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Resection versus ablation for hepatocellular carcinoma: role of initial treatment

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Hepatic Oncology

In almost all clinical practice guidelines for hepatocellular carcinoma (HCC), percutaneous ablation is the first-line treatment for those with limited tumor extension (e.g., solitary tumor ≤ 5 cm or 2–3 tumors none of which exceed 3 cm) not suitable for hepatic resection or liver transplantation [1–4]. Among various ablative methods for HCC, radiofrequency ablation (RFA) is the *de facto* standard supported by cumulative evidence including randomized and nonrandomized studies [5–8]. However, it is still controversial whether RFA can provide equivalent outcome in patients who have indication for resection. Several randomized controlled trials have been conducted to provide the answer to the question; some concluded resection was superior to RFA and some reported that these two were comparable [9–11]. However if one looks at the details of these studies, there are substantial problems in the implementation process. First, high conversion rates from RFA to resection and vice versa are noticed [9,11]. As a potential reason for

treatment conversion after randomization, Feng *et al.* wrote that many patients and physicians in China strongly believe that surgical resection is a more definitive treatment for HCC [11]. Although RCT should provide the highest grade of evidence with the smallest bias, this kind of selection bias is hardly avoided in comparing such different treatments where blinding to both patients and physicians is fundamentally infeasible. The second problem is proficiency in treatment procedures. An RCT conducted in a surgical department reported 1-year survival rate of 86.96% in RFA group whereas that of resection group was 98.26%. Because RFA is safer treatment than resection, 1-year survival rate should be higher or at least comparable (in this scenario $>95\%$) in RFA group [7,8] because patients with above-mentioned criteria rarely die of cancer within 1 year. Survival difference might appear in the long run after tumor recurrence. As shown here, it is not easy to reproduce the outcome of resection or ablation reported from high volume

KEYWORDS:

- hepatic resection
- overall survival
- radiofrequency ablation
- recurrence

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centers, because considerable experience and expertise exist behind the reported results.

Apparently, hepatic resection enable a more secure removal of tumor than RFA. Therefore physicians have to achieve complete ablation of target tumor with sufficient margin by careful evaluation of treatment efficacy in all cases in whom resection is feasible. For that purpose, second or third session of RFA are sometimes unavoidable. If RFA team in an institution does not have enough skills to ablate tumors in difficult location completely [12], they should refer patients to the surgical department if resection is feasible or other high volume centers of RFA. Comparison of two treatments is possible only when both of them are performed at a sufficient standard. When we prepared for nation-wide multicenter RCT comparing resection and RFA [13], there were only a few institutions that are ranked in the top 20 in both resection and RFA. In some cases, inter-hospital matching of departments would be necessary.

Even when complete ablation is achieved by RFA, hepatic resection has still advantage as it enables the systematic removal of a hepatic segment containing the tumor. Although the superiority of anatomical resection to limited resection in overall survival has not been fully proved [14,15], it is theoretically correct that removal of larger amount of liver parenchyma leads to lower risk of recurrence related to intrahepatic metastasis when patients have sufficient liver function reserve. In this meaning, superiority of resection to RFA in terms of recurrence-free survival is evident before conducting RCTs. Indeed in our cohort study, 20% of all recurrence after curative RFA were confined to the same subsegment of the original tumor [16]. Instead of the inferiority of RFA to resection in local tumor control, RFA has an advantage of safeness. A nation-wide survey using reimbursement database in Japan reported that in-hospital mortality of partial hepatectomy and segmentectomy for HCC were 1.94 and 2.34%, respectively whereas that of RFA was 0.25% [17]. Considering more than a few in-hospital deaths are liver-related, this figure may represent long-term difference in mortality affected by deterioration of liver function between the two treatments.

Across all solid tumors, the outcome of the initial treatment is undoubtedly the most important predictor of overall survival.

However it is also known that even after anatomical resection for HCC, the cumulative recurrence rate at 5 years is as high as 50–70% due to intrahepatic metastasis as well as *de novo* carcinogenesis in the remnant liver. Therefore, the survival curves of either resection or ablation never become plateau 5 years or even 10 years after the initial treatment [7,18]. However even after tumor recurrence, unlike other gastrointestinal cancers in which patients are only indicated for systemic therapy, resection or ablation can be applied to a large proportion of HCC patients. Easiness in repeat treatment is also an advantage of RFA over resection. The feasibility of secondary liver resection for recurrent HCC was reported as 8.8 to 44% even in high volume centers [19]. In contrast RFA were indicated in more than 80% of patients with secondary to quaternary recurrence in our series [7].

The impact of initial treatment of HCC would be relatively smaller than other solid tumors. In other words, sophisticated follow-up protocol after ablation and prompt treatment for recurrence are quite important to improve the overall survival of patients. For example, surveillance program that comprises dynamic CT of 4-month interval combined with three tumor markers enabled detection of recurrent tumors smaller than 2 cm in diameter in 86.7% of patients and 92% of patients could be treated by RFA [20]. In repeated treatment for recurrence, the advantage of RFA over resection in maintaining liver function reserve and wider indication for Child-Pugh B patients would be enhanced.

It would take a long time to have a solid answer to the first question whether RFA can provide equivalent outcome to resection as an initial treatment for small HCCs. However it seems that physicians have already known the way to maximize the advantage of resection and RFA. For example, the advantage of liver resection decreases according to deterioration of liver function. In terms of local cure, smaller tumors are better for RFA. The weight of initial treatment would be larger in patients with lower risk of recurrence, whereas the weight of repeat treatment for recurrence would be larger in those with higher risk such as multiple tumors or advanced liver fibrosis. There is no one-size-fits-all treatment for HCC. Needless to say, our common goal is to improve the survival of patients.

“...even after anatomical resection for hepatocellular carcinoma, the cumulative recurrence rate at 5 years is as high as 50–70%...”

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

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