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Microwave Ablation for Liver Malignancy: A Literature Review

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Abstract

Hepatocellular carcinoma (HCC) is a common cancer, especially in the East. Patients with HCC are unique in that they are usually suffering from two afflictions: cancer and liver cirrhosis. This combination makes the management of their condition challenging. Surgery is the mainstay of treatment for HCC patients but for those who are not fit to undergo operation, other options are available. Ablation therapy has emerged as a viable alternative to the open surgery. Radiofrequency ablation has been around for many years and there is ample amount of research to support its use. Microwave ablation is a newer technology with many theoretical advantages. The review article describes the mechanism, equipment, technical advantages and indication of microwave ablation. It also summarizes the findings of different studies which compared the use of microwave with radiofrequency ablation.

Keywords: Microwave ablation; Liver; HCC

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Introduction

HCC

Hepatocellular carcinoma (HCC) is the fifth most common cancer with around 750,000 new patients every year [1,2]. It accounts for the third most cancer-related deaths in Hong Kong [3]. Hepatitis B cirrhosis is common in Asia, where HCC is endemic. Other risk factors for the development of HCC include Hepatitis C infection, alcoholic cirrhosis, hereditary hemochromatosis and primary biliary cirrhosis. Although it used to be a disease primarily affecting Eastern countries due to the prevalence of chronic hepatitis B viral infection in the area, its incidence in Western countries has been rising in recent years [4,5]. The annual incidence of HCC in hepatitis B carriers is around 0.5%. The incidence in patients with liver cirrhosis is even higher at around 2.5% annually [6,7].

Treatment of HCC

The patients who are hepatitis B/C virus carriers should be offered regular surveillance in order to identify small tumors that may be potentially treatable. However, most patients with small HCCs do not have symptoms. Hepatic resection forms the cornerstone of the surgical management of HCC and is regarded as the standard treatment with curative intent for HCC as suggested by Asia Pacific Association for the Study of Liver Disease guideline [8]. The operative mortality is less than 5% for major hepatectomy and the 5-year survival is 50% [9]. Anatomical resection for HCC proposed by the Makuuchi et al. [10] is the gold standard for the surgical treatment for HCC. However, not all patients are suitable for surgical resection [11]. In fact it is only possible in 25% of patients because the disease is usually so advanced upon presentation. The presence of multifocal disease, proximity of tumor to major vascular and biliary structures preventing adequate resection margin, metastatic disease on presentation are all contra-indications to major resection [12]. Another unique impediment to liver resection is the issue of liver remnant as HCC is often associated with cirrhosis, making resection difficult if not possible at times. Hence the prognosis for the majority of HCC patients remains dismal. Liver transplantation provides an alternative curative treatment for a selected group of HCC patients, but the paucity of liver grafts limits the application of the approach [13,14].

Even for those who are fit to undergo resection, cure is far from guaranteed. Post-resection tumor recurrence is common with 5-year recurrence rate over 50% [6]. Salvage treatment (defined as treatment given for recurrent disease after resection) for recurrent HCC poses several challenges, especially when tumor recurrence occurs in a small and cirrhotic remnant liver. Factors such as inadequate liver reserve (both in terms of volume and function), presence of adhesions from previous operations, and tumor location in the vicinity of major hepatic vessels or bile ducts in the liver remnant are all major challenges to further resection. Therefore, alternative treatments are needed.

The Role of Ablation Therapy

The advent of local ablative therapy revolutionized the treatment protocol for HCC over the last decade [7]. With technological advances, local ablative therapy using various energy sources has emerged as a viable treatment alternative for patients for whom conventional surgery is not suitable. These include cryo-ablation therapy, interstitial laser therapy, high intensity focused ultrasound (HIFU) ablation, and radiofrequency ablation (RFA). Recently, microwave ablation (MWA) has emerged as a relatively new form of local ablative therapy. This innovative treatment entails the delivery of electromagnetic waves with frequencies ranging from 900 MHz to 24 GHz into targeted area resulting in hyperthermia which in turn leads to coagulative necrosis of tumor cells. This technique was first described in 1994 and has emerged as a potential alternative to RFA in treating small HCC (less than 3cm in size). Over the past two decades, marked improvement in percutaneous and operative technique together with better localization of lesion and more efficient delivery of energy has resulted in improved outcomes. MWA has been predominantly employed in China and Japan but the technique is becoming more popular in the West. One major advantage of the MWA technique over RFA is the reduced "heat sink" effect. Heat sink is defined as the loss of temperature (and hence energy source) in peripheries of the tumor close to blood vessels. Other advantages include its ability to reach high temperature faster and to maintain the intra-tumoral temperature longer, thereby producing a deeper and faster penetration over a larger volume.

Mechanism of microwave ablation

MWA manipulates the property of electromagnetic wave to induce tumor destruction. This microwave ablation instrument emits energy, in the form of heat from electromagnetic waves of frequencies greater than 900 MHz [15]. The rotational movement of dipole molecules of water accounts for heat generated during MWA [16,17]. Water is a charged molecule. The dipoles within the water molecule possess asymmetrical electric charge distribution, and they attempt to rotate continuously at the same frequency as the microwave oscillating electromagnetic field. Therefore, electromagnetic microwaves burn tissue (in this case, tumor cells) by agitating water molecules inside the cells, producing friction and heat, thus resulting cell death via coagulation necrosis. Currently, two types of frequencies are used for MWA: 915 MHz and 2450 MHz A frequency of 2450 MHz is more widely used, which is also the frequency used in conventional microwave ovens [17]. The theoretical advantage of microwaves of 915 MHz is that it can penetrate tissue deeper than 2450 MHz microwaves [18], therefore, the low frequency MWA may be able to create larger areas of ablation zones.

Technical advantages

Radiofrequency ablation is currently the most well-established form of ablation therapy. Other forms include high intensity focused ultrasound, cryo-ablation therapy and MWA. MWA displays some theoretical advantages over RFA. First of all, the active heating of tissue by RFA is limited to a few millimeters surrounding the operating electrode; the remainder of ablation zone relies entirely on the conduction of electricity and heat through the tissue [16]. MWA use electromagnetic waves to generate heat, resulting in a much larger area of energy propagation (up to 2 cm surrounding the antenna). The waves agitate the polar water molecules within tissue to reorient rapidly to achieve primarily active heating and the active heating zone is much larger, regardless of tissue conductivity [15]. The energy delivered by RFA is limited when there is an increase in impedance with tissue boiling and charring [16], since water vapor and char are effectively electrical insulators. Since the propagation of electromagnetic waves in MWA differs from the conduction of heat by RFA, MWA is not subject to the limitation from presence of char and water vapor. Therefore, high temperature such as those greater than 100°C is readily achieved [19]. A third advantage is that MWA can achieve higher temperatures within the target tumor, larger ablation volumes, and shorter ablation times, due to its superior active heating ability [19-22]. Furthermore, since the heat dissipation by blood flow is most obvious within the zone of conduction rather than active heating, MWA is theoretically less affected by blood-vessel-mediated cooling, also known as the heat-sink effect. Therefore, MWA can potentially secure a more consistent tumor necrosis within the ablation zone, both within the targeted zone and perivascular tissue [22,23]. MWA device permits the use of multiple probes simultaneously to reduce the duration of treatment and increase the diameter of ablation zone [15,16,19]. MWA does not use grounding pads (which are required in RFA in order for the electric current to complete the circuit) during the procedure and the electrical energy is delivered into the target tissue only, which avoids unnecessary energy loss or potential skin burns. MWA is also not contraindicated by the presence of the metallic materials like surgical clips or pacemaker since there is no electric circuitry.

As one of the newer options in the field of ablation therapy, MWA is not without flaws. The higher thermal efficiency of MWA can be a victim of its own success. The energy can easily result in injury near the adjacent critical tissues because the tissue surrounding the antenna is rapidly ablated and heated to very high temperature. In other words, advantages which make the method powerful are also cause for safety concerns.

All of the above are postulations based on physics and biochemical behavior of electromagnetic waves and tissue property. On a cellular level, the induction of pro-inflammatory cytokines including interleukin-1 and interleukin-6 by microwave ablation is minimal compared with that induced by RFA and cryo-ablation in an animal model [24]. In humans, there is a significant inverse correlation between survival outcome and the extent of immune cell infiltration in patients treated with microwave ablation for HCC [25]. Apart from theoretical comparison of these two different ablation techniques, in the reviewing the limited comparative trials between MWA and RFA, both modalities achieved similar tumor necrosis effects and survival [26-29].

Equipment

All MWA devices are made up of three components: the generator, a connecting cable, and the microwave probe. The electromagnetic waves are generated by a magnetron in the generator (similar to ones used in commercial kitchen microwaves). The antenna probes are connected to the generator by a low-loss cable and are responsible to transmitting the electromagnetic waves from the magnetron onto the tissue. Antennae are classified into three types based on their physical features and radiation properties: they are dipole, slot, and monopole [30]. The various antenna shapes include straight, loop and tri-axial. Design of the antenna is crucial to the therapeutic efficacy. Currently, the design has focused largely on needle-like, thin, coaxial-based antennae [30,31], which are appropriate for percutaneous use to create large ablation zones.

To prevent over-heating of the shaft which might lead to skin burn, and to permit further propagation of energy into tissues with low impedance during ablation, cooled-shaft antennae are developed. This new design has made strides in obtaining larger ablation zones [19,32]. The diameter of the antenna can range from 1.6 to 2.8 mm (i.e. 10 to 16G); the most commonly used diameter clinically is from 14G to 16G.

Most types of radiofrequency devices have a thermometer coupled with the electrode tip to measure the temperature during the procedure. Temperature monitoring ensures that the maximum energy is applied [33]. The MWA system is also coupled to a temperature monitoring device which provides real time measurement during the procedure. There are multiple reasons for this type of real time monitoring. The measuring needle is inserted under image guidance about 5-10 mm from the outer edge of the tumor. Total necrosis can be quantified when the temperature remains at 54°C for at least 3 min or reaches 60°C instantly. For tumors that are in close proximity to vital structures (i.e. less than 5 mm from bile ducts, the gastrointestinal tract, gallbladder, and major blood vessels), the real-time monitoring at the tumor margins ensures that temperature outside the target lesion does not reach a damaging level for collateral vital structures. In patients with virgin abdomen, the ablation therapy will stop momentarily when the temperature reaches 54°C. The transmission of microwaves resumes when the tissue cools to 45°C, and then repeats in cycles until the entire target is completely encompassed by hyperechoic water vapor.

Indication for microwave ablation

In the management of hepatocellular carcinoma, MWA therapy can be curative, palliative or bridging in its treatment intent.

For patients who are not surgical candidates for a variety of reasons, ablation therapy is a suitable alternative either as primary or salvage treatment. HCC patients are often not fit for operation due to reasons such as inadequate liver remnant volume, multi centricity of tumor, tumors located at anatomically unsuitable locations, and concomitant liver failure etc. For patients who are fit to undergo surgery, resection is still the good standard of treatment. However, percutaneous ablation offers some benefits such as shorter hospital stay, increased preservation of surrounding liver tissue, and decreased morbidity. Previously ablation therapy has proven to be successful with regards to small liver tumors less than 3 cm in largest diameter [34-36]. With advancement of technology and management strategies, larger tumor (namely 5 to 8 cm in size) can be ablated with success [37]. According to BCLC (Barcelona Clinic Liver Cancer Staging System), for very early and early stage hepatocellular carcinoma, ablation is curative. The inclusion criteria is a single lesion less than 5 cm, or 3 separate lesions, each no larger than 3 cm, combined with the absence of major vascular invasion and extrahepatic metastases. If patient is outside these criteria, then the intent of MWA therapy is palliative in nature.

MWA can be also used as salvage treatment for HCC recurrence after resection. In case of recurrent disease, only patients with Child Pugh class cirrhosis, and selected patients with Child- Pugh class B cirrhosis, should be considered for re-resection. The usual indication for re-resection is a solitary or oligonodular tumor within the same single section of the liver in the presence of sufficient future liver remnant. Re-resection should be avoided in the presence of gross ascites, an indocyanine green retention rate more than 15% at 15 minutes, a platelet count lower than 100 x 109/L or inadequate liver remnant. Percutaneous MWA is therefore considered a viable option when the recurrent tumor is in a deep-seated location where anatomical resection will sacrifice a large amount of functional liver parenchyma. MWA should be considered as an alternative ablative option for this group of patients in the setting of salvage treatment for HCC. To conclude, for the treatment of HCC smaller than 3 cm (either in the setting of primary or salvage treatment), MWA ablation offers excellent oncological outcome which is comparable to the results achieved with percutaneous RFA. This relatively new method can offer hope to patients with poor liver function and advanced cirrhosis, when other therapies are not curative.

Bridging therapy arose out of the need to suspend tumor progression and to enable patients to remain within the transplantation criteria as long as possible, in order to qualify for a liver graft. Effective bridging therapy is particularly limited for patients whose treatment options are restricted by poor liver reserve and portal hypertension. TACE (transarterial chemoembolization) and RFA are the most popular bridging therapies. TACE is a standard bridging therapy at some centers, achieving a rate of down-staging of tumor of around 40%. However, about 20% of the tumors progress after TACE, leading to these patients being delisted for transplantation. MWA can be used as a bridging therapy. A bridging therapy must not cause further liver decompensation and TACE and RFA are not safe for patients with severe cirrhosis with gross ascites and thrombocytopenia. The role of MWA for these patients is an area of research to be explored. Whether MWA as a bridging therapy is superior to RFA or TACE has yet to be determined.

Comparison between RFA and MWA

Studies done in USA after the MWA system using 2.4GHz was FDA approved showed that it is a safe treatment and the local recurrence is uncommon for tumors smaller than 3cm in diameter (1% for lesion less than 1cm and 9% for tumor ranging from 1 to 3 cm) and for tumors which are not located close the major vessels [38]. For large HCCs (defined as 5 to 7 cm), a small study of 26 patients showed that percutaneous microwave ablation is safe and effective. Overall survival (21.5 months) and local tumor control (as defined by the rate of local recurrence of 23%) were acceptable [37]. Another study including 45 patients also showed that MWA for large HCC (5 to 8 cm) appears safe and effective. Local recurrence of 24% was observed within one year and 1st and 2nd year survival rates were 96% and 87% respectively. There were no mortality associated and major complications such as bleeding, rupture or abscess were not reported. HBV-DNA (signifying viral disease activity) and proximity to risk area are the only independent predictors of local tumor recurrence [39]. An Egyptian study including 111 patients showed both RFA and MWA are safe treatment and the rates of complete ablation were similar (94% for RFA vs. 96% for MWA). The overall survival of the rates did not show statistically significant differences. However, MWA group achieved better local control as demonstrated by the lower local recurrence rate (4% in MWA vs. 14% in RFA group) [40]. While Japanese researchers thought RFA had a tumor control advantage in small liver lesions [33,34], another study by German group led by Vogl which included 53 patients showed no difference in term of treatment success in tumors less than 2 cm. Complete response rates, and recurrence rates and survival were all similar [41]. RFA and MWA are both widely used as curative treatment for HCC. They are both effective and safe but MWA may be more effective in preventing local tumor progression when treating larger tumor according to one meta-analysis which contains 10 comparative studies [42]. Another systemic review by Faccioirusso which included 7 trials and 774 patients also shows a similar efficacy, local recurrence rates between the two technique with an apparent superiority of MWA for larger lesions [43]. However, randomized controlled trials with large samples and long-term follow-up are still lacking. In the absence of robust evidence, it is difficult to recommend one treatment over the other.

Conclusion

Significant improvements over the past decade allow the treatment of more patients with advanced HCC who were previously deemed unfit for surgery. As of now, resection or transplantation when suitable is still the gold standard of treatment for HCC. However, for patients who are not fit for surgery or outside transplantation criteria, ablation is a good alternative. Locoregional treatments such as RFA, MWA, HIFU or cryotherapy make up the backbone of ablation therapy for HCC, a malignancy that affects up to a million people per year worldwide. RFA and MWA differ in their mechanism of action. RFA uses electrical current as opposed to MWA which uses electromagnetic wave. The end results of both modalities are the same: heat resulting in coagulative necrosis of tumor cells. RFA is an establish technique with proven results. Microwave is a newer technology which has many theorectical advantages. MWA does not use grounding pads; therefore it carries no risk of skin burns. Since an electrical circuit is not needed, the presence of metallic surgical clips or a pacemaker is not a contraindication to the procedure. It creates a rapid and homogenous heating effect despite tissue charring and boiling and results in a more predictable ablation area. It reaches higher temperatures faster and is less susceptible to the heat-sink effect of nearby major vessels. Simultaneous treatments of multiple lesions are possible, leading to shorter procedural time while covering larger ablation volume. Finally, a faster procedure correlates to less peri-procedure pain. However, all of the above potential benefits have not been proven to confer clear-cut superior clinical results in terms of local control, recurrence rates, and completeness of ablation or survival. In other words, there is still no solid proof to support the advantage of one treatment over the other. The future technological advances in medical instruments together with a multidisciplinary approach to patient management will allow better patient selection that would maximize treatment benefit.

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