) 3 years after LA [21]. Dossing et al. evaluated the

long-term efficacy of LA in 78 solitary benign euthyroid nodules and found that the overall median nodule volume decreased from 8.2 ml (range, 2.0–25.9 ml) to 4.1 ml (range, 0.6–33.0 ml) and the median VRR was 51 % [22]. LA appears to be valid and safe not only in euthyroid nodules but also in nodules with hyperthyroidism. Disappearance of clinical signs related to hyperthyroidism and normalization of T3, fT4, and TSH serum levels were discovered in seven patients with autonomously functioning thyroid nodule after LA [39].

Conclusion

MWA is a safe and effective alternative technique for benign thyroid nodules. It is important to maximize efficacy and minimize complications. Its efficacy can be maximized by complete necrosis of thyroid nodules, which is essential in order to effectively reduce the size of tumors. Consideration of possible complications and available preventative techniques is important to minimize complications. However, the current literatures have limitations, so prospective randomized studies with large sample and long-term follow-up period are necessary to determine efficacy, safety, cost/benefit balance, and quality of life.

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Microwave Ablation of Adrenal Tumors

20

Bing Feng, Mengjuan Mu, and Ping Liang

Abstract

Adrenal tumors comprise a broad spectrum of benign and malignant neoplasm, including functional adrenal adenomas, pheochromocytomas, malignant adrenocortical carcinomas, myelolipomas, and adrenal metastases. The traditional treatment of adrenal tumors including open and laparoscopic resection has been proven to be potentially curative and to offer survival benefits; however, many patients are not surgical candidates. Therefore, less invasive techniques have been used in an attempt to treat adrenal neoplasm. As one of minimally invasive techniques, percutaneous image-guided microwave ablation has achieved optimistic effect in treatment of primary and metastatic adrenal tumors. In the following chapter, we review the patient selection, pre-procedure management, equipment, microwave ablation procedures, post-ablation observation, imaging follow-up, and therapeutic efficacy assessment of microwave ablation on adrenal tumors, in comparison to surgery, radiofrequency ablation, cryoablation, laser ablation, and chemical ablation.

Keywords

Adrenal neoplasm • Microwave ablation • Radiofrequency ablation • Laser ablation • Percutaneous ethanol injection

Abbreviations and Acronyms

CT	Computed tomography
MWA	Microwave ablation
RFA	Radiofrequency ablation
US	Ultrasound

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20.1 Introduction

Incidental adrenal tumors are identified in up to 3 % of the population in middle age and up to 10 % in the elderly [1]. The most common adrenal tumors are nonfunctioning adenomas. Metastatic lesions, functional adrenal neoplasms, and other benign adrenal neoplasm are much less common [2]. Adrenal metastases can be found in various primary malignancies of the lung, stomach, liver, and so on; metastasis to the adrenal

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gland is regarded as a late-stage manifestation of tumor progression [3].

Surgical resection for an isolated adrenal tumor has been advocated by some authors, although this treatment remains controversial [4, 5]. There is accumulating evidence that resection of adrenal malignancies offers a survival benefit. Toniato et al. noted that the median survival after adrenalectomies for 9 primary adrenal carcinomas and 16 adrenal metastases were 30 months and 28 months, respectively [6]. However, many patients are not surgical candidates; in addition, complication rates are approximately 10.9 % with open adrenalectomy and 25.2–28 % with laparoscopic approach [7]. Therefore, less invasive techniques have been used in an attempt to treat adrenal neoplasm. These techniques include selective arterial embolization [8], chemical ablation with ethanol or acetic acid [9], radiofrequency ablation (RFA) [2], laser ablation [10], and microwave ablation (MWA) [11]. MWA is one of the thermal ablation techniques which have been increasingly used in primary and metastatic solid tumors. The preliminary study revealed that MWA can yield complete tumor necrosis and effective local tumor control for adrenal tumors [3]. This chapter describes techniques of MWA of adrenal primary and metastatic tumors including functional tumors and discusses clinical studies in this field.

20.2 Inclusion Criteria and Exclusion Criteria

Recent reports have described the clinical utility of MWA in controlling both functional adrenal tumors and adrenal metastasis. Patients with functional adrenal adenoma who meet the following inclusion criteria can be included: (1) age of 18 years or more, (2) Eastern Cooperative Oncology Group performance status of 0 or 1, (3) unresectable abdominal tumors, and (4) blood pressure less than 140 mmHg.

The inclusion criteria for patients with adrenal metastasis are as follows: (1) unilateral adrenal tumor of 5 cm or smaller, (2) complete eradication of primary tumor, (3) no tumor thrombus and extra-adrenal metastases, (4) an appropriate microwave antenna needle path on US, and (5) prothrombin activity higher than 40 % and prothrombin time less than 25 s [3].

The exclusion criteria are as follows: patients in whom the platelet count was 50,000 μl or less and whom the prothrombin time/international normalized ratio was greater than 1.5 are excluded.

20.3 Pre-procedure Management

The pathological diagnosis is obtained by biopsy in all tumors before MWA. Before treatment, all patients receive contrast-enhanced computed tomography (CT), magnetic resonance imaging, and ultrasound (US) examination. Contrast-enhanced US is performed on Sequoia 512 system (Siemens Ultrasound, Mountain View, CA) equipped with contrast pulse sequencing software. The US contrast agent is sulfur hexafluoride (SonoVue, Bracco, Milan, Italy). All patients need to receive routine laboratory examinations including complete blood count, blood biochemistry, viral titers, and coagulation profile examinations. Specific laboratory tests are also needed for patients with functional adrenal tumors. Most functional adenomas are represented by primary hyperaldosteronism and Cushing's syndrome [12]. In cases of primary hyperaldosteronism, serum aldosterone and plasma renin activity are measured by radioimmunoassay. For Cushing's syndrome, measurement of post-suppression plasma cortisol, urinary cortisol, and salivary cortisol levels by chemiluminescence confirms the diagnosis.

20.4 Equipment and MWA Procedures

The MWA system (KY2000, Kangyou Medical Instruments, Nanjing, China) is capable of producing 1–100 W of power at 2,450 MHz and driving two microwave antennas simultaneously. The 15G cooled-shaft antenna is coated with Teflon to prevent adhesion. The microwave system is equipped with 21 G thermocouple needles

which can be inserted into the designated places with the guidance of US to monitor real-time temperature during MWA.

For US-guided percutaneous MWA of adrenal tumors, the appropriate microwave antenna needle path should be chosen before MWA procedure. For left adrenal tumor, the patient is laid in right decubitus position and a posterior microwave antenna path is chosen carefully to evade the spleen; for right adrenal tumor, the patient is laid in left decubitus position and a transhepatic approach is adopted to access the adrenal tumor [3]. MWA is performed under local anesthesia (1 % lidocaine, at the site of skin puncture) combined with intravenous anesthesia (a combination of propofol and ketamine). Prior to MWA, a core biopsy needle (18-gauge or 21-gauge Surecut biopsy needle, TSK laboratory, Tochigi, Japan) is placed in the target nodule lesion by US guidance and two or three pieces of core biopsy specimen are obtained for pathological examination. Then microwave antenna is percutaneously inserted into the tumor and placed at the designated place under US guidance. A single antenna needle is used for small lesions. For adrenal nodules with the diameter equal to or greater than 2 cm, two antennas are used with an inter-antenna distance of no more than 1.8 cm, which are activated simultaneously to obtain confluent ablation zones [3]. One thermocouple needle is percutaneously placed at the tumor border and is not moved around during MWA emission, from which temperature is monitored continuously. Treatment can be considered complete if the entire tumor is enveloped by hyperechoic microbubbles and the temperature of thermocouple needle tip reaches 54 °C for at least 3 min [3]. After MWA of adrenal malignant tumors, the antenna needle path should be routinely cauterized to avoid bleeding and tumor seeding. Requirements for benign and malignant tumors are different. Safe and conformal ablation is needed for benign adrenal tumors; however, enough margin of at least 0.5 cm is necessary when MWA is applied to treat malignant tumors [3].

MW thermal stimulation would lead to increased release of adrenaline (catecholamines), which can cause rapid heartbeat and hypertension. To prevent possible hypertensive crisis, the following measures should be noted: (1) Blood pressure should be within normal range before MWA treatment. (2) Blood pressure, electrocardiogram, heart rate, and oxygen saturation are monitored by anesthetists during MWA treatment. Various rescue medication and equipments should be prepared adequately. If the systolic pressure exceeded 170 mmHg during MWA procedure, microwave emission should be suspended and antihypertensive drug (labetalol hydrochloride) should be given intravenously. MWA can be resumed until the systolic pressure decreased to baseline level [3]. (3) MWA is started at a power output of 20 W, and then the power is gradually increased to 50 W when patients adapt to thermal stimulation and their blood pressure is stabilized. (4) For patients with functional pheochromocytoma, phenoxybenzamine (20 mg, 3/d) should be taken orally for 2 weeks before MWA.

20.5 Post-ablation Observation and Imaging Follow-Up

Vital signs such as blood pressure, heart rate data, and peripheral blood oxygen saturation are closely observed after the procedure and for the first 4 h once the patients return to their ward. If the patient experienced intolerable pain after the procedure, drug as acetaminophen or meperidine hydrochloride is injected intramuscularly. To evaluate the efficacy of treatment, contrast-enhanced US examination is performed 1 day after MWA. If enhancement is found on contrast-enhanced US, a further MWA session would be planned.

The first post-ablation CT examination is performed 1–30 days after treatment. Thereafter, follow-up CT examinations are performed at 3-, 6-, and 12-month interval. Within the ablated area, the lack of enhancement is indicative of successful treatment, and any focal area of soft tissue enhancement greater than 1 cm in short axis is considered as local tumor progression [13]. For adrenal metastases, 18F-fluorodeoxyglucose positron emission tomography combined with computer tomography is also performed to assess metastatic foci and systemic

disease progression [13]. For biochemical functional adrenal tumors, hormonal production is routinely monitored.

20.6 Therapeutic Efficacy Assessment

MWA of the adrenal gland is a promising technique for percutaneous treatment of adrenal tumors, although there is limited experience reported in the literature. Wang et al. treated five patients with pathologically proven unilateral adrenal metastases by US-guided percutaneous MWA [3]. The tumor size ranged from 2.3 to 4.5 cm and the mean size was 3.5 cm. All adrenal metastases were ablated completely after scheduled MWA sessions (mean 1.2 sessions, ranged from one to two sessions; total time ranged from 240 to 720 s). No major complications occurred. During a median follow-up of 19 months (range from 8 to 31 months), persistent absence of enhancement was observed in all treated tumors. One patient developed new intrahepatic nodule and pathological fracture on the right femoral neck. Li et al. performed CT-guided percutaneous MWA on nine patients with adrenal malignant carcinoma including one primary adrenocortical carcinoma and eight metastatic carcinomas (four from lung cancer, two from hepatocellular carcinoma, one from left tibial osteosarcoma, and one from intrahepatic cholangiocarcinoma) [11]. Of the eight metastatic cases, seven were unilateral and one was bilateral. The tumor diameters ranged from 2.1 to 6.1 cm and the average diameter was 3.8 cm. The number of ablation sites ranged from one to three sites (mean, 1.5 sites) and the accumulated ablation time was from 4 to 15 min (average, 7.7 min). One patient experienced hypertensive crisis during treatment, and the crisis was controlled after the immediate pause of ablation and two times of intravenous injection of 5 mg phentolamine mesylate. At the average follow-up period of 11.3 months (from 3 to 37 months), no patient experienced recurrent tumor at the treated site, but all patients had progression of metastatic disease at extra-adrenal sites. Five of the eight patients with adrenal metastatic tumors died from the progression of their primary tumor or its metastasis to other organs.

According to our latest study data, we evaluated the feasibility and effects of MWA in 26 patients (M:F = 18:8; mean age, 54 ± 10 years; range 34–76 years) with 28 adrenal tumors (mean diameter, 3.9 ± 3.0 cm; range, 1.4–16.2 cm). The cases included 6 adrenocortical adenomas, 3 pheochromocytomas, and 17 metastatic carcinomas (from lung cancer, hepatocellular carcinoma, renal cell carcinoma, rectum adenocarcinoma, and liposarcoma). Twenty tumors were on the right side and eight were on the left side. All adrenal tumors were ablated after scheduled MWA sessions (ranged from one to four sessions; total time ranged from 120 to 2,640 s). During MWA procedure, the blood pressure reached 195/100 mmHg (systolic blood pressure/diastolic pressure) in one patient with pheochromocytoma, and it decreased to baseline level when MWA emission was suspended. No major complications occurred; minimal to moderate pain was experienced in four patients, slight fever was found in two patients, and transaminase increased notably in one patient with metastatic tumor near the diaphragm. After the MWA treatment, enhancement was found in one patient with metastatic tumor near the diaphragm which was then treated with radioactive seed. During a follow-up period that ranged from 1 to 31 months, persistent absence of enhancement was observed in all treated tumors. One patient developed new retroperitoneal lymph node metastasis. No local recurrence and extra-adrenal metastasis were found in other patients (Figs. 20.1 and 20.2).

20.7 Other Treatments of Adrenal Tumors

20.7.1 Radiofrequency Ablation

RFA is performed by using the alternating current via radiofrequency pulses to create friction, which can result in the heating of cells and resultant cell death and/or tissue necrosis [7]. RFA is being increasingly used for cure or palliation of

different tumors in the liver, kidney, lung, musculoskeletal system, and adrenal glands. However, percutaneous RFA of adrenal tumors is still a relatively new procedure compared with the more widespread application for hepatic and renal tumors [14]. For adrenal tumors, RFA has been used a little more widely than MWA. The literatures demonstrate the successful use of RFA as a technique in the adjuvant treatment of primary functional adrenal neoplasm and adrenal malignancies. According to the study of Mendiratta et al., RFA was employed in 13 patients with symptomatic functional adrenal neoplasm no more than 3.2 cm in diameter. (Ten patients with aldosteronoma, one patient with cortisol-secreting tumor, one patient with testosterone-secretingtumor,

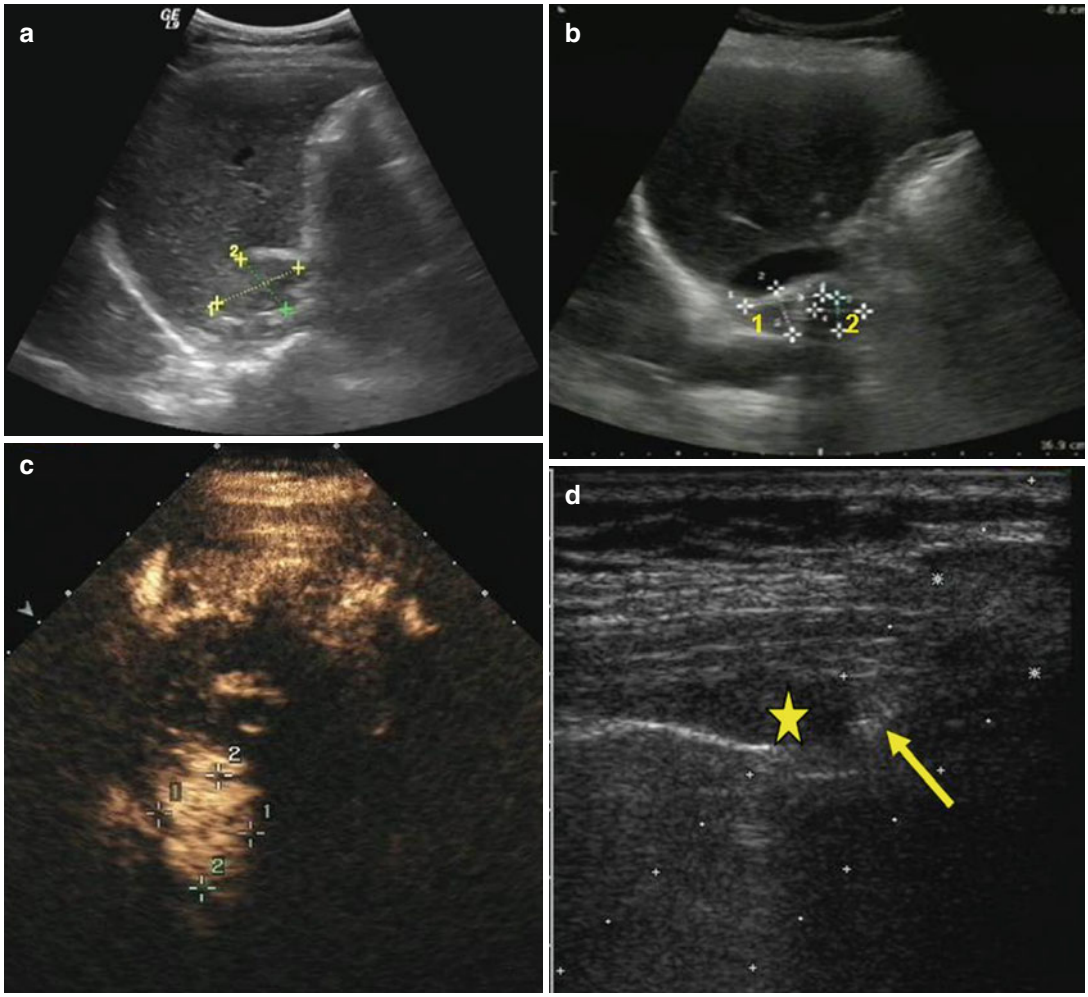

Fig. 20.1 Procedures of microwave ablation (MWA) in a 50-year-old woman with recrudescent pheochromocytoma, who had undergone surgical resection for right pheochromocytoma (size, 10×8×6 cm). (**a**) Six months after the surgery, conventional ultrasound scan shows a right adrenal lesion with the size of 3.2×2.3 cm, which is then treated with MWA. (**b**) Thirty months after the first MWA, the ablated lesion (*1*) volume is decreased, and a new lesion (*2*) is found. (**c**) Contrast-enhanced ultrasound before the second MWA shows tumor enhancement in arterial phase with the size of 3.0×2.5 cm. (**d**) Through artificial liquid chest catheterization (*arrow*), normal saline (*star*) is injected between the right lung and liver, which may prevent the right lung from heat injury during MWA. (**e**) MWA procedure is performed. (**f**) Contrast-enhanced US shows no enhancement of the ablation zone 3 days after MWA

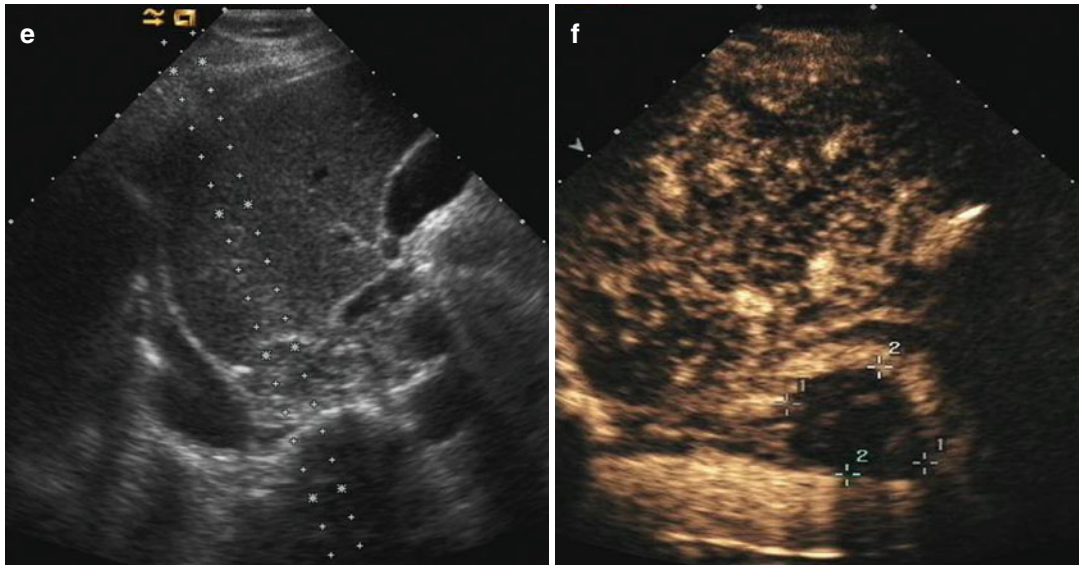

Fig. 20.1 (continued)

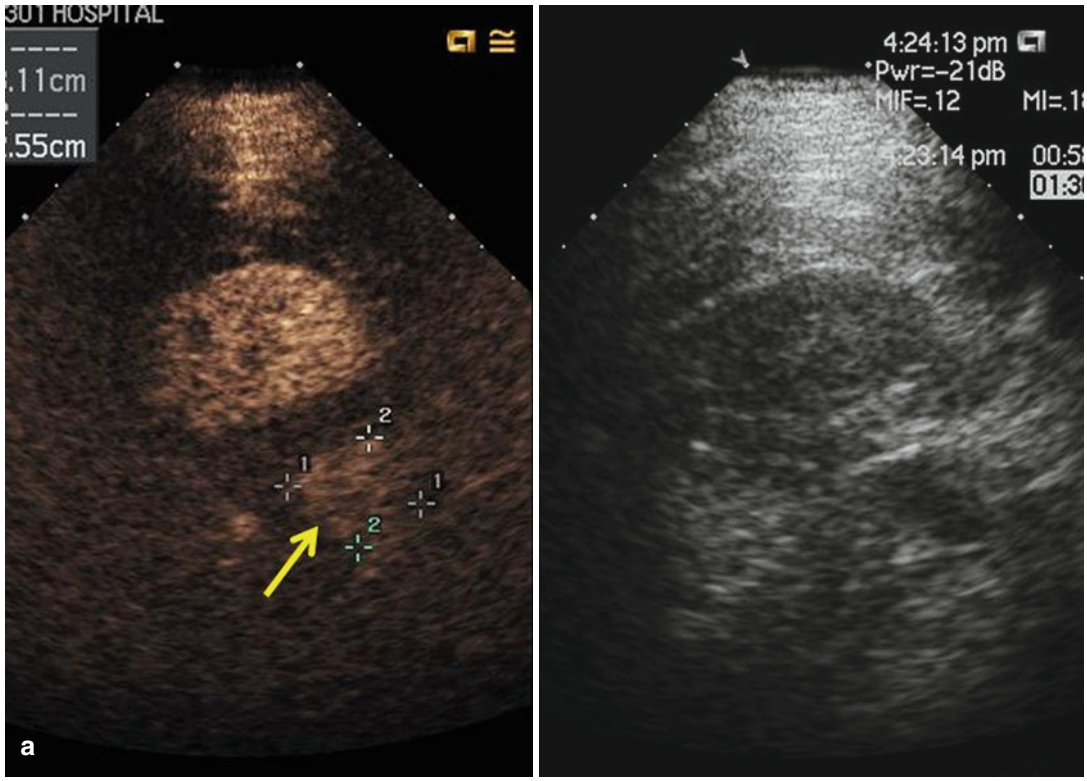

Fig. 20.2 MWA in a 64-year-old man with left adrenal metastasis (3.1×2.6 cm), who had hepatocellular carcinoma treated with transarterial chemoembolization 1 year ago. (**a**) Contrast-enhanced ultrasound scan obtained before ablation shows tumor enhancement (*arrow*) at arterial phase. (**b**) T2WI on MRI scan obtained before ablation shows a well-demarcated tumor (*arrow*) on the left adrenal. (**c**) MRI scan obtained 6 months after ablation shows hypointense ablation zone (*arrow*) at the site of treated left adrenal tumor, suggesting the absence of new tumor progression. (**d**) MRI scan obtained 15 months after ablation shows hypointense ablation zone (*arrow*) of treated left adrenal tumor

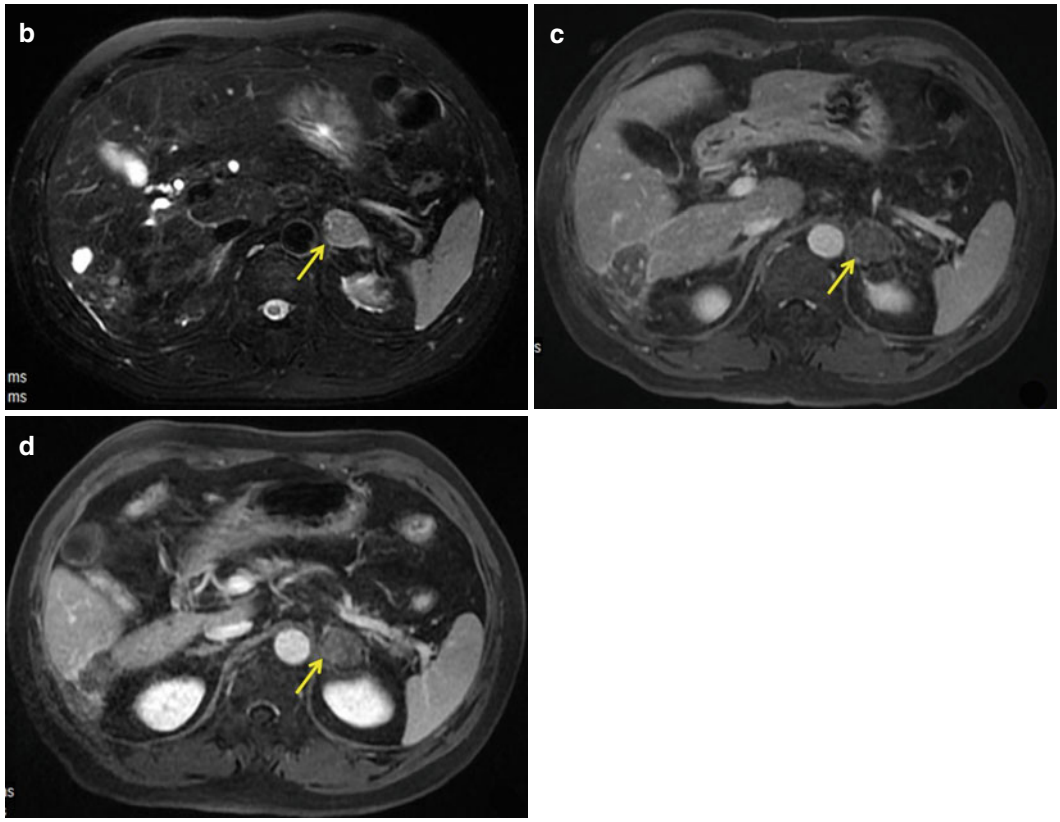

Fig. 20.2 (continued)

and one patient with pheochromocytoma) [7]. All patients experienced resolution of clinical symptoms or syndromes including hypertension, hypokalemia, Cushing's syndrome, or virilizing symptoms. Technical success was confirmed in all cases by immediate post-procedure imaging. The mean clinical follow-up was 41.4 months (range, 12–106 months). All patients demonstrated resolution of clinical findings 1 year after treatment. For the patients with aldosteronoma, improvements in hypertension management were noted. The mean blood pressure before ablation was 149/90 mmHg, which decreased to 122/77 mmHg at a mean of 2.8 months after ablation and 124/75 mmHg at a mean of 41.4 months. There were two minor complications including one small pneumothorax and one limited hemothorax, neither of which required overnight admission. Lo et al. performed CT-guided RFA on a 71-year-old patient with painful bilateral adrenal metastases from lung cancer [15]. The left adrenal mass was 4.7 cm and right mass was 4.3 cm. The patient experienced marked relief in pain bilaterally after the treatment. On further follow-up of 6 months, the patient noted a lack of endocrine sequelae and continued pain relief.

RFA treatment has limitations. It is difficult to treat all adrenal tumors because some of them are hypervascular and the size of tumor is too big. Combination therapy with RFA and adrenal arterial chemoembolization has been confirmed as a safe therapeutic option that can lengthen survival among patients with adrenal metastasis from hepatocellular carcinoma [16]. Six patients with eight adrenal metastatic lesions were treated. The mean maximum diameter was 5.2 ± 1.8 cm (range, 3.5–8.0 cm). One patient has isolated adrenal metastatic lesions, but the other five patients had four associated intrahepatic lesions and three extra-adrenal distant metastatic lesions.

Tumor enhancement of all eight adrenal tumors ceased on contrast-enhanced CT scans and no major complications were related to combination therapy. During the mean follow-up period of 37.7 ± 27.6 months (range, 4.0–70.9 months), two of eight adrenal tumors (25 %) had local tumor progression. The median survival time was 24.9 months; however, three patients treated for both intrahepatic and extrahepatic lesions survived longer than 4 years.

Brook et al. described the imaging findings after RFA of 14 patients with adrenal tumors [2]. Immediate soft tissue findings after RFA included fat stranding around the adrenal gland in 13 patients (93 %) and air bubbles in 12 patients (86 %). A fat rim sign was found in 60 % of patients at long-term follow-up. In addition, the author reported that the expected side effects were found in 35 % of patients: in two patients adjacent liver parenchyma was ablated, in two patients the diaphragmatic crus was injured, and in two patients local hematoma occurred (in one patient, both adjacent liver and diaphragmatic crus were ablated). Complication rate was 14 %, including one case of small pneumothorax and one case of small hemothorax.

20.7.2 Cryoablation

Cryoablation relies on rapid freezing and thawing to cause rupture of cell membranes resulting in cell death [1]. Cryoablation probes are inserted in the target lesion and temperatures from −80 °C to less than −150 °C are achievable by rapidly propelling argon gas at high pressures through the probe into an area of lower pressure [17]. This change from the high to low pressure system necessitates absorption of heat from the surrounding tissues via the Joule-Thomson effect, which creates the surrounding ice ball [1]. Advantages of cryoablation rather than heat thermal ablation are the ability to see ice ball on CT and decreased degree of pain [1].

Cryoablation of the adrenal gland is a promising technique for percutaneous treatment of adrenal metastasis, with limited experience reported in the literature. Twelve patients with single adrenal metastasis were treated with percutaneous adrenal cryoablation [17]. Local control was achieved in 11 of 12 tumors (92 %) after treatment. One patient with adrenal insufficiency underwent conservative ablation and developed adrenal recurrence which was retreated. Six patients developed hypertensive crisis during or immediately after cryoablation procedure. Patients with adrenal cryoablation experienced a significant increase in systolic blood pressure, pulse pressure, and mean arterial pressure compared with kidney cryoablation patients.

20.7.3 Laser Ablation

Laser is an acronym for light amplification by stimulated emission of radiation. Laser technology directs collimated, monochromatic, coherent, and powerful light energy to a well-delimited area of tissue in a predictable, precise, and controlled manner [18]. About 80 % of tissue is destroyed by energy absorption; and because of coagulation of microvessels and ischemic injury, cell death may continue for up to 72 h after laser ablation [18]. The maximum diameter of the near-spherical lesions can reach 1.2–1.6 mm with a bare fiber; lesion size can be increased by simultaneous deployment of multiple fibers in an array [18].

Laser ablation is not widely used in adrenal tumors as RFA according to searchable literatures. Vogl et al. performed CT-guided Nd:YAG laser ablation on nine patients with nine unilateral adrenal metastases from primaries comprising colorectal carcinoma, renal cell carcinoma, esophageal carcinoma, carcinoid tumors, and hepatocellular carcinoma [10]. The mean diameter of tumors was 4.3 cm. The average number of laser applicators per tumor was 1.9 (range, 1–4) and mean applied laser energy was 33 KJ (range, 15.3–94.6 KJ). All patients tolerated the procedure well with local anesthesia and no complications occurred. Complete ablation was achieved in seven lesions; progression was detected in two lesions in the follow-up.

20.7.4 Chemical Ablation

Ethanol and acetic acid are the most common chemical ablation agents, which accomplish tumor necrosis by degenerating cellular

cytoplasm, denaturing cellular proteins, and developing irreversible vascular thrombosis of small vessels supping the tumor [19]. Although chemical ablation has been used to treat neoplasm of the liver, lung, thyroid, and other organs [20–22], only a few reports treated with chemical ablation for adrenal tumor have been published [9, 19]. Percutaneous ethanol or acetic acid injection may be useful for small lesions, but they are not sufficiently effective for larger tumors. In the article of 37 patients with 46 adrenal tumors treated with CT-guided percutaneous chemical ablation [19], the complete response rate was 92.3 % (24/26) and partial response rate was 7.7 % (2/26) for primary tumors, but for metastasis, complete response rate was 30 % (6/20) and partial response rate was 70 % (14/20). Their results suggested that benign tumors less than 3 cm in diameter can be treated completely with one to three percutaneous ethanol injections, and for tumors more than 3 cm in diameter, tumor size regressed gradually after acetic acid injection. For malignant tumors, acetic acid may control or delay the malignant progression because they may be associated with higher incidence of residual or recurrent tumors [19]. For functional tumors, the level of corticosteroid in five patients with Cushing's syndrome was normal 3 months after the procedure. However, for functional aldosteronomas, blood pressure did not decrease obviously after the procedure because of arteriolar sclerosis caused by long-term hypertension [19].

Studies of different ablations in primary and metastatic adrenal tumors are listed (Table 20.1). The clinical efficacy of chemical ablation for adrenal tumors is not very satisfactory, and it has side effects related to the leakage of ethanol or acetic acid outside the capsule of tumor; therefore, only a few reports about chemical ablation for adrenal tumor have been published. The advantage of laser ablation and cryoablation includes well-defined area of complete tissue ablation with a regular, homogeneous, and reproducible pattern, so the clinical efficacy is better than chemical ablation, but its use is not as widely as RFA. For adrenal tumors, RFA and MWA have been used relatively widely, and the technical success rate is higher than other techniques. Pros and cons of each ablative technique in adrenal tumors

Table 20.1 Studies of ablation in primary and metastatic adrenal tumors

Author	No. of pts (Ts)	Treatment type	Tumor type	Tumor size (cm)	Session	Technical success rate (%)	Follow-up (m)	Complication rate (%)	Local progression rate (%)
Wang et al. [3]	5	MWA	Met	2.3–4.5	1–2 (1.2)	100	8–31 (19)	0	0
Li et al. [11]	9 (10)	MWA	Met + primary[a]	2.1–6.1 (3.8)	1–2 (1.1)	100	3–37 (11.3)	0	0
Wolf et al. [13]	22 (23)	RFA + MWA	Met + primary[b]	1–8	N/A	100	1–91 (45.1)	13.6	4
Mendiratta-Lala et al. [7]	13	RFA	Primary[b]	1.0–3.2	1	100	12–106 (28)	15.3	0
Brook et al. [2]	14	RFA	Primary + met	1–3.3 (1.9)	N/A	100	12–38	14.3	7.1
Nunes et al. [12]	11 (12)	RFA	Primary[b]	1.2–3.4 (1.9)	1	100	N/A	18.1	N/A
Welch et al. [17]	12	Cryoablation	Met	1.2–4.5 (2.7)	1–2	92	3–55	50	N/A
Vogl et al. [10]	9	Laser	Met	4.3	N/A	78	14	0	22.2
Xiao et al. [19]	37 (46)	Ac + ethanol	Primary + met	1.9–8.6 (4.2)	N/A	65	24	0	N/A

Note: *Met* metastasis, *Primary* primary adrenal tumors, *Ac* acetic acid, *Pts* patients, *Ts* tumors, *m* months, *N/A* not available

[a]Primary adrenocortical carcinoma

[b]Functional adrenal adenoma

require more investigation. A combination of different ablation methods, surgery, and other treatments is necessary according to the condition of patients.

Conclusion

Percutaneous MWA of adrenal tumors appears to be an effective and safe technique in regard to local tumor control and ability to treat hormonally active tumors with clinical syndromes. Current literatures regarding adrenal tumors are limited, and larger multicenter studies with long-term follow-up are required to determine the clinical efficacy.

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Ultrasound-Guided Microwave Ablation for Superficial Malignant Tumors

21

Cai Qi and Xiao-ling Yu

Abstract

Image-guided microwave ablation has received substantial attention for the treatment of many focal malignancies, but there are few reported assessments about the image-guided microwave ablation for superficial malignant tumors. As a relatively new technology, microwave ablation can achieve favorable results for the superficial malignant tumors with different compositions because of its high ablation efficiency, its low complication rate, and its short treatment period. Increasing interest has been accompanied by continual advances in the type of antenna and therapeutic combinations with other treatments. In this chapter, the review outlines device, indications, patient preparation, procedures, clinical results, and complications of microwave ablation on superficial malignant tumors in comparison to other treatments, such as surgery, radiofrequency ablation, and high-intensity focused ultrasound.

Keywords

Superficial malignant tumor • Microwave ablation • Radiofrequency ablation • High-intensity focused ultrasound

Abbreviations and Acronyms

CT	Computed tomography
HIFU	High-intensity focused ultrasound
MWA	Microwave ablation
SMTs	Superficial malignant tumors

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21.1 Introduction

Superficial malignant tumors (SMTs) are usually located close to the skin, hypodermis, and muscle. They can be recurrent or metastatic tumors or primary ones. Clinically, the incidence of primary malignant superficial tumors is low. Metastasis or local infiltration is the major cause of SMTs.

Surgical excision is currently the most common option for treating SMTs [1]. It is generally thought that the benign tumors can achieve radical

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cure by operation. But for SMTs, especially the recurrent or metastatic ones, reoperation can significantly reduce immunity and increase the chance of recurrence and metastasis. Tumor size also plays an important role in the resection. Small lesions can be easily resected, whereas it is technically difficult for radical excision of large lesions, especially those invading muscles. Radical resection may sacrifice a large area of skin and muscle which may influence the integrity of the skin, and a significant number of patients require abdominoplasty for larger superficial tumors [2–5].

Other traditional treatments have been used for SMTs, such as chemotherapy and radiotherapy. But for a lot of malignant tumors, especially recurrent or metastatic ones whose primary tumors are removed by surgery, it is very difficult to achieve complete response with traditional chemotherapy because of their superficial location and poor blood supply. In addition, the dosage limit is an important concern when treating SMTs: skin ulcers, skin necrosis, and infection are common when the radiotherapy dosage reaches high levels [6]. Therefore, a minimally invasive yet effective therapy may be of value for the treatment of SMTs. Thermal ablation has been widely used for the treatment of multi-position malignant tumors in the past decades and is well established [7–9]. The common energy sources include radiofrequency, microwave, and HIFU. Microwave ablation is one of the effective localized thermal ablation techniques that has been used to treat benign and malignant tumors of the liver, kidney, adrenal gland, spleen, and lung [10–14]. However, no report assesses the efficacy and safety of MWA for SMTs apart from other groups. This chapter describes the therapeutic efficacy of ultrasound-guided MWA for the treatment of SMTs in our department.

21.2 Microwave Device

Microwave generator is the same as that used for the liver as described in the previous chapter. The antenna is designed to minimize power feedback and provide tissue with optimal energy deposition. Three types of antennas are applied according to the size and location of the tumor with the antenna emitting tip length of 5, 7, and 11 mm, respectively. For tumors smaller than 2 cm, an antenna tip of 5 mm is chosen, while for tumors larger than 3 cm, a tip of 11 mm is selected, and the antenna tip of 7 mm is used for the tumor size in between. Multi-needles are usually used in tumors measuring 2 cm or greater during MWA. The microwave system is also equipped with thermocouple needles which can monitor temperature in real time during ablation.

21.3 Indications and Pre-ablation Workup

MWA can be used to treat both metastatic and primary malignant tumors. The indications for MWA of superficial tumors are as follows: (a) The tumor is histopathologically confirmed (via biopsy) or clinically confirmed as superficially malignant tumors; (b) the lesions can be clearly seen on ultrasound; (c) the tumor is located more than 5 mm from the skin; (d) patients can tolerate anesthesia; (e) for tumors smaller than 4 cm, radical treatment is the therapeutic goal; (f) metastatic neoplasms undergo systemic chemotherapy before MWA; and (g) patients have no contraindication for magnetic resonance imaging (or PET-CT, CT). The exclusion criteria are as follows: (a) severe malfunction of the heart, kidney, or liver; (b) severe coagulation abnormalities (prothrombin time more than 25 s, prothrombin activity higher than 40 %, and platelet count higher than 40 cells $\times 10^9$/L); (c) tumors widely spread to the skin or subcutaneous tissue, or beoken is present; (d) heavily scarred skin or radiation-injured skin; and (e) cachexia.

All patients should undergo image examination, such as ultrasound, contrast-enhanced ultrasound, or gadolinium-enhanced magnetic resonance imagining (magnetic resonance imaging) to delineate the target tumor before MWA. The maximum diameter of nodules should be measured by enhanced imaging. Patients are informed of the mechanism, procedures and precautions of MWA and written consent

are obtained from all patients before MWA treatment. Twelve-hour fasting and 8-h water deprivation are required before treatment.

21.4 MWA Procedure

Before treatment, an appropriate puncture route is chosen on ultrasound. After local anesthesia with 1 % lidocaine, ultrasound-guided biopsy is performed first by using an automatic biopsy gun with an 18-gauge cutting needle for the tumors with no pathology confirmed, and specimens are taken from different parts of the tumor (one to three pieces). Subsequently, the antenna is percutaneously inserted into the tumor along the long axis and placed at the desired location, guided with ultrasound, and the antenna type is chosen by the tumor size. After correct placement of antennas the general anesthesia (Propofol, 6–12 mg/kg per hour; Ketamine, 1–2 mg/kg) is applied, and microwaves than emit [15, 16]. The thermal monitoring system can measure temperature in real time during ablation. For tumors not adjacent to important organs, if the measured temperature at the site 5–10 mm away from the tumor margin reaches 60 °C or remains above 54 °C for at least 3 min, complete tumor necrosis is considered. If the tumor is adjacent to the bowel, skin, important blood vessels, and other important organs, the temperature cutoff of ablation is set at 50 °C. The results of study [17] demonstrate that tissue coagulation can be induced by focal tissue heating to approximately 50 °C for less than 5 min; this has become a standard surrogate endpoint for thermal ablation therapies in both experimental studies and current clinical paradigms. An increased gray scale or strong echoes are indications of effective treatment. Insert the antenna in the deepest area of the tumor and increase the angle of puncture between the antenna and transducer to avoid skin injury. If the tumor is adjacent to the bowel, gallbladder, or other important tissues, a 21-gauge thermocouple is inserted close to these tissues for real-time temperature monitoring. The treatment session will be ended when the transient hyperechoic zone between antennas merges and covers the whole lesion on grayscale ultrasound; an ice bag is placed on the skin since the beginning of MWA to avoid scalding; besides, MWA will be ended if skin redness, edema, and even exudate appear during MWA.

21.5 Posttreatment Observation

After MWA, patients should be carefully monitored for possible complications such as skin edema, skin burn, organ injury, abscess, and side effects such as pain, fever, and pleural effusion. All patients undergo contrast-enhanced imaging 1–3 days after MWA. If residual tumor (hyperenhanced area on contrast-enhanced imaging) is found, a further session is planned or patients enter the follow-up protocol.

21.6 Therapeutic Efficacy Assessment

Therapeutic efficacy is assessed by contrast-enhanced imaging and serum tumor marker levels. The technique effectiveness is defined as the "complete ablation" of macroscopic tumor proved by imaging follow-up after ablation. Local tumor progression is defined as in completely treated viable tumor continuing to grow or a new viable tumor growing at the edge of the ablation zone during the follow-up; contrast-enhanced follow-up study performed 1 month after MWA has documented adequate ablation and an absence of viable tissue in the target tumor and surrounding ablation margin by imaging criteria.

Between August 2007 and September 2012, a total of 32 patients (20 male and 12 female) of 58 tumors with a mean age of 55 years (range, 16–87 years) were treated by MWA in our department. Tumor diameters varied from 0.9 to 10.0 cm (mean3.33 ± 2.26), including 35 ≤3 cm nodules (35/58, 60.3 %), 11 nodules >3 to ≤5 cm (11/58, 19.0 %), and 12 nodules >5 to ≤10 cm (12/58, 20.7 %). The palliative treatment are usually for the tumors larger than 5 cm as a therapeutic goal. All superficial tumors were metastasis or local infiltration. Sixteen lesions were located on the chest wall, 40 were located

Table 21.1 Patient's general characteristics

Category	
Age (years)	55.12 ± 14.08
Sex (M/F)	20/12
Original/metastasis	9/49
Tumor number (1/2/3)	58
≤3 cm/3–5 cm/>5 cm	35/11/12
Tumor diameter (cm)	3.33 ± 2.26
Tumor location (abdominal wall/chest wall/groin)	42/13/3
Ablation power (W)	45.26 ± 7.58
Ablation needle	1.57 ± 0.6
Ablation session	1.1 ± 0.34
Follow-up (months)	13.28 ± 7.54

on the abdominal wall, and 3 were located on the groin. The primary tumors were as follows: liver tumors (17), renal and adrenal tumors (5), bladder tumors (2), intestinal tumors (2), ovarian tumors (3), and other primary tumors (3). Before MWA, all patients were treated with other therapies, such as chemotherapy, radiotherapy, surgery, and so on.

All selected patients chose MWA on the basis of tumor stage which made them inoperable or had comorbidities, advanced age, or refused to undergo surgery (Table 21.1). The follow-up period was calculated starting from the beginning of MWA in all patients, which consisted of contrast-enhanced CT, magnetic resonance imaging, and/or contrast-enhanced ultrasound 1, 3, and 6 months after MWA and every 6 months thereafter.

Ultrasound-guided MWA was performed for 58 tumors in 32 patients. The follow-up time was 3–26 months (13.28 ± 7.54 months). The observation period was less than 6 months for six patients (6/32, 18.75 %), 6 months to 1 year for nine patients (9/32, 28.13 %), 1–2 years for 13 patients (13/32, 40.63 %), and 2–3 years for four patients (12.5 %). Indications for MWA in these 32 patients were advanced age or poor surgical candidates with significant comorbidities (seven patients), poor liver or renal function (eight patients), other ineffective therapies (five patients), and patient preference (12 patients).

Microwave ablation output power ranged from 30 to 50 W, and an output setting of 50 W was routinely used during ablation sessions, relatively lower than that used in liver lesions. Desired temperatures were attained in no more than 1,180 s (range 120–1,180). Thermocouple was used during ablation for the tumors adjacent to the high-risk locations. In this study, four tumors were adjacent to the gallbladder, three tumors were adjacent to the intestinal tract, and three tumors were adjacent to the pleuroperitoneum. We used one thermocouple to monitor the temperature, and the maximum was 50 °C in these tumors. The mean treatment session was 1.1 per person (1–3).

On the basis of follow-up imaging finding, technique effectiveness was achieved in 54 of 58 (93.1 %) tumors. Four lesions with local tumor progression were discovered at 1, 3, 4, and 15 months after MWA, with the ablation nodule size of 4, 6.2, 7.4, and 7.9 cm, respectively (Table 21.2). Therapeutic options offered to patients with local tumor progression included chemotherapy for one patient and iodine-125 seed implantation for three patients.

No major complications occurred during or immediately after MWA. Ten patients experienced grade 1 pain according to the standardization of terms and reporting criteria for image-guided tumor ablation [18] after the treatment, and no analgesic medication was needed. Minimal asymptomatic pleural effusion and ascites was found in three patients, which was resolved spontaneously in 1 week. Post-ablation fever was encountered in 13 patients, but the temperature of 12 of the patients was lower than 38 °C. The last patient had peritonitis and the temperature reached 41.2 °C; oral antipyretic was administrated for 3 days and the patient recovered. No skin burns were observed in the treated area; however, the treated area was slightly swollen in five patients, and no extra treatment was applied.

During the follow-up period, eight patients died of primary tumor progression during 6–24 months after MWA, and two patients died of cardiovascular at 7 months after MWA and cerebrovascular at 10 months after MWA. In the other patients, the ablation zones were well defined on contrast-enhanced imaging and gradually shrank with time.

Table 21.2 Comparison of ablation results in different tumor sizes

Parameters	≤3 cm	3–5 cm	>5 to ≤10 cm	*p* value
Tumor number	35	11	12	N/A
Tumor size (cm)	1.9 ± 0.6	3.8 ± 0.6	7.0 ± 1.6	0.0001
Number of antenna insertions	1.3 ± 0.5	1.8 ± 0.6	2 ± 0.6	0.11
Emission time (s)	395.1 ± 213.1	877.3 ± 409.9	1,115.3 ± 345.3	0.0001
Technique effectiveness (%)	100 (35/35)	90.9 (10/11)	75 (9/12)	0.01
LTP (%)	0 (0/35)	9.1 (1/11)	25 (3/12)	0.01

LTP is defined as a new viable tumor at the edge of the ablation zone

21.7 Comparison with Other Treatments

Local recurrence and distant metastasis present a great challenge for treating malignant tumors after conventional surgery, radiotherapy (external beam radiotherapy), and chemotherapy. Effective treatments are needed to prolong survival and improve the quality of life for recurrent or metastatic superficial tumors.

Surgical resection is the most invasive method for superficial tumors, but open surgery brings about the risk of hemorrhage and possible postoperative incision hernia. Meanwhile, if the resection margin is inadequate, reoperation of SMTs can significantly reduce immunity and increase the chance of recurrence and metastasis. Some patients may not be surgical candidates due to poor medical condition [19]. Reoperation of SMTs can significantly reduce immunity and increase the chance of recurrence and metastasis; sometimes surgery provides only temporary treatment for recurrent or metastatic SMTs without prolonging survival time [20].

Minimal invasive treatments are suitable for treating such tumors. The management of superficial malignant tumors underwent a dramatic evolution in the last decade [18, 21]. Transarterial embolization is used for tumors larger than 4 cm in diameter at present, especially for patients who are nonsurgical candidates [21]. However, superficial tumors have relatively poor blood supply than the solid ones, and it cause difficult to the embolization. In addition, it is difficult to create a safety margin to eradicate possible microscopic tumor and it may cause ischemic changes. Thus, it is rarely used in superficial tumors. The local and minimal invasive treatments must be applied to overcome these treatments preclude, which should have image precise monitoring system and image-guided thermal ablation system.

HIFU ablation is a noninvasive technique for the treatment of localized tumors [22, 23]. HIFU is a conformal extracorporeal treatment which can generate thermal coagulation necrosis of the target lesion without surgical exposure or insertion of applicators. There have been many clinical studies using HIFU for alleviation of solid tumors recently and has obtained effective local tumor control [24–27]. In the treatment of superficial tumors, it also achieved a satisfying result, with the technique effectiveness ranging from 57.9 to 100 % [28–30]. But it also has some limitations; HIFU treatment takes more time, hence increasing the incidence of complication, and ablation is influenced by the acoustic pathway, which cannot treat undetectable tumors.

MWA, which is the newer technique, is technically similar to radiofrequency ablation. Radiofrequency ablation remains the most widely used ablative technique [31–33], and MWA has its own advantages. Microwave power can be continually applied to produce extremely high (>150 °C) temperatures, which improves ablation efficacy by increasing thermal conduction into the surrounding tissue [34]. Microwaves also heat tissue more efficiently than does radiofrequency energy, microwaves do not require ground pads, and multiple antennas can be operated simultaneously [35]. But it is unable to compare the pros and cons among these treatment methods in the treatment of SMTs, for it has relatively limited studies and lacking of systemic and strict controlled studies.

^{125}I seed implant brachytherapy is a relatively new radiotherapy treatment; it has become one of the standard treatments of prostate cancer [36, 37]. With the improvement of the technique, ^{125}I seed implant brachytherapy has been used for various kinds of tumors [38–40]; however, no report assesses the efficacy and safety of ^{125}I seed implant brachytherapy for SMTs; it can be used as an adjunctive therapy during MWA.

21.8 Technique Key Points

On account of the previous experience in MWA for solid tumors, the ultrasound-guided MWA was used for the SMTs. The treatment effectiveness was 93.1 %, and 54 of 58 lesions were successfully treated. Tumor size was an important factor to influence the efficiency. When the tumor diameter was <4 cm, the tumor effectiveness was 97.9 %; however, when the tumor diameter was ≥4 cm, the effectiveness was 75 %. This might result from an inadequate ablation dosage, and the larger tumors have more relatively abundant blood supply. In order to achieve the same effect, tumors larger than 4 cm needed several sessions. Results suggest that microwave may be effective for superficial tumors like other techniques; it may also represent a competitive alternative to surgical and other therapies.

Some important points need attenting during the ablation: (1) Though an antenna is sufficiently for tumors less than 1.5 cm, when the tumors have abundant nourishing vessel, another antenna is required to successfully treat the entire tumor and ablative margin. In order to improve the ablation efficiency, we also made some progress with the antenna. Three types of antenna were used in this study; according to the tumor size and location, the antenna tips were 0.5, 0.7, and 1.1 cm, respectively. Based on the preliminary experiments, the reform antenna tip of 0.7 and 0.5 cm can ablate smaller zones than the common tip of 1.1 cm, which can be used for the superficial tumors, especially for the smaller ones. (2) It must be concerned in and after the ablation for the older patients or the patients with hypertension medical history, cardio-cerebrovascular condition status. (3) Enough rehydration salt is needed for the patients with abnormal renal function to avoid the renal insufficiency or acute renal failure. Microscopic hematuria must be observed after ablation. (4) Palliative ablation is taken for tumor larger than 4 cm to reduce the tumor burden. The whole tumor could not be ablated in one treatment session. The larger ablation zone we ablated, the more complications for patients. The biggest or the remarkable clinical symptoms of tumor are first treated during ablation to alleviate the clinical symptom. The patient needs to be discharged from the hospital for a period (usually 1 to 2 months) when ablating a number of tumors, and further treatment is administered if necessary. (5) Patients with primary tumors that are prone to develop in multiple organs are unlikely to be successfully treated with local therapy; regardless of how successfully individual lesions are destroyed. Treatment failure in these cases is due largely to uncontrolled growth of previously undetected metastases. Systemic treatment and close follow-up are needed for all patients, especially for those with recurrent or metastatic tumors. (6) Sometimes, for the tumor which is relatively superficial or it have special structure of the skin, the skin edema, hematoma and even burn will be account during and after the MWA for SMTs. The patients skin edema and hematoma will be relief from the cold compresses and the use of repercussive after MWA; (7) Combining therapies (such as chemotherapy and radiation) could be used in MWA; it acts with synergistic effects which are able to reduce the ablative margin (Figs. 21.1 and 21.2).

No major complications occurred, but a special complication abdominal wall edema was observed after MWA. In our study, five cases of abdominal wall were encountered and the ablated tumors were all located in shallow muscles with subcutaneous invasion. Compared with solid organs, muscle tissue cannot accumulate heat during the ablation for it lacks relative capsules and the heat overflow can readily lead to edema. In order to achieving surgical treatment margins, a rim of normal tissue (such as fatty tissue or muscle tissue) surrounding the tumor should be destroyed and it may cause edema in

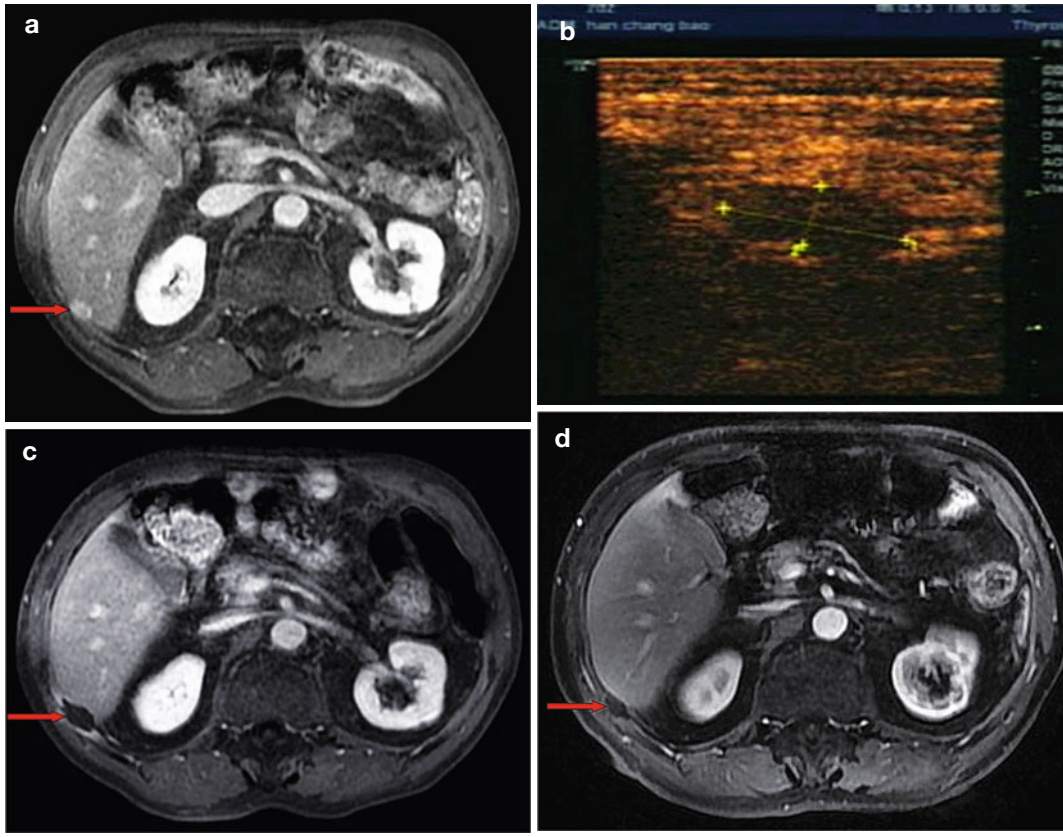

Fig. 21.1 Microwave ablation (MWA) in a 71-year-old man with right abdominal wall metastatic tumor, post operation of colon cancer, splenectomy of spleen metastasis, and radiofrequency ablation (RFA) for the liver metastasis. (**a**) Pre-ablation arterial-phase magnetic resonance imaging (MRI) scan shows one round-like enhancement neoplasm (*arrow*) near the right abdominal wall with the size of 2.2×1.4 cm. (**b**) Contrast-enhanced ultrasound shows no enhancement of the ablation zone at 3 days after treatment. (**c**) Arterial-phase MRI scan obtained 2 months after ablation shows hypoattenuating ablation zone (*arrow*) without enhancement. (**d**) Scan obtained 6 months after ablation shows hypoattenuating ablation zone (*arrow*) without enhancement corresponding to treated region

the superficial tumors. In this study, all edema were occurred in abdominal wall tumors, for these parts have more fat. Fortunately, the abdominal wall edema seen in five patients was mild and all patients recovered within a short time (1–3 months) without special treatment. There are also some key points to reduce the complications during the ablation. (a) The microwave antenna should be inserted in the deepest area of the tumor and along the tumor long axis to avoid the skin injury. (b) For tumors with subcutaneous invasion, the transient hyperechoic zone should not exceed the dermal layer in the gray-scan ultrasound, and an ice bag was placed on the skin to avoid scalding. Special attention should be taken for abdominal wall tumors, especially for the patient with thick subcutaneous fat to avoid fat liquefaction. (c) For functional tumor, such as pheochromocytoma, the ablated power from 30 W to high power and changed the power according to the blood pressure. The antihypertensive drugs were used during the procedure, as the functional tumor can release catecholamine which could result in blood pressure fluctuation. (d) For tumors adjacent to the gastrointestinal tract protective temperature monitor could be used during the ablation, and the peritoneal irritation and the

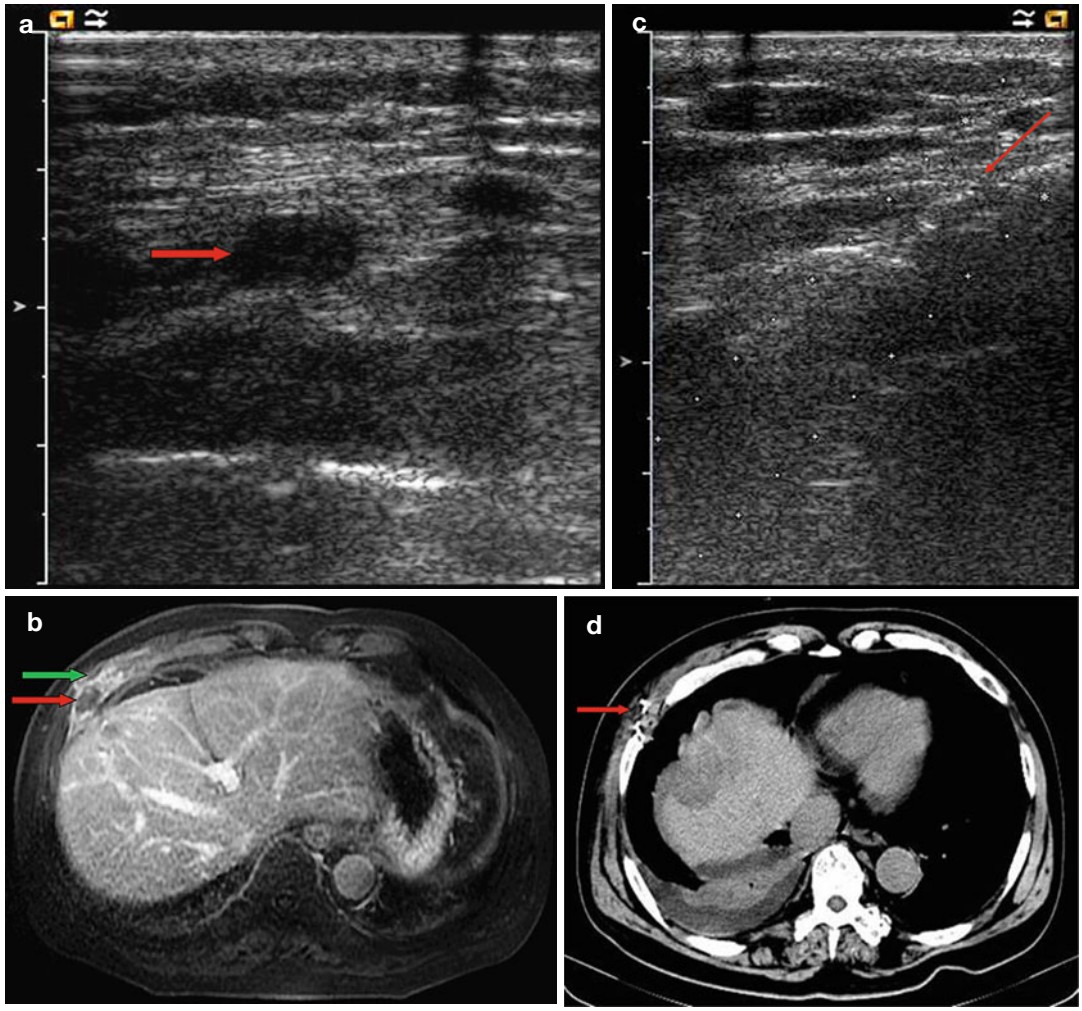

Fig. 21.2 Iodine-125 seed implantation combined with MWA for a 62-year-old man with right chest wall metastatic tumor. (**a**) Conventional ultrasound scan shows a hypoechoic lesion (*arrow*) with the size of 2.3 × 1.6 cm. (**b**) Pretreatment MRI scan shows the chest wall lesion still alive after MWA (the *red arrow* shows necrosis zone and the *green arrow* shows residual zone). (**c**) Conventional ultrasound shows one puncture needle for seed implantation is placed in the tumor. (**d**) CT scan shows the treated lesion is not clear and the neat rows of hyperechoic seeds (*arrow*)

defecation condition should be observed after the ablation; anhydrous alcohol injection could be used as a adjunctive therapy for these tumors.

Conclusions

Minimally invasive percutaneous ablation has been well recognized as an important tool in the treatment of SMTs. Efficacy may be optimized by complete necrosis of SMTs. Considering possible complications and available preventative techniques is important to minimize complications. As with other thermo-ablative techniques, controlled trials evaluating local control, symptom palliation, and survival are necessary. MWA for SMTs is still in its infancy, and further developments and clinical implementation will help improve the care of patients with SMTs.

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Microwave Ablation on Spleen

22

Chao Cheng, Jie Yu, and Ping Liang

Abstract

Microwave ablation has been accepted in the area of solid tumors, especially in liver cancer. With the development of microwave equipment, it is safer and more effective for spleen ablation. In this chapter, we review the equipment, indications, patient preparation, procedures, assistant techniques, clinical results, and complications of microwave ablation on the spleen, in comparison to other thermal ablations such as radiofrequency ablation and high-intensity focused ultrasound ablation.

Keywords

Microwave ablation • Hypersplenism • Spleen tumor • Spleen trauma

Abbreviations and Acronyms

ALB	Serum albumin
CEUS	Contrast-enhanced ultrasonography
CT	Computed tomography
HIFU	High-intensity focused ultrasound ablation
MHz	Megahertz
MWA	Microwave ablation
PLT	Platelets
RBC	Red blood cell
RFA	Radiofrequency ablation
STP	Serum total protein
WBC	White blood cell

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According to the high prevalence of hepatic cirrhosis, secondary hypersplenism is quite common worldwide, which can cause thrombocytopenia and a severe coagulation disorder and makes it difficult to stanch upper gastrointestinal hemorrhage. Splenic tumors, as another splenic disease, whether benign or malignant, are relatively rare entities [1, 2]. Classic splenectomy is regarded as the first line of choice over the years [3]. However, the spleen is known as an important immune organ in defending against infection. High operative risk and serious complications secondary to classic splenectomy includes a 25 % incidence rate of portal vein thrombosis, high rate of bacterial infections, and overwhelming postsplenectomy sepsis [4–7]. Preservation of 25–50 % of the spleen ensures an adequate physiological function, especially its immune function [8, 9]. Preserving

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part of the spleen is taken into consideration in the situations of hypersplenism, splenic tumor, and trauma. A variety of minimally invasive treatments are in clinical investigation, such as transcatheter selective splenic arterial embolization [10], absolute alcohol or ethanolamine oleate intrasplenic ablation [11, 12], and thermal ablation including radiofrequency ablation [13], microwave ablation [14], and high-intensity focused ultrasound ablation [15].

22.1 Equipment

22.1.1 The Microwave System

Not the same as in liver tumors, the frequency of 915 MHz is more commonly adopted for spleen MWA, as it covers larger ablation zone and has a higher thermal efficiency [16–18], in the in vivo porcine spleen model [19] and in a canine splenic artery hemorrhage model [16]. The generator is capable of producing 1–100 W of power at 915 MHz. The needle antenna has a diameter of 1.9 mm and a tip length of 22 mm. If the maximum diameter of the splenic tumor is <5 cm, it is better to use a frequency of 2,450 MHz according to our experience.

During ablation, a thermocouple system attached to MW equipment can be used to measure the temperature in real time.

22.2 Indications

22.2.1 Secondary Splenomegaly and Hypersplenism

The presence of secondary hypersplenism is caused by liver cirrhosis in adults: platelet (PLT) counts between 15×10^9 cells/L and 100×10^9 cells/L (normal level, $100–300\times10^9$ cells/L) and white blood cell (WBC) counts between 1.5×10^9 cells/L and 10×10^9 cells/L (normal level, $4–10\times10^9$ cells/L); splenic volume less than 1,500 mL (patients with a splenic volume of <700 mL are suitable for percutaneous MW ablation, while the ones with a splenic volume >700 mL are suitable for laparoscopic MW ablation); no severe esophageal varices that are treated by endoscopic sclerotherapy and ligation; no portal vein or hepatic vein thrombosis; and a prothrombin time less than 22 s (normal time, 1,216 s) [14, 20].

22.2.2 Spleen Tumor

The application of the microwave ablation technique in splenic tumor treatment is limited. Only the team of Liang et al. [21] had reported such. According to the limited experience, patients with the following conditions can be taken into consideration: For splenic malignancy, imageological examination shows a single tumor of 3 cm or smaller, three or fewer multiple lesions with a maximum diameter of 2 cm or less, and no extensively extra-splenic metastases. For benign tumors, the maximum diameter can expand up to 5 cm. The general condition of the patient permits MW ablation [21].

22.2.3 Splenic Trauma

Microwave ablation in splenic trauma is seldom reported. Only Guoming Zhang et al. [16] performed a percutaneous microwave coagulation in a canine splenic artery hemorrhage model to prove that microwave coagulation therapy is efficient in splenic hemorrhage. Combined with the experience of radiofrequency ablation, these considerations should be followed: splenic injury clearly indicated by ultrasound or CT, no other organ involvement or severe systemic complications, anticoagulated blood present in the abdominal cavity, and manifestation of hemorrhagic shock remaining after sufficient rehydration [22]. The grade of splenic injuries is classified as 1–3 by Moore classification [23]. No lesions of major vessels or avulsion of the hilum is detected [24]. The absence of contraindications for laparotomy is necessary for patients who will undergo laparoscopic MWA.

22.3 Patient Preparation

Written informed consent should be obtained from each patient. Patients would be informed of the possibilities of conversion to open surgery and the postoperative complications [22]. Before MW ablation, laboratory examinations, imaging workups, and other preparations should be done. On laboratory examination, routine blood counts (PLT, WBC, and RBC counts), urine routine, liver function data (serum alanine aminotransferase, aspartate aminotransferase, albumin, total protein, total bilirubin, and direct bilirubin levels), renal function data (serum creatinine and serum urea nitrogen levels), serum amylase levels, and serum lipase levels should be obtained. All patients are treated as inpatients after fasting for 12 h before MW ablation. For patients receiving splenic MW ablation via laparoscopy, nasogastric tubes and urethral catheters should be placed. For secondary splenomegaly and hypersplenism, the splenic volume of each patient is calculated on 3D plain CT before MV ablation. Patients with a splenic volume of <700 mL are suitable for percutaneous MW ablation, while the ones with a splenic volume between 700 and 1,500 mL are suitable for laparoscopic MW ablation. The reason is that laparoscopic procedure can provide more room for applicators, direct view on hemorrhage, and protection against injury of surrounding organs [14]. For splenic tumors, computed tomography, ultrasound or magnetic resonance imaging, and contrast-enhanced ultrasound, if necessary, should be performed to locate the tumor. For splenic tumor, definite pathological diagnosis must be obtained before MWA. Tumor markers will be helpful in differential diagnosis and to assess the therapeutic efficacy. For trauma, CT, MRI, and CEUS can all help to clearly indicate splenic injury.

22.4 MWA Procedures

A detailed protocol that contains the operation method, appropriate approach, placement of the applicators, power output, and ablation time should be planned at first. For percutaneous splenic MWA, patients are placed in the right supine oblique position in the interventional ultrasound suite. The procedure is performed under intravenous sedation combined with propofol and ketamine via the peripheral vein, combined with local anesthesia with 1 % lidocaine. As the puncture site must be kept away from the diaphragm, lung, and large vessels at the hilum of the spleen, the lower part of the spleen is considered as the preferred path [14, 20, 25]. The upper polar of the spleen can be taken into consideration once the treatment efficacy is not satisfying after the ablation of the lower part of the spleen in hypersplenism. The spleen is accessed via the left subcostal approach under US guidance. 2D ultrasound and color Doppler are performed again to guarantee the safety of the path, which cannot traverse major hilar vasculature or pleura.

For patients undergoing MW ablation via laparoscopy, general anesthesia with endotracheal intubation and mechanical ventilation is administered. For hypersplenism, two applicators are placed in the lower part of the spleen at a distance of 2.5–3.5 cm [14]. The set of energy output varies from literatures. The reported set of power output is normally 70–90 W for 10–40 min due to different volumes of the spleen (Table 22.1). The bleeding during puncture can be stopped by emitting MW for 1–3 min [19]. After the emission, pull back the applicator for about 2 cm. Keep emitting until the distance between the ablation zone and the splenic surface is less than 2 cm. Thus, the overlapping areas of applicators end up with one insertion [14]. According to some doctors' experience, they ablate the margin of the spleen first, with an output of 70–80 W for 2 min. Once there is no hemorrhage, the needle can be inserted into the deeper splenic parenchyma and ablate for 5 min. Then retreat the needle to the edge. Repeat the second step for about five times to achieve a fan-shaped ablation area. For spleen tumor, the antenna is percutaneously inserted into the tumor and placed at the designated place under US guidance. According to Liang's experience, for tumors less than 1.5 cm, one antenna is inserted; for tumors measuring 1.5 cm or greater,

Table 22.1 Clinical studies reporting outcomes of microwave ablation for hypersplenism

Author	No of pts	Power (W)	Ablation time (mins)	Spleen ablation ratio (%)	WBC level	PLT level	Fever (%)	Pain (%)	Hydrothorax (%)	Transient hemoglobinuria (%)	Delayed hemorrhage (%)	Ecchymosis (%)
Liang P et al. [14]	20	70–90	10	30.9 ± 13 (16–58)	Peaked at 7 days then decreased	Peaked at 14 days then decreased	80	70	20	70	No	No
Jiang YZ et al. [32]	5	70–120	27.2 (10–44)	7.04–28.60	Peaked at 2–3 days then decreased	Peaked at 6 months then remained at normal level	No	No	No	No	20	No
Han JB et al. [33]	13	60	30	34.20 ± 1.72	Higher significantly	Increased significantly	No	No	No	No	No	No
Yi YX et al. [34]	16	60	30	35.73 ± 4.04	Higher significantly	Increased significantly	No	No	No	No	20	13

STP serum total protein, *ALB* albumin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *NA* not available

two antennae are inserted with an inter-antenna distance of no more than 1.8 cm. A 20-gauge thermocouple, with the system attached to microwave, is inserted about 0.5–1.0 cm away from the tumor for real-time temperature monitoring during MW ablation. The routine power output used is 50–60 W for 600–1,000 s. If the heat-generated hyperechoic water vapor does not completely encompass the entire tumor and if the measured temperature does not reach 60 °C or remain above 54 °C for at least 3 min, prolonged MW emission is applied until the desired temperature is reached [21]. For trauma, only an experiment on dogs was reported by Ping Liang et al. [16]. They performed the CEUS-guided percutaneous MWA procedures as follows: The animals received 1.2–1.5 mL of contrast agent, followed by 5 mL of normal saline bolus via femoral vein injection. Then, percutaneous CEUS-guided microwave coagulation therapy was initiated by inserting the electrode along the puncture guidewire to reach the trauma area. Microwave generator power was 80 W. At the end of treatment, the cautery needle tract and the generator were removed. According to our experience with RFA [22], we suggest the procedure as follows: For ruptures with a depth <5 mm and a clear margin, place the electrode 5 mm beneath the rupture surface and stop the power once bubbles achieved; repeat it till the hemorrhage ceased. For ruptures with a depth >5 mm and irregular margins, remove the damaged tissue before inserting the needle 5–10 mm into the spleen. The power output is 40 W. Repeat the procedure until the hemorrhage ceased.

22.5 Assistant Techniques

Thermal monitor instrument can be used for avoiding overheating and assessing accurate treatment efficacy. Put one to two thermocouples about 0.5 cm away from the target and the hilar vessels. It can reduce the occurrence rate of residues and injury of major vessels.

For tumors located in the upper pole of the spleen or hypersplenism which have no approach toward the lower pole of the spleen, establishment of the left artificial pleural effusion before ablation can help keep the approach safe by exposing the lesion clearly. Besides, it can effectively reduce the pulmonary complications and referred pain. The detailed procedure is just the same as artificial pleural effusion combined with MWA of liver tumors. The volume of the normal saline is usually about 500–1,000 mL.

22.6 Therapeutic Efficacy Assessment

For secondary splenomegaly and hypersplenism, the coagulation size and volume of one ablation can be estimated according to the results of a previous in vivo study [19], while the exact ablated splenic volume can be calculated using 3D contrast-enhanced CT scans with a section thickness of 1.25 mm 7 days after ablation. For microwave ablation of spleen tumors, all patients undergo CEUS examination 1 day after MVA to assess the efficacy. Once residues are found, further course is planned. Patients without residues enter the follow-up protocol which consisted of contrast-enhanced CT/MRI and/or CEUS at 1, 3, and 6 months after MW ablation and every 6 months thereafter. For thermal ablation for trauma, blood routine and CT are helpful to assess the status of hemorrhage.

22.7 Clinical Efficacy of MWA

22.7.1 Secondary Splenomegaly and Hypersplenism

Results of selected clinical studies are summarized in Table 22.1. Most of the reports showed a result that the more volumes were ablated (over 40–50 %), the better the clinical outcomes were. WBC level, PLT level, and liver functions reached a peak level at a short time after treatment, but decreased overtime. According to Duan et al. [26], partial MW ablation of the spleen improved levels of peripheral lymphocyte subsets. Percentages of $CD3^+$ and $CD4^+$ cells increased rapidly one month after MW

ablation therapy. According to the latest study data in China, they evaluated the effects of MWA in 38 patients (M:F = 25:13; age range, 45–65 years) with hepatic cirrhosis caused by hepatitis B and C (30:8). At a follow-up period that ranged from 3 to 24 months, the ratio of ablation volume ranged from 20 to 40 %. Blood cells (mainly PLT and WBC) started to increase at the 1st week, and 45 % (17/38) of patients peaked at 3 months, 32 % (12/38) at 6 months, 13 % (5/38) at 12 months, and 10 % (4/38) at 24 months. The clinical symptoms of fatigue, bleeding gums, and skin ecchymosis definitely improved.

22.7.2 Spleen Tumor

According to our latest study data, we evaluated the feasibility and effects of MWA in seven patients (M:F = 2:5; age range, 32–56 years) with two benign splenic nodules (diameter range, 5.9–6.3 cm) and six malignant nodules (diameter range, 1.3–2.9 cm). A single antenna was used in two patients and two antennae were used in five patients. The power outputs were 50–60 W for 420–1,030 s. For some patients with the nodules located in the upper pole of the spleen (3/4), establishment of the left artificial pleural effusion was taken. All the eight nodules showed no progress for 4–48 months (Fig. 22.1). Almost half of the patients (4/7; 2 are benign and 2 are malignant) were still alive at the end of follow-up. The other three malignant patients died from primary tumor progression.

22.8 Complication

Possible complications including intraperitoneal hemorrhage, pleural effusion, fever, pain, and skin burn should be closely observed. For trauma, only one case of massive postoperative bleeding 24 h after laparoscopic RFA was reported, which finally underwent laparotomy for a total splenectomy. For splenic metastasis, there exists the possibility of residuum, peritoneal metastasis, and abdominal incision.

22.9 Other Local Thermal Ablations on the Spleen

22.9.1 Radiofrequency Ablation (RFA)

RFA is more widely used in the spleen worldwide according to the literature published. The indications of RFA for spleen ablation are quite similar with MWA [25], and the application is explored. It is mainly used in hypersplenism, spleen tumor, and spleen trauma at present. Hashemieh M et al. [27] studied the use of RFA on the spleen due to thalassemia, with a result that RFA reduced thrombocytopenia in thalassemic patients with splenomegaly but did not change the hemoglobin levels or transfusion intervals. For hypersplenism, the splenic RF ablation shows good short-term effects. But in the long term, outcomes depended on the ablation volume. Feng et al. [20] demonstrated that hypersplenism syndromes in patients with more than 50 % of the spleen ablated were well controlled. The results were even more prominent when the ablation volume was greater than 70 %. Based on 5 years of follow-up data, after weighing risks and benefits, they concluded that the ideal ablation volume should be between 50 and 70 %. For splenic tumors, Marangio et al. [28] performed RFA on colorectal splenic metastasis. The pathological analyses showed a complete necrosis in the core of the ablated tumor lesion and vital tumor in the peripheral zone. But the result was still encouraging. For splenic injury, Stella M et al. [24] reported the first case of conservative management of a spleen trauma using a cool-tip needle electrode with radiofrequency at 2005. Then Dai et al. [29] reported a case of RF-assisted hemostasis from iatrogenic splenic injury at 2010. A tear at the splenic tip was made during an abdominal operation on the colon. After a failure of using hemostatic agents, 4 min of RF ablation was performed. CT scan of the abdomen showed a minimal degree of splenic infarction. Julien Jarry [30] showed three cases on radiofrequency fulguration of the spleen under laparoscopy to stop iatrogenic hemorrhage. Complete hemostasis was achieved in a median

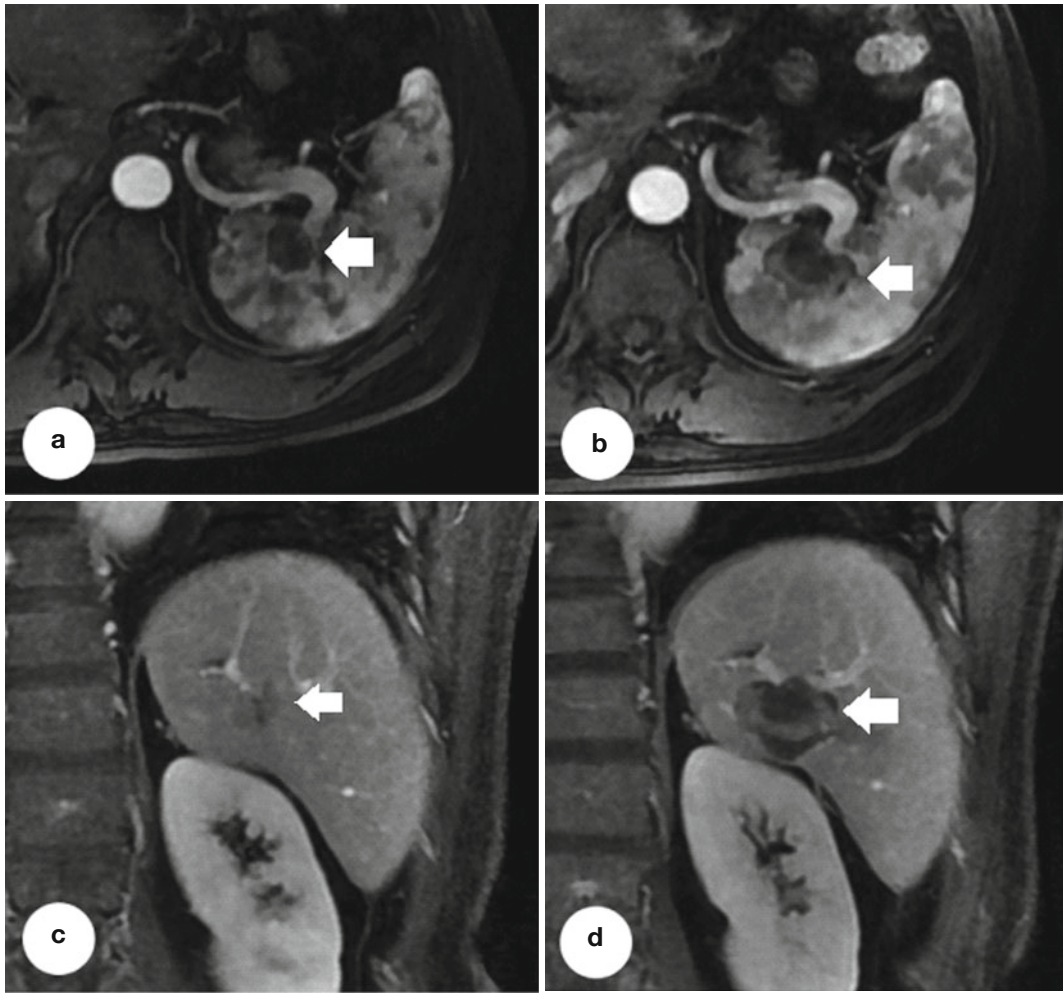

Fig. 22.1 Transverse images and coronal images in a 58-year-old man with a single-focus (2.1 × 1.9 cm) colon cancer metastasis. Transverse contrast-enhanced magnetic resonance imaging (*MRI*) scan (**a**) and coronal contrast-enhanced MRI scan (**c**) before ablation show a well-demarcated tumor (*arrow*) adjacent to the splenic hilum with mild hyperintensity at arterial phase. Transverse contrast-enhanced MRI scan (**b**) and coronal contrast-enhanced MRI scan (**d**) obtained 12 months after ablation show a hypointense zone (*arrow*) corresponding to treated region

time of 10 min without additional treatments. The blood loss was minimal with no blood transfusion, and splenic hemorrhage is not recurrent during the 20-month follow-up period.

22.9.2 High-Intensity Focused Ultrasound Ablation (HIFU)

The application of HIFU in the spleen is seldom reported. Only Zhu et al. [31] reported nine cases regarding the use of HIFU on hypersplenism complicated by hepatocellular carcinoma. The main parameters they used for splenic ablation were configured as follows: therapy frequency of 0.85 MHz, focal length of 140 mm, therapy power of 300–400 W, and average ablation time of 1,806 s (range, 601–4,328 s). The mean ratio of ablation volume was 28.76 % ± 6.1 %. Results of laboratory examination include the WBC, PLT, and liver functions that were substantially improved during the 4-year follow-up period. Symptoms such as epistaxis and gingival bleeding were ameliorated or even eliminated as well.

The main complications were dermal ecchymosis of the treated area, hydrothorax, pleural and peritoneal effusions, low fever, and abnormal pain, which disappeared within 2 weeks after expectant treatment. No death or other severe complications like gastrointestinal perforation, peritonitis, splenic rupture, and splenic abscesses occurred.

Although HIFU cost less, the long ablation time and a stereotypic posture increase the suffering of the patients.

Conclusions

Microwave ablation is safe and efficient in the treatment of splenic diseases. Even though there are no reports on the efficacy comparison of MWA, RFA, and HIFU for the spleen, due to the higher thermal efficacy of MWA, there is more potential advantage of microwave on the splenic disease with rich blood supply. The application of this new ablation technique in the spleen is worth expanding and discussing.

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Microwave Ablation for Adenomyosis

23

Yu Yang, Xia Ma, Jing Zhang, and Hong-yu Zhou

Abstract

Several minimally invasive ways, including uterine artery embolization, high-intensity focused ultrasound, radiofrequency ablation, microwave ablation, and so on, have been used to reduce the patients' symptoms of adenomyosis in the recent years. To evaluate the safety and efficacy of ultrasound-guided percutaneous microwave ablation in treating symptomatic adenomyosis, the technique's indications, contraindications, instruments, the whole procedure of ultrasound-guided microwave ablation, and the efficacy after this therapy will be shown in this paper. At the end of the paper, other techniques about the treatment of symptomatic adenomyosis are also reviewed.

Keywords

Adenomyosis • Microwave • Ultrasound • Conservative treatments

Abbreviations

ce-MRI	Contrast-enhanced magnetic resonance imaging
CEUS	Contrast-enhanced ultrasound
HIFU	High-intensity focused ultrasound ablation
MWA	Microwave ablation
UAE	Uterine artery embolization

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23.1 Introduction

Adenomyosis is a common benign disease; the prevalence in hysterectomy specimens can range from 10 to 18 % [1–3]. The disease was defined by Bird et al. in the 1970s as "benign invasion of endometrium in the myometrium, producing a diffusely enlarged uterus, which microscopically exhibits ectopic, non-neoplastic, endometrial glands and stroma surround by hypertrophic and hyperplastic myometrium"[4]. There are several hypotheses about etiologies in adenomyosis, and the most popular one is the invagination of endometrium into the myometrium [5]. Menorrhagia and dysmenorrhea as the common symptoms always need clinical intervention, and the severity

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of symptoms correlates roughly with the extent of disease [6].

Several treatments are commonly used to relieve patients' suffering. The first line is medicine treatments, such as oral contraception, progestins, levonorgestrel intrauterine device, danazol, gonadotropin-releasing hormone agonists, aromatase inhibitors, all of which are nonsurgical alternatives. They can temporarily induce regression of adenomyosis [7, 8] and should be offered before more invasive procedures [9]. Hysterectomy is the standard and the most effective treatment for adenomyosis. Although bladder injury [10], ureteral injury [11], postsurgical adhesions, and pelvic floor dysfunction can occur after operation, in general, hysterectomy has a high satisfaction and quality rate [9]. But the inevitable damage in women's fertility is obvious, so it is not suitable for the patients who have further desire of fertility. Minimally invasive treatments of adenomyosis have developed in parallel with improvements of imaging technology. The current approach to conservative surgery relies on accurate localization of focal disease or the more commonly seen diffuse adenomyosis. Treating adenomyosis in minimally invasive ways includes uterine arterial embolization (UAE), high-intensity focused ultrasound ablation (HIFU), radiofrequency ablation (RFA), microwave ablation (MWA), and laparoscopic myomectomy, all of which belong to the cytoreductive surgery.

MWA has been used in the treatment of symptomatic fibroids and adenomyosis [12–14], and the effectiveness is satisfactory. Thus we will introduce this technique from several aspects including indications, contraindications, instruments, the whole procedure of the treatment, as well as the effectiveness.

23.2 Indications

The indications of MWA for adenomyosis are as follows: (1) younger than 45 years and no clinical signs of menopausal transition, (2) with adenomyosis-related symptoms (e.g., menorrhagia, dysmenorrhea, bulk pressure, or urinary frequency) longer than 1 year, and (3) symptoms that cannot be relieved by noninvasive ways (e.g., drugs (Mirena)).

23.3 Absolute Contraindications

The following are contraindications to this therapy: (1) menstrual period, pregnancy, or lactation; (2) with contraindications in + a history of malignant tumor; (3) pelvic infection; (4) intravenous anesthesia and invasive therapy; and (5) diagnosis of cervical intraepithelial neoplasia level 3.

23.4 Relative Contraindications

Patients in the following situations are not advised to relieve adenomyosis-related symptoms by MWA: (1) had clinical signs of the menopausal transition, (2) underwent the symptoms less than 1 year, and (3) didn't complete childbearing but have further desire of fertility.

23.5 Instruments

The MW tumor coagulator is the same as that used in the liver. Contrast-enhanced ultrasound (CEUS) is a real-time evaluation method that can be performed after percutaneous MWA during the ablation procedure. The microbubble contrast agent such as SonoVue (Bracco, Milan, Italy) should be infused into the median cubital vein in a rapid bolus in the dose of 2.0–2.4 ml, followed immediately by 5 ml of normal saline.

23.6 Pre-ablation Preparation

1. All patients must be notified of the potential risks and benefits of MWA and possible alternative treatments.
2. Before ablation all patients should finish the essential examinations, including routine blood, urine, and stool tests; electrocardiogram; and chest X-rays. Serum gonadal hormone, cancer antigen 125 (CA125), ultrasonography, CEUS (Fig. 23.1c), contrast-enhanced magnetic resonance imaging

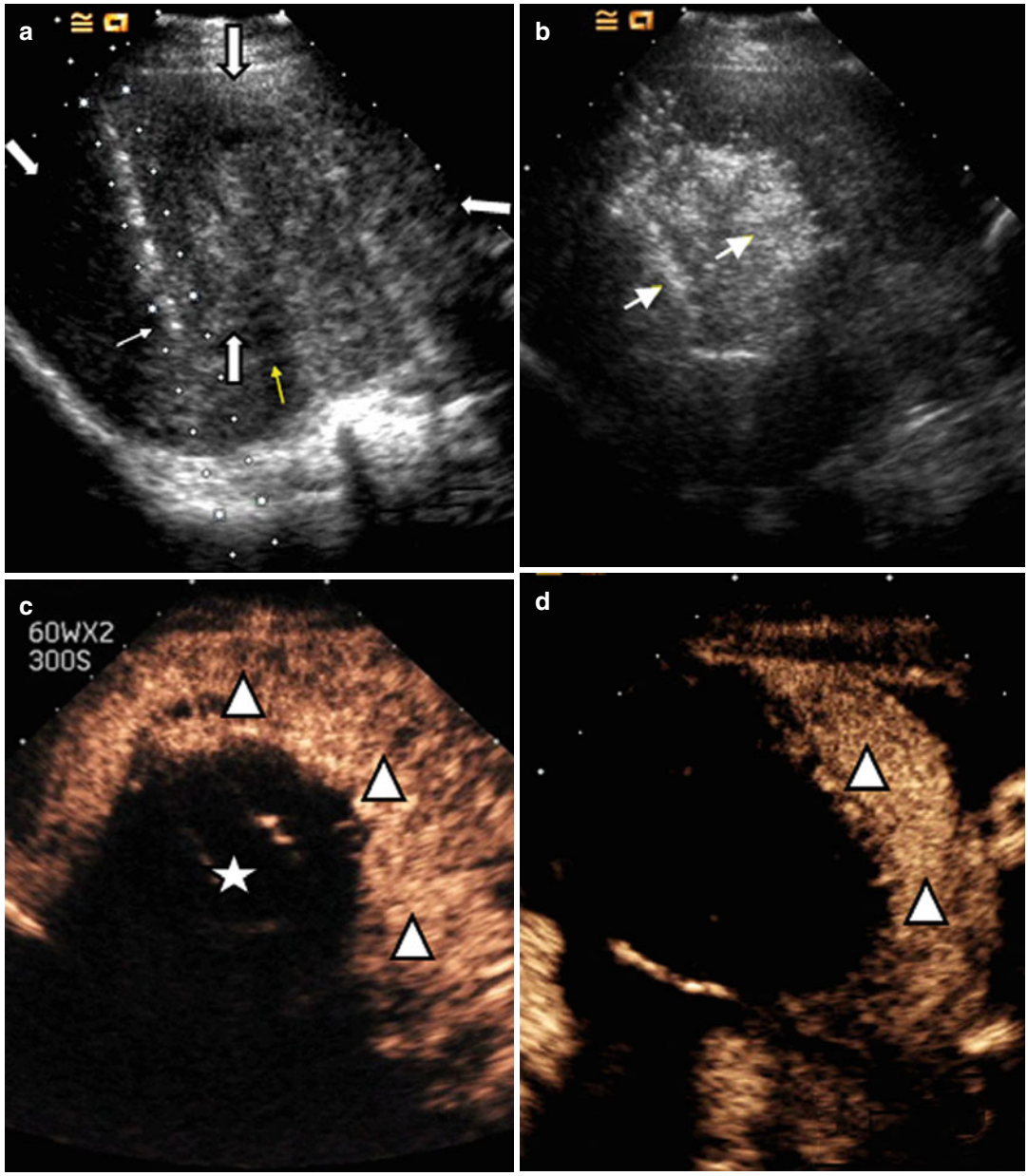

Fig. 23.1 A 39-year-old woman who suffered from adenomyosis for about 5 years, with visual analogue scale (*VAS*) of 10, hemoglobin 106 g/l. Her uterine size was 11.5 cm × 9.0 cm × 11.3 cm, and the lesions are mainly located in the anterior wall. For her desire to reserve her uterus, she accepted microwave ablation (*MWA*). (**a**) Microwave antenna inserted into endometrial-myometrial area and the needle tip (*small arrow*) close to the far end of lesions (area between *large arrows*; the *yellow arrow* indicates endometrium). (**b**) Two microwave antennas (*arrows*) worked and the surrounding area turned to hyperechogenic (**c**) After 60 W × 300 s, by two antennas, the non-perfused area (*white star*) in contrast-enhanced ultrasound (*CEUS*) was insufficient, and the *triangle* means the area that needs supplementary treatment. (**d**) After supplementary treatment, CEUS was performed again. The non-perfused area was 62.22 % of the lesion, and the *triangles* indicate the residual disease. (**e**) Magnetic resonance imaging (*MRI*) (*T2WI*) before MWA, which shows the enlargement of the junctional zone (greater than 12 mm) especially in anterior wall with ill-defined margins. And the area between the *white long arrows* is the target area that needs to be ablated. (**f**) ce-MRI, 3 days after MWA; the non-perfused area size was sufficient. (**g**) Three months after MWA, CEUS shows the non-perfused area (between *white arrows*). The hyperechoes (*yellow arrows*) in the grayscale sonography are antenna passages. Her menstrual VAS declined to 0, and hemoglobin reached 134 g/l

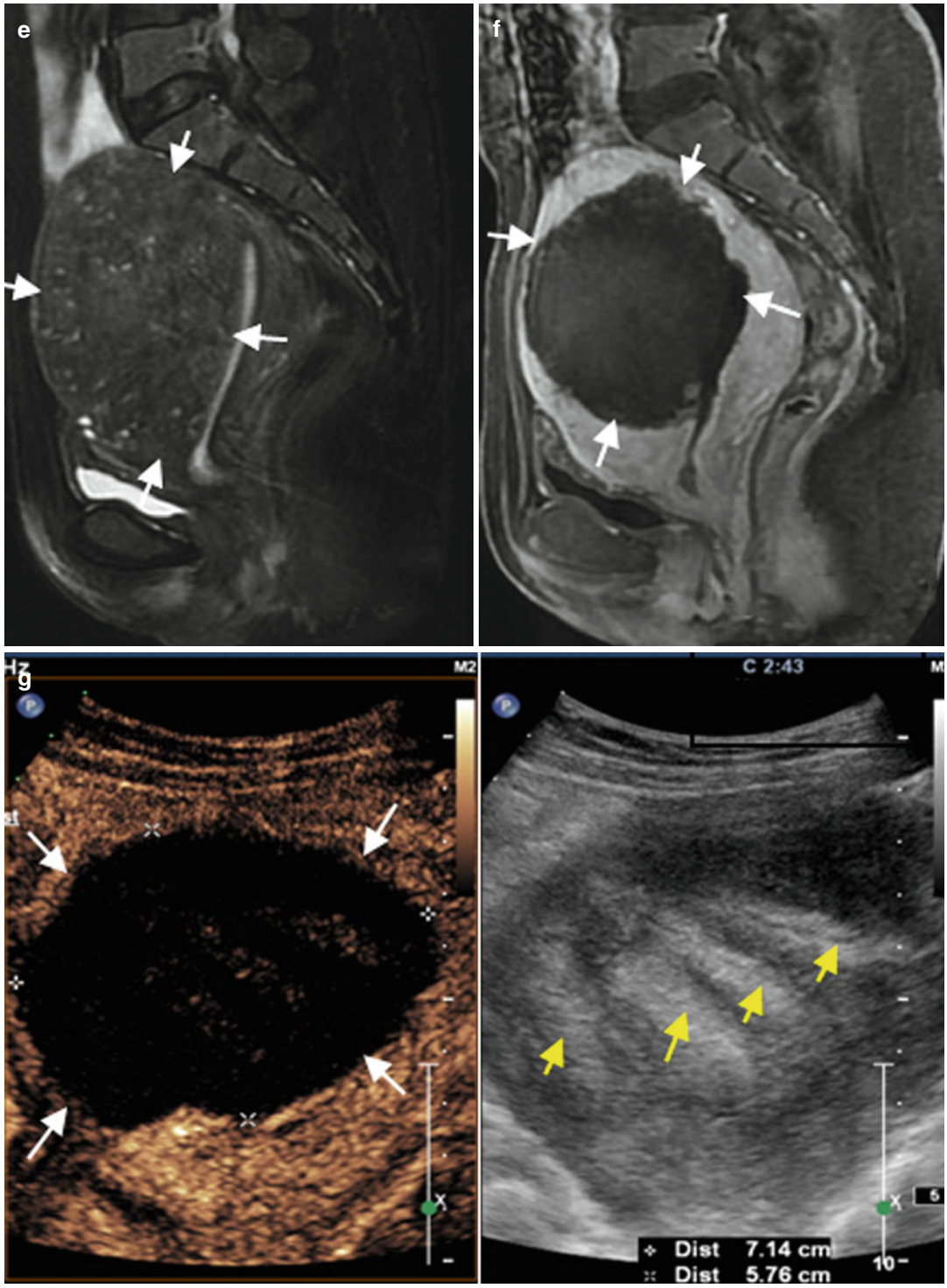

Fig. 23.1 (continued)

(ce-MRI) (Fig. 23.1e), as well as the questionnaire Uterine Fibroid Symptom and Quality of Life [15] and the visual analogue scale(VAS) [16] are used to assess the treatment effectiveness. Uterine volume is calculated according to ultrasonography (volume=4/3*π*r3, where r is the mean radius).

3. To avoid damage of the intestinal tract, patients should fast at least 12 h before ablation. Besides, people who have thick abdominal wall always need a bowel preparation. The bladder is another easily injured organ, especially when it is evacuated. Indwelling urinary catheter and occlusion for more than half an hour can solve this matter properly. Because the fully filled bladder can be recognized readily under ultrasound, it can avoid being bladder punctured directly by MWA antenna. The second function of the urinary catheter is to adjust the position of the uterus slightly and make the antenna reach the optimal point. What's more, the operator needs to observe the color of urine during the therapy.
4. To avoid vaginal mucosa scalding by thermal gas from the uterine cavity during ablation (once occurred in fibroid ablation), fold fine mesh gauze into ball and infiltrate with cold normal saline, and put two or three of these balls into the patient's vagina. Besides, these gauze balls also can adjust the uterus' position to some extent.
5. For the patients with no clear endometrium under US, putting urinary catheter into the uterine cavity is a commonly used way to make the uterine cavity easy to distinguish. Thus, when MWA is performed, the operator can keep the hyperecho away from the catheter and protect the endometrium easily.

23.7 Therapy Procedures

US-guided MWA should not be performed during the menstrual or ovulatory period.

Patients adopt a supine position. Ablation is performed under intravenous conscious sedation using sodium propofol. Although intestinal tract preparation is done before therapy, a percutaneous approach could have the risk of inadvertently puncturing the bowel in some patients. Pushing the abdominal wall little by little, using a pressed probe before percutaneous puncture, keeps the intestinal tract away from the antenna. Of note is that the shapes of coagulation necrosis are spheroid but not a rigorous sphere. Thus, the needle tip is not inserted into the center of the endometrial-myometrial area, but close to the far end (Fig. 23.1a). Although the border may be poorly defined, the presence of subendometrial linear striations, subendometrial echogenic nodules, asymmetric myometrial thickness, and inhomogeneous hypoechoic areas can be used to identify the margin of nidus in the myometrium [17]. Besides, MRI can also help to recognize the lesion. When the endometrial-myometrial area is less than 3 cm, one antenna is enough, while if it is larger than 3 cm, two antennas are suitable. 50–60 W is the commonly used power in the treatment. The whole procedure is under ultrasonogram monitoring [18]. The antenna could be repositioned until the hyperechogenic signal reaches 3–5 mm from the serosa (Fig. 23.1b) and CEUS shows the non-perfused area reached at least 50 % of the endometrial-myometrial area (Fig. 23.1d). However, once the hyperechogenic signal is found in the uterine cavity, the ablation should be stopped immediately to avoid endometrium impairment.

All vital signs need to be monitored during the whole procedure. The color of urine and gauze balls also should be observed to monitor the bleeding timely.

23.8 Post-ablation Observation

Patients' temperature, hemorrhage, abdominal pain, and routine blood, urine, and stool tests should be paid close attention to after ablation. From these results, the doctor should judge whether infection and surrounding organ injury have occurred.

Post-ablation ce-MRI is performed within 3 days to evaluate both the possible injury to the surrounding organs accurately and the range of the non-perfused area [19] (Fig. 23.1f). Figures 23.1, 23.2, and 23.3 show the changes of different types of adenomyosis after MWA.

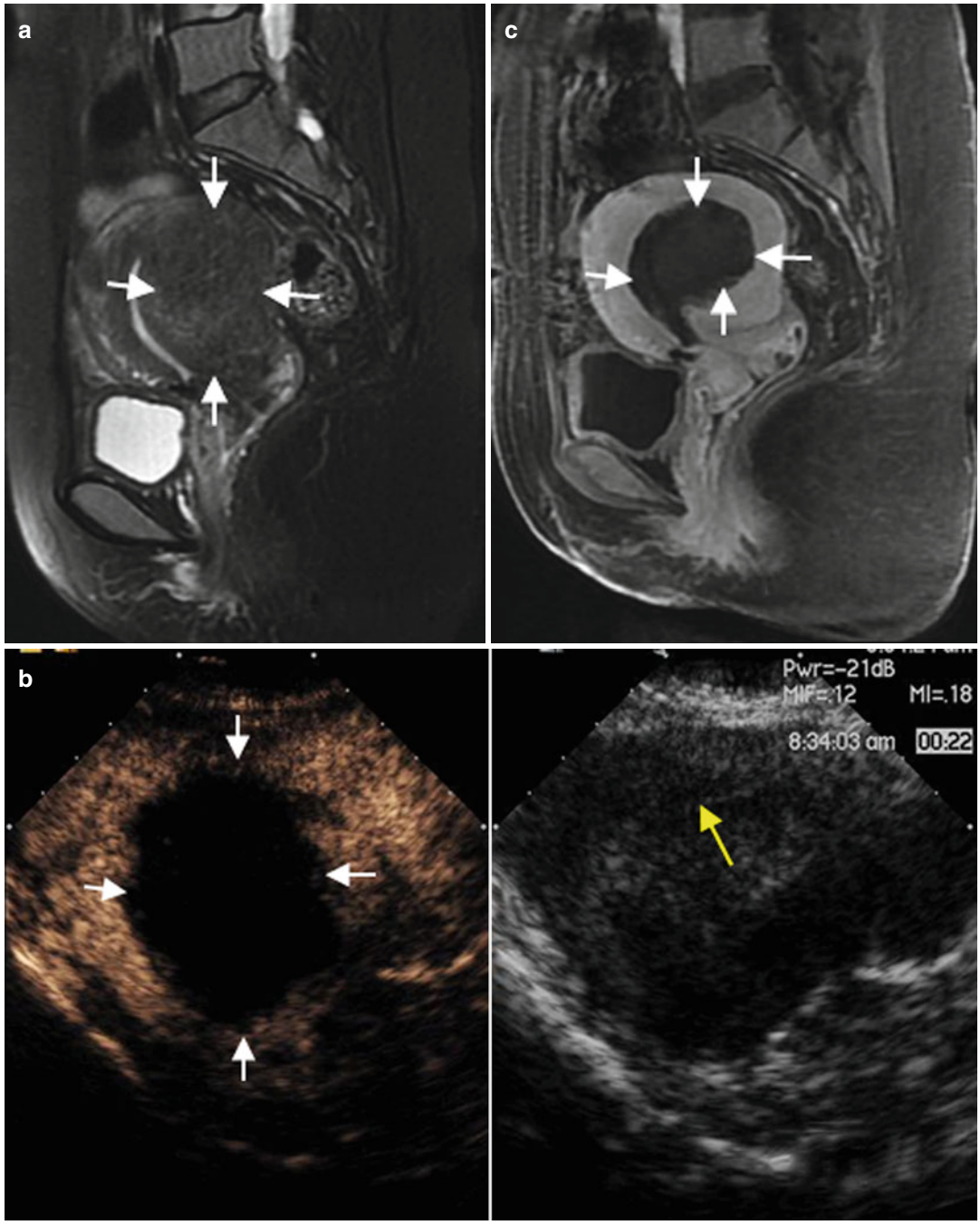

Fig. 23.2 A 35-year-old woman who suffered from adenomyosis with severe dysmenorrhea (VAS 10), hemoglobin 82 g/l. Her uterine size was 8.0 cm×7.3 cm×8.2 cm, and the lesions are mainly located in the posterior wall. (**a**) MRI (T2WI) before MWA, enlargement of the junctional zone especially in the posterior wall, the area between the *white arrows* is the target area that needs to be ablated. (**b**) After ablation CEUS was performed and the area between the *white arrows* shows the non-perfused lesions. The *yellow arrow* indicates endometrium. (**c**) ce-MRI, 3 days after MWA; the area between the *white arrows* shows the lesions in the posterior wall turned to non-perfused

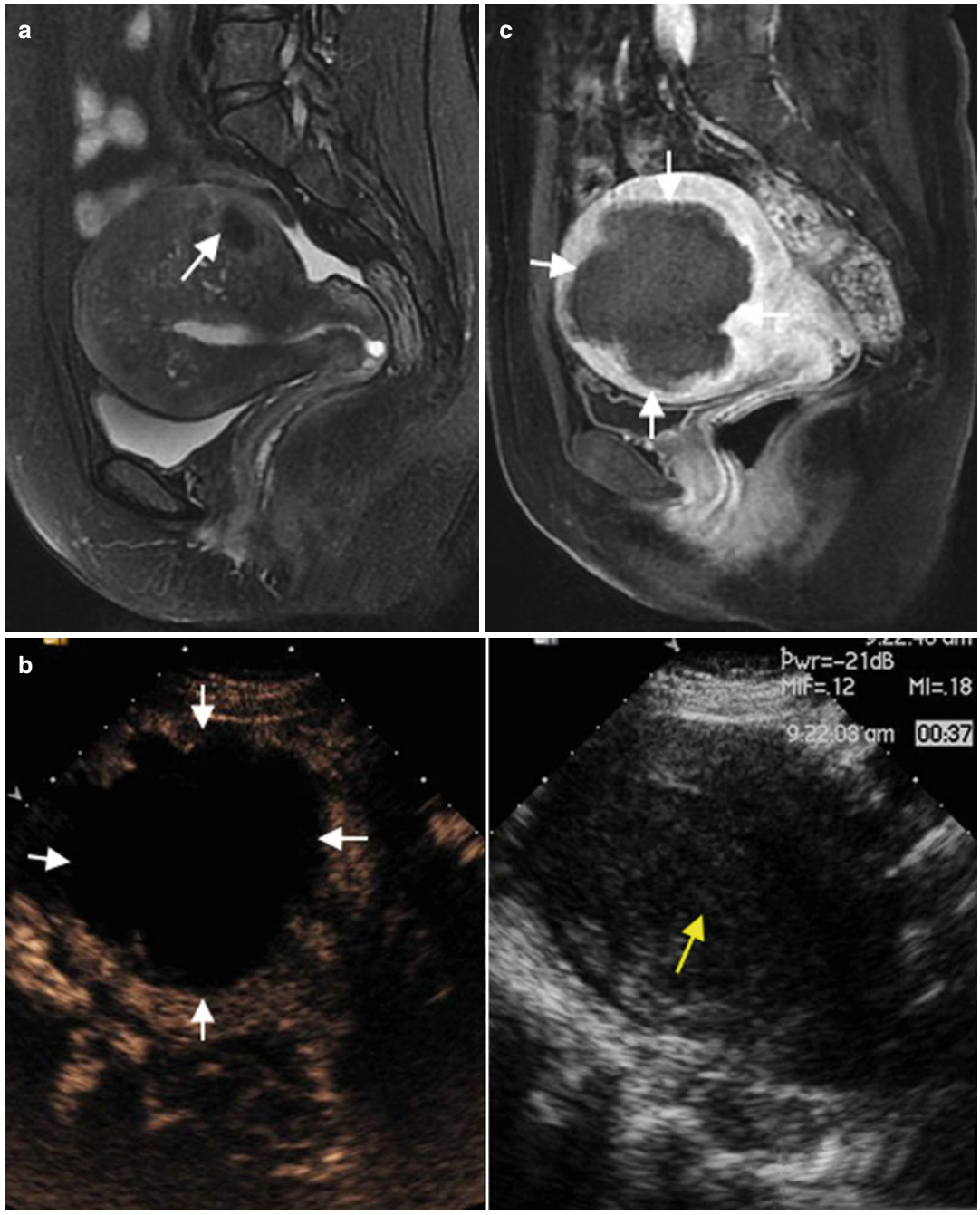

Fig. 23.3 A 43-year-old woman with diffused adenomyosis. Her uterine size was 10.5 cm × 8.7 cm × 7.9 cm. (**a**) MRI (T2WI) before MWA, enlargement of the diffused junctional zone in the whole uterus; in the posterior wall a small leiomyoma could be found (*white arrow*). (**b**) After ablation CEUS was performed and the area between the *white arrows* shows the non-perfused lesions. The *yellow arrow* indicates endometrium. (**c**) Three days after MWA, ce-MRI shows most of the area of the uterus turned to non-perfused (between *arrows*)

Table 23.1 Comparison of minimally invasive therapy of adenomyosis

Author	No. of patients	Therapy	Operating time (min)	Non-perfused volume ratio (%)	Improvement of symptoms (%)	
					Within 1 year	Over 1 year
Kim et al. [30]	43	UAE	N/A	72.1	93	N/A
Chen et al. [34]	168	UAE	N/A	N/A	N/A	82.4–83.9
Pelage et al. [35]	18	UAE	N/A	N/A	80–94	55
Zhang et al. [32]	202	HIFU	102	71.6±19.1	79.2	79.8
Fan et al. [20]	10	HIFU	120–240	62.5±21.6	N/A	N/A
Zhang et al. [12]	21	MWA	12	60–80	99.3	N/A
Yin et al. [33]	178	RFA	N/A	N/A	N/A	93.3–96.4

UAE arterial embolization, *HIFU* high-intensity focused ultrasound, *RFA* radiofrequency ablation, *N/A* not available

Uterine volumes, hemoglobin, CA125, the questionnaire Uterine Fibroid Symptom and Quality of Life, and dysmenorrhea levels could be used to evaluate effectiveness. Also, serum gonadal hormonal changes and possible complications related to MWA should also be recorded.

According to the reported references, our department has performed the largest number of cases in adenomyosis ablation, so the therapeutic efficacy and experiences of our department will be introduced to make a reference (Table 23.1).

Uterine enlargement, menorrhagia, and dysmenorrhea are the three most common clinical presentations of adenomyosis. Thus, the decrease of uterine volume and dysmenorrhea level as well as the increase of hemoglobin (hb) can conclude the treatment is effective directly. In our latest perspective study, we performed MWA in 145 patients with a median age of 39.38 years, average uterine size was 278.76 cm^3. Most of them show notable improvements after ablation. The size of uterus at 3, 6, 12, and 18 months' follow-up indicates a decrease of 46.75, 46.88, 44.53, and 32.84 %, respectively, when compared with baseline. And the 3 months' reduction rate reached 46.75 %, which is much more than UAE and HIFU in literatures [20–22]. These may be because MWA has a relative high thermal efficiency.

The average level of hb increased from 93.87 ± 16.51 g/l before ablation to 108.60 ± 17.75 g/l 3 months after ablation. And the VAS of dysmenorrhea also decreased significantly from an average of grade 8 to grade 3 [23].

The changes about cancer antigen 125 were also calculated; although the value had reduced significantly, it still reached as high as above 60 U/ml.

As most of symptoms of adenomyosis are similar to those of uterine leiomyoma, we used the questionnaire Uterine Fibroid Symptom and Quality of Life to evaluate the outcomes after MWA. There are two sections in the questionnaire, including the Symptoms Severity Score and Health-Related Quality of Life. And the latter part consists of eight subsections, including concern, activities, energy/mood, control, self-consciousness, and sexual function. All of the sections and subsections improved after MWA. At 3, 6, 12, and 18 months' follow-up, Symptoms Severity Score had improved by 40.15, 44.82, 28.66, and 41.21 %, and Health-Related Quality of Life by 35.63, 31.77, 28.91, and 40.22 %, respectively.

In order to evaluate ovarian function after MWA, patients younger than 45 years old [24] with no clinical signs of the menopausal transition and with no hormonal treatment for 3 months are selected for statistics. No significant differences were shown between the pre-ablation and follow-up in serum follicle-stimulating hormone and estradiol levels. Five patients gestated spontaneously after MWA and none of them has given a birth till now.

23.9 Side Effects and Complications

Mild lower abdominal pain and excessive fluid are two of the most common side effects. After ablation, patients would experience mild lower

abdominal pain and most of them would relieve spontaneously within 6 h. Excessive fluid discharging is complained by about two-thirds of the patients, and this phenomenon usually appears just after menstruation. Most of the patients' fluid disappeared within three menstrual cycles, but that of few patients would last for more than half a year. In our study the concentration of hemoglobin in one patient decreased from 83 to 41 g/l within 7 days after ablation. We considered the uterus of this patient huge (15.3 cm × 11.0 cm × 12.1 cm), and the abundant necrotic tissues interfered the contraction properly. She had recovered after hemostasis and uterotonics were given. Endometrium damages were found in one patients in our research. The patient (0.7 %) was diagnosed to have cervix adhesion at 2 months after microwave ablation. Transcervical resection of adhesion was performed and then the menstrual cycle became regular. The trauma to the basal layer of endometrium may cause the adhesion [25].

23.10 Multi-technology Comparison of Adenomyosis Treatment

Hysterectomy has long been the only definitive and permanent treatment for adenomyosis. Moreover, it is the only way in which a diagnosis of adenomyosis can be confirmed. In spite of the emerging use of less invasive treatment options, hysterectomy remains the approach of choice for women who do not desire future pregnancy [26]. However, hysterectomy is not readily performed in patients who wish to have their own children or refuse to lose their uteruses. These patients are more willing to accept minimally invasive treatment for adenomyosis. Options include endomyometrial ablation, UAE, HIFU, RFA, MWA, and so on.

Endometrial ablation by intrauterine access is only for submucous or superficial localized adenomyosis. Patients without or with minimal endometrial penetration of <2.5 mm only (superficial adenomyosis) have good responses after thermal ablation. However, the symptoms are usually persistent in patients with deep endometrial penetration of >2.5 mm (deep adenomyosis) [27]. It indicates that it is difficult for these minimally invasive therapies to treat deep adenomyosis due to technical limitations.

UAE has been reported to be effective and associated with high patient satisfaction rates. Popovic et al. [28] analyzed 15 available studies with 511 patients, and symptom improvements were reported by 387 patients (75.7 %) with the median follow-up of 26.9 months. It concluded that UAE as treatment for adenomyosis shows significant clinical and symptomatic improvements on short- and long-term bases. Possible side effects and drawbacks associated with UAE were also reported in some studies [29–31]. It includes post-embolization syndrome, pain, nausea, vaginal discharge, hematoma at the femoral puncture site, and premature ovarian failure and bladder and kidney damage. Although there exists a low stochastic radiation risk, exposure amounts of approximately 20 cGy of radiation are reported.

As a noninvasive approach, there is less published research on specific treatment of adenomyosis by HIFU, and all of them have satisfactory results. Zhang et al. [32] reported their study of using HIFU for the treatment of 120 focal adenomyosis patients and 82 diffuse adenomyosis patients; it contains the largest number of cases by far. In the research, the treatment was successfully completed without any complication, and the rates of overall relief of dysmenorrhea at 1, 3, 6, 12, and 18 months were 82.3, 84.9, 77.2, 79.2, and 79.8 %, respectively. The remaining researches about treatment of adenomyosis by HIFU have small sample with no long-term follow-up. So the therapeutic effectiveness, complications, and side effects still need a study for further examination.

Reports, mostly from China, confirmed that MWA and RFA are effective therapies for adenomyosis. We performed MWA in 145 patients, and all patients tolerated the therapy well; the patients presented significant clinical improvements during the follow-up period. At 3, 6, 12, and 18 months' follow-up, Symptoms

Severity Score had improved by 40.15, 44.82, 28.66, and 41.21 %, and Health-Related Quality of Life by 35.63, 31.77, 28.91, and 40.22 %, respectively. Studies of image-guided RFA for the treatment of adenomyosis are mainly reported in China; Yin et al. [33] reported a clinical trial of using RFA ablation for 122 patients with adenomyoma and 56 patients with adenomyosis, which contains the largest number of cases by far. The dysmenorrhea relief rate was 93.3 % in adenomyoma and 96.4 % in adenomyosis in an 18-month follow-up. It seems that MWA and RFA represent a new, safe, and effective method for the ablation of adenomyotic tissue. Although the results have been very encouraging, larger-scale, randomized trials producing high-quality data will be necessary to determine the true value of this treatment.

Conclusion

For decades hysterectomy was the main therapeutic option available to women with leiomyomas and adenomyosis, and this diagnosis was verifiable at tissue examination of the removed uterus. However, as imaging and minimally invasive diagnostic methods are pursued and developed, new and less aggressive therapeutic options are introduced including laparoscopic, UAE, HIFU, MWA, and RFA. They are all considered as ways to decrease uterine size and lead to a reduction of endometrium, which may contribute to the alleviation of symptoms. And our research demonstrates that MWA is a convenient, efficient, safe, and minimally invasive method in treating symptomatic adenomyosis.

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Microwave Ablation for Symptomatic Uterine Fibroids

24

Yanli Hao, Xia Ma, and Jing Zhang

Abstract

Minimally invasive uterine-conserving treatments have been proposed to relieve the symptom and improve quality of life of patients with fibroids. Therefore, it is crucial to use minimally or noninvasive therapy which is safe and could provide a good therapeutic result. The article will review the principles, procedure, outcomes, and complications of microwave ablation of uterine fibroids. The importance of the evaluation pre and post procedure of the patient will be emphasized. At the end of the paper, other techniques about the treatment of symptomatic uterine fibroids are also reviewed.

Keywords

Microwave ablation • Ultrasonography, interventional • Uterine leiomyoma

24.1 Introduction

Uterine fibroids are common benign tumors that arise from the smooth muscle cells of uterus. They are clinically apparent in about 25 % of women [1]. Traditionally, treatment for symptomatic uterine fibroids is hysterectomy which ensures permanent relief of fibroid-related symptoms, but it is associated with significant morbidity and guarantees infertility [2, 3]. Even women without a desire for future pregnancies might not wish to lose their uterus for various reasons. Many patients would like to look for modalities to permanent alleviation of symptoms rather than surgical radical hysterectomy for this benign disease [4].

Minimally invasive uterine-conserving treatments such as laparoscopic myomectomy (LM), uterine artery embolization (UAE), high-intensity focused ultrasound (HIFU), and radiofrequency ablation (RFA) have been proposed [5–8].

Cheng Xiangyun et al. firstly reported transvaginal microwave ablation (MWA) for pedunculated submucosal fibroids into the vagina in 1977 as a minimally invasive treatment [9]. Jing Zhang et al. firstly reported the ultrasound-guided percutaneous microwave ablation (PMWA) as a treatment for symptomatic uterine fibroid in 2007 [10]. Since then, PMWA as a minimally

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invasive management technique has been developed and improved in uterine fibroid therapy within the last several years [11]. Now in clinical, MWA as a treatment for fibroids has been used mainly by ultrasound-guided percutaneous. Hence this article will focus on PMWA. The potential advantages of MW technology include consistently higher intratumoral temperatures, larger tumor ablation volumes, and faster ablation times [12, 13]. This technology has been widely used to treat solid tumors in multiple organs other than the uterus, such as liver, thyroid, lung, kidney, adrenal gland, and so on [14–16].

Since uterine fibroids are benign, treatment is focused on symptom relief, fertility reserve, and quality of life improvement [17]. Therefore, it is crucial to use minimally or noninvasive therapy which is safe and could provide a good therapeutic result. The uterus is adjacent to the rectum and the bladder, so it is important to avoid thermal damage to the adjacent tissues during treatment procedures [18].

24.2 Indications

Patients who are diagnosed as with uterine fibroids by MRI, classified as type 0–6 according to international FIGO classification [19] (Table 24.1) and with the following symptoms:

1. Menorrhagia. Defined as prolonged or excessive bleeding at regular intervals, generally blood loss greater than 80 ml per cycle [20] and the blood routine test showing HGB <110 g/L
2. "Bulk" symptoms. Including excessive pelvic fullness often resulting in urinary tract symptoms (e.g., urinary urgency and frequency), gastrointestinal symptoms (e.g., constipation), and low back pain secondary to pressure
3. Patients younger than 45 years old and have the strong demand to reserve uterus
4. Reproductive dysfunction. Patients who are with infertility due to uterine fibroids and require to give birth after treatment
5. Patients, nulliparous, younger than 30 years old, with average diameter of fibroids >5 cm, though without obvious clinical symptoms and not suitable for treatment under laparoscope and hysteroscope

Table 24.1 The International Federation of Gynecology and Obstetrics (FIGO) classification

Type 0	Pedunculated intracavitary
Type 1	<50 % intramural
Type 2	≥50 % intramural
Type 3	Contacts endometrium, 100 % intramural
Type 4	Intramural
Type 5	Subserosal ≥50 % intramural
Type 6	Subserosal <50 % intramural
Type 7	Subserosal pedunculated
Type 8	Others (specify, e.g., cervical, parasitic)

Type 0 to type 2 fibroids are defined as submucosal fibroids, type 3 and type 4 as intramural, and type 5 to type 7 as subserosal

24.3 Contraindications

1. Menstrual period, gestation, or lactation period.
2. Fibroids enlarge quickly in short time and cannot rule out canceration.
3. Patients with uncontrolled pelvic inflammatory disease.
4. Severe coagulation disorders, platelet less than 50×10^9/L, prothrombin time >25 s, prothrombin activity <40 %.
5. Cancer cells found out by cervix TCT examination.
6. Fibroids classified as type 7 or type 8 according to FIGO classification.

24.4 Evaluation of the Patient for PMWA

24.4.1 Preablation Preparation

All patients considering PMWA require a thorough gynecologic evaluation. The treatment procedures, the expected curative effect, and the potential complications as well as the potential hazardous effect on fertility and adjacent organs are needed to explain in detail to the patients. The applications for treatment and written informed consent will be signed by all the patients. The patients need to take routine blood, urine, and stool examinations along with a test measuring bleeding and clotting time and electrocardiography (ECG).

Contrast-enhanced magnetic resonance imaging (ce-MRI), 2D gray-scale and color Doppler ultrasonography, and pre-contrast-enhanced ultrasonography (CEUS) are performed to evaluate the site, size, and blood supply of the fibroid.

24.4.2 Preclinical Assessment and Imaging

Diagnostic imaging studies are essential not only to confirm the suspected diagnosis of fibroids but also to rule out other malignancies. ce-MRI and transabdominal and endovaginal ultrasounds are extremely helpful in identifying and localizing uterine fibroids. A very small percentage of patients with uterine fibroids will develop leiomyosarcomas (0.2–0.3 %) [21]. If clinical concern for uterine sarcoma exists, image-guided biopsy is indicated.

Women with multiple large fibroids are often adequately evaluated. We devoted specifically to the risk of recurrence after PMWA because of the multiplet [22]; for the sake of safety, we just, in one procedure, ablate the dominant fibroids (the larger fibroids and the main reason of symptoms) and leave alone the smaller ones (<4 cm and not for the symptom reason). For the large type 2 to type 6 fibroids with the diameter >8 cm, we must inform patients the risk of re-ablation, because of the theoretical reason that large coagulation necrosis area may lead to persistent vaginal discharge or bleeding risk.

24.5 MW Ablation Therapy Procedures

24.5.1 Equipments and Procedures

24.5.1.1 MW Tumor Coagulator

A KY 2,000 MW tumor coagulator (Kangyou Medical instruments, Nanjing, China) with a frequency of 2,450 MHz can radiate continuous and pulse MW emission modes. The needle antenna is 15 G in diameter and 20 cm in length. The distance from the aperture of the MW emission to the needle tip is 5–11 mm; the emission aperture is 1 mm. For the antenna, an internal water cycle cooling system is used to lower the temperature of the needle shaft.

24.5.1.2 Sonography System

Using sonography system with a puncture-guided device and low MI contrast-enhanced function. The frequency of the probe is 2.5–4.5 MHz.

The ablation is performed under intravenous conscious sedation. A catheter is inserted and the bladder is filled for a half hour prior to the ablation in order to observe the location of the urinary bladder and its wall before the ablation. The patients receive a supine position. Under ultrasound guidance, if we cannot exclude the possibility of carcinomatous change of fibroid, a biopsy of the fibroid is performed via percutaneous puncture with an 18-gauge core needle for three slips of pathological diagnosis. Along the path of the biopsy, the MW antenna is then inserted into the center of the fibroid. For temperature measurement in real time during the ablation, one thermal couple is placed at a site of 0.5 cm inside the tumor adjacent to the urinary bladder if the fibroid is located at the anterior wall of the uterus, or adjacent to the rectum if the fibroid is located at the posterior wall. The output energy of the MW is set at 50 W. Based on experience from the previous study [23–26] of using MW ablation in vivo griskin, coagulation zones can be induced covering 4.3 cm × 3.1 cm × 2.8 cm (one antenna,50 w, 300 s), 5.1 cm × 3.6 cm × 4.1 cm (one antenna,50 w, 600 s), 5.7 cm × 5.6 cm × 4.8 cm (two antennae,50 w,300 s), and 6.7 cm × 5.9 cm × 5.3 cm (two antennae,50 w, 600 s). A single antenna is used for fibroids with mean diameters <5 cm and with lower perfusion; double antennas are used with an inter-antenna distance of 1 cm for fibroids with mean diameters ≥5 cm or those <5 cm in mean diameter but with rich blood supply. For larger fibroids with mean diameters ≥5 cm, the ablation is first performed using two antennas with 50 W for 300 s, then the antennas are withdrawn by 1 cm for a second ablation. For fibroids with non-spherical volumes, the margin of the thermal field is controlled at the shortest axis diameter, and the antenna is then withdrawn along the long axis or reinserted into the unablated zone for another ablation session. Computer-aided dynamic temperature

measurement of microwave-induced thermal distribution is used during multiple-electrode coagulation [27].

During the ablation, variations in the echo from the fibroid are monitored by real-time ultrasonography. The MW therapy is stopped when the hyperecho (caused by microbubbles generated during MW emission and representing roughly the ablation zone) covers the whole nodule [26] or when the measured temperature reaches 60 °C [27], because temperature correlates well with the extent of the coagulation necrosis to ensure that the tumor tissue is completely necrosed. The surveillance of the three-dimensional margin of the high echo was achieved with 2D imaging through continuous scanning in cross sections. When the MW therapy ended, the CEUS is performed. If the CEUS showed the non-perfusion volume ≥80 %, the treatment can be stopped.

24.6 Post-ablation Care

After the PMWA procedure, the patient is transferred to the recovery room and given immediate oxygen and electrocardiograms (ECG) for 30 min.

After recovery, the patient is transferred to the ward and kept for 12 h under close observation for side effects and complications. During the observation time, the patients have access to painkillers and antibiotics. The necessary conditions will be discussed in another section below.

24.7 Efficacy Assessment and Patient Follow-Up

The therapeutic efficacy of PMWA has been documented by:

1. Assessment of enhanced imaging
2. Volume reduction of the ablated fibroids
3. Dosage of HGB
4. Patients' reported symptom and quality of life (use UFS-QOL to assess the changes of patients' symptoms and quality of life [28])
5. Ovarian function (sex hormone and fertility)
6. Recurrence or reoperation
7. Adverse reactions and complications

The patients' menstrual information during the first few days after PMWA were recorded. Patients are requested to come back for a recheck at regular intervals thereafter (3, 6, and12 months and then 1 year). An ultrasound scan, appropriate blood work, and the UFS-QOL assessments were obtained at every follow-up visit. MRI and CEUS are the imaging modalities of choice after PMWA [29]. Generally speaking, submucosal fibroids have a higher chance to discharge necrotic masses and larger discharged tissue volume than intramural fibroids, while the subserous uterine fibroids are nearly impossible to discharge necrotic masses because of no connection with the vagina [30]. There are reports of women with pedunculated subserosal fibroids who have sloughed necrotic fibroids into the pelvis after UAE [31, 32]. Hence, we do not recommend PMWA for fibroids of this type. The long-term effect of PMWA on ovarian function has not been completed understood; however, studies on ovarian-related hormone and effects on fertility are under way.

24.8 Possible Adverse Effect and Complications of PMWA and Defensive Measures

24.8.1 Infection and Fever

Strict aseptic manipulation could reduce the risk of hospital-borne infections, while large area of necrotic tissue may lead to absorption fever. If the fever is caused by infection, we can give no special handling except for drinking more water. Otherwise, some measures can be taken.

24.8.2 Pelvic Pain

Use the visual analog scale to assess the pain. If the score is higher than 5–6, painkiller could be used.

The visual analog scale (VAS) is a line 10 cm in length with each end anchored by extreme descriptive. Patients are asked to mark on the line that represented their level of perceived pain intensity [33].

24.8.3 Watery Vaginal Discharge or Colporrhagia

Reduce the risk of uterine infection. When the symptom lasts for a short time, instruct the patients to pay attention to sanitation, and generally, the symptom would disappear automatically. If not or the fluid has smell, some clinical intervening measure must be taken.

24.8.4 Skin or Vaginal Mucous Membrane Burn

For skin security, water-cooled microwave ablation instrument has been applied in clinical to protect skin burn. We can stuff several vaginal yarn balls doused in physiological saline before PMWA which can protect the vagina mucosa from the hot liquid discharged from vaginal.

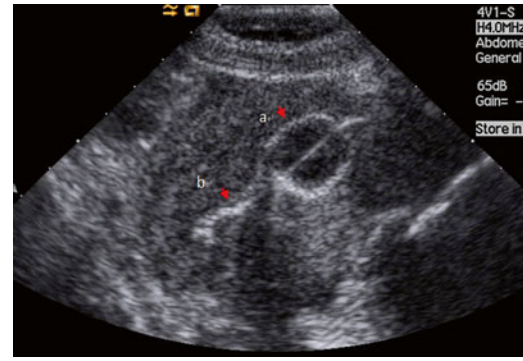

Fig. 24.1 Percutaneous microwave ablation (*MWA*) in a 29-year-old woman with two type 3 fibroids with the sizes of 3.4×3.1 cm and 4.2×4.8 cm who was nulliparous. Because the fibroids are in contact with the endometrium, some defensive measures were taken to protect the endometrium. A 5 F double-lumen balloon urinary catheter was placed into the cavity. The balloon was filled with 1.5 ml of saline solution (*arrow a*). Then, 1 ml sterile ultrasound gel was slowly injected through the urethral catheter to mark the endometrium (*arrow b*). On the same section of ultrasound, the fibroids cannot be shown

24.8.5 Transient and Permanent Amenorrhea

Protecting the endometrium is considered as the core measures. Some defensive measures can be taken. A 5 F double-lumen balloon urinary catheter is placed into the cervix under direct visualization. The balloon is filled with 1–1.5 ml of saline solution to fix the catheter and prevent saline backflow. Then, 1 ml sterile ultrasound gel is slowly injected through the urethral catheter. Endometrium can be marked and covered with this "protective film" from microwave heat by taking this exploratory measure. However, it is presently on its trial stage (Fig. 24.1).

24.8.6 Uterine Perforation or Injuries to Adjacent Organs

First, before PMWA, nursing crux includes gastrointestinal preparation. Second, fill the posterior vaginal fornix with gauze rolls soaked in sterile physiological saline, which play a role similar to uterine manipulator. Third, if the fibroids are close to the intestine or the patient has a retroverted uterus, the investigator can puncture the posterior vaginal fornix then inject sterile physiological saline into the uterus-rectum nest before ablation to separate the fibroids from the surrounding tissue to protect the adjacent organs from heat.

24.9 Results

PMWA is a minimally invasive technique for the treatment of uterine fibroid and adenomyosis by inducing tissue necrosis through heat. Most of the heat generated during MWA was accounted for the rotation of dipole molecules. The preablation 2D grey-scale US showed fibroids of low echogenicity and CEUS showed enhancement within the fibroid. Immediately after MWA, the 2D grey-scale US showed the scheduled treated area was covered with hyperechoic zone and the CEUS showed no enhancement in the ablation zone and with circle enhancement in the periphery of the fibroid (Fig. 24.2). The preablation ce-MRI showed the fibroid was obviously

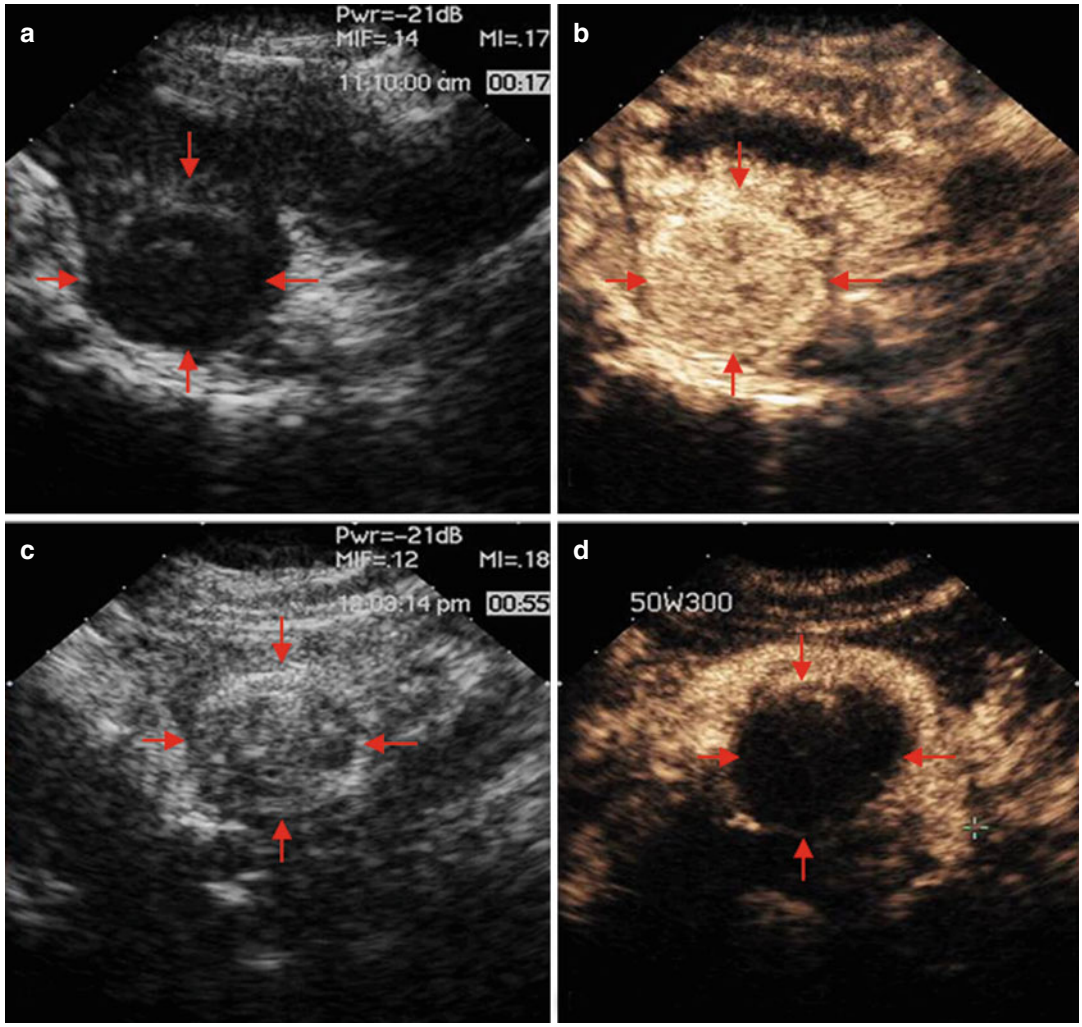

Fig. 24.2 Percutaneous MWA in a 31-year-old woman with a single subserous fibroid in posterior uterine wall. (**a**) Preablation two-dimensional gray-scale ultrasonography shows the hypoechoic fibroid (*arrows*) with the size of 4.4×4.9 cm. (**b**) Pre-contrast-enhanced ultrasonography scan obtained during the early phase after contrast injection, and at 17 s it shows homogeneous hyper-enhancement (*arrows*). (**c**) Two-dimensional gray-scale immediately after MWA shows the scheduled treated area is covered with hyperechoic zone (*arrows*). (**d**) Post-contrast-enhanced ultrasonography immediately after microwave ablation shows the ablation area is consecutively non-enhanced (*arrows*)

enhanced (Fig. 24.3). After the ablation, ce-MRI showed no enhancement in the ablated zone like "black hole." Several studies have been reported. The results are listed in Table 24.2. All of them used US to evaluate the fibroid volume. A paper published in 2011 [18] showed the shrinkage rates of the fibroid were 61.8 %, 78.7 %, 73.2 %, and 93.1 % at 3, 6, 9, and 12 months after ablation, respectively. 15 % (6/40) of patients felt pain in their lower abdomens or waists within 12 h post ablation, and the discomfort rapidly disappeared. 17.5 % (7/40) of patients had a small amount of vaginal bloody secretions within 1–2 weeks after treatment, and they recovered from the bleeding without any therapy after 1 week.

Based on our previous study, from October 2007 to October 2013, 240 patients were treated

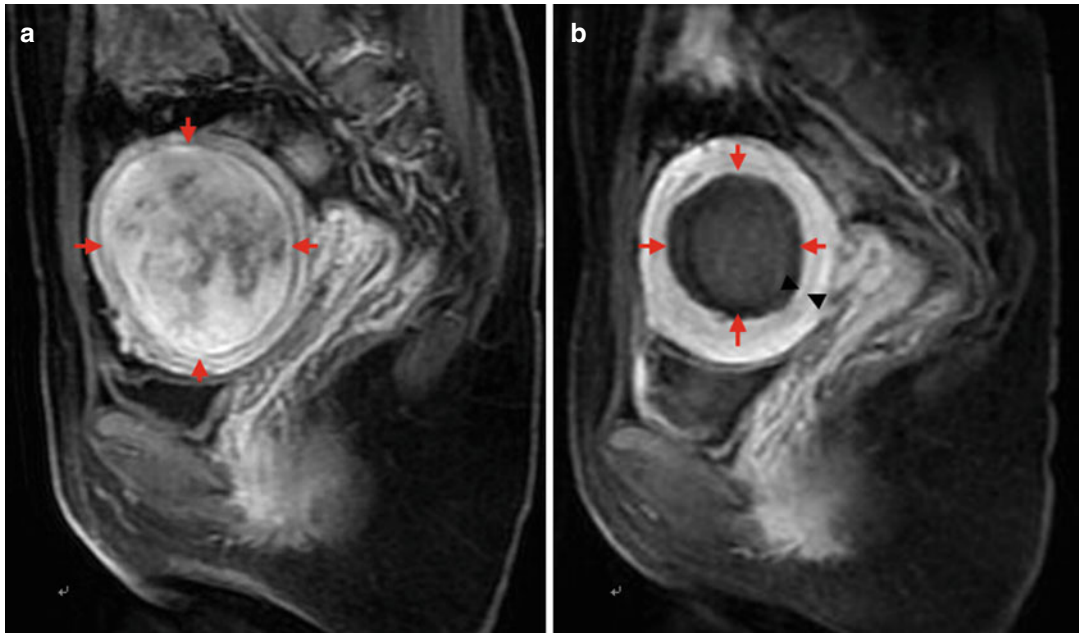

Fig. 24.3 Percutaneous MWA in a 39-year-old woman with an intramural fibroid who suffered from menorrhagia and refused surgical treatment.MWA was implemented to relieve her symptom. (**a**) Preablation sagittal T1W1 contrast-enhanced magnetic resonance imaging (ce-MRI) scan showed one enhancement intramural fibroid (*arrows*) with the size of 7.9×6.9 cm. (**b**) Scan obtained 3 days after ablation shows the ablated fibroid (*red arrows*) without enhancement shrink to 4.9×4.5 cm, which is surrounded by the unablated belt (*black arrows*) with 0.5 cm in width

Table 24.2 Shrinkage rates of the fibroids treated by microwave ablation

Study	Number of fibroids	Baseline (cm^3)	Shrinkage rates of the fibroids			
			3-month	6-month	12-month	24-month
Zhang et al. [18]	40	140.1 ± 87.4	61.80 %	78.70 %	93.10 %	N/A
Qu et al. [34]	17	137.6 ± 61.3	N/A	N/A	44.70 %	N/A
Chunying et al. [35]	20	69.3 ± 7.3	N/A	75.20 %	N/A	N/A
Jun et al. [36]	16	47.8 ± 26.0	57.30 %	66.80 %	79.90 %	92.50 %

N/A not available

with PMWA in our departments (22 patients with 22 submucosal fibroids, 128 patients with 157 intramural fibroids, and 90 patents with subserosal 120 fibroids). 239 patients completed the therapy in a single ablation. One with a large fibroid diameter of 10.2 cm underwent two steps of PMWA to ensure the safety (4 months between two treatments), and the outcomes are satisfactory. All the patients with submucosal fibroids and 30 ones with intramural fibroids had iron deficiency anemia. The dosages of HGB are all recovered normally at mean 6-month follow-up.

Patient-reported symptom severity decreased from baseline (56.3 ± 19.3) to 24 months (11.8 ± 6.9), and health-related quality of life improved from baseline (50.0 ± 10.8) to 24 months (86.0 ± 12.3).

Two (0.8 %) patients encountered recurrence at 9-month and 13-month follow-up respectively and received re-ablations (recurrence is defined as the appearance of a fibroid on ultrasound examination or identification of fibroid during subsequent surgery after the initial ablation [37]).

Fifty-one patients in 240 women (21.3 %) passed necrotic fibroids at approximately 1-day

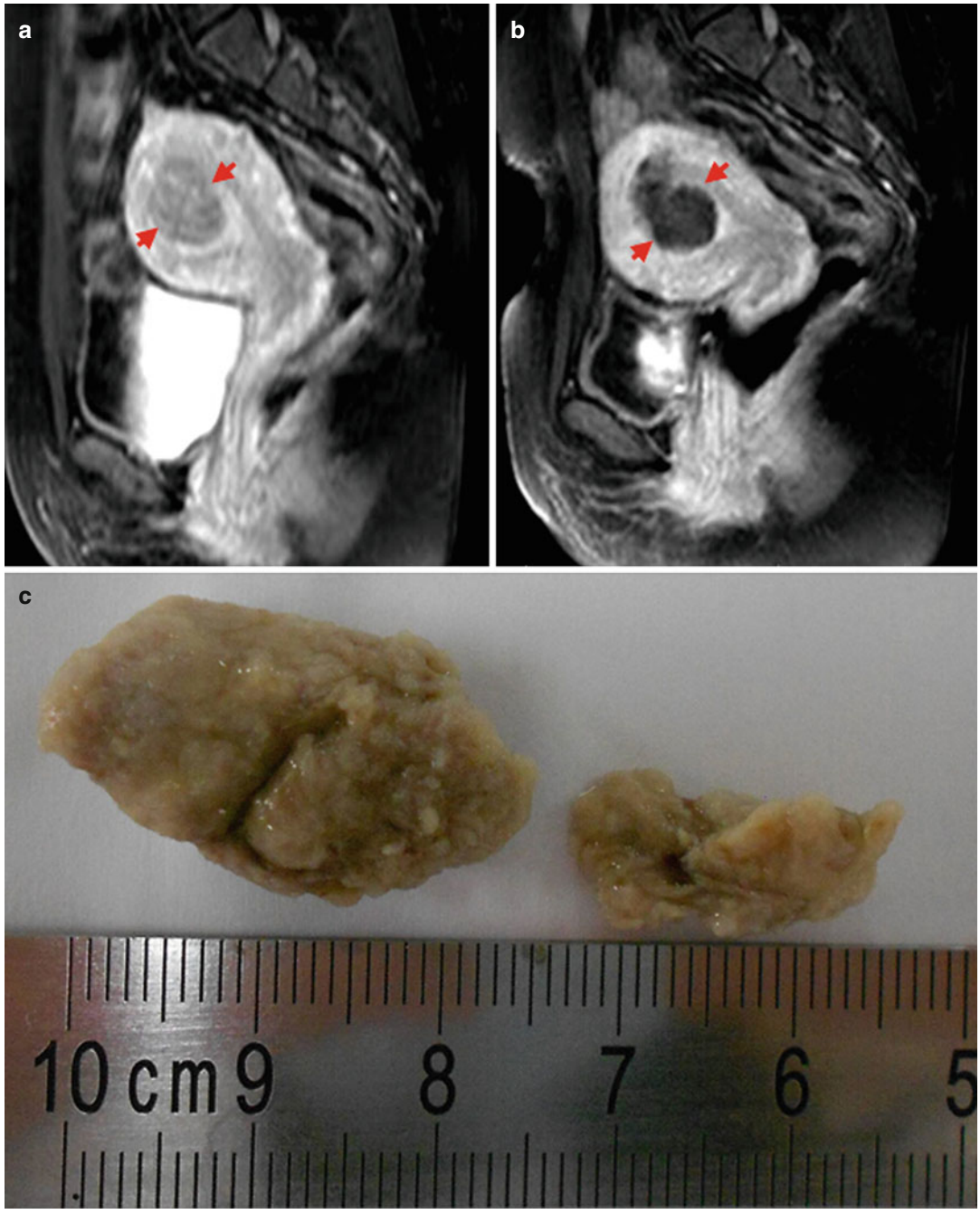

Fig. 24.4 Percutaneous MWA in a 37-year-old woman with a submucosal fibroid who suffered from menorrhagia and refused hysteroscopic myomectomy. MWA was implemented to relieve her symptom. (**a**) Preablation sagittal T1W1 ce-MRI scan showed one enhancement submucosal fibroid (*arrows*) with the size of 3.9×3.3 cm. (**b**) Scan obtained 3 days after ablation shows the ablated fibroid (*arrows*) without enhancement shrinks to 3.5×3.3 cm. (**c**) Two pieces of tissue discharged from vagina with the menstrual blood 1 month after the ablation, then the symptom of menorrhagia was relieved

to 24-month follow-up (Fig. 24.4) (21 patients (95.5 %) with submucosal, 30 (23.4 %) patients with intramural fibroids, and 0 (0 %) with subserous fibroids).

Now, no studies of the impact of PMWA on ovarian function have been published. However, there were five spontaneous pregnancies in four women (one woman conceived twice) in our departments. Two women delivered full-term healthy babies at 13-month and 26-month follow-up respectively. Wang Xiuli et al. [38] have reported that a 29-year-old woman with a fibroid 9.2 cm × 8.7 cm became pregnant and had normal full-term infant at 1-year follow-up.

Two (0.8 %) patients with fibroid >10 cm suffered from colporrhagia 10 days and 20 days after ablation respectively; however, the ce-MRI showed good imaging results but the symptoms persisted. They chose the transabdominal myomectomy to remove the ablated fibroids 20 days and 25 days after ablation respectively. One (0.4 %) patient with a 6 cm submucosal fibroid suffered from severe pain caused by lesion discharging from vagina 7 days after ablation and received an emergency hysteroscopy for removal of the large piece of necrotic tissue. Twenty eight (11.7 %) patients encountered lower abdominal pain in which eight patients got 6–8 scores and took painkillers. No measures were taken to the other 20 patients. Fourteen (5.8 %) encountered absorption fever with normal blood routine results. Fifty-seven (23.8 %) encountered watery vaginal discharge, and symptoms persisted for 3–10 days. No severe complications such as uterine perforation or injuries to adjacent organs happened.

24.10 Discussion

24.10.1 Multi-technology Comparison of Uterine Fibroid Treatment

For decades hysterectomy has been the main therapeutic option available to women with fibroids, and this diagnosis is verifiable at tissue examination of the removed uterus. However, as imaging and minimally invasive diagnostic methods are pursued and developed, new and less aggressive therapeutic options are introduced including LM, UAE, HIFU, RFA, PMWA, and so on.

Following the initial application of LM in 1979 by Semm [5], this minimally invasive technique has become more and more popular worldwide. The procedures include excision of the fibroid(s), repair of myometrium, and removal of the fibroid from the abdomen [39]. Landi et al. [40], in a prospective large sample study, evaluated 368 women undergoing LM. Their mean operating time was 100.78 + 43.83 min, mean decreases in hemoglobin and hematocrit were 1.38 + 0.93 and 4.8 + 2.9 g/100 ml, respectively, and the mean length of hospital stay was 2.89 + 1.3 days. They reported 12 (3.34 %) intraoperative complications, with an intraoperative transfusion of autologous blood required in ten patients. Recurrence rates reported in recent studies ranged from 20.3 % to 22.9 % [41] and the risk of recurrence appears to increase with multiple fibroids and nulliparity [42].

UAE was first introduced in 1974 [6] and involves femoral artery catheterization and intra-arterial infusion of embolization particles, producing ischemia of the fibroid uterus and subsequently decreasing the volume of fibroids [43, 44]. The treatment of symptomatic uterine fibroids is in evolution. Since the Ravina et al. [45] description of UAE as an effective treatment potential, numerous short- and long-term studies have validated the safety, efficacy, and benefits of the procedure when compared with traditional surgical options. All large studies including comparative trials between UAE and hysterectomy have reported 70–90 % symptom improvement for menorrhagia, pain, and bulk-related symptoms, with the mean decrease in the fibroid volume of 42–64 % at 6 months [46–49]. Its major side effect is severe pain after the procedure; other complications include radiation risk (exposure amounts of approximately 20 cGy of radiation), severe infection leading to hysterectomy (1.5 %) and ovarian failure, and low-grade fevers

due to the ischemic necrosis; nausea and vomiting are also not uncommon with postembolization syndrome [50–55].

HIFU refers to the use of tightly focused high-energy ultrasound waves to induce focal thermal effects, ablation, or thermocoagulation in vivo [53]. Some clinical trials showed that there is a correlation between amount of treated fibroid volume and lower likelihood of subsequent treatments: the greater the treatment volume, the better the response achieved [53]. In the study of Stewart [56], 109 patients underwent HIFU and less than 10 % of fibroid volume was ablated. The results showed that 71 % of patients reached the targeted symptom reduction at 6 months with a 13.5 % reduction in fibroid volume, and 51 % reached this point at 12 months. However, in the report by Gorny KR [57], the mean percent of non-perfused volume ratio was 45.4 % immediately upon completion of HIFU treatment. At 3 months' follow-up, 85.7 % reported symptom improvement and 13.3 % reported no symptom relief. At 6 months' follow-up, 92.9 % reported symptom improvement and 7.1 % reported no relief. At 12 months' follow-up, 87.6 % reported overall symptom improvement and 12.4 % had no improvement. The rate of side effects is generally low, including skin burns, lower abdominal pain, nerve palsy, and so on [58].

Ablation of solid tumors with RFA results from heating that is produced when ions follow the oscillations of a high-frequency alternating electric field, and the heat causes coagulation necrosis of local tissue [59]. Guido et al. [60] reported on 124 patients treated with RFA, which had the largest sample size by far. One hundred twelve subjects were followed through 24 months. Patient-reported symptom severity decreased from baseline (61.1 ± 18.6) to 24 months (25.4 ± 20.6), and health-related quality of life improved from baseline (37.3 ± 19.1) to 24 months (79.3 ± 21.7). Iversen et al. [61] reported their experience treating 43 fibroids with RFA; improvements in fibroid symptoms and quality of life were measured by the uterine fibroid symptom and quality of life questionnaire scores at baseline, and 3, 6, and 9 months after the intervention, mean symptom severity scores decreased from 60.7 ± 17.8 to 31.2 ± 19.5. The total health-related quality of life score improved by 46.4 % from 55.6 ± 20.9 to 81.4 ± 16.6. The studies showed that RFA of uterine fibroids is an effective and safe minimally invasive treatment.

To date, the only indications for total LM are pedunculated and subserosal lesions sometimes can even be used for intramural fibroids, depending on the position of the fibroid and the skills of the surgeon. It is believed that subserosal pedunculated fibroid is a relative contraindication to UFE, PMWA, and RFA because of the risk of separation from the uterus. That is, the potential for stalk necrosis and detachment of the leiomyoma could lead to peritonitis, persistent pain, or infection. Compared with LM, UAE, and HIFU, RFA and MWA have many advantages, such as less blood loss, faster recovery, diminished postoperative pain, and shorter hospital stay (Table 24.3). LM and UAE are associated with more and severer complications than RFA and PMWA (Table 24.3). HIFU is a noninvasive therapy for treatment of uterine fibroids and had better cosmetic effects, but it can treat only one fibroid at a session, and one treatment procedure lasts up to 3 h. A large area of necrosis can be achieved in a single access with MWA, and therefore, compared to the other therapy, it is relatively time efficient. When a greater percentage of a fibroid's volume is ablated, symptomatic relief is more pronounced and quality of life increases. Hence improvement of symptoms is different in different research centers because of the different lesion volume reduction.

Table 24.3 Comparison of minimally invasive therapeutic options for fibroid

Author	No. of pts	Therapy	Operating time (min)	Blood loss (ml)	Recovery time	Reduction in fibroid volume (%)			Improvement of symptoms (%)		Major complications (%)
						6-month	12-month	24-month	Within 1 year	Over 1 year	
Landi et al. [40]	368	LM	100.7 ± 43.83	N/A	10.58 ± 6.68 days	N/A	N/A	N/A	N/A	N/A	4.7
Holzer et al. [62]	19	LM	99 ± 37	71 ± 80	2.9 ± 1.8 weeks	N/A	N/A	N/A	N/A	N/A	N/A
Volker et al. [49]	88	UAE	N/A	N/A	N/A	42.1	54.5	60.5	88.9 ~ 91.3	96.3	4.7
Hehenkamp et al. [63]	81	UAE	79	30.9	2.0 days	N/A	N/A	N/A	N/A	N/A	8.64
Ren et al. [64]	145	HIFU	N/A	N/A	N/A	47.9	50.3	N/A	85.5	N/A	4.1
Iversen et al. [61]	43	RFA	N/A	N/A	N/A	N/A	64.7 ~ 78.4	71.4 ~ 82.7	64.3 ~ 76.2	N/A	0
Ghezzi et al. [65]	25	RFA	20 ~ 45	N/A	N/A	68.8	77.9	77.9	N/A	N/A	0
Zhang et al. [18]	240	MWA	8 ~ 12	N/A	N/A	82.9	78.70	93.10	N/A	N/A	2

LM laparoscopic myomectomy, *UAE* uterine artery embolization, *HIFU* high-intensity focused ultrasound, *RFA* radiofrequency ablation, *MWA* microwave ablation, *N/A* not available

Conclusion

A marked shrinkage in post-fibroid volume and a novel improvement on symptom and quality of life are some of the benefits achieved. Totally the technique is a safe, feasible, and effective minimally invasive therapeutic option in the management of women with symptomatic uterine fibroids. The risk of transient or permanent menopause appears related to the age of the patient at the time of ablation. Further studies will hopefully provide us with answers to many questions, including the optimal population groups, the durability of the procedure, and the influence on ovarian function and fertility.

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Microwave Ablation in Other Tumors (Lung, Breast, and Bone)

25

Xiao-lin Cao and Ping Liang

Abstract

Microwave ablation (MWA) has been applied to treating tumors of the liver, spleen, kidney, thyroid, and adrenal gland, and it was recognized as an effective therapy for these types of tumors. In recent years there has been a growing interest in MWA for the treatment of tumors in the lung, breast, and bone. MWA therapy of lung, breast, or bone tumors can be curative, neoadjuvant, and palliative and/or symptomatic. This chapter describes the applications of MWA in lung, breast, and bone tumors.

Keywords

Microwave • Ablation • Lung • Breast • Bone

Abbreviations

CT	Computed tomography
MWA	Microwave ablation

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25.1 MWA in Lung Tumor

Lung cancer is the most common cancer diagnosed worldwide with 1.3 million cases newly diagnosed every year. However, only 20 % of all diagnosed lung tumors are resectable. Since the first reported use of thermal ablation for lung cancer in 2000, there has been an explosive use of the procedure, and by 2010 the number of procedures to treat thoracic malignancy is expected to exceed 150,000 per year [1]. In all thermal ablation methods, radiofrequency ablation remains to date the most widely used, but MWA has its own distinct advantage.

The lower permittivity and conductivity of aerated lung allows deeper microwave penetration than in other organs, such as liver and kidney. Preclinical studies have shown that microwaves can actively heat larger volumes of normal lung

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than radiofrequency devices comparable in size and form [2–4]. Another conceivable advantage of using microwaves in the lung is that the increased thermal gradient created by microwaves may provide better passive heating of the tumor margin. Several groups have successfully applied MWA in the treatment of primary lung cancer or lung metastases (Table 25.1). The rate of complete necrosis observed in lung tumor was about 56.25–94.12 % [5–12]. Computed tomography (CT) is the usual guidance method. Ultrasonography guidance is only for ultrasonographically visible lung cancer at the peripheral location. MWA of lung tumor is usually carried out under conscious sedation and local anesthesia. The probes used for lung tumor MWA are usually 14–16 gauge. The probes can be either used alone or simultaneously depending on the tumor size. Tumors that are <2 cm in maximal diameter can be treated with a single antenna which is placed in the center of the tumor. Tumors that are 2 cm or larger can be treated with two to three different sites based on tumor size and shape in order for the ablation range to completely cover the tumors [6]. Ablation margin around the tumor should be created with at least 5 mm although greater than 10 mm is preferable. After MWA, patients need to be observed for potential complications and to be followed up with either CT, contrast-enhanced CT, or positron emission tomography CT. CT is widely available, and imaging is usually performed at 0, 1, 3, 6, 9, and 12 months, followed by every 3–4 months afterwards (Fig. 25.1). The most common complication is pneumothorax. The incidence rate of pneumothorax was about 6.25–63 % [5–12]. Other common complications after MWA include chest pain, hemoptysis, skin burns, fever, pleural effusion, pulmonitis, and so on, but severe complications are rare.

The advantages of MWA in the treatment of lung tumors are its safety, efficiency, less invasiveness, easy performance, low cost, and decreased associated hospitalization as compared with traditional pneumonectomy. MWA represents a potential safe and effective percutaneous technique in the treatment of lung malignancies, with a potential optimistic impact on patients' survival. MWA may be a valid treatment option in lung malignancies and it may improve survival in patients that are not suitable to surgery.

25.2 MWA in Breast Cancer

As widespread screening for breast cancer is detecting more women at younger ages and earlier stages, the need for minimally invasive, cosmetically preferable approaches to its treatment is growing. For small breast carcinomas, the survival difference between mastectomy and breast-conserving surgery with combined radiation therapy is not striking, and the latter approach has been accepted as a standard of care by both patients and doctors. However, about 20 % of patients are not satisfied with the cosmetic outcomes after such breast-conserving therapies.

Ablative techniques are now being applied to the treatment of primary breast tumors, perhaps offering an alternative to surgical excision. Clinical experiences of using MWA for breast cancer are limited. Focused microwave phased array thermotherapy was used in the treatment of breast tumor before 2010, with a complete ablation rate of 0–8 % [13–15]. This microwave treatment system uses transcutaneous opposing microwave waveguide applicators and produces a phase-focused microwave field in the compressed breast to heat and destroy high-water-, high-ion-content tumor tissue with tumoricidal temperature over 43 °C by externally focused 915 MHz microwave energy [16, 17]. The first pilot study of the feasibility and efficacy of ultrasonography-guided percutaneous microwave coagulation of small breast cancers was carried by Zhou and colleagues in 2012 [18]. Thirty eight (93 %) of 41 cases patients were diagnosed with invasive ductal carcinoma and three (7 %) were diagnosed with ductal carcinoma in situ. The mean greatest diameter of the tumor was 2.5 cm ± 0.8 (range, 1.0–4.0 cm). The microwave irradiation frequency is 2,450 MHz and output power of 40 W was selected. The irradiating segment of 2 mm in length is 1 cm away from the shaft tip. The mean time to reach complete ablation was 4.48 min, ranging from 3 to 10 min. Thirty seven

Table 25.1 Results of clinical studies published in the literature regarding microwave ablation of lung tumors

Authors	No. of patients	Tumor size (cm)	Image guidance	Microwave frequency (MHz)	Output power (W)	Follow-up period (month)	Complete ablation (%)	Local treatment response (%)	Survival rate		
									1	2	3 years
He et al. [5]	12	2.0–6.0	Ultrasound	2,450	100	20 (6–40)	56.3 %	100 %	N/A	N/A	N/A
Lu et al. [6]	69	2.2 (0.8–5.5)	CT	915	60	36	N/A	78.3 %	66.7 %	44.9 %	24.6 %
Little et al. [7]	23	1.9 (0.8–5.7)	CT	2,450	180	7.3 (3–19)	N/A	88 %	N/A	N/A	N/A
Carrafiello et al. [8]	16	3.8 (2.8–4.7)	CT	915	45	1–18	94.1 %	N/A	N/A	N/A	N/A
Liu et al. [9]	15	2.4 (0.8–4.0)	CT	2,450	180	12 (6–18)	56 %	69 %	N/A	N/A	N/A
Wolf et al. [10]	50	3.5 ± 1.6	CT	915	60	10	N/A	67 ± 10 %	65 %	55 %	45 %
Belfiore et al. [11]	56	3.0 ± 0.9	CT	N/A	55	3–36	N/A	100 %	69 %	54 %	49 %
Feng et al. [12]	20	3.7 (2.0–4.6)	CT	2,450	65	12.4 (3–24)	57.1 %	100 %	40 %	10 %	N/A

CT computed tomography, *N/A* not available

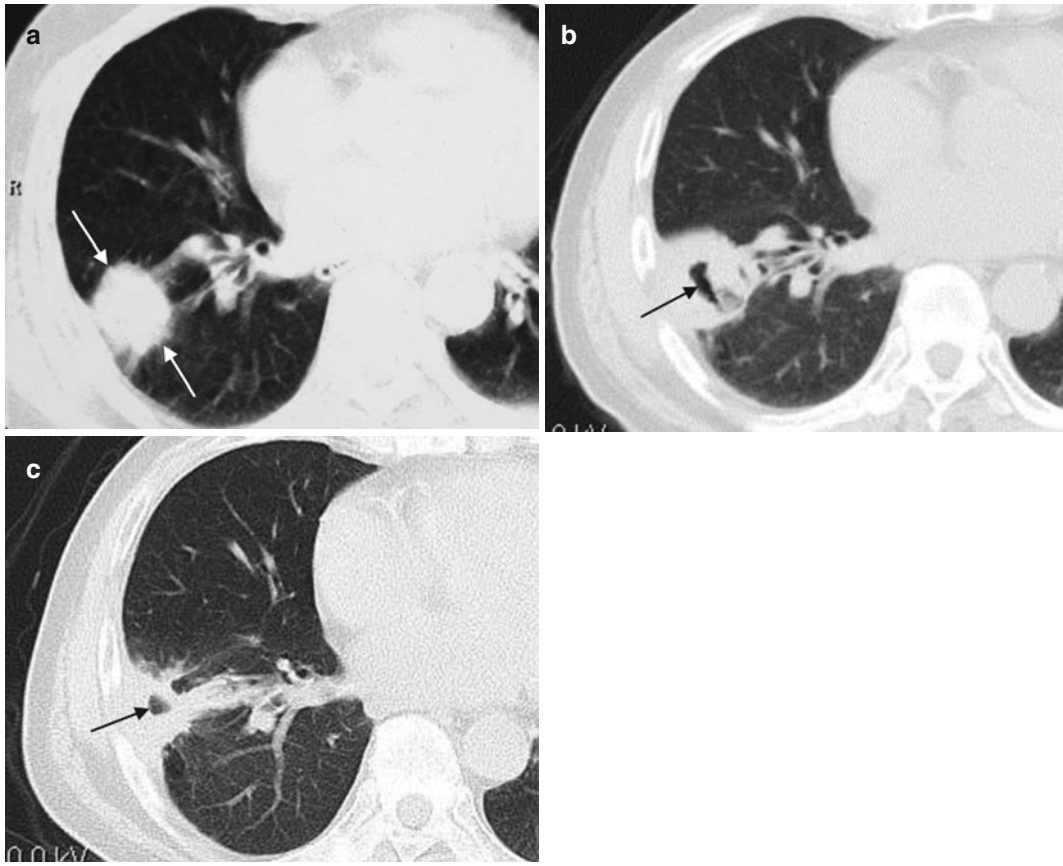

Fig. 25.1 Images of a 76-year-old patient with right lobe squamous cell carcinoma who had complete response from microwave ablation. (**a**) Computed tomography scan pre-microwave ablation shows the approximately 3.7×2.9 cm mass with high attenuation in the right lobe (*arrow*). (**b**) Computed tomography scan at 1 month shows that the ablation range completely covers the tumor and a cavitating structure developing at the site of the ablated lesion (*arrow*). (**c**) Computed tomography scan at 12 months shows the tumor shrank with complete necrosis, along with small persistent cavitation (*arrow*)

of 41 cases (90 %) showed complete tumor coagulation. Of three ductal carcinoma in situ cases, only one (33 %) achieved complete tumor necrosis. Complete ablation was achieved in 36 (95 %) of 38 invasive ductal carcinoma cases. To avoid heat injury to the overlying skin, noninvasive skin surface temperature probes were applied to the skin and fans provided constant air cooling [13]. All of the trials conducted up to now have followed ablative therapies with surgical excision, and axillary dissection was performed if the sentinel node contained metastatic cancer or if no sentinel node was found [17]. In this manner, both the completeness of ablation and the margin status can be assessed.

Recently, we treated one patient with breast fibroadenoma 1.2×0.6×1.1 cm with percutaneous MWA under ultrasound guidance (Fig. 25.2a–d). The microwave irradiation frequency was 2,450 MHz, and output power of 20 W was selected. The total radiation time was 250 s. Postprocedural contrast-enhanced ultrasound examination showed complete ablation of the mass (Fig. 25.2e, f). The only side effect in the patient was pain, which did not require any treatment and resolved spontaneously. The patient was satisfied with the cosmetic result after treatment. The use of ultrasonography-guided percutaneous MWA in the management of breast fibroadenoma is safe and with favorable cosmetic results compared to surgical treatment, although

it may require long-term follow-up. The limited follow-up and the fact that only one patient was treated make it incapable to assess the long effects of the mass reduction degree and local sensation change. Several concerns should be considered in MWA. First, patient selection before ablation is very important. Patients with ductal carcinoma in situ are unsuitable for MWA. Second, ultrasonography may underestimate the extent of the tumor, which can cause incomplete ablation. MR imaging should be considered to evaluate the extent of the tumor, guide the placement of the antenna, monitor the procedure, and evaluate the efficacy of the therapy. Third, the time and extent of sentinel lymph node mapping and complete axillary dissection should also be taken into consideration before ablation. The absence of cellular viability in the tumor tissue must be demonstrated by the long-term follow-up in patients who do not undergo surgery. Comparison of the local tumor progression and survival rates between patients treated with MWA and patients treated with the standard therapy should also be assessed. However, MWA represents exciting new approach to in situ tumor treatment.

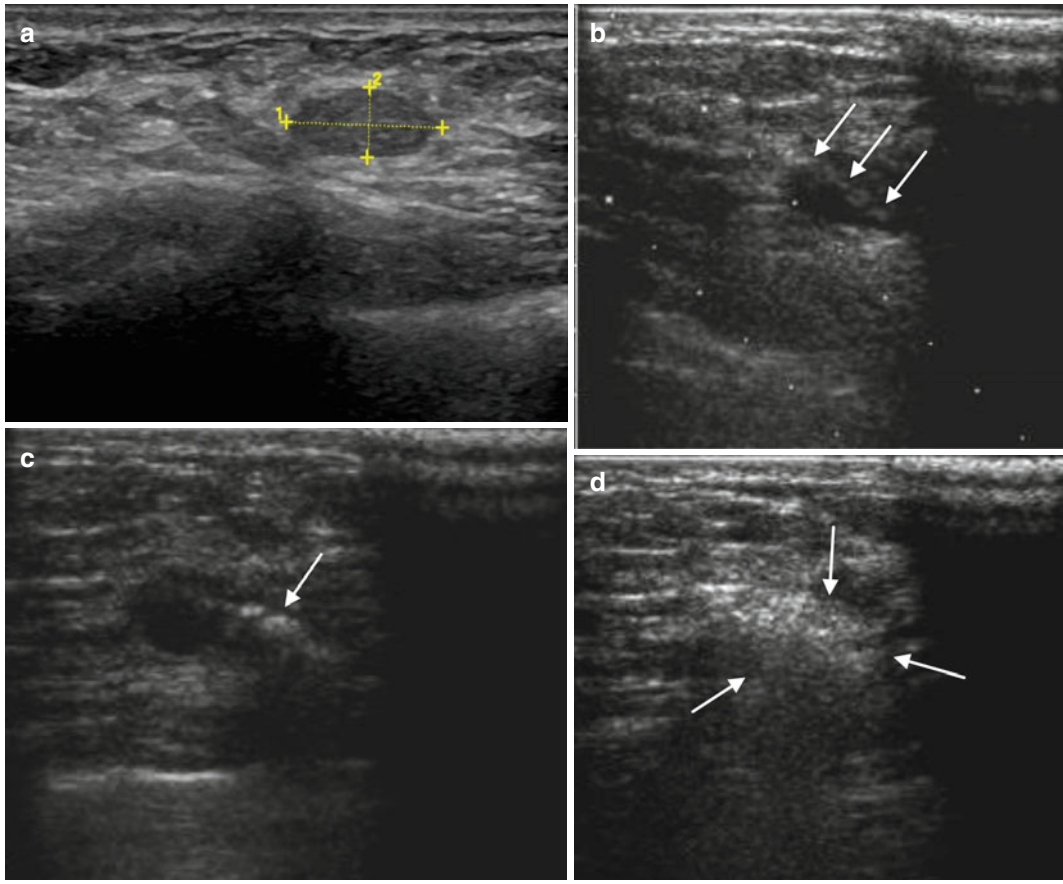

Fig. 25.2 Images of a 43-year-old woman with left breast fibroadenoma treated by microwave ablation. (**a**) Sonogram shows a well-circumscribed oval-shaped solid mass with the size of 1.2×0.6×1.1 cm. (**b**) Sonogram shows successful placement of the antenna (*arrow*). (**c**) Sonogram shows increased echogenicity of the mass near the irradiating segment of the antenna at the beginning of microwave ablation (*arrow*). (**d**) Sonogram shows a gradual and diffuse increase in the echogenicity of the mass from the irradiating segment to the whole mass during microwave ablation (*arrow*). (**e**) Pre-ablation contrast-enhanced ultrasound scan shows hyper-enhancement of the mass (*arrow*). (**f**) One day after ablation contrast-enhanced ultrasound shows the whole mass with no enhancement continuously (*arrow*)

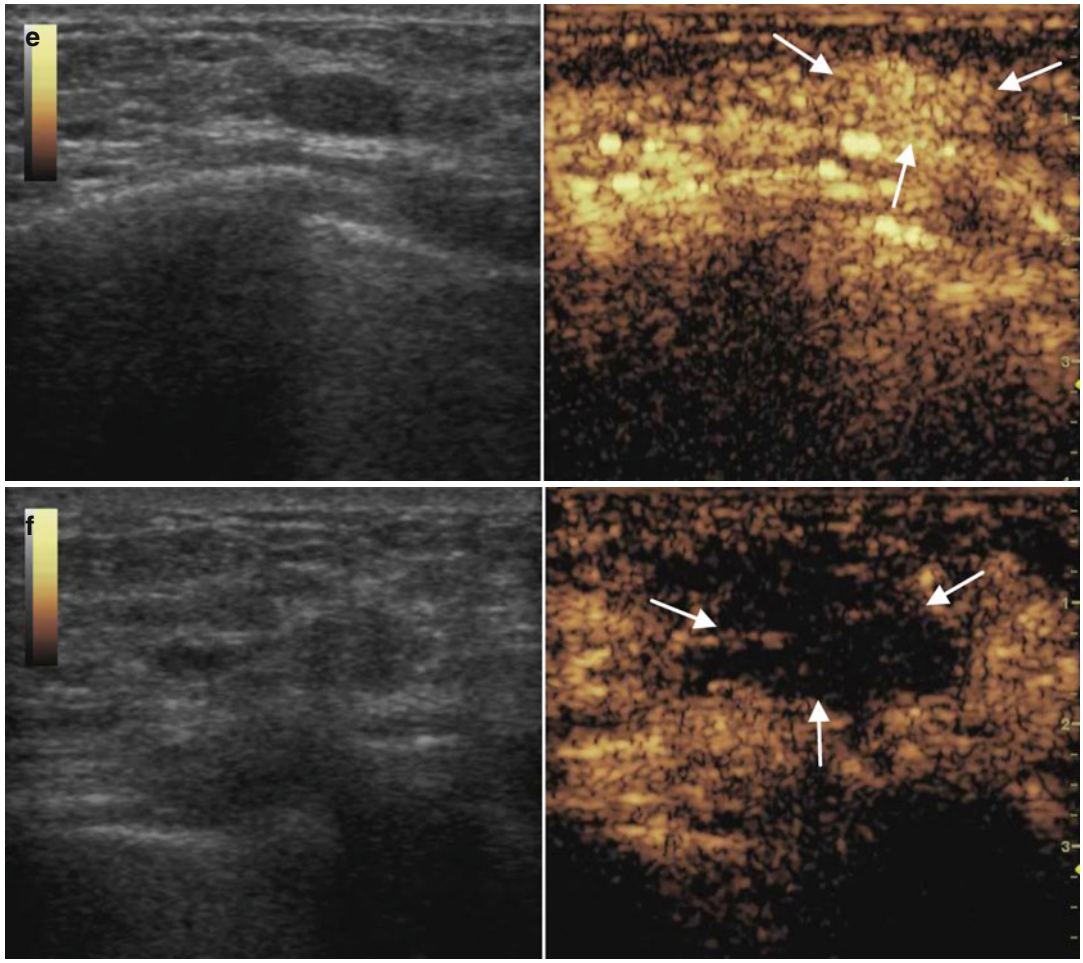

Fig. 25.2 (continued)

25.3 MWA in Bone Tumor

MWA is increasingly being used to treat benign and malignant tumors in the musculoskeletal system with either curative or palliative intent, though the reported literatures are not very sufficient. Reports of MWA of skeletal tumors have appeared with promising results. Benign primary musculoskeletal tumors, such as osteoclastoma, osteoid osteoma, and neurofibromatosis, have been successfully treated with MWA [19]. Series of ablation of bone malignancy, most commonly osteosarcoma and chondrosarcoma, have also been reported [20, 21].

MWA systems use 11–17 gauge antennas to deposit electromagnetic microwaves (915 MHz or 2,450 MHz), resulting in oscillation of water molecules to produce heat. MWA has been applied in surgical resection of bone tumors, and recently its percutaneous use has been reported [19–23]. CT and magnetic resonance are the usual guidance methods in bone tumor ablation. Fan and his colleagues [21] carried out the largest available clinical study of 213 patients with various malignant bone tumors in the operative setting using MWA. After isolating the tumor-bearing bone and the extraosseous mass from surrounding normal tissues with a proper margin, microwave energy was delivered into the

tumor with 2,450 MHz frequency output and 0–200 W power. The total duration of hyperthermia usually was 30–40 min. The core temperature and surface temperature reached 108 °C and 65 °C, respectively, while the normal tissue temperature was cooled to below 39 °C by real-time monitoring using thermocouples inserted into the tumor, the joint cavity, and the normal tissues. The survival rate was 73.9 %. The functional results were good or excellent and the cosmetic results were acceptable in the majority of patients. Recently, percutaneous MWA was applied in musculoskeletal tumors in 18 patients with 21 skeletal metastases with a 2,450 MHz MWA device, under CT guidance [20]. There was no complication, and during 3 months of follow-up, mean pain score reduced by 92 % with 72 % patients pain-free. To evaluate the efficacy of MWA in the treatment of ten patients with osteoid osteomas, 3D dynamic contrast-enhanced MR imaging was used in a recent study [19]. 3D MR imaging was performed before and after MWA. No minor or major complications developed during the intervention or during follow-up. All patients were free of pain within 1 week after intervention, without any recurrence during the 6 months of follow-up. Therapeutic success can be objectively monitored by 3D MR imaging. MWA is a novel and effective way to treat bone tumors in selected patients. Initial results suggest that ablation can produce significant reductions in pain levels and analgesic requirements [19, 20, 24]. The use of MWA is limited in patients with poor bone quality to maintain function, even with prophylactic stabilization. If the bone is weight bearing and there is a risk of fracture, consolidation with cementoplasty or surgery is needed. In these patients arthrodesis using is a better option and is reliable for restoring limb function.

Appropriate use of MWA in the treatment of patients with musculoskeletal tumors requires proper patient and lesion selection, knowledge of relevant anatomy, and understanding of the advantages and limitations of the ablative techniques. The oncological and functional results of MWA in bone tumors are encouraging. MWA is an effective, simple, and inexpensive method. MWA applications in bone tumors should deserve more attention than it has in the clinical practice.

Conclusion

In summary, MWA is an exciting technique in the application for the treatment of tumors in the lung, breast, and bone. The fact remains that the study of microwave ablation for these tumors is limited. The safety and efficacy of MWA in the treatment of these tumors are still currently ongoing. Randomized multicenter trials to compare it with other ablative techniques and traditional surgery are necessary to confirm long-term effectiveness of MWA in these tumors.

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Part VI

Application of Imaging in Percutaneous Microwave Ablation

26 Three-Dimensional Visualization Technology and Therapy Planning System for Microwave Ablation Therapy of Liver Tumor

Jin Xue, Wenbo Wu, and Ping Liang

Abstract

Three-dimensional (3D) visualization technology has been increasingly applied in image-guided therapy, and computerized 3D medical imaging is more intuitive and rich in anatomical details of minimally invasive therapy. Under the assistance of 3D visualization technology, 3D medical imaging can be displayed on the screen. Radiologists can perform various operations on 3D medical imaging (such as calculating, measuring, rotating, moving, scaling, hiding, and visualizing), so as to optimize the preoperative planning. Extensive experiments have been performed on phantom, porcine livers. Clinical researches also have been performed, and the actual necrosis zone is measured in postoperative contrast-enhanced CT images of patients. In the following chapter, the capabilities of 3D visualization technology are exploited for microwave ablation (MWA) of liver tumor by using a self-developed 3D computer-assisted therapy planning system.

Keywords

Microwave ablation • 3D visualization 3D medical imaging • 3D preoperative planning • Planning evaluation

Abbreviations and Acronyms

3D	Three-dimensional
CT	Computed tomography imaging
GUI	Graphical user interface
MRI	Magnetic resonance imaging
MWA	Microwave ablation
ROI	Region of interest
US	Ultrasound
VR	Virtual reality

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26.1 Introduction

Microwave ablation (MWA) is a promising minimally invasive technique with several advantages, such as flexible therapy approaches, good tolerability, predictable necrotic areas, high thermal

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efficiency, higher capability of coagulating blood vessels, faster ablation time, and an improved convention profile [1–8]. However, MWA is commonly guided with the 2D imaging patterns currently, such as ultrasound (US), computed tomography imaging (CT), and magnetic resonance imaging (MRI). Moreover, the preoperative planning has often been designed through the imaging based on 2D preoperative CT or MRI too. 2D medical imaging can provide valuable information about the anatomical structure, but they lack the spatial detail of volumetric data and the anatomical details of risk structures that the interventional radiologists need to know for therapy. The radiologists perform the puncture by freehand. Freehand ablator antenna positioning depends on the experience and the 3D conception of the radiologists [9]. Currently, 2D imaging is the basis of recreating the spatial relationship between the ablator antennas and the anatomical structure. Interventional radiologists are demanded to mentally reconstruct the 3D spatial scene of the target lesion and hepatic anatomy from 2D imaging well. Results of human errors, such as weakness in spatial sense and imperfect hand–eye coordination, usually lead to imprecise antenna positioning. Moreover, there are still two problems that are worthy of high concern in the 2D image-guided MWA. (1) One is collateral damage to adjacent healthy tissues. (2) The main problem in the current MWA is the lack of reliable therapy planning. Some research showed that insufficient spatial information on the 2D imaging, inaccurate manual positioning of the ablator antennas, excessive dependence on operating experience of the interventional radiologist, and imprecise ablation spheres of the preoperative planning limited further application of the MWA therapy [10, 11]. By transforming 2D image slices to 3D graphics or images, patient-specific 3D medical imaging can be displayed on the screen. Since its introduction in the late 1970s, 3D medical imaging has attracted more and more attention. The main clinical applications include the preoperative planning for resection of the liver, pancreatic, and kidney tumors; living donor liver and renal transplantation; and tumor ablation of the liver and kidney [12]. 3D medical imaging can display the space structure and dynamic characteristics to make up the shortage of 2D imaging display and can determine the quantitative information about the properties of the anatomy of the tissues. Wealthy hidden information of 2D imaging is described in an illustrative, vivid, and effective manner on the 3D scene. Interventional radiologists can view and analyze 3D medical imaging from multi-angle and multi-hierarchy. The application of 3D visualization technologies has succeeded as shown in computerized 3D imaging of spatial relationship analysis for liver therapy [13–19].

Successful MWA of the liver also requires an understanding of the patient-specific characteristics, including the shape and the maximum diameter of the tumor, vessel distribution, and spatial relationships with other relevant organs. 3D medical imaging can offer the exact visualization of the vessels in the region of interest (ROI) with complex and variable vascular anatomy, demonstration of possible ablation margins, and prediction of operational risks in MWA. So the first problem of high concern in MWA under US guidance can be solved by transforming 2D imaging into 3D imaging.

Our experimental results showed that 3D medical imaging also could offer assistance in diagnosis and preoperative planning and facilitate crucial decisions and ablation evaluation for MWA [20–22]. Radiologists who conduct repeated preoperative planning may optimize the therapeutical procedure, improve therapeutical skills and safety, and reduce therapeutical complications [16, 21, 23, 24]. The application of 3D visualization technology can intuitively display preoperative planning to avoid thermal damage of the surrounding structures in MWA under US guidance. To solve the second problem of prominent concern in MWA under US guidance, a 3D computer-assisted therapy planning system is developed to optimize the preoperative planning.

This 3D computer-assisted therapy planning system has integrated the relevant technologies of image processing for the transformation of 2D imaging into 3D imaging. It has functions to visualize the spatial relationship of the tumor and the surrounding structures in a 3D scene. It has the ability to process and analyze the 2D image

and 3D image. Furthermore, it can calculate the results of important parameters for MWA therapy including the distances from the tumor to the surrounding vital structures or organs, the best puncture path, and the minimum number of insertions. The assistant platform and the evaluation platform for 3D preoperative planning have also been designed for this system.

26.2 Relevant Technologies of Medical Image Processing Technologies

The qualities of 3D medical imaging depend on the medical image processing technologies. The main technologies of the medical image processing technologies include segmentation and 3D visualization. The purpose of segmentation is to extract the interesting region from the surroundings. Segmentation is the basis on the visualization of 3D imaging. The main task of 3D visualization in medical applications is to display segmented 2D imaging into 3D imaging. Methods of 3D visualization include surface rendering reconstruction and volume rendering reconstruction.

There are five principal preprocessing steps for 3D imaging reconstruction. The steps involve segmentation of 2D CT images, surface rendering reconstruction, data analysis of the 3D spatial relationships, volume rendering reconstruction, and combining surface rendering and volume rendering reconstruction. In addition, the virtual reality (VR) technique is used to establish a simulated therapy environment for MWA under US guidance in this study. In this simulated therapy environment, radiologists can perform and optimize preoperative planning repeatedly without the patient's participation in the operating room. Relevant clinical trial studies have been performed for MWA therapy.

26.2.1 Segmentation of 2D Preoperative CT images

Segmentation of 2D CT images is the foundation for 3D visualization. Accurate and robust segmentation of hepatobiliary structures from medical imaging is a prerequisite for hepatic disease diagnosis and therapy planning. The segmentation results directly affect the subsequent quantitative analysis. The main tasks of segmentation consist of eliminating noise, defining ROI, categorizing the liver and tumors, and extracting the vessel. In computer-assisted therapy 3D system, the semiautomated segmentation is utilized to outline the hepatic artery, hepatic veins, portal vein, gallbladder, and the tumors and liver on the CT images. After segmentation, each structure is established as a layer and is outlined by contour line with a different color. Every image is segmented like this and each hepatobiliary structure is assigned an anatomical name as a data node.

26.2.2 Surface Rendering Reconstruction and 3D Medical Imaging

Surface rendering is used for the visualization of anatomical structures in the patient's body. Based on the contour of the segmented structures, surface rendering techniques can extract the isosurface from the 2D slice data and can represent the surface of the anatomical structures by a mosaic of connected polygons. The marching cubes algorithm is applied to place surface patches or tiles at each contour point, and with hidden surface removal and shading, the surface is rendered visible. The visual effects such as gray scale, color, and texture also appeared. Then the surface of these segmented structures can be projected on the screen. After surface rendering, the 3D medical imaging of anatomical structures in the ROI is reconstructed. 3D medical imaging is the foundation of data analysis of the 3D spatial relationships.

Some research showed that patient-specific image-based 3D medical imaging could resolve some important problems by permitting preoperative planning of the simulated thermal ablation based on preoperative images of the lesion [25, 26]. These problems include inaccurate puncture needle positioning, heat-sink effect

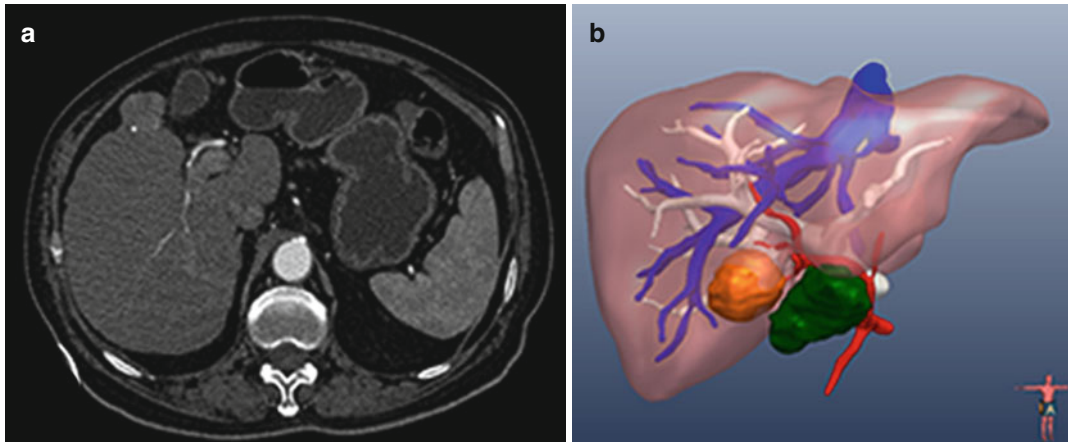

Fig. 26.1 2D CT image and the relevant 3D images. (**a**) The original CT image of the patient. (**b**) The surface rendering image of the liver (*brown*), the tumor (*yellow*), the bile ducts, the gallbladder (*green*), and the important pipeline structures (HA, *red*; HV, *blue*; PV, *white*)

from large blood vessels, and injury to adjacent organs. The original CT image of the patient and the 3D medical imaging created by computer-assisted 3D therapy system are shown in Fig. 26.1.

26.2.3 Data Analysis of the 3D Spatial Relationships

After reconstruction of the 3D medical imaging, the interventional radiologists can now perform various operations on the 3D medical imaging, such as hiding, visualizing, moving, scaling, rotating, and measuring. Data analysis can be carried out, and the 3D spatial relationships of the tumor and surrounding vital structures can be visualized in a 3D scene of the 3D computer-assisted therapy planning system. As shown in Fig. 26.2, from the graphical user interface (GUI) of the 3D computer-assisted therapy planning system, the interventional radiologists were able to see that the volume of the tumor was 8.6 ml; the maximum diameter of the tumor was 29.5 mm; and the shortest distance from the tumor to the HA, HV, PV, and gallbladder was 20.2, 2.4, 19.4, and 2.5 mm respectively.

26.2.4 Volume Rendering Reconstruction

Volume rendering technique is considered as the standard method in 3D medical image processing [27]. Surface rendering techniques can reconstruct the surface contours of the anatomical structures, but the internal information about the structures is disregarded. Volume rendering techniques can provide a volumetric display by rendering the entire volume of the data. Each attenuation value is attributed to a relative shading of opacity and color. The brightness of each voxel is determined by calculating a virtual light source [28]. Because the color and opacity of each attenuation value can be modified interactively, volume rendering is particularly helpful for the visualization of complex anatomical structure such as bones, vessels, tumors, and livers [12].

Because the contour of the structure does not need to be extracted beforehand and the voxel is used as the basic modeling unit, the reconstructed 3D medical imaging of the volume rendering reconstruction can be rendered and viewed directly. Using volume rendering techniques, the anatomical structures can be shown on the screen with rich internal details. 3D medical images of the volume rendering reconstruction

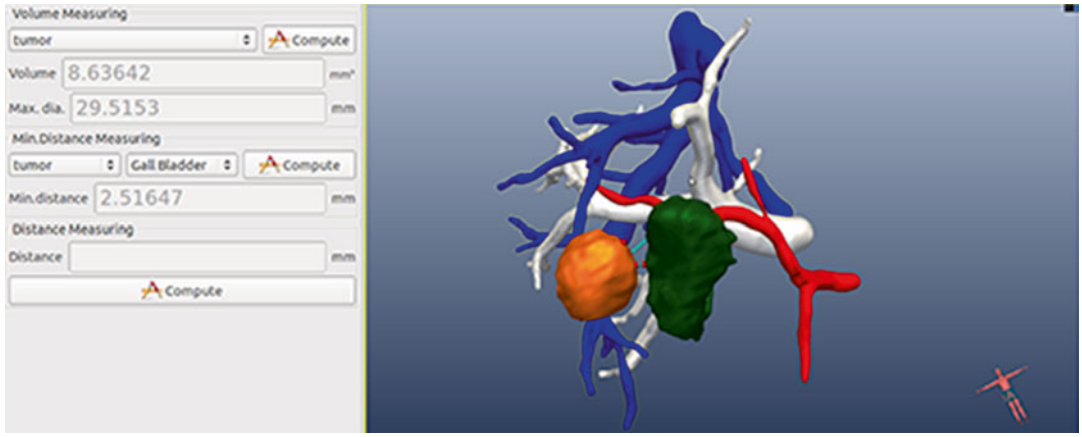

Fig. 26.2 From the 3D image navigation software, tumor volume, maximum diameter of the tumor, and minimum distance from the tumor to the surrounding duct system are calculated and displayed in the 3D scene

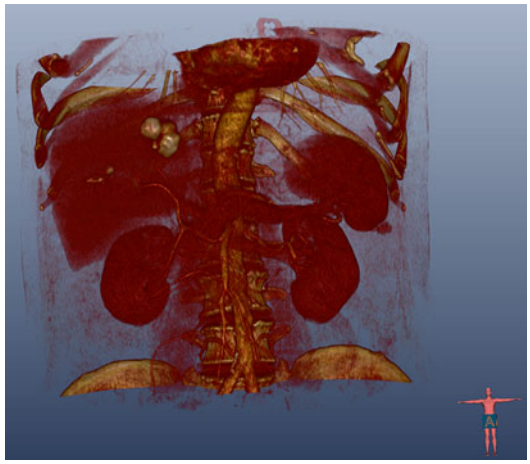

Fig. 26.3 The volume rendering imaging of CT data. These 3D images have more rich internal details than the surface rendering 3D images, but their interactive performance and efficiency of the algorithm are poor

are all of high quality, but the quantity of an operation is too large and the volume rendering process is slow. Volume rendering imaging can offer spatial information to assist interventional radiologists to determine the entry point and direction of the MW antennas without blocking the ribs.

Using volume rendering reconstruction tools, 3D medical images from the CT data of the patient are displayed in the GUI as shown in Fig. 26.3.

26.2.5 Combining Surface Rendering and Volume Rendering Reconstruction

According to the need of the preoperative plan, we combined surface rendering technique with volume rendering technique to reconstruct the anatomical structures for MWA. The liver, the tumor, the gallbladder, the HA, the HV, and the PV are reconstructed by surface rendering; other relevant anatomical structures of the abdomen in the CT image data are reconstructed by volume rendering.

As shown in Fig. 26.4, the tumor, the liver, the gallbladder, and the important pipeline structures (surface rendering) are displayed on the GUI, and its surrounding organs and structures (volume rendering) are displayed on the GUI simultaneously in the original place.

26.2.6 Virtual Reality

Virtual reality (VR) refers to a technique which uses a computer interface to simulate the 3D medical imaging of the anatomical structures, in a synthetic environment, a real or imaginary world, through the computer operator's senses. These are most commonly visual, tactile (haptic), or auditory senses and allow for an interactive,

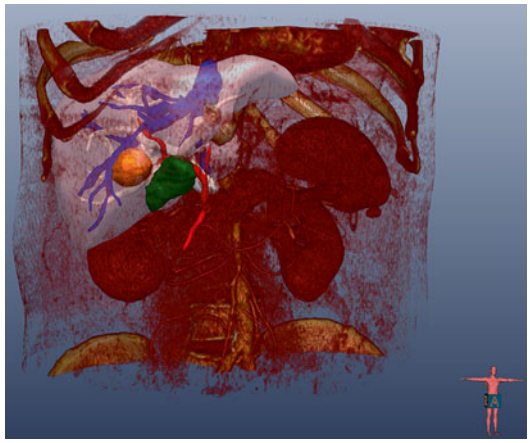

Fig. 26.4 Combining display of the tumor, the liver, the gallbladder, and important pipeline structures (surface rendering) and its surrounding organs and structures (volume rendering) in the original place. The combining display method provides fast interaction by surface rendering and displays the relevant organs and structures by volume rendering simultaneously

virtual environment. VR can simulate environments and create the effect of an interactive three-dimensional world in which virtual instrumentation can be used to perform therapeutical procedures in the simulated environments (Fig. 26.5).

26.3 Assistant Platforms

On the basis of 3D medical imaging and a patient-oriented risk analysis by using objective parameters, a virtual preoperative planning of the operation and an ablation evaluation of the risk–benefit analysis can be helpful in improving patient selection, reducing postoperative complications, and offering a potential new basis for therapeutic strategies. Combined with the 3D visualization technology and the VR technique,

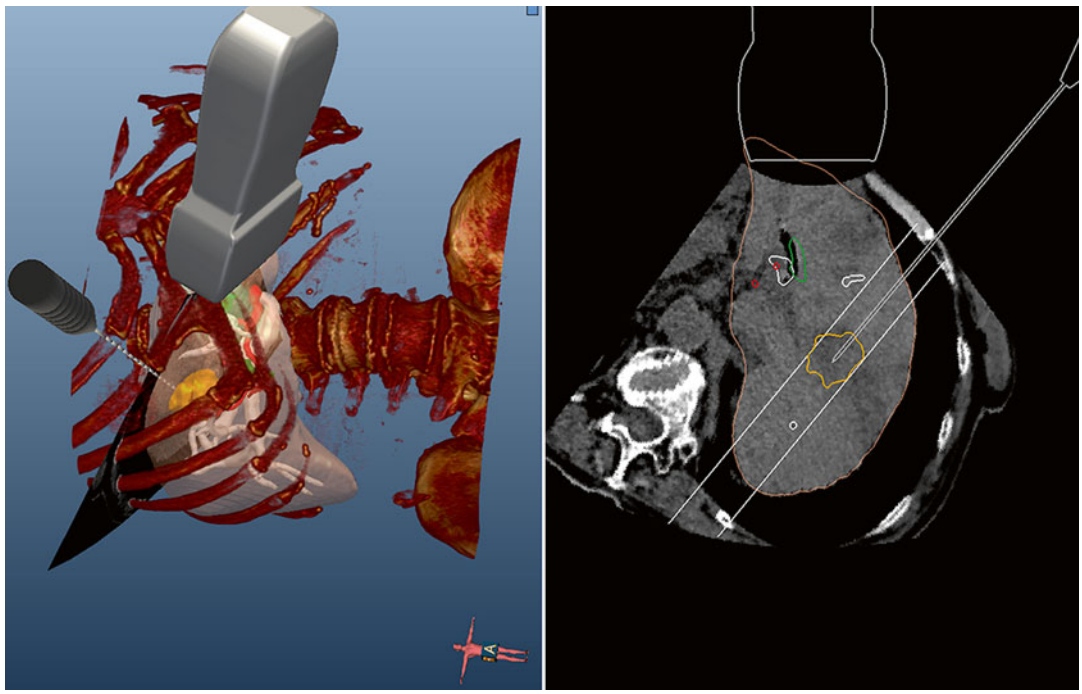

Fig. 26.5 The interactive graphical user interface of virtual reality environment. During the simulation puncture operation, the 3D models of the US probe, ablator antenna, and anatomical structures are showed in real time on the 3D GUI; and the corresponding CT image and the contours of the 3D models are showed in real time on the 2D GUI too

an assistant platform for 3D preoperative planning and an evaluation platform for 3D preoperative planning are established.

26.3.1 Assistant Platform for 3D Preoperative Planning

For MWA therapy, planning of puncture routes, antenna number, and locations of zones and any possible monitoring points need to be laid out carefully in advance. In a published study, regular prism and regular polyhedron models for preoperative planning are created for liver tumor ablation to minimize the number of ablation spheres, optimize the overlapping mode, and determine MW antenna placement [7]. 3D preoperative planning is performed by the interventional radiologist in an interactive way, until the optimal therapy plan is achieved. The plan includes the pose of the microwave probe and the microwave working time and power [29]. The purpose of preoperative planning is to predict the time–temperature profile and tumor-free safety margins before MWA. An accurate planning can assist interventional radiologists to improve the accuracy of the therapy, lower the rate of complications, and improve long-term survival outcomes.

Many researchers [30–33] reported that preoperative planning methods based on the 3D image data were feasible for thermal ablation. Computer 3D medical imaging of thermal therapy taking into account patient-specific anatomies was developed for hyperthermia applications [26, 29, 34–36]. In our self-developed 3D computer-assisted therapy planning system, preoperative planning is performed in a VR simulation environment based on patient-specific CT data. After finishing segmentation, surface rendering reconstruction, data analysis of the 3D spatial relationships, and volume rendering reconstruction, the VR simulation environment is established.

In the GUI of computer-assisted therapy planning system, interventional radiologists can adjust (including axial, rotate, and panning adjustment) the antenna path in accordance to the need for MWA.

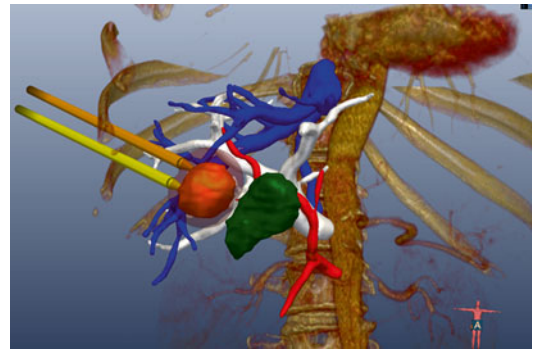

Fig. 26.6 The 3D preoperative planning is achieved, and two antennas are needed to ablate the tumor completely

According to our previous study [37–39], we set the power at 50 W and described the ablation zone as ellipsoid (when the emission time is 10 min, the short ellipse diameter (S) is 3 cm, and the long ellipse diameter (L) is 3.5 cm). The volume of the ablation zone is calculated in the 3D computer-assisted therapy planning system.

The GUI of the 3D preoperative plan is displayed in real time as shown in Fig. 26.6.

26.3.2 Evaluation Platform for 3D Preoperative Planning

The tumor map method by Rieder et al. [40] is selected in our system as one of our ablation evaluation tools. The tumor map is a pseudo-cylindrical mapping of the tumor surface onto a 2D image. It is used in a combined visualization of all ablation zones to allow a trustworthy therapy assessment. In the ablation evaluation platform, the safety margin of the ablation zone is 5 mm around the tumor surface, three ablation zones (see Fig. 26.7) in the spatial extent of the tumor are determined, and a light color scheme is used to emphasize the ablation state. The light color scheme is described as follows:

I. The ablation zone of the tumor inside of the safety margin is marked with green.
II. The ablation zone of the tumor outside of the safety margin is marked with yellow.
III. The zone of the tumor which could not be ablated is marked with red.

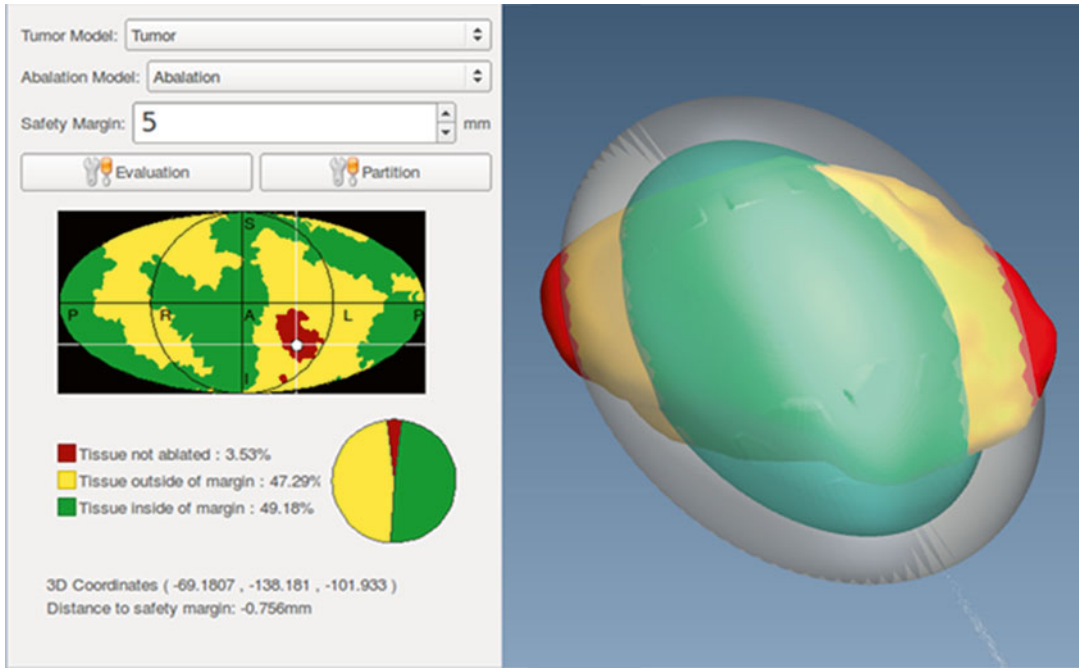

Fig. 26.7 The 3D tumor model and color scheme of the coagulation zones. *Red*, not ablated tumor tissue; *yellow*, tissue outside of margin; *green*, tissue inside of margin

Under the assistance of the ablation evaluation platform, interventional radiologists can interact with the virtual instrumentation to evaluate and optimize the preoperative planning in a 3D VR environment.

26.3.3 The Principles for 3D Preoperative Planning

In order to validate the clinical value of the application of 3D visualization technology, relevant clinical trial studies have been performed for MWA therapy. Enrolment conditions for the patients were as follows: liver cancer patients who met the indications for MWA and patients exhibiting close relationship between the tumor and the surrounding organs on 2D CT images.

The preoperative planning of MWA must abide the following principles:

I. The sum of the composite of the predefined ellipsoid-shaped ablation zones must cover the entire tumor.
II. The critical organs must not be transgressed or ablated.
III. The number of MW antenna insertions is minimized.
IV. The occurrence of damage to the surrounding pipeline structures is avoided strictly in the puncturing.

Conclusion

Using medical image 3D visualization technique, the CT data of patients was processed with the assistance of 3D computer-assisted therapy planning system. 3D medical imaging of the tumor, liver, HA, HV, PV, and gallbladder can be displayed stereoscopically on a PC and can be observed with a stereoscope. 3D medical imaging can also be displayed in multiple colors. They can be displayed alone, with other structures, or as a whole, or some of the structures being transparent, and can be continuously rotated in 3D space at different angles. They can fully reveal the complex relations between the structures of the liver.

Volume rendering model of the liver and its adjacent structures can assist interventional radiologists to select the puncture point and optimize therapy planning. Currently, ultrasound is an ideal tool with which interventional radiologists can attain anatomical information on the vessel and tumors in the liver during MWA. Its sensitivity and provision of real-time scanning allow tissue to be scanned while procedures are underway. However, 2D ultrasound imaging becomes increasingly difficult to target deep structures accurately. Because liver anatomy is complex, the optimal approach of instruments and MW antennas to tumors often cannot be achieved in exact alignment with the 2D ultrasound imaging. So, 3D medical imaging is an important visual aid to the interventional radiologist in order to facilitate crucial decisions and to lower the operative risk. By applying 3D visualization techniques, superior accuracy in MWA has been achieved with the assistance of 3D computer-assisted therapy planning system. Therefore, the application of the medical image 3D visualization technique has a relatively sharp clinical application value.

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27 Clinical Application of Three-Dimensional Visualization Techniques in Microwave Ablation for Liver Cancer

Fang-Yi Liu and Ping Liang

Abstract

This chapter introduces a three-dimensional (3D) visualization navigation system and its clinical application in preoperative planning, intraoperative positioning, and postoperative assessment during microwave ablation of liver tumors, respectively. Compared with two-dimensional preoperative planning group, the 3D visualization preoperative planning group has a higher successful rate of first ablation and less number of sessions. The 3D visualization navigation system has the advantage of image fusion in commercial navigation system; in addition, 3D visualization image will provide more information for microwave ablation and enhance ablation efficacy and decrease the complication. In postoperative assessment, 3D visualization navigation system could visually and quantitatively display the postoperative efficacy of microwave ablation in liver cancer. Therefore, the 3D visualization navigation system has a relatively high clinical application value in the whole process of microwave ablation for liver cancer.

Keywords

Microwave • Ablation technique • Three-dimensional visualization Preoperative treatment planning • Liver cancer

Abbreviations and Acronyms

2D Two-dimensional
3D Three-dimensional

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27.1 Introduction

With the techniques development, thermal ablation has been a curative method in the treatment of liver cancer [1]. To obtain a good clinical efficacy, scientific preoperative planning, precise intraoperative positioning, and accurate postoperative assessment are three key steps of thermal ablation. The whole ablation procedure has usually been performed using two-dimensional (2D) imaging data [2]. The radiologist must

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reconstruct a three-dimensional (3D) image in their own perception during thermal ablation for liver cancer. However, this is dependent on their spatial awareness and experience, which is highly subjective. If the radiologist's judgment is not consistent with the actual situation, it will lead to treatment failure or major complications.

In order to overcome the shortcomings of 2D imaging techniques for thermal ablation, 3D imaging techniques have been developed over recent years [3, 4]. At first, 3D imaging techniques were used in surgical operation, and so far there have been a number of methods and software systems for 3D surgical planning for liver surgery [5, 6]. In particular, the application of 3D visualization technology allows the physicians to perform various operations on the image, such as rotation, scaling, and moving, to see more intuitively the internal complexity of the structure of the human tissue. The doctor may conduct repeated preoperative planning in the individual 3D model of surgical planning, to optimize the surgical program, improve surgical skills, improve the safety of surgery, and reduce surgical complications [7–10].

The 3D surgical planning method is not available for the image-guided percutaneous thermal ablation, due to the differences in operation way between the image-guided percutaneous thermal ablation and surgical resection. Besides quantitative calculation of the tumor volume and the distance between the tumor and surrounding vital structures, accurate simulation of 3D thermal field, and the planning of puncture path are required for image-guided thermal ablation therapy as well. 3D visualization preoperative planning method has been applied to thermal ablation in liver cancer [11–13], which could intuitively display ablation planning through the segmentation of tumor and vascular and 3D volume reconstruction and avoid thermal damage to surrounding structures. A novel 3D visualization preoperative surgery planning method was proposed for percutaneous hepatic microwave ablation by Zhai [14]; however, the preoperative planning system reported for the puncture path planning was only based on computed tomography (CT) image or/and 3D visual image, which cannot satisfy the requirements of multi-modality image guidance. On the basis of the characteristics and clinical application requirements of image-guided percutaneous thermal ablation for liver tumor, we combined 3D image processing and analysis methods with navigation technology, to establish a 3D visualization navigation system in microwave ablation for liver tumors. In this part, we will introduce the application of the 3D visualization navigation system in microwave ablation procedures for liver tumors, including preoperative planning, intraoperative positioning, and postoperative assessment.

27.2 Composition of a 3D Visualization Navigation System

A computer-assisted 3D visualization navigation system is developed that integrated electromagnetic tracking technology with guidance and planning software. The system enables the operator to load the preprocedural images, perform offline tumor segmentation, and create a treatment plan. The system is developed based on a commercially available electromagnetic tracking system (Aurora; Northern Digital, Ontario, Canada). The system also includes a simulation model (Model071, CIRS, USA), an ultrasound probe, and appropriate computer hardware. There are two sensors, one attached to the ultrasound probe and the other attached to the simulation model (Fig. 27.1).

27.3 Image Guidance Software and Tumor Segmentation

The image guidance software package was developed by our research team. The software provides the basic components needed for rapid prototyping and the development of image-guided microwave ablation applications. The graphical user interface displays the real-time simulation ultrasound 2D guided planning and the 3D visualization planning, as well as the

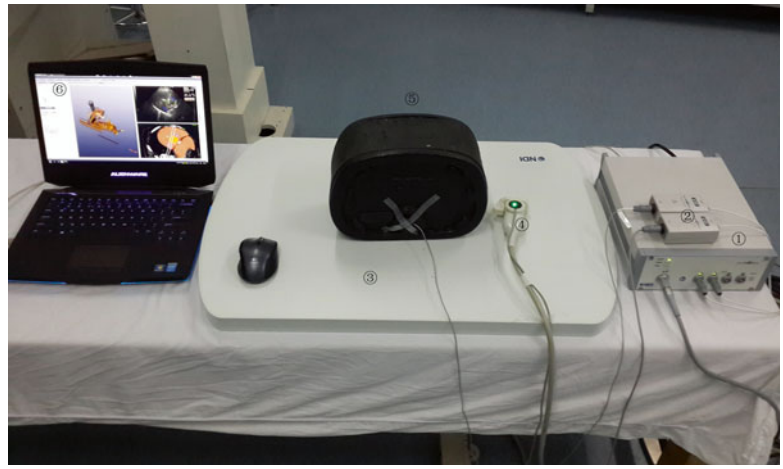

Fig. 27.1 Physical setup and components of three-dimensional (3D) visualization preoperative treatment planning system. Legend: ① a control unit of the electromagnetic tracking system ② two sensor interface devices of the electromagnetic tracking system ③ a field generator of the electromagnetic tracking system ④ tracked ultrasound probe ⑤ a simulation model ⑥ screen

planning path from the transverse, coronal, and sagittal plane. The tumor is segmented in a semi-automatic manner using the open source program FITME (http://www.fitme.org). The same user interface is also employed to allow the interventional radiologist to contour the tumor. Additionally, the system could visually display the tumor size and the distance between the tumor and the surrounding pipeline structure and organization.

27.4 Function of 3D Visualization Navigation System

Preoperative planning could be performed based on not only the 2D imaging but also 3D visualization model using this system, which could avoid the shortcomings of 2D imaging planning. Our approach to covering the entire tumor with a series of ablation spheres is based on the following guiding objectives: (1) covering the entire tumor plus a predefined ablative margin with a composite of spherical thermal fields, (2) minimizing the number of ablations, (3) minimizing the number of electrode insertion trajectories, and (4) avoiding any critical organ transgression or ablation. The planning software is designed to iterate through these goals until a complete treatment plan was finalized.

3D visualization navigation system combined with 3D visualization and navigation technology, focusing on the research of navigation parameters interface and image registration fusion. This system achieves the fusion of 2D ultrasound image and 3D visualization graphics and the display of navigation parameters interface, and it could be applied in image-guided intraoperative positioning in thermal ablation. In addition, this system could execute the preoperative planning accurately and improve the positioning capability of beginners by using it.

The quantitative assessment of postablation has always been a difficult point. 3D visualization navigation system could intuitively and quantitatively show the relationship between the tumor and ablation zone after ablation, realize quantitatively assessing ablation efficacy. The results of our simulated experiments showed that the accuracy rate of estimating tumor ablation efficacy by using this system was significantly higher than that by using conventional 2D imaging method.

27.5 Clinical Application of 3D Visualization Navigation System

3D visualization techniques can be used in every step of microwave ablation for liver cancer, including preoperative planning, intraoperative positioning, and postoperative assessment. We

will introduce separately the clinical application of 3D visualization navigation system in three steps as follows.

27.5.1 Preoperative Planning

Preoperative treatment planning as the first step in the thermal ablation process acts to lower the rate of complications, ensure tumor-free safety margins after ablation, and improve long-term survival outcomes. The procedure of application of 3D visualization navigation system in preoperative planning is as follows: first, 3D visualization images are acquired according to the CT imaging data of patients in DICOM format; second, processing and analysis of the CT images is performed, and simulated ultrasound images are acquired; third, image registration is performed; fourth, doctors perform the preoperative planning using 3D visualization preoperative treatment planning system. The planning results are completed, including the number of planning insertions, the depth of insertions, angle of needles, and so on.

Liu et al. [15] reported the clinical application of 3D visualization preoperative planning in microwave ablation in liver cancer. Ninety-four enrolled patients with liver cancer were divided into two groups. The 3D preoperative planning group included 36 patients with 44 lesions, who underwent microwave ablation with the aid of the self-developed 3D visualization navigation system. The 2-dimensional (2D) preoperative planning group included 58 patients with 64 lesions, who underwent microwave ablation according to conventional 2D image preoperative planning method. After microwave ablation, therapeutic efficacy was assessed by contrast-enhanced imaging during follow-up. Results showed that the 3D preoperative planning group has a higher successful rate of first ablation than 2D preoperative planning group ($p=0.01$). The sessions are more in 2D preoperative planning group than that in 3D preoperative planning group ($p=0.002$). There were no significant differences in technique effectiveness rate between the 2D preoperative planning group (96.55 %) and 3D preoperative planning group (100 %) according to the contrast-enhanced images follow-up after microwave ablation ($p=0.64$). There were no significant differences in the rate of local tumor progression between the 2D preoperative planning group and 3D preoperative planning group ($p=0.64$) during 3–12 months' follow-up (median, 6 months). Compared with 2D preoperative planning group, the 3D preoperative planning group has a higher successful rate of first ablation and less number of sessions. The application of 3D visualization preoperative planning system reduced the number of sessions compared with conventional 2D imaging preoperative planning method. Less session of ablation means less risk and less cost of hospitalization and shorter hospital stay, so the application of 3D visualization preoperative planning system is beneficial to patients with liver tumors. Meanwhile, based on the results, the 3D preoperative planning improved the accuracy of the positioning and may strengthen doctors' confidence in ablation therapy. Therefore, the 3D visualization navigation system has a relatively high clinical application value in preoperative treatment planning of microwave ablation for liver cancer (Fig. 27.2).

27.5.2 Intraoperative Positioning

Intraoperative positioning is the second key step of microwave ablation for liver cancer. Precise intraoperative positioning could be realized by using the navigation techniques. The 3D visualization navigation system achieved the fusion of 2D ultrasound image and 3D visualization graphics and the display of navigation parameters interface. This system could execute the preoperative planning accurately and improve the positioning capability of beginners by using it. The 3D visualization navigation system has the advantage of commercial navigation system; in addition, 3D visualization image will provide more information for microwave ablation and enhance ablation efficacy and decrease the complication.

From August 2012 to December 2013, 31 patients with 39 hepatocellular carcinoma nodules, consisting of 25 males and 6 female aged 35–82 years (mean, 57.8 ± 10.3 years), were performed microwave ablation assisted with 3D visualization navigation system in our

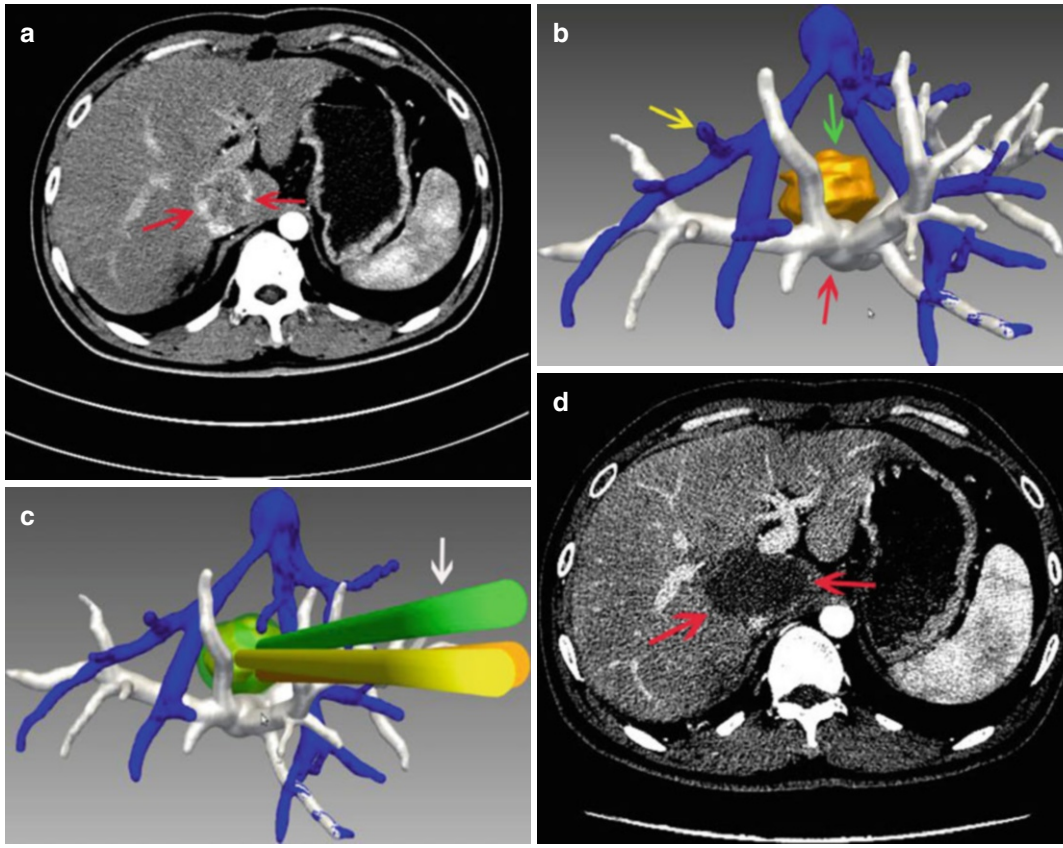

Fig. 27.2 Images in a 45-year-old patient with a tumor in the caudate lobe. (**a**) Preoperative CT image showed that the tumor (*red arrows*) was close to portal vein. (**b**) The 3D visualization images visualized the spatial relationship of tumor and the surrounding pipe in multi-angle. (*yellow arrow*: hepatic vein; *green arrow*: tumor; *red arrow*: portal vein) (**c**) The preoperative planning was achieved through 3D visualization of preoperative planning system, and three needles (*white arrow*) were needed to ablate the tumor completely. (**d**) The contrast-enhanced CT showed complete tumor necrosis (*red arrows*) a month after microwave ablation (MWA)

department. The maximum diameter of the hepatocellular carcinoma nodules ranged from 15 to 63 mm (mean, 28 ± 2.3 mm). The follow-up time was 3–16 months (median, 8 months) in our study. All nodules were positioned precisely, and microwave ablation was performed successfully. Local recurrence was observed only in one patient during follow-up (Fig. 27.3).

27.5.3 Postablation Evaluation

The assessment of ablation efficacy, whether tumor is ablated completely or not and whether residual tumor or marginal recurrence occurred or not, is performed by the doctor based on two-dimensional contrast-enhanced imaging before and after treatment, such as contrast-enhanced CT, magnetic resonance imaging, and contrast-enhanced ultrasound. It is difficult to determine the original location of the lesion after ablation, so it is difficult to conduct a comprehensive and accurate safety margin assessment. In addition, this assessment method greatly depends on the doctor's personal experience, which has become a technical problem of the evaluation of tumor ablation efficacy. We have established a three-dimensional visualization evaluation platform that will unify the spatial information of preoperative and postoperative enhanced imaging into the same coordinate system, and the distance between the tumor margin and the ablation

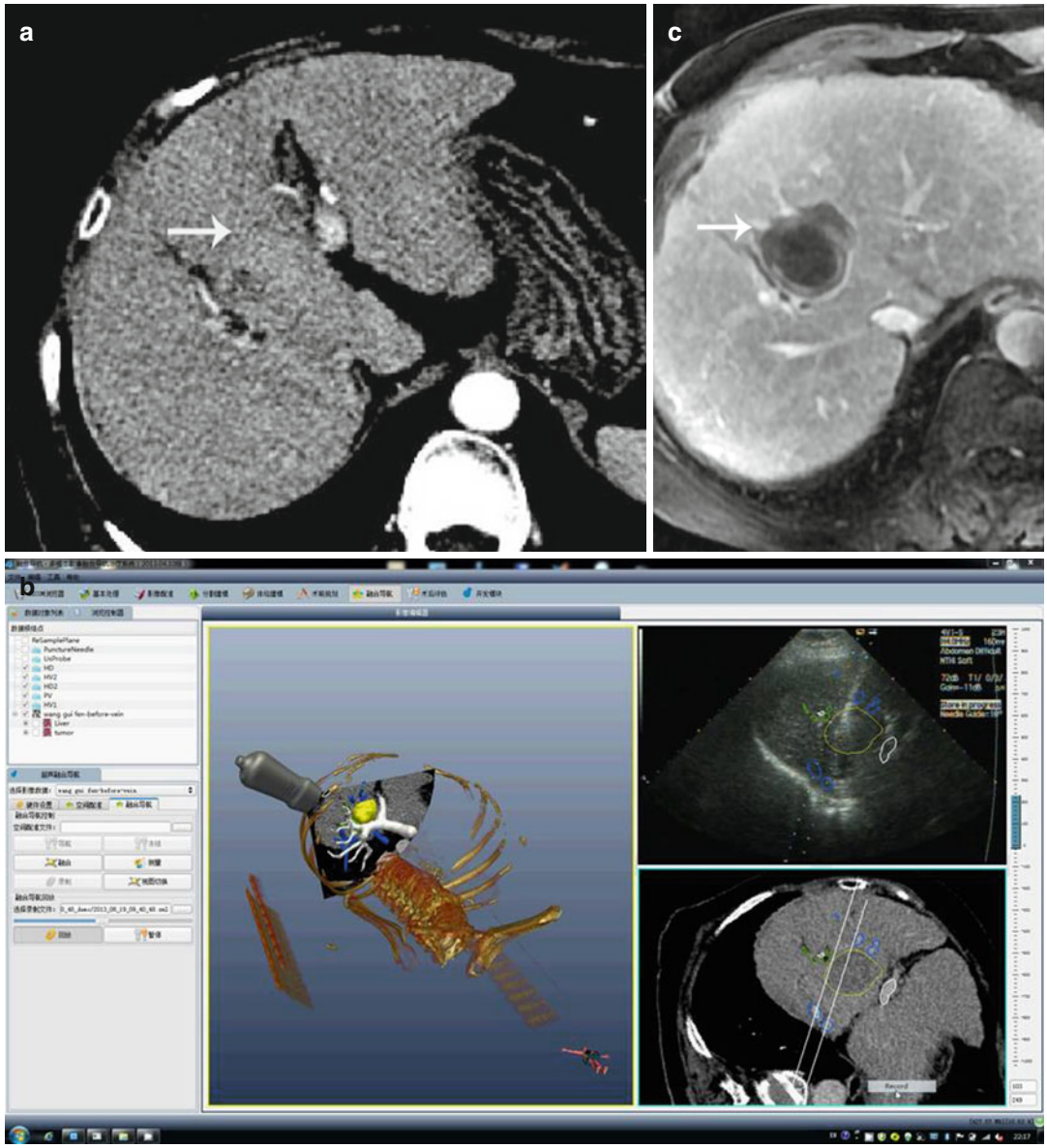

Fig. 27.3 Images in a 75-year-old patient with a tumor in the liver segment VIII. (**a**) Preoperative CT image showed that the tumor (*white arrow*) was close to portal vein. (**b**) The patient was performed MWA assisted with 3D visualization navigation system. (**c**) The contrast-enhanced magnetic resonance imaging showed complete tumor necrosis (*white arrow*) a month after MWA

zone boundary can be quantitatively calculated. Our preliminary clinical application showed that 3D visualization navigation system could visually and quantitatively display the postoperative efficacy of microwave ablation in liver cancer (Fig. 27.4).

27.6 Discussion

In recent years, 3D image techniques have been applied to thermal ablation [11–13]. Sato et al. [16] and Morikawa et al. [17] reported a preoperative planning method which is feasible for

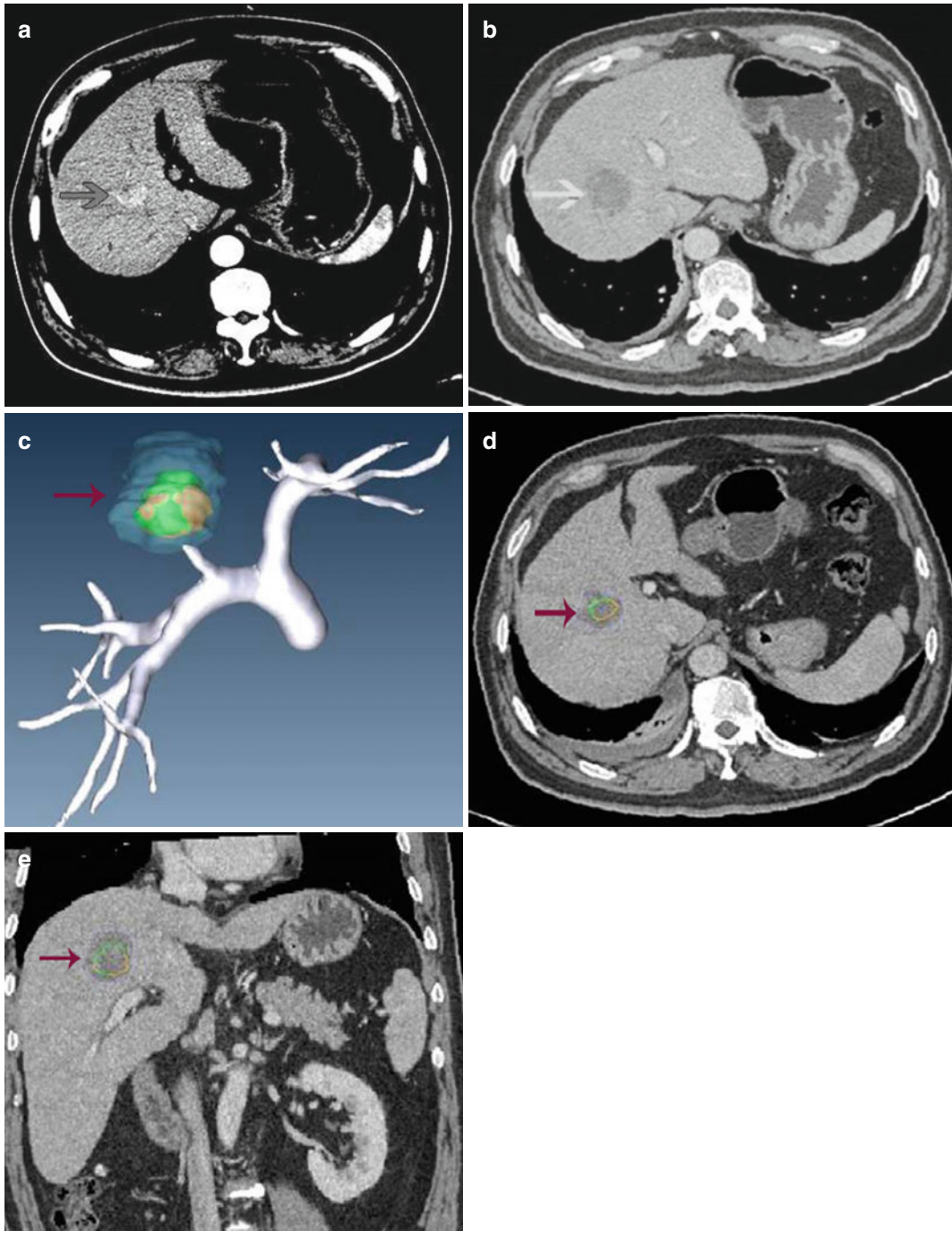

Fig. 27.4 Images before and after ablation therapy and 3D visualization curative effect evaluation results. (**a**) Preoperative enhanced CT showed right anterior lobe of the liver mass (*arrow*); (**b**) ablation zone (*arrow*) was unenhanced after ablation; (**c**) 3D visualization image showed ablation efficacy of the ablation zone covering the original tumor (*arrow*). Green area reached a security boundary, and the yellow area did not reach the safety margin; (**d, e**) two-dimensional display of ablation efficacy results (*arrow*). The green line represents that safety margin of the tumor was reached and the yellow line area represents that safety margin was not reached

MR-guided microwave ablation of liver tumors, while complete 3D visualization information was not included. Keserci et al. [18] reported a dedicated temperature imaging feedback control system to guide and assist in a thermal liver ablation procedure; although target visualization, treatment planning and monitoring, and temperature and thermal dose visualization with the graphical user interface of the thermal ablation software were demonstrated, the system can only be applied in magnetic resonance imaging-guided liver thermal ablation therapy.

A 3D visualization navigation system introduced above can visualize the spatial relationship of the tumor and surrounding structures in a 3D manner, calculate the distance from the tumor to the surrounding vital structures or organs, and provide the minimum number of insertions and the best needle path and other parameters of the treatment. Preoperative planning can be repeated in the 3D visualization system, to optimize treatment planning, which may improve the success rate of ablation therapy and reduce the incidence of complications. Compared with commercial 3D image system, the 3D visualization navigation system can provide real 3D visualization information and can be applied in not only preoperative planning but also intraoperative positioning and postoperative assessment.

Conclusions

In preoperative planning, compared with 2D preoperative planning group, 3D visualization preoperative planning group has a higher successful rate of first ablation and less number of sessions. In intraoperative positioning, 3D visualization navigation system has the advantage of commercial navigation system; in addition, 3D visualization image will provide more information for microwave ablation and enhance ablation efficacy and decrease the complication. In postoperative assessment, 3D visualization navigation system could visually and quantitatively display the postoperative efficacy of microwave ablation in liver cancer. Therefore, the 3D visualization navigation system has a relatively high clinical application value in the whole process of microwave ablation for liver cancer.

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Microwave Ablation Assisted by a Real-Time Virtual Navigation System for Liver Cancer

28

Fang-Yi Liu, Ping Liang, Xiao-ling Yu, Zhi-Gang Cheng, Zhi-Yu Han, and Jie Yu

Abstract

Imaging-based navigation is a new technology that allows the fusion of real-time ultrasonography and preoperative positron emission tomography or computed tomography or magnetic resonance imaging data. We reviewed the application of navigation system in microwave ablation for hepatocellular carcinoma. Navigation systems for ablation bring the opportunity for standardization and accuracy that extend the operator's ability to use imaging feedback during procedures and the indications of ablation. Navigation techniques will play an important part in microwave ablation in the future, especially in the application of integrated ablation treatment plans. Such standardization should decrease the variability of practice patterns and even enable less experienced operators to deliver precise ablations.

Keywords

Microwave ablation • Real-time virtual navigation • Hepatocellular carcinoma

Abbreviations and Acronyms

CT	Computed tomography
EM	Electromagnetic
MRI	Magnetic resonance imaging
MW	Microwave
US	Ultrasonography

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28.1 Introduction

Thermal ablation therapy, such as radiofrequency ablation or microwave (MW), is a widely used method for solid tumors, especially for liver tumors, which has been a curative method for small liver cancer [1]. MW ablation is a promising minimally invasive treatment method for liver tumors, which has been performed by using ultrasonography (US), computed tomography (CT), or magnetic resonance imaging (MRI) guidance [2–4]. US is real time and allows to scan the body from different positions and angles, so compared with CT or MRI guidance, MW

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ablation under the guidance of US is more convenient. However, there are occasions when liver lesions are inconspicuous to US imaging, but are only optimally visualized on positron emission tomography or contrast-enhanced CT and MRI, due to the texture or the location of the lesion [5–7]. In this situation, the physician conventionally makes use of this information by mentally registering the anatomic information from offline modalities (contrast-enhanced CT or MRI) to the modality (US) used for guiding the actual procedure. This process can be inexact and may be prone to human error and inaccuracies [8].

Imaging-based navigation is a new technology that allows the fusion of real-time US and preoperative positron emission tomography or CT or MRI data. This multimodality matching, which has been used in nuclear medicine, radiotherapy, and neurosurgery [9–11], can provide more useful integrating information, such as intuitive 3D information. With the development of magnetic navigation system, it brings the opportunity for standardization and accuracy that extends the operator's ability to use imaging feedback during ablation procedures, with its own specific operational conditions [12–14]. In this part, we review the application of navigation system in MW ablation for hepatocellular carcinoma.

28.2 Navigation System

There are several methods by which to enable navigation during image-guided procedures with codisplay of multiple data sets. Each method includes (1) the capability to import previously acquired image data sets to be registered with a selected real-time imaging modality and (2) the ability to display the position of the procedure device in the fused data sets in static or real-time fashion. Electromagnetic (EM) tracking and optical tracking provide real-time position data for tracked instruments in a virtual space. Optical systems are inspired by parallax satellite systems and use infrared or laser light-emitting diodes localized on (or reflected from) instruments within the field of view of an infrared camera [15, 16]. The advantage of optical systems is higher accuracy; however, their widespread use has been precluded by the "line of sight" requirement, which is the necessity of a direct unimpeded pathway between camera and tracked instrument [14–16]. Due to the limitation of optical systems, the tracking system in the clinical application mostly is EM tracking system. EM tracking is sometimes referred to as "medical GPS" [14, 17] and relies on Faraday's law of induction. The benefit of EM tracking (vs. optical) is that the device can reside out of sight and within the patient's body without erosion of signal. A generator creates numerous weak and differential magnetic fields that turn on and off within a work volume of approximately $500 \times 500 \times 500$ mm. Two major vendors manufacture the EM tracking equipment: Northern Digital (Waterloo, California) and Ascension Technology (Milton, Vermont). Multiple vendors have EM tracking solutions for percutaneous procedures with varying degrees of complexity: Philips Healthcare (Eindhoven, The Netherlands), Siemens (Erlangen, Germany), GE Healthcare (Milwaukee, Wisconsin), Veran Medical (St. Louis, Missouri), Esaote (Indianapolis, Indiana), CIVCO (Kalona, Iowa), Hitachi (Twinsburg, Ohio), Sentinelle (Toronto, Ontario, Canada), Ultrasonix (Richmond, British Columbia, Canada), and Traxtal (Toronto, Canada). Take a commercially available multimodality fusion imaging system (MyLab90 System equipped with Virtual Navigator, Esaote SpA, Genoa, Italy) for example. The real-time virtual navigation system consists of a transmitter and two magnetic sensors. The transmitter is fixed to the operation bed. One magnetic sensor is applied to the sonographic probe (3.5-MHz curvilinear probe), which can detect the position of the sonographic probe. The other one is mounted on the microwave antenna, which can detect the position of the microwave antenna (Fig. 28.1). The information from the tracking device and the DICOM volume data of the second modality (CT or MRI) is combined to compute a virtual slice image that is spatially consistent with the displayed US image. Virtual Navigator displays on the monitor both the ultrasound and the second modality image in the same dimension and cut plane.

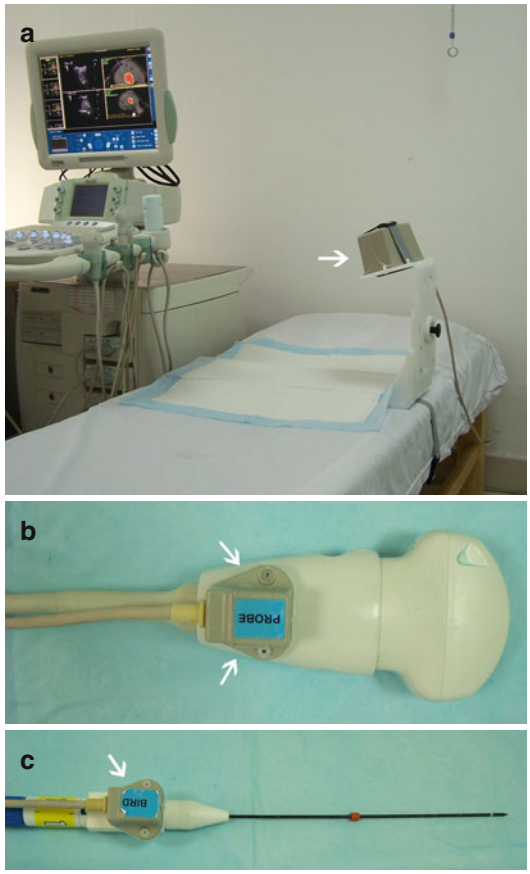

Fig. 28.1 (**a**) A real-time virtual navigation system. The transmitter is fixed to the operation bed (*arrow*). (**b**) A magnetic sensor is applied to the sonographic probe (*arrow*). (**c**) A magnetic sensor is mounted on the microwave (MW) antenna

There are three registration methods of a second modality images data to intraprocedural US images: internal markers method, external markers (the markers will cling to the surface of patients' abdomen before CT or MRI examination) method, and topographical (xiphoid, sternum, and umbilicus) landmarks method. Among those, internal markers method is used mostly.

The accuracy of navigation system in biopsy and ablation procedures has been reported in a range that is consistent with clinical utility [17–19]. In the study by Penzkofer et al. [20], 23 patients underwent image-guided interventions using EM tracking navigation with a reported spatial accuracy of 3.1 ± 2.1 mm. Our previous ex vivo experimental results [21] showed the accuracy of the matched US-CT images was very satisfactory in the fact that it was found there was a mean discrepancy of 1.63 ± 1.06 mm. Therefore, the accuracy of navigation system could satisfy the condition of MW ablation.

28.2.1 Microwave Ablation Procedures Assisted by Navigation System

MW ablation procedures assisted by navigation system are introduced as follows based on the virtual navigation system (taking MyLab90 System equipped with Virtual Navigator, Esaote SpA, Genoa, Italy as example). Prior to MW ablation, DICOM volume data from MRI (or CT) were loaded on the fusion imaging system apparatus. The patient lay in the operation bed with supine position which is the same to the CT or MRI examination. B-mode ultrasound images and the second modality images (MRI or CT images) are synchronized using the internal markers at the best timing of the inspiration. First, a US image is selected as the first marker plane (sagittal part of portal vein, spleen vein, etc.) while the probe is perpendicular to the abdominal wall of the patient, and then the US image and the second modality image are adjusted in order to make the two displayed planes overlap completely. Second, another US image is selected as the second marker plane (right branch of portal vein, cysts, etc.), and the US image and the second modality image are made to overlap completely with the fine-tuning mode. Last, whether the fusion image is satisfied or not is verified, using the larger vessels of liver as a reference, when the patient was at the end of calm inspiration. If the distance of the same point between US image and the second modality image was less than 5 mm, the fusion image was considered successful; otherwise, we readjust the US image and the second modality image until the fusion image was satisfied. The time required for image fusion was recorded.

After the fusion image is completed, the MW ablation is performed under real-time virtual navigation system guidance with the patients under unconscious intravenous anesthesia (propofol

and ketamine) in the operating room. A detailed protocol including the placement of the antennae, power output setting, emission time, and appropriate approach is worked out for each patient on an individual basis before treatment. Sterilizable biopsy kit (ABS 421, Esaote, Genoa, Italy) and sterilizable mounting brackets with disposable needle guide (DBS421/431, Protek Medical, Coralville IA, USA), with biopsy needle angles of 20° and 30°, have been used to guide the needle insertions. The tumors, well visible in the CT or MRI (and inconspicuous on US), have been "targeted" using the information coming from the fusion image. A 15G MW antenna (Kangyou Corporation, China) is inserted into the liver using real-time guidance and biopsy kit. The virtual needle is displayed computing its projection on the biopsy line. In general, MW ablation is performed at 50 W using one to two cooled-shaft antennae simultaneously. During MW ablation the hyperechoic area of ablation is monitored using gray-scale sonography, because the second modality image may be overlapped on the current ultrasound situation. The treatment session would be ended if the transient hyperechoic zone between antennae on gray-scale US merged and covered the target region. When withdrawing the antennae, the needle tracks are routinely cauterized to avoid tumor seeding and bleeding.

28.2.2 Clinical Use of Navigation System

The potential clinical indications for the use of navigation technique during microwave ablation are as follows: lesions seen only on CT or MR imaging and lesions not seen at all on US; composite ablations requiring multiple needle insertions, complex geometries, or difficult treatment plan; identification of safest pathway, given complex angle of insertion; and dome lesions or lesions under the ribs. Electromagnetic navigation is forbidden to use for the patient with a pacemaker, while optical navigation is available for this.

Navigation technique offers a distinct advantage in cases where the target lesion is not readily visible with conventional imaging guidance, such as ultrasound and CT, without iodinated contrast administration. Several studies have reported the usefulness of navigation technique for lesions that are indistinct, heterogeneous, or only visible on PET-CT [14, 22, 23]. Navigation technique may enhance ablation planning and execution, especially if US visualization is hindered by ablation gas. Ablation-planning software enables visualization of the potential ablation zone, depending on probe type, number, and position, to facilitate attempts for complete tumor coverage. Moreover, there may be advantages in terms of delivering a prescribed treatment plan or adding together multiple individual ablations to fully envelop a tumor with a composite ablation (i.e., multiple overlapping ablation volumes) [24–26].

From October 2009 to December 2012, 34 patients with 36 HCC nodules, consisting of 32 males and 2 female aged 42–78 years (mean, 59.1 ± 9.3 years), were performed microwave ablation assisted with navigation in our department. Of all patients, 33 patients had hepatitis B- or C-induced liver cirrhosis, and one patient had biliary cirrhosis (Child-Pugh A, 32; Child-Pugh B, 2). HCC was diagnosed using imaging analysis, including dynamic contrast-enhanced CT or MRI. The maximum diameter of the HCC nodules ranged from 9 to 38 mm (mean, 19.2 ± 7.3 mm). Among the 34 patients, five had received TACE within 1 month before MWA in this series.

We synchronized successfully B-mode ultrasound images with the second modality images (MRI or CT images) using the internal markers at the best timing of the inspiration for all the patients. The target HCC nodule and viable portion of the HCC could be detected with fusion image in all patients. The time required for image fusion was 5–30 min (mean, 12.2 ± 5.5 min). MWA was successfully performed in all patients. Of all 36 lesions, 35 lesions were successfully ablated according to the contrast-enhanced imaging 1 month after ablation. The technique effectiveness rate was 97.22 % (35/36). For the other one patient, the lesion was not ablated completely according to the contrast-enhanced MRI, and the ablated area was close to the lesion. Another MW ablation was performed for the patient. After MW ablation, mild pain and fever were noted,

but no severe complications occurred. Even the tumor lesions directly beneath the diaphragm were ablated without side effects such as injury of the diaphragm. No thermal injuries to adjacent structures or organs occurred. The follow-up time was 6–24 months (median, 12 months) in our study. No local recurrence was observed in any patients (Figs. 28.2 and 28.3).

28.3 Advantage and Limitation of Navigation Techniques

The real-time virtual navigation system has several important features in the application of MW ablation therapy, which assure the MW ablation performed successfully. The first is compatibility. The real-time US imaging modality can be registered with preoperative CT or MRI data, the

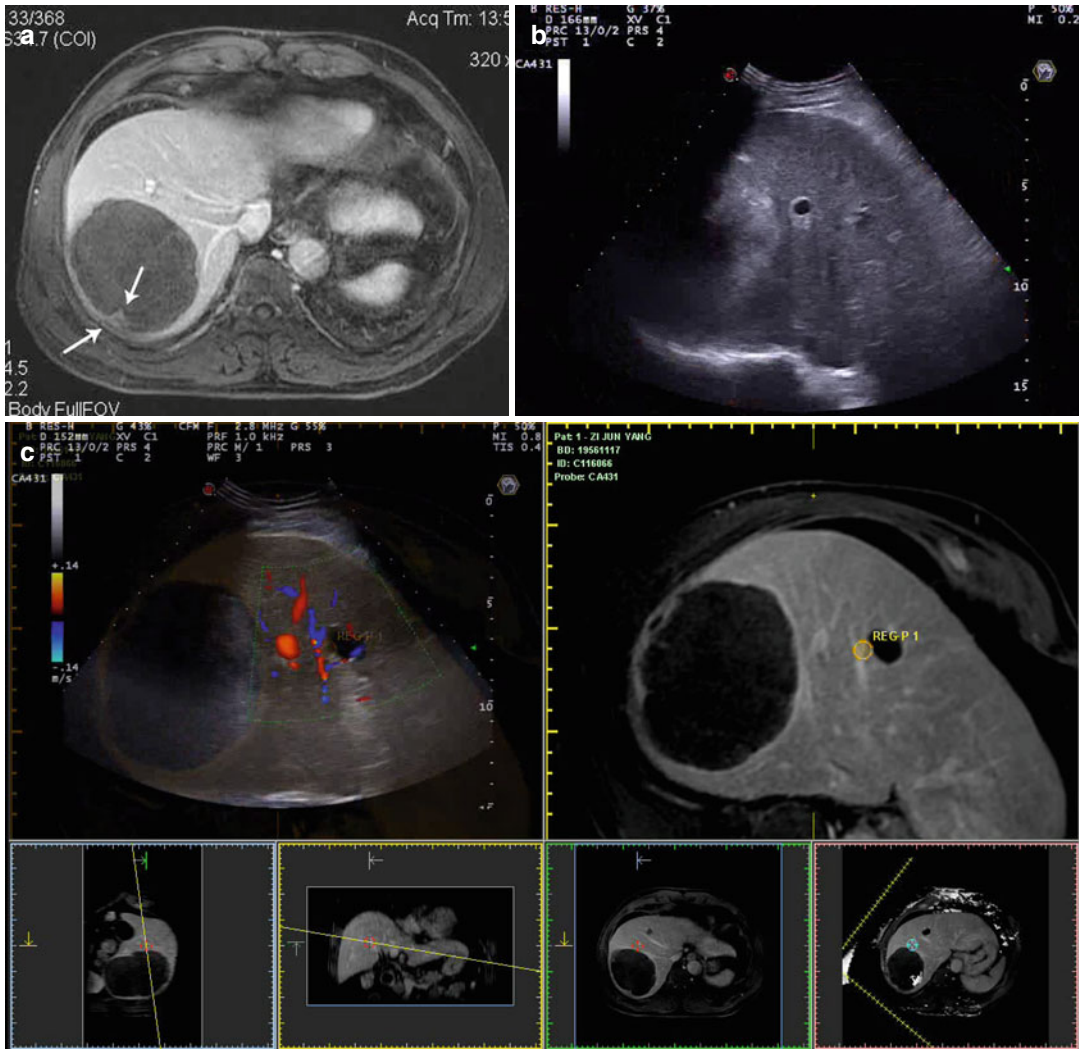

Fig. 28.2 Images in a 54-year-old male with a 1.4 × 1.3 cm residual tumor of hepatocellular carcinoma (HCC) after transcatheter arterial chemoembolization in segment VII of the liver. (**a**) Contrast-enhanced magnetic resonance imaging (MRI) shows a residual tumor (*arrows*) adjacent to the diaphragm. (**b**) Conventional US could not detect the lesion. (**c**) Ultrasound (US) images and MR images were synchronized using the internal markers at the best timing of the inspiration. (**d**) MW antenna was inserted into the tumor under real-time virtual navigation system guidance. The virtual needle was displayed on the biopsy line (*arrows*). (**e**) Contrast-enhanced MRI obtained 1 month after MW ablation shows complete necrosis of the residual tumor (*arrows*)

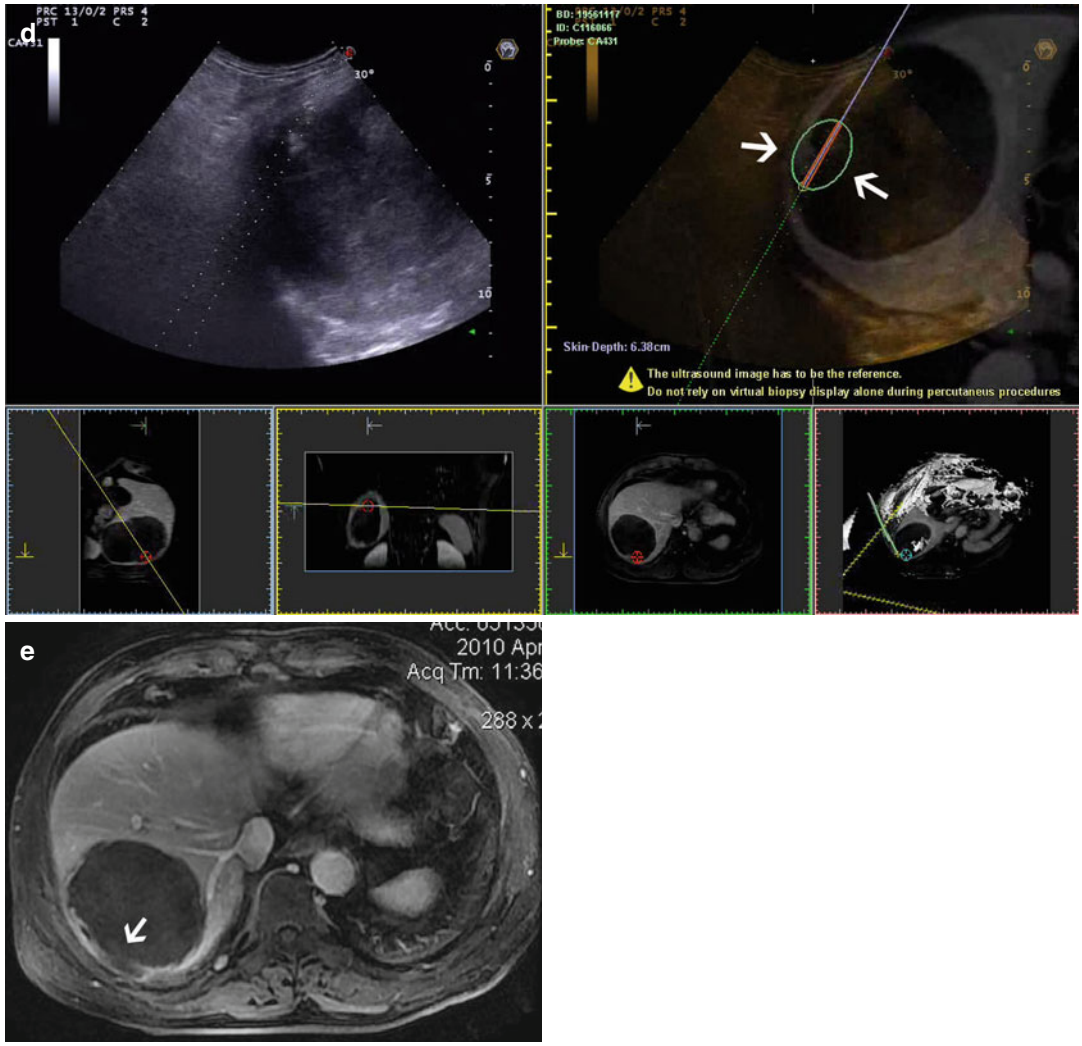

Fig. 28.2 (continued)

benefits of which are the simultaneous acquisition of high-resolution image, 3D spatial orientation, and real-time image. The second feature is synchronicity. This guidance technique is based on immediate feedback to point out lesions that cannot be clearly visualized with US. The second modality image could be overlapped on the current ultrasound situation, so during MW ablation we could monitor the ablation using gray-scale sonography to assess whether the hyperechoic area of the ablation covered the tumor. The third is precise guidance. The sensor which was mounted on the microwave antenna can detect the position of the microwave antenna, and the virtual needle was displayed computing its projection on the biopsy line, so the MW antenna could be inserted into lesions inconspicuous on US using this technique.

Although the real-time virtual navigation system was very useful to assist the MW ablation for the lesions inconspicuous on US, there were some limitations in the clinical application. First is the limitation of patients' position. The patients must keep the same position as the CT or MRI examination, so when the lesion is close to the back, the insertion of antenna could not

be conveniently performed. Second, the respiratory excursion and patients' motion will affect the accuracy of registration and insertion of the MW antenna as well. US images and the second modality images (MRI or CT images) were synchronized using the internal markers when the patient was at the end of calm inspiration. When the registration was completed, the CT or MR image was stable while the US image was changing following with the patients' respiratory. When the MW antenna was inserted into the lesion, the patient must keep the same breath condition as the registration (at the end of calm inspiration) so as to achieve full integration of images instantly. Several techniques may be available to decrease the influence of respiratory excursion and patients' motion: first, a real-time 3D US image acquisition and display will add more merits to the proposed multi-image modality algorithm; second, a minimally invasive fiducially, noninvasive miniature position sensor directly on the liver surface, or the internal anatomic landmarks of the liver can be a possible candidate tool for tracking liver movement.

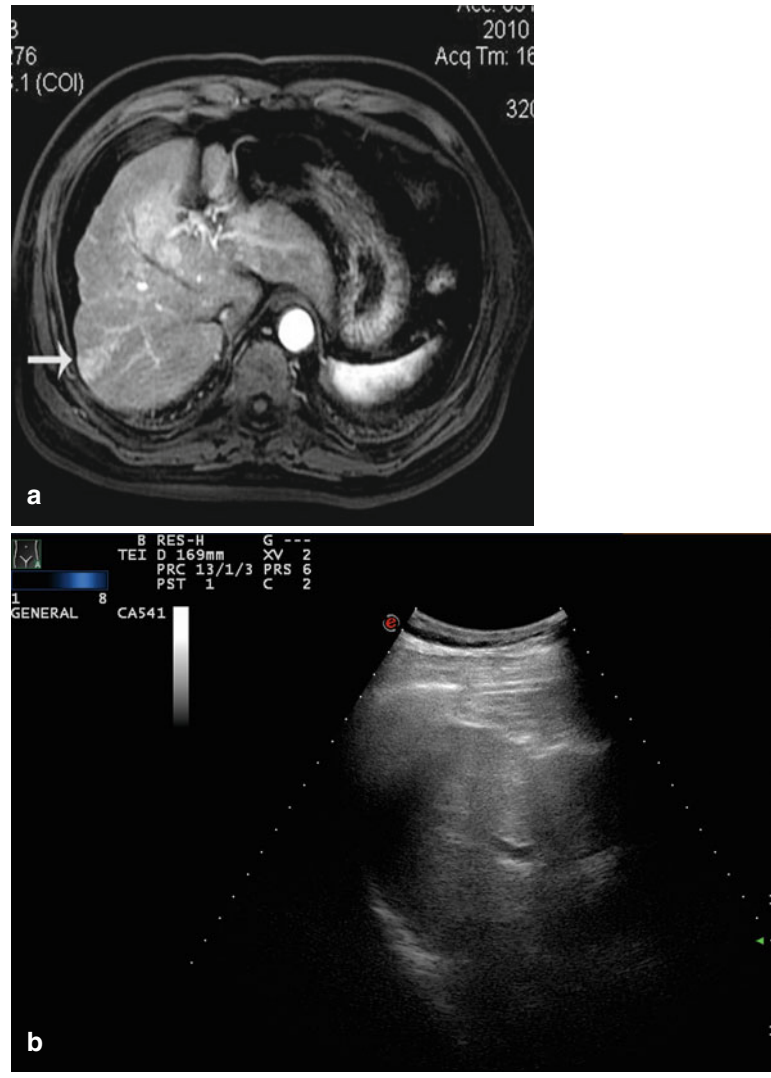

Fig. 28.3 Images in a 58-year-old male with a 2.0×1.5 cm lesion in segment VII of the liver. (**a**) Contrast-enhanced MRI shows a hyper-vascular tumor (*arrows*) in segment VII of the liver. (**b**) Conventional US could not detect the lesion. (**c**) US images and MR images were synchronized using the internal markers at the best timing of the inspiration. (**d**) MW antenna was inserted into the tumor under real-time virtual navigation system guidance. (**e**) Contrast-enhanced MRI obtained 1 month after MW ablation shows complete necrosis of the tumor (*arrows*)

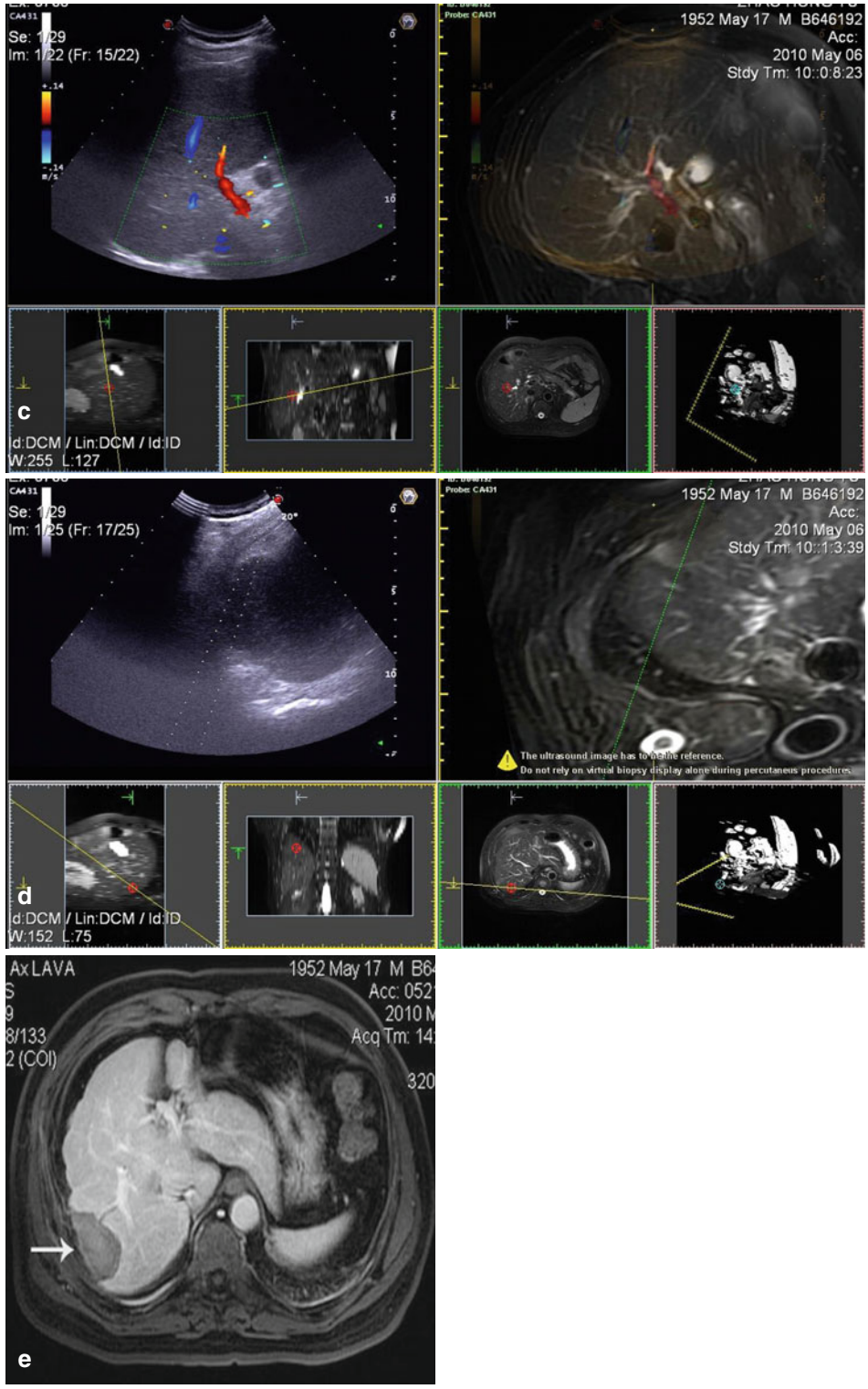

Fig. 28.3 (continued)

Conclusions

Before the application of navigation techniques, thermal ablation was highly dependent on operator experience and spatial skills. Navigation systems for ablation bring the opportunity for standardization and accuracy that extends the operator's ability to use imaging feedback during procedures and the indications of ablation. Navigation techniques will play an important part in microwave ablation in the future, especially in the application of integrated ablation treatment plans. Such standardization should decrease the variability of practice patterns and even enable less experienced operators to deliver precise ablations.

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29 Contrast-Enhanced Ultrasound-Guided Microwave Ablation for Hepatic Tumors Inconspicuous on Conventional Ultrasound

Xiao-Wei Yang, Xiao-ling Yu, and Ping Liang

Abstract

Microwave ablation is one of the newly developed techniques for the treatment of hepatic tumors and has been a curative method for small liver cancer. The accurate imaging guidance plays a critical role in the success of this technique. Compared with computed tomography or magnetic resonance imaging guidance, microwave ablation under ultrasound guidance is more convenient. However, the target lesions cannot always be visualized on B-mode ultrasound, due to the texture of the lesion. Also, residual tumor is difficult to be differentiated from the treated area of tumors after thermal ablation on ultrasound. Therefore, contrast-enhanced ultrasound was introduced in recent years to help in guiding microwave ablation of hepatic tumor. The purpose of this chapter is to present an overview, introduce the main technique, and evaluate the effectiveness as well as application status of contrast-enhanced ultrasound in guiding percutaneous microwave ablation in patients with hepatic tumors.

Keywords

Contrast-enhanced ultrasound • Microwave • Ablation • Liver cancer

Abbreviations and Acronyms

CT	Computed tomography
CEUS	Contrast-enhanced ultrasound
HCC	Hepatocellular carcinoma
MRI	Magnetic resonance imaging
MWA	Microwave ablation
RFA	Radiofrequency ablation

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29.1 Introduction

Microwave ablation (MWA) is one of the newly developed techniques for the treatment of hepatic tumors [1, 2]. Confident visualization of the target lesion and accurate image guidance are prerequisites for successful application of MWA. Until now, the guidance methods mainly include

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ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) guidance [3–5]. US is the most commonly used imaging guiding technique and has advantages of convenience, safety, low cost, and lack of ionizing radiation compared with computed tomography (CT) and magnetic resonance imaging (MRI) [6]. However, the target lesions cannot always be visualized on conventional B-mode US in several kinds of situations [7]. The first is that residual hepatic tumor nodules exist after ablation, for B-mode US cannot adequately differentiate between treated and viable residual tumor tissue. The second is that naïve hepatic tumor nodules present among many large regenerated nodules in cirrhotic liver. Color Doppler and power Doppler have increased the sensitivity of hepatic lesion detection compared to that using gray-scale US. However, these modalities do not provide levels of sensitivity comparable to those of contrast-enhanced CT or MRI [8]. Therefore, multiple sessions of MWA therapy are often required for small HCCs, which are poorly defined on conventional B-mode US alone [9]. According to a review [10] on diagnostic B-mode US for hepatocellular carcinoma (HCC), the reported per-lesion sensitivity ranges from 33 to 84 %. A study [11] reported that tumors could not be visualized on preprocedural planning B-mode US in 30 % of the patients referred for percutaneous radiofrequency ablation (RFA) of HCC. A meta-analysis [12] reported that diagnostic B-mode US had limited per-patient sensitivity [55 %; 95 % confidence interval, 41–68 %] in detecting hepatic metastases from cancers of the gastrointestinal tract.

In recent years, contrast-enhanced US (CEUS) has been introduced to help in guiding MWA. It has been shown to depict tumor vascularity sensitively and accurately. It allows better visualization of focal hepatic lesions that cannot be clearly visualized on B-mode US [13–15]. Specifically, second-generation US contrast agents enable real-time continuous imaging of focal hepatic lesions for several minutes [16], which dramatically broaden the scope of US diagnosis of hepatic tumors [17]. However, few clinical researches concerning CEUS-guided MWA for the treatment of hepatic tumors have been reported until now. In this chapter, we will present an overview, introduce the main technique, and evaluate the effectiveness as well as application status of CEUS in guiding percutaneous MWA in patients with hepatic tumors.

29.2 The Indications for CEUS-Guided MWA

The indications for CEUS-guided MWA usually include (a) nodules undetectable on conventional US but detectable by intravenous contrast-enhanced CT or MRI and (b) no allergy to contrast media. Others are same as the general indications of liver cancer ablation.

29.3 CEUS Application Technique During MWA

With second-generation contrast media, real-time CEUS is performed through all vascular phases: the arterial (early) phase (15–35 s after injection), the portal (venous) phase (35–90 s), and the sinusoidal (parenchymal or late vascular) phase (90–240 s). On real-time images, contrast medium is seen arriving in the hepatic artery and rapidly spreading through its branches. Liver parenchymal echogenicity increases consistently from the arterial to the portal phase and then decreases slightly during the sinusoidal phase. Lesion echogenicity is defined with respect to the surrounding parenchymal echo levels at the same imaging time and depth. Lesions are either hyperechoic, isoechoic, or hypoechoic relative to the adjacent parenchyma. In addition, lesions can be compared with the blood pool, being hypervascular when demonstrating the same echogenicity as contrast material-enhanced vessels and hypovascular when demonstrating a lower echogenicity (Figs. 29.1, 29.2, and 29.3).

With CEUS guidance, the tumor is localized, and microwave antennas are placed directly into the tumor. During MWA, the hyperechoic area of ablation is usually monitored using gray-scale sonography. The treatment session will be ended if the transient hyperechoic zone between antennas on gray-scale US merges and covers the

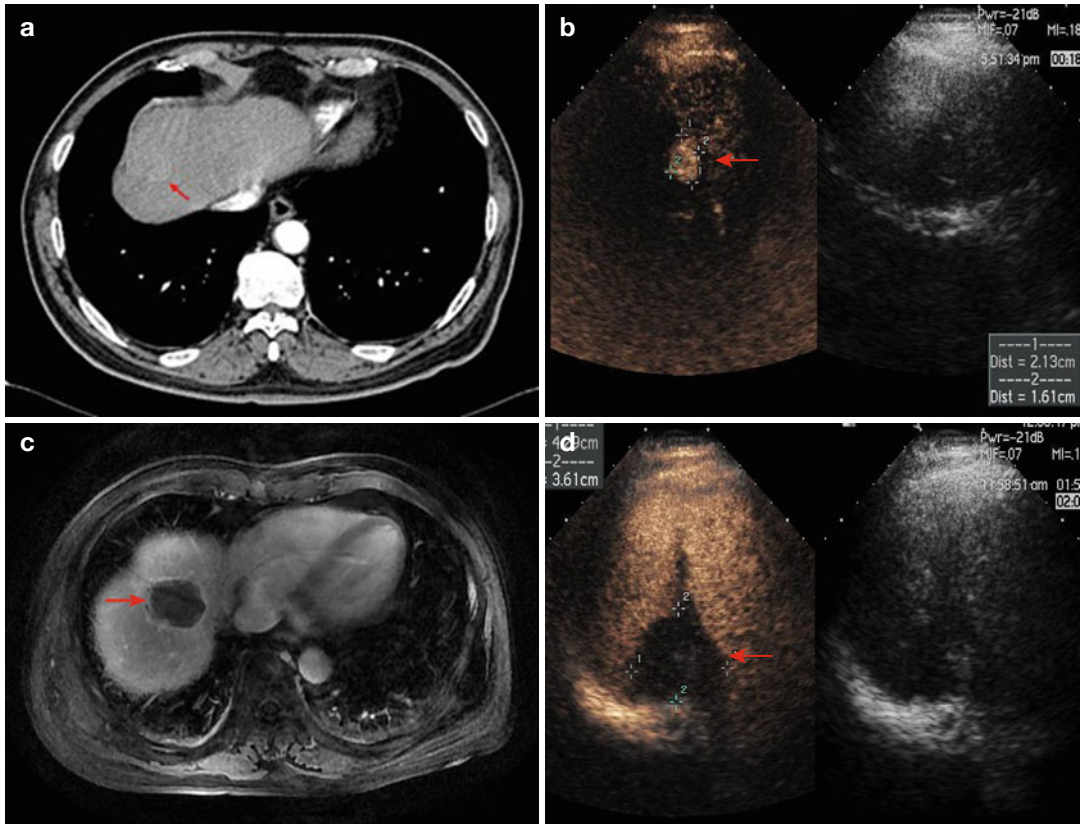

Fig. 29.1 Images in a 58-year-old man who underwent contrast-enhanced ultrasound (*CEUS*) guidance microwave ablation (*MWA*) of hepatocellular carcinoma (*HCC*). (**a**) Contrast-enhanced computed tomography (*CT*) shows a local nodule (*arrows*) in the right hepatic lobe. (**b**) Conventional ultrasound could not detect the tumor, but the CEUS arterial phase image shows a 2.1×1.6 cm tumor in the right hepatic lobe (*arrow*). (**c**) Arterial phase of contrast-enhanced magnetic resonance imaging (*MRI*) obtained 3 months after MWA shows complete necrosis of the tumor (*arrow*). (**d**) Arterial phase of CEUS obtained 3 months after MWA shows complete necrosis of the tumor (*arrow*)

target region. After ablation, every patient receives CEUS to evaluate treatment response. Successful treatment is defined when no focal and/or irregular enhancement within the treated lesion during the dynamic study is detected, whereas treatment failure is defined by the presence of nodular enhancement in arterial phase and washout in late vascular phase within the treated lesion.

29.4 Effect of CEUS in Guiding Ablation

MWA with CEUS guidance has demonstrated the potential to dramatically broaden the scope of US diagnosis of hepatic tumors [17, 18] and decrease the number of sessions required for ablation of HCC in difficult cases [19]. Masuzaki et al. [20] reported in a large-scale study that the detectability of tumor nodules was 83.5 % in conventional US and 93.2 % in contrast-enhanced US ($P=0.04$). In a randomized controlled study [21], the number of treatment sessions was significantly lower in the contrast harmonic US group (mean, 1.1 ± 0.2 vs. 1.4 ± 0.6, $P=0.037$). Treatment analysis showed that the complete ablation rate after a single treatment session was significantly higher in the CEUS group than in the B-mode US group (94.7 % vs. 65.0 %, $P=0.043$).

Our previous studies evaluated the efficiency and feasibility of CEUS-guided MWA

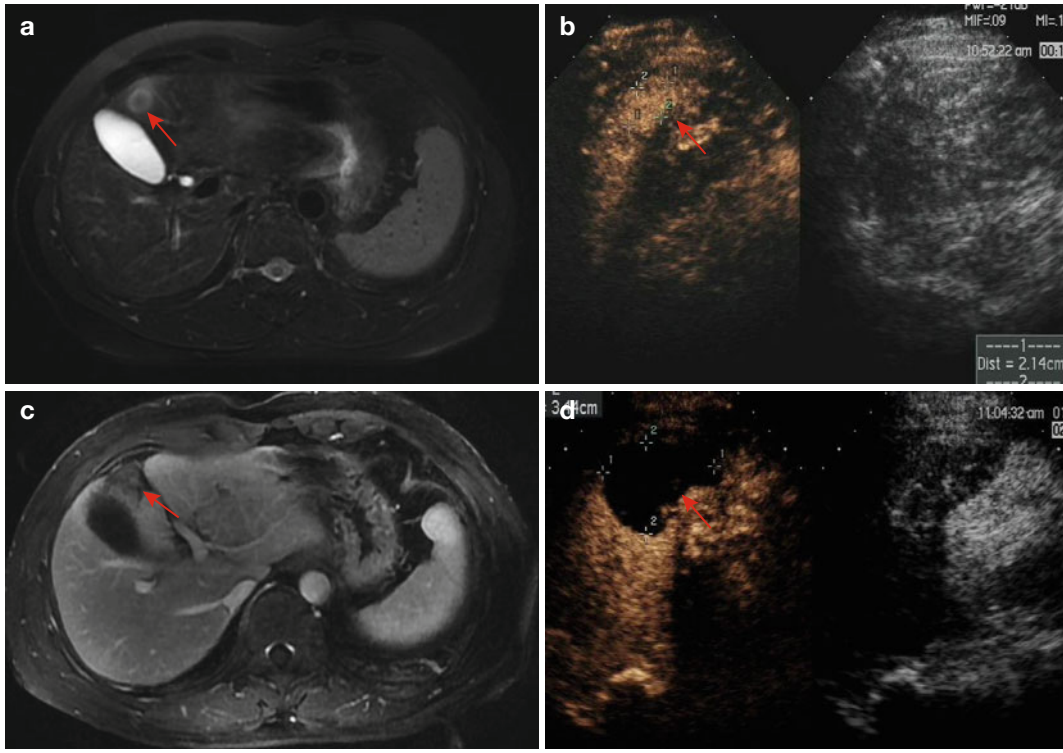

Fig. 29.2 Images in a 50-year-old man who underwent CEUS guidance MWA of HCC. (**a**) Contrast-enhanced MRI shows a local nodule (*arrow*) in the left hepatic lobe. (**b**) Conventional ultrasound could not detect the tumor, but the CEUS arterial phase image shows a 2.1 × 1.4 cm tumor in the left hepatic lobe (*arrow*). (**c**) Arterial phase of contrast-enhanced MRI obtained 6 months after MWA shows complete necrosis of the tumor (*arrow*). (**d**) Arterial phase of CEUS obtained 6 months after MWA shows complete necrosis of the tumor (*arrow*)

for hepatocellular carcinoma inconspicuous on conventional US [22]. In that study, we performed MWA under CEUS guidance for 109 patients with 109 HCC nodules inconspicuous on conventional US. We found that CEUS-guided microwave ablation is an efficient and feasible treatment method for patients with HCC inconspicuous on conventional US.

Before its application in MWA, CEUS has been used for a long time in guiding RFA. Other studies reveal that CEUS does allow a reliable and immediate assessment of therapeutic efficacy of percutaneous RFA of malignant liver lesions [23]. Meanwhile, pretreatment evaluation with CEUS is effective for percutaneous RFA of HCCs with poor conspicuity on conventional US [24].

29.5 Comparison with Other Guiding Techniques

Besides CEUS, CT or MRI guidance can also be used for the guidance of MWA. Compared with other techniques, CEUS guidance has many advantages: (a) US equipment is smaller, which makes it more convenient to use in clinical work. (b) CEUS guidance is real time. (c) CEUS is easy to operate and allows scanning the body from different positions and angles. (d) CEUS emits no ionizing radiation. (e) CEUS is less expensive than other guiding techniques. (f) Few allergies happen during CEUS guidance. (g) The therapeutic effect can be evaluated in real time under CEUS guidance (Table 29.1).

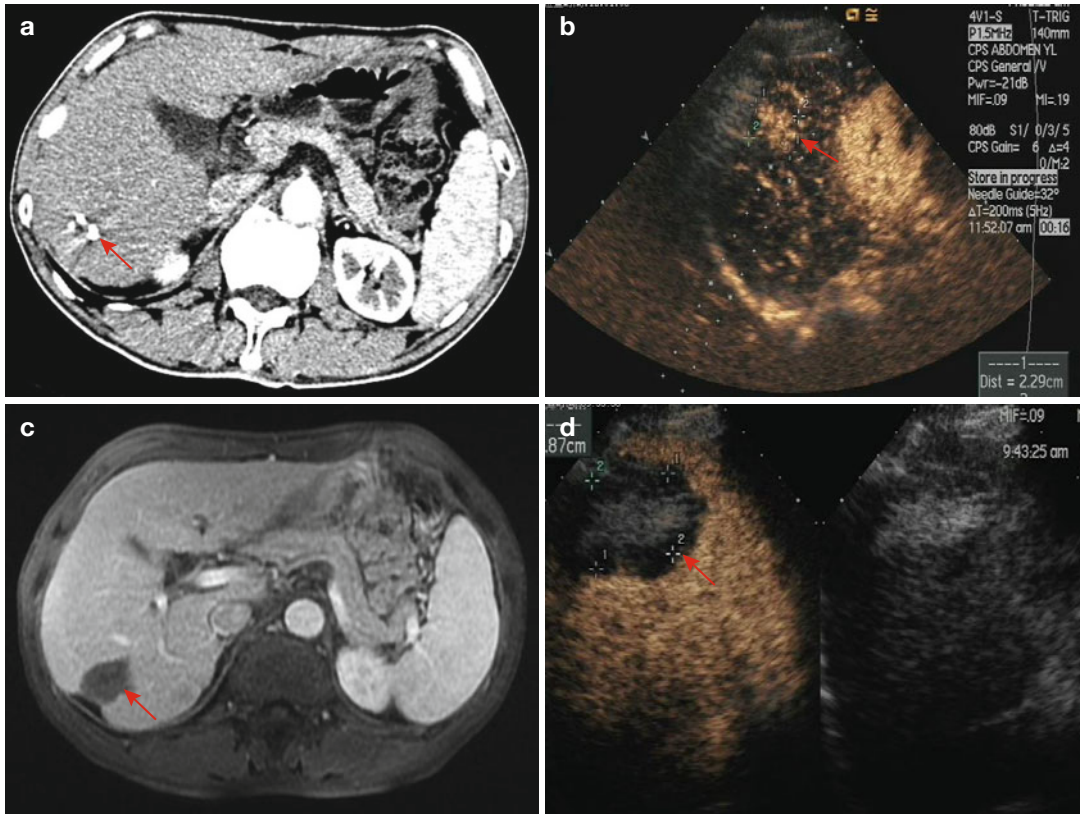

Fig. 29.3 Images in a 56-year-old man who underwent CEUS guidance MWA with a 2.4×2.3 cm local residual lesion of HCC after TACE. (**a**) Contrast-enhanced CT shows a local residual lesion in the right hepatic lobe after TACE (*arrow*). (**b**) Conventional US could not detect the tumor, but the CEUS shows arterial phase adjacent to the TACE zone indicative of local residual lesion (*arrow*). And MWA was inserted along the guideline under CEUS guidance (*arrow*). (**c**) Arterial phase of contrast-enhanced MRI obtained 3 months after MWA shows complete necrosis of the local residual lesion (*arrow*). (**d**) Arterial phase of CEUS obtained 3 months after MWA shows complete necrosis of the local residual lesion (*arrow*)

Table 29.1 The comparison among CEUS, CT, and MRI for the guidance of MWA

	Guiding techniques		
Features	CEUS	CT	MRI
Convenience	Yes	No	No
Multiangle scan	Yes	No	No
Ionizing radiation	No	Yes	No
Expensive	No	Yes	Yes
Allergy	Few	More	More
Real time	Yes	No	No

CEUS Contrast-enhanced ultrasound, *MWA* Microwave ablation, *MRI* Magnetic resonance imaging, *CT* Computed tomography

Compared to CEUS, CT and MRI have been used for a long time in guiding MWA (Table 29.2). CT has high spatial resolution, good contrast, wide field of view, good reproducibility, and applicability to bony and air-filled structures. The use of a CT-guided method can be expected to reduce the rate of local tumor progression associated with percutaneous ablation therapy. We reviewed several well-performed studies. Laspas et al. [31] reported that the ablation success rate was 87.3 % (281/322 HCC nodules), and the survival rates at 1 year, 3 years, and 5 years were

Table 29.2 Ablation treatment results of HCC patients under different guiding techniques

Author	Guiding technique	No. of patient	Size (cm)	Technique effectiveness rate (%)	Locoregional recurrence rate (%)	1-year survival rate (%)	2-year survival rate (%)	3-year survival rate (%)	Mean follow-up (month)
Dong et al. [3]	CEUS	234	4.1	93	31	92.70	81.60	72.85	27.9
Liang et al. [25]	CEUS	288	3.75	91	35	93	82	72	31.4
Lu et al. [26]	CEUS	50	2.7	94	48	96	83	73	18.1
Li et al. [27]	CT	320	N/A	99	38	73.4 %	41.1 %	30 %	23
Lencioni et al. [28]	CT	50	≤5	82.6	38	96	88	N/A	22.4
Li et al. [29]	MRI	96	≤4	94.8	18.8	N/A	N/A	N/A	15–17.5
Zhang et al. [30]	MRI	112	2.5	98.2	8	65.8	53.6	53.6	26

HCC

94.8, 73.1, and 51.1 %, respectively. Despite the advantages of CT, there are several limitations such as the increased time that is necessary for the procedure and exposure of the patient to ionizing radiation.

MRI with its high soft tissue contrast can be advantageous and the capability of MRI for multiplanar imaging can be of value for needle placement and surveillance of the ablation procedure. A study performed by Wu et al. [32] reported that MRI and optical navigation system-guided ablation procedures were successfully performed on all 32 patients (36 tumor sites), and the 6- and 12-month overall survival rates were 96.8 and 90.6 %, respectively. Although MRI can be used to obtain reference images in ablation therapy, radiofrequency needle puncture is actually performed under sonographic guidance. Therefore, an MRI-guided system can be used for ablation monitoring, but not for puncture guidance.

Conclusions

CEUS-guided MWA is found to be a safe and efficient treatment approach for hepatic tumors that are not clearly demarcated by conventional B-mode US. In future, the extensive application of this technique might dramatically improve the prognosis of patients with hepatic tumors.

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30 Application of Contrast-Enhanced Ultrasound in the Evaluation of Clinical Effect of Microwave Ablation of Hepatocellular Carcinoma: Comparison with Other Imaging Modalities

Peng Qu, Xiao-ling Yu, Ping Liang, Zhigang Cheng, Zhiyu Han, Fangyi Liu, and Jie Yu

Abstract

Image-guided percutaneous ablation therapy for hepatocellular carcinoma has been used worldwide, and the most widely used modalities are radiofrequency ablation (RF) and microwave ablation (MA). Multiphasic contrast-enhanced CT, dynamic MRI, and contrast-enhanced ultrasound are accepted as reliable modalities for evaluating the adequacy of radiofrequency and microwave ablation and early detection of tumor recurrences. In this session, we evaluate the clinical utility of low mechanical index contrast-enhanced ultrasound in assessing percutaneous microwave ablation response in patients with hepatocellular carcinoma by comparing the results to contrast-enhanced magnetic resonance imaging and prove that contrast-enhanced ultrasound examination is a safe and easy modality in assessing therapeutic effect of microwave ablation.

Keywords

Hepatocellular carcinoma • Microwave ablation • Contrast-enhanced ultrasound • Magnetic Resonance Imaging

30.1 Introduction

Hepatocellular carcinoma is the second leading cause of death with more than 200,000 victims each year in China. Image-guided percutaneous ablation therapy for hepatocellular carcinoma has been used worldwide, and the most widely used modalities are radiofrequency ablation and microwave ablation [1–4]. The success of ablative treatment is strongly dependent on complete tumor destruction, which requires both accurate

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placement of ablative probes in the lesion and thorough understanding of the ablative range [5, 6]. In order to evaluate the therapeutic effect and to detect residual tumor, much effort has been made on the identification of an imaging technique that can permit early localization of surviving tumor tissue post therapy.

30.2 Application Status

Nowadays ultrasound has been widely used as an effective imaging modality to guide the treatment due to its real-time, easiness of use, noninvasiveness, and lack of ionizing radiation. However, conventional ultrasound is of little help in the assessment of both pretreatment tumor vascularity and post-treatment therapeutic response. Assessment of tissue perfusion is crucial to differentiate necrotic from viable residual tumor. CEUS has been used in some locoregional therapies, which conventionally include ablation and transarterial chemo-/radioembolization, and plays a key role in the management of patients with liver malignancies, both HCC and metastases. At present, most studies have used CEUS or CEMRI/CECT to assess the efficacy of ablation treatment. The enhancement patterns observed during the arterial, portal venous, and late phases are generally similar among CEUS, CECT, and CEMRI. The real-time nature of CEUS allows depiction of early arterial phase enhancement which is sometimes missed on CT and MRI because they have lower frame rates. Discordance has also been shown in some lesions during the portal venous and late phases when CT and MRI contrast materials diffuse into the tumor interstitium and may conceal washout. On the other hand, postvascular phase imaging with Sonazoid® (made by Schering AG) shows patterns similar to those described with superparamagnetic iron oxide (SPIO) MRI. The aims of application of CEUS are as follows: (1) assessment of the lesions to be treated by ablation (number, size and enhancement characteristics of the lesions, and the presence of feeding vessels) to define the eligibility of the patient for treatment and the best ablation strategy, (2) depicting undetectable lesions under conventional US and guiding probe puncture, and (3) detecting viable tumor following locoregional treatment (either ablation or chemo-/radioembolization). In this section, we will discuss this in more detail below, focusing primarily on this part.

30.3 Periprocedural Assessment of Treatment Response

In the pretreatment stage, the assessment of tumor size must include the perilesional hypervascular halo. Tumor margins are better detected by CEUS than conventional US because definition of its relationships with surrounding structures is improved; thus, CEUS can help define the size and margin and the nourishing blood vessels of the lesion to develop appropriate treatment strategies and reduce the risks of complications. Hence, pretreatment CEUS is essential for comparison of the patterns before and after treatment.

In the follow-up investigation to assess tumor recurrence stage, it is often difficult to depict local tumor recurrence after ablation using conventional US alone. Here, scanning in the late or postvascular phase of the lesion, with subsequent reinjection of contrast agent to confirm tumor enhancement in any suspicious region, is useful to identify the viable tumor adjacent to the ablated volume. This can be used to guide biopsy and complementary treatment. While CEUS may be extremely useful to define local recurrence in a treated nodule, CT and MRI provide a better overview of the liver to detect distant intra- and extrahepatic tumor and cannot be replaced by CEUS.

Therapeutic effect was assessed by the result of MRI after ablation, the proved serum tumor marker levels, and additional follow-up. Completely treated lesions show no contrast enhancement by dynamic CT or MRI, which indicates the disappearance of blood flow in the

lesion. If the treatment is incomplete, the residual tumor is detected by contrast enhancement in the treated area [14]. The criteria used for determining tumor response to ablation treatment in CEMR imaging during follow-up period were (1) complete tumor necrosis if no foci of enhancement were seen within and in the peripheral ablated area on CEMR imaging [14] or (2) presence of residual, incompletely treated tumor, if during the CEMRI arterial phase, the presence of a hyper-dense area was seen, becoming progressively iso- and hypo-dense with respect to the surrounding parenchyma. For CEUS, when a lesion had the appearance of enhancement in the hepatic arterial phase lesion and was identified within or adjacent to the treated area during the follow-up, it was defined as a local recurrence. Two experienced radiologists who were blinded to clinical and imaging information of the patients and not involved in the CEMRI scan or ablative treatment procedure evaluated the findings of post-treatment CEMRI in consensus. CEUS digital clips were retrospectively analyzed in consensus by two experienced sonographers who were blinded to the other imaging information of the patients.

In the early postablative evaluation (within the first 30 days), a thin, uniform enhancing rim can be visible along the periphery of the necrotic region, similar to the findings on CECT or CEMR. It could be considered as the perilesional congestion zone and the misinterpretation of it as residual viable tumor needs to be avoided. The imaging indicator of complete ablation is the disappearance of any previously visualized intralesional enhancement on CEUS. This must be assessed throughout the whole volume of each tumor which has undergone ablation. The volume of the necrosis achieved should be compared with the pretreatment volume of the tumor(s). Simultaneous display of tissue and contrast is of particular value for follow-up of treated lesions. The volume of necrosis achieved can be compared with the pretreatment volume of the same lesion on CECT or CEMRI using real-time fusion imaging (Figs. 30.1 and 30.2).

30.4 Recommended Uses and Indications

CEUS can be used as a new method as CECT and/or CEMRI for pretreatment staging and assessment of target lesion vascularity. Also, it could be used in the evaluation of the immediate treatment effect after ablation and guidance for immediate re-treatment of residual unablated tumor and in the assessment of local tumor progression when follow-up CECT or CEMRI is contraindicated or not conclusive. In addition to CECT and/or CEMRI, CEUS may be used in follow-up protocols. All patients should undergo conventional ultrasound, CEUS, contrast-enhanced CT, and/or gadolinium-enhanced magnetic resonance imaging (MRI) to delineate the target tumor before microwave ablation. Baseline liver assessment should be performed in each patient using conventional gray-scale ultrasound and color/power Doppler to evaluate and record the number, location, size, shape, border, and internal echogenicity of the lesion and the intralesional blood supply. The measurements of maximum diameters for the index tumors are performed on CEUS image during the portal venous phase before the MW ablation because the necrotic zone in this phase is avascular. To determine if the persistence of tumor was present, ablated lesions were assessed in all vascular phases. CEUS examinations were carried out using low mechanical index (MI $\leq$ 0.2) contrast dedicated methods – contrast pulse sequencing [CPS – Siemens, Mountain View, CA, USA]. The contrast agent used in this study was SonoVue (Bracco, Milan, Italy). It consisted of an aqueous suspension of phospholipid-stabilized sulfur hexafluoride (SF6) gas microbubbles supplied as a lyophilized powder [7, 8]. Contrast-enhanced images (all vascular phases) were acquired digitally on the hard disk of the US system in addition to the continuous imaging on digital video tape and were evaluated in consensus by two expert doctors who had at least 5 years experience using CEUS and were blinded to clinical and imaging information of the patients [9–12]. All MR studies were carried out with the same

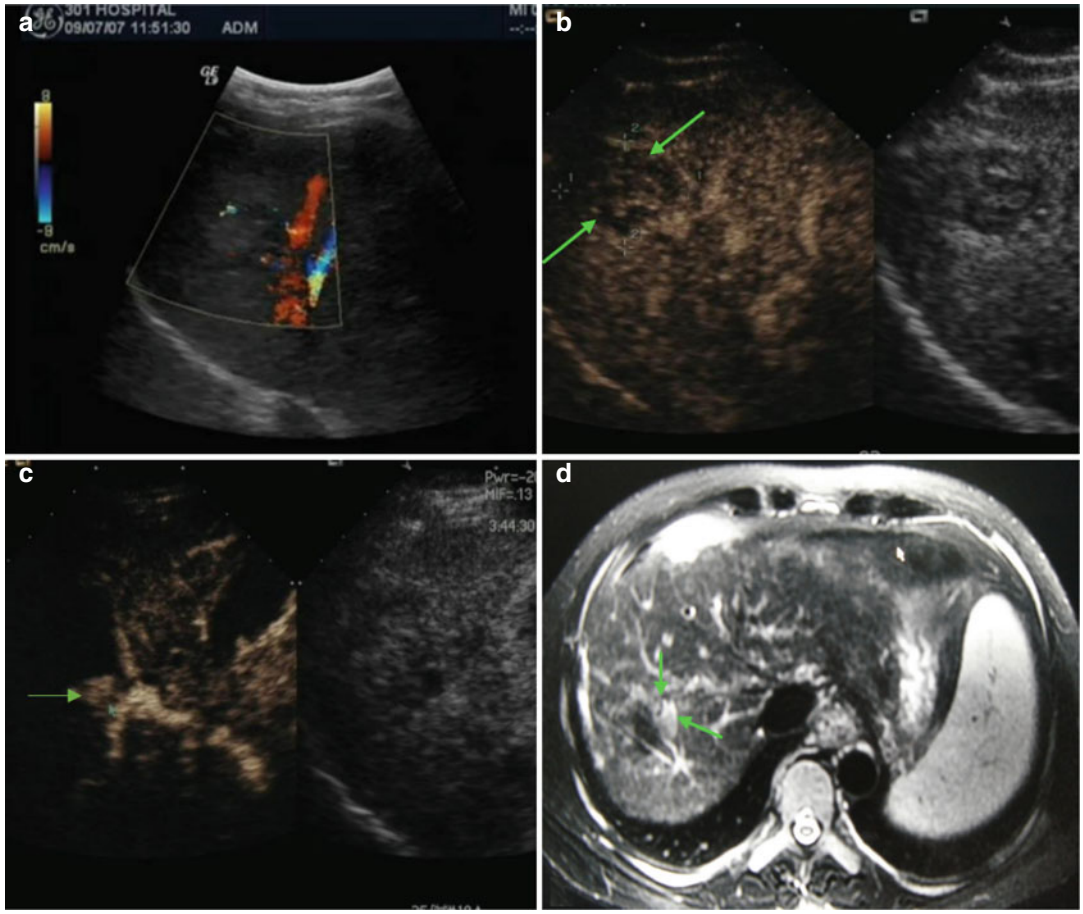

Fig. 30.1 The patient is male, 73 years old, diagnosed as with hepatocellular carcinoma (*HCC*) (3.3×2.2 cm) for 1 month, underwent the contrast-enhanced ultrasound (CEUS) and contrast-enhanced magnetic resonance (CEMR) before the operation. After the necessary examination, the patient underwent microwave ablation (MA). Both the CEUS and the CEMR showed recurrence of the lesion after 2 months, and the patient was treated by microwave ablation again. (**a**) Hypoechoic lesion in the right lobe of the liver on B-mode sonography and the blood signals of the lesion on CDFI. (**b**) Intratumoral enhancement in the early arterial phase of CEUS. (**c**) The presence of residual carcinoma showed enhancement in the arterial phase of CEUS (*red arrow* showed ablative zone; *green arrow* showed residual carcinoma). (**d**) MRI T2WI shows a hyperintense nodule (*green arrow*) beside the ablative area (*green arrow*)

1.5 T unit (signal Echo-speed, GE Medical Systems), contrast medium (Magnevist, Schering; 0.1 mmol/kg body weight), and sequences. According to at least two modalities of contrast imaging, all lesions were hypervascular. Histological diagnosis of all lesions was obtained by ultrasound-guided tumor biopsy using an 18-gauge needle in all patients. In patients with multiple nodules that had the same manifestation on contrast-enhanced images, at least one biopsy was performed and they were definitely diagnosed by follow-up.

30.5 Results

Until now, there are few studies that have compared the imaging features and the roles of contrast-enhanced ultrasound and contrast-enhanced MRI in assessing therapeutic response of HCC after microwave ablation. According to our latest study data, a total of 182 patients with 231 lesions diagnosed as suspected or known hepatic malignancies were enrolled Table 30.1. The final diagnosis was confirmed by MRI, serum tumor marker levels, and additional

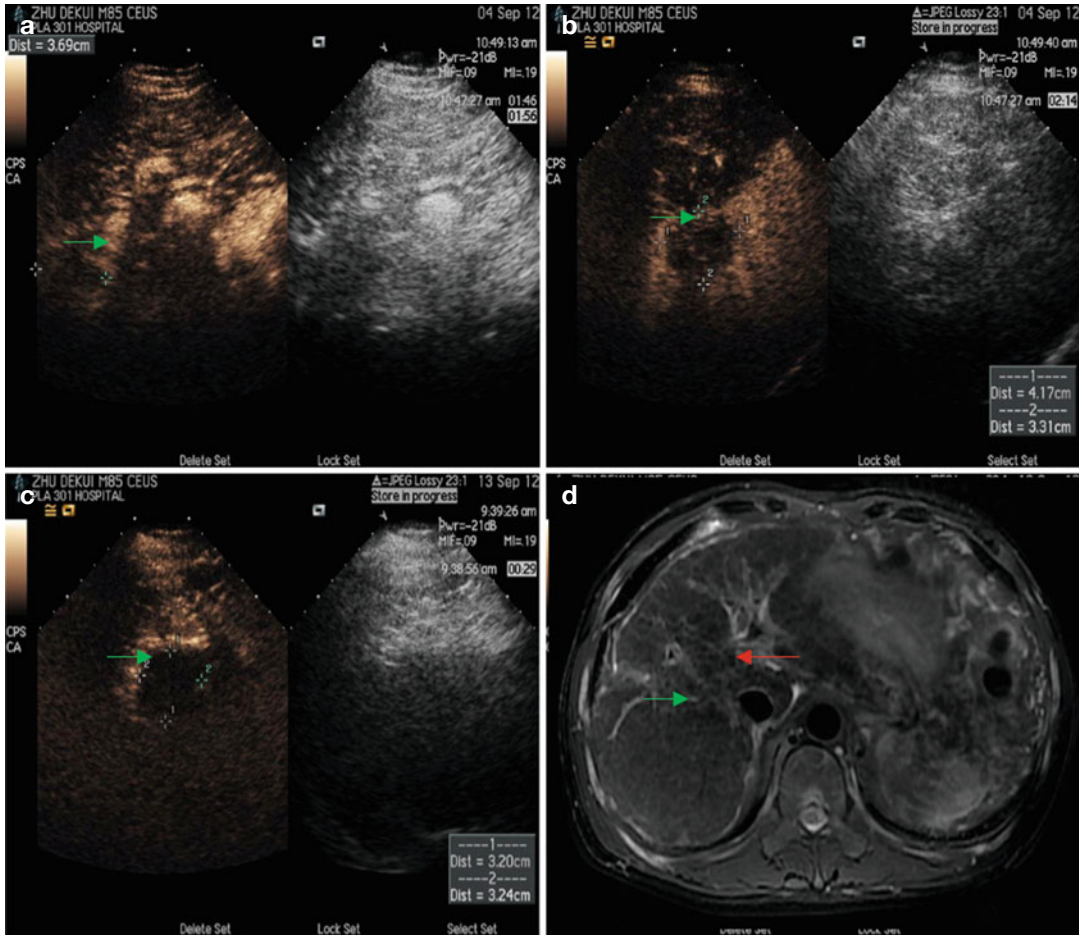

Fig. 30.2 The patient is male, 57 years old, diagnosed as with HCC (3.5 × 2.5 cm) for 2 months. He underwent MA, and after 1 month, the CEUS showed no recurrence, but the CEMR showed recurrence. The pathology result showed there was no recurrence. (**a**) Intratumoral enhancement in the early arterial phase of CEUS before ablation. (**b**) Hypoechoic lesion compared to the peripheral liver tissue in the late phase of CEUS before ablation. (**c**) It showed no enhancement in the lesion in arterial phase of CEUS after being treated for 1 month. (**d**) MRI T2WI image shows a hyperintense nodule beside the ablative area (*green arrow*)

follow-up. In 1 month after ablative treatment, 179/231 (77.5 %) lesions had obtained complete necrosis and 52/231 (22.5 %) lesions had not been treated completely (Tables 30.2 and 30.3); 213/231 (92.2 %) lesions had same diagnostic results by these two imaging methods. 175/231 (75.8 %) had showed complete tumor necrosis both in CEUS and CEMRI. The concordance between CEUS and CEMRI on the presence of residual carcinoma vascularization was observed in 38 patients. While in six patients residual

Table 30.1 Baseline clinical characteristics of our patients

	Number
Age (years)	
Mean±SD (range)	58.1 ± 10.3
Sex	
Male/female	150/32
Etiology of liver chronic diseases	
None/HBV/HCV/HBV+HCV	25/123/28/6
Hepatic cirrhosis/none	154/28
Max diameter of lesions (cm)	
Mean±SD (range)	2.6 ± 1.4

Table 30.2 Comparison of diagnostic results: CEUS vs. final diagnostic results

	Final diagnostic		
	Positiveness	Negativeness	
CEUS	($n=52$)	($n=179$)	Total
Positiveness ($n=10$)	45	3	48
Negativeness ($n=67$)	7	176	183
Total	52	179	231

Table 30.3 Comparison of diagnostic results: CEMRI vs. final diagnostic results

	Final diagnostic		
CEMRI	Positiveness ($n=52$)	Negativeness ($n=179$)	Total
Positiveness ($n=12$)	44	2	46
Negativeness ($n=65$)	8	177	185
Total	52	179	231

Table 30.4 Combination of CEUS and CEMRI in evaluating ablation treatment

Combination result			
CEUS	CEMRI	Local recurrence	Total necrosis
Positiveness	Positiveness	38	0
Positiveness	Negativeness	7	3
Negativeness	Positiveness	6	2
Negativeness	Negativeness	1	174
Total number		52	179

Table 30.5 The result of combination of CEUS and CEMRI in assessment ablation therapy

Imaging modality	Sensitivity (%)	Specificity (%)	Accuracy (%)
CEUS	86.5	98.3	95.7
CEMRI	84.6	98.9	95.7
Combination of CEUS and CEMRI	98.1	97.2	97.8

carcinoma vascularization was detected only by CEMR and not by CEUS, in other seven patients, residual carcinoma vascularization was detected by CEUS and not by CEMRI. One patient with residual carcinoma vascularization was not detected by either CEUS or CEMRI, but residual vascularization was shown by CEUS 3 months later and by CEMRI 6 months later. In our study, the sensitivity in evaluating the therapeutic effect of malignant hepatic masses with CEUS and CEMRI was 86.5 % vs. 84.6 %, the specificity 98.3 % vs. 98.9 %, and the accuracy 95.7 % vs. 95.7 %. There was no significant statistical disparity between CEUS and CEMRI ($P=0.01$). The sensitivity has been improved greatly to 98.1 % and the specificity has a slight decrease to 97.2 % by a combination of CEUS and CEMRI in the evaluation of the therapeutic effect of malignant hepatic masses ($P>0.05$) (Tables 30.4 and 30.5). In the ROC curve, combination of these two methods has a larger AUC (area under the curve) (Area = 0.991) than that of CEUS (Area = 0.953) ($P<0.05$) and CEMRI (Area = 0.936) ($P<0.05$) (Fig. 30.3). It means that the combination of CEUS and CEMRI is superior to CEUS or CEMRI alone in the evaluation of the therapeutic effect after microwave ablation.

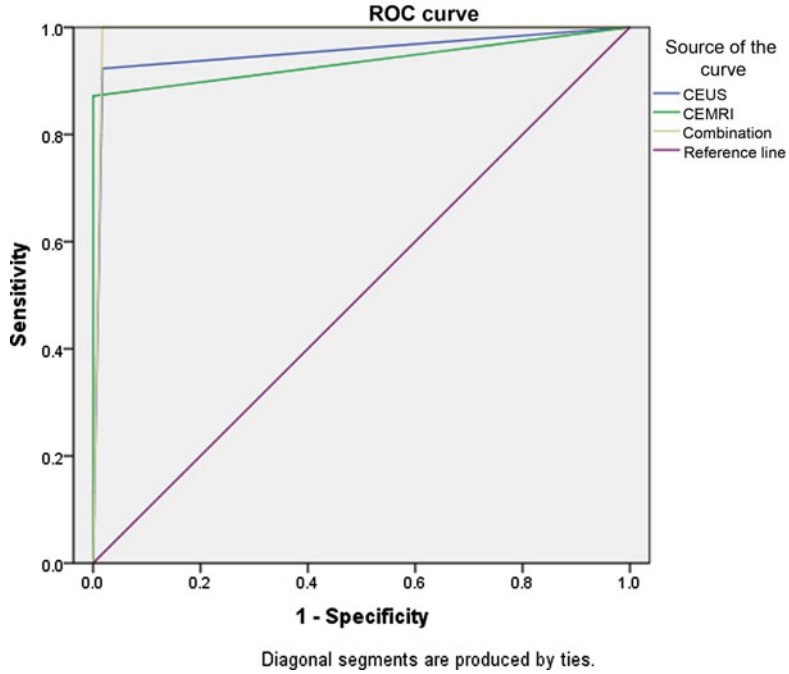

Fig. 30.3 ROC curve to compare the sensitivity and specificity of CEUS, CEMRI, and their combination. In the ROC curve, combination of these two methods has a larger AUC (Area = 0.991) than that of CEUS (Area = 0.953) ($P < 0.05$) and CEMRI (Area = 0.936) ($P < 0.05$)

30.6 Other Local Imaging Techniques for Evaluation

Other local imaging techniques have been employed to evaluate thermal efficacy.

30.6.1 MRI

Nowadays, imaging methods have played an important role in the procedure of percutaneous ablation treatment for hepatocellular carcinoma. Multiphasic contrast-enhanced CT and dynamic MRI are accepted as reliable modalities for evaluating the adequacy of radiofrequency ablation and early detection of tumor recurrences [15–18]. Recently the method of follow-up is more based on contrast-enhanced magnetic resonance imaging (MRI) with dynamic acquisitions [19, 20]. The higher sensitivity of MR imaging over CT is mostly due to the T2-weighted images. The superior sensitivity of T2-weighted imaging could be explained by an increase in contrast between the coagulated area which shows low signal intensity and the viable residual tumor which shows high signal intensity. Moderate (different from a fluid signal) hyperintensity on T2-weighted images may correspond to the presence of residual viable tumor. Therefore, T2-weighted imaging is demonstrated to be highly specific. Moreover, the moderately hyperintense area on T2-weighted images associated with corresponding enhancement on contrast-enhanced T1-weighted images offers optimal specificity (100 %) for residual viable tumor in all cases. Most studies that have directly compared CT and MRI, using either gadolinium or SPIO (superparamagnetic iron oxide) as the contrast agent, reported no significant differences in sensitivity. They have, however, reported a higher specificity of MRI than of CT in detecting hepatic lesions, especially in terms of the accuracy in discriminating between malignant lesions and pseudotumors such as perfusion defects [13, 21, 22].

30.6.2 CT

At present, contrast-enhanced computed tomography (CT) is the most generally used imaging method for evaluating the efficacy of ablation, while the ablated margin can be determined by CT both before and after the thermal ablation [23, 24]. The sensitivity, specificity, and accuracy in evaluating therapeutic effect of HCC with CECT were 96.7, 83.3, and 95.5 % [25]. However, CT imaging is significantly limited by its ionizing radiation exposure, and both of them are expensive and confined by side effects from contrast agents [26]. Until now, most studies have used CECT or CEMRI separately to assess the efficacy of ablation treatment, but to our knowledge, the study comparing the characteristics of these two modalities was seldom reported.

Conclusion

The sensitivity, specificity, and accuracy of real-time CEUS in the assessment of the therapeutic response to microwave ablation after 1 month have been shown to be comparable to those of CEMRI, suggesting that these two modalities may have comparable evaluation efficacy for MWA of HCC, and a combination of two modalities can complement each other perfectly and improve the sensitivity and accuracy in the evaluation of the MWA response.

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31 Effectiveness of Contrast-Enhanced Ultrasound in Evaluating Microwave Ablation of Renal Cell Carcinoma

Xin Li and Ping Liang

Abstract

Percutaneous ablative therapies guided by imaging techniques are considered nowadays curative treatment for small renal cell carcinoma in patients who are not candidates for surgical resection and willing to accept ablation personally. The final goal of all ablative treatments is to obtain complete destruction of neoplastic tissue. The best noninvasive way to evaluate the efficacy of ablative therapies is to demonstrate no blood supply both inside the lesions and the peripheral renal parenchyma of the tumor. The timely and accurate evaluation of the therapeutic effects is also momentous for promoting the survival. Contrast-enhanced computed tomography/magnetic resonance imaging as traditional imaging in evaluating the ablation treatment efficacy has some intrinsic limitations. Contrast-enhanced ultrasound with second-generation contrast agents is effective in depicting the residual and recurrent tumor after ablation. The unique advantages of contrast-enhanced ultrasound have been well documented, including its safety, simplicity, well tolerance, no radiation, and real-time multiplanar imaging. In this chapter, we will review the clinical efficiency and feasibility of low-mechanical-index contrast-enhanced ultrasound in assessing the therapeutic effect of renal cell carcinomas following ultrasound-guided percutaneous microwave ablation.

Keywords

Renal cell carcinoma • Contrast-enhanced ultrasound • Microwave ablation

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Abbreviations and Acronyms

CEUS	Contrast-enhanced ultrasound
CT	Computed tomography
MRI	Magnetic resonance imaging
MWA	Microwave ablation
RCC	Renal cell carcinoma
RFA	Radiofrequency ablation
US	Ultrasound

The image-guided thermal ablation has been widely used for renal lesions treatment on account of the technology promotion and obtained a favorable curative effect parallel to nephron-sparing surgery especially for small ones [1, 2]. To achieve radical clinical results after microwave ablation (MWA) of renal tumors, it is important to select suitable patients. Indications for MWA of renal cell carcinoma (RCC) include patients with small lesions (size less than 4 cm), patients of advanced age or who are poor surgical candidates due to significant comorbidities, those with single kidney or multiple tumors in both kidneys, and patients with ablation preference. In addition, the timely and accurate evaluation of the therapeutic effects is also momentous for promoting the ablation effect. The evaluation of therapeutic efficacy after percutaneous ablation methods for RCC is essential for the determination of subsequent treatment and follow-up strategy. Computed tomography (CT)/magnetic resonance imaging (MRI) as traditional imaging in evaluating the ablation treatment efficacy has some limitations. CEUS with the second-generation contrast agent SonoVue (Bracco, Milan, Italy) as a useful, convenient, no-hepatotoxicity and no-nephrotoxicity tool has been widely used and provided abundant diagnosis and assessment information, especially suitable for renal function impaired patients. There were several reports on CEUS assessment of RFA or cryoablation of renal lesions [3–5], but in the MWA field, the study is seldom. In this chapter, we review the clinical efficiency and feasibility of low-mechanical-index CEUS with SonoVue in assessing the therapeutic effect of RCC following ultrasound-guided percutaneous MWA.

31.1 Evaluation Methods of RCC Treatment Response After Percutaneous Ablation

The final goal of all ablative treatments is to achieve complete destruction of neoplastic tissue and avoid complications related to procedure. The success rate of ablation for RCC depends on tumor's size and the location [2, 6]. It is generally accepted that RCC with a maximum diameter of 4 cm or less (T1a) has a higher probability of complete ablation than that of RCC larger than 4 cm [7].

Tumor location can be classified into three types (exophytic, parenchymal, and endophytic). Some reporters indicated that tumors located endophyticly close to hilar regions have more ablation difficulty and have an increased risk of incomplete ablation or radiographic recurrence [8, 9]. One intrinsic setback for thermal ablation is that major renal vessel proximity to renal tumor distributes heat away from the tumor (heat-sink phenomenon). This may result in incomplete local ablation [10]. In contrast, exophytic RCC may be more likely to be completely ablated than parenchymal or endophytic RCC as perirenal fat can produce a thermally insulating effect, resulting in more efficient thermal ablation [8]. The best noninvasive way to assess the therapeutic efficacy of any ablative treatments is to demonstrate that the blood supply for the tumor has been disrupted both inside and at the periphery via imaging methods [11]. Imaging modalities such as contrast-enhanced CT and MRI have been regarded as reliable and accurate tools for post-procedural surveillance and follow-up [12]. However, both contrast-enhanced imagings have some intrinsic limitations, such as hepatic and renal toxicity, allergic reactions, and excessive exposure to radiation, which always concern both clinicians and patients [13]. And it is contraindicated for patients who have an implanted arthroprosthesis or pacemaker. Additionally, contrast-enhanced CT and MRI are relatively expensive.

The second-generation US contrast agent SonoVue is a blood pool sonographic contrast

agent that consists of microbubbles of sulfur hexafluoride gas with a phospholipid membrane. The development of second-generation microbubble contrast agent as purely intravascular agent has created the ability for US to show the enhancement features of renal lesions. And kidney itself is a blood-rich organ. CEUS technique could significantly demonstrate the visualization of micro- and macro-vascularization pattern in renal lesions [14]. Compared to contrast-enhanced CT/MRI, one major advantage of CEUS is that the microbubble can be metabolized through the respiratory system, safely used in patients with known hepatic or renal failure, and another advantage is the ability to characterize an indeterminate renal lesion detected during US examination and immediately after the ablation procedure. CEUS has been widely used in liver lesions and provided excellent image information [15, 16]. A few reports were published on the assessment of the efficiency of RFA or cryoablation of renal lesions by CEUS [14, 17, 18], but no research on evaluation of MWA by CEUS is reported. MWA shows more thermal efficiency than RFA [17, 18]. For kidney is an blood-rich organ, MWA may appear a different CEUS patterns in the tumor necrosis boundary.

31.2 CEUS Examination

The CEUS imaging technique employs a contrast pulse sequencing software to depict lesion blood perfusion with a real-time manner. In order to avoid microbubble disruption, performing this technique needs to be under the condition of low mechanical index (MI < 0.1). The recommended contrast agent is SonoVue (Bracco, Milan, Italy), an aqueous suspension of phospholipid-stabilized sulfur hexafluoride (SF6) gas microbubbles supplied as a lyophilized powder. 1.0–1.2 ml of a microbubble contrast agent is administrated with a bolus injection by a 20-gauge cannula implanted in the antecubital vein. Injection of SonoVue is followed by flush of 5 ml 0.9 % sodium chloride solution. The procedure is stored digitally on the hard disk of the US system, as well as continuously on digital video tape, and is analyzed in consensus by two expert radiologists.

31.3 Follow-Up

Follow-up interval and duration of CEUS, CT, and MRI may vary depending on institutions. The timing of initial scan varies among institutions from as early as immediately [6, 15] to 1 week [19] after thermal ablation procedure, in order to assess treatment adequacy and baseline size of the ablated tumor and ablation zone. Subsequent follow-up is often performed at 6 months' interval [6] or yearly thereafter [20].

31.4 Image Analysis

The image is evaluated according to previous report [21]. The criteria for CEUS imaging are as follows: inflammatory congestion caused by MWA displayed uniformly circular enhancement around the necrosis zone. If irregular peripheral enhancement in scattered, nodular, or eccentric pattern is noted, this is thought to indicate the presence of residual, incompletely ablated tumor [22]. This finding indicates the incomplete local treatment and a further ablation is considered if the patient still meets the criteria for MWA. Completely treated lesions exhibit no contrast enhancement by CEUS, which indicates the absence of blood flow in the lesion, and the lesions shrunk gradually over time.

31.5 Results of CEUS in Evaluating RCC Ablative Treatment

We performed MWA in 103 RCC patients with the tumor size of 0.6–7.8 cm. Ninety-four lesions were ablated completely for the first session (94/109, 86.2 %), and 15 lesions were ablated completely 2 days after first-time ablation by percutaneous MWA under CEUS guidance (15/109, 13.8 %). No severe procedure-related complications (including hematuria, pneumothorax,

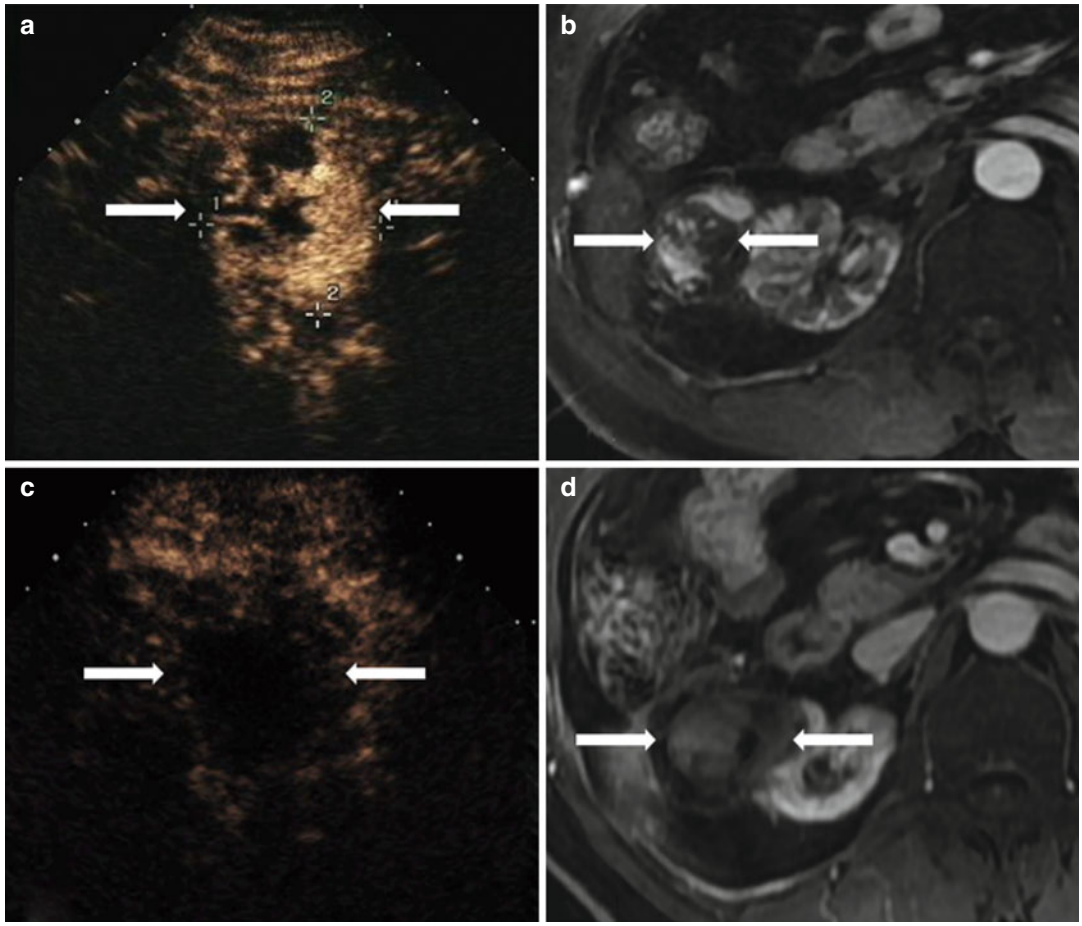

Fig. 31.1 Images in a 53-year-old female with a renal clear cell carcinoma (*RCC*) (4.8 cm×4.5 cm) in the right kidney treated with microwave ablation (*MWA*). (**a**) Pre-ablation contrast-enhanced ultrasound (*CEUS*) shows a heterogeneous hyper-enhancement lesion (*arrow*) in cortical phase. (**b**) Magnetic resonance imaging (*MRI*) shows a heterogeneous hyper-intense lesion in renal parenchyma (*arrow*) in arterial phase. (**c**) One month after ablation, CEUS shows the ablation zone no-enhancement (*arrow*) in cortical phase. (**d**) MR imaging showed hypo-intensity in the ablation zone (*arrow*) in arterial phase one month after ablation

sepsis, renal infarction, skin burns, seeding, and so on) were observed.

On the third day after MWA, the image results of 94 lesions were consistent with CEUS and synchronous CT/MRI after the first ablation (Fig. 31.1). Fifteen residual lesions were revealed by CEUS, but only 12 residual lesions were demonstrated by CT/MRI. Thirteen residual lesions were verified by pathology with biopsy samples (Fig. 31.2), and the second CEUS-guided ablation was implemented. Above results demonstrated that one residual lesion was found by CEUS and did not appear on CT/MR image. Two "residual lesions" were not verified by pathology. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of CEUS were 100, 97.9, 98.2, 86.7, and 100 %, compared to that of CT/MRI which were 100, 98.9, 99.1, 93.3, and 100 %, respectively.

During the median follow-up period of 23 months (range 3–90 months), 93.6 % (102/109) lesions showed completed ablation (Fig. 31.3). Six of seven recurred lesions were found by both CEUS and CT/MRI (6/109, 5.5 %). The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of recurred tumor

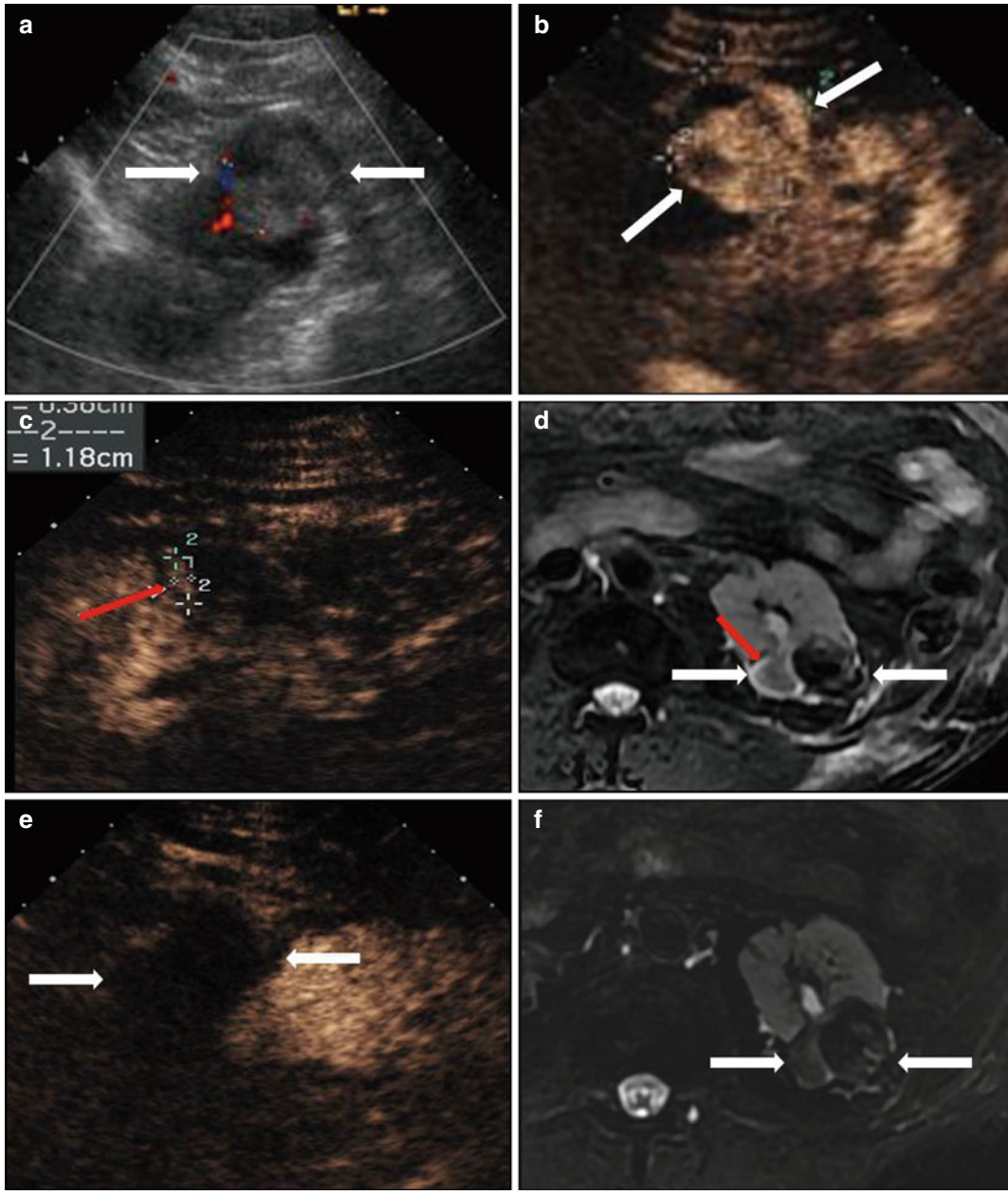

Fig. 31.2 Images in a 81-year-old female with a RCC (3.6 cm×3.4 cm) in the left kidney treated with MWA. (**a**) Pre-ablation US scan shows one hypo-echo parenchymal lesion (*arrow*). (**b**) CEUS scan shows one heterogeneous hyper-enhancement lesion (*arrow*) in cortical phase. (**c**) Three days after ablation, CEUS shows a very small hyper-enhancement lesion adjacent to the ablation zone (*arrow*) in cortical phase. (**d**) MR imaging shows a hyper-intense lesion at the same location on T2 image, considered as residual tumor (*red arrow*), (**e**) then no-enhancement on CEUS (*arrow*) in cortical phase after another ablation. (**f**) Hypo-intense on MRI after another ablation (*arrow*) on T2 image

detection by CEUS were 85.7, 99.0, 98.2, 85.7, and 99.0 %, respectively. Our results indicate that CEUS may be an effective alternative to CT/MRI in the follow-up of RCC after percutaneous MWA, which is similar to the results after RFA reported by Maria Franca Meloni in 2008 [17].

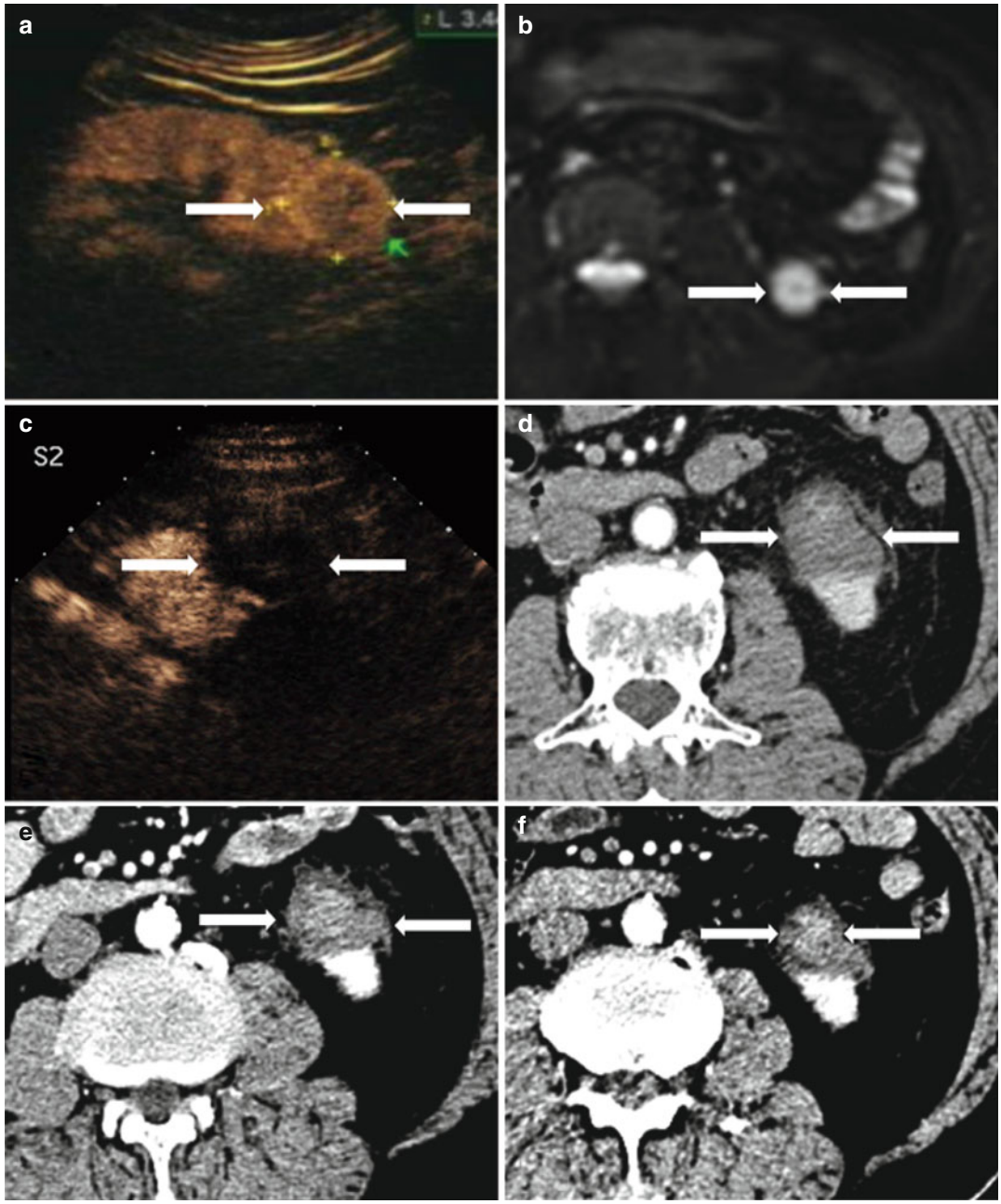

Fig. 31.3 Images in a 73-year-old female with a RCC (3.4 cm × 3.4 cm) in the left kidney treated with MWA. (**a**) Pre-ablation contrast-enhanced CEUS shows a hyper-enhancement in cortical phase. (**b**) MR imaging showed one hyper-intense lesion exophyticly in the inferior pole of the kidney (*arrow*) on T2 image. (**c**) Three days after ablation, CEUS showed the whole lesion no-enhancement continuously in cortical phase. Computed tomography (*CT*) imaging showed one hypo-intense lesion in arterial phase 1 month (**d**), 3 months (**e**), and 12 months (**f**) after ablation, and the lesion shrunk gradually obviously (*arrow*)

Meanwhile several studies reported that CEUS played a promising role in evaluating the short-term and long-term therapeutic effects of RCC following different ablations. As shown in Tables 31.1 and 31.2, CEUS is an effective method in assessing the therapeutic effect during

Table 31.1 The CEUS evaluation performance on assessment of the ablation effect for RCCs in short-term (<3 months) follow-up

Author	Num	Ablation	Follow-up (days)	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
Hoeffel et al. [3]	66	RFA	1	64	98	N/A	82	92
Hoeffel et al. [3]	66	RFA	42	79	100	N/A	100	95
Li et al. [24]	83	MWA	3	100	97.9	98.2	86.7	100
Barwari et al. [23]	45	Cryoablation	90	NA	92	N/A	N/A	77

CEUS contrast-enhanced ultrasound, *RCC* renal cell carcinoma, *RFA* radiofrequency ablation, *MWA* microwave ablation, *PPV* positive predictive value, *NPV* negative predictive value, *N/A* not available

Table 31.2 The CEUS evaluation performance on assessment of the ablation effect for RCCs in long-term (>3 months) follow-up

Author	Num	Ablation	Follow-up (months)	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
Meloni et al. [17]	28	RFA	4–67	96.6	100	100	95.8	98.1
Kong et al. [4]	64	RFA	2–34	100	96	N/A	50	100
Li et al. [24]	83	MWA	3–74	85.7	99.0	98.2	85.7	99.0
Barwari et al. [23]	45	Cryoablation	12	NA	90	N/A	N/A	100

the follow-up of RCC followed with RFA, MWA, and cryoablation [3, 4, 17, 23, 24]. Just as conventional US, CEUS is subject to unclear lesion display for abdominal gas shielding or relative operator dependence of US. Sometimes it could be avoided by changing the posture of patient and cleaning the bowel. Otherwise, this situation may affect the assessment of the therapeutic efficiency after ablation.

The study about CEUS, as a relative new technique in the assessment of ablation effect in RCC, has some limitations as well. Firstly, post-ablation biopsy with pathological results was not performed for all the lesions to prevent the risk of bleeding because of the nature of the kidney being rich in blood supply. And some authors had pointed out that the use of needle biopsy had some limitation in depicting residual lesions after thermal ablation [25]. Secondly, to some extent, the CEUS imaging evaluation was dependent on the experience and diagnosis level of the radiologists. Thirdly, larger series and long follow-up period are needed to further confirm the result. Thus, further investigation is mandatory.

Conclusions

Ultimately, the post-procedural CEUS with second-generation contrast agents establishes imaging method to assess the efficacy of ablative treatment. Its high assessment accuracy in depicting the residual tumor with no adverse effects makes it one of the methods of choice to evaluate ablation response in short term (2 days after percutaneous MWA). And in the long-term follow-up (longer than 3 months after percutaneous MWA), CEUS shows a comparable assessment accuracy with CT/MRI. CEUS appears to be a convenient, repeatable, less-toxic technology with high diagnosis accuracy and plays a promising role in evaluating the therapeutic effect of RCC following percutaneous MWA.

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