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Thermal ablation of large unresectable hepatocellular carcinoma in cirrhotic patients

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common and lethal malignancies worldwide. Surgery is the mainstay of treatment, but less than 20%-30% of patients are good candidates. Actually, thermal ablation is considered the best treatment with curative intent for cirrhotic patients with unresectable HCC ≤ 3 cm. Unfortunately, radio frequency efficacy in obtaining the complete ablation of HCC nodules diminishes with increasing tumor size and local tumor progression is more frequent in larger nodules. To overcome these problems, higher-powered generators, different devices and techniques have been attempted. Furthermore, microwave ablation has been introduced with the promise of a large ablative capacity. The aim of this review is to describe the role of thermal ablation for the treatment of large unresectable HCC.

Keywords: Hepatocellular carcinoma, hypertermic ablation, radiofrequency, microwave ablation

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common and lethal malignancies worldwide. Surgery is the mainstay of treatment, but less than 20%-30% of patients are good candidates mainly due to cancer multifocality, position of nodules, liver insufficiency, and severe portal hypertension[1]. When feasible, resection ensures better local control of cancer and longer disease-free survival, but it carries a higher rate of complication as compared to local ablation[2,3]. In early 1990's, thermal ablation with radiofrequency (RFA) has been introduced for the treatment of HCC. This technique has become increasingly popular and a large amount of studies have been published confirming its efficacy. Actually, thermal ablation is considered the best treatment with curative intent for cirrhotic patients with unresectable HCC ≤ 3 cm[4-8].

In nodules up to 2 cm in size, RFA allows the complete ablation in more than 90% of cases and may obtain results comparable to surgery[9-11]. Randomized studies have shown higher efficacy of RFA as compared to chemical ablation with ethanol achieving the complete necrosis of HCC nodules ≤ 3 cm with fewer sessions and reducing the rate of local cancer progression[12-14]. Unfortunately, RFA efficacy in obtaining the complete ablation of HCC nodules diminishes with increasing tumor size and local tumor progression is more frequent in larger nodules[15,16]. The lower efficacy of ablation in nodules larger than 3 cm is also due to a more aggressive biological behaviour of large cancers, as high levels of biomarkers, poor histological grade or capsule invasion[17]. Viable tumor cells after partial ablation may develop "resistance" to heat and may exhibit a more aggressive growth[18]. Furthermore, the position of nodules and the amount of blood flow inside and at periphery of nodules may affect the ablative effect of RFA (heat-sink effect)[19,20]. To overcome these problems, higher-powered generators, different devices and techniques have been attempted. Furthermore, microwave ablation (MWA) has been introduced with the promise of a large ablative capacity. The treatment of large HCC lesions represents a great challenge for clinicians because the late diagnosis of such cancer is not rare despite the use of surveillance. A careful multidisciplinary evaluation of liver function, cancer characteristics, and patient status is needed to establish the best treatment in the single case.

The aim of this review is to describe the role of thermal ablation ablation for the treatment of large unresectable HCC.

RADIO FREQUENCY ABLATION

In a seminal study by Livraghi and Coll, 114 patients with 126 nodules larger than 3.0 cm were treated with single or triple cluster of cool-tip monopolar electrodes. Complete ablation was achieved in 61% of nodules in the size range 3.1-5.0 cm, and only in 24% of nodules 5.1-9.5 cm[21]. To improve these results, a protocol derived from a mathematic model was applied to calculate preoperatively the site and the number of needle insertions[22]. The model was based on the analysis of how many overlapping ablation spheres were needed to cover the HCC nodule. To ablate nodules sized 3.6-7.0 cm, 1-13 electrode placements were performed. The success rate in 121 nodules was 87%. A limitation of the application of such protocol was the difficulty in determining the accurate placement of needles in larger lesions. Using an open approach and single or cluster cool-tip needles a complete ablation rate of 91% may be achieved in nodules of 3.5-8.0 cm[23]. "Surgical RFA" as compared to percutaneous RFA showed similar efficacy in small nodules, but was associated to better survival rates in patients with larger HCC[24]. However, with this approach the rate of complications and post-RFA liver impairment was higher as compared to patients treated percutaneously. The highest rate of complete ablation using cool-tip needles has been reported in a large Asian cohort. The authors achieved a complete necrosis in 98.9% of 360 treatments for HCC 3.1-5.0 cm, and in 97.7% of 44 treatments for tumors > 5.0 cm[25]. These results have never been reproduced in a Western study. In order to increase the ablation area bipolar and multipolar electrodes have been attempted. The use of bipolar devices may allow a better distribution of temperature inside the tissue[26]. In a small prospective study including 26 patients with 27 tumors 5.0-8.5 cm, three separate bipolar internally cooled electrodes achieved the complete ablation in 22 among 27 nodules (81%), including three tumors that showed segmental portal vein invasion[27]. However, multipolar electrodes resulted more effective than monopolar devices in obtaining the complete necrosis of nodules up to 4.5 cm, but in larger tumors the efficacy was comparable[28]. Another way to increase the ablation area is the use of expandable electrodes and interstitial saline infusion that may create lesions significantly larger than not cooled needles[29]. However, in small HCC internally cooled electrodes compared to expandable electrodes had similar effectiveness[30]. A strategy to increase the efficacy of RFA in larger nodules is the insertion of multiple needles inside the tumor that may be alternatively activated using a swichting algorytm[31,32]. However, with the devices actually available, RFA ablative capacity in nodules > 5 cm is scarce. To overcome the limited efficacy of RFA in larger nodules, combination treatments of RFA plus percutaneous ethanol injection or plus transarterial chemoembolization (TACE) have been attempted. In Eastern studies, in combining these treatments, a higher rate of cancer ablation and a better overall and recurrence-free survival than RFA alone have been reported[33-41].

Another possibility may be the combined treatment with sorafenib and RFA or triple combination also with TACE, with the aim of increasing the necrosis and reducing the rate of recurrence[42-44]. Regarding complications of RFA ablation, in a large survey 6 deaths (0.3%) were observed. Five of these patients had large HCC complicating cirrhosis, in 3 patients the cancer nodules were located in risky areas and two had Child-Pugh B cirrhosis[45]. Therefore, caution should be observed in such cases. Major and minor complications occurred in 2% and 5%, respectively. Similar rates have been observed in more recent studies[46,47]. A pre-RFA value of bilirubin > 2.5 mg/dL may predict liver decompensation after treatment[48].

MICROWAVE ABLATION

Due to the advancement of microwave technology and the development of cooled electrodes, percutaneous microwave ablation (MWA) is actually considered a safe and effective alternative to RFA for thermal ablation of HCC[49,50]. As compared to RFA, MWA has theoretical advantages including the shorter procedural time, very rapid increase in tissue temperature, and it is less affected by tissue impedance and the heat-sink effect[51]. Both in ex vivo and in vivo porcine liver model, MWA produced larger coagulation zones than bipolar RFA[52].

Two metanalyses comparing the two techniques have been published[53,54]. Chinnaratha *et al.*[54] analyzing three studies including 450 patients with HCC nodules > 5.0 cm or more than 3 nodules found a benefit for MWA as compared to RFA with a pooled OR of 1.88[55-57]. Furthermore, MWA treatment was associated with a lower rate of local tumor progression in large HCC as compared to RFA. The evaluation of studies including larger HCC and the metanalysis of Facciorusso et al confirmed that MWA was significantly more effective than RFA in inducing the complete necrosis of tumours[58,59]. Also other authors confirmed MWA is safe and effective in the treatment of large HCC[60,61] and subcapsular lesion[62].

A recent randomised controlled trial did not show superiority of MWA over RFA in terms of efficacy, major complications and local tumour progression at 2 years of follow-up in patients with hepatocellular carcinoma lesions of 4 cm or smaller[63], confirming a previous study published in 2002[64]. Chong *et al.*[65] suggested to apply ALBI score for the selection of patients in order to identify the cases with worse liver function in whom to prefer MWA to surgery.

More than overlapping insertions, the placement of multiple antennas may obtain larger ablation areas, mainly when simultaneous activation is used[66]. This is an advantage as compared to RFA that do not allow the simultaneous activation of multiple electrodes. Another approach is the insertion of electrode under laparoscopic guidance. This technique resulted effective in small nodules, but it might be useful for the treatment of large nodules with an exophytic growth[67]. A study in 14 centers on 736 patients treated with MWA using the AMICA system found 22 (2.9%) major complications, 54 (7.3%) minor complication, and no deaths[47].

LASER ABLATION

Laser ablation (LA) is the less popular technique for performing thermal ablation and there is only one case-control study designed to evaluate the efficacy of this treatment in large HCC. This study compared LA with the multifiber technique and TACE for the treatment of solitary large HCC with a diameter of 4.0-7.5 cm[68]. LA approach resulted more effective than TACE in inducing complete tumour necrosis. Overall, 26 (63.4%) patients from the LA group and 8 (19.5%) from the TACE group showed a complete response to treatment ($P < 0.001$). In univariate analyses, baseline predictors of complete response were Child-Pugh class A and treatment modality with LA. Furthermore, the rate of local cancer progression was observed in 19.5% of LA successfully treated patients and in 75% of TACE treated ($P < 0.001$). In nodules with a median diameter of 5.2 cm (3.1-9.6 cm), combined treatment with LA performed before TACE obtained the complete ablation in 90% of 45 tumours in 30 patients[69]. In our Unit, a study evaluating the use of sorafenib as neoadjuvant

therapy in patients with large HCC who receive LA is ongoing. A multicenter Italian study evaluated the rate and type of complications after LA with the multifiber technique. Among 520 patients and 1004 sessions, 4 deaths (0.8%), 15 major complications (1.5%), and 62 minor complications (6.2%) were observed. All deceased patients had intermediate or large tumours and 2 of these were in Child-Pugh C class[70].

CONCLUSION

Thermal ablation is a very popular technique for the treatment of unresectable HCC in patients with cirrhosis. In small HCC sized < 3.0 cm, RFA may achieve good results that in some cases are comparable to that of surgical resection. Compared to surgery, local ablation features, mini-invasive approaches, with less impact on liver function less morbidity and hospital stay and less costs. The applicability of thermal ablation in nodules > 3 cm which constitutes the objective of this review, is still a matter of debate. During the last 25 years, technical advances have increased the efficacy of such technique, expanding the range of its application. However, the level of evidence is poor due to the scarcity of appropriated designed randomized studies. A main problem in inducing the complete necrosis of large HCC nodules is the lack of very experienced operators. In fact it is evident that a single needle insertion is insufficient in inducing the complete necrosis of large tumors. The increase in the potency emitted by a single source may be insufficient to ablate the periphery of large nodules and may be risky causing unwanted complications. In this setting, overlapping electrode placements and multiple needle insertions are the better way to increase the treatment effectiveness. The correct placement of electrodes inside the nodules is crucial for obtaining the therapeutic success. The simultaneous activation of inserted needles seems more effective than alternate activation in inducing larger and confluent coagulation areas. Therefore, theoretically MWA and LA might be favored as compared to RFA in the treatment of large tumors. A strategy frequently used in clinical practice is the use of combined treatments, mainly percutaneous ablation and TACE. The sequential use of such treatments seems to achieve a better local tumor control, but randomized studies are awaited to define its applicability.

DECLARATIONS

Authors' contributions

Concept and design of study, drafting the article, final approval of the version to be published: Di Costanzo GG

Acquisition of data or analysis and interpretation of data; drafting the article, final approval of the version to be published: Tortora R

Acquisition of data or analysis and interpretation of data; revising it critically for important intellectual content; final approval of the version to be published: Opramolla A

Concept and design of study; revising it critically for important intellectual content; final approval of the version to be published: Guarracino M

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Conflicts of interest

All authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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