Comparison of open liver resection and RFA for the treatment of solitary 3-5 cm hepatocellular carcinoma: a retrospective study

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- Hepatocellular carcinoma, liver, resection, radiofrequency ablation
Abstract

Aim: The goal of this study was to compare the postoperative results of liver resection and radiofrequency ablation (RFA) for the treatment of small hepatocellular carcinoma (HCC) (3-5 cm).

Patients and methods: We retrospectively collected 122 patients with small solitary HCC treated at our center from Jan 2011 to Dec 2015, with diameters in the range of 3-5 cm. According to the treatment program received at our center, they were divided into the liver resection group (72 patients) and the RFA group (50 patients).

Result: In comparison with the RFA group, the resection group had a longer operative time, and greater intra-operative blood loss (P<0.01), more hepatic inflow occlusion, and longer postoperative hospital stay (P<0.01). The 1-, 3-, and 5-year expected overall survival rates and tumor-free survival rates were comparable between the 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 3-5 cm in diameter, RFA can achieve better in-hospital clinical results and similar long-term outcomes, and RFA can be considered for wide application, especially for central cases.

Introduction

Hepatocellular carcinoma (HCC) ranks No. 5 in the global incidence of malignant tumors, and HCC-related mortality rate ranks No. 3[1]. The burden imposed by the 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 not only removes the lesion but also removes the substrate for the growth of the tumor, and it is generally considered the most effective method[3]. Liver
resection and RFA are the main treatments for early HCC. The comparison of safety and effectiveness between liver resection and RFA has been the subject of strong 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 tumors with a diameter ≤3 cm, the long-term survival and tumor recurrence are similar[5]; for liver tumors with a diameter >5 cm, it is currently believed that RFA cannot achieve the effect of radical treatment[6]. However, for liver tumors with diameters of 3–5 cm, there is still considerable controversy on the effect of RFA[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 an issue that we must consider when selecting the treatment option. Therefore, this study was performed to comprehensively study the efficacy and safety of liver cancer (diameter 3–5 cm) treatment with liver resection and RFA using the data collected at our center.

Data And Methods

Patients

This retrospective study was performed after approval from the Ethics Committee of our Hospital. Written informed consent was obtained from the patient for the publication and any accompanying images and videos. We retrospectively collected all the liver cancer cases admitted to our hospital from Jan 2011 to Dec 2015, and these cases were screened according to the inclusion and exclusion criteria (shown in Table 1). In the end, we collected 122 patients for the grouped analysis in our study.

According to the treatment strategies received by the 122 patients, we divided them into the liver resection group and the RFA group. In particular, the liver resection group included 72 patients, and the RFA group included 50 patients. We compared the relevant
intra-operative data for the two groups: surgical time, blood loss due to hepatic portal occlusion, and transfusion rate; we also compared the relevant postoperative data: total days of hospitalization and total hospital expenses. The focus was the occurrence of postoperative complications; we used the Clavien evaluation system to assess the occurrence of postoperative complications. Finally, we focused on comparing the long-term tumor follow-up for the patients: 1-, 3-, and 5-year overall survival rates and tumor-free survival rates, and the recurrence and 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.

**Surgical procedures**

Surgery in our center is personally implemented by the chief physician or deputy chief physician who each have more than ten years of surgical experience. The choice between these two procedures (either liver resection or RFA) was made mainly on the basis of the location of the tumor, followed by the consideration of the preservation of hepatic function. Usually, when the shortest distance between the edge of the target and the edge of the liver was greater than 3 cm, the cases is considered a central case in our center, and RFA is recommended. To avoid migration, all surgical resection or RFA is performed by laparotomy. The resection is performed as other reports[10], with the clamp method or ultrasonic knife to implement the standard resection of a liver lobe or liver segment (anatomical resection) with hemihepatic vascular occlusion, and the resected section is at least 1–2 cm from the border of the tumor (R0). There was no intra-operative radiotherapy, and portal vein intubation chemotherapy was not used. During the surgery, we applied B-mode ultrasound at the same time intra-operative localization of the resection and examination after the resection. We treated our patients with RFA 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 after the ablation. All RFA cases were treated with a single needle and a single puncture on the liver surface. The duration of every RFA is determined by the size of the tumor and generally lasts at least 10 minutes. After the ablation, we used the intra-operative B-mode ultrasound to evaluate the range of ablation and the possible remaining tumor tissue, and before closing the abdomen, we again used B-mode ultrasound to inspect the whole liver to prevent the omission of lesions or incomplete ablation[11].

Follow-up
After the post-operative patients left the hospital, they visited our clinic on a regular basis: within three months after the surgery, they came to the clinic for relevant monthly follow-up examinations, including abdominal ultra-sonography, AFP testing, liver function testing, and regular blood examinations. In the third month after the surgery, we conducted routine enhanced CT scanning of the abdomen to further identify any recurrence of the tumor; during the period from three months to one year after the surgery, according to the pathological classification of the tumor and the condition of the patients, we conducted one re-examination every 2–3 months. More than one year after the surgery (postoperative observation occurred until death or loss to follow-up), we conducted re-examinations every 3–6 months. The re-examinations mainly consisted of imaging, followed by liver function tests, regular blood tests, and other relevant inspections. When the color ultra-sonography indicated suspected recurrence, we advised the patients to undergo enhanced CT or MRI scanning in combination with testing of the AFP level. If there was recurrence, we recommended the relevant treatment plan (e.g., re-resection, re-RFA, or intervention surgery) to the patients according to the basic condition of the patients, characteristics of the tumor, and other relevant factors[12].

Statistical analysis
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 the mean ± SD and were compared and calculated by using the non-parametric Wilcoxon test because some of the measurements did not have normal distributions. Categorical data are expressed as frequencies and were compared by using the Chi-squared test or Fisher’s exact test, as appropriate. Ranked data were compared by using the 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 the log-rank test. Univariate analysis was performed to identify factors predicting overall and tumor-free survival. All variables with P< 0.05 were included in the multivariate analysis to assess the independent predictive factors using Cox regression. Two-sided P values <0.05 were considered statistically significant. However, eventually, we must combine biological characteristics and common sense to determine the clinical significance.

Results

Clinical and pathological characteristics

According to the comparison in Table 2, we found no significant difference in the demographic baseline characteristics of the 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 was not statistically significant. Regarding the comparison of cancer characteristics, the cases incorporated into our analysis are all single lesions. Our comparison indicates that the tumor diameter for the RFA group was slightly larger than the tumor diameter for the resection group (3.8 vs. 3.7 cm), but this difference was not statistically significant (P = 0.528). Regarding the position of the tumor in the liver, for the resection group, the tumor was located on the
edge in 53 cases (73.6%), while for the RFA group, there were only 12 cases (24.0%) in which the tumor was 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.

Intraoperative and short-term outcomes

As shown in Table 3, we compared the relevant intra-operative and post-operative data for the resection group and RFA group. The operative time of the resection group was significantly longer than that of the RFA group (4.0 vs. 2.7 h, P<0.001). The intra-operative blood loss was significantly greater for the resection group than for 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 that of the RFA group (P<0.001). We also found that the average hospital stay of the resection group was 6.3 days, which was 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 patients with complications, for a total occurrence rate of complications of 25%; in the RFA group, there were 8 patients with complications, and the total occurrence rate of complications was 16%. Although the occurrence rate of complications for the resection group was higher than that 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.

**Long-term outcome**

During the follow-up period, the 1-, 3-, and 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. The differences were not statistically significant (P = 0.968). The 1-, 3-, and 5-year expected tumor-free survival rates were 87.5%, 62.5%, and 55.6% vs 88%, 68%, and 60% in the resection and RFA groups, respectively. As shown in Figure 2, the difference between the two groups was also not statistically significant (P = 0.620).

During the follow-up period, 41 patients died and 52 patients experienced HCC recurrence. The most common recurrence or metastasis location of postoperative tumors was the liver (55%). Extrahepatic recurrence and metastasis occurred mostly in the lung (30%), followed by intra-abdominal metastasis (7.5%); bone metastasis was rare (5%), as was metastasis to other parts of the body (2.5%). The most common treatment for tumor recurrence was 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), and radiotherapy (1 case)} were rare. The most common factor causing the death of patients during the postoperative follow-up period was tumor recurrence and metastasis (78%), followed by liver function failure (19.5%); other causes were rare (2.4%).

**Univariate and multivariate analysis**

As shown in Table 5, univariate analysis identified the pre-operative neutrophil-lymphocyte ratio (NLR) $\geq$4 (P<0.001), AFP $\geq$400 ng/ml (P = 0.014), intra-operative blood loss $\geq$400 ml (P = 0.029), poor histological grade (P<0.029), central tumor location (P = 0.044), and microvascular invasion (P<0.001) as significant factors contributing to overall survival after the operation. Multivariate analysis of the five factors found to be
significant in univariate analysis further identified NLR≥4 (P = 0.020) and poor histological grade (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 shown in Table 5, univariate analysis identified pre-operative platelet counts <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, and 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 liver condition and function, postoperative complications also need to be taken into account. RFA surgery is a relatively safe treatment approach, but the stability and thoroughness of RFA for treating liver cancer are difficult to determine[13, 14]. Although the evaluation of effectiveness between the two approaches is still under debate, in Western countries, especially in the United States, the treatment guidelines for liver cancer consistently recommend surgical resection for early liver cancer if the liver function allows it and if there is not high vein pressure[15]. However, the guidelines also mention that due to the nearly 3% mortality rate after liver resection surgery, the use of other therapies to treat small liver tumors may be appropriate, of which ablation treatment is preferred. At present, the relevant mature ablation treatment method is RFA. 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, we believe that the effect of RFA depends on the maximum
diameter of the tumor. Current studies mostly define the gold standard for RFA to be smaller than 2.3–3 cm. For a single tumor with a diameter smaller than 3 cm, RFA can achieve similar results to resection, and the safety of the patient is ensured[16-18]. However, for a tumor with a diameter in excess of 5 cm, 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 that is 3–5 cm in diameter, and for these tumors, the treatment effectiveness of RFA and resection remain to be further investigated. Our study was conducted 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 RFA 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 in the left lateral lobe; in contrast, RFA ablation is prone to injuring other surrounding tissues, such as the stomach or colon[6]. In addition, the implementation of RFA for peripheral small liver tumors is more prone to cause tumor rupture and result in metastasis[4, 19]. When the tumor is located in the center of the liver, however, especially at the junction of the donor in segments V, VI, VII, and VIII of the right side of the liver, liver resection will result in the loss of a large amount of normal liver tissue, leaving too small a volume in the residual liver[19]. Because most of the liver is often cirrhotic in these patients, postoperative liver function cannot satisfy 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 poor 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, the surrounding tissue and the
background liver condition to achieve better results.

Although a 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 the two groups. Because the trauma of resection is relatively great, 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 ischemia-reperfusion.

However, in our analysis and comparison, although the intra-operative time was short, the blood loss during surgery was small, and the postoperative hospital stay was short, there was still a significant difference between the total treatment expense in the RFA group and the resection group, mainly because the domestic hospitals usually use imported RFA needles. The RFA needle costs nearly 10,000 RMB Yuan, which accounts for most of the treatment cost of the RFA treatment, whereas the overall expense of surgical resection is low. Hence, there was no difference in the total treatment expense between the resection group and the RFA group. Through the observation of postoperative complications, we found that although the occurrence rate of postoperative complications and the occurrence rate of serious complications were both higher in patients in the resection group 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 underwent abdominal surgery. Therefore, in comparison with other statistical analyses, our data are more objective and accurate. However, this topic still needs a multi-center randomized comparison and a large sample to further explore the occurrence of postoperative complications for the two methods.

Our analysis indicates that the postoperative 1-, 3-, and 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 a similar result to resection for liver tumors smaller than 2 cm but also for liver tumors that are 2-5 cm in diameter; their observations extended up to 10 years[20]. Meanwhile, our univariate and multivariate analyses of the factors contributing to the overall survival and tumor-free survival rates indicated that resection or RFA did not contribute to overall survival or tumor-free survival. Our study again corroborates this point.

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

Conclusion

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

Abbreviations

ICU: Intensive care unit; NLR: Neutrophil-lymphocyte ratio; AFP: alpha-fetoprotein; BMI:
Declarations

Ethics approval and consent to participate:
This retrospective study was performed after approval from the Ethics Committee of West China Hospital of Sichuan University. Written informed consent was obtained from the patient for the publication and any accompanying images and videos.

Consent to publish:
All authors have read and approved the manuscript.

Availability of data and materials:
All of the raw data and materials can be got from sending E-mail to the corresponding author (ljydoctor11@163.com).

Competing interest:
No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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Authors Contributions:
Lei Jianyong and Li Dajiang collected the clinical data, Wang Wentao and Yan Lunan done the surgery.

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Tables

Table 1. **Main inclusion/exclusion criteria of the study**

| Inclusion criteria                                                                 |
|-----------------------------------------------------------------------------------|
| Single tumor                                                                      |
| 3 cm \(\leq\) diameter of tumor < 5 cm                                            |
| ECOG score 0-1                                                                    |
| Liver function of grade Child A or B                                              |
| Receiving the first treatment in our center: liver resection or RFA               |
| All cases were accomplished with laparotomy                                       |
| Able to receive the complete postoperative regular follow-up visit or inspection |

| Exclusion criteria                                                                 |
|-----------------------------------------------------------------------------------|
| Tumor thrombus in major vessels                                                   |
| Multiple tumors, or distant metastasis                                           |
| The heart and lung function of the patients cannot tolerate surgical treatment    |
| Cannot take the surgery due to other diseases                                     |
| Cases with preoperative intervention of HIFU knife on the lesion or other preoperative relevant downgrade treatment |
| Liver function at level C (patients achieving levels A or B after liver-protection treatment can be incorporated) |
| 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 |
|--------------------------|-----------------------|-----------|---------|
| 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/m²)              | 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) | 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)      | 4.1±1.2               | 4.1±1.2   | 0.411   |
| Preoperative AFP level (ng/ml) | 3.9±1.5       | 3.8±0.5   | 0.528   |
| Preoperative AFP (-/++/+++/++++) | 3.7±0.5      | 4716.6±14813.6 | 0.725 |
| Degree of tumor differentiation (low/moderate/high) | 3781.9±14 | 19/8/8/15 | 0.444   |
| Tumor location (edge/center) | 105.9           |           |         |
| Microvascular invasion (yes/no) | 33/10/10/1 | 16/19/15 | 0.116   |
|                           |                       | 9         | 0.000   |
|                           |                       | 12/38     |         |
|                           |                       | 17/33     | 0.813   |
|                           |                       | 53/19     |         |
|                           |                       | 23/49     |         |

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      |
| Intra-operative blood loss (ml)| 364.6±180.1     | 102.0±105.9 | .00     |
| Intra-operative transfusion (Yes/No) | 9/63          | 3/47      | 1       |
| Hepatic inflow occlusion (whole liver/half liver/non-blocking) | 9/36/27       | 2/4/44    | <0     |
| ICU care (Yes/No)              | 5/67            | 3/47      | 1       |
| Total number of days in hospital | 6.3±2.2       | 4.7±1.8   | 0.2    |
| Total cost of hospitalization (RMB Yuan) | 35542±2456.9 | 33453.2±1986.6 | <0 |

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).
TABLE 5: Univariate analyses contributing to overall survival and tumor-free survival rate after RFA or Resection.

| Condition                                      | Resection group | RFA group |
|------------------------------------------------|----------------|-----------|
| **Clavien level I (without drugs, conservative treatment)** |                |           |
| Incision fat liquefaction                      | 2              | 1         |
| Wound infection                                | 2              | 1         |
| Pleural effusion                               | 2              | 0         |
| Biliary fistula                                | 5 (6.9%)       | 2 (4%)    |
| **Clavien level II (simple medicine treatment)** |                |           |
| Wound infection                                | 2              | 1         |
| Postoperative pulmonary infection               | 1 (1.4%)       | 0 (0%)    |
| **Clavien level IIIa (therapeutic operation under local anesthesia)** |                |           |
| Pleural effusion                               | 2 (2.8%)       | 1 (2%)    |
| **Clavien level IIIb (operational treatment under general anesthesia)** |                |           |
| Abdominal hemorrhage                           | 1 (1.4%)       | 0 (0%)    |
| Biloma                                         | 1              | 0         |
| **Clavien level IVa (single organ function failure)** |                |           |
| Respiratory failure                            | 1              | 0         |
| Liver failure                                  | 1 (1.4%)       | 0 (0%)    |
| **Clavien level IVb (multiple organ failure)**  |                |           |
| Hepatorenal syndrome                           | 0 (0%)         | 0         |
| **Clavien level V (death)**                    |                |           |
| Septic shock                                   | 0 (0%)         | 0         |
| 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                    |
| Intra-operative blood loss≥400ml (yes/no)| 57/65   | 0.044                 | 0.358                    |
| Histological grading (well/moderate/poor)| 38/84   | 0.029                 | 0.161                    |
| 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 (yes/no)| 1.219        | 0.829-2.083  | 0.398   |
| Histological grading (well/moderate/poor)|              |              |         |
| Well                                     | 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

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