Comparison of outcome between liver resection, radiofrequency ablation, and transarterial therapy for multiple small hepatocellular carcinoma within the Milan criteria

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INTRODUCTION

Liver resection has been a mainstay of treatment for hepatocellular carcinoma (HCC). It provides a chance of long-term outcome, with 5-year survival rate of more than 50% [1]. However, only 30%–40% of patients with HCC undergo liver...
Resection as the initial treatment [2] either due to decreased liver function or advanced tumor stage. For patients presenting with multiple tumors, liver resection is not recommended as the best option by European Association for Study of the Liver [3], American Association for the Study of Liver Diseases [4], and Korean Association for the Study of the Liver guidelines [5] even if patient has preserved liver function. High chance of recurrence after liver resection and concern for small future liver volume are reasons for not considering liver resection as the best option. However, with recent advances in surgical techniques and perioperative care, surgical mortality for HCC resection has been reduced to less than 1% [6]. Several previous reports have also suggested that liver resection can be an option for multiple HCCs as it may provide better outcome than other treatment modalities [7,8].

For multiple HCCs, radiofrequency ablation (RFA) can also be considered if tumor number is 2–3 nodules and tumor size is less than 3 cm which can be defined as a tumor within the Milan criteria. For those presenting multiple HCCs within the Milan criteria (small but multiple tumors), resection, RFA, or TACE can be considered. Several previous studies have reported outcomes according to treatment modality for HCC patients diagnosed within the Milan criteria. Some studies have reported that resection can provide more favorable outcomes in survival and recurrence than RFA [9-12]. On the other hand, other studies have reported similar outcomes between resection and RFA [13-16]. Similarly, when RFA is compared to transarterial chemoembolization (TACE), some studies have reported better outcome in RFA while others have reported similar outcome between RFA and TACE [17,18]. Although the subjects in these studies were diagnosed within the Milan criteria, these studies included the patients with a single tumor less than 5 cm or included those with impaired liver function. As the risk of recurrence can be different between single and multiple tumors [8,19,20], HCC patients diagnosed within the Milan criteria need to be separately analyzed for single and multiple tumors. To date, few data have focused on the outcome between treatment modality for multifocal small tumors (2–3 nodules, less than 3 cm).

Therefore, the objective of this study was to compare long-term outcome according to the initial treatment modality (resection, RFA, or TACE) for multifocal small HCCs within Milan criteria to determine whether resection could be considered as the best option.

**METHODS**

**Study design, setting, and participants**

This was a single-center retrospective cohort study conducted at Samsung Medical Center (SMC), Seoul, Korea. A total of 4,089 consecutive HCC patients who were registered at SMC HCC registry between 2009 and 2013 were screened. SMC HCC registry is a prospective registry that collects baseline characteristics and initial treatment modality for newly-diagnosed HCC patients managed at SMC. Among them, 406 HCC patients were diagnosed within the Milan criteria defined by 2–3 nodules and tumor size ≤3 cm without vascular invasion, bile duct invasion, or extrahepatic metastasis. Of them, we excluded 130 patients who had Child-Pugh class B or C and patients who received treatment other than resection, RFA, or TACE were excluded. Finally, a total of 276 patients with multiple HCCs diagnosed within the Milan criteria with preserved liver function defined by Child-Pugh class A and received resection (n = 48), RFA (n = 87), or TACE (n = 141) as initial treatment were analyzed (Fig. 1). We also generated propensity-score (PS) matching cohort in a 1:1:1 ratio based on age, platelet count, albumin-bilirubin (ALBI) grade, number of tumors, alpha-fetoprotein (AFP), and protein induced by vitamin K absence-II (PIVKA-II). Matching variables were composed of factors which differed in the baseline characteristics between treatment arms or factors that were associated with outcomes. The PS matching resulted in 93 patients who received hepatic...
Diagnosis of HCC was based on regional HCC guidelines during study period. In high-risk group, HCC can be diagnosed for nodules ≥1 cm in diameter if 1 or 2 of dynamic contrast-enhanced CT/MRI show typical features of HCC. Typical features of HCC included arterial phase enhancement with washout in the portal or delayed phase [5].

All patients underwent staging workup including enhanced CT scan and/or gadolinium-enhanced MRI. Treatment selection was determined by physician in charge of the patient. After treatment, CT scan or MRI was conducted every 3–4 months for the first 1–2 years and every 4–6 months thereafter during the follow-up period, until March 2019. Liver function, serum AFP, and PIVKA-II levels were also monitored.

The study protocol was reviewed and approved by the Institutional Review Board at Samsung Medical Center (2018-04-044). As the study used only de-identified data routinely collected during hospital visits, the requirement to obtain informed patient consent was waived.

### Variables

The primary outcome of the study was overall survival (OS). OS was measured from the date of diagnosis to the date of death or the last follow-up. Secondary outcome was recurrence-free survival (RFS). RFS was defined as the interval between the date of diagnosis and the date of the first recurrence, last follow-up, or death.

Exposure was the initial treatment modality which was either resection, RFA, or TACE. Liver resection included single or multiple segmentectomies aiming to remove all macroscopic tumors. Minor resection, defined as the resection of 2 or fewer liver segments. Resection of 3 or more segments was considered a major hepatic resection. For possible confounders or mediators, the following variables were used: age, sex, etiology of liver disease, Child-Pugh score, platelet count, ALBI grade, tumor size, tumor number, and serum AFP and PIVKA level at the time of HCC diagnosis. ALBI grade was calculated using albumin and bilirubin levels as described in a previous study [21]. We also reviewed treatment response after initial treatment. Complete response (CR) was defined when complete resection was done for resection, complete ablation at immediate follow-up CT after RFA, and CR by modified response evaluation criteria in solid tumors (mRECIST) criteria after TACE (either by 1 or 2 dynamic phases of contrast-enhanced MRI).

### Table 1. Baseline characteristics of overall and propensity-score matched cohort

| Characteristic | Overall cohort (n = 276) | Propensity-score matched cohort (n = 93) |
|----------------|-------------------------|----------------------------------------|
|                | Resection (n = 48)      | RFA (n = 87)                           | TACE (n = 141) |
|                |                         | RFA (n = 31)                           | TACE (n = 31) |
| Age (yr)       | 54.5 (50.2–61.7)        | 59.0 (51.0–68.0)                      | 62.0 (54.5–67.0) |
|                | 0.007                   | 0.007                                  | 0.007         |
| Male sex       | 37 (77.1)               | 72 (82.8)                             | 112 (79.4)    |
|                | 0.720                   | 0.700                                  | 0.700         |
| Hepatitis B    | 41 (85.4)               | 67 (77.0)                             | 98 (69.5)     |
|                | 0.070                   | 0.070                                  | 0.070         |
| Child-Pugh score, 5 | 43 (89.6) | 75 (86.2)               | 118 (83.7)    |
|                | 0.590                   | 0.590                                  | 0.590         |
| Platelet (×10^3/μL) | 140.0 (115.5–167.0) | 116.0 (87.0–157.0)   | 107.0 (82.0–143.0) |
|                | 0.001                   | 0.001                                  | 0.001         |
| ALBI grade 1   | 46 (95.8)               | 63 (72.4)                             | 92 (65.2)     |
|                | 0.130                   | 0.130                                  | 0.130         |
| Tumor size (cm) | ≤2                     | 21 (43.8)                             | 52 (59.8)     |
|                | 14 (45.2)               | 17 (54.8)                             | 16 (53.4)     |
|                | <0.001                  | 0.070                                  | 0.070         |
| Tumor number   | 2                       | 27 (56.3)                             | 35 (40.2)     |
|                | 17 (45.8)               | 13 (41.9)                             | 14 (45.2)     |
|                | 0.220                   | 0.220                                  | 0.220         |
| AFP (ng/mL)    | 13.8 (6.1–109.5)        | 11.8 (5.4–55.7)                      | 13.1 (6.3–51.9) |
|                | 0.830                   | 0.830                                  | 0.830         |
| PIVKA-II (mAU/mL) | 39.5 (24.5–143.2) | 25.0 (17.0–54.0)                    | 26.0 (17.0–57.0) |
|                | 0.005                   | 0.005                                  | 0.005         |
| Complete response | 46 (95.8) | 87 (100)                       | 127 (90.1)    |
|                | 0.007                   | 0.007                                  | 0.007         |

Values were presented as median (interquartile range) or number (%).

RFA, radiofrequency ablation; TACE, transarterial chemoembolization; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II.

* Included 3 patients with HBV and HCV coinfection.
Treatment-related complications were stratified according to the Clavien-Dindo classification [22], and complication grade III or higher were collected.

**Statistical analysis**

Values are expressed as median (interquartile range) or number (%). Student t-test or analysis of variance (ANOVA) was used to compare continuous variables while chi-square test or Fisher exact test was used to compare categorical variables. Unadjusted hazard ratio (HR) and adjusted HR analysis were performed using Cox-regression analysis. OS and RFS curves were estimated with the Kaplan-Meier method and compared using Log-rank test. Discrete variables were computed directly whereas continuous variables were classified into binary categorical data. Cut-off points for ALBI grade was determined according to a previous study [21]. Age, platelet count, AFP, and PIVKA-II were determined according to receiver operating characteristic curve: low platelet (≤100 × 10^3/μL) and high platelet (>100 × 10^3/μL), low AFP (≤10 ng/mL) and high AFP (>10 ng/mL), low PIVKA-II (≤40 mAU/mL) and high PIVKA-II (>40 mAU/mL). PS matching cohort was generated to balance baseline characteristics and control potential selection bias due to nonrandom treatment assignment. The 1:1:1 PS model was constructed [23] with the use of multivariable logistic regression. The 3 exposures of resection, RFA, and TACE yield 3 possible matches: resection vs. RFA, RFA vs. TACE, and TACE vs. resection. We began with pairwise approach and produced 3 PS-matched populations. We considered resection to be the referent treatment. Using the resection vs. RFA and the TACE vs. resection PS-matched populations from the prior step, we extracted patients treated with RFA or TACE who had a common match of a patient who was treated with resection. Then, a single cohort of these patients and their resection matches were created. All statistical analyses were performed using IBM SPSS Statistics ver. 24.0 (IBM Corp. New York, NY, USA). Statistical significance was considered at P < 0.05.

**RESULTS**

**Baseline characteristics**

Clinical characteristics of patients with multiple HCCs within Milan criteria are shown in Table 1. Their median age was 59.0 years (range: 53.0–66.0 years). Patients who received resection were younger than those in other groups (P = 0.007). Although all patients belonged to Child-Pugh class A, liver resection group had more preserved liver function assessed by ALBI grade and platelet count (P = 0.013 and P = 0.001, respectively). Surgical resection group also showed different tumor characteristics. This group had more patients with 2 tumors and higher PIVKA-II levels compared to RFA or TACE group. Resection was rarely performed for those with ALBI grade 2 (n = 2). Among patients who received resection, 41.6% of patients received major resections and 58.4% of patients received minor resections.

The 1:1:1 PS-matched analysis generated 31 pairs, and the baseline characteristics of the 3 groups were described in Table 1. The median age of resection group, RFA group, and TACE group was 56.0, 57.0, and 57.0 respectively (P = 0.720). Among patients, 29 (93.5%) of resection group, 29 (93.5%) of RFA group, and 30 (96.8%) of TACE group showed ALBI grade 1. Most patients had 2 tumors and half of the patients had tumors less than 2 cm.

**Overall survival according to treatment modality**

During a median of 5.2 years (range: 3.1–7.0 years) of follow-up, mortality was observed in 104 patients (37.7%). The OS was 81.7% at 3-year and 63.0% at 5-year. OS rates were different according to treatment modality. Resection group showed significantly better OS than RFA or TACE group. Three-year and
### Table 2. Factors associated with overall survival in overall and propensity-score matched cohort

| Factor                      | Overall cohort (n = 276) | Propensity-score matched cohort (n = 93) |
|-----------------------------|-------------------------|----------------------------------------|
|                             | Unadjusted HR (95% CI)  | P-value | Adjusted HR (95% CI)  | P-value | Unadjusted HR (95% CI)  | P-value |
| Age, >60 yr (vs. ≤60 yr)    | 1.84 (1.25–2.71)         | 0.002  | 1.53 (1.02–2.31)       | 0.038   | 1.96 (0.93–4.11)        | 0.070   |
| Male sex (vs. female sex)   | 0.82 (0.51–1.32)         | 0.420  | 0.98 (0.57–1.71)       | 0.901   | 0.80 (0.31–2.06)        | 0.651   |
| HBV (vs. others)            | 0.58 (0.21–1.58)         | 0.290  | 0.73 (0.29–1.92)       | 0.487   | 0.70 (0.25–2.02)        | 0.497   |
| Platelet, >100,000 (vs. ≤100,000) | 0.68 (0.46–1.01) | 0.060  | 0.77 (0.35–1.77)       | 0.510   | 0.35 (0.16–0.77)        | 0.009   |
| ALBI grade 1 (vs. 2)        | 0.46 (0.31–0.68)         | <0.001 | 0.54 (0.35–0.82)       | 0.004   | 0.36 (0.20–0.69)        | 0.090   |
| Tumor size, 2–3 cm (vs. ≤2 cm) | 1.08 (0.73–1.59) | 0.670  | 1.60 (1.01–2.56)       | 0.049   | 1.38 (0.85–2.24)        | 0.191   |
| Tumor number, 3 (vs. 2)     | 1.01 (0.65–1.56)         | 0.950  | 1.69 (1.01–2.80)       | 0.043   | 1.54 (0.62–4.03)        | 0.340   |
| AFP, >10 (vs. ≤10)          | 1.64 (1.09–2.47)         | 0.017  | 1.31 (0.86–2.00)       | 0.200   | 1.96 (0.88–4.35)        | 0.090   |
| PIVKA-II, >40 (vs. ≤40)     | 1.62 (1.10–2.38)         | 0.014  | 1.79 (1.19–2.69)       | 0.005   | 1.75 (0.83–3.69)        | 0.130   |

**Initial treatment modality**

| Resection | Unadjusted HR (95% CI) | P-value | Adjusted HR (95% CI) | P-value | Unadjusted HR (95% CI) | P-value |
|-----------|------------------------|---------|----------------------|---------|------------------------|---------|
| RFA       | 2.46 (1.13–5.36)       | 0.023   | 2.37 (1.06–5.32)     | 0.036   | 1.26 (0.45–3.50)       | 0.640   |
| TACE      | 3.39 (1.62–7.07)       | 0.001   | 2.39 (1.08–5.26)     | 0.030   | 2.09 (1.11–5.26)       | 0.110   |

| LT during follow-up | Unadjusted HR (95% CI) | P-value | Adjusted HR (95% CI) | P-value |
|---------------------|------------------------|---------|----------------------|---------|
| None                | 0.54 (0.24–1.24)       | 0.150   | 0.38 (0.05–2.84)     | 0.350   |
| Recurrence          |                        |         |                      |         |
| None                | Reference              |         |                      |         |
| Recurrence*         | 1.88 (1.00–3.53)       | 0.049   | 1.34 (0.69–2.60)     | 0.370   |

| LT during follow-up | Unadjusted HR (95% CI) | P-value | Adjusted HR (95% CI) | P-value |
|---------------------|------------------------|---------|----------------------|---------|
| None                | Reference              |         |                      |         |
| Recurrence*         | 3.05 (0.72–12.96)      | 0.130   |                      |         |

HR, hazard ratio; CI, confidence interval; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; LT, liver transplantation.

*Included 16 patients without complete response after resection, RFA, or TACE.
5-year OS rates were 93.7% and 86.8% in the resection group, 82.5% and 63.6% in the RFA group, and 77.1% and 54.7% in the TACE group, respectively (Fig. 2A, P = 0.002). By multivariate analysis, resection was independently associated with a significantly lower risk of death.

In PS matching cohort, the median follow-up period was 5.8 years (range, 3.4–7.1 years). Five-year OS rates were 79.5%, 72.3%, and 62.0% for resection, RFA, and TACE groups, respectively (Fig. 2B). Compared to those who received RFA or TACE, the difference of OS was not statistically significant in PS cohort (P = 0.232). Multivariate analysis also showed that initial treatment modality was not an independent factor for OS (Table 2).

**Recurrence-free survival according to treatment modality**

Among 260 patients who achieved CR after initial treatment, 205 patients (78.8%) experienced HCC recurrence during a median of 1.2 years of follow-up (range, 0.7–3.3 years). The number of intrahepatic recurrences was 197 (75.8%), extrahepatic recurrence was 7 (2.7%), and vascular recurrence was 12 (4.6%). Eight patients (3.1%) were retreated with resection. 53 patients (20.4%) were retreated with RFA, and 109 patients (41.9%) were retreated with TACE. Five patients (1.9%) underwent LT and 30 patients (11.5%) were retreated with other treatments (Supplementary Table 1). RFS was different according to initial treatment modality. Resection group showed significantly better RFS than RFA or TACE group. RFS rates at 3-year and 5-year were 65.7% and 56.0% for those who received resection, 36.5% and 18.9% for those who received RFA, and 11.6% and 4.5% for those who received TACE, respectively (Fig. 3A, P < 0.001). By multivariate analysis, resection was independently associated with a significantly better RFS.

In PS matching cohort, 93 patients who achieved CR after initial treatment. recurrence was observed in 67 patients (72.0%) during a median 1.5 years of follow-up (range, 0.8–4.0 years). Five-year RFS rate were 51.9%, 22.0%, and 3.4% for patients who received resection, RFA, and TACE, respectively (Fig. 3B, P < 0.001). By multivariate analysis, initial treatment modality was independent factor associated with RFS (Table 3).

**Major complications according to treatment modality**

In overall, 7 patients experienced a major complication, defined as more than Clavien-Dindo grade III complication: 3 (6.3%) in resection group, 2 (2.3%) in RFA group, and 2 (1.4%) in TACE group (P = 0.170). In resection group, one patient experienced hepatic encephalopathy, requiring lactulose enema, and 2 patients experienced hepatic failures, which required subsequent LT. All of the 3 patients underwent major hepatectomy. In RFA group, 2 patients experienced 3rd-degree atrioventricular block and dyspnea due to large amount of pleural effusion, requiring thoracentesis. In TACE group, 1 patient experienced contrast anaphylaxis, and 1 patient experienced acute cholecystitis and ischemic colitis, requiring diagnostic endoscopy. After PS matching, major complication remained in 5 patients (3 in resection group, 2 in RFA group, and zero in TACE group; P = 0.360).

**DISCUSSION**

This study focused on the long-term outcome after treatment for those who had multiple small HCCs (2–3 nodules and ≤3 cm) with preserved liver function. In the present study, liver resection was associated with better OS than RFA or TACE for patients with multiple small HCCs. Since the resection group
Table 3. Factors associated with recurrence-free survival in overall cohort propensity-score matched cohort

| Factor                             | Overall cohort (n = 276) | Propensity-score matched cohort (n = 93) |
|------------------------------------|-------------------------|----------------------------------------|
|                                     | Unadjusted HR (95% CI)  | P-value | Adjusted HR (95% CI) | P-value | Unadjusted HR (95% CI) | P-value | Adjusted HR (95% CI) | P-value |
| Age, >60 yr (vs. ≤60 yr)           | 1.58 (1.21–2.07)        | 0.001   | 1.42 (1.08–1.86)    | 0.011   | 1.30 (0.79–2.13)       | 0.280    |
| Male sex (vs. female sex)          | 1.07 (0.75–1.51)        | 0.700   | 0.96 (0.71–1.32)    | 0.420   | 1.44 (0.69–3.02)       | 0.650    |
| HBV (vs. others)                   | 0.79 (0.35–1.80)        | 0.580   | 0.76 (0.42–1.38)    | 0.370   | 0.94 (0.50–1.65)       | 0.760    |
| Platelet, >100,000 (vs. ≤100,000) | 0.70 (0.53–0.93)        | 0.015   | 0.92 (0.68–1.23)    | 0.590   | 0.76 (0.42–1.38)       | 0.370    |
| ALBI grade 1 (vs. 2)               | 0.64 (0.48–0.87)        | 0.004   | 0.96 (0.71–1.32)    | 0.840   | 0.65 (0.23–1.82)       | 0.420    |
| Tumor size, 2–3 cm (vs. ≤2 cm)     | 1.08 (0.82–1.41)        | 0.560   | 1.36 (0.84–2.20)    | 0.200   | 1.42 (1.08–1.86)       | 0.001    |
| Tumor number, 3 (vs. 2)            | 1.67 (1.23–2.26)        | 0.001   | 1.04 (0.76–1.43)    | 0.760   | 1.89 (1.02–3.49)       | 0.040    |
| AFP, >10 (vs. ≤10)                 | 1.25 (0.95–1.64)        | 0.100   | 1.23 (0.76–1.99)    | 0.380   | 1.04 (0.76–1.43)       | 0.001    |
| PIVKA-II, >40 (vs. ≤40)            | 0.96 (0.72–1.27)        | 0.780   | 1.03 (0.63–1.69)    | 0.880   | 1.04 (0.76–1.43)       | 0.001    |

Excluded 16 patients without complete response after resection, RFA, or TACE.

HR, hazard ratio; CI, confidence interval; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.
selected appropriately.

Our data warrants careful interpretation as this is an observational study. The better outcome of resection might be due to careful selection of patients. Resection can only be considered when remnant volume is adequate, and when multiple tumors are located in right or left liver (unilobal tumors). Also, in this study, we noticed that almost all patients who received resection showed ALBI grade 1. ALBI grade offers a simple, evidence-based, and objective method for assessing liver function in HCC [28]. It has shown low mortality rate after resection among patients with preserved liver function assessed by ALBI grade [28,29]. Hence, better outcome in resection group might not be from treatment modality itself, but from selection of better patients. Other limitations of this study include its retrospective design and analysis of patients in a single center. In this study, OS was better in overall cohort, not in PS-matched cohort. We used PS matching to minimize heterogeneity between groups. However, PS matching cannot completely remove heterogeneity between groups, and PS-matched cohort became small (n = 93) to make definite conclusion. All cases in the resection group were histologically confirmed cases, while tumors treated by TACE or RFA were not histologically confirmed cases. This study did not assess subsequent quality of life after treatment which might be another important issue in choosing treatment option. In addition, following treatment after recurrence can influence OS, which we could not adjust in the study, due to relatively small number of patients with recurrence (n = 23) in the resection group. Despite these limitations, the present data may have some advantages in terms that we can provide evident results compared to other studies where heterogeneous population included.

In summary, resection was associated with a significantly lower risk of recurrence compared with RFA or TACE and showed better or comparable OS in multiple HCC patients within the Milan criteria. These findings suggest that surgical resection can be considered as a first-line option for multiple small HCCs if patients are selected appropriately. However, considering retrospective nature of the study, prospective studies are warranted to see the risks and benefits of each treatment option, in order to find out patients who may best benefit from resection of multiple small HCCs.

SUPPLEMENTARY MATERIAL

Supplementary Table 1 can be found via https://doi.org/10.4174/astr.2020.99.4.238.

ACKNOWLEDGEMENTS

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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