Comparison open liver resection and RFA on the treatment of solitary 3-5cm hepatocellular carcinoma

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Abstract

Aim The goal of this study is to compare the postoperative results of liver resection and radiofrequency ablation (RFA) for the treatment of small hepatocellular carcinoma (HCC) (3-5cm). Patients and methods We retrospectively collected 122 patients with small solitary HCC treated at our center, with diameters in the range of 3-5cm. According to the treatment program received at our center, they are divided into the liver resection group (72 cases) and the RFA group (50 cases). Result In comparison with the RFA group, the resection group requires a longer operative time, and the intra-operative blood loss is more (P<0.01); there is also more hepatic inflow occlusion, and the postoperative days of hospital stay are significantly longer (P<0.01). The 1-, 3-, and 5-year expected overall survival rates and tumor-free survival rates are comparable between two groups. Cox regression analysis showed that resection or RFA was not a significant risk factor for overall or tumor-free survival for HCC. Conclusions For solitary HCC of 3-5cm, RFA can achieve better hospital clinical results and similar long-term outcome, and RFA can be considered for wide application especially for central cases.

Background

Hepatocellular carcinoma (HCC) ranks No.5 in the global incidence of malignant tumors, and its mortality rate ranks No.3[1]. The burden of diagnosis of liver cancer is particularly prominent in China[2]. For the treatment of early stage liver cancer, the commonly accepted radical treatments include liver transplant (LT), liver resection, and RFA. LT cannot only remove the lesion but also remove the soil for the growth of the tumor, and it is generally considered the most effective method[3]. liver resection and RFA are the main approaches of treatment for early HCC. The comparison of safety and effectiveness between liver resection and RFA has been the subject of greatest research interest for the past several years[4].

Although a unified understanding has not been reached, the analysis of its effectiveness generally indicates that for small liver cancer with diameter ≤3cm, the long-term survival and tumor recurrence are similar[5]; for liver cancer with diameter >5cm, it is currently believed that RFA difficulty achieve the effect of radical treatment[6]. However, for liver cancer with diameter of 3-5cm, there is still considerable controversy on its effect[7-9]. Additionally, most studies that compare these two methods focus on the treatment or control of the tumor, while the safety of two treatment methods is ignored. However, safety is still a question that we must consider while selecting the treatment option. Therefore, this study aims to comprehensively study the efficacy and safety of liver cancer (diameter 3-5cm) treatment with liver resection and RFA using the data collected at our center.

Methods

This retrospective study was performed after approval from the Ethics Committee of our Hospital. In addition, due to the retrospective characteristic, no consent was obtained from participants, but patient records or information was anonymized and de-identified prior to analysis. We retrospectively collected all the liver cancer cases admitted to our hospital, and these cases were screened according to the following
inclusion and exclusion criteria (As shown in Table 1). In the end, we collected 122 cases of patients for the grouped analysis in our study.

According to the treatment strategies received by the 122 cases of patients, we divided them into the liver resection group and the RFA group. In particular, the liver resection group includes 72 cases, and the RFA group includes 50 cases. We compared the relevant intra-operative data for the two groups: surgical time, blood loss due to hepatic portal occlusion, and transfusion rate, and the postoperative relevant data: total hospital days, and total hospital expense. The focus is the occurrence of postoperative complications; we used the Clavien evaluation system to assess and measure the occurrence of postoperative complications. Finally, we focused on comparing the long-term tumor follow-up situation for the patients: 1-, 3-, 5- year total survival rates, tumor-free survival rates, and occurrence or features of the tumor, as well as the treatment of recurring tumors. The Cox Proportional hazards model was used for multivariate analysis of factors that were considered significant in univariate analysis.

The surgery in our center is personally implemented by the chief physician or deputy chief physician with more than ten years of surgical experience. The selection of these two procedures (either liver resection or RFA) was made mainly on the basis of the location of the tumor and then the preservation of hepatic function. Usually, when the shortest distance between edge of the target and the edge of the liver was larger than 3cm, these cases may be considered as the central cases in our center and would be recommended to RFA. To avoid migration, all surgical resection or RFA is performed by laparotomy. The resection adopts the clamp method or ultrasonic knife to implement the standard resection of a liver lobe or liver segment, and the section of resection is at least 1-2 cm from the border of the tumor. There was no intra-operative radiotherapy, and the portal vein intubation chemotherapy is not used. During the surgery, we applied B-ultrasonic at the same time for the intra-operative localization and examination after the resection. We treated our patients with RFA by using a commercially available system (Radionics, Cool-Tip System, Burlington, MA USA), all procedures were performed under general anesthesia; we located and evaluated the tumor situation after the ablation. According to the size and location of the tumor, we selected a single needle or 3-pin ablation needle. The time of every RFA is determined by the size of the tumor, and generally it is at least 10 minutes. After the ablation, we used the intra-operative B ultrasound to evaluate the range of burning and the possible remaining situation, and before closing the abdomen, we again used B ultrasound to inspect the whole liver, to prevent the omission of lesions or incomplete burning.

After the post-operative patients have left the hospital, they visit our clinic department on a regular basis: within three months after the surgery, they come to the clinic of our hospital for relevant monthly follow-up examinations, including abdominal ultra-sonography, AFP, liver function, and regular blood examination; in the third month after the surgery, we conducted routine enhanced CT scanning of the abdomen to further clarify the recurrence of the tumor; during the period of three months to one year after the surgery, according to the pathological classification of the tumor and the situation of the patients, we conduct one re-examination every 2-3 months; following one year after the surgery, we conduct re-examination every 3-6 months. The content of re-examination is mainly imaging, followed by liver
function, regular blood tests, and other relevant inspections. When the color ultra-sonography indicates suspicious recurrence, we advise the patients to undergo enhanced CT or MRI inspection in combination with the AFP level. If there is indeed recurrence, we will recommend the relevant treatment plan (e.g., resection, re-RFA, or intervention surgery) to the patients according to the basic situation of the patients, characteristics of the tumor, and other relevant factors.

We adopted SPSS 17.0 (SPSS Inc. Chicago, IL, USA) for the statistical analysis of the data, the patients’ baseline characteristics and other continuous variables are expressed as mean ±SD, and compared and calculated by using non-parametric Wilcoxon test because some of the measurements did not follow a normal distribution, and as frequencies for categorical data, and compared by using the Chi-squared test or Fisher’s exact test, if necessary, ranked data were compared by using Mann-Whitney U test. Overall survival and tumor-free survival rates were obtained by Kaplan-Meier survival analysis, and differences in survival curves between two groups were statistically compared by log-rank test. Univariate analysis was performed in order to identify factors predicting overall and tumor-free survival. All variables with P< 0.05 were included in multivariate analysis to assess the independent predictor factors by using the Cox regression. The bilateral P<0.05 was considered to be statistically significant. However, eventually we must combine biological characteristics and common sense to determine the statistical significance.

**Results**

According to the comparison in Table 2, we found no significant difference in the demographic baseline level of patients in the two groups (P>0.05). According to either the Child scoring system or the MELD scoring system, the difference in the preoperative liver function between the two groups is not statistically significant.

Regarding the comparison of oncology characteristics, the cases incorporated into our analysis are all single lesion. Our comparison indicates that the tumor diameter for the radiofrequency group was slightly larger than the tumor diameter for the resection group (3.8 vs. 3.7 cm), but this difference is not statistically significant (P=0.528). Regarding the position of the tumor in the liver, for the resection group, the tumor located on the edge in 53 cases (73.6%), while for the radiofrequency group, there were only 12 cases (24.0%) where the tumor is located on the edge (P<0.01). This difference is mainly because the advantages and disadvantages of RFA and resection cause the surgeon to adopt the optimal treatment plan before or during the surgery.

As shown in Table 3, we compare the relevant intra-operative and post-operative data for the resection group and radiofrequency group. The operative time of the resection group was significantly longer than the RFA group (4.0 vs. 2.7h, P<0.001). The intra-operative blood loss was significantly more for the resection group than the RFA group (364.6 vs. 102.0 ml, P<0.001); the hepatic portal occlusion of the resection group was also significantly more than the RFA group (P<0.001). We also found that the average hospital stay of the resection group was 6.3 days, which is significantly longer than 4.7 days for the RFA group (P=0.001).
We adopted the Clavien system to summarize and compare the occurrence of postoperative complications between the two groups. Table 4 shows our comparison of the occurrence of postoperative complications for the two groups. It was found that the resection group included 18 cases with complications, for a total occurrence rate of complications of 25%; in the RFA group, there were 8 cases with complications, and the total occurrence rate of complications as 16%. Although the occurrence rate of complications for the resection group was higher than for the RFA group, the difference between them was not statistically significant (P=0.284). The occurrence rate of serious complications (≥ level III) was 8.3% for the resection group and 4% for the RFA group, with no significant difference between the two groups (P=0.344). In the RFA group, there was one case with postoperative fever. Color ultra-sonography and CT showed the formation of biloma with abscess, and we performed laparotomy abdominal inspection to conduct a partial liver resection.

During the follow-up period, the 1-, 3-, 5-year expected overall survival rates of the resection group were 94.4%, 77.8%, and 70.8% VS 90%, 76%, and 68% in the RFA group, as shown in Figure 1, this difference is no statistically significant (P=0.968). For the 1-, 3-, 5-year expected tumor-free survival rates, resection group were 87.5%, 62.5%, and 55.6% VS 88%, 68%, and 60% in the RFA group, As shown in Figure 2, the difference between the two groups is also no statistically significant (P=0.620). During the median 3.6 years (range from 0.3-7.5 years) follow up period, 41 patients died and 52 patients’ HCC recurred. The most common recurrence or metastasis position of postoperative tumors is intrahepatic metastasis or recurrence (55%). Extrahepatic recurrence and metastasis occur mostly in the lung (30%), followed by intra-abdominal metastasis (7.5%); bone metastasis is rare (5%), as is metastasis to other parts of the body (2.5%). The most common treatment for tumor recurrence is TACE intervention (28 cases), followed by re-resection (11 cases) or RFA (21 cases), while LT (2 cases), HIFU knife (3 cases), and other treatment programs (including sorafenib (2 cases), chemotherapy (1 case), radiotherapy (1 case)) are rare. The most common factor causing the death of patients during the postoperative follow-up period is tumor recurrence and metastasis (78%), followed by liver function failure (19.5%); other cases are rare (2.4%).

As showed in Table 5, univariate analysis identified pre-operative NLR≥ 4 (P<0.001), AFP ≥400ng/ml (P=0.014), Intra-operative blood loss≥ 400ml (P=0.029), poor histological grading (P<0.029), central tumor location (P=0.044), microvascular invasion (P<0.001) as significant factors contributing to overall survival after operation, multivariate analysis of the five factors found to be significant in univariate analysis further identified NLR≥ 4 (P=0.020), poor Histological grading (P<0.001) as significant contributors to overall survival. The hazard ratios (HRs) and 95% confidence intervals (CIs) for these factors are detailed in Table 6.

As showed in Table 5, univariate analysis identified Pre-operative Platelet ≥100*10^9/L (P=0.029), NLR≥4 (P<0.001), and Microvascular invasion (P<0.001) as significant factors contributing to tumor-free survival after operation. Multivariate analysis of the three factors found to be significant in univariate analysis confirmed NLR≥ 4 (P<0.001) and Microvascular invasion (P=0.002) as significant contributors to tumor recurrence, the HRs and 95% CIs for these factors are detailed in Table 6.
Discussion

Generally, Surgical resection is a more radical treatment approach than RFA. However, due to the limitations of the background of liver and the liver function situation, postoperative complications also need to be taken into account. RFA surgery is the relatively safe treatment approach, but the stability and thoroughness for RFA to treat liver cancer are difficult to determine[10, 11]. Although the evaluation of effectiveness between the two approaches is still in debate, in Western countries, especially in the United States, the treatment guidelines on liver cancer consistently require surgical resection for early liver cancer if the liver function allows and if there is no high vein pressure[12]. However, the guidelines also mention that due to the nearly 3% mortality rate after the liver resection surgery, other therapies to treat small liver cancer may be appropriate, of which ablation treatment is preferred. At present, the relevant mature ablation treatment is RFA treatment. There have been many studies on the effectiveness and reliability of the treatment of liver cancer using RFA and surgical resection. Although a unified opinion has not yet been reached, at present, we believe that the effect of RFA depends on the maximum diameter of the tumor. Current studies mostly define the gold standard of RFA to be smaller than 2.3-3cm. For a single tumor with diameter smaller than 3cm, RFA can achieve similar results to resection, and its safety can be ensured[13-15]. However, for a tumor with diameter in excess of 5cm, although some reports claim that three-dimensional RFA can achieve similar results to resection, at present most reports in the literature indicate the use of resection instead of RFA[4]. However, the focus of the current debate is on a single liver tumor of 3-5cm, and the treatment effectiveness of RFA and resection remains to be further investigated. Our study aims to promote an in-depth discussion of this subject.

Regarding tumor characteristics, there were more cases with the tumor located in the center of liver in the radiofrequency group than in the resection group, mainly due jointly to preoperative CT evaluation and intra-operative examination of tumor features and liver cirrhosis: when the tumor is located in the periphery of the liver, surgical resection is relatively easy, especially for a tumor of left lateral lobe; in contrast RFA ablation is prone to injure other surrounding tissues, such as the stomach or colon[6]. In addition, the implementation of RFA surgery on peripheral small liver cancer is more prone to cause tumor rupture and result in metastasis[4, 16]. When the tumor is located in the center of liver, however, especially at the junction of the donor on the segments V, VI, VII, and VIII of the right liver, liver resection will lose many normal liver tissues, leaving too small a volume of the residual liver[16]. Because most of the liver suffers from the cirrhosis background, the postoperative liver function cannot satisfy the organ metabolism, leading to liver function failure or even death. Moreover, when the tumor is close to large blood vessels, the result of using RFA is not good and often leaves behind part of the tumor tissue. Therefore, in the clinical application of RFA, we need to consider not only the diameter of the tumor but also its location, surrounding tissue and the background liver situation to achieve better results.

Although the small incision means that RFA surgery leads to significantly less blood loss, cases requiring blood transfusion are rare because the blood loss during resection surgery is also small in our hospital. Therefore, although the blood loss was different for the two groups, there was no significant difference in the rate of blood transfusion for two groups. Because the trauma of resection is relatively large, the
surgery requires partial occlusion. The most commonly used method is semi-liver occlusion, which can prevent injury to the remaining liver due to continuous occlusion by the ischemia-reperfusion. However, in our analysis and comparison, although the intra-operative time is short, the blood loss during surgery is small, and the postoperative hospital stay is short, there is still a significant difference between the total treatment expense of the radiofrequency group and that of resection group, mainly because the domestic hospitals mostly use imported RFA needles. The RFA needle costs nearly 10,000 RMB Yuan, which accounts for most of the treatment cost of radiofrequency treatment, whereas the overall expense of surgical resection is low. Hence, there is no difference in the total treatment expense between resection group and radiofrequency group. Through the observation of postoperative complications, we found that although the occurrence rate of postoperative complications and the occurrence rate of serious complications for cases with resection surgery were both higher than in the RFA group, this difference was not statistically significant. One possible reason could be that our sample size is not large enough, and all our cases of RFA employed abdominal surgery. Therefore, in comparison with other statistical analyses, our data are more objective and accurate. However, this topic still needs a multi-center random comparison and study of a large sample to further explore the occurrence of postoperative complications for the two methods.

Our analysis indicates that the postoperative 1-, 3-, 5-year survival rates are similar for the RFA group and the resection group, which is similar to the results of the 18th national statistical analysis of Japan: they conducted a statistical analysis of over 10,000 cases of liver cancer with level A liver function. They found that RFA not only achieves the similar result to resection for the liver cancer smaller than 2cm but also that for liver cancer of 2-5cm, its effect is similar, and their observations have been as long as 10 years[17]. Meanwhile, our univariate and multivariate analyses contributing to overall survival or tumor-free survival rate indicated the resection or RFA did not contribute to overall survival or tumor-free survival. Our study again corroborates this point.

There are still some limitations on this study: although the sample size in this study is relatively large, all the cases are from a single center, and the study of cases from multiple centers is more persuasive; the essence of this study is a retrospective analysis. We retrospectively collected and compared the characteristics of two groups of cases. Because our selection of resection and RFA before and during the surgery is mainly determined according to the tumor position found by pre-operative CT and during the surgery, it cannot be assigned randomly. Therefore, a multi-center random comparative study with a large sample will be more persuasive, and this goal is also the direction of our future work.

Because there are fewer complications after RFA surgery, which has better intra-operative and post-operative data performance and a post-operative survival rate comparable to the resection surgery, abdominal RFA can be considered for wide application to single tumors with diameters of 3-5cm especially for central cases.
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Tables

Table 1. Main inclusion/exclusion criteria of the study

| Inclusion criteria | Exclusion criteria |
|--------------------|--------------------|
| Single tumor       | Tumor thrombus in major vessels |
| 3 cm≤ diameter of tumor<5cm | Multiple tumors, or distant metastasis |
| ECOG score 0-1     | The heart and lung function of the patients cannot tolerate surgical treatment |
| Liver function of grade Child A or B | Cannot take the surgery due to other diseases |
| Receiving the first treatment in our center: liver resection or RFA | Cases with preoperative intervention of HIFU knife on the lesion or other preoperative relevant downgrade treatment |
| All cases were accomplished with laparotomy | Liver function at level C (patients achieving levels A or B after liver-protection treatment can be incorporated) |
| Able to receive the complete postoperative regular follow-up visit or inspection | Cases with postoperative diagnosis of biliary carcinoma or other non-liver-cell liver cancer |
|                    | Cases that received other treatment means |
|                    | Cases without follow-up after the surgery |
|                    | Other treatment cases that adopted intravenous chemotherapy or took sorafenib after the surgery |
|                    | Other surgical contraindications, such as coagulation disorders |

Table 2. Comparison between baseline data and oncological features of patients in resection group and RFA group.
|                                | Liver resection group | RFA group | P value |
|--------------------------------|-----------------------|-----------|---------|
|                                | 72                    | 50        |         |
| Age                            | 46.7±10.3             | 45.8±12.0 | 0.664   |
| Gender (male/female)           | 61/11                 | 42/8      | 0.914   |
| Weight (Kg)                    | 68.1±9.5              | 66.8±10.0 | 0.474   |
| Height (cm)                    | 166.9±8.4             | 163.5±8.4 | 0.057   |
| BMI (kg/m^2)                   | 23.3±2.4              | 23.8±1.8  | 0.252   |
| Ethnicity (Han/Tibet/Yi/Others)| 63/4/2/3              | 45/2/2/1  | 0.665   |
| Virological examination (B/C/negative) |                     |           |         |
| HBV-DNA (negative/positive)    | 67/1/4                | 46/4/0    | 0.899   |
| Child score (A/B/C)            | 28/39                 | 25/21     | 0.191   |
| MELD score                     | 47/25/0               | 37/13/0   | 0.308   |
| Ishak score                    | 5.5±2.2               | 5.4±1.5   | 0.688   |
| Tumor diameter (cm)            | 3.9±1.5               | 4.1±1.2   | 0.411   |
| Preoperative AFP level (ng/ml) | 3.7±0.5               | 3.8±0.5   | 0.528   |
| Preoperative AFP (−/+;++/+++:+) | 3781.9±14104.9        | 4716.6±14813.6 | 0.725 |
| Degree of tumor differentiation (low/moderate/high) | 33/10/10/19 | 19/8/8/15 | 0.444   |
| Tumor location (edge/center)   |                       |           |         |
| Microvascular invasion (yes/no)| 15/27/30              | 16/19/15  | 0.116   |
|                                | 53/19                 | 12/38     | 0.000   |
|                                | 23/49                 | 17/33     | 0.813   |

HBV DNA negative: <1.0E+03 copies/ml, positive: ≥1.0E+03 copies/ml

Other ethnicities: Qiang and Mongolian
Preoperative AFP level: -: <12ng/ml; +: 12ng/ml ≤ <400ng/mL; ++: 400ng/ml < ≤1200ng/mL; +++: ≥1200ng/ml

Continuous variables compared and calculated by using non-parametric Wilcoxon tests, frequencies for categorical data, and compared by using the Chi-squared test or Fisher’s exact test if necessary, ranked data were compared by using Mann-Whitney U test.

**Table 3.** Comparison of relevant intra-operative data and post-operative short-term recovery situation between the two groups.

|                                | Resection group | RFA group | P value |
|--------------------------------|----------------|-----------|---------|
| Operation time (hours)         | 4.0±1.2        | 2.7±0.8   | <0.001  |
| Intra-operative blood loss (ml)| 364.6±180.1    | 102.0±105.9| <0.001  |
| Intra-operative transfusion (Yes/No) | 9/63       | 3/47      | 0.238   |
| Hepatic inflow occlusion (whole liver/half liver/non-blocking) | 9/36/27 | 2/4/44 | <0.001 |
| ICU care (Yes/No)              | 5/67           | 3/47      | 0.836   |
| Total number of days in hospital | 6.3±2.2       | 4.7±1.8   | 0.001   |
| Total cost of hospitalization (RMB Yuan) | 35542±2456.9 | 33453.2±1986.6 | 0.939   |

ICU: Intensive care unit

Continuous variables compared and calculated by using non-parametric Wilcoxon tests, frequencies for categorical data, and compared by using the Chi-squared test or Fisher’s exact test if necessary,

**Table 4.** Comparison of post-operative complication occurrence for resection group and radiofrequency group (Clavien scoring system).
| Clavien level | Description | Resection group | RFA group |
|--------------|-------------|----------------|----------|
| I            | Incision fat liquefaction | 7 (9.7%) | 4 (8%) |
|              | Wound infection | 2 | 1 |
|              | Pleural effusion | 1 | 2 |
|              | Biliary fistula | 2 | 1 |
| II           | Clavien level II (simple medicine treatment) | 2 | 0 |
|              | Wound infection | 5 (6.9%) | 2 (4%) |
|              | Postoperative pulmonary infection | 2 | 1 |
|              | Postoperative abdominal hemorrhage | 1 | 1 |
| IIIa         | Clavien level IIIa (therapeutic operation under local anesthesia) | 2 | 0 |
|              | Pleural effusion | 1 (1.4%) | 0 (0%) |
| IIIb         | Clavien level IIib (operational treatment under general anesthesia) | 1 | 0 |
|              | Abdominal hemorrhage | 1 | 0 |
|              | Biloma | 1 (1.4%) | 1 (2%) |
| IVa          | Clavien level IVa (single organ function failure) | 1 | 0 |
|              | Respiratory failure | 1 | 0 |
|              | Liver failure | 0 | 1 |
| IVb          | Clavien level IVb (multiple organ failure) | 2 (2.8%) | 1 (2%) |
| Hepatorenal syndrome | 1 | 0 |
| V            | Clavien level V (death) | 1 | 1 |
| Septic shock | 1 (1.4%) | 0 (0%) |
TABLE 5: Univariate analyses contributing to overall survival and tumor-free survival rate after RFA or Resection.

| Variables                                      | N (122) | Overall survival rate | Tumor-free survival rate |
|------------------------------------------------|---------|-----------------------|--------------------------|
|                                                 |         | P Value               | P Value                  |
| Age ≥60 (yes/no)                               | 19/103  | 0.398                 | 0.961                    |
| Gender (M/F)                                   | 103/19  | 0.398                 | 0.652                    |
| Race (Han/other)                               | 108/14  | 0.170                 | 0.083                    |
| BMI≥26 (yes/no)                                | 13/109  | 0.821                 | 0.751                    |
| Causes of liver diseases (HBV/other)           | 113/9   | 0.150                 | 0.419                    |
| Child Score (A/B)                              | 84/38   | 0.255                 | 0.389                    |
| Hemoglobin ≥120 g/L (yes/no)                   | 44/78   | 0.480                 | 0.766                    |
| Platelet ≥100*10^9/L (yes/no)                  | 40/74   | 0.194                 | 0.029                    |
| NLR≥4 (yes/no)                                 | 62/60   | 0.001                 | 0.001                    |
| AFP ≥400ng/ml (yes/no)                         | 52/70   | 0.014                 | 0.059                    |
| Tumor diameter (3-4/4-5)                       | 56/66   | 0.488                 | 0.296                    |
| Radical therapy (RFA/ Resection)               | 50/72   | 0.940                 | 0.629                    |
| Tumor location (center/edge)                   | 57/65   | 0.044                 | 0.358                    |
| Intra-operative blood loss≥400ml (yes/no)      | 38/84   | 0.029                 | 0.161                    |
| Histological grading (well/moderate/poor)      | 44/45/33| 0.001                 | 0.212                    |
| Microvascular invasion (yes/no)                | 40/82   | 0.001                 | 0.001                    |
NLR: Neutrophil-lymphocyte ratio; AFP: alpha-fetoprotein; BMI: body mass index; HBV: hepatitis B virus; M: male; F: female

**TABLE 6: Multivariate analyses contributing to overall survival and tumor-free survival rate.**

| Variables                              | Hazard ratio | 95% CI         | P-value |
|----------------------------------------|--------------|----------------|---------|
| **Prognostic factors for overall survival** |              |                |         |
| NLR≥4                                   | 1.453        | 1.072-2.287    | 0.020   |
| AFP ≥400ng/ml                           | 1.864        | 1.021-3.210    | 0.102   |
| Intra-operative blood loss≥400ml        | 1.219        | 0.829-2.083    | 0.398   |
| **Histological grading**               |              |                |         |
| Well                                    |              |                |         |
| Moderate                                | 2.211        | 1.806-3.127    | 0.046   |
| Poor                                    | 2.680        | 1.346-4.632    | 0.001   |
| Tumor located central                   | 1.458        | 1.091-1.762    | 0.469   |
| Microvascular invasion                  | 2.209        | 1.210-3.290    | 0.016   |
| Treatment modality (Resection/RFA)      | 1.542        | 1.105-3.026    | 0.895   |
| **Prognostic factors for tumor-free survival** | |                |         |
| Platelet ≥100*10^9/L                    | 1.782        | 1.142-2.891    | 0.142   |
| NLR≥4                                   | 1.374        | 1.201-2.347    | 0.001   |
| Microvascular invasion                  | 1.618        | 1.082-2.289    | 0.015   |
| Treatment modality (Resection/RFA)      | 1.762        | 1.052-2.217    | 0.651   |

NLR: Neutrophil-lymphocyte ratio; AFP: alpha-fetoprotein
Cox regression was used in multivariate analysis

**Abbreviations**

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ICU: Intensive care unit; NLR: Neutrophil-lymphocyte ratio; AFP: alpha-fetoprotein; BMI: body mass index; HBV: hepatitis B virus; M: man; F: female; HCC: Hepatocellular carcinoma, RFA: radiofrequency ablation, MELD: model for end-stage liver disease, HIFU: high-intensity focused ultrasound, LT: liver transplantation

Declarations

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Figures
Figure 1

Comparison of 1-, 3-, 5-year expected overall survival rates for the treatment of small liver cancer with diameter of 3-5 cm between the abdominal RFA and resection groups does not show significant difference: for the resection group, the values are, respectively, 94.4%, 77.8%, and 70.8%, and for the radiofrequency group, the values are 90%, 76%, and 68% (P=0.968).
Comparison of 1-, 3-, 5-year expected tumor-free survival rates for patients in resection group and radiofrequency group with respect to small liver cancer with diameter of 3-5 cm: for resection group, these values are, respectively, 87.5%, 62.5%, and 55.6%, and for the RFA group, these values are 88%, 68%, and 60% (P=0.620).

Figure 2