

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

Felix F. Widjaja, Kemal F. Kalista, Juferdy Kurniawan

Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:

Juferdy Kurniawan, MD. Division of Hepatology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital. Jl. Diponegoro 71, Jakarta 10430, Indonesia. email: felixfw@gmail.com.

ABSTRAK

Latar belakang: radiofrequency ablation (RFA) saat ini semakin luas dipergunakan sebagai terapi alternatif reseksi pada pasien dengan karsinoma sel hati (KHS). Bahkan pada ukuran nodul kurang dari 2 cm, RFA dapat menjadi lini utama pada kasus tersebut. Reseksi merupakan terapi utama dan salah satu terapi kuratif pada nodul dengan kriteria Milan, tetapi harus dipertimbangkan toleransi operasi pada pasien yang akan menjalani reseksi. Pada laporan kasus berdasar bukti ini kami bertujuan memperlihatkan efektivitas RFA dibandingkan reseksi dalam hal kesintasan, tetapi pada KHS nodul tunggal berukuran lebih dari 5 cm. **Metode:** pencarian artikel dilakukan dengan menggunakan mesin pencari PubMed, Scopus, Web of Science, dan CINAHL dari EBSCO dengan kata kunci “hepatocellular carcinoma”, “single nodule”, “radiofrequency ablation”, “resection”, dan “survival”. Artikel dibatasi pada artikel berbahasa Inggris dengan pertanyaan klinis “Pada pasien dengan KHS nodul tunggal berukuran lebih dari 5 cm, apakah RFA lebih baik dibandingkan dengan reseksi untuk memperpanjang kesintasan?” **Hasil:** didapatkan tiga artikel penelitian retrospektif dengan satu artikel menggabungkan terapi RFA dan injeksi etanol dalam analisis dan satu penelitian menggabungkan RFA dengan transarterial chemoembolization (TACE) dalam analisisnya. Dari ketiga penelitian tersebut memperlihatkan penurunan risiko absolut 33% sampai peningkatan risiko absolut 60,6%. **Kesimpulan:** seluruh penelitian menjadikan RFA sebagai alternatif reseksi bila reseksi tidak dapat dilakukan yang berarti tingkat keparahan lebih tinggi pada RFA, sehingga sulit mengambil kesimpulan bahwa RFA memberikan kesintasan lebih buruk.

Kata kunci: karsinoma sel hati, radiofrequency ablation, reseksi.

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 $\geq 100,000/\text{ml}$ 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.⁴

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} ILCSG² and EASL³ 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 aspirin. 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 positive, 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 cm³ 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?

Table 2. Search strategy according clinical question conducted in December 11th 2017

Search engine	Description	No. of articles
Web of Science	TOPIC: (single nodule) AND TOPIC: (hepatocellular carcinoma) AND TOPIC: (radiofrequency ablation) AND TOPIC: (resection) AND TOPIC: (survival) Refined by: DOCUMENT TYPES: (ARTICLE) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI.	66
PubMed	((("single person"[MeSH Terms] OR ("single"[All Fields] AND "person"[All Fields]) OR "single person"[All Fields] OR "single"[All Fields]) AND nodule[All Fields]) AND ("carcinoma, hepatocellular"[MeSH Terms] OR ("carcinoma"[All Fields] AND "hepatocellular"[All Fields]) OR "hepatocellular carcinoma"[All Fields] OR ("hepatocellular"[All Fields] AND "carcinoma"[All Fields]))) AND (radiofrequency[All Fields] AND ablation[All Fields])) AND resection[All Fields] AND English[lang]	19
CINAHL (EBSCO)	(single nodule) AND (hepatocellular carcinoma) AND (radiofrequency ablation) AND (resection) AND (survival)	27
Scopus	ALL ("single nodule") AND ALL ("Hepatocellular carcinoma") AND ALL ("radiofrequency ablation") AND resection AND ALL ("survival") AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English"))	104

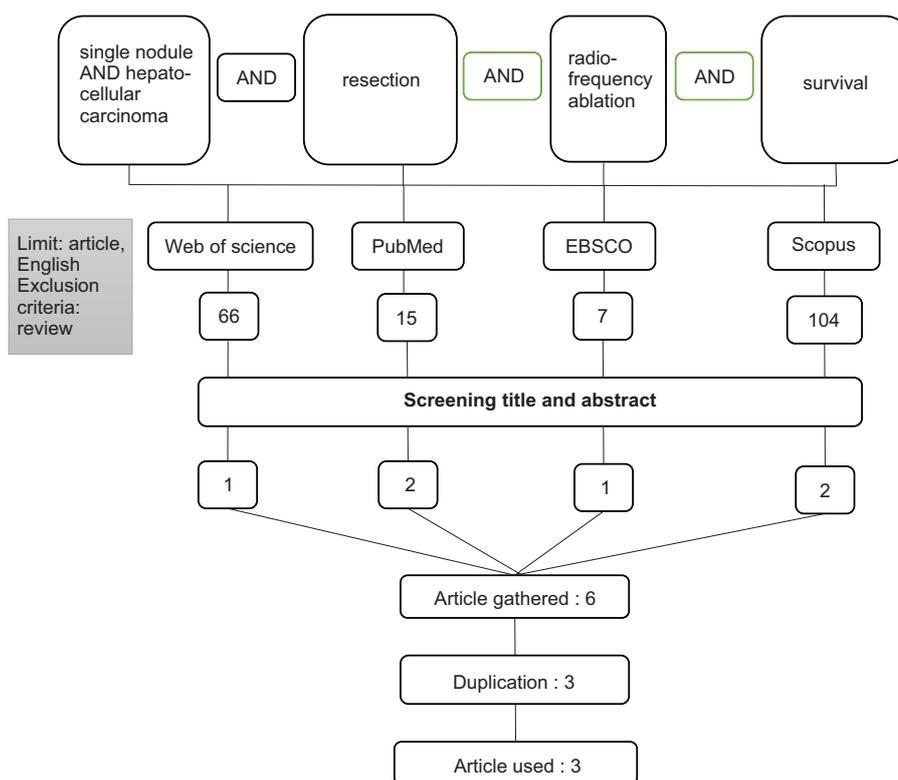


Figure 1. Flow chart of search strategy *without keyword of survival

METHODS

The articles were searched in PubMed, CINAHL (EBSCO), Web of Science, and Scopus on 11th Desember 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 al⁵ 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 >5 cm, 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 al⁶ 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—16) for disease-free survival.

Jung, et al⁷ 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 \pm TACE, and 68 patients (54.8%) undergone TACE alone. Child-Pugh B was in 5% resection cases, 13% in RFA \pm TACE, and 18% in TACE alone. Median of overall survival was 84.2 months for resection, 74.1 months for RFA \pm 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 \pm 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.

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 is quite hard to compare resection and RFA because resection is still recognized as a

Table 2. Critical appraisal of all three studies

Articles (Year)	Relevance					Validity			Importance (5-year survival)				
	Patient	Intervention	Comparison	Outcome	Random	Long follow-up	All patients analyzed	blind	Treated equally	Similar at start	RRR	ARR	NNT
Ogihara, et al ⁵ (2005)	±	RFA	resection	OS, disease free survival	-	+	+	-	+	-	89%	33% (65% vs 37%)	3
Ruizenente, et al ⁶ (2012)	+	RFA or PEI	resection	OS, disease-free survival	-	+	+	-	+	+	-88%	-60.6% (7.8% vs 68.4%)	-1.6
Jung, et al ⁷ (2016)	±	RFA±TACE	resection	OS	-	+	+	-	+	?	-15%	-10% (65% vs 75%)	-10

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).

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 study⁸ in San Francisco, 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 al⁶, 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's⁶ and Jung, et al's⁷ studies showed resection was more superior, otherwise Ogihara, et al's⁵ study showed RFA was more superior. RFA was also superior in the meta analysis of Changyong, et al⁹ which included 4812 patients with HCC size of ≤ 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 ≤ 7 cm and one study of ≤ 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 ≤ 5 cm.

In two studies which showed resection was more superior, there were also some notes. Ruzzenente, et al⁶ combined two LAT, e.g.: RFA and PEI in the analysis, meanwhile Jung, et al⁷ 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 al¹¹ showed combination of RFA and TACE for tumor size ≤ 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 al⁶ 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 al¹⁴ in Perugia, Italy compared RFA and resection in single nodule with size of >3 and ≤ 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 al⁵ 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 >5cm. 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 al⁵ mentioned the technique of RFA that was done clearly.

In the point of view of quality of life, Chie, et al¹⁵ 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

1. Omata M, Cheng A-L, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int*. 2017;11(4):317-70.
2. Indonesian Liver Cancer Study Group. Konsensus Nasional Penatalaksanaan Karsinoma Sel Hati. In: Hasan I, Loho IM, eds. Jakarta: Perhimpunan Peneliti Hati Indonesia; 2017.
3. Dufour JF, Greten TF, Raymond E, et al. Clinical practice guidelines EASL – EORTC clinical practice guidelines: Management of hepatocellular carcinoma European Organisation for Research and Treatment of Cancer. *J Hepatol*. 2012;56(4):908-43.
4. Wong LL, Hernandez BY, Shvetsov YB, Kawano Y, Tang ZY, Ji JF. Liver resection for early hepatocellular cancer: Comparison of centers in 3 different countries. *World J Hepatol*. 2016;8(31):1327-35.
5. Ogihara M, Wong LL, Machi J. Radiofrequency ablation versus surgical resection for single nodule hepatocellular carcinoma: Long-term outcomes. *Hpb*. 2005;7(3):214-21.
6. Ruzzenente A, Guglielmi A, Sandri M, et al. Surgical resection versus local ablation for HCC on cirrhosis: Results from a propensity case-matched study. *J Gastrointest Surg*. 2012;16(2):301-11.
7. Jung YK, Jung CH, Seo YS, et al. BCLC stage B is a better designation for single large hepatocellular carcinoma than BCLC stage A. *J Gastroenterol Hepatol*. 2016;31(2):467-74.
8. Ho EY, Cozen ML, Shen H, et al. Expanded use of aggressive therapies improves survival in early and intermediate hepatocellular carcinoma. *Hpb*. 2014;16(8):758-67.
9. Changyong E, Wang D, Yu Y, Liu H, Ren H, Jiang T. Efficacy comparison of radiofrequency ablation and hepatic resection for hepatocellular carcinoma: A meta-analysis. *J Cancer Res Ther*. 2017;13(4):625.
10. Tanaka M, Ando E, Simose S, et al. Radiofrequency ablation combined with transarterial chemoembolization for intermediate hepatocellular carcinoma. *Hepatol Res*. 2014;44(2):194-200.
11. Pan T, Mu L-W, Wu C, et al. Comparison of combined transcatheter arterial chemoembolization and CT-guided radiofrequency ablation with surgical resection in patients with hepatocellular carcinoma within the up-to-seven Criteria: a multicenter case-matched study. *J Cancer*. 2017;8(17):3506-13.
12. Hocquelet A, Seror O, Blanc J-F, et al. Transarterial chemoembolization for early stage hepatocellular carcinoma decrease local tumor control and overall survival compared to radiofrequency ablation. *Oncotarget*. 2017;8(19):32190-200.
13. Zhong J-H, Xiang B-D, Gong W-F, et al. Comparison of long-term survival of patients with BCLC Stage B hepatocellular carcinoma after liver resection or transarterial chemoembolization. *PLoS One*. 2013;8(7):e68193.
14. Parisi A, Desiderio J, Trastulli S, et al. Liver resection versus radiofrequency ablation in the treatment of cirrhotic patients with hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int*. 2013;12(3):270-7.
15. Chie W-C, Yu F, Li M, et al. Quality of life changes in patients undergoing treatment for hepatocellular carcinoma. *Qual Life Res*. 2015;24(10):2499-506.