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Editorial

Resection or ablation of small hepatocellular carcinoma: What is the better treatment? ☆

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See Article, pages 589–594

Hepatocellular carcinoma (HCC) is the third most common cause of death from cancer in men and the sixth most common cause in women [1]. The incidence of HCC is currently increasing in the US [2]. Chronic inflammatory liver disease caused by viral hepatitis is the background of HCC in the majority of cases but also alcoholic liver disease, non-alcoholic steatohepatitis, and diabetes mellitus are important risk factors for HCC [2]. The incidence of HCC is rising faster than most other cancers owing to the increasing prevalence of hepatitis B (HBV) and C (HCV) infection worldwide. While the oncogenetic mechanism of hepatitis B is thought to result from genomic instability following integration of HBV DNA into the hepatocyte host genome, hepatocarcinogenesis of hepatitis C is related to the necroinflammatory hepatic response to viral infection. Although, HCC is mostly present under cirrhotic conditions, a minority of tumors occur in livers with non-cirrhotic parenchyma.

An evolution in therapeutic techniques occurring over the past 3 decades has broadened available treatment options for patients with HCC. If HCC is localized and not multifocal, total tumor extirpation is the primary principle of therapy, which can be achieved by nonsurgical and surgical therapies. Nonsurgical techniques that have been shown to be effective for local tumor control include radiofrequency ablation (RFA), cryoablation, percutaneous ethanol (EI) and acetic acid injection, as well as transarterial chemoembolization (TACE). All of these locoregional techniques result in local tumor destruction without the need of tumor and liver tissue removal. Although surgical removal either *via* resection or orthotopic liver transplantation (OLT) is considered today as the gold standard for HCC treatment, only the minority (approximately 20%) of patients are candidates for these therapies. The choice of the suitable treatment is not only dependent on the tumor stage but also on the severity of the underlying liver disease. Among the surgical treatments liver transplantation achieves the best results but can be offered only to a small proportion of patients due to graft availability, selection criteria, and high cost. Therefore, in specialized centers, liver resection is the mainstay of surgical therapy in patients with well preserved liver function (Child-Pugh A-B) and absence of portal hypertension [3–5].

In experienced hands surgical resection for HCC can be performed safely with a mortality rate below 2% and a 5-year postoperative survival rate of 40–70% [3,6,7]. On the other hand, percutaneous RFA and EI have been shown to be effective for local tumor control and do not require general anesthesia and hospitalization [5,8,9]. These advantages have made both percutaneous techniques popular and both entered clinical practice before these therapies had been proven to be equivalent or superior to hepatic resection in randomized controlled

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Abbreviations: EI, ethanol injection; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; RCT, randomized contolled trial; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

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trials (RCT). Despite the encouraging results of RFA, this technique has its clear limitations when the tumor is located in close proximity to major vascular and biliary structures regardless of the tumor size. However, there is evidence from several studies, including three RCTs, that indicate that percutaneous RFA is superior to EI [10–12]. Since the introduction of percutaneous ablation techniques, their efficiency compared to surgery or ablation in the treatment for small HCC has been debated. This question is addressed in the study by the Liver Cancer Study Group of Japan that appears in the current issue of this Journal [13]. In this large, prospective study, 7185 patients with HCC were divided into those undergoing hepatic resection ($n = 2857$) versus percutaneous ablation with RFA ($n = 3022$) or EI ($n = 1306$) for HCC. The majority of patients had hepatitis C as the underlying liver disease. All patients exhibited Child's A or B liver function and had no more than 3 tumors with each not larger than 3 cm in diameter. The comparison of all three groups showed that the time-to-recurrence rate was significantly lower for the resection group. Locoregional ablation by RFA or EI was an independent predictor of poorer outcome in terms of recurrence compared to resection in the multivariate analysis. Despite these favorable results for the resection group, these findings had no impact on overall survival that was comparable for all three groups. This might be the result of the relatively short follow-up. Although this is not a RCT, the strength of this study is the large number of patients analyzed within a relatively short study period (2000–2003) and the clear definition of the degree of tumor extent. On the other hand, this study also has significant drawbacks which are related to the nature of a survey study. Furthermore, the comparative analysis showed that patients in the resection group had better liver function reflected by the Child-Pugh score and indocyanine green retention at 15 min. This difference implies that the groups are not homogenously comparable and associated with some degree of selection bias.

There are many retrospective studies comparing resection *versus* ablation for small HCC [14–19] (Table 1). The majority of these studies used percutaneous RFA and demonstrated better results for patients who undergo resection [14–16,18,19]. However, a subgroup analysis of smaller tumors (less than 2–3 cm) showed an equivalent outcome for resection and RFA in three of these studies [14,16,18]. Because of the retrospective and non-randomized nature of these studies, the findings have to be carefully interpreted due to the lower level of evidence. Surprisingly, only two RCTs comparing resection and ablation have been published so far [20,21] (Table 1). The RCT by Huang et al. [20] used percutaneous EI as the ablative method while RFA was used in the RCT by Chen et al. [21]. Both studies showed equivalent recurrence and survival data for the resection and percutaneous ablation group. Despite the nature of a RCT, both trials had significant drawbacks. The trial by Huang

Table 1
Studies comparing hepatic resection *vs.* local ablation for small HCC

Author, year	Study type	Study period	Comparison	Tumor number	Tumor size	Liver function	Outcome
Vivarelli, 2004	Retrospective	1998–2002	Resection ($n = 79$) *vs.* RFA ($n = 79$)	ND	ND	Child A/B	Better disease-free and overall survival for resection
Hong, 2005	Retrospective	1999–2001	Resection ($n = 93$) *vs.* RFA ($n = 55$)	1	⩽4 cm	Child A	Lower tumor recurrence for resection
Huang, 2005	RCT	1998–2002	Resection ($n = 38$) *vs.* EI ($n = 38$)	⩽2	⩽3 cm	Child A/B	Equivalent recurrence and survival
Wakai, 2006	Retrospective	1990–2002	Resection ($n = 85$) *vs.* Ablation ($n = 64$)	ND	⩽4 cm	ND	Lower tumor recurrence and better survival for resection
Chen, 2006	RCT	1999–2004	Resection ($n = 90$) *vs.* RFA ($n = 71$)	1	⩽5 cm	Child A, $ICG\text{-}R_{15} < 30\%$	Equivalent overall and disease-free survival
Lupo, 2007	Retrospective	1999–2006	Resection ($n = 42$) *vs.* RFA ($n = 60$)	1	3-5 cm	Child A/B	Equivalent overall and disease-free survival
Guglielmi, 2008	Retrospective	1996–2006	Resection ($n = 91$) *vs.* RFA ($n = 109$)	ND	⩽6 cm	Child A/B	Better disease-free and overall survival for resection
Abu-Hilal, 2008	Matched cohort[&]	1991–2003	Resection ($n = 34$) *vs.* RFA ($n = 34$)	1	1–5 cm	Child A/B	Better disease-free survival for resection
Schwarz, 2008	SEER database study	1998–2003	Resection ($n = 426$) *vs.* Ablation[#] ($n = 328$)	Milan[*]	Milan[*]	ND	Better overall survival for resection
Current study, 2008	Prospective survey study	2000–2003	Resection ($n = 2,857$) *vs.* RFA ($n = 3,022$) *vs.* EI ($n = 1,306$)	⩽3	⩽3 cm	Child A/B	Lower tumor recurrence for resection

ND, not defined; RCT, randomized controlled trial; SERR, surveillance, epidemiology, and end results; RFA, radiofrequency ablation; EI, ethanol injection; $ICG\text{-}R_{15}$, indocyanine green retention at 15 min; [&], matched for gender, age, tumor size, and Child-Pugh score; [#], included RFA, EI, cryosurgery, and other ablation techniques; [*], Milan criteria (single lesion ⩽5 cm, or no more than three lesions ⩽3 cm).

et al. [20] had a small sample size and was not based on a power calculation, while 19 of 90 patients (21%) who were randomized for ablation converted to liver resection in the other RCT [21]. These facts demonstrate the need for further RCTs comparing hepatic resection *versus* percutaneous ablation for small HCC in patients with preserved liver function and absence of portal hypertension.

Another interesting series that was recently published comes from the Surveillance, Epidemiology and End Results (SEER) database [22] (Table 1). During the period of 1998–2003, patients with HCC within the Milan criteria (single lesion $\leqslant$5 cm, or no more than three lesions $\leqslant$3 cm) were selected based on absence of extrahepatic disease and vascular invasion. In this series, the actuarial overall survival was compared for OLT ($n = 428$), liver resection ($n = 426$), and ablation ($n = 328$). As expected, OLT had the best outcome followed by resection and locoregional ablation. Although the 1-year survival rate was similar for resection and ablation, resection had a significant better long-term survival compared to ablation. These findings were also consistent with the multivariate analysis where resection was superior to ablation. However, these findings have to be interpreted carefully since the ablation group was composed of different techniques including RFA, EI, cryosurgery, and other locoregional techniques. Therefore, the exact value of each technique can not be assessed against liver resection.

In conclusion, hepatic resection and local ablation such as RFA and EI are effective treatment modalities for small HCC. Although two RCTs found equivalent outcomes for resection and ablation (RFA, EI), there is evidence from the large US [22] and Japanese series [13] reviewed herein that resection offers better outcome than locoregional ablation. There is also evidence that percutaneous RFA is superior to EI and should be preferred for the treatment of small HCC among available ablation techniques. Since the majority of data comes from retrospective studies, further RCTs are warranted to define the exact value of resection and ablation for small HCC.

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