Radiofrequency Ablation versus Resection in Large Single Nodule of Hepatocellular Carcinoma: an Evidence-based Case Report

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ABSTRACT

Background: nowadays, radiofrequency ablation (RFA) is applied widely as an alternative therapy of resection in patient with hepatocellular carcinoma (HCC). Moreover, in single nodule with size of less than 2 cm, RFA may be the primary treatment. Although resection is the main treatment and one of the curative treatments in nodule meeting Milan criteria, it needs consideration of risk stratification for surgical resection. This report was aimed to search evidence of RFA compared with RFA in term of survival in patient with HCC single nodule size of more than 5 cm. Methods: the searching was done using PubMed, Scopus, Web of Science, dan CINAHL from EBSCO with keyword of “hepatocellular carcinoma”, “single nodule”, “radiofrequency ablation”, “resection”, and “survival”. The limitation of the article was English with clinical question of “In patient with HCC single nodule size of more than 5 cm, was RFA more superior in resection in term of survival?”. Results: there were three articles with retrospective studies. One of the article combined RFA and percutaneous ethanol injection in the analysis, meanwhile another article combined RFA and transarterial chemoembolization. These articles showed conflicting
data that showed absolute risk reduction of 33% till absolute risk increment of 60.6%. **Conclusion:** all studies used RFA as the alternative of resection when the tumor was unresectable which means the severity was higher in RFA group. Hence, we can not solely conclude that RFA resulted in worse survival.

**Keywords:** hepatocellular carcinoma, radiofrequency ablation, resection.

**INTRODUCTION**

Hepatocellular carcinoma is responsible for 90% of liver cancer and is the second highest cause of cancer mortality in the world. Most of HCC are caused by hepatitis B and/or hepatitis C, mainly in patients with liver cirrhosis.\(^1\)

Therapy for HCC includes resection, liver transplant, local ablation (includes radiofrequency ablation), transarterial chemoembolization (TACE), radiation, and systemic therapy. The decision of treatment depends on nodule size, nodule number, vascular invasion, metastasis, liver function (Child-Pugh score), and also performance status. National, regional, or international guideline has their own algorithms that have some differences. Meanwhile, in some condition, the treatment is needed to be decided by the multidisciplinary team.

According to Asia Pacific Association for the Study of the Liver (APASL)\(^1\) and Indonesian Liver Cancer Study Group (ILCSG),\(^2\) resection is the first-line curative treatment for HCC in patient of Child-Pugh A, but ILCSG along with European Association for the Study of the Liver (EASL)\(^3\) has less strict criteria that include normal bilirubin, platelet ≥100,000/ml and without portal hypertension (≤10 mmHg). It is recommended that the resection is done using Milan criteria, of which diameter less than 5 cm or maximal three nodules with size of less than 3 cm without any vascular invasion or metastasis.\(^1,2\) ILCSG stated resection may be done in single nodule with size of more than 5 cm and located in peripheral liver.\(^2\) It is clear that nodule size of more than 5 cm which was resected had worse outcome.\(^3\)

Ablation, particularly radiofrequency ablation (RFA) is recommended in HCC patient with Child-Pugh A or B and multiple nodule ≤3 of size ≤3 cm. Moreover, it is the main treatment in nodule with size of ≤2 cm.\(^1,2\) ILCSG\(^2\) and EASL\(^3\) recommend RFA as alternative in patient with single nodule size of ≤5 cm. There is still no recommendation about the applicability of RFA in single nodule >5 cm.

There are also no clear recommendation about the treatment choice in patient with HCC single nodule size of >5 cm. Hence, this evidence-based case report was aimed to search the evidence whether RFA was better than resection in single nodule size of >5 cm.

**CLINICAL QUESTION**

A-62 year old man was diagnosed with HCC when he was screened for surveillance with ultrasound because of hepatitis B infection. The patient had a comorbid of coronary artery disease and underwent coronary bypass 5 years ago and still consumes clopidogrel and aspilet. The patient also had hypertension and it was controlled with amlodipin 10mg once daily. There was no complaint of sleep disturbance or other complaints of hepatic encephalopathy. No abnormality was found in physical examination. Ascites was not found at physical or radiological examination. AFP showed 4.7 IU/mL, HBsAg was positif, albumin 4.0 mg/dL, bilirubin total 0.47 mg/dL, and INR 1.02. The liver status was Child-Pugh A. Triple-phase abdominal computed tomography showed single nodule with size of 5.4x4.2x3.9 cm\(^3\) in segment 4A of liver. There was no metastasis. The patient asked whether there was another option (like RFA) than resection considering the comorbidity of the patient.

Based on the information from the presented case, the formulation of clinical question and PICO framework are as follows:

- **P:** Hepatocellular carcinoma single nodule size of >5 cm.
- **I:** Radiofrequency ablation
- **C:** Resection
- **O:** Survival

In HCC patients with single nodule size of >5 cm, how was the survival between RFA and resection?
METHODS

The articles were searched in PubMed, CINAHL (EBSCO), Web of Science, and Scopus on 11th December 2017, with keywords of hepatocellular carcinoma, single nodule, radiofrequency ablation, resection, and survival, but in PubMed we omitted the survival because of the lack of results (Table 1). Search strategy and the description including the inclusion and exclusion criteria was described in Figure 1.
Selection

After searching the articles, we found six articles from four search engines. Three articles were duplicated, so there are three articles that were available and being appraised. All three articles are retrospective study.

RESULTS

Ogihara et al. did the study retrospectively in two health centres in Honolulu, Japan. Total subjects were 87 HCC patients with single nodule recruited from period of 1995 until 2003. Of total 40 patients undergone RFA, 36 patients had unresectable lesions or low healthy liver volume and 4 patients refused to undergo surgery. They divided to two groups, lesion with ≤5 cm or >5 cm and resection or RFA so there are four groups. In this report, we only discuss the part of the study that the size of nodule >5cm, so there were 29 patients in resection group and 14 patients in RFA group. This study also showed disease-free survival as an outcome. Patients who had recurrence were treated depends on the lesion. Overall 1-year, 3-year, 5-year survival for therapy RFA vs resection were 65% vs 82%, 65% vs 67%, 65% vs 37%, respectively. The median were >63 months in RFA vs 47 months in resection. Moreover, disease-free 1-year, 3-year, 5-year survival were 53% vs 64%, 44% vs 40%, 0% vs 30% with median 20 months vs 28 months in RFA vs resection, respectively. In RFA group, mean of age was older than resection group (72±10 years vs 60±13 years), but the tumor size was bigger in resection group than RFA group (10.2±4.7 cm vs 7.1±3.7 cm). Liver condition was worse in RFA group showed by more Child-Pugh B in RFA group than resection (43% vs 10%). The stage of HCC according to TNM classification was also more advance in RFA than resection (64% vs 7%).

Ruzzenente, et al. also did a cohort study retrospectively from period of 1995—2009 in a hospital in Verona, Italy. The advantage of the study is they did a propensity case-matched study, so the baseline characteristics were similar. They included percutaneous local ablative therapies (LAT) and combined RFA and ethanol injection (PEI). In that period, there were total 181 patients undergone RFA and 297 patients undergone LAT (214 RFA and 83 PEI). The indication of LAT in this study were indicated when the location of the tumor was difficult or the patients refused to undergo liver resection, but all patients did not have absolute contraindication for resection. If the tumor relapsed, patients would be evaluated and undergone new treatment according to the indication. Unfortunately, in this study the tumor size was only maximum of 6 cm. After matching was done, there were 88 patients had resection and 88 had LAT. In LAT group, 88.6% of subjects were undergone RFA and 11.4% PEI. For single nodule with tumor size of ≥5 cm, there were only 13 cases undergone resection and 15 cases undergone LAT. The overall 1-year, 3-year, 5-year survival in LAT group versus resection group were 78.3% vs 76.9%, 31.3% vs 68.4%, and 7.8% vs 68.4%. Meanwhile for disease-free 1-year, 3-year, 5-year survival in group LAT versus resection were 20% vs 83.3%, 6.7% vs 52.9%, 6.7% vs 31.7%. Moreover, in case of single nodule with size of ≥5 cm, LAT gave hazard ratio of 3.8 (CI 95%: 1.3—11.2) for overall survival and 5.6 (CI 95%: 2.6—16) for disease-free survival.

Jung, et al. also did a study retrospectively by taking the data in three hospitals in South Korea in 2004—2009 with total patients of HCC of 2131 patients. The treatment choice for resection was evaluated based on the location of the tumor, Child Pugh A or B, and indocyanine green retention rate at 15 minutes <25% which means there was no portal hypertension. Patients whose tumor was unresectable and who refused surgery would have RFA and transarterial chemoembolization (TACE). There were 124 patients with single nodule with size of >5 cm and 41 patients (33.1%) undergone resection, 15 patients (12.1%) undergone RFA ± TACE, and 68 patients (54.8%) undergone TACE alone. Child-Pugh B was in 5% resection cases, 13% in RFA ± TACE, and 18% in TACE alone. Median of overall survival was 84.2 months for resection, 74.1 months for RFA ± TACE, and 28.9 months for TACE alone. We measured the overall survival from the Kaplan Meier graphical analysis, because the authors did not write the data explicitly. The overall 1-year, 3-year, and 5-year survival for RFA ± TACE vs resection were 91% vs 97.5%, 65% vs 85%, 65% vs 75%.
Critical Appraisal

The appraisal forms obtained from toolkit in http://www.cebm.net/blog/2014/06/10/critical-appraisal/ and presented in Table 2. All critical appraisals used therapy category in all articles although the studies were only retrospective.

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<tr>
<th>Articles (Year)</th>
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<th>Validity</th>
<th>Importance (5-year survival)</th>
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<td>RFA</td>
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<tr>
<td>Ruzzenente, et al (2012)</td>
<td>+</td>
<td>RFA or PEI</td>
<td>resection</td>
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OS: overall survival; RFA: radiofrequency ablation; PEI: percutaneous ethanol injection; RRR: relative risk reduction (survival rate in intervention minus in comparison and then divided to survival rate in intervention); ARR: absolute risk reduction (survival rate in intervention minus in comparison); NNT: number needed to treat. Negative numbers mean favor to resection RRR become RRI (relative risk increase), ARR become ARI (absolute risk increase) and NNT become NNH (number needed to harm).

DISCUSSION

From three articles that was found, none of the studies used randomized clinical trial, only retrospective studies, so the level of evidence is 2b. It quite hard to compare resection and RFA, because resection is still recognized resection not RFA.
curative treatment of HCC, although the usage of RFA is more widely used. RFA may have good prognostic as showed in Ho, et al’s study\(^4\) in San Fransisco, United States that showed in patients with HCC BCLC B, RFA had lower hazard ratio in 1-year survival than other locoregional therapy (TACE, transarterial embolization {TAE}, and PEI) (0.17 vs 0.38), but higher hazard ratio in 5-year survival (0.63 vs 0.31).

In all studies found in this report, resection was the main treatment given to the patient if the tumor was resectable and the patients agreed, so the comparison between main treatment and alternative treatment was hard to be similar at the baseline. Only in the second study by Ruzzenente, et al\(^6\), the comparison may be thought similar because they were doing propensity matched study.

It was difficult to make head to head comparison as HCC patients might had a relapse and there would be other treatment applied to the patient. Hence it is difficult to make sure that the outcome was the result from the first treatment or the subsequent treatment.

The interesting result of this report is the wide range results of three studies. Ruzzenente, et al’s\(^6\) and Jung, et al’s\(^7\) studies showed resection was more superior, otherwise Ogihara, et al’s\(^5\) study showed RFA was more superior. RFA was also superior in the meta analysis of Changyong, et al\(^9\) which included 4812 patients with HCC size of \(\leq 7\) cm (2419 patients in RFA group and 2393 patients in resection group), but there is no specific analysis among group with nodule \(>5\) cm. They showed overall 3-year and 5-year survival was significantly better in RFA group, but we need to put note that from 25 studies included in the meta analysis, only two studies had tumor size of \(\leq 7\) cm and one study of \(\leq 6\) cm.

Ogihara, et al\(^5\) showed there was decreasing of overall survival of resection in patient with single nodule \(>5\) cm among 1-year, 3-year, 5-year survival from 82% to 67% to 37%, meanwhile in RFA groups, the overall survival was stagnan of 65% among till 5 years. The most common cause of death of resection and RFA were secondary to liver failure in 35% of deaths and 100% of deaths among each group. Unfortunately the authors did not differentiate the cause of death between nodule \(>5\) cm and \(\leq 5\) cm.

In two studies which showed resection was more superior, there were also some notes. Ruzzenente, et al\(^6\) combined two LAT, e.g.: RFA and PEI in the analysis, meanwhile Jung, et al\(^7\) combined RFA with/without TACE, so the efficacy of the treatment is not RFA alone. From Jung, et al’s study,\(^7\) it is clear that by adding RFA would increase survival than TACE alone. Combination RFA and TACE in HCC intermediate class (beyond Milan criteria, include single nodule \(>5\) cm) was proved to increase survival in another study with difference in median reached 31.7 months than supportive therapy alone.\(^10\) Moreover, in a study by Pan, et al\(^11\) showed combination of RFA and TACE for tumor size \(\leq 7\) cm beyond Milan criteria was significantly increased median overall survival when compared with resection (52 months vs 45 months). Meanwhile, in the earlier stage of HCC that is still included in Milan criteria, RFA showed more superior than TACE alone both in overall survival and also progression-free survival, particularly after one year.\(^12\) Among HCC BCLC B with single nodule with size of \(>5\) cm, TACE alone was not better than resection in terms of overall 1-year, 3-year, and 5-year survival.\(^13\)

The advantage of the study by Ruzzenente, et al\(^6\) is they did matching in the analysis, comparison to similar in baseline characteristics, but the largest tumor size in this studies only 6 cm. Other study by Parisi, et al\(^14\) in Perugia, Italy compared RFA and resection in single nodule with size of \(>3\) and \(\leq 6\) cm, but no specific analysis in size of \(>5\) cm. It showed that among Child-Pugh A, resection and RFA was not different in median survival (40 months vs 40 months), but resection was significantly better than RFA among patients with Child-Pugh B (44 months vs 30 months). From those studies, we may infer that resection was still superior in tumor up to 6 cm than RFA, although it is not proven in Child-Pugh A group.

On the other hand, Ogihara, et al\(^5\) showed that the baseline characteristics were worse in RFA group in terms of age, Child-Pugh and TNM stage, but not in tumor size. With these baseline, they found RFA was better than resection in
single nodule size of >5 cm. Moreover, only in this study, the RFA is not combined with other modalities. We also need to consider the technique of RFA and the type of the machine and puncture, because it will also affect the result. Only Ogihara, et al. mentioned the technique of RFA that was done clearly.

In the point of view of quality of life, Chie, et al. showed ablation was worse than surgery and embolization. The components of quality of life that were lower were dyspnea, loss of appetite, body image, and role of life. Meanwhile, in surgery, the component of quality of life that was impaired was only pain. They also performed the adjustment for patients’ characteristics and severity of cases and still found ablation had worse outcome quality of life, but there was no explanation the cause of this result.

CONCLUSION

We may conclude from this report that RFA can still be used in the single nodule with a size of >5 cm, although resection is still the first-line treatment when the patient has the proper criteria and reachable location. Resection may be still superior till size of 6 cm. RFA combined with TACE when the size is bigger may have more benefit than RFA alone.

REFERENCES