

Long-Term Outcome of No-Touch Radiofrequency Ablation for Treating AFP-Positive Small Hepatocellular Carcinoma

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Objective: This study aimed to evaluate the short- and long-term efficacy of no-touch radiofrequency ablation (NT-RFA) in treating patients with AFP-positive, solitary hepatocellular carcinoma (HCC) with a diameter of ≤ 3 cm, and to assess its effect on AFP levels.

Methods: A retrospective analysis was conducted on 245 AFP-positive HCC patients treated with NT-RFA (n=78) and Conventional RFA (C-RFA) (n=167) at our center between 2015 and 2023. The changes of AFP levels were compared. Statistical analysis was conducted on the overall survival(OS), recurrence free survival(RFS), and tumor recurrence status of the two groups at 1 to 5-years post-RFA.

Results: The decrease in postoperative AFP levels was significantly greater in the NT-RFA group than that in the C-RFA group (P=0.009), and the postoperative AFP seronegative rate in the NT-RFA group was significantly higher than that in the C-RFA group (P=0.020). The OS rates at 1-, 3-, and 5-years were 100.00%, 71.07%, and 54.07% for NT-RFA group, while 95.21%, 62.06%, and 30.80% for C-RFA group. Significant differences existed between the two groups (P=0.026). The 1-, 3-, and 5-year RFS rates in the NT-RFA group were 79.49%, 46.36%, and 29.96%, while 65.87%, 30.99%, and 21.20% in the C-RFA group. Significant differences existed between the two groups (P=0.025). The 1-, 3-, and 5-year local tumor progression-free survival (LTP-FS) rates were 89.67%, 83.31%, 81.06% in the NT-RFA group and 79.01%, 64.61%, 63.10% in the C-RFA group. Significant differences existed between the two groups (P=0.002). But there was no significant difference in intrahepatic distant recurrence-free survival (IDR-FS) between the two groups (P=0.819).

Conclusion: Compared with C-RFA, NT-RFA treatment for AFP positive HCC ≤ 3 cm is more effective in reducing postoperative AFP levels and improving the rate of AFP conversion to negative. Meanwhile, NT-RFA significantly increased RFS and OS. It can replace C-RFA as the primary treatment method for AFP-positive small HCC.

Keywords: hepatocellular carcinoma, radiofrequency ablation, no-touch, alpha-fetoprotein, survival rate

Introduction

Alpha-fetoprotein (AFP) serves as the most classic serum biomarker for hepatocellular carcinoma (HCC), occupying a central role in the diagnosis, treatment efficacy assessment, and prognosis evaluation of HCC.¹⁻³ Extensive clinical evidence indicates that AFP-positive HCC patients typically exhibit greater tumor biological aggressiveness, manifested as more active tumor cell proliferation, higher microvascular invasion (MVI) rates, and significantly poorer long-term survival outcomes.^{4,5} Data confirm that patients with AFP levels ≥ 400 ng/mL face a postoperative recurrence risk over 2.3 times higher than those with normal AFP levels. Elevated AFP is also strongly associated with adverse pathological features such as tumor multicentric origin and early intrahepatic metastasis.^{6,7} As one of the curative treatments for HCC,

radiofrequency ablation (RFA) yields suboptimal long-term efficacy for these invasive AFP-positive HCC,^{8–10} facing critical challenges such as high local recurrence rates and low AFP conversion rates.^{11,12}

In recent years, “no-touch” RFA (NT-RFA) technology has gradually been adopted in clinical practice. The advantage of this technique lies in avoiding the risk of iatrogenic tumor cell dissemination that may result from direct puncture of the tumor lesion, while also facilitating the achievement of a sufficient and uniform ablation safety margin (SM). This is crucial for eliminating potential microsatellite foci and MVI within the peritumoral liver tissue.¹³ Multiple studies have confirmed that NT-RFA effectively reduces the local tumor progression (LTP) rate in both primary and recurrent HCC.^{14,15} Given that AFP levels reflect not only tumor burden but also serve as a sensitive indicator of tumor cell activity, invasiveness, and potential intrahepatic metastatic tendency,^{16,17} a critical clinical-scientific question arises: Can NT-RFA, leveraging its “no-touch” tumor principle and superior local ablation efficacy, effectively induce postoperative serum AFP decline or even seroconversion in AFP-positive HCC patients, thereby significantly improving long-term outcomes for this population?

Given the indicative value of AFP on long-term outcomes following HCC treatment, this study aims to select AFP-positive HCC cases treated with either NT-RFA or conventional RFA (C-RFA) as subjects. Through long-term follow-up, we will compare the long-term efficacy of both treatment methods to evaluate whether NT-RFA can effectively improve the long-term prognosis of AFP-positive HCC patients. Concurrently, by comparing changes in preoperative and postoperative AFP levels between the two treatment methods, we will evaluate whether NT-RFA can more effectively reduce AFP levels.

Patients and Methods

Patients Inclusion

This retrospective, single center study screened AFP-positive HCC patients who underwent RFA treatment at First Affiliated Hospital of Army Medical University from September 2015 to December 2023. Initial screening identified 256 cases (82 in the NT-RFA group and 174 in the C-RFA group). After applying inclusion and exclusion criteria, 245 cases were ultimately enrolled (78 in the NT-RFA group and 167 in the C-RFA group, [Figure 1](#)). All patients had no absolute contraindications for RFA, voluntarily selected their treatment modality. This study was approved by the Ethics

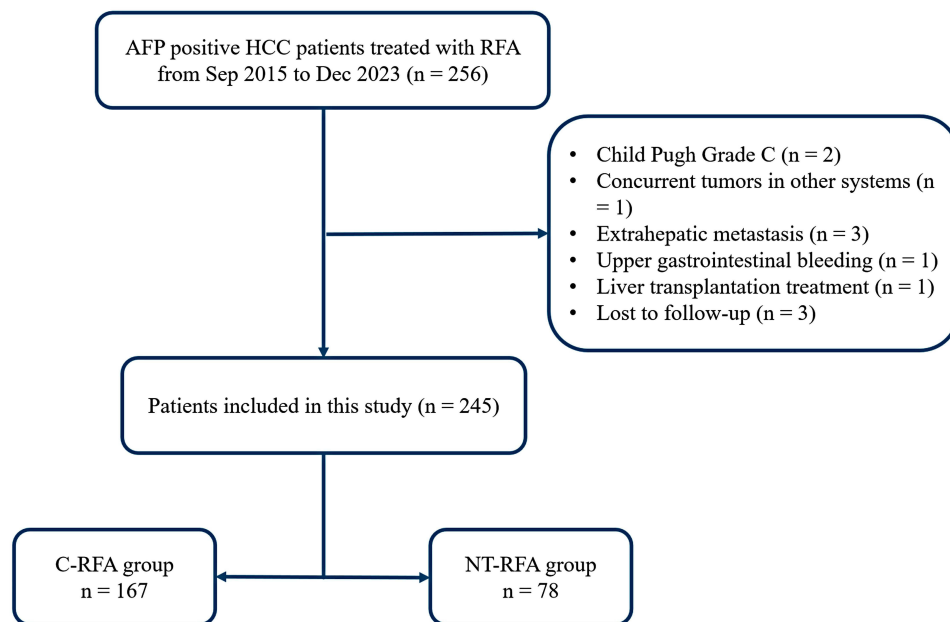


Figure 1 Patient selection process.

Committee of Southwest Hospital of Army Medical University (Approval No.: KY2024183). Due to the retrospective nature of this study, the committee waived the informed consent.

Inclusion and Exclusion Criteria

Inclusion Criteria: 1) HCC was diagnosed by Chinese Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2022 Edition);¹⁸ 2) Single lesion with diameter ≤ 3 cm; 3) AFP > 20 ng/mL and detected within 72 hours prior to RFA treatment; 4) Tumor has not invaded the portal vein or main trunk/secondary branches of the hepatic veins; 5) Child-Pugh grade A/B, ECOG performance status score of 0–1; 6) No severe coagulation disorders (platelet count $>30 \times 10^9/L$, prothrombin time prolongation <4 seconds or INR <1.5).

Exclusion Criteria: 1) Concurrent extrahepatic metastasis, lymph node metastasis, or tumors in other systems; 2) Receiving liver transplantation preoperatively or postoperatively; 3) Liver function Child-Pugh grade C, or gastrointestinal bleeding; 4) Patients lost to follow-up.

Equipments and Materials

RFA Equipment: Multipolar Radiofrequency Generator (LDRF-120S, Lead Electron Corporation, Mianyang, China), Internally Cooled Wet Electrode (LDDJS1-0200200, Lead Electron Corporation, Mianyang, China), Ultrasonic scanning equipment (EUB-405, Hitachi, Japan).

AFP Detection System: Fully Automated Chemiluminescent Immunoassay Analyzer (Alinity i-series, Abbott, USA), with Chemiluminescent Microparticle Immunoassay Kit (Abbott, Ireland Diagnostics Division).

C-RFA and NT-RFA Procedures

Patients were required to fast for 8 hours before the procedure. Positioned supine or on the left side, the procedure was performed under anesthesia monitoring by three senior hepatobiliary surgeons from our center (with cumulative RFA experience exceeding 1000 cases). The location of the lesion and its maximum cross-section were first identified using ultrasound scanner, and the optimal needle insertion path was selected, with the insertion site being marked. The local anesthesia was performed using 2% lidocaine that was injected subcutaneously.

For C-RFA, 1 or 2 electrodes were directly inserted into the lesion. The ablation power was set at 120W and maintained until maximum impedance was reached, which marked the end of one treatment session. The procedure could be repeated, with real-time ultrasound monitoring until the lesion area was covered by a hyperechoic zone.

For NT-RFA, two single-needle electrodes were inserted into the tumor-free areas on both sides of the lesion's maximum cross-section under ultrasound scanner. The distance between the electrodes could be adjusted based on tumor size, with the same ablation time and power as in C-RFA. During the procedure, the electrode positions could be adjusted based on the severity of the lesion, and multiple ablations were performed; however, the electrodes could not be inserted directly into the lesion.

No matter in NT-RFA or C-RFA, track ablation was performed to achieve hemostasis upon electrode withdrawal. Vital signs were monitored in real-time during the procedure. Contrast-enhanced ultrasound was performed 20 minutes postoperatively to determine whether there were residual lesions. Any residual lesions were immediately treated by repeating the procedure until complete ablation was achieved.

RFA Efficacy Evaluation

Short-term efficacy is evaluated in terms of both ablation efficiency and safety. Operation time and the number of ablation sessions reflect the efficiency of the procedure. On the first postoperative day, AFP, liver function, coagulation function, and complete blood count were rechecked. On the third postoperative day, contrast-enhanced ultrasound was performed to confirm the absence of residual lesions, and the ablation range (AR, the maximum cross-sectional area) and the safety margin (SM, the minimum distance that the ablation zone extended beyond the original lesion boundary) were also measured. AR and SM were used to evaluate the efficacy of ablation, while the safety of the two groups was assessed by monitoring postoperative complications and length of hospital stay.

Follow-Up

All patients were followed up regularly at the outpatient clinic (1 month postoperatively, then every 2 months during the first year, and every 3 months thereafter). Routine follow-up indicators included AFP and HBV-DNA, and imaging examination (contrast-enhanced ultrasound, contrast-enhanced CT or MRI) were performed. Recurrence-free survival (RFS) time and overall survival (OS) time were recorded, and RFS rates and OS rates were calculated. Local tumor progression (LTP) or intrahepatic distant recurrence (IDR) were discriminated based on comparing the new and old lesion location. Information on retreatment after recurrence and causes of death was also collected.

Statistical Analysis

Categorical data are expressed as frequencies and percentages. Comparisons between groups were performed using the Pearson's chi-square test. Quantitative data with normal distribution were expressed as mean \pm standard deviation ($\bar{x} \pm SD$), and intergroup comparisons were performed using the independent samples *t*-test. Data not normally distributed were expressed as median (interquartile range) [M (Q1, Q3)], and intergroup comparisons were performed using the Mann-Whitney *U*-test. Kaplan-Meier methods were used to plot cumulative incidence curves for OS, RFS, LTP-free survival (LTP-FS) and IDR-free survival (IDR-FS). Survival curves between groups were compared using the Log rank test. Univariate and multivariate analyses were performed by employing Cox proportional hazards regression models. Variables with $P < 0.05$ in univariate analysis were included in multivariate analysis to identify independent risk factors for RFS. Factor correlation is represented by HR (95% CI), with $HR > 1$ indicating a risk factor and $HR < 1$ indicating a protective factor. All hypothesis tests were two-sided, with $P < 0.05$ considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 19.0 software.

Results

Basic Clinical Information

By applying inclusion and exclusion criteria, 245 cases were ultimately enrolled in this study, with 78 in the NT-RFA group and 167 in the C-RFA group (Figure 1). Among the included patients, 198 were male (80.8%) and 47 were female (19.2%), with a male-to-female ratio of 4.2:1. The mean age in the NT-RFA group was 52.77 ± 10.05 years, comprising 65 males and 13 females. The C-RFA group had a mean age of 51.43 ± 10.68 years, comprising 133 males and 34 females.

Preoperative AFP levels within 3 days prior to surgery were > 200 ng/mL in 106 cases (41 in the NT-RFA group, 65 in the C-RFA group). The median preoperative AFP in the NT-RFA group was 221.08 (75.8, 556) ng/mL, while the C-RFA group was 123.00 (56.8, 334) ng/mL. The difference between groups was statistically significant ($P=0.045$). No significant differences were observed between groups for other preoperative indicators such as liver function, coagulation function, or lesion diameter (Table 1), indicating comparable baseline characteristics.

Short-Term Outcomes

All included cases achieved complete ablation on imaging during the same hospitalization. Among these, 19 cases underwent two ablation procedures (5 in the NT-RFA group, 6.41%; 14 in the C-RFA group, 8.38%), with no significant difference between the two groups ($P=0.591$). The NT-RFA group demonstrated significantly superior mean AR ($P<0.001$) and SM ($P=0.001$) compared to the C-RFA group. A total of 43 postoperative complications occurred across both groups (11 in the NT-RFA group, 14.1%; 32 in the C-RFA group, 19.2%), and all classified as Clavien-Dindo grade I-II¹⁹ (34 grade I, 9 grade II). No grade III or higher severe complications or in-hospital deaths occurred. The difference in complication rates between groups was not statistically significant ($P=0.332$). These results indicate that NT-RFA demonstrates good safety and efficacy (Table 2).

Survival Outcomes

The OS duration in the NT-RFA group ranged from 12 to 72 months, with a median survival of 59 months. The 1- to 5-year OS rates were 100.00%, 92.11%, 71.07%, 58.52%, and 54.07%, respectively. In contrast, the C-RFA group

Table 1 Basic Clinical Data of Two Groups

| Category | NT-RFA Group (n=78) | C-RFA Group (n=167) | χ^2/t | P value |
|------------------------------------|------------------------|-------------------------|------------|--------------------|
| Sex (Male/Female) | 65/13 | 133/34 | 0.468 | 0.494 |
| Age (years) | 52.77±10.05 (36–76) | 51.43±10.68 (24–82) | 0.931 | 0.353 |
| Viral infection (no/HBV or HCV) | 7/71 | 9/158 | 1.120 | 0.290 |
| Child–Pugh grade (A/B) | 70/8 | 160/7 | 3.161 | 0.085 |
| Tumor size (mm) | 18.63±5.23 (6–30) | 18.54±5.42 (7–30) | 0.113 | 0.910 |
| Cirrhosis (no/yes) | 12/66 | 25/142 | 0.007 | 0.933 |
| ALT (U/L) | 41.99±38.84 (3.5–197) | 37.17±29.58 (6.6–215.8) | 1.072 | 0.285 |
| Serum albumin (g/L) | 41.38±5.02 (28.5–52.2) | 41.27±5.62 (26.7–54.6) | 0.149 | 0.881 |
| γ -GT (U/L) | 91.15±111.23 (11–665) | 114.31±167.85 (11–1496) | 1.110 | 0.268 |
| Total bilirubin (umol/L) | 21.26±12.73 (8.5–96.3) | 19.57±9.47 (5.8–58) | 1.162 | 0.246 |
| Platelet count ($\times 10^9/L$) | 111.47±48.45 (32–217) | 113.69±47.74 (37–277) | 0.337 | 0.737 |
| Prothrombin time (s) | 12.92±1.48 (10–18) | 12.98±1.46 (10.4–17.5) | 0.289 | 0.773 |
| Preoperative AFP level (ng/mL) | 221.08 (75.8, 556) | 123.00 (56.8, 334) | 2.342 | 0.019 [▲] |
| HBV-DNA (positive/negative)* | 15/63 | 31/136 | 0.016 | 0.901 |

Notes: *means HBV-DNA>1000cps/mL was considered positive. [▲]The preoperative AFP level in the NT-RFA group was significantly higher than that in the C-RFA group. Independent sample t test for continuous variables and Pearson chi-square test for discrete variables.

Table 2 Short-Term Outcomes of Two Groups

| Category | NT-RFA Group (n=78) | C-RFA Group (n=167) | χ^2/t | P value |
|-----------------------------------|-------------------------|------------------------|------------|--------------------|
| Operation time (min) | 6.04±1.53 (2–10) | 5.88±1.71 (2–12) | 0.700 | 0.485 |
| Number of ablation (1/2 or above) | 73/5 | 153/14 | 0.289 | 0.591 |
| Ablation range (cm ²) | 15.19±4.42 (8.4–33) | 10.31±4.52 (1.3–24.84) | 7.937 | 0.000 [▲] |
| Safety margin (mm) | 10.56±4.25 (3.00–26.00) | 8.39±4.70 (1.00–21.00) | 3.470 | 0.001 [▲] |
| Complications (no/yes) | 67/11 | 135/32 | 0.940 | 0.332 |
| Length of hospital stay (days) | 8.08±4.12 (2–19) | 8.71±5.24 (2–49) | 0.934 | 0.351 |

Notes: [▲]There were significant differences in Ablation range and Safety margin between the two groups. Independent sample t test for continuous variables and Pearson chi-square test for discrete variables.

showed OS ranging from 8 to 75 months with a median survival of 49 months. The 1- to 5-year OS rates were 95.21%, 78.13%, 62.06%, 50.03%, and 30.80%, respectively. The difference between the two groups was statistically significant (P=0.026; Figure 2A).

The RFS of NT-RFA group ranged from 1 to 72 months, with a median RFS of 29 months. The 1- to 5-year RFS rates were 79.49%, 56.95%, 46.36%, 33.29%, and 29.96%, respectively. While the C-RFA group had RFS ranging from 1 to 78 months, with a median RFS of 19 months. The 1- to 5-year RFS rates were 65.87%, 42.15%, 30.99%, 23.77%, and 21.20%, respectively. The RFS rates in the NT-RFA group was significantly higher than that in the C-RFA group (P=0.025; Figure 2B).

Changes in AFP Levels

The preoperative AFP levels in the NT-RFA group were significantly higher than those in the C-RFA group (P=0.019), and the proportion of cases with AFP \geq 200 ng/mL in the NT-RFA group was significantly higher than that in the C-RFA group (P=0.045). However, postoperative mean AFP levels (P=0.908) and the number of cases with AFP \geq 200 ng/mL showed no significant differences between the two groups (P=0.598). Thus, the postoperative decrease in AFP was significantly greater in the NT-RFA group than in the C-RFA group (P=0.009).

Furthermore, the overall AFP negativity rate was significantly higher in the NT-RFA group (39.74%) compared to the C-RFA group (25.15%) (P=0.020). Notably, 61 cases exhibited postoperative AFP elevation rather than reduction, with 49 cases (26.35%) in the C-RFA group significantly exceeding the 12 cases (15.38%) in the NT-RFA group (P=0.019).

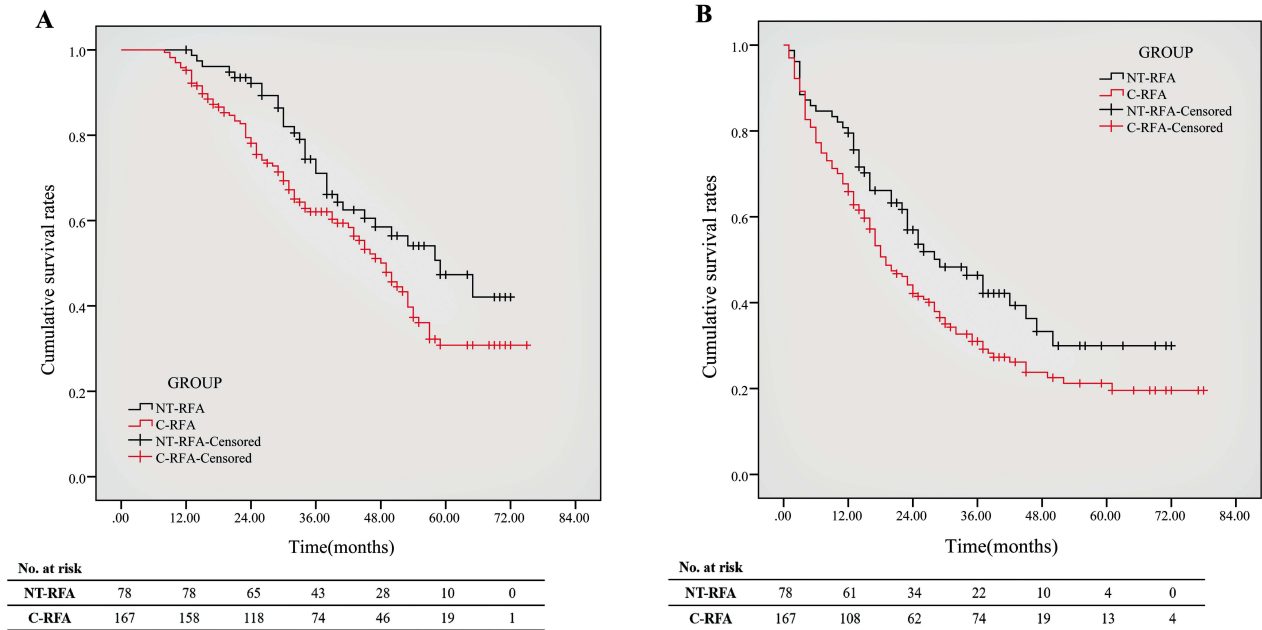


Figure 2 OS and RFS curves for NT-RFA group vs. C-RFA group. **(A)** Cumulative OS rates in NT-RFA group (n=78) and C-RFA group (n=167). There was a significant difference between the two groups ($\chi^2=4.960$, $P=0.026$, Log rank test); **(B)** Cumulative RFS rates in the two groups. There was a significant difference between the two groups ($\chi^2=5.026$, $P=0.025$, Log rank test).

This indicates that NT-RFA more effectively reduces serum AFP levels in AFP-positive patients, potentially supporting improved patient outcomes (Table 3).

HCC Recurrence

During follow-up, a total of 163 patients (66.53%) were diagnosed with recurrent HCC, including 44 cases (56.41%) in the NT-RFA group and 119 cases (71.26%) in the C-RFA group, with a significant difference between the two groups ($P=0.022$). Among these, 70 cases were classified as LTP (13 in the NT-RFA group and 57 in the C-RFA group), with a statistically significant difference between groups ($P=0.005$). The 1- to 5-year LTP-FS rates in the NT-RFA group were 89.67%, 85.12%, 83.31%, 81.06%, and 81.06%, while 79.01%, 65.36%, 64.61%, 63.10%, and 63.10% in the C-RFA group, with a statistically significant difference between groups ($P=0.002$; Figure 3A).

A total of 93 patients experienced IDR (31 in the NT-RFA group and 62 in the C-RFA group), with no significant difference between groups ($P=0.565$). The 1- to 5-year IDR-FS rates in the NT-RFA group were 89.74%, 75.32%,

Table 3 Analysis of Changes in AFP Levels

| Category | | NT-RFA Group (n=78) | C-RFA Group (n=167) | χ^2/Z | P value |
|--------------------------------------|---------------|---------------------|---------------------|------------|--------------------|
| Average AFP level (ng/mL) | Preoperative | 221.08 (75.8, 556) | 123.00 (56.8, 334) | 2.342 | 0.019 [▲] |
| | Postoperative | 101.59 (15.2, 290) | 60.69 (20.3, 229) | 0.116 | 0.908 |
| AFP (<200/≥200ng/mL) | Preoperative | 37/41 | 102/65 | 4.031 | 0.045 [▲] |
| | Postoperative | 53/25 | 119/48 | 0.278 | 0.598 |
| AFP turned negative* (yes/no) | | 31/47 | 42/125 | 5.413 | 0.020 [▲] |
| Postoperative AFP elevation (yes/no) | | 12/66 | 49/118 | 5.539 | 0.019 [▲] |
| AFP change amplitude (ng/mL) | | 74.2 (13.5, 267) | 27.9 (-13.71, 144) | 2.627 | 0.009 [▲] |

Notes: * means Postoperative AFP < 20 ng/ml was considered AFP turned negative. [▲] indicates statistical significance ($P < 0.05$). AFP data, being non-normally distributed, were analyzed using the Mann-Whitney U-test. Non-continuous variables were assessed using Pearson chi-square test.

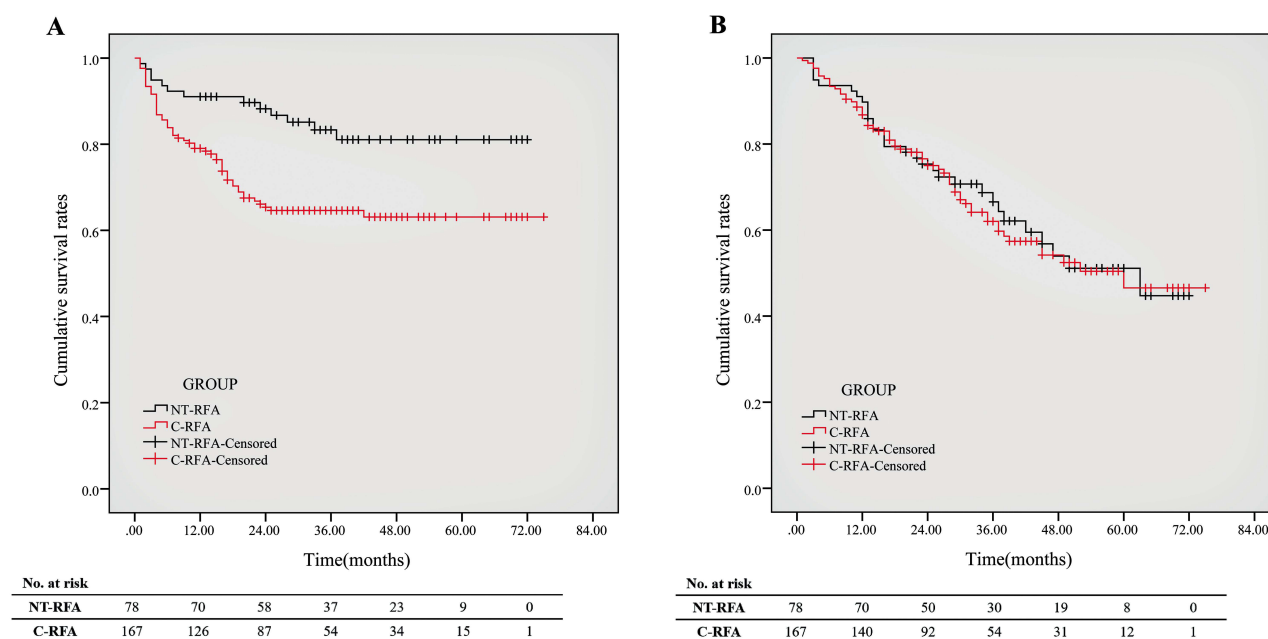


Figure 3 LTP-FS and IDR-FS curves for NT-RFA group vs. C-RFA group. **(A)** Cumulative LTP-FS rates for NT-RFA group and C-RFA group; significant differences existed between groups ($\chi^2=9.706$, $P=0.002$, Log rank test); **(B)** Cumulative IDR-FS rates in NT-RFA group and C-RFA group; no significant differences were observed between groups ($\chi^2=0.052$, $P=0.819$, Log rank test).

66.54%, 53.97%, and 51.13%, while 86.77%, 74.98%, 62.03%, 54.20%, and 46.56% in the C-RFA group. Differences between groups were not statistically significant ($P=0.819$; Figure 3B).

Risk Factors for RFS

Univariate analysis revealed seven factors significantly associated with RFS: hepatitis virus infection, cirrhosis, lesion diameter > 2 cm, SM < 5 mm, preoperative AFP \geq 200 ng/mL, postoperative AFP \geq 200 ng/mL, and the NT-RFA. Multivariate analysis revealed four independent significant factors influencing RFS: lesion diameter > 2 cm, SM < 5 mm, postoperative AFP \geq 200 ng/mL, and the NT-RFA (Table 4). Notably, NT-RFA emerged as a crucial protective factor for RFS.

Discussion

AFP levels, the most classic serum biomarker for HCC, exhibit a strong correlation with tumor biological behavior. While current research on ablation therapy for AFP-positive HCC primarily emphasizes the diagnostic utility and prognostic evaluation value of AFP,^{20,21} investigations into the impact of different treatment modalities on pre- and post-treatment AFP dynamics, as well as the clinical relevance between AFP dynamics and long-term survival outcomes, remain severely inadequate. The biological characteristics of AFP confer its unique position in HCC treatment. Not only AFP is secreted by HCC cells, with its levels directly correlating to tumor burden and invasive capacity, but it also reflects the malignant transformation potential of the hepatic microenvironment. Even in small HCCs, AFP positivity indicates a higher risk of recurrence.²² RFA, one of the definitive treatments for HCC, also carries a high risk of recurrence when used for AFP-positive HCC, and this recurrence risk is positively correlated with AFP concentration.⁸ This stems from the limited ablation range achieved by C-RFA, which results in residual tumor tissue and consequently affects AFP conversion rates.²³ Moreover, C-RFA directly punctures the tumor lesion, violating the principle of tumor-free and potentially facilitating tumor dissemination and metastasis. NT-RFA technology improves upon C-RFA by modifying the needle placement technique, thereby offering a new pathway to enhance AFP conversion rates and improve prognosis.²⁴ Numerous studies have confirmed that this technique improves RFS in HCC, but it cannot improve the OS.^{25,26} Two previous studies at our center have also reached the same conclusion.^{13,27} Therefore, we further explore the population of HCC patients who can benefit significantly from

Table 4 Univariate and Multivariate Analyses Influencing RFS

| Variables | Univariate Analysis | | Multivariate Analysis | |
|-------------------------------|---------------------|--------------------|-----------------------|--------------------|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| Viral infection (yes) | 2.697 (1.192–6.105) | 0.013 [▲] | 1.748 (0.742–4.120) | 0.202 |
| Child–Pugh grade B | 0.671 (0.342–1.314) | 0.241 | | |
| Tumor size>2cm | 2.023 (1.486–2.756) | 0.000 [▲] | 1.729 (1.251–2.390) | 0.000 [▲] |
| Cirrhosis (yes) | 1.928 (1.218–3.052) | 0.004 [▲] | 1.541 (0.940–2.527) | 0.087 |
| Safety margin<5mm | 1.870 (1.368–2.555) | 0.000 [▲] | 1.857 (1.332–2.590) | 0.001 [▲] |
| ALT>40U/L | 0.969 (0.694–1.352) | 0.854 | | |
| Total bilirubin>17.1umol/L | 0.977 (0.718–1.328) | 0.881 | | |
| Preoperative AFP (≥200ng/mL) | 1.365 (1.003–1.857) | 0.047 [▲] | 1.051 (0.728–1.515) | 0.791 |
| Postoperative AFP (≥200ng/mL) | 1.688 (1.231–2.316) | 0.001 [▲] | 1.465 (1.010–2.125) | 0.044 [▲] |
| HBV-DNA (positive) | 0.973 (0.703–1.347) | 0.869 | | |
| Treatment method (NT-RFA) | 0.696 (0.492–0.984) | 0.039 [▲] | 0.530 (0.366–0.766) | 0.001 [▲] |

Notes: [▲]Indicates statistical significance ($P < 0.05$). Univariate and Multivariate analyses used Cox proportional hazard model.

Abbreviations: CI, confidence interval; HR, Hazard ratio.

NT-RFA in terms of OS. Based on the high risk of recurrence in AFP positive HCC patients, we speculate that NT-RFA may significantly improve their long-term survival. This study evaluates the efficacy of NT-RFA in controlling AFP levels and improving long-term outcomes for AFP-positive HCC by comparing pre- and post-treatment AFP changes and long-term efficacy differences between NT-RFA and C-RFA, and further verifying the long-term efficacy advantage of NT-RFA in AFP positive HCC patients. This study differs from the previous two studies conducted by our center in terms of research subjects, research methods, and research results. Furthermore, no studies have yet reported on the dynamic changes in AFP levels before and after NT-RFA treatment for HCC and their correlation with long-term survival outcomes.

Elevated AFP levels not only reflect a larger tumor burden but also indicate the presence of intrahepatic micro-metastases and MVI, which are risk factors for HCC recurrence.^{28,29} Within our cohort, 43.27% (106/245) had preoperative AFP ≥ 200 ng/mL. Univariate analysis revealed that preoperative/postoperative AFP ≥ 200 ng/mL was an independent risk factor affecting RFS, aligning with previous literatures. Consequently, for the treatment of AFP-positive HCC, effectively reducing AFP levels is a key indicator for evaluating therapeutic efficacy. In this study, the postoperative AFP conversion rate was significantly higher in the NT-RFA group than in the C-RFA group (38.46% vs. 26.35%, $P=0.020$). Moreover, the reduction in AFP levels was significantly greater in the NT-RFA group ($Z=2.627$, $P=0.009$). Despite higher baseline AFP levels in the NT-RFA group, it demonstrated superior postoperative AFP reduction and a significantly improved conversion rate, clearly indicating superior AFP control efficacy compared to C-RFA. Effective postoperative control of AFP suggests more thorough tumor inactivation, which is based on the technical advantages of NT-RFA in achieving a larger AR and SM, more effectively clearing micrometastases and preventing residual tumors.³⁰ Conversely, 26.35% of patients in the C-RFA group experienced postoperative AFP elevation, a rate significantly higher than the NT-RFA group ($t=5.539$, $P=0.019$), indicating C-RFA carries a risk of accelerating tumor dissemination or metastasis. The presumed mechanism involves direct tumor puncture during C-RFA potentially elevating intra-tumoral pressure, thereby promoting cancer cell dissemination into the bloodstream or implant metastasis. In contrast, No-touch RFA avoids direct contact with the tumor through circumferential ablation, prioritizing the destruction of peritumoral vessels to block the pathway for tumor cells entering the bloodstream. Additionally, it prevents increased mechanical pressure within the tumor, reducing the driving force for tumor cell dissemination while also minimizing the risk of cancer cell seeding along the needle tract.^{25,31,32} This represents a potential mechanism by which no-touch RFA reduces the risk of postoperative AFP elevation.

Previous investigations have largely concluded that NT-RFA confers advantages limited to superior local tumor control, without improving OS compared to C-RFA.^{13,33} However, survival analysis in this study demonstrates that NT-RFA not only significantly enhances RFS and LTP-free survival in AFP-positive patients but also unexpectedly improves OS, resulting in comprehensive long-term survival benefits. In this study, the median OS in the NT-RFA

group reached 59 months, representing a significant 10-month extension compared to the 49 months observed in the C-RFA group. Furthermore, the 5-year OS rate in the NT-RFA group (54.07%) was significantly higher than that in the C-RFA group (30.80%). These findings differ from the results of most current studies. Elevated AFP levels are typically associated with stronger tumor proliferative activity, higher MVI incidence, and more extensive potential microsatellite foci.³⁴ We believe that for AFP-positive patients with highly invasive or high risk of recurrence HCC, the technical advantages of NT-RFA are more pronounced, yielding more significant long-term efficacy benefits. Therefore, compared to C-RFA, NT-RFA represents a superior choice for this patient population.

Our analysis of HCC recurrence revealed that NT-RFA significantly improves RFS primarily by substantially reducing LTP, consistent with most current studies. The technique employs a standardized circumferential ablation strategy to achieve expanded SM, more effectively covering high-risk areas at tumor margins (MVI-prone zones). This substantially reduces tumor residue and local recurrence due to insufficient SM, thereby enhancing the thoroughness of local tumor ablation.^{35,36} Notably, No-touch RFA fails to improve IDR, suggesting its occurrence is likely driven more by systemic or hepatic background factors than by the choice of local ablation technique. Potential drivers of IDR include: 1) Persistent carcinogenic factors: such as high levels of HBV/HCV replication, which drive new tumor formation.³⁷ 2) Deterioration of the intrahepatic microenvironment: The severity of underlying liver disease (eg, significant fibrosis/cirrhosis) creates a pro-carcinogenic microenvironment that increases the risk of tumors with multiple origins.³⁸ 3) Undetected occult micrometastases: These lesions may already exist at the time of ablation but lie beyond the capabilities of current imaging techniques and the reach of local ablation.

Of course, this study has limitations. Firstly, as a retrospective study, treatment choices for patients were not randomly assigned, which may introduce certain biases. The findings of this study require further validation through multicenter, prospective, randomized controlled trials. Secondly, the lesions included in this study were all ≤ 3 cm. For larger tumors, the ablation efficiency of NT-RFA may be reduced. For AFP-positive HCC patients with a diameter >3 cm, the application value of NT-RFA still requires further investigation. Finally, this study did not address the molecular mechanisms underlying AFP regulation. In the future, we may combine pathological immunohistochemistry analysis to explore the impact of NT-RFA on the tumor microenvironment.

Conclusion

For AFP-positive HCC with a diameter ≤ 3 cm, NT-RFA demonstrates superior short-term and long-term efficacy when strictly adhering to operational protocols. Key advantages include: 1) Enhanced ablation efficacy: Achieves a larger AR and SM. 2) Reduced recurrence risk: Effectively lowers serum AFP levels, significantly decreasing recurrence probability. 3) Superior long-term outcomes: markedly improving long-term RFS and OS rates. Therefore, for AFP-positive HCC with a diameter ≤ 3 cm meeting the indications, NT-RFA can be considered the preferred ablation therapy over C-RFA.

Patient Confidentiality Statement

All patient data were fully anonymized before analysis. All personal identifiers, including names, medical record numbers, dates of birth, and hospital identification codes, were removed to protect patient privacy. This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Patient confidentiality was strictly maintained throughout the research process, and all data were used solely for scientific research purposes.

Abbreviations

HCC, Hepatocellular carcinoma. RFA, Radiofrequency ablation. NT-RFA, No-touch radiofrequency ablation. C-RFA, Conventional radiofrequency ablation. OS, Overall survival. RFS, Recurrence-free survival. LTP-FS, Local tumor progression-free survival. IDR-FS, Intrahepatic distant recurrence-free survival. MRI, Magnetic resonance imaging. CT, Computed tomography. US, ultrasound. AFP, Alpha-fetoprotein. AR, Ablation range. SM, Safety margin.

Data Sharing Statement

The data that support the findings of this study are not publicly available due to patient privacy reasons but are available from the corresponding author upon reasonable request.

Ethics Statement

This single-center, retrospective study was approved by the Ethics Committee of Southwest Hospital of Army Medical University (approval No.: KY2024183). Due to the retrospective nature of this study, the committee waived the informed consent.

Patient Consent for Publication

This is a retrospective study. The informed consent of patients in this clinical trial has been approved for exemption by the Ethics Committee of Southwest Hospital of Army Medical University. We will strictly adhere to the Helsinki Declaration and the International Ethical Guidelines for Biomedical Research Involving Human, and any publication of the results of this study will not disclose the personal identity of the patients.

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Disclosure

The authors declared that they have no conflicts of interest to this work.

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