

Propensity score-matched comparison of non-anatomical resection and radiofrequency ablation for hepatocellular carcinoma in patients with up to three tumours, each measuring up to 3 cm in diameter

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Background: Non-anatomical liver resection (NAR) and radiofrequency ablation (RFA) are treatment options for early-stage hepatocellular carcinoma (HCC). The aim was to compare the outcomes of NAR and RFA for HCC in patients with three or fewer tumour nodules, each measuring not more than 3 cm in maximum diameter.

Methods: Eligible patients undergoing NAR or RFA with curative intent between September 2002 and December 2014 were identified. A propensity score-matching analysis was performed to reduce bias, and outcomes in these patients were analysed.

Results: From a total of 199 patients, 1:1 propensity score matching identified 70 matched pairs. Patients having NAR had a longer hospital stay (median 10 days *versus* 4 days for those who had RFA; $P < 0.001$) and a higher morbidity rate (24 *versus* 10 per cent respectively; $P = 0.042$). Patients who had NAR had slightly better recurrence-free survival but this failed to reach statistical significance in univariable analysis ($P = 0.064$). There was no significant difference in overall survival between the two groups ($P = 0.475$). RFA was identified as an independent risk factor for recurrence-free survival (hazard ratio (HR) 1.57; $P = 0.041$) in multivariable analysis. Local recurrence was significantly more common in patients receiving RFA (23 *versus* 1 per cent; $P < 0.001$).

Conclusion: RFA was an independent risk factor for shorter recurrence-free survival, with a significantly higher local recurrence rate than NAR. Despite these differences, overall survival was not affected.

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Introduction

Hepatectomy can be performed with low operative mortality and morbidity rates^{1,2}. Surgical resection is therefore considered the standard treatment for hepatocellular carcinoma (HCC) in patients with adequate hepatic functional reserve, and offers patients the chance of long-term survival^{3,4}. Radiofrequency ablation (RFA) has become a popular treatment option for patients with early-stage HCC owing to its low complication rate and cost-effectiveness^{5,6}, particularly in patients with multiple small tumours^{7,8}. The American Association for the Study

of Liver Diseases guidelines⁹ and European Association for the Study of the Liver (EASL)¹⁰ recommend RFA together with surgical resection for early-stage HCC.

Whether surgical resection or RFA should be selected as the first therapeutic choice for patients with early-stage HCC remains controversial. To date, three RCTs^{11–13} and several retrospective studies^{14–16} comparing RFA with surgical resection have been reported, with contradictory findings reflecting different inclusion criteria.

Regarding method of hepatectomy, the EASL recommends anatomical resection and, although some studies^{17–20} have reported survival benefits with

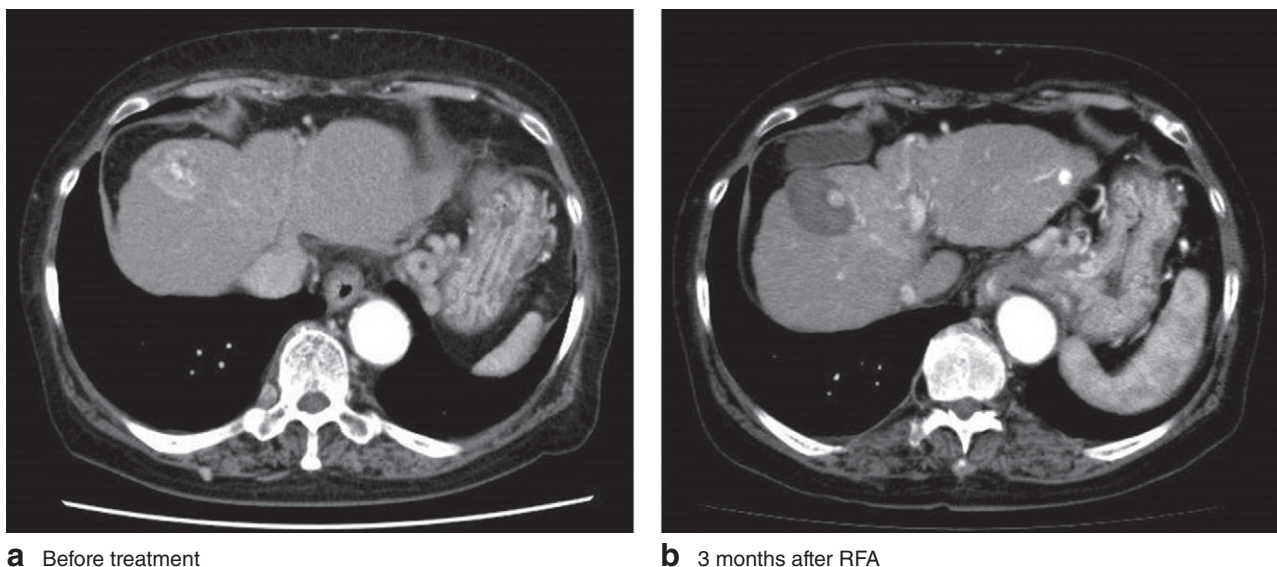


Fig. 1 CT images: **a** hepatocellular carcinoma 25 mm in diameter in segment VIII before treatment and **b** viable lesion at the site of ablation identified 3 months after radiofrequency ablation (RFA)

anatomical resection, others^{21–24} have been unable to do so. Non-anatomical resection (NAR) is an attractive treatment option for patients with cirrhotic livers, so a comparison of NAR and RFA seems appropriate in the context of achieving local control. Only one study²⁵, which included only 17 patients in each group after matching, has compared RFA with NAR.

The purpose of this study was to compare the long-term outcomes of patients treated with NAR and RFA as initial therapy for HCC in patients with three or fewer tumours, each with a maximum diameter of not more than 3 cm, using propensity score matching.

Methods

Patients with HCC who had three or fewer tumours, each measuring not more than 3 cm, were identified from the surgical database of hepatectomies undertaken at the Division of Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Centre Hospital, between September 2002 and December 2014. Patients who underwent anatomical resection were excluded and the remaining patients formed the NAR group. Patients who had undergone RFA as initial treatment at the Division of Interventional Radiology, Shizuoka Cancer Centre Hospital, in the same interval were identified, and those with the same tumour characteristics as the NAR group selected for comparison to achieve 1:1 matching. The institutional review board approved this study and waived the need for informed consent.

Pretreatment blood samples were drawn on admission (in principle within 2 days before treatment). Serum albumin values were measured, as well as total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase, α -fetoprotein (AFP), des- γ -carboxy prothrombin (DCP), hepatitis C virus antibody, hepatitis B virus surface antigen, platelet count and prothrombin time. Other patient-related variables included age, sex and Child–Pugh classification²⁶.

The diagnosis of HCC was predominantly based on imaging. Patients underwent ultrasonography, dynamic CT and dynamic MRI. Liver nodules showing hyperattenuation in the arterial phase of the dynamic study and washout in the portal or delayed phase were considered HCC. When a dynamic enhanced pattern was inconclusive, contrast-enhanced ultrasonography was added.

Treatment

Indications for treatment were based on the size, number and location of tumours, and hepatic reserve assessment, discussed at a weekly conference involving surgeons, oncologists and radiologists. The extent of hepatectomy was largely determined using Makuuchi's criteria²⁷, and was usually undertaken by ultrasonic dissection in combination with a Pringle manoeuvre, with clamping for 15 min followed by 5 min declamping.

Patients in the RFA group were treated percutaneously using a 17-G Cool-tip™ RFA system (Covidien, Tokyo, Japan) or LeVeen™ RF system 3000™ (Boston Scientific,

Table 1 Patient demographics and preoperative laboratory analyses after propensity score matching

| | NAR (n = 70) | RFA (n = 70) | P† |
|---|-------------------|-------------------|--------|
| Age (years)* | 68 (39–79) | 70 (27–85) | 0.482 |
| Sex ratio (M:F) | 55:15 | 53:17 | 0.841‡ |
| Multiple tumours | 11 (16) | 10 (14) | 1.000‡ |
| Tumour size (mm)* | 20 (9–30) | 20 (6–30) | 0.604 |
| Hepatic virus infection (B or C) | 56 (80) | 61 (87) | 0.362‡ |
| Child–Pugh grade B | 1 (1) | 1 (1) | 1.000§ |
| α-Fetoprotein (ng/ml)* | 13.3 (1.4–2813.3) | 12.8 (2.0–4556.4) | 0.728 |
| Des-γ-carboxy prothrombin (arbitrary units/ml)* | 32 (1–12 300) | 22 (1–5280) | 0.075 |
| Albumin (g/dl)* | 4.2 (2.9–4.9) | 4.1 (3.1–5.0) | 0.792 |
| Aspartate aminotransferase (units/l)* | 39 (16–143) | 41 (15–141) | 0.431 |
| Alanine aminotransferase (units/l)* | 44 (11–281) | 40 (7–196) | 0.331 |
| Total bilirubin (mg/dl)* | 0.7 (0.3–2.3) | 0.7 (0.2–1.5) | 0.618 |
| Platelet count (× 10 ⁴ /μl)* | 12.4 (4.8–26.6) | 13.4 (3.3–85.0) | 0.341 |
| Prothrombin time (%)* | 88 (59–117) | 85 (60–108) | 0.748 |

Values in parentheses are percentages unless indicated otherwise; *values are median (range). NAR, non-anatomical resection; RFA, radiofrequency ablation. †Mann–Whitney *U* test, except ‡ χ^2 test and §Fisher’s exact test.

Marlborough, Massachusetts, USA). Generator settings were set in accordance with the manufacturer’s instructions, which were based on impedance. For example, if a 3-cm needle was used with the Cool-tip™ system, ablation was started at 40 W and increased by 10 W/min

Table 2 Complications, recurrences and further treatments

| | NAR (n = 70) | RFA (n = 70) | P‡ |
|---|-----------------|-----------------|---------|
| Duration of hospital stay after treatment (days)* | 10 (3–55) | 4 (1–9) | <0.001§ |
| Morbidities | 17 (24) | 7 (10) | 0.042 |
| Additional RFA | 0 | 4 | |
| Pneumothorax | 0 | 1 | |
| Fever | 3 | 1 | |
| Liver dysfunction | 0 | 1 | |
| Bile leakage | 4 | 0 | |
| Ascites | 5 | 0 | |
| Pleural effusion | 1 | 0 | |
| Wound infection | 2 | 0 | |
| Other complications | 2 | 0 | |
| Patients with any recurrence† | 42 (60) | 47 (67) | 0.482 |
| Remnant liver (except local area) | 41 (59) | 29 (41) | 0.063 |
| Local recurrence in liver | 1 (1) | 16 (21) | <0.001¶ |
| Lung | 1 (1) | 1 (1) | |
| Bone | 1 (1) | 1 (1) | |
| Peritoneum | 0 (0) | 1 (1) | |
| Treatment for local recurrence | 1 | 16 | |
| Surgical resection | 0 | 3 | |
| RFA | 0 | 8 | |
| TACE | 1 | 5 | |

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Some patients had more than one type of recurrence. NAR, non-anatomical resection; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization. ‡ χ^2 test, except §Mann–Whitney *U* test and ¶Fisher’s exact test.

until ablation was complete. Ultrasound-guided puncture was usually performed, although CT-guided puncture was used when the tumours could be detected only by CT.

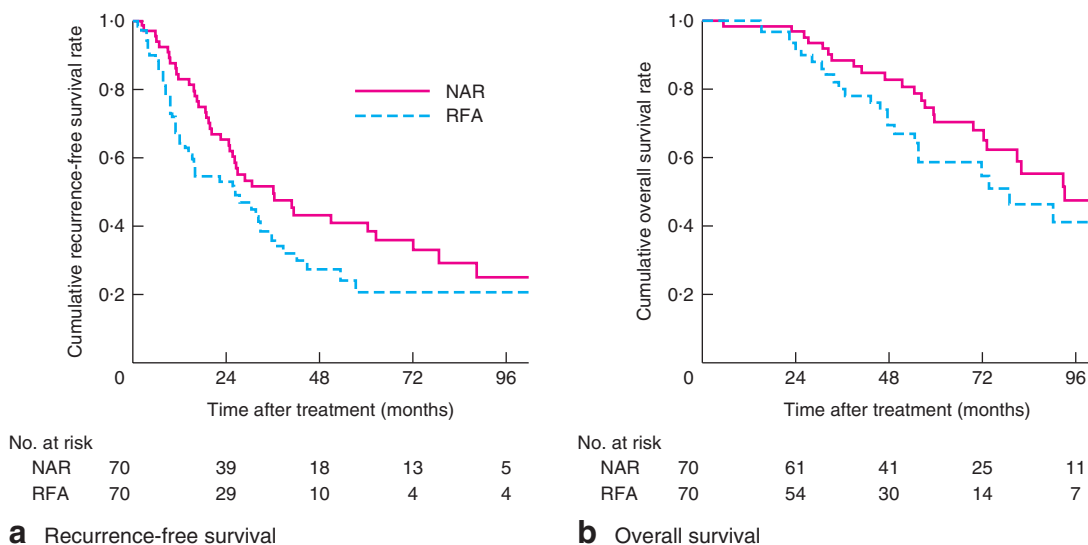


Fig. 2 Survival analysis according to treatment group: **a** recurrence-free and **b** overall survival in patients who had non-anatomical liver resection (NAR) or radiofrequency ablation (RFA). **a** *P* = 0.064, **b** *P* = 0.475 (log rank test)

Table 3 Univariable and multivariable analyses for recurrence-free and overall survival

| | n | Recurrence-free survival | | | Overall survival | | |
|---|-----|--------------------------|-------------------------|-------|------------------|-------------------------|-------|
| | | Univariable P* | Multivariable analysis† | | Univariable P* | Multivariable analysis† | |
| | | | Hazard ratio | P | | Hazard ratio | P |
| Age (years) | | | | | | | |
| ≥ 70 | 73 | 0.192 | | | 0.003 | 2.24 (1.23, 4.06) | 0.008 |
| < 70 | 67 | | | | | 1.00 (reference) | |
| Sex | | | | | | | |
| M | 108 | 0.991 | | | 0.356 | | |
| F | 32 | | | | | | |
| Tumour number | | | | | | | |
| Multiple | 21 | 0.347 | | | 0.979 | | |
| Solitary | 119 | | | | | | |
| Maximum tumour size (mm) | | | | | | | |
| ≥ 19 | 81 | 0.130 | | | 0.070 | 1.63 (0.84, 3.19) | 0.151 |
| < 19 | 59 | | | | | 1.00 (reference) | |
| Hepatic virus infection (B or C) | | | | | | | |
| Yes | 117 | 0.018 | 1.27 (0.59, 2.77) | 0.536 | 0.096 | 1.11 (0.55, 2.31) | 0.532 |
| No | 23 | | 1.00 (reference) | | | 1.00 (reference) | |
| α-Fetoprotein (ng/ml) | | | | | | | |
| ≥ 17 | 61 | 0.088 | 1.14 (0.58, 1.96) | 0.630 | 0.112 | | |
| < 17 | 79 | | 1.00 (reference) | | | | |
| Des-γ-carboxy prothrombin (arbitrary units/ml)* | | | | | | | |
| ≥ 36 | 58 | 0.086 | 1.64 (1.06, 2.53) | 0.026 | 0.102 | | |
| < 36 | 82 | | 1.00 (reference) | | | | |
| Albumin (g/dl) | | | | | | | |
| < 4.0 | 50 | 0.001 | 1.83 (1.17, 2.86) | 0.008 | 0.002 | 2.17 (1.23, 3.83) | 0.007 |
| ≥ 4.0 | 90 | | 1.00 (reference) | | | 1.00 (reference) | |
| Aspartate aminotransferase (units/l) | | | | | | | |
| ≥ 42 | 63 | < 0.001 | 2.06 (1.32, 3.21) | 0.001 | 0.026 | 2.08 (0.91, 3.52) | 0.061 |
| < 42 | 77 | | 1.00 (reference) | | | 1.00 (reference) | |
| Alanine aminotransferase (units/l) | | | | | | | |
| ≥ 41 | 72 | 0.004 | 1.08 (0.52, 2.24) | 0.850 | 0.266 | | |
| < 41 | 68 | | 1.00 (reference) | | | | |
| Total bilirubin (mg/dl) | | | | | | | |
| ≥ 0.7 | 74 | 0.320 | | | 0.531 | | |
| < 0.7 | 66 | | | | | | |
| Platelets (× 10 ⁴ /μl) | | | | | | | |
| < 10.7 | 46 | 0.021 | 1.21 (0.72, 2.04) | 0.468 | 0.165 | | |
| ≥ 10.7 | 94 | | 1.00 (reference) | | | | |
| Prothrombin (%) | | | | | | | |
| < 80 | 47 | 0.251 | | | 0.568 | | |
| ≥ 80 | 93 | | | | | | |
| Treatment | | | | | | | |
| RFA | 70 | 0.064 | 1.57 (1.02, 2.42) | 0.041 | 0.475 | | |
| NAR | 70 | | 1.00 (reference) | | | | |

Values in parentheses are 95 per cent confidence intervals. RFA, radiofrequency ablation; NAR, non-anatomical resection. *Log rank test; †Cox proportional hazards model.

Contrast-enhanced CT was carried out the day after RFA to confirm the adequacy of the ablated margin. If residual tumour was detected, RFA was repeated that day.

Patients subsequently underwent physical examinations and blood tests for AFP and DCP every 3 months. Serial CT or liver ultrasonography was performed in each patient every 3–6 months. Local recurrence in the liver was diagnosed when a tumour was identified at or adjacent to the initial treatment site (*Fig. 1*). Patients with recurrence were re-treated subject to their performance status and

wishes. Recurrence-free survival (RFS) was defined as the time between the first curative treatment of HCC and confirmation of recurrence. Overall survival (OS) was defined as the time between the first curative treatment and death from any cause.

Statistical analysis

To reduce the influence of potential confounders, propensity scores were generated using binary logistic regression.

Independent variables entered into the propensity model included age, Child–Pugh grade, serum albumin level, serum AST level and prothrombin time.

Continuous variables, presented as median (range), were compared using the Mann–Whitney *U* test. The χ^2 test or Fisher's exact test, as appropriate, was used for analysis of categorical variables. Cumulative RFS and OS curves were calculated using the Kaplan–Meier method and compared using the log rank test. A Cox proportional hazards model was used for univariable and multivariable analyses; all factors found to be significant predictors of recurrence and survival ($P < 0.100$) in the univariable analysis were entered into the multivariable model. The multivariable analysis was performed according to the logistic regression method using a backward stepwise selection model. All statistical analyses were undertaken in SPSS® version 24.0 (IBM, Armonk, New York, USA), and $P < 0.050$ in two-tailed tests was considered significant.

Results

Of 199 patients who underwent NAR (70) or RFA (129) as the initial treatment for HCC, and who satisfied the entry criteria, 70 in the RFA group were matched with 70 patients in the NAR group. The pretreatment factors became balanced between the two groups (Table 1).

The duration of hospital stay after treatment was significantly longer in the NAR group than in the RFA group (median 10 *versus* 4 days respectively; $P < 0.001$). Postoperative morbidity occurred more frequently in the NAR group (24 *versus* 10 per cent; $P = 0.042$). The specific morbidities were characteristic of each treatment (Table 2).

Median RFS was 26.1 and 16.1 months in the NAR and RFA groups respectively, although this did not reach statistical significance ($P = 0.064$) (Fig. 2a). Among factors with $P < 0.100$ for RFS in the univariable analysis, multivariable analysis indicated that RFA was independently associated with shorter RFS (hazard ratio (HR) 1.57, 95 per cent c.i. 1.02 to 2.42; $P = 0.041$), along with serum DCP level at least 36 arbitrary units/ml, serum AST level 42 units/l or more, and serum albumin level below 4.0 g/dl (Table 3).

Median OS times were 59.5 and 45.4 months in the NAR and RFA groups respectively, with no significant difference between the groups ($P = 0.475$) (Fig. 2b). Multivariable analysis showed that age at least 70 years (HR 2.24, 1.23 to 4.06; $P = 0.008$) and serum albumin level below 4.0 mg/dl (HR 2.17, 1.23 to 3.83; $P = 0.007$) were independently associated with OS (Table 3), but RFA treatment was unrelated to OS.

Forty-two patients (60 per cent) in the NAR group and 47 (67 per cent) in the RFA group developed recurrence in the

liver or at any other site over the entire observation period (Table 2). Local recurrence was significantly less frequent in the NAR group than in the RFA group (1 *versus* 23 per cent; $P < 0.001$), with local recurrences in one and 16 patients respectively. All patients who had local recurrence underwent additional treatment to the local sites in the liver (Table 2).

Discussion

The present study showed that, in matched patient groups, RFA treatment was an independent risk factor for local recurrence in the liver, but without impact on overall survival.

A recent meta-analysis²⁸, including three RCTs^{11–13} and several retrospective studies^{14–16} comparing RFA with surgical resection, concluded that RFA was comparable to surgical resection in terms of survival, with lower complication rates but higher recurrence rates, consistent with the present results. A study²⁹ comparing RFA with surgical resection for solitary small HCC using a propensity score model showed that surgical resection provided better OS and RFS than RFA. Most reports included patients who underwent anatomical resection in the surgical resection group; such patients would generally have better liver function and performance status. The present study deliberately focused on patients thought able to tolerate NAR as an alternative to RFA.

The study showed that NAR resulted in a better RFS than RFA, but was not superior to RFA in terms of OS. The similar OS rates may reflect aggressive further treatments designed to achieve local control, such as repeated RFA and salvage surgical resection. These were used in more than two-thirds of patients with local recurrence in the RFA group.

The Barcelona Clinic Liver Cancer (BCLC) group³⁰ classifies single HCC smaller than 2 cm into very early-stage disease, and a single lesion or nodules not larger than 3 cm into early-stage HCC³⁰. The Japan Society of Hepatology (JSH)³¹ recommends surgical resection or RFA for HCC with a maximum diameter of 3 cm and three or fewer tumours, embracing the very early and early-stage in the BCLC classification. The inclusion criteria for the present study matched the definition of the treatment algorithm of the BCLC and JSH.

The present study suggested that NAR should be considered in patients with a lower serum DCP level or a lower serum AST level on the basis of the multivariable analysis for RFS. On the other hand, RFA should be considered in older patients or those with a lower serum albumin

level, based on the results of multivariable analysis for OS. Shorter hospital stay and lower rates of morbidity after RFA may be important because of their association with survival in the actual clinical setting.

Despite the present study being balanced and comparative by applying propensity score matching, several limitations warrant mention. The total number of patients was relatively small in both groups (70 patients each). The decision to choose NAR or RFA as the initial treatment was dependent on the patient's and clinician's preferences. As a non-randomized observational single-centre study, there was still a possibility of selection bias despite the use of propensity score matching. An RCT to determine the survival benefit of RFA compared with surgical resection is currently in progress (registered at the University Hospital Medical Information Network, identifier UMIN000001795).

The present study showed superiority of NAR compared with RFA with regard to RFS, but not in terms of OS in patients with early-stage HCC. Clinicians should, nevertheless, consider biochemical profiles and differences in likely complication and recurrence rates when advising patients about these treatments.

Disclosure

The authors declare no conflict of interest.

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