Radiofrequency ablation in the treatment of hepatocellular carcinoma

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ABSTRACT

Objective: The purpose of this article is to discuss the use, comparative efficacy, and research progress of radiofrequency ablation (RFA), alone or in combination with other therapies, for the treatment of hepatocellular carcinoma (HCC).

Method: To search and summarize the basic and clinical studies of RFA in recent years.

Results: RFA is one of the radical treatment methods listed in the guidelines for the diagnosis and treatment of HCC. It has the characteristics of being minimally invasive and safe and can obtain good local tumor control, and it can improve the local immune ability, improve the tumor microenvironment and enhance the efficacy of chemotherapy drugs. It is commonly used for HCC treatment before liver transplantation and combined ALPPS and hepatectomy for HCC. In addition, the technology of RFA is constantly developing. The birth of noninvasive, no-touch RFA technology and equipment and the precise RFA concept have improved the therapeutic effect of RFA.

Conclusion: RFA has good local tumor control ability, is minimally invasive, is safe and has other beneficial characteristics. It plays an increasingly important role in the comprehensive treatment strategy of HCC. Whether RFA alone or combined with other technologies expands the surgical indications of patients with HCC and provides more benefits for HCC patients needs to be determined.

Introduction

Since Rossi et al. first reported percutaneous radiofrequency ablation (RFA) in 1993, most studies suggest that RFA is a mainstay treatment for early-stage HCC, and it can achieve a long-term effect that is close to surgical resection for HCC with diameters less than 3 cm. In general, RFA should be the first choice for patients with a central single nodule HCC that has a diameter of less than 3 cm because surgical resection will sacrifice a large part of the normal liver parenchyma. However, for tumors in special locations (those adjacent to important organs and ducts, that are subcapsular liver and multiple tumors in the same liver segment), RFA easily causes residual tumors, so surgical resection should be selected. It can act as a primary curative therapy or as a bridge therapy for patients waiting to undergo a liver transplant. New ablation modalities and combining tumor ablation with other therapies, such as transarterial chemoembolization, can improve clinical outcomes and allow for the treatment of larger lesions. Combining thermal ablation with systemic chemotherapy, including immunotherapy, is an area of future development.

Clinical application of RFA in the treatment of HCC

RFA as a primary treatment

RFA has been written into the guidelines for HCC treatment as a therapeutic method for early-stage HCC [1]. In early reported experiences, RFA was most effective for the treatment of HCC smaller than 2 cm (very early HCC) and 3 cm (early HCC), and RFA achieved complete necrosis rates of 90% [2]. The complete necrosis rates have historically been noted to decrease to approximately 70% in lesions between 3 and 5 cm, to approximately 24% in lesions larger than 5 cm and even lower in infiltrative tumors [3]. For tumors \( \leq 3 \text{ cm} \), local tumor progression at the ablative margin has been reported to occur in approximately 10% of patients, predominantly within the first 12–18 months after treatment [4]. In contrast, HCC larger than 3 cm has historically had poorer local tumor control rates and long-term outcomes using RFA. Aggressive tumor biological activity, as reflected by microvascular invasion, high levels of biomarkers (\( \alpha \)-fetoprotein and \( \alpha \)-fetoprotein L3), or poorly differentiated morphologic findings on pathologic analysis, is associated with higher...
rates of local tumor progression and worse overall survival, even for smaller tumors. Indeed, an increasing tumor size is associated with higher rates of microvascular invasion (>60% in tumors larger than 4 cm), which is associated with worse overall long-term survival [5]. The median postrecurrence survival was 22 months in early/intermediate patients initially treated with RFA. Child–Pugh score, performance status, sum of tumor diameters at recurrence and recurrence patterns were independent predictors of postrecurrence survival [6]. The 5-year overall survival ranged from 61 to 86% in patients with preserved liver function (Child–Pugh class A and tumors ≤3 cm) [7–9]. At 10 years of follow-up, two previous studies reported the survival of patients with preserved liver function (Child–Pugh class A), and the survival rates were 61.2% in patients with tumors ≤3 cm and 33.6% in patients with tumors up to 5 cm [10,11].

The basic principle of RFA is thermal ablation, and its local tumor control ability is affected by the heat sink effect. The heat sink effect is an important factor affecting the recurrence of HCC after RFA [12]. Intraoperative radiofrequency can be carried out after blocking hepatic blood flow, which is conducive to reducing the heat sink effect. Assisted ablation of the tumor blood supply artery before radiofrequency ablation can reduce the local recurrence rate of tumors, but the disadvantage is that it may increase the risk of bleeding due to damage to the tumor blood supply artery [13]. We can use bipolar electrodes because bipolar radiofrequencies were less affected by the heat sink, while monopola RFA was the most affected [14]. In addition, treatment combined with TACE can also reduce the heat sink effect. However, artificial ascites did not show a heat-sink effect [15].

In addition, the safety margin is also the main factor affecting the efficacy of RFA for HCC. Surgeons usually define the safety margin as 1 cm, and radiologists usually define it as 0.5 cm [16]. For early HCC with a diameter ≤3 cm, the ideal safety margin is 2 cm; for HCC with a diameter >3 cm, the ideal safety margin is at least 3 cm. Fusion imaging (FI) is a newly developed imaging method that integrates CT/MRI accurate imaging and matches the characteristics of real-time ultrasound imaging, thereby providing a new approach to guide tumor ablation therapy [17]. The ablation safety margin [18] or even the minimal ablative margin (MAM) [19] can be evaluated by FI technology. FI may have some effects on improving the efficacy and safety of thermal ablation in HCC patients relative to ultrasound [20]. In addition, contrast-enhanced ultrasound (CEUS) guidance can make it difficult to see HCC lesions. 3D US/CEUS- US/CEUS fusion imaging [21], three-dimensional reconstruction techniques using CT imaging [22], and fused MRI imaging [23] can effectively evaluate the security margin. Therefore, with the development of fusion image guidance technology, we can obtain a better security margin of RFA.

Radiofrequency ablation is widely used in the clinic, with less intrahepatic and distant metastasis. The recurrence site is mainly next to the original ablation focus, but we also need to pay attention to its systemic pro-oncogenic effects. This kind of situation is generally seen in insufficient RFA. Insufficient RFA can promote the rapid growth of residual cancer through autophagy [25,26] and epithelial mesenchymal transformation [27,28]. It can also promote liver cancer metastasis [29]. With the development of image-guided technology and the improvement of radiofrequency ablation instruments and electrodes, it is generally required to obtain a sufficient safety margin in clinical practice. Therefore, insufficient radiofrequency ablation is rare, and systematic pro-oncogenic effects from RFA are also rare.

Radiofrequency-assisted liver resection and ALPPS

The heat energy produced by RF generators can cause coagulation necrosis of liver tissue and seal the microvessels and bile ducts. In 2002, Habib creatively applied RFA in hepatectomy patients. The results showed that blood loss was significantly reduced and the number of hepatic hilar occlusions was reduced [30]. RF-assisted liver resection allows for a nonanatomical liver resection with reduced blood loss, a low proportion of patients needing blood transfusions, and reduced mortality and morbidity rates [31] and offers the opportunity for a combination of resection and ablation. The analysis of 857 consecutive open and laparoscopic elective RF-assisted liver resections for benign and malignant liver tumors showed that RF-assisted liver resection has evolved into a feasible and safe technique of liver resection with an acceptable incidence of perioperative morbidity and a low incidence of postoperative liver failure and related mortality [32]. Open and laparoscopic radiofrequency-assisted liver resections were not significantly different [33]. RF-assisted liver resection did not show increased liver injury or postoperative morbidity or mortality [34], even in patients who had liver cirrhosis [35]. It is a safe and feasible surgical resection method for patients with cirrhosis and concomitant HCC [36].

However, a study showed that the use of RF generators does not significantly reduce intraoperative and postoperative complications [37]. We should note that this kind of operation is still associated with a high death rate and rare serious postoperative complications, mainly liver failure [38], major bile duct injury [39], bile leakage and cross-section effusion [40]. The incidence of bile leakage at the resection margin and postoperative liver failure is 2.8 and 1.5%, respectively [32]. Postoperative complications were noted in 16.9% of patients, and the postoperative mortality was 1.9% [41]. This method should be used with caution in patients with concomitant cirrhosis. Therefore, some scholars have pointed out the need for future well-designed RCTs to further investigate the efficacy and safety of RF devices in liver resection [42].

Clinical studies have reported superior disease-free survival following RF-assisted resection of HCC compared to conventional liver resection. HCC often develops secondary
to chronic inflammation and in a complex immunosuppressive network that is characterized by increased regulatory T cells, impaired CD8$^+$ T cells and the secretion of immunosuppressive cytokines. A study previously showed that patients undergoing RF-assisted liver resection with Habib$^\text{TM}$ 4X had a significant decrease in inhibitory Treg cells, circulating TGF-$\beta$ and IL10 and a significant increase in CD8$^+$ T lymphocytes, CD4$^+$CD45RO$^+$CD4$^+$ memory T cells, IFN-gamma and IL-17 compared to those patients undergoing liver resection with CUSA. Liver resection with the RF-assisted device Habib$^\text{TM}$ 4X was associated with positive immunomodulatory changes in circulating immune cells and circulating cytokines, which could explain the significant improvement in disease-free survival [43]. The new internal cold circulation bipolar radiofrequency (New-RF) is a safe and efficacious auxiliary device for liver resection with a faster speed of resection, a lower carbonization rate of the electrode needle, and a more precise range of coagulation than Habib-4X bipolar radiofrequency (Habib-4X) [44].

The standard procedure of this technique is to use a bipolar RF electrode to cauterize a 1 cm wide continuous ablation band on both sides of the predetermined resection line on the liver surface and then cut off the liver parenchyma. However, this method will lose more functional liver parenchymal cells, especially for the cirrhotic liver, and the incidence of liver failure is significantly increased. For HCC patients with cirrhosis, especially in Asia and South Africa, this ablation method will undoubtedly increase the risk of liver failure. According to our experience, it is suggested that the two ablation bands should be reduced to one and should be as close to the tumor as possible to reduce the loss of functional liver parenchymal cells and the incidence of postoperative complications.

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a new, safe and feasible surgical method in recent years that provides the opportunity for radical resection in HCC patients who have an insufficient residual liver volume [45,46]. The classic ALPPS one-stage operation includes liver partition and portal vein ligation. The main complications are postoperative bile leakage and abdominal infection. The reasons for these complications are that two large wounds are formed in the amputated liver tissue, and the incidence of bile leakage is doubled. These not only result in extensive and serious postoperative abdominal adhesions but also cause great difficulties for the second-stage operation. Because of the emergence of many complications, many patients cannot be treated with a secondary resection. In view of the above drawbacks, we [47] optimized ALPPS (that is, radiofrequency-assisted ALPPS, RALPPS): in the first stage, the radiofrequency electrode was continuously cauterized along the preresection line after ligation of the right branch of the portal vein to form an ablation band between the tumor and the remaining liver tissue to isolate the liver tissue. Although the liver tissue is not completely isolated, RFA can stimulate the liver to secrete a large number of cell growth factors, thus promoting the rapid growth of the contralateral liver. In addition, the intra-abdominal adhesions after the one-stage operation were less severe, which created favorable conditions for the second-stage resection of the tumor. RALPPS has successfully treated massive HCC patients [48], and case reports have described the use of totally laparoscopic RALPPS [49]. However, the general opinion is that RALPPS is not recommended for HCC patients because of the long waiting time between the two stages [46]. However, rescue RFA/PEI may provide an alternative to trigger further growth of the future liver remnant (FLR) in patients with cirrhosis-related HCC showing insufficient FLR after RALPPS stage-1 [50]. Percutaneous RF-assisted liver partitioning with portal vein embolization in staged liver resection (RALPPS) is a feasible procedure in pigs [51]. Subsequent clinical studies suggested that the short-term outcomes were similar for PRALPPS and PVE in terms of safety. However, remnant hypertrophy was achieved more rapidly by PRALPPS [52].

**Role of RFA in liver transplantation**

Liver transplantation (LT) is the best treatment for HCC according to the Milan criteria. However, due to the serious shortage of donor organs, patients often have to wait for a long time. If the waiting time is more than 6 months, it is necessary to take measures (such as RFA and TACE) to delay the progression of the tumors [53]—a strategy that is referred to as bridging to transplant. As early as 2001, scholars [54] have tried to use RFA to delay the progression of HCC before LT and have achieved good results. For tumors less than 3.5 cm, it is suitable to use RFA as a bridge treatment to prolong the waiting period of HCC patients. Since then, many scholars have reported the efficacy of RFA as a bridge therapy before LT, but the results are not the same. Compared with the average waiting time of LT, RFA can prolong the average waiting time by 4.5-8.2 months without increasing the risk of metastasis or death [55,56]. In a pathological study of diseased livers in LT patients receiving RFA before surgery, Schroeder et al. [57] found that 38% of HCC patients did not have their disease effectively controlled. In another study [58], imaging examinations after 3 weeks showed that the complete destruction rate of the tumor was 82.6%, while pathological examination of the diseased liver showed that only 74% of the tumors were completely destroyed. N’Kontchou et al. [59] compared the curative effect between patients who received RFA followed by salvage LT and those patients who received LT only and found that there was no significant difference in prognosis between the two groups. Therefore, a two-step strategy was proposed for LT patients; that is, RFA should be the first choice, followed by salvage LT after recurrence. RFA and/or TACE were used for tumor reduction before LT in patients exceeding the Milan criteria, and approximately 30% of the patients failed to receive LT because of tumor progression. These studies suggest that our ‘ablation and wait’ strategy may be useful in identifying patients with high-grade liver cancer, and these patients will not benefit from LT [60]. The effect of RFA on tumor reduction is closely related to the complete tumor destruction rate. With the development of modern RFA technology, the complete ablation rate of tumors less
than 5 cm in diameter can reach more than 90%. Therefore, currently, the main problems are tumors that are in special locations and small lesions that cannot be found by preoperative imaging. Laparoscopic RFA can solve the above problems [61]. RFA allows patients to be maintained longer on the waiting list without negative consequences on drop-off and without a decrease in survival compared with patients with no treatment [62].

Percutaneous RFA is safe and effective for intrahepatic recurrent HCC after LT, especially for those patients without limited extrahepatic metastasis [63]. However, RFA cannot decrease the frequency of new tumors or extrahepatic metastasis. The AFP level and tumor number before RFA should be considered to predict the outcome [64]. RFA, as a first-line stand-alone bridge therapy to LT, achieves excellent long-term overall and tumor-specific survival, and RFA has a low dropout rate from tumor progression despite the long wait list times and has a sustained low tumor recurrence rate with a post-LT follow-up of up to 10 years [65]. For HCC recurrence after LT, RFA is preferable when surgical resection is contraindicated or when technically infeasible and provides a comparable long-term survival compared with surgery [66]. The same is true for patients with metastatic liver cancer after LT [67].

However, with the development of technology and the development of antitumor drugs, the concept of liver cancer treatment is constantly being updated. At present, the treatment of liver cancer has gradually developed from a single treatment mode to a comprehensive treatment mode. The comprehensive treatments include technology combinations, technology and drug combinations, drug combinations and so on. Here, we introduce the progress of RFA combined with other technologies and combined with drug therapy.

**RFA combined with hepatectomy**

Multicentric tumors have always been a key problem that has restricted the efficacy of surgery. Due to the impaired functional reserve of the cirrhotic liver, it is impossible to resect all tumors, especially small HCCs located in the center of the liver parenchyma. As early as 1998, Elias et al. [68,69] tried to use RFA to ablate small lesions not including the main focus in hepatectomy and achieved good results. Choi et al. [70] reported that the 1-year, 3-year and 5-year survival rates of RFA combined with hepatectomy to treat multiple focus liver cancer were 87, 80, and 55%, respectively, which were comparable to those of surgical resection alone. Meanwhile, it was found that the diameter of the main lesion was an independent risk factor related to postoperative efficacy. Cheung et al. [71] reported that the 1- and 3-year survival rates of the RFA combined with hepatectomy group were 88.8 and 62.6%, respectively, and those of the simple hepatectomy group were 88.9 and 51.8%, respectively. Hepatectomy combined with intraoperative RFA (IORFA) could be a safe and effective treatment option for patients with multiple HCCs, and it is comparable to extended hepatectomy alone [72]. However, it should be noted that although RFA is much less likely to cause liver failure than extended hepatectomy, surgical death may still occur after ablation of multiple tumor nodules. Therefore, we should carefully select the appropriate patients for RFA. At present, patients with a liver lobectomy less than 10% or patients with an ICG-15 less than 10% are considered to be the appropriate patients [73]. Patients with a limited ablation size (≤2 cm), a limited number of ablations (≤2), and an adequate surgical margin should be considered candidates for combination therapy [74]. Combining hepatectomy and IORFA could provide comparable survival rates for patients with multiple unresectable colorectal liver metastases (CRLMs) compared to patients with resectable CRLMs treated with hepatectomy alone [75]. Therefore, for metastatic liver cancer, combining RFA with hepatectomy should be considered an option to achieve cure [76].

**RFA combined with TACE**

An additional strategy to improve the efficacy of thermal ablation for larger tumors (size, 3–5 cm) has been to combine it with other liver-directed therapies, such as transarterial chemoembolization (TACE) [77] and transarterial embolization (TAE) with particles or ethiodized oil. Although treatment algorithms have classically used TAE or TACE in a palliative capacity for patients with HCC that is not amenable to ablation, the use of chemoembolization in concert with ablation has been studied as a possible means of potentiating the curative effects of ablation. The order and timing of TACE relative to RFA is a matter of debate, with theoretical advantages associated with various protocols, including reducing the overall perfusion to the tumor to overcome perfusion-mediated heat sink effects (if TAE or TACE is performed first) or by targeting residual areas of the tumor at the ablative margin that have not been completely treated with ablation (if the ablation is performed first). There is evidence to suggest that greater tumor necrosis is achieved with the ablation-first approach [78]. The role of combined TACE and ablation treatment of tumors ≤7 cm is a statistically significant benefit in overall survival and recurrence-free survival [79]. For medium-to-large HCC, TACE + RFA has the long-term beneficial effect of retarding tumor progression and improving PFS and OS [80]. These studies have shown success in achieving a complete response for lesions larger than 3 cm with the use of combination therapy. However, less than 3 cm in diameter is controversial because some studies have suggested that there is no significant advantage over ablation alone [81]. For small HCCs, the tumor response rate after TACE-RFA seems to be similar to that of RFA but better than that of TACE monotherapy. Thus, TACE-RFA for treating small HCCs may be required for selected patients, especially patients with a small HCC that are ineligible for RFA monotherapy [82].

Combined TACE plus RFA is safe and as effective as hepatectomy for patients with HCC within the Milan criteria [83], and it may be an alternative treatment [84]. However, there are also studies that point out that hepatectomy was associated with better overall and recurrence-free survival than TACE + RFA [85]. For patients with HCC beyond the Milan
criteria, TACE with RFA is superior to hepatectomy [86]. TACE combined with RFA is helpful in improving the survival rate of patients with primary and recurrent HCC [87–89] and advanced HCC [90]. DEB-TACE + RFA achieved better treatment responses and OS than DEB-TACE alone in HCC patients [91]. The tumor response of TACE + RFA seems to be similar to that of RFA and better than that of TACE mono-therapy [92].

RFA combined with drug therapy

**Sorafenib**

The negative results of the STORM trial: The study indicated that sorafenib is not an effective intervention in the adjuvant setting for HCC following resection or ablation [93]. The STORM trial is a reminder that there remains no established role for sorafenib as an adjuvant therapy for patients with HCC after liver-directed therapy. Sorafenib at the approved starting dose was intolerable in the fit, adjuvant population of the STORM study. We should reassess the optimum starting dose of sorafenib to avoid decreasing and discontinuation liabilities for future trials and for patients across disease stages [94]. The benefit of sorafenib treatment in patients is largely empirical, and precise treatment according to the specific activated pathway is urgently needed to select the subclasses of patients who will benefit from sorafenib treatment. In the adjuvant setting, both patients with residual disease and specific molecular markers of tumors should be identified to ensure personalized treatment. Furthermore, the dose of sorafenib may be decreased through drug combinations to improve the patients’ quality of life [95].

RFA with sorafenib is safe and effective for unresectable remnant large HCCs after TACE because it can control tumor progression and prolong survival better than sorafenib alone [96]. Combined therapy with sorafenib-RFA was associated with a lower incidence of post-RFA recurrence and better OS than RFA alone in patients with BCLC stage 0–B1 HCC [97]. A systematic review and meta-analysis suggested that the RFA-sorafenib combination may not be a better approach for patients with HCC [98]. Although these findings suggest that sorafenib and RFA are safe and effective for the treatment of early HCC, prospective and randomized controlled trials are needed to validate these treatments. Furthermore, the earlier the application, the better the results [99]. Sorafenib inhibited the EMT of HCC cells after insufficient RFA and may be used to prevent the progression of HCC after RFA [100].

Regorafenib as a second-line agent after sorafenib failure in HCC patients. The meta-analysis showed that the median overall survival was 11.08 months (9.46–12.71). The pooled objective response rate was 10.1% (7.8–12.5%), while the disease control rate was 65.5% (61.3–69.7%) for regorafenib. It represents a valuable and relatively safe therapeutic option in intermediate/advanced HCC patients who progress on sorafenib [101]. However, regorafenib combined with RFA has not been reported in the literature.

**Immunologic preparation**

A combination of immune checkpoint inhibitors with biologic therapy seems to be promising for a new therapeutic standard of care for patients with unresectable HCC [102]. However, the PD-L1-PD-1 axis plays a critical role in dampening RFA-induced antitumor immune responses, and combined therapy with RFA and anti-PD-1 antibodies significantly enhances T-cell immune responses, resulting in stronger antitumor immunity and prolonged survival [103]. RFA treatment reduced the proportions of immunosuppressive cells, including regulatory T cells, tumor-associated macrophages and tumor-associated neutrophils, whereas it increased the percentages of functional T cells in distant non-RFA tumors. Moreover, RFA treatment also altered the gene expression at the single-cell level in each cell cluster. In addition, immune checkpoints, including PD-1 and LAG3, were upregulated in the T cells in distant non-RFA tumors after RFA treatment. These data indicate that RFA treatment induced remodeling of the tumor immune microenvironment in distant non-RFA tumors in a pancreatic cancer mouse model and suggest that combining RFA with immune checkpoint inhibitors may be an effective treatment approach [104]. Incomplete RFA (iRFA) is associated with earlier new metastases and poor survival in patients with HCC, and the administration of a CCR2 antagonist or the loss of CCL2 expression in tumor cells enhances the antitumor activity of PD-1 blockade, providing a salvage alternative for residual tumors after iRFA [105].

**Clinical comparative study of RFA**

**Comparison of RFA and surgical resection**

The efficacies of RFA and surgical resection have been debated for a long time, especially in the treatment of small HCCs. Many clinical studies have been carried out in recent years, but the conclusions are not uniform [11,106–108]. Three randomized controlled prospective trials have compared RFA with surgical resection for small HCCs, and two of the three studies reported the equivalency of both therapies [107–109]. Chen et al. [109] first reported that RFA has the same effect as surgical resection for single liver cancers less than 5 cm in diameter. Huang et al. [107] found that liver resection was superior to RFA in terms of the cumulative survival rate and tumor-free survival rate for patients who met the Milan criteria. Feng et al. [108] found that overall survival was statistically equivalent in both groups (75% for resection vs. 67% for RFA at 3 years).

A large number of retrospective studies have shown that the recurrence rate post-RFA is significantly higher than that of hepatectomy, especially the short-term recurrence rate, but for the long-term survival rate, the conclusions have not been the same. Livraghi et al. [110] showed that for HCC tumors ≤2 cm, RFA can be used in place of surgical resection with similar results: a sustained complete response in 97.2% of patients, with a 5-year survival of 68.5% (with surgical series at that time reporting a 5-year survival of 62–70%). A meta-analysis [106] found that the recurrence of HCC in situ
for RFA compared to surgical resection and that in the ectopic recurrence, hepatectomy was significantly higher than RFA. The postoperative complications of RFA are significantly less frequent than those of hepatectomy, and RFA has better economic benefits [111].

Imai et al. [112] considered that the 5-year disease-free survival rate and cumulative survival rate of surgical resection are significantly better than those of RFA for single small HCC, especially those with a diameter of 2–3 cm. Meta-analysis indicated that in treating small HCC, surgical resection treatment led to a higher long-term survival rate and a lower long-term recurrence rate, while RFA led to a lower complication rate than surgical resection [113–115]. RFA in the treatment of small HCCs has achieved the same effect as hepatectomy [116,117]. For patients with HCC who met the Milan criteria, RFA exhibited similar clinical efficacy to surgical resection. However, RFA was superior to surgical resection in terms of minor trauma and may be recommended as the first choice for tumors <4 cm in diameter [118,119]. Surgical resection offers better long-term oncological outcomes than RFA [120]. Surgery provides better results in long-term oncological outcomes than ablation in elderly patients (>70 years) with HCC according to the Milan criteria, but surgery has a longer length of stay and a higher rate of severe postoperative complications [121]. Repeat hepatic resection offers a longer OS and PFS than RFA for patients with recurrent HCC, but no statistically significant difference was observed for single recurrent HCCs that are ≤3 cm [122]. The advantages of fewer major complications may render RFA an alternative treatment option for selected patients [123].

Large retrospective studies that include patients with small HCC tumors of less than 3–5 cm who might also be considered candidates for surgical resection (on the basis of tumor location, liver function, and a lack of overt portal hypertension) have reported 5-year survival rates after ablation that are similar to those after surgical resection. However, as the tumor size increases, particularly when tumors are larger than 4 and 5 cm, the long-term outcomes are more favorable with surgical resection [85,124]. Patients with MVI who had undergone RFA were more vulnerable to recurrence than those who had undergone surgical resection [125]. For perivascular HCC (<3 cm), surgical resection provides better long-term tumor control and OS than RFA, particularly for periportal tumors [126].

Comparison of RFA and microwave ablation

RFA and microwave ablation (MWA) have a similar efficacy, and MWA has an apparent superiority in larger neoplasms [127]. MWA should be considered the technique of choice when the tumor is ≥3 cm in diameter or when it is close to large vessels, independent of its size [128–130]. MWA is at least as safe and effective as RFA for treating liver cancer and has demonstrated significantly reduced local tumor progression rates [131]. MWA has shown an efficacy similar to that of RFA for ablation of HCCs smaller than or equal to 2 cm, with an overall patient survival of 78.3% noted at 5 years and with no significant differences in recurrence-free survival or local tumor or survival or local tumor progression compared with RFA [132]. The superiority of MWA over RFA remains unclear and needs to be confirmed by high-quality evidence [133]. MWA was not more effective than RFA for the treatment of HCC lesions of 4 cm or smaller, and the proportion of lesions with local tumor progression at 2 years of follow-up was low with MWA and RFA [134].

No-touch RFA

The commonly used RFA technique for treating HCC is monopolar. This requires the insertion of the RF electrode directly into the tumor tissue, which increases the risks of tumor track seeding (TTS). Recently, one way to overcome TTS has been by employing bipolar RFA implemented in the no-touch mode. In the no-touch mode, two RF electrodes are inserted into the healthy tissue that surrounds the tumor. The distance between the electrodes and the tumor was defined as the no-touch gap. A larger no-touch gap may result in incomplete tumor destruction because the central region of the tumor is not directly affected by the Joule heating phenomenon, which is more prominent around the electrodes. This suggests that an improperly selected no-touch gap may result in a reduced efficiency of the no-touch bipolar RFA [135]. Research has shown that no-touch RFA provides a higher 2-year tumor-free survival rate than conventional RFA but is as safe as conventional RFA [136]. A large number of studies have confirmed that no-touch multibipolar RFA (NTM-RFA) represents a novel therapy that surpasses standard RFA for HCC. No-touch RFA using twin internally cooled wet (TICW) electrodes in bipolar mode demonstrated significantly lower cumulative local tumor progression (LTP) rates than conventional RFA for small HCCs [137]. Compared to surgical resection (SR), research has shown that the morbidity was higher (67.9% vs. 50.0%) and the hospital stay was longer (12 [IQR 8–13] vs. 7 [IQR 5–9] days) after SR. The local recurrence rates at one and three years were 5.5 and 10.0% after NTM-RFA and 1.9 and 1.9% after SR, respectively. The rates of systematized recurrence (within the treated segment or in an adjacent segment within a 2 cm distance from the treatment site) were higher after NTM-RFA (7.4 vs. 1.9% at one year, 27.8 vs. 3.3% at three years). The overall survival (86.7% after NTM-RFA, 91.4% after SR at three years) and disease-free survival (40.8% after NTM-RFA, 56.4% after SR at three years) were similar because most patients with recurrence were eligible for rescue treatment [138]. In a proof of concept study, in the rabbit VX2 subcapsular hepatic tumor model, no-touch RFA led to lower rates of peritoneal seeding and showed a tendency toward better local tumor control than direct tumor puncture RFA [139]. The no-touch pincer ablation procedure has the potential to prevent intrasubsegmental recurrence after RFA for patients with HCC (<3 cm) to the same degree as partial resection [140]. One large multicenter case-matched study showed that NTM-RFA provided better primary RFA success and sustained the local tumor response without increasing the severe complication rates for HCCs.
that were ≤5 cm in cirrhotic patients compared to monopolar RFA [141]. NTM-RFA for HCC tumors that meet the Milan criteria provides a high local tumor progression-free survival rate [142]. No-touch RFA is an effective and safe treatment method for small HCC (≤2.5 cm), with a 1.6% cumulative incidence of local tumor progression at 2 years [143]. No-touch ablation appears to be an ideal method for the prevention of intrahepatic dissemination [144]. A switching monopolar no-touch RFA technique is a favorable treatment option and provides lower local tumor progression after RFA compared with conventional RFA for small HCCs [145].

Noninvasive RFA

A solid-state radiowave machine consisting of a power generator and transmitting/receiving couplers that transmit radiowaves at 13.56 MHz was used. Gold nanoparticles were produced by citrate reduction and were exposed to the RF field. Nanoparticles were directly injected into the tumor to focus the radiowaves for select heating. These data show that noninvasive radiowave thermal ablation of cancer cells is feasible when facilitated by gold nanoparticles. Future studies will focus on tumor selective targeting of nanoparticles for in vivo tumor destruction [146]. They used a hybrid core-shell nanostructure comprised of IONPs as the core and AuNPs as the shell (IO@Au) for targeted RF ablation therapy. Due to the magnetic core, the nanohybrid can be directed toward the tumor through a magnet. In vitro cytotoxicity experiments showed that the combination of IO@Au and a 13.56-MHz RF field significantly reduced the viability of cancer cells. Next, during an in vivo experiment, they demonstrated that magnetic targeting of IO@Au to the tumor and subsequent RF exposure dramatically suppressed tumor growth. This method can improve the effectiveness of RF ablation therapy. Moreover, IONPs enable the nanohybrid to be used as a magnetic resonance imaging (MRI) contrast agent [147]. An amine-functional gold ion complex (GIC), [Au(III)(diethylenetriamine)Cl]Cl2, which generates heat upon RF exposure, was conjugated to carboxyl-functional poly(acrylic acid)-capped iron-oxide nanoparticles (IO-PAA NPs) to form IO-GIC NPs that are ~100 nm in size, and these show good promise as a theranostic agent for magnetic resonance imaging and noninvasive RF hyperthermia for cancer [148]. Multifunctional fluorescent FeQCs therefore show good promise as a novel therapeutic agent for RF hyperthermia and drug loading [149]. However, the appropriate balance of safety and efficacy for diagnosis, therapy, and therapeutic monitoring with these nanoparticles remains to be fully elucidated [150].

Basic application research of enhanced RFA damage volume

The RFA combined with 30-nm tumor necrosis factor-alpha and polyethylene glycol-coated gold nanoparticle group had a larger zone of complete cell death and a smaller partially ablated tissue zone than the RFA-only group when measured on microscopic examination [151]. In addition, combined D-sorbitol has the same effect [152]. The ablated liver volume that was treated using microbubble-enhanced ultrasound (MEUS) combined with RFA was 2.8 times greater than the ablated liver volume after treatment using RFA alone [153]. Therefore, some thermal materials are mainly used to enhance the damage volume of the RFA.

Progress in basic research of RFA

Dan et al. found that hepatectomy is more likely to lead to the reactivation of hepatitis B virus than RFA [154]. In a mouse model study, Meredith et al. found that hepatectomy can increase the secretion of hepatocyte growth factor (HGF) and basic fibroblast growth factor (bFGF) and promote tumor growth. However, after RFA ablation, the abovementioned factors decreased [155]. In contrast to hepatectomy, RFA can induce an immune response. Many scholars have carried out many animal and clinical trials [156–158]. Zerbini et al. [159,160], found that RFA can activate tumor-specific T lymphocytes and enhance the killing ability of natural killer cells toward hepatoma cells. However, there are many aspects worthy of attention regarding the biological effects of RFA on liver cancer. Nijkamp et al. [161,162] found that the growth and invasion ability of residual cancer were significantly enhanced after RFA because the transitional zone of RFA provided a special microenvironment for residual cancer cells. However, tumor cells undergoing heat shock without apoptosis can enhance proliferation and invasion by upregulating the expression of some cytokines (PCNA, MMP-9, VEGF, HGF, IL-6, etc.) in the secondary persistent hypoxic environment [163]. Sublethal heat can induce the epithelial mesenchymal transition of hepatoma cells, which leads to an increase in invasion ability [28]. Tumor cells that remain viable after partial heating also develop genetic features that are associated with more aggressive growth [164].

ICAM-1 activates platelets and promotes endothelial permeability in TAECs through VE-cadherin after insufficient RFA, and antiplatelet and anti-ICAM-1 therapy can be used to prevent the progression of HCC after insufficient RFA [165]. ATPase inhibitory factor 1 promotes EMT and angiogenesis and attenuates HCC cell sensitivity to sorafenib after insufficient RFA through the NF-κB signaling pathway [166]. Therefore, targeting ATPase inhibitor factor 1 may improve the efficacy of RFA.

Long noncoding RNAs play an important role in the occurrence and development of liver cancer. The IncRNA expression profile of sublethal heat-treated hepatoma cells suggests that many changes in IncRNA expression may be involved in the occurrence and development of hepatomas after RFA [167].

Summary

Hepatectomy is still the first choice of curative treatment for patients with early- and medium-term HCC. However, with the progress of RFA equipment and technology and the accumulation of clinician experience, many patients with early HCC can obtain comparable curative effects after RFA.
In the future, technologies such as artificial intelligence-guided precise ablation and preoperative MVI noninvasive evaluation will undoubtedly make important contributions to improving the therapeutic effect of RFA for HCC. Regardless of the kind of treatment, the key to improving the curative effect is to minimize the incidence of residual cancer during the operation, have a comprehensive treatment after the operation, perform a close follow-up and have active treatment after recurrence.

Disclosure statement

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