Radiofrequency ablation in the treatment of hepatocellular carcinoma – a clinical viewpoint

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Hepatocellular carcinoma (HCC) is not only the fifth most common cancer in the world, accounting for 5.4% of all human cancer (1), but it is also a disease with increasing prevalence due to the widespread distribution of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, the main causes of cirrhosis and hepatocellular carcinoma (2,3). HCC is also a tumor with a high mortality rate (4) due to its chemoresistance and the underlying cirrhosis, which in itself has a high mortality.

Although 6-monthly screening programs (using alpha-fetoprotein and liver ultrasound) pick up the appearance of small nodules (5–7), larger nodules or multiple nodules are often recognized only during follow up, despite screening. This is because HCC can have a multifocal origin (8) with a very variable and unpredictable doubling growth interval (9), which is poorly correlated with survival (10). Survival is related more to the functional reserve of the liver than to the size and number of tumors (11), at least in the early and intermediate stages of HCC (10–12). Thus, all therapeutic options have to be weighed against the underlying functional hepatic reserve.

Background

Many therapeutic options have been proposed in the last two decades, and from the numerous studies published some general guidelines have been generated and used in clinical practice.

In patients with HCC and non-cirrhotic liver, the treatment of choice is surgical resection. In patients with cirrhosis, for whom liver function is a determinant of outcome, the therapeutic choice needs necessarily to take into account both tumor size and the functional reserve of the liver. If the tumor is single and small and the patient has well-preserved liver function, surgical resection is the best choice, providing a 5-year survival rate ranging from 47.1 to 60.5% (13–16). With a further selection of patients, excluding from surgery those with portal hypertension which is the most reliable predictor of survival after resection (17), an even higher survival rate has been achieved (18). Unfortunately, due to the multicentric nature of HCC, the recurrence rate is high (19). Furthermore, many HCC’s, although small, are unresectable, being multiple, centrally located in the liver or associated with poor liver function.

Liver transplantation (OLT) is usually reserved for patients with more advanced liver impairment, in whom OLT is also indicated for liver failure. Performing OLT at an early stage of disease (one nodule ≤5 cm or three nodules ≤3 cm) a 4-year actuarial survival of 75% and a 4-year recurrence-free survival of 82% have been obtained (20), and these figures are even better (5-year survival of 90%) when HCC are discovered incidentally by pathological examination in an otherwise tumor-free liver (21). However, although the recurrence rate is significantly lower with transplantation than resection (22), the operative mortality is higher (23,24). Moreover, using “an intention-to-treat” basis, survival after OLT is worse than survival of patients carefully selected for resection. This is because of dropouts, the number of whom increases with lengthening waiting lists (18). Thus, OLT is a difficult therapeutic regimen to apply, with a potential benefit for only a few patients.

If a patient with a small tumor is not eligible for resection or OLT, percutaneous ethanol injection (PEI) seems to be the best option (25,26). PEI has the advantage of being cheap, with few complications. In unselected patients with Child’s A cirrhosis with a small tumor, results are similar to those in patients treated with resection, in terms of complication and mortality (27–30), as well as in terms of recurrence rate (26). The treatment of large HCC in patients with a good functional reserve is controversial. The role of PEI in such patients is still uncertain (31,32) and transcatheter arterial chemo-em-
bolization (TACE) is not recommended (26). In three randomized controlled trials assessing embolization (two with and one without chemotherapy) in unresectable HCC in cirrhotic patients with well-preserved liver function, TACE reduced tumor growth but did not improve survival (33-35).

Patients with more advanced liver disease who are not OLT or resection candidates invariably have a dismal prognosis. The role of TACE requires further study (36) and, although PEI is used, the survival benefit is uncertain. Furthermore, the anti-estrogen drug tamoxifen and systemic chemotherapy are ineffective (26).

With this background in mind, the optimal therapeutic option should be based on prognostic survival models. The classification of Okuda et al. (11) is largely used in clinical practice. It combines characteristics related to liver function (serum albumin, serum bilirubin and ascites) and to HCC (tumor volume). This classification, however, was constructed on an empirical basis and necessitates the assessment of tumor size relative to total liver volume, a difficult parameter to assess. Several new prognostic models for the prediction of survival in patients with HCC have been elaborated in the last decade. There are two types: with variables in the model derived from an unselected (37-39) or a selected (40) cohort of patients. Unfortunately, at present there are no data supporting their validity, and this and their applicability are currently being tested. At present, the independent predictors of survival in patients selected for a particular treatment need to be considered when recommending treatment. For example, Llovet et al. (18) have shown a 5-year survival of 51% in cirrhotic patients with well-preserved liver function and with a single small HCC treated with surgical resection on an intention-to-treat basis, but this figure is 74% in patients without clinically relevant portal hypertension (HVPG less than 10 mmHg) and with serum bilirubin ≤1 mg/dl, portal hypertension and bilirubin being independent survival predictors after resection.

Radiofrequency Ablation (RFA): What We Know Now
Several percutaneous interstitial ablation systems, either chemically-mediated or thermally-mediated, have recently been proposed as an alternative to PEI. Thermally-mediated interstitial ablation systems, able to induce tissue necrosis by means of heat, use 2 types of energy according to the frequency of waves emitted from a generator and delivered through an electrode into the liver.

In the microwave ablation system a wave frequency of 2450 MHz ± 50 MHz is usually used, whereas the radiofrequency ablation system (RFA) uses a wave frequency of 480–500 KHz. RFA delivers energy into the tumor by an electrode, which is electrically insulated along its length except for the 1–3 cm of the distal portion of the shaft, which is percutaneously introduced into the tumor. Ultrasound guidance is the modality more extensively used, although both computed tomography (CT) and magnetic resonance (MRI) (provided there is MR compatibility of the equipment) can be used (41-43). After emission from an appropriate generator, the radiofrequency energy is delivered to the distal non-insulated portion of the electrode and converted into heat, which causes coagulative necrosis of surrounding tissue. Compared to ethanol injection, RFA induces a more homogeneous area of necrosis within the tumor, with less coagulation than expected in surrounding cirrhotic tissue. It has been hypothesized that cirrhotic tissue around the tumor has a thermal insulator effect, increasing heat retention within the tumor and preventing dispersal of heat to outside the tumor (44), but to date there are no data to prove this. On the other hand, the vascular patterns of both HCC and surrounding cirrhotic tissue also play an important role in establishing the volume of tissue ablated, because of the negative effect of blood flow on lesion size (45).

Technical improvements have overcome the limitation in tissue coagulation of the first conventional monopolar RFA electrodes, with cooled-tip and saline-infusion electrodes and J-hook needles (46). The infusion of saline through sideholes in the electrode tip during the production of the thermal lesion achieves a larger area of necrosis, probably because of reduced tissue impedance. The cooled-tip device, marketed by Radionics (Burlington, Mass), uses an internally cooled, straight needle alone or in a three-needle cluster. The J-hooks are curved needle electrodes advanced from a movable hub, and are able to provide a more homogeneous and controllable diffusion of heat. There are two types of multiple electrode needles: the current RITA system (Radiofrequency Interstitial Thermal Ablation Medical System, Mountain View, CA, USA) consists of 7 curved prongs (6 hooks and a central prong), each of which has a thermistor on its tip able to monitor the temperature produced in the heated tissue; the Radiotherapeutics device (RF 2000 system, RadioTherapeutics Corp., Mountain View, CA, USA) deploys 10 curved prongs, which are reported to induce a more uniform thermal injury than the system with fewer prongs. This latter device measures solely the impedance to gauge the extent of the thermal injury produced (42,47). The use of multiple or clustered internally cooled electrodes, such as the three-needle cluster,
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and multiprong electrodes, offer the possibility of larger volume coagulation necrosis (even >5 cm), but so far there have been no studies that demonstrate the advantage of one RFA probe over another (42).

RFA is performed under both local and general anesthesia, depending on the location (central rather than close to the capsule), the number of nodules (one rather than multiple) and the modality (percutaneous rather than intraoperative). The extent of coagulative necrosis can be checked immediately by using CT and/ or MRI, or even color or power Doppler after intravenous administration of contrast (41,48–50). If the tumor is not completely necrosed, the treatment can be repeated immediately or within the next 24 h. Follow-up assessment of response to treatment is performed by using CT or MRI at 1-, 3- and then 6-monthly intervals (41,44,46,49,51,52), with variations reported by some authors.

Recently, several reports on RFA have been published, including both HCC and liver metastases. Apart from the study of Livraghi et al. (44), which is a randomized controlled trial versus PEI, all the other studies are preliminary reports or clinical series without a control group of patients treated with a different option. The data derived from the studies with more details of patient characteristics (particularly stage of cirrhosis), tumor size, details of efficacy, recurrence rate and with a sufficient follow up, are summarized in Table 1.

Despite this selection, these studies are poorly comparable because of different types and usually small numbers of patients, different techniques and different modalities of approach and often too short a follow up. Rossi et al. (49) report a longer experience (with a mean follow up of 23 months) with mono or bipolar electrodes with an estimated survival rate of 94%, 86%, 68% and 40% at 1, 2, 3 and 5 years, respectively. All the other studies were performed with cooled-tip or multiple-electrode needles, and only two of them had a mean follow up longer than 12 months (53,54). As a consequence of such a short follow up, there is only information about the recurrence rate, but not about survival. As expected, the recurrence rate is a function of the length of follow up, varying from 0% in the study of Allgaier et al. (55), with a mean follow up of 5 months, to 41% in the study of Rossi et al. (49), with a mean follow up of 23 months (Table 1).

The papers from surgical groups (54,56,57) which used both a percutaneous and an intraoperative approach are of interest. The latter is combined with the Pringle maneuver (58) (clamping of the porta hepatitis during ablation, thus interrupting hepatic arterial and portal venous flow to the liver) in order to obtain better control of tissue cooling. Curley et al. (54) treated 75 patients with liver metastasis and 48 patients with HCC. Among the patients with HCC, there were 26 with a single small tumor (<3 cm in diameter) (23 of whom were Child B), who were treated percutaneously and 22 (one Child B and 21 Child A) who were treated intraoperatively. In many patients treated intraoperatively with RFA, open surgical treatment was used to enable treatment of both multiple and bilobar tumors. No death and only one RFA-related complication were reported during the follow up. The mean follow up was 15 months, but as the authors did not consider separately the development of new hepatic lesions in patients with HCC as opposed to liver metastasis, the recurrence rate for HCC cannot be calculated. Jiao et al. (56) treated eight patients with HCC percutaneously and intraoperatively, only one of whom had a solitary lesion. Although seven of the eight patients were reported to have stable disease during a mean follow up of 10 months, no clear information on recurrence rate was provided. Nicoli et al. (57) treated 47 patients with both small and large HCC's (1–6 cm in diameter) and reported an actuarial survival rate of 83% at 24 months.

Another surgical group has reported an anecdotal experience on laparoscopic ultrasound-guided RFA.

TABLE 1
Clinical studies on radiofrequency ablation (RFA) which have well documented description of patient characteristics, tumor size, efficacy of ablation, recurrence rate and follow up

<table>
<thead>
<tr>
<th>Patients</th>
<th>Child A (%)</th>
<th>Tumor size (mm)</th>
<th>Single nodule (%)</th>
<th>RFA technique</th>
<th>RFA modality</th>
<th>Mean follow up (months)</th>
<th>Recurr. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rossi et al. (49)</td>
<td>39</td>
<td>54</td>
<td>≤30</td>
<td>96</td>
<td>Monobipolar</td>
<td>P</td>
<td>23</td>
</tr>
<tr>
<td>Rossi et al. (51)</td>
<td>23</td>
<td>–</td>
<td>13–35</td>
<td>88</td>
<td>RITA J-hook</td>
<td>P</td>
<td>10</td>
</tr>
<tr>
<td>Francica et al. (53)</td>
<td>15</td>
<td>86</td>
<td>10–43</td>
<td>75</td>
<td>Cooled-tip</td>
<td>P</td>
<td>15</td>
</tr>
<tr>
<td>Curley et al. (54)</td>
<td>48</td>
<td>50</td>
<td>&lt;30</td>
<td>93</td>
<td>Radioth. J-hook</td>
<td>P+I</td>
<td>15</td>
</tr>
<tr>
<td>Allgaier et al. (55)</td>
<td>12</td>
<td>75</td>
<td>–</td>
<td>92</td>
<td>RITA J-hook</td>
<td>P</td>
<td>5</td>
</tr>
<tr>
<td>Nicoli et al. (57)</td>
<td>47</td>
<td>71</td>
<td>10–60</td>
<td>77</td>
<td>RITA J-hook</td>
<td>P+I</td>
<td>12</td>
</tr>
</tbody>
</table>

P=percutaneously; I=intraoperatively. RFA=radiofrequency ablation.
Of 10 patients with unresectable tumors (two with HCC and eight with metastasis) treated, eight appear free of tumor with a follow up ranging from 6 to 20 months (59). More recently, a 12% local failure rate has been reported with this technique (60).

Other uncontrolled studies report very differing results. Rhim et al. (47) used RFA in 25 patients with HCC and 17 with liver metastasis, with an overall 69% complete ablation and a major complication rate of 9%. Rose et al. (61) treated 30 patients (three with HCC with a total of 6 lesions and 27 with liver metastasis with a total of 87 lesions) using RFA combined with other therapeutic techniques (resection, cryosurgical ablation and hepatic artery infusion pump placement). They had only an overall 3% complication rate. However, objective information on the efficacy of RFA is not easy to gauge due to the complexity of the treatment protocol.

The most informative paper is that of Livraghi et al. (44), a prospective randomized trial comparing RFA with PEI. These authors treated 52 small HCC (≤3 cm of diameter) in 42 cirrhotic patients (39 Child A) with cooled tip RFA and 60 HCC of similar size in 44 cirrhotic patients (38 Child A) with PEI. Unfortunately, this study had a short follow up (ranging from 4 to 28 months with a mean of 10 months) and reported data only on short-term efficacy in terms of complete necrosis rate (Table 2). This is as high with RFA (90%) as that obtained with PEI (80%; \( p=0.12 \)); and 3 out of 5 treatment failures were nodular HCC's. Thus, 6% of single small nodular HCC's were not treatable with this technique, in the hands of an expert group. The authors concluded that RFA, despite the higher number of complications (10% versus 0% of PEI), was more effective than PEI. However, apart from the information that more patients showed a radical ablation at 4 months based on CT images, there is no other information to support the superiority of RFA, since the evaluation of effectiveness should take into account not only the initial technical success, but also the morbidity and survival rates. In fact, as shown in Table 2, the only significant result was the lower number of sessions necessary to ablate the lesions, together with a higher rate of complications with RFA. These data suggest that, at least at present, RFA may be a time-saving procedure but that it has a higher rate of complication than PEI. This may have a negative impact in terms of cost effectiveness.

More recently, a clinical trial in large HCC has been performed from the same authors (62), using RFA alone. One hundred and twenty-six HCC's in 114 patients, with a mean diameter of 5.4 cm, were treated with cooled-tip single or triple-cluster electrodes (for lesions larger than 4 cm in diameter). Complete necrosis was obtained in 47% of patients, whereas nearly complete (90%–99%) and partial (50%–89%) necrosis was achieved in 31% and 20%, respectively. No data are available regarding the outcome. As regards the treatment of large HCC, RFA has also been used with transcatheter arterial embolization (TAE), with the rationale of inducing less dispersal of heat from the vasculature of the embolized tributary and therefore increasing the volume of tissue ablated. With this approach, Buscarini et al. (63) treated 14 cirrhotic patients with large HCC (mean diameter of 5.2 cm); 11 patients were ablated with only one session of RFA 3 days after undergoing segmental TAE. Eleven of the 14 patients were still alive after a mean follow up of 13 months, although four had to be re-treated for recurrence.

Currently, from the data available in the literature on RFA, the message appears to be that it is an emerging technology with some physico-chemical advantages over PEI. However, as happened at the start of PEI, data are always enthusiastically reported at first. In fact, although RFA appears to be an easy procedure to perform, with the potential to eradicate tumors if small (64), hard endpoints are still not available to allow clinicians to decide on whether it is better than other techniques (65).

Although RFA should be considered first as an alternative percutaneous technique to PEI, it might be a useful tool also in the hands of surgeons, enabling them to ablate small or surgically inaccessible lesions discovered by intraoperative ultrasound (66). However, this approach is not a "minimally invasive" technique and it should be applied if detecting additional disease during the resection of the primary neoplasm. During intraoperative RFA, the possibility of performing the Pringle maneuver (by clamping the hepatoduodenal peduncle) or other forms of blood flow control, can achieve larger necrotic areas than that obtained in the presence of natural blood flow (67), since both portal

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**TABLE 2**

Efficacy and complications in the randomized trial comparing radiofrequency ablation (RFA) and percutaneous alcohol injection (PEI). From Livraghi et al. (44).

<table>
<thead>
<tr>
<th></th>
<th>RFA</th>
<th>PEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>Total no. of lesions</td>
<td>52</td>
<td>60</td>
</tr>
<tr>
<td>No. of sessions×lesion</td>
<td>1.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Complete necrosis (%)</td>
<td>90</td>
<td>*80</td>
</tr>
<tr>
<td>Major complication (%)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Minor complication (%)</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Total complication (%)</td>
<td>10</td>
<td>*0</td>
</tr>
</tbody>
</table>

\* \( p=0.12 \) (Fisher's exact test). \* \( p=0.00026 \) (Fisher's exact test).
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and arterial blood flow dissipate heat by convection and then reduce the temperature at the periphery of the nodule (45, 67, 68). Furthermore, intraoperative RFA should also be compared with cryoablation, which is a current surgically applied ablative technique. A recent prospective non-randomized study comparing RFA and cryoablation showed that RFA had a lower rate for both complications and recurrence than cryoablation (69).

Further controlled therapeutic studies comparing RFA versus PEI and RFA versus surgery must be performed to guide selection of patients for treatment of HCC. An appropriate sample size must be achieved based on the expected efficacy of PEI and surgery in the particular group of patients selected for study. Hopefully, the next monothematic conference of the European Association of the Study of the Liver, to be held in Barcelona in September 2000, will provide an important forum to debate many of the questions posed by radiofrequency ablation as a new treatment for hepatocellular carcinoma.

References


