Radiofrequency ablation or percutaneous ethanol injection for the treatment of liver tumors

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Abstract

The liver is a common location of both primary and secondary malignancies. For unresectable liver cancer, many local ablative therapies have been developed. These include e.g., percutaneous ethanol injection (PEI), percutaneous acetic acid injection, radiofrequency ablation (RFA), cryoablation, microwave ablation, laser-induced thermotherapy, and high-intensity focused ultrasound. RFA has recently gained interest and is the most widely applied thermoablative technique. RFA allows more effective tumor control in fewer treatment sessions compared with PEI, but with a higher rate of complications. However, there are certain circumstances where PEI therapy represents a better strategy to control liver tumors than RFA, especially in situations where RFA is difficult, for example when large vessels surround the tumor. In the context of hepatocellular carcinoma (HCC), both RFA and PEI are feasible and of benefit in non-operable patients. RFA seems superior to PEI in HCC > 2 cm, and the combination of interventions may be of benefit in selected patients. Liver resection is superior to RFA for patients with HCC meeting the Milan criteria, but RFA can be employed in tumors ≤ 3 cm and where there is an increased expected operative mortality. In addition, some lines of evidence indicate that RFA and PEI can be employed as a bridge to liver transplantation. The use of RFA in colorectal liver metastases is currently limited to unresectable disease and for patients unfit for surgery. The aim of this article is to summarize the current status of RFA in the management of liver tumors and compare it to the cheap and readily available technique of PEI.

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Key words: Colorectal liver metastases; Hepatocellular cancer; Liver resection; Percutaneous ethanol injection; Radiofrequency ablation

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the third highest cause of cancer-related death and the incidence appears to be rising[14]. Partial hepatectomy and liver transplantation are potential curative options, but only a minority (10%-20%) are candidates for these therapies[9]. For inoperable cases, sorafenib (Nexavar®) is now available, inhibiting tumor-cell proliferation and tumor angiogenesis, as well as increasing the rate of apoptosis. It acts by inhibiting the serine-threonine kinase Raf and the receptor tyrosine kinase activity of vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptor β[15]. Sorafenib increased median survival
and the time to radiological progression by nearly three months (7.9-10.7 mo and 2.8-5.5 mo, respectively) in patients with inoperable HCC. The effect of sorafenib has been reproduced. Furthermore, sorafenib has been reported to be cost-effective as compared to best supportive care in HCC. Its multikinase inhibition, which is effective in RAS-mediated signal transduction pathways, is potentially applicable in other tumors. Currently, the combination of sorafenib and various other chemotherapeutic agents in HCC is under investigation. In the future, sorafenib might become an adjuvant following resection or local ablation of HCC.

Liver metastases occur in almost half of cases with colorectal cancer. Resection is the treatment of choice for the 20% to 30% that have metastatic disease limited to the liver. Novel local treatment, embolization, and not least, neoadjuvant radiochemotherapy have increased the number of resectable cases. For those with initially unresectable colorectal liver metastases (CLM), downstaging with chemotherapy followed by rescue liver resection is safe and effective. The role of chemotherapy in resectable CLM is not entirely certain. The use of perioperative FOLFOX has been associated with improvement of 3-year progression-free survival.

Over the years, local ablative methods have been developed for patients that are not surgical candidates because of multifocal disease, an inadequate liver remnant (size, function), or co-morbid conditions. These techniques include percutaneous ethanol injection (PEI), percutaneous acetic acid injection, radiofrequency ablation (RFA), cryoablation, microwave ablation, laser-induced thermotherapy, high-intensity focused ultrasound, and irreversible electroporation. RFA has recently received increased attention, and is the most studied of the thermal ablation techniques. This article reviews the current role of RFA in the treatment of liver tumors and compares it to PEI, which is a safe, cost-efficient, and readily available alternative to RFA.

RADIOFREQUENCY ABLATION AND PERCUTANEOUS ETHANOL INJECTION

Modern RFA for the treatment of liver tumors has been available since the early 1990s. RFA induces thermal injury to the target tissue using electromagnetic energy with a frequency < 900 kHz. An electrode is placed into the lesion and a high-frequency alternating current is delivered. The current causes ionic agitation and frictional heat, leading to irreversible cellular changes, such as protein denaturation and coagulative necrosis of tumor cells. Optimal ablation results are achieved when local temperatures of 60 °C to 100 °C are employed. At temperatures above 100 °C, the increase in the electrical impedance because of tissue carbonization and vaporization limits the amount of energy that can be delivered. Internally cooled-wet electrodes have been developed that combine interstitial saline infusion and intra-electrode cooling, thereby avoiding tissue desiccation around the electrode tip and maintaining low impedance during treatment, while increasing the ablative zone. RFA can be performed either percutaneously or intraoperatively with laparoscopy or laparotomy. The percutaneous approach is less invasive and may be associated with reduced postoperative pain, fewer complications, shorter hospital stay, and reduced costs. However, surgical RFA allows more accurate cancer staging because of the direct macroscopic visualization of tumors and the use of intraoperative ultrasound. In patients with small HCC (≤ 3 cm), percutaneous and surgical RFA had similar complete ablation rates and the overall and disease-free survival were comparable at 1 and 3 years. However, for larger tumors (3.1-5 cm), the surgical approach was associated with better overall survival. In addition, surgical RFA may be preferred for HCC occurring in high-risk locations, defined as less than 5 mm from a large vessel or an extrahepatic organ.

PEI was described for the first time in 1983. PEI is performed under local anesthesia using a 21-gauge needle guided by ultrasound or computed tomography. Ethanol diffuses into the tumor cells and causes dehydration and protein denaturation, resulting in coagulative necrosis. This is followed by microvascular thrombosis and subsequent tumor ischemia. The amount of ethanol required can be calculated using the formula of a sphere, where the 0.5 is added to provide extra safety margin: $V = \frac{4}{3} \times \pi \times (r + 0.5)^3$. The advantages of PEI are its relative safety, simplicity, and low cost. However, PEI is limited to small lesions and requires multiple sessions because of its reduced diffusion capacity over intratumoral septa.

Tumor seeding has occasionally been reported following RFA and PEI, but the risk remains low (< 2%) when an adequate ablation technique is employed and there is no previous biopsy. Several studies have confirmed the safety of RFA and PEI in patients awaiting liver transplantation. According to the practice guidelines from the American Association for the Study of Liver Diseases (AASLD), there is level II evidence to support the use of RFA and PEI as a bridge to liver transplantation. However, the actual value of local therapies before liver transplantation remains controversial. It has been suggested that bridging therapies such as RFA or PEI should be reserved for patients with a predicted waiting list time of more than 6 mo.

RADIOFREQUENCY ABLATION VS LIVER RESECTION

Two recent systematic reviews showed no significant differences in survival between RFA and resection for HCC within the Milan criteria, although RFA was associated with higher recurrence rates. When RFA was used for tumors outside the Milan criteria, overall and disease-free survival rates were significantly better after resection. Zhou et al performed a meta-analysis of one randomized controlled trial (RCT) and nine controlled studies comparing RFA and liver resection for HCC
(Table 1). Seven hundred and forty-four patients treated with RFA and 667 treated with resection were included. The 5-year overall survival rate was borderline significant at 5 years [OR 0.60 (0.36-1.01)]. RFA was associated with higher local recurrence [OR 4.50 (2.45-8.27)] and the disease-free survival rates were significantly better for resected patients. A recently published RCT by Huang et al[46] based on 230 patients fulfilling the Milan criteria, confirmed the superiority of surgical resection. The benefits of liver resection are further supported by data concerning quality of life adjusted survival, which seem to favor resection over RFA, at least in cirrhotic patients[47]. However, although current evidence favors liver resection for the treatment of early HCC (within the Milan criteria), percutaneous RFA can be used as a first-line treatment when the tumor is ≤ 3 cm and the expected operative mortality rate is above 3%[65].

Data concerning RFA vs resection for CLM are accumulating. A recent meta-analysis by Wu et al[63] compared RFA and liver resection for solitary CLM (Table 1). Liver resection was better than RFA in terms of 5-year overall survival, as well as local control of the disease. There were no statistically verified differences regarding the rate of adverse events. According to the study by Gazelle et al[51], liver resection is more effective in terms of quality-adjusted life year (QALY) as compared to RFA.

| Author | Diagnosis | Treatment | n | Tumor response (OR) | Complications (OR) | Local recurrence (OR) | Overall survival (OR) |
|--------|-----------|-----------|---|---------------------|---------------------|-----------------------|-----------------------|
| Zhou et al[50] | HCC | RFA resection | 744 | - | 0.29 (0.13-0.65) | 4.50 (2.45-8.27) | 0.60 (0.36-1.01) (5 yr) |
| Wu et al[59] | CLM | RFA resection | 667 | - | 0.32 (0.07-1.52) | 4.89 (1.73-13.87) | 0.41 (0.22-0.90) (5 yr) |
| Bouza et al[66] | HCC | RFA PEI | 396 | 1.10 (1.04-1.17) | Total: 2.55 (1.8-3.65) | 0.37 (0.23-0.59) | 1.24 (1.05-1.48) (4 yr) |

**Table 1 Summary of meta-analyses of radiofrequency ablation vs liver resection and radiofrequency ablation vs percutaneous ethanol injection**

PEI: Percutaneous ethanol injection; RFA: Radiofrequency ablation; OR: Odds ratio; HCC: Hepatocellular carcinoma; CLM: Colorectal liver metastases.

**PERCUTANEOUS ETHANOL INJECTION VS LIVER RESECTION**

PEI is suggested to be as safe and effective as resection in early-stage HCC (n = 76)[57]. On the other hand, Cho et al[58] reported that liver resection had a better survival profile as compared to PEI in 230 HCC patients (5-year overall survival 49% vs 19%). Repeated single-session PEI is effective in patients with advanced HCC and a combination of transcatheter arterial chemoembolization (TACE) and PEI results in longer survival[53].

The effectiveness of PEI for the treatment of CLM is unclear. It was reported that in more than 50% of cases of liver metastases < 4 cm, complete necrosis can be obtained by means of PEI[59]. Giorgio et al[60] reported that the survival rates of patients with liver metastases who underwent PEI were 94%, 80%, 80%, and 44% at 12 mo, 24 mo, 36 mo, and 44 mo, respectively. However, Livraghi et al[61] reported that PEI was ineffective for the treatment of colorectal metastases. The main difficulty is that liver metastases are typically scirrhous and the alcohol tends to spread into the "soft" adjacent liver parenchyma. HCC is often surrounded by a cirrhotic parenchyma and is more vascularized than CLM, allowing for a better local effect of PEI[62,63].

**RADIOFREQUENCY ABLATION VS PERCUTANEOUS ETHANOL INJECTION IN HEPATOCELLULAR CARCINOMA**

Giorgio et al[60] recently conducted an RCT of percutaneous RFA and PEI in 285 HCC patients with tumors ≤ 3 cm. The primary endpoint was 5-year survival. In the RFA and PEI groups, the 5-year survival rates were 70% and 68%, respectively (not significant). The local recurrence rates were also not significantly different. The overall costs of RFA and PEI were 171 000 Euros and 1359 Euros, respectively (P < 0.0001). According to pooled data from two previous RCTs[60,61], RFA and PEI are equally effective for tumors ≤ 2 cm[63]. However, the effect of RFA is more predictable than PEI when considering all tumor sizes. The meta-analysis by Bouza et al[66] included a total of 396 patients treated by RFA and 391 treated by PEI (Table 1). RFA yielded a better overall survival (1 year, 2 year, 3 year, and 4 year), as well as disease-free survival (1 year, 2 year, and 3 year). The risk of local recurrence was reduced in the RFA group. Total complications were increased for RFA, but major complications were not significantly different. In terms of cost-effectiveness of PEI over RFA, data are still controversial. Brunello et al[64] reported that mean direct hospital costs were 6540 Euros for RFA treated patients and 4097 Euros for the PEI group (P < 0.001), whereas Seror et al[65] reported that RFA was the most cost-effective option.

**RADIOFREQUENCY ABLATION-IMPROVEMENT WHEN COMBINED WITH PERCUTANEOUS ETHANOL INJECTION**

RFA enables more effective tumor necrosis in fewer treatment sessions, albeit with a higher rate of complications than with PEI therapy. Nevertheless, there are certain circumstances or clinical situations that PEI therapy
offers a better strategy to control liver tumors than RFA, especially in situations where RFA is difficult. PEI can be useful when tumors are in close vicinity (< 1 cm) to vital structures, including biliary ducts, stomach, intestinal loops, and kidney, and whose location make them difficult to treat with thermal ablative techniques. In addition, PEI is useful for lesions that remain undetected by ultrasound, such as masses in the hepatic dome or small nodules, or when the tumor is located subcapsularly or exophytically or surrounded by major vessels. The efficacy of RFA in HCC can be improved if combined with PEI. The combination of RFA and PEI was shown to be more effective than RFA alone for high risk locations. The combination of RFA and PEI can also be used for recurrent HCC (diameter > 3 cm). Furthermore, RFA and PEI can be combined with other locoregional therapies. TACE and RFA were as effective as liver resection for HCC in a recent study, with similar 1-, 3-, and 5-year overall and recurrence-free survival rates. The combination of microwave ablation and PEI was safe and effective for the treatment of liver tumors adjacent to the hepatic hilum.

CONCLUSION

Liver resection still remains the gold standard for the treatment of liver tumors. RFA and PEI are feasible and of benefit in non-operable patients, and as bridging therapies before liver transplantation. RFA seems superior to PEI in HCC > 2 cm and the combination of both interventions may be of benefit in selected patients. Liver resection is superior to RFA for patients with HCC meeting the Milan criteria, but RFA can be employed in tumors ≤ 3 cm and where there is increased expected operative mortality. Using RFA as the primary treatment of resectable CLM is still not recommended; however, RFA may have a role in unresectable lesions and for patients unfit for surgery. Newer advancements in the field of local ablative therapies are to be expected, requiring constant evaluation of the different techniques. In the future, local ablative approaches may be combined with systematically administered molecular targeted therapies (e.g., sorafenib) to further improve the outcomes of patients with liver malignancies.

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