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Liver Resection vs Nonsurgical Treatments for Patients With Early Multinodular Hepatocellular Carcinoma

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IMPORTANCE The 2022 Barcelona Clinic Liver Cancer algorithm currently discourages liver resection (LR) for patients with multinodular hepatocellular carcinoma (HCC) presenting with 2 or 3 nodules that are each 3 cm or smaller.

OBJECTIVE To compare the efficacy of liver resection (LR), percutaneous radiofrequency ablation (PRFA), and transarterial chemoembolization (TACE) in patients with multinodular HCC.

DESIGN, SETTING, AND PARTICIPANTS This cohort study is a retrospective analysis conducted using data from the HE.RC.O.LE.S register (n = 5331) for LR patients and the ITA.LI.CA database (n = 7056) for PRFA and TACE patients. A matching-adjusted indirect comparison (MAIC) method was applied to balance data and potential confounding factors between the 3 groups. Included were patients from multiple centers from 2008 to 2020; data were analyzed from January to December 2023.

INTERVENTIONS LR, PRFA, or TACE.

MAIN OUTCOMES AND MEASURES Survival rates at 1, 3, and 5 years were calculated. Cox MAIC-weighted multivariable analysis and competing risk analysis were used to assess outcomes.

RESULTS A total of 720 patients with early multinodular HCC were included, 543 males (75.4%), 177 females (24.6%), and 350 individuals older than 70 years (48.6%). There were 296 patients in the LR group, 240 who underwent PRFA, and 184 who underwent TACE. After MAIC, LR exhibited 1-, 3-, and 5-year survival rates of 89.11%, 70.98%, and 56.44%, respectively. PRFA showed rates of 94.01%, 65.20%, and 39.93%, while TACE displayed rates of 90.88%, 48.95%, and 29.24%. Multivariable Cox survival analysis in the weighted population showed a survival benefit over alternative treatments (PRFA vs LR: hazard ratio [HR], 1.41; 95% CI, 1.07-1.86; P = .01; TACE vs LR: HR, 1.86; 95% CI, 1.29-2.68; P = .001). Competing risk analysis confirmed a lower risk of cancer-related death in LR compared with PRFA and TACE.

CONCLUSIONS AND RELEVANCE For patients with early multinodular HCC who are ineligible for transplant, LR should be prioritized as the primary therapeutic option, followed by PRFA and TACE when LR is not feasible. These findings provide valuable insights for clinical decision-making in this patient population.

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Supplemental content

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Hepatocellular carcinoma (HCC) represents the third leading cause of cancer-related deaths, and an increase of 55% in HCC-related fatalities is predicted over the period 2020 through 2040, reaching 1.3 million deaths by 2040.[1,2] Advances in surveillance have increased the early detection of HCC,[3] but a subset of individuals diagnosed with early-stage (ie, small HCC in compensated cirrhosis) have a multinodular HCC (ie, 2-3 nodules, each measuring ≤3 cm), a condition that poses a therapeutic dilemma. Although liver resection (LR) is considered the gold standard curative treatment for early-stage HCC, its applicability and efficacy in multinodular disease are debated. On one side, Asia-Pacific guidelines suggest evaluating LR before any other therapy in all patients with HCC and compensated cirrhosis without extrahepatic metastases, irrespective of vascular invasion, tumor size, and number of nodules[4]; therefore, this recommendation is valid even for patients with early multinodular HCC. Conversely, the updated 2022 Barcelona Clinic Liver Cancer (BCLC) treatment algorithm states that in these patients, when transplant is not feasible, percutaneous radiofrequency ablation (PRFA) is recommended, and if this is not feasible, transarterial chemoembolization (TACE), thus excluding LR as a therapeutic approach.[5] The 2022 BCLC algorithm has been recently acknowledged by the 2023 guidelines for HCC from the American Association for the Study of Liver Diseases.[6]

A similar debate also exists in the literature. Although a large amount of solid indirect evidence suggests the superiority of LR over PRFA or TACE regardless of BCLC stage,[7-10] direct evidence comparing these 3 treatments in the subgroup of early multinodular HCC is relatively poor. Only 3 studies were designed to analyze this specific population,[11-13] and small samples limit the robustness of their results. Other direct comparisons between these treatments in patients with early multinodular HCC are only obtainable from subgroup analyses of studies designed for larger populations.[14-18]

Based on these premises, an observational study on this topic is justified. Therefore, a large multicenter cohort of Italian patients was used to compare the effectiveness of LR, PRFA, and TACE in early multinodular HCC.

Key Points

Question In patients with early multinodular hepatocellular carcinoma (HCC), does liver resection provide a significant survival benefit over percutaneous radiofrequency ablation (PRFA) or transarterial chemoembolization (TACE)?

Findings In a cohort study including 720 patients, liver resection demonstrated significantly higher 1-, 3-, and 5-year survival rates than PRFA and TACE. Liver resection exhibited a significant survival benefit over PRFA and TACE.

Meaning Liver resection should be considered the first therapeutic option in patients with early multinodular HCC who are not eligible for transplant.

Methods

HE.RC.O.LE.S and ITA.LI.CA database management conforms to past and current Italian legislation regarding privacy. Approval for observational studies based on these registries was obtained from the institutional review boards of the participating centers. Patient consent specific to the current study was waived because patient approval is not needed for retrospective analysis, according to the institutional review boards. However, patients did provide written informed consent for every diagnostic and therapeutic procedure. This study adhered to ethical principles outlined in the Declaration of Helsinki. Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.[19]

Study Groups and Variables

We aimed to validate the concept of therapeutic hierarchy[20] in the specific subgroup of patients with multinodular HCC. In particular, we compared outcomes of LR with those of PRFA and TACE in patients with resectable multinodular early HCC. The primary end point of the study was overall survival (OS). Data collection was performed using 2 large Italian multicenter databases: HE.RC.O.LE.S (Hepatocarcinoma Recurrence on the Liver Study group, 39 centers) for LR patients (study group), and ITA.LI.CA (Italian Liver Cancer group, 24 centers) for patients undergoing PRFA or TACE (control groups).

From January 1, 2008, to December 31, 2020, 5331 and 7056 patients with a new diagnosis of HCC were included in HE.RC.O.LE.S and ITA.LI.CA registries, respectively. The exclusion criteria were BCLC stage other than A, absence of cirrhosis, a single nodule, previous treatments for HCC, and combined therapy.

Moreover, to avoid crossovers between groups, we considered LR, PRFA, and TACE as the main treatments in each population in a hierarchical order. In other words, in the LR group, we excluded patients undergoing a hierarchically superior treatment during the follow-up (ie, liver transplant). Similarly, in the PRFA group, we excluded patients undergoing surgery to treat HCC recurrences. Finally, in the TACE group, we excluded patients undergoing surgery or PRFA during the follow-up. A total of 720 patients with early-stage multinodular HCC (2 or 3 nodules ≤3 cm) were finally selected (eFigure 1 in Supplement 1).

The following clinical and treatment-related variables were recorded: age, sex, comorbidities (Charlson Comorbidity Index),[21] disease cause (hepatitis B virus, hepatitis C virus, or alcohol), severity of liver disease (Model for End-stage Liver Disease [MELD] score, Child-Pugh class, platelet count, clinically relevant portal hypertension), and tumor characteristics (number and size of nodules, α-fetoprotein levels). Clinically relevant portal hypertension was defined as splenomegaly, varices, ascites on imaging, or platelet count less than 100 000/mL.[22] For the LR group, some technical details were also recorded (anatomic resection, major resection, and mini-invasive approach). We also recorded the main HCC treatments after first-line therapy. In this description, second-line therapies were described following the hierarchical therapy concept. For example, only LR was mentioned if the patient had LR, PRFA, and TACE during the follow-up. Similarly, only

ablation was mentioned if the patient had PRFA, TACE, and systemic therapy, and only intra-arterial therapy was mentioned if the patient had TACE and systemic therapy during the follow-up (eTable in Supplement 1).

HCC diagnosis was based on the European Association for the Study of the Liver (EASL) criteria.[23] Thus, noninvasive radiologic criteria were used in patients with cirrhosis and nodules larger than 1 cm, and when noninvasive criteria were not applicable, a tumor biopsy was performed. The response to treatment evaluation was also based on the EASL criteria.[23]

Treatment and Follow-Up

Standardized techniques and posttreatment follow-up protocols were not pre-established for the LR, PRFA, and TACE groups. However, all therapeutic and diagnostic interventions across various centers can be regarded as reasonably comparable and dependable because they were conducted in institutions affiliated with the HE.RC.O.LE.S and ITA.LI.CA registries, which possess substantial and long-lasting expertise in HCC management. PRFA was ultrasound-guided. Both conventional and drug-eluting bead TACE procedures were performed.

The efficacy of LR, PRFA, and TACE was evaluated with computed tomography or magnetic resonance imaging 1 month after the procedures. If a complete response was achieved, the follow-up computed tomography or magnetic resonance imaging was usually repeated every 3 months for the first 2 years and every 6 months after that.

Statistical Analysis

Categorical-nominal variables are expressed as frequencies (%), while continuous variables are median (IQR). For group comparisons, categorical and continuous variables were compared using Pearson χ^2 and Kruskal-Wallis rank sum test, respectively. The OS was calculated from the date of the therapeutic procedure to the date of the patient's death or the end of follow-up (December 2020). The length of the follow-up of survivors is expressed as median (IQR). The OS curves were calculated using the Kaplan-Meier technique and compared with the log-rank test.

The comparison of treatments across separately and differently collected datasets (HE.RC.O.LE.S and ITA.LI.CA) may be biased by cross-dataset differences. Propensity score analysis is usually used for matching uneven populations before comparison. In this study, it was not possible to use this method because of the intrinsic characteristics of the analysis. A necessary assumption to perform propensity score matching is that the variable treatment is exogenous, meaning that any treatment should be considered feasible in every patient included in the analysis. This study did not satisfy this assumption because patients eligible for PRFA and TACE may not always be suitable for LR based on considerations about portal hypertension, residual liver function, and tumor nodule location. Therefore, the comparative analysis was performed using a matching-adjusted indirect comparison (MAIC),[24] which should be applied for matching when the variable treatment is not exogenous.

MAIC created PRFA and TACE weighted populations that were similar and comparable with the reference LR population. Among the available variables in the 2 datasets, we selected the most relevant for clinical decision-making. Thus, the following variables were weighted to process 2 balanced pseudo-populations of PRFA and TACE compared with the LR group: age, sex, Charlson Comorbidity Index, Child-Pugh class, MELD score, clinically relevant portal hypertension (yes/no), cause of cirrhosis (viral/not viral), number and diameter of nodules, and serum α-fetoprotein levels. Continuous variables were dichotomized using relevant values derived from the literature to perform the MAIC.[24]

The results of the comparison between groups and weighted groups were reported using an effect size measure (*d*). Values less than 0.1 indicate minimal differences between means, values between 0.1 and 0.3 show negligible differences between means, values between 0.3 and 0.5 indicate moderate differences, and values greater than 0.5 indicate substantial differences. Univariable and multivariable Cox proportional hazard models were used to calculate the survival benefit of LR compared with alternative therapies.

Both unweighted and weighted Cox models were performed. All selected relevant variables were included in the multivariable analysis. Missing data for covariates involved less than 10% of patients and were estimated using the multiple imputation estimation method.[25]

Since the prognosis of patients with HCC is influenced not only by cancer-related death but also by liver failure and extrahepatic causes of death, weighted competing-risk analyses were performed using the methodology provided by Fine and Gray.[26] Although the primary end point of this study was OS, this analysis was important to better understand the pathophysiology of the potential benefit of LR over PRFA and TACE in the study population. Cancer-related death represents a surrogate for the potential oncological benefit of surgery. Conversely, extrahepatic causes of death represent a surrogate for the potential harm of LR related to liver hepatic failure or comorbidities.

Moreover, because OS could be influenced by the management of incomplete responses to first-line treatments or tumor recurrence after a complete response, a subgroup survival analysis was also performed in patients who had received only the first-line therapy for HCC. A subgroup OS analysis in patients with Child-Pugh class B cirrhosis was also performed.

A *P* value less than .05 was considered statistically significant. All statistical calculations were performed using Stata SE version 18.0. The Stata package ebalance was used for MAIC processing. Data were analyzed from January to December 2023.

Results

Patient Characteristics

A total of 720 patients with multinodular HCC were included, 543 males (75.4%), 177 females (24.6%), and 350 individuals older than 70 years (48.6%). There were 296 patients in the LR group, 240 who underwent PRFA, and 184 who underwent TACE. LR included 38.18% anatomic, 6.76% major, and 30.74% laparoscopic cases. The demographic and clinical characteristics of the patients are summarized in the eTable in Supplement 1 and **Table 1**.

Table 1. Demographic and Clinical Characteristics for Patients Before and After MAIC Weighting

Characteristic	No. (%)				
	LR (n = 296)	PRFA (n = 240)	Effect size	TACE (n = 184)	Effect size
Before weighting					
Age >70 y	132 (44.6)	129 (53.8)	−0.184	89 (48.4)	−0.076
Sex					
Male	227 (76.7)	181 (75.4)	0.030	135 (73.4)	0.077
Female	69 (22.3)	59 (24.6)		49 (26.6)	
CCI score>4	203 (68.6)	189 (78.8)	−0.232	136 (73.9)	−0.118
High-volume center	166 (56.1)	191 (79.6)	−0.519	137 (74.5)	−0.392
Viral cause	207 (69.9)	163 (67.9)	0.043	117 (63.6)	0.135
MELD score ≥8	199 (67.2)	170 (70.8)	−0.078	129 (70.1)	−0.062
Child-Pugh class B	28 (9.5)	62 (25.8)	−0.439	56 (30.4)	−0.543
Platelet ≤100 × 10^3/μL	73 (24.7)	88 (36.7)	−0.262	88 (47.8)	−0.495
Diameter ≥2 cm	242 (81.8)	153 (63.8)	0.412	123 (66.9)	0.345
Three nodules	59 (19.9)	50 (20.8)	−0.022	75 (40.8)	−0.464
AFP ≥20 ng/mL	98 (33.1)	97 (40.4)	−0.152	94 (51.1)	−0.370
After weighting					
Age >70 y	132 (44.6)	108 (45.0)	−0.008	83 (45.0)	−0.008
Sex					
Male	227 (76.7)	185 (77.1)	−0.007	142 (77.0)	−0.007
Female	69 (22.3)	55 (22.9)		42 (23.0)	
CCI score >4	203 (68.6)	166 (69.2)	−0.010	127 (69.0)	−0.009
High-volume center	166 (56.1)	134 (55.8)	0.002	103 (56.0)	0.002
Viral cause	207 (69.9)	168 (70.0)	−0.001	129 (70.0)	−0.001
MELD score ≥8	199 (67.2)	161 (67.1)	0.005	123 (67.0)	0.005
Child-Pugh class B	28 (9.5)	22 (9.2)	0.012	17 (9.0)	0.011
Platelet ≤100 × 10^3/μL	73 (24.7)	60 (25.0)	−0.007	46 (25.0)	−0.008
Diameter ≥2 cm	242 (81.8)	197 (82.1)	−0.006	151 (82.0)	−0.005
Three nodules	59 (19.9)	48 (20.0)	−0.002	37 (20.0)	−0.002
AFP ≥20 ng/mL	98 (33.1)	79 (33.0)	0.002	61 (33.0)	0.002

Abbreviations: AFP, α-fetoprotein; CCI, Charlson Comorbidity Index; MAIC, matching-adjusted indirect comparison; MELD, Model for End-Stage Liver Disease; LR, liver resection; PRFA, percutaneous radiofrequency ablation; TACE, transarterial chemoembolization.

Hepatitis C virus was the primary cause of liver disease, more prevalent in the PRFA group (63.3%) and followed by alcohol abuse. Hepatitis B virus infection was more common in the LR group (15.9%). Median MELD scores were 8 (LR) and 9 (PRFA and TACE), with a similar proportion of MELD scores of 8 or higher. Platelet counts were highest in LR (134 × 10^3/μL) and lowest in TACE (103 × 10^3/μL). Clinically relevant portal hypertension was less common in LR. Three nodules were more common in TACE and less in LR. Most LR and PRFA patients had α-fetoprotein levels less than 20 ng/mL, which was lower in TACE.

The number of incompletely treated cases (eTable 1 in Supplement 1) among patients with LR (positive margins, 10.1%) was significantly lower than in nonsurgical patients (imaging at 1 month showing residual HCC disease, 18.3% in PRFA, 49.5% in TACE). During follow-up, LR required significantly fewer second-line treatments (44.6%) compared with PRFA (74.2%) and TACE (60.3%). After MAIC matching (Table 1), the differences between groups consistently diminished (eFigure 2 in Supplement 1).

Overall Survival Analysis in the Unweighted Population

After a median follow-up for survivors of 67 months (LR), 77 months (PRFA), and 77 months (TACE), the Kaplan-Meier OS rates were as follows: LR, 1 year = 89.11%, 3 years = 70.98%, and 5 years = 56.44%; PRFA, 1 year = 90.74%, 3 years = 57.66%, and 5 years = 34.00%; TACE, 1 year = 84.35%, 3 years = 42.31%, and 5 years = 20.18%. Median OS was 69 months for patients who had LR, 41 months for those who had PRFA, and 31 months for those who had TACE. Kaplan-Meier curves are shown in **Figure 1**. Cox multivariable survival analysis showed LR was independently associated with a lower risk of death than PRFA and TACE (**Table 2**): PRFA had an HR of 1.77 (95% CI, 1.41-2.23; $P < .001$), and TACE had an HR of 2.52 (95% CI, 1.98-3.20; $P < .001$). Other factors independently linked to worse OS were high center volume, Child-Pugh class B, and α-fetoprotein levels of 20 ng/mL or higher (Table 2).

Overall Survival Analysis in the MAIC-Weighted Population

After MAIC adjustment, the 1-, 3-, and 5-year Kaplan-Meier OS rates were, respectively, as follows: LR (89.11%, 70.98%, 56.44%), PRFA (94.01%, 65.20%, 39.93%), and TACE (90.88%, 48.95%, 29.24%). Median OS was 69 months for patients who had LR, 54 months for those who had PRFA, and 34 months for those who had TACE. Kaplan-Mayer survival curves for the MAIC-weighted population are shown in **Figure 2**. Multivariable Cox survival analysis in the weighted population confirmed higher mortality risk with PRFA (HR, 1.41; 95% CI, 1.07-

1.86; *P* = .01) and TACE (HR, 1.86, 95% CI, 1.29-2.68, *P* = .001) compared with LR. The only other significant independent prognostic factor was Child-Pugh class B.

Competing Risk-Weighted and Subgroup Survival Analyses

Patients who were treated with LR had a lower risk of HCC-related death than those who had PRFA (HR, 1.38; 95% CI, 0.98-1.95; *P* = .07) and TACE (HR, 1.91; 95% CI, 1.20-3.02; *P* = .006) (eFigure 3A in Supplement 1). Conversely, non-HCC-related deaths showed no significant difference between LR and PRFA (HR, 1.08; 95% CI, 0.70-1.67; *P* = .74) and between LR and TACE (HR, 1.11; 95% CI, 0.61-2.01; *P* = .73) (eFigure 3B in Supplement 1).

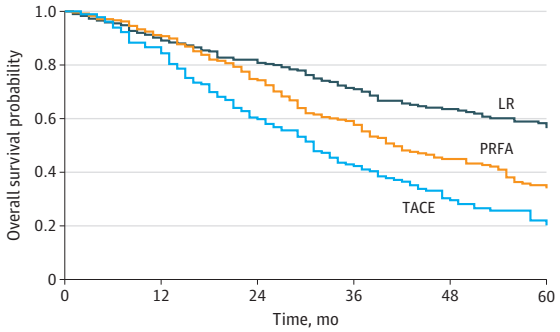
We then considered the subgroup of patients undergoing only first-line therapy (n = 318). There were 164 patients undergoing LR, 67 undergoing PRFA, and 87 undergoing TACE (eFigure 4 in Supplement 1). In this subgroup of patients, LR provided a significantly better OS (eFigure 4A in Supplement 1) than PRFA (HR, 1.96; 95% CI, 1.39-2.75; *P* < .001) and TACE (HR, 2.18; 95% CI, 1.58-3.01; *P* < .001). Competing risk analysis in this subgroup confirmed LR's clear superiority in preventing HCC-related deaths over PRFA (HR, 2.74; 95% CI, 1.70-4.43; *P* < .001) and TACE (HR, 2.84; 95% CI, 1.77-4.58; *P* < .001) (eFigure 4B in Supplement 1), with no significant differences in non-HCC-related deaths (eFigure 4C in Supplement 1). We also performed a subgroup survival analysis in patients with Child-Pugh class B cirrhosis (eFigure 5 in Supplement 1). In this subgroup of patients, LR provided a significantly better OS than TACE (HR, 2.79, 95% CI, 1.56-5.00; *P* = .001), while OS was similar to patients undergoing PRFA (HR, 1.44; 95% CI, 0.82-2.54; *P* = .21).

Discussion

The present comparative study enrolled the largest matched cohorts of patients with BCLC stage A multinodular HCC who had LR, PRFA, and TACE and represents the first Western study in this setting to our knowledge. We found only 1 study in the literature directly comparing LR vs PRFA and TACE[27]; it was a retrospective single-center Korean study involving a total of 276 patients (LR, n = 48; RFA, n = 87; TACE, n = 141) with early multinodular HCC, treated between 2009 and 2013.[11] OS and recurrence-free survival (RFS) were significantly higher with LR than with PRFA and TACE before propensity score matching. Still, after this adjustment, LR remained markedly better than PRFA and TACE only for RFS. However, the tiny sample size (reduced to 31 patients in each treatment group after adjustment) remarkably decreased the statistical power of this study.

The second study that directly compared only LR and PRFA (but not TACE) in patients with early multinodular HCC showed a better RFS and similar OS for LR compared with PRFA before and after propensity score matching (140 patients with LR vs 140 patients with PRFA).[13] A third comparative study between LR and PRFA (but not TACE) in these patients disclosed a slightly better OS and RFS for LR after propensity score

Figure 1. Probability of Overall Survival in the Unweighted Populations of the Liver Resection (LR), Percutaneous Radiofrequency Ablation (PRFA), and Transarterial Chemoembolization (TACE) Groups



No. at risk

LR	296	250	206	155	118	94
PRFA	240	212	162	122	81	59
TACE	184	153	101	69	42	24

Table 2. Univariate and Multivariate Cox Model of Overall Survival in the Unweighted Population

	Univariate		Multivariate	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Treatment group				
LR	1 [Reference]		1 [Reference]	
PRFA	1.77 (1.41-2.23)	<.001	1.54 (1.21-1.96)	<.001
TACE	2.52 (1.98-3.20)	<.001	2.17 (1.68-2.81)	<.001
Age >70 y	1.17 (0.97-1.41)	.10	1.12 (0.89-1.40)	.33
Male sex	1.07 (0.87-1.33)	.52	1.17 (0.93-1.46)	.18
CCI score>4	1.09 (0.88-1.36)	.42	0.89 (0.68-1.15)	.37
High-volume centre	1.43 (1.15-1.77)	.001	1.27 (1.01-1.58)	.04
Viral cause	0.98 (0.80-1.20)	.88	1.03 (0.84-1.28)	.76
MELD score ≥8	1.32 (1.07-1.63)	.01	1.24 (0.99-1.55)	.06
Child-Pugh class B	1.84 (1.49-2.29)	<.001	1.56 (1.23-1.96)	<.001
Platelet ≤100 × 10^3/μL	1.27 (1.05-1.54)	.02	1.09 (0.89-1.34)	.41
Diameter ≥2 cm	1.08 (0.87-1.33)	.48	1.17 (0.94-1.45)	.15
Three nodules	1.22 (0.99-1.50)	.06	0.96 (0.77-1.20)	.74
AFP ≥20 ng/mL	1.33 (1.10-1.61)	.003	1.30 (1.06-1.59)	.01

Abbreviations: AFP, α-fetoprotein; CCI, Charlson Comorbidity Index; HR, hazard ratio; LR, liver resection; MELD, Model for End-Stage Liver Disease; PRFA, percutaneous radiofrequency ablation; TACE, transarterial chemoembolization.

matching. Still, the study's power was meager because of the small sample size (20 patients with LR vs 20 patients with PRFA).[12]

The main result of the current study is the indisputable superiority of LR over PRFA and TACE in terms of OS, supported by a high effect size (HR 1.41 for PRFA vs LR and 1.86 for TACE vs LR) (**Table 3**). This clear superiority of LR over nonsurgical therapies in patients with early multinodular HCC is at variance from 3 previous studies indicating a clear superiority of LR only for RFS.[11-13] However, as these results are robustly supported by an adequately large sample size and by the use of the MAIC technique that reduced the selection bias in comparing treatment groups, the findings of this study are more probative than the previous ones. The previous limited "direct" evidence and the characteristics of the present multicenter investigation attribute to its results a considerable value in the evolutionary management of HCC, supporting the superiority of LR over ablation and TACE, regardless of the number and size of nodules.[7-10,28]

This assumption is supported by the study by Kawaguchi et al,[7] where 3 large populations were compared: patients who underwent resection (n = 15 313), those who underwent ablation (n = 15 216), and those who underwent TACE (n = 15 375). The study showed that the predicted 5-year survival was consistently higher after LR than in the other 2 groups, regardless of the number of nodules and the diameter of the main nodule. In general, there is a convergence of the literature toward the superiority of LR over nonsurgical therapies. The current study falls within this perspective, validating the concept of treatment hierarchy, which means that treatment is an ordinal variable (ordered from surgery to best supportive care) statistically independent from HCC stages as its prognostic value is maintained within each BCLC stage.[20]

The conceptual framework of the treatment hierarchy conflicts with that of the "stage hierarchy" of the BCLC algorithm, where the HCC stage dictates treatment choice.[20,29] The treatment indications of this algorithm exclude LR from the treatment of multinodular early HCC, and the results of this study would suggest the risk of incurring undertreatment if the BCLC indications are followed.

This risk may be reduced by adding more flexibility to the stage hierarchy with "treatment stage migration" and "treatment stage alternative," which improves flexibility and adherence. However, even these variants focus on a single main therapy for each stage or substage based on the available evidence, although other therapies with better survival benefits may be available.[20,29] On the other hand, the indiscriminate application of therapeutic hierarchy has the risk of exposing patients to overtreatment. Considering these observations and that therapeutic algorithms typically do not include factors significantly influencing therapeutic decisions in real-life scenarios, such as patient frailty,

Figure 2. Probability of Overall Survival in the Liver Resection (LR), Percutaneous Radiofrequency Ablation (PRFA), and Transarterial Chemoembolization (TACE) Populations After Matching-Adjusted Indirect Comparison Adjustment

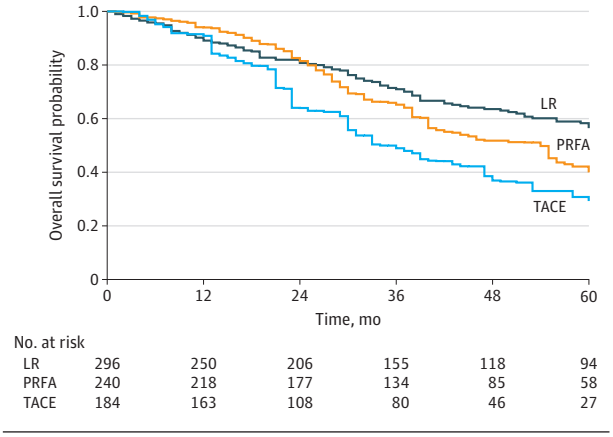


Table 3. Univariate and Multivariate Cox Model of Overall Survival in the MAIC-Weighted Population

	Univariate		Multivariate	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Treatment group				
LR	1 [Reference]		1 [Reference]	
PRFA	1.60 (1.24-2.07)	<.001	1.41 (1.07-1.86)	.01
TACE	1.96 (1.42-2.71)	<.001	1.86 (1.29-2.68)	.001
Age >70 y	1.02 (0.80-1.29)	.90	0.96 (0.70-1.32)	.82
Male sex	1.17 (0.87-1.56)	.30	1.12 (0.78-1.61)	.55
CCI score>4	1.03 (0.79-1.33)	.85	1.07 (0.75-1.53)	.71
High-volume center	1.21 (0.90-1.64)	.20	1.22 (0.88-1.68)	.22
Viral cause	1.00 (0.78-1.29)	.98	1.00 (0.74-1.36)	>.99
MELD score ≥8	1.38 (1.06-1.80)	.02	1.24 (0.90-1.69)	.19
Child-Pugh class B	1.55 (1.10-2.18)	.01	1.57 (1.03-2.39)	.04
Platelet ≤100 × 10^3/μL	1.03 (0.81-1.30)	.84	1.00 (0.77-1.30)	.98
Diameter ≥2 cm	1.28 (0.97-1.68)	.08	1.25 (0.93-1.66)	.14
Three nodules	0.98 (0.75-1.28)	.89	1.00 (0.74-1.35)	.98
AFP ≥20 ng/mL	1.27 (0.99-1.63)	.06	1.30 (0.96-1.77)	.09

Abbreviations: AFP, α-fetoprotein; CCI, Charlson Comorbidity Index; HR, hazard ratio; LR, liver resection; MAIC, matching-adjusted indirect comparison; MELD, Model for End-Stage Liver Disease; PRFA, percutaneous radiofrequency ablation; TACE, transarterial chemoembolization.

comorbidities, critical tumor location, and technical or logistical difficulties, a multiparametric model has been recently proposed.[20] It guides the decision-making process of a specialized multidisciplinary group according to the above-mentioned clinical variables, switching the strategy from stage-centered to patient-customized therapy, as envisioned by precision medicine.

Limitations

The present study has several limitations. It may be affected by the selection bias due to potential "hidden" variables that were not collected in the centers' databases. Unfortunately, recurrence data were available only for the HE.RC.O.LE.S and not for the ITA.LI.CA registry. For this reason, we analyzed only cancer-related deaths in the competing risk analysis. However, the end point cancer-related death could be considered a good surrogate of aggressive recurrence after HCC treatment.

Not all patients included in the study were potentially treatable with all 3 proposed alternatives. In particular, only a randomized clinical trial could ensure all enrolled patients were resectable. Conversely, in this retrospective study, a relevant proportion of patients enrolled in the PRFA and TACE groups were probably unresectable for portal hypertension, residual liver function, and tumor nodule location. Using the MAIC procedure limited this relevant drawback, eliminating the differences between treatment groups and making the PRFA and TACE populations as superimposable as possible to the LR population regarding patients, liver function, and tumor characteristics (Table 1).

Another potential limitation is inherent to the study design (applying the concept of therapeutic hierarchy), excluding from each study group patients undergoing hierarchically superior therapies during the follow-up (ie, transplant in the LR group, surgery in the PRFA group, surgery or PRFA in the TACE group). In reality, the relative proportions of excluded crossover patients were very low (<5%) and thus not relevant for our prognostic analysis.

Moreover, because of the retrospective nature of this study, we cannot say with certainty that all nonsurgical therapies were adopted with curative intent, particularly TACE. All these limitations were also more relevant because surgical and nonsurgical patients were derived from different databases. Lastly, as the studied population came from Italian centers, the results of the present study need to be confirmed in different patient cohorts to extend their generalizability.

Conclusions

For patients with early multinodular HCC ineligible for transplant, LR is the preferred first-line treatment, followed by PRFA and TACE if surgery is not feasible. While our results show LR's superiority over nonsurgical therapies, further confirmation from large prospective studies is needed.

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Invited Commentary

What Is the Best Local Therapy for HCC?
It Actually Matters More How They All Work Together

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Screening and surveillance strategies allow us to diagnose hepatocellular carcinoma (HCC) at early stages.[1] This disease, which is the third highest killer of human cancers, is now being diagnosed when the tumor is small and highly treatable. However, even when discovered by surveillance and screening, the presentation of HCC is often multinodular. This has led to a debate on which local therapy is best in the setting of multifocal presentation. Most Eastern guidelines recommend resection of the hepatic resection when possible,[2] while Western guidelines often recommend thermal ablation or transarterial chemoembolization.[3] The article in this issue of *JAMA Surgery* by Vitale et al[4] is a superb multicenter collected series composed of data from 2 large Italian registries collected between 2008 and 2020. By univariate and multivariate analysis, the investigators present convincing data that liver resection leads to superior 3- and 5-year survivals.[4] They also demonstrate on multivariate analysis that outside of baseline liver function, resection is the most important factor for long-term survival.

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The clinical situation, however, is usually much more complicated than deciding which of these 3 suitable local therapies is best. Clearly, baseline liver function plays into the decision-making. In the supplemental data provided by the authors, patients with a Child-Pugh B baseline liver function class had a very high (25%) first-year mortality.[4] Thus, ablative therapy is likely better in this setting. In clinical practice, patients will rarely receive only one of these therapies unless they are cured. Most patients on recurrence will have additional local therapies, which could range from embolization of multifocal disease to reresection or transplant for solitary lesions.[5] There is also increasing data that combinations of ablations and transarterial chemoembolization render a much higher likelihood of durable local response and a higher rate of potential cure. At many centers, multifocal disease is likely to be treated with upfront combined ablation and embolization.[6]