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Systematic Review

Liver resection *versus* radiofrequency ablation or trans-arterial chemoembolization for early-stage (BCLC A) oligo-nodular hepatocellular carcinoma: meta-analysis

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Abstract

Background: The 2022 Barcelona Clinic Liver Cancer (BCLC) algorithm does not recommend liver resection (LR) in BCLC A patients with oligo-nodular (two or three nodules ≤3 cm) hepatocellular carcinoma (HCC). This sharply contrasts with the therapeutic hierarchy concept, implying a precise treatment order exists within each BCLC stage. This study aimed to compare the outcomes of LR *versus* radiofrequency ablation (RFA) or trans-arterial chemoembolization (TACE) in BCLC A patients.

Methods: A meta-analysis adhering to PRISMA guidelines and the Cochrane Handbook was performed. All RCT, cohort and case–control studies that compared LR *versus* RFA or TACE in oligo-nodular BCLC A HCC published between January 2000 and October 2023 were comprehensively searched on PubMed, Embase, the Cochrane Library and China Biology Medicine databases. Primary outcomes were overall survival (OS) and disease-free survival (DFS) at 3 and 5 years. Risk ratio (RR) was computed as a measure of treatment effect (OS and DFS benefit) to calculate common and random effects estimates for meta-analyses with binary outcome data.

Results: 2601 patients from 14 included studies were analysed (LR = 1227, RFA = 686, TACE = 688). There was a significant 3- and 5-year OS benefit of LR over TACE (RR = 0.55, 95% c.i. 0.44 to 0.69, $P < 0.001$ and RR 0.57, 95% c.i. 0.36 to 0.90, $P = 0.030$, respectively), while there was no significant 3- and 5-year OS benefit of LR over RFA (RR = 0.78, 95% c.i. 0.37 to 1.62, $P = 0.452$ and RR 0.74, 95% c.i. 0.50 to 1.09, $P = 0.103$, respectively). However, a significant 3- and 5-year DFS benefit of LR over RFA was found (RR = 0.70, 95% c.i. 0.54 to 0.93, $P = 0.020$ and RR 0.82, 95% c.i. 0.72 to 0.95, $P = 0.015$, respectively). A single study comparing LR and TACE regarding DFS showed a significant superiority of LR. The Newcastle–Ottawa Scale quality of studies was high in eight (57%) and moderate in six (43%).

Conclusions: In BCLC A oligo-nodular HCC patients, LR should be preferred to RFA or TACE (therapeutic hierarchy concept). Additional comparative cohort studies are urgently needed to increase the certainty of this evidence.

Introduction

Primary liver cancer stands as the third foremost contributor to cancer-related fatalities. Projections anticipate a 55% surge in mortality between 2020 and 2040, culminating in a staggering 1.3 million cases by 2040[1,2].

Although significant advancements have been achieved in the surgical treatment of hepatocellular carcinoma (HCC) in the last 20 years[3], liver resection (LR) remains the victim of current Western hepatological guidelines[4,5]. The Barcelona Clinic Liver Cancer (BCLC) algorithm still does not consider liver resection a valuable treatment option for HCC patients with intrahepatic vascular invasion or multinodular tumours. However, solid evidence nowadays supports such a treatment strategy[6,7]. The discrepancy between Western hepatological guidelines and real-world surgical indications is well documented in large international, multicentre surgical series such as the one published by Roayaie *et al.*[8], where more than 70% of patients underwent liver resection beyond the BCLC guidelines. In contrast, the role of liver resection is completely different in Eastern guidelines[9], where the variable 'resectability' is hierarchically superior to vascular invasion or the number of nodules in the proposed treatment algorithm.

Most importantly, several pieces of evidence clearly show a relevant survival benefit of LR over non-surgical therapies independent of tumour stage[10,11]. This evidence is in line with the concept of therapeutic hierarchy, meaning both that treatment choice is independent of the HCC stage and that a precise hierarchical order of treatment exists (liver transplantation > LR > ablation > intra-arterial therapies > systemic therapies > best supportive care) within each BCLC stage[12,13]. A recent policy review[13] underlines that the therapeutic hierarchy approach should be adopted only in expert multidisciplinary tumour boards, where a multiparametric decisional process can be applied for personalized treatment decisions.

The present study focuses on the subgroup of HCC patients with oligo-nodular BCLC-A HCC (that is, two or three nodules under 3 cm and well-compensated cirrhosis). The 2022 BCLC algorithm does not recommend resection for these patients. Rather, trans-arterial chemoembolization (TACE) is preferred if

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the first treatment (liver transplantation or ablation) option is not feasible[4]. This means that the treatment hierarchy rule is not respected for this specific BCLC subgroup of patients. A systematic review and meta-analysis were therefore performed to compare the outcome of LR with either radiofrequency ablation (RFA) or TACE in patients with resectable oligo-nodular BCLC-A HCC with the aim to validate the treatment hierarchy concept for patients with early oligo-nodular HCC.

Materials and methods

Systematic review design

The key question developed according to the Population, Intervention, Comparison, Outcomes (PICO) acronym was the following:

Does LR provide a significant survival benefit over RFA or TACE in early (BCLC-A) resectable oligo-nodular (two or three nodules under 3 cm) HCC patients?
P (population): patients with a resectable early (BCLC-A) oligo-nodular HCC
I (intervention): LR
C (comparator): RFA or TACE
O (outcome): overall survival and disease-free survival

The review was conducted on the relevant literature published from 1 January 2000 to 1 February 2023 on PubMed, Embase, the Cochrane Library, and China Biology Medicine databases following the PRISMA guidelines. It was registered on the PROSPERO register (CRD42023413492). The search strategy included the following keywords: (MeSH) '((resection) OR (hepatectomy)) AND ((HCC) OR (hepatocellular carcinoma) OR (hepatoma) OR (liver malignancy) OR (liver tumor)) AND ((multifocal) OR (multinodular) OR (multiple HCC))'.

Inclusion criteria for articles were as follows: RCT, cohort or case–control studies published within the range 2000/January/01–2023/October/01; comparison between liver resection or RFA or TACE; patients with multinodular (2 or 3) HCC BCLC-A; analysis of overall survival (OS) or recurrence-free survival (DFS).

Exclusion criteria for articles were as follows: other types of studies outside those listed in the inclusion criteria; publication in languages other than English; the population belonging to the inclusion criteria has not been clearly defined or not analysed; combined therapy.

The studies underwent an inclusion evaluation process with a double-blind check conducted by two reviewers (P.R. and M.B.) using Rayyan software[14], first through titles and abstracts and then analysing the whole text at the end of the selection process. Any discrepancies were resolved by a discussion including two auditors and a third investigator (A.V.).

Data extraction and quality assessment

Two reviewers (P.R. and M.B.) independently extracted and summarized data from the included studies using a predefined data extraction module. Any conflicts that arose during this process were resolved through discussion or with the consent of a third-party auditor (A.V.).

The following information was recorded: general information, including first author, year of publication, study design, and status; population characteristics, including the number of patients, reference demographic characteristics, follow-up time, postoperative mortality and morbidity, Child class, model for end-stage-liver disease (MELD) score, MELD-sodium score, clinically relevant portal hypertension (CRPH), alcohol abuse, HCV or HBV infection, non-alcoholic-steato-hepatitis, cirrhosis presence and outcomes for each treatment group.

The methodological quality of case–control and retrospective studies was evaluated using the Newcastle Ottawa Scale (NOS). Eight items were assessed in three key domains: patient selection, comparison of study groups and outcome. The quality of the studies was categorized into three levels according to the number of points obtained: low (<4 points), moderate (between 4 and 6 points) and high (≥7 points)[15]. The evaluation was conducted in duplicate and independently by two reviewers (P.R. and M.B.). Disagreements were resolved through consensus.

Statistical analysis

The report of this meta-analysis was carried out in line with the PRISMA statement and with the Cochrane guide. The Engauge Digitizer software (version 4.1, M Mitchell, http://markummitchell.github.io/engauge-digitizer/) was used to extract survival data from Kaplan–Meier curves for studies that did not show HR and 95% c.i. In studies where the number of events at different time intervals was not available, it was calculated from the at-risk patients using the formula described by Tierney *et al.*[16].

Continuous variables were expressed as medians and interquartile ranges; categorical variables were expressed as absolute numbers and percentages. All results were reported with 95% c.i. A proportion meta-analysis with random or fixed-effects models evaluated information from studies comprising more than three patients. Variables included in the meta-analysis were: overall survival at 3 and 5 years and DFS at 3 and 5 years.

Risk ratio (RR) was computed as a measure of treatment effect to calculate common and random effects estimates for meta-analyses with binary outcome data. The Mantel–Haenszel method[17,18] was used to calculate the common effect estimate. The Paule–Mandel estimator was used to estimate $\tau 2$, the between-study variance[19].

In order to obtain a simple estimate of the overall effect of hepatic resection, RFA and chemoembolization on the population studied, the meta-analysis of proportions was used to pool the risk of mortality or recurrence at 3 and 5 years for each type of treatment. For descriptive purposes, the effect size was expressed as the number needed to treat (NNT = 1/risk difference, where the risk difference (RD) is calculated as RD = mortality or recurrence rate in control group (RFA and TACE)−mortality or recurrence rate in treatment group (liver resection, LR)). The lower the NNT, the higher the overall and disease-free survival benefits.

Heterogeneity was evaluated using the I^2 test. According to the Cochrane revision guidelines, if there is moderate or severe heterogeneity (that is, $I^2 > 25\%$ or >50%, respectively)[20], a random-effect model was used. Otherwise ($I^2 < 25\%$), a fixed-effect model was used. Publication bias was evaluated through a funnel plot. Statistical significance was defined as $P < 0.05$. RStudio 4.3.0 (2023) software was used for statistical analysis and graphical representation.

Results

Literature search and characteristics of included studies

The study flow chart summarizes the process of selecting studies (*Fig. S1*)[21].

A total of 1825 studies were retrieved from the bibliographic database search. After removing duplicates, 1762 studies were screened, and 68 potentially eligible studies were identified for full-text review. A further 45 articles were excluded based on a wrong publication type.

Moreover, a further search was conducted through bibliography searches in relevant papers and guidelines, and the results were

Table 1 Summary of studies included in the meta-analysis with the outcomes of OS and DFS

First author	Design	Study period	No. of patients oligo-nodular BCLC A			3-year OS (%)			5-year OS (%)			3-year DFS (%)			5-year DFS (%)			Follow-up (months)
			LR	RFA	TACE	LR	RFA	TACE	LR	RFA	TACE	LR	RFA	TACE	LR	RFA	TACE	
Zhang, 2022[22]	MR	2009–2019	38	40	–	–	–	–	–	–	–	29.6	20.7	–	20.6	12	–	50.8
Oh, 2020[23]	R	2009–2013	48	87	141	93.7	82.5	77.1	86.8	63.6	54.7	65.7	36.5	11.6	56	18.9	4.5	62.4
	PS		32	31	31	90.4	83.3	84.5	79.5	72.3	62	60.2	41.3	7.7	51.9	22	3.4	69.6
Fukami, 2020[24]	MR	2000–2007	435	–	434	86.9	–	77.6	70.7	–	53.3	–	–	–	–	–	–	19.2
Min, 2018[25]	R	2004–2009	26	62	–	92.4	83.4	–	88.5	61.5	–	69.4	26.5	–	46.2	24.4	–	78
	PS		20	20	–	100	84.7	–	100	63.3	–	75.2	30.0	–	60	30	–	
Guo, 2017[26]	R	2003–2012	21	–	11	71.4	–	9.1	35.1	–	0	–	–	–	–	–	–	39
Jiang, 2015[27]	R	2008–2013	224	160	–	71.7	72.7	–	36.3	37.8	–	53.1	34	–	20.1	9.7	–	29.8
	PS		140	140	–	72.9	74	–	38.9	38.9	–	52.4	35.8	–	18.9	10.1	–	
Desiderio, 2013[28]	MR	2004–2012	30	25	–	96.6	52	–	30	16	–	70	36	–	13.3	8	–	51.7
Ruzzenente, 2012[29]	R	1995–2009	13	9	–	62.9	60	–	62.9	60	–	39.2	47.6	–	19.6	–	–	33.8
Tashiro, 2011[30]	R < 2cm	2001–2007	30	5	–	92	92	–	69	73	–	22	18	–	22	18	–	35
	R > 2cm		27	11	–	96	75	–	43	78	–	28	0	–	22	0	–	
Huang, 2010[31]	RCT	2003–2005	26	31	–	80.8	58.1	–	69.2	45.2	–	–	–	–	–	–	–	37.2
Ueno, 2009[32]	MR	2000–2005	13	54	–	67	93	–	–	63	–	29	35	–	–	22	–	35.0
Ho, 2009[33]	R	1981–2000	95	–	71	64.8	–	43.6	41.2	–	16.4	–	–	–	–	–	–	20.2
Guglielmi, 2008[34]	R	1996–2006	7	6	–	50	75	–	–	37	–	–	–	–	–	–	–	32
Vivarelli, 2004[35]	MR	1998–2002	2	5	–	100	33	–	–	–	–	100	33	–	–	–	–	28.9

OS, overall survival; DFS, disease-free survival; BCLC, Barcelona Clinic Liver Cancer; LR, liver resection; RFA, radiofrequency ablation; TACE, trans-arterial chemoembolization; PS, propensity score cohort; R, retrospective; MR, multicentric retrospective.

included in the second branch of the flow chart (*Fig. S1*). Finally, 23 studies remained. Papers that lacked multinodular BCLC-A population analysis or did not show the correct result were excluded, so 12 studies were finally included. An identical step-by-step process was followed for studies found through bibliography searches in relevant papers and guidelines, including two additional studies.

Study and patients' baseline characteristics

Finally, 14 studies were included[22–35], three of which analysed the study's target population[23,25,27], whereas the remainder focused on subgroups that met the inclusion criteria. Among these, 13 were retrospective studies[22–30,32–35], three presented a propensity score analysis and one was an RCT[31]. The studies were conducted in Eastern (China, Japan, Korea, Taiwan) and Western (Italy) centres.

A total of 2601 patients from the 14 included studies were analysed, with 1227 patients undergoing LR, 686 patients treated with RFA and 688 patients undergoing TACE. Duration of follow-up ranged from 32 to 78 months. The main characteristics of the included studies are reported in *Table 1*.

Study quality assessment

The assessment of the quality of the studies and the scores in each of the eight domains of the NOS scale are specified in *Table S1*. In summary, eight studies (57%) obtained a NOS score of ≥7 stars, indicating high methodological quality, while six studies (43%) were considered to be of moderate quality.

Overall survival benefit

Liver resection versus *radiofrequency ablation*

A total of 10 reports were included for the analysis of the OS benefit between the LR ($n = 482$) and RFA ($n = 490$) groups.

Figure 1a shows a non-significant 5-year OS benefit of LR over RFA (RR 0.74, 95% c.i. 0.50 to 1.09, $P = 0.103$), with a high heterogeneity between the studies ($I^2 = 52.5\%$ (0.0% to 79.8%), $P = 0.049$, *Fig. S2a*).

Similarly, *Fig. 1b* shows a non-significant 3-year OS benefit of LR over RFA (RR = 0.78, 95% c.i. 0.37 to 1.62, $P = 0.452$) and high heterogeneity between the studies ($I^2 = 51.3\%$ (0.0% to 77.2%), $P = 0.037$, *Fig. S2b*).

Liver resection versus *chemoembolization*

A total of four reports were included for the analysis of OS between the LR ($n = 599$) and TACE ($n = 657$) groups.

Figure 1c shows a significant 5-year DFS benefit of LR over TACE (RR 0.57, 95% c.i. 0.36 to 0.90, $P = 0.030$) and a moderate heterogeneity between the studies ($I^2 = 48.5\%$ (0.0% to 82.9%), $P = 0.120$, *Fig. S2c*).

Figure 1d shows a significant 3-year DFS benefit of LR over TACE (RR = 0.55, 95% c.i. 0.44 to 0.69, $P < 0.001$) and a low heterogeneity between the studies ($I^2 = 2.5\%$ (0.0% to 85.1%), $P = 0.380$, *Fig. S2d*).

NNT benefit analysis

The 3-year mortality rates derived from the meta-analysis of proportions were 0.17 (0.11; 0.27) for LR, 0.22 (0.19; 0.26) for RFA and 0.44 (0.08; 0.88) for TACE (*Fig. S3*). The 5-year mortality rates were 0.37 (0.23; 0.53) for LR, 0.47 (0.42; 0.52) for RFA and 0.71 (0.15; 0.97) for TACE (*Fig. S4*).

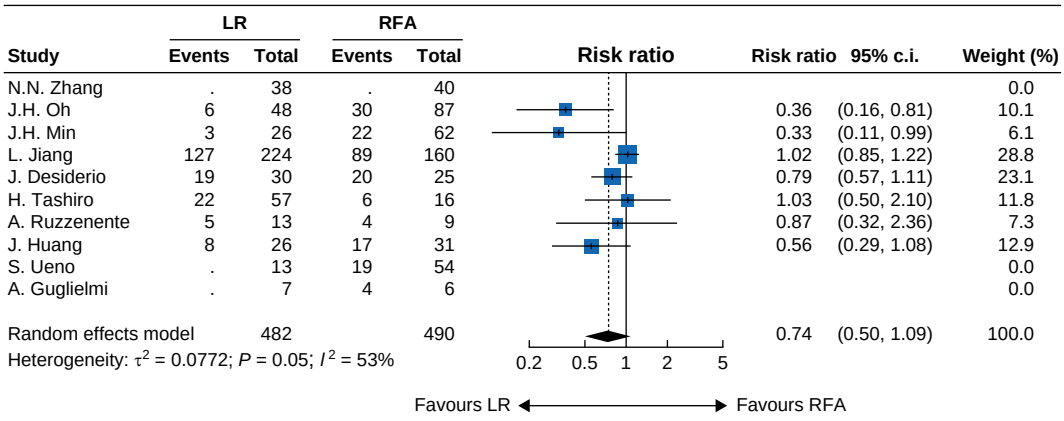
Overall survival benefits of LR over the other treatment modalities were calculated as NNT. The NNT values expressing the 3-year LR OS benefit were 20 over RFA and 3.70 over TACE. The NNT values expressing the 5-year LR OS benefit were 10 over RFA and 2.94 over TACE (*Table S1*).

Disease-free survival benefit

Liver resection versus *radiofrequency ablation*

A total of seven reports were included for the analysis of DFS between the LR ($n = 436$) and RFA ($n = 399$) groups.

a



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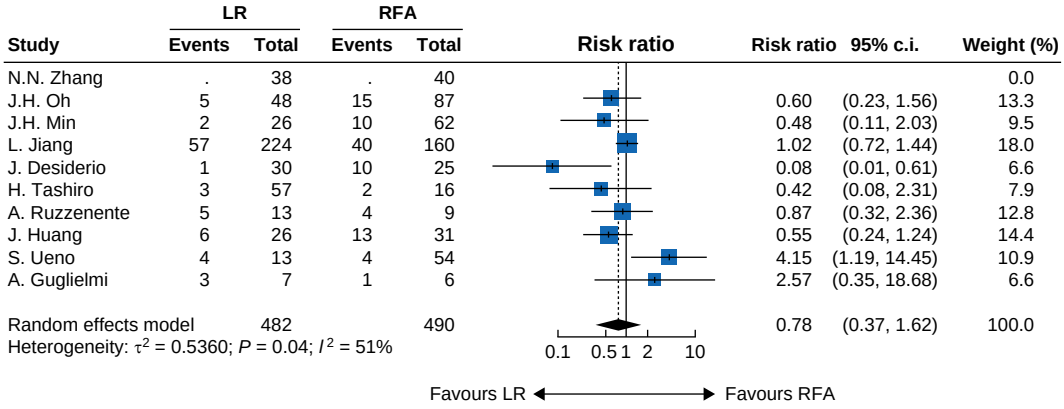

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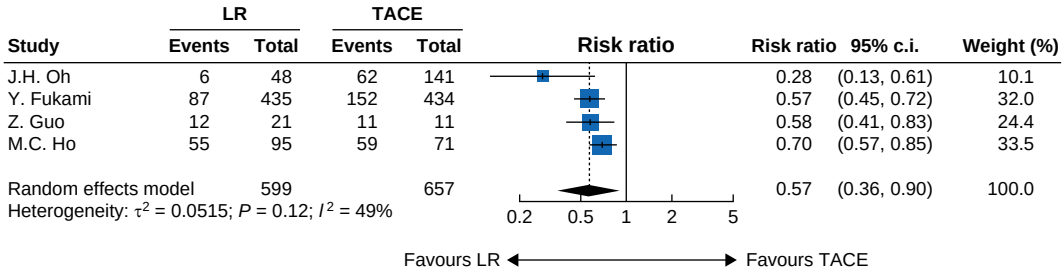

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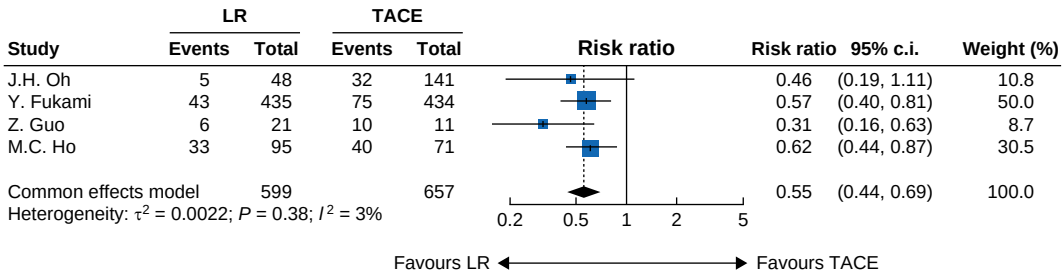
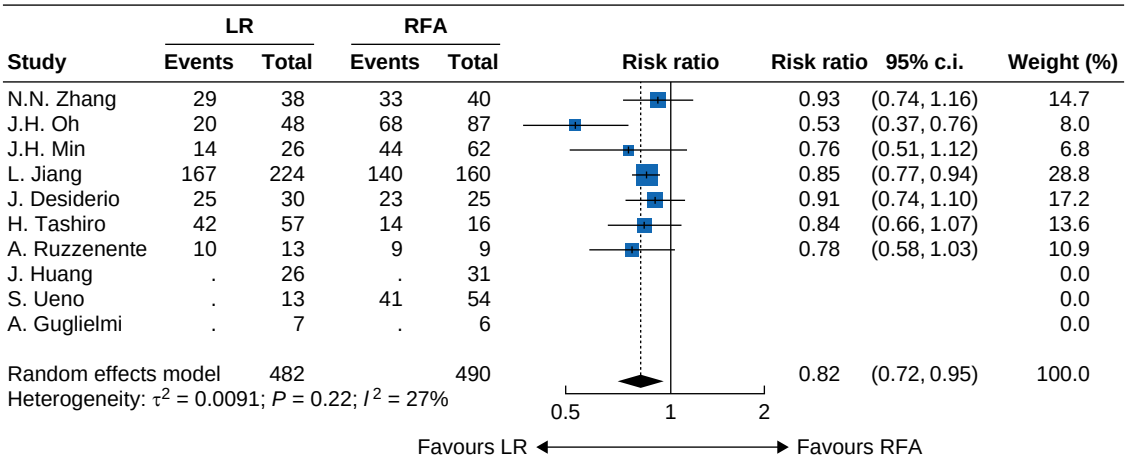


Fig. 1 Overall survival results

a Five-year overall survival liver resection (LR) *versus* radiofrequency ablation (RFA). **b** Three-year overall survival LR *versus* RFA. **c** Five-year overall survival LR *versus* trans-arterial chemoembolization (TACE). **d** Three-year overall survival LR *versus* TACE.

a



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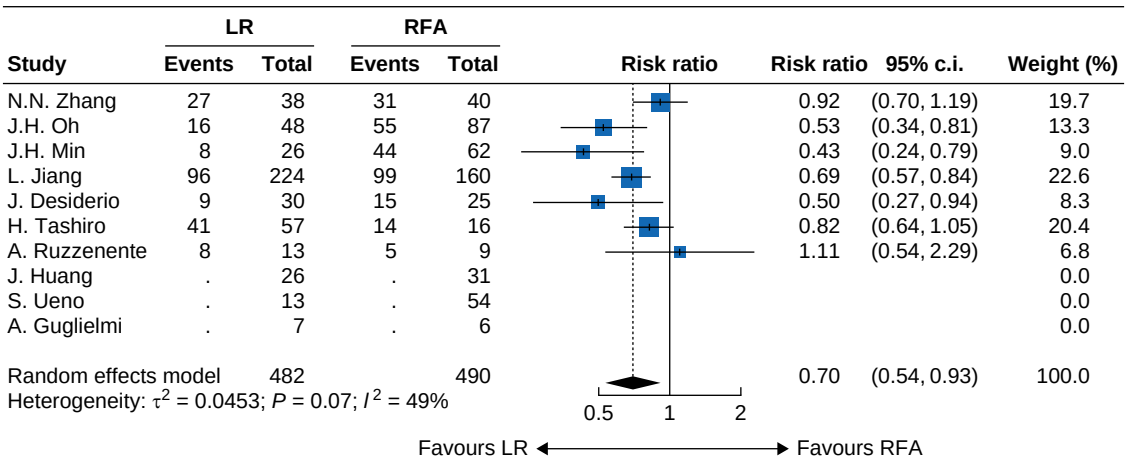

Fig. 2 Disease-free survival results

a Five-year disease-free survival liver resection (LR) *versus* radiofrequency ablation (RFA). **b** Three-year disease-free survival LR *versus* RFA.

As shown in *Fig. 2a*, a significant 5-year DFS benefit of LR over RFA was observed (RR 0.82, 95% c.i. 0.72 to 0.95, $P = 0.015$) and the heterogeneity between the studies was moderate ($I^2 = 27.4\%$ (0.0% to 68.6%), $P = 0.220$, *Fig. S5a*).

Figure 2b shows a significant 3-year DFS benefit of LR over RFA (RR = 0.70, 95% c.i. 0.54 to 0.93, $P = 0.020$) but with a high heterogeneity between the studies ($I^2 = 49.1\%$ (0.0% to 78.5%), $P = 0.067$, *Fig. S5b*).

Liver resection versus *chemoembolization*

Because DFS was reported only in a cohort study[23] involving LR ($n = 48$) and TACE ($n = 141$) treatment groups, a meta-analysis for this endpoint was not performed. In the study by Oh *et al.*[23], after propensity score, 3- and 5-year DFS rates were 60.2% and 51.9% for LR and 7.7% and 3.4% for TACE, respectively ($P < 0.001$). After multivariable Cox analysis, the reported propensity score-adjusted hazard ratio was 4.86 (95% c.i. 2.42 to 9.76), describing a consistently higher risk of death after TACE than LR.

NNT benefit analysis

The 3-year recurrence rates derived from the meta-analysis of proportions were 0.47 (0.31; 0.64) for LR, 0.66 (0.61; 0.70) for RFA and 0.89 (0.83; 0.93) for TACE (*Fig. S6*). The 5-year recurrence rates were 0.69 (0.55; 0.81) for LR, 0.82 (0.78; 0.85) for RFA and 0.96 (0.92; 0.99) for TACE (*Fig. S7*). The NNT values expressing the 3-year LR DFS benefit were 5.26 over RFA and 2.38 over TACE. Conversely, the NNT values expressing the 5-year LR DFS benefit were 7.69 over RFA and 3.70 over TACE (*Table S1*).

Discussion

The results of this meta-analysis show that LR offers better outcomes for BCLC A patients with two or three nodules smaller than 3 cm (early oligo-nodular HCC) when compared to RFA and TACE. LR was statistically superior to TACE in terms of OS benefit, while significant OS benefit differences were not observed upon comparison of LR with RFA. However, as shown in a recent meta-analysis mainly focused on single small HCCs[36], the study's superiority of LR over RFA was more evident in regard to DFS. Along the same line, the single study[23] comparing LR and TACE in terms of DFS showed an overwhelming superiority of LR (that is, 5-year DFS was 51.9% for LR *versus* only 3.4% for TACE), supporting the hypothesis that TACE is more a palliative than a curative therapeutic option. Together, these results confirm the existence of a precise treatment hierarchy (LR > RFA > TACE) also in oligo-nodular early (BCLC-A) HCC.

Table 2 Summary of cohort studies supporting the superiority of LR over RFA or TACE independent of tumour stage (indirect evidence)

First author, year, location	Study design, study cohort (No.)	Therapies (No.)	Survival outcome measures	Comments
Vitale, 2015, Italy[10]	Observational 1181 Child A	*Very early BCLC stage*	*Median survival (months)*	Multivariate log-logistic parametric survival analysis including patient, liver function, and tumour-related variables and using treatment as stratifying covariate
		Resection (23)	92	
		Ablation or TACE (70)	62	
		Early BCLC stage		
		Resection (147)	72	
		Ablation or TACE (314)	50	
		Single > 5 cm		
		Resection (45)	55	
		Ablation or TACE (25)	42	
		Intermediate BCLC stage		
		Resection (83)	52	
		Ablation or TACE (207)	41	
Serper, 2017, USA[11]	Observational 3988		*Hazard ratio (95% c.i.)*	Multivariable time varying Cox analysis including BCLC staging
		No therapy (1436)	1.00 Reference	
		LT (160)	0.18 (0.13,0.25)	
		Resection (160)	0.31 (0.13,0.25)	
		Ablation (439)	0.50 (0.42,0.60)	
		Transarterial therapy (1755)	0.72 (0.65,0.80)	
		Sorafenib (1555)	1.70 (1.54,1.86)	
Vitale, 2018, Italy[38]	Observational 1196		*Hazard ratio (95% c.i.)*	Multivariable Cox analysis including ITA.LI.CA score performed at restaging before additional treatment decision
		LT (41)	1.00 Reference	
		Resection (37)	2.10 (0.85,5.45)	
		Ablation (164)	2.93 (1.47,6.68)	
		Transarterial therapy (446)	3.66 (1.90,8.20)	
		Sorafenib (253)	3.57 (2.87,12.52)	
		Other (79)	5.70 (2.78,13.29)	
		No therapy (176)	6.30 (3.17,14.36)	
Vitale, 2019, Italy[37]	Observational controlled with IPTW 4867		*Hazard ratio (95% c.i.)*	Multivariable IPTW Cox analysis including ITA.LI.CA staging
		No therapy (1210)	1.00 Reference	
		LT (174)	0.19 (0.18,0.20)	
		Resection (645)	0.40 (0.37,0.42)	
		Ablation (1546)	0.42 (0.40,0.44)	
		Transarterial therapy (1085)	0.58 (0.55,0.61)	
		Sorafenib (207)	0.92 (0.87,0.97)	
Kawaguchi, 2021, Japan-Italy-USA[7]	Observational controlled with IPTW 43,904		*5-year survival (95% c.i.)*	Multivariable IPTW Cox analysis including tumour burden
		Resection (15,313)	46.2% (44.0%,48.3%)	
		Ablation (15,216)	33.4% (31.1%,35.7%)	
		Trans-arterial therapy (13,375)	27.4% (25.0%,29.8%)	

LR, liver resection; RFA, radiofrequency ablation; TACE, trans-arterial chemoembolization; BCLC, Barcelona Clinic Liver Cancer; LT, liver transplantation; ITA.LI.CA, Italian liver cancer; IPTW, inverse probability of treatment weighting.

The results regarding DFS expose a need for comparative studies to analyse this outcome. This meta-analysis shows that the direct evidence comparing LR with RFA or TACE has room for improvement. First, only 14 studies have data comparing LR and RFA or TACE in oligo-nodular early HCC. Second, only three of the 14 studies identified by this meta-analysis were designed to analyse the study target population of early oligo-nodular HCC. At the same time, the other 11 studies were focused on larger populations, forcing us to derive the data for this meta-analysis from subgroup analyses. In these 11 studies, the three treatment subpopulations (LR *versus* RFA *versus* TACE) had only the multinodular BCLC-A stage in common. Still, they might differ in age, gender, co-morbidities and other characteristics. For this reason, the results of this paper (that is, the superiority of LR over RFA and TACE) could be affected by a not negligible selection bias due to unknown confounding factors.

Moreover, confounding variables, including the considerable heterogeneity among patients or disparities in LR techniques and management protocols across various institutions, could impact the results of this meta-analysis. In particular, the location of the HCC nodules represents an unknown variable in these studies that greatly impacts treatment choice. For example, percutaneous RFA is often unfeasible in superficial exophytic nodules, making LR a favourable option. The influence of latent variables necessitates careful consideration, thus warranting further investigation into this subject matter for enhanced clarity.

However, the present results should be evaluated in the context of the available literature concerning all HCC stages. This study presents indirect evidence from studies that compare LR with RFA or TACE but do not focus on the specific subgroup of BCLC-A multinodular HCC patients. From this larger perspective, the study's results are supported by a large amount of indirect solid evidence suggesting the superiority of LR over RFA or TACE regardless of the BCLC stage (*Table 2*)[7,10,11,37,38]. Supposing LR is superior to RFA or TACE in most BCLC stages, in that case, there are no solid pathophysiological reasons to hypothesize an exception only for BCLC A patients with oligo-nodular HCC.

Therefore, this study falls within that line of research, validating the concept of treatment hierarchy. Treatment hierarchy means that both treatments are an ordinal variable

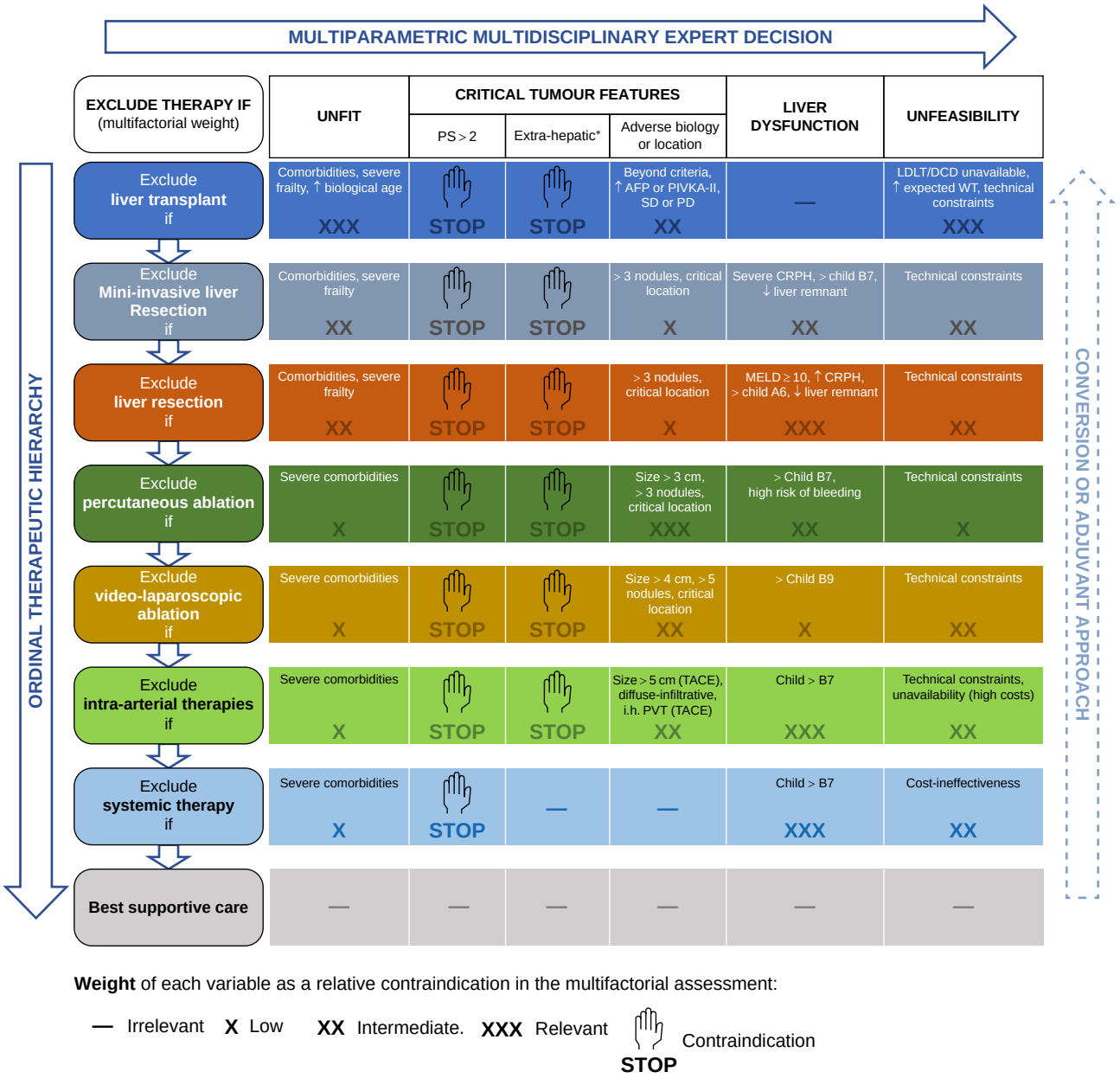

Fig. 3 Concepts of multiparametric and converse therapeutic hierarchy

Figure reproduced with permission from Elsevier[13]. PS, performance status; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin-K absence-II; SD, stable disease; PD, progression disease; LDLT, living donor liver transplantation; DCD, donor after circulatory death; WT, waiting time; DBD, donor after brain death; MELD, model for end-stage liver disease; CRPH, clinically relevant portal hypertension; TACE, trans-arterial chemoembolization; PVT, portal vein thrombosis.

(ordered from liver transplant to best supportive care) statistically independent by HCC stages, but also that this prognostic hierarchy of treatments is maintained within each BCLC stage[12] (*Table 2*). The conceptual framework of treatment hierarchy is clearly in contrast with stage hierarchy, where the HCC stage dictates treatment choice[12,13]. The specific treatment indications for patients with oligo-nodular early HCC in the last BCLC 2022 update, excluding the option of LR for these patients, are a clear example of stage hierarchy. From this perspective, this current study also validates the treatment hierarchy concept within the specific subgroup of early oligo-nodular HCC.

The risk associated with stage hierarchy is the potential undertreatment of patients, leading to the denial of hierarchically superior treatments that offer better survival benefits[13]. For instance, this situation may arise in cases of oligo-nodular early HCC, where a decision is made to offer TACE to a patient eligible for surgical resection[3]. Conversely, a liberal treatment hierarchy approach carries the risk of overtreating patients. For this reason, the treatment hierarchy approach must be balanced by a multiparametric evaluation done by an expert multidisciplinary team, as suggested in *Fig. 3*, taken by a recently published policy review[13]. In the specific LR setting, this is the best example of a multiparametric treatment decision for HCC patients[39]. This aspect is well described in the last guidelines of the European Association for the Study of the Liver[40], introducing the multiparametric concept of 'optimal surgical candidate'. However, the same concept was not acknowledged by the BCLC authors, mainly maintaining a monoparametric vision of LR treatment allocation.

In the context of the multiparametric LR decision, the newly proposed scheme (Fig. 3) suggests another crucial point favouring the choice of LR over RFA or TACE for early oligo-nodular HCC patients, particularly in recent years, which is the possibility of adopting a minimally invasive surgical approach. The multiparametric treatment hierarchy scheme considers minimally invasive LR hierarchically superior to open LR (Fig. 3). This important novelty of this scheme is supported by the recent literature showing that a minimally invasive approach improves the mid–long-term outcomes of LR over an open approach[41–43]. Moreover, other studies show that the minimally invasive approach may also increase the indications of LR in patients with borderline liver function[44,45]. Because the studies included in this meta-analysis do not account for a pivotal prognostic variable, namely the potential adoption of a minimally invasive approach, it is plausible that the outcomes presented might underestimate the authentic survival advantages of LR compared to RFA or TACE. Thus, it becomes imperative to initiate additional investigations that have the potential to elucidate the prospective benefits that minimally invasive techniques could contribute to the existing findings.

Other crucial variables to be considered in the multiparametric decision for LR included in the novel scheme (Fig. 3) but not evaluated in the studies included in the present meta-analysis are patients' fitness and location of nodules. These two variables are particularly important to orientate the clinician's decision towards a surgical or a non-surgical option in patients with multinodular BCLC-A HCC.

Finally, the novel scheme suggests another relevant point favouring LR over RFA or TACE, supporting this study's results. Resectability and transplantability can also be considered appropriate clinical endpoints to be reached after successful conversion therapy. This is the concept of converse therapeutic hierarchy, where surgery represents the final step. In contrast, systemic and loco-regional non-surgical therapies represent the tools to achieve surgical treatment[13]. From this perspective, BCLC-A oligo-nodular stage can be considered not at first diagnosis but as the consequence of a downstaging process promoted by non-surgical therapies. This possibility (that is, conversion/downstaging of unresectable tumours to a resectable BCLC-A oligo-nodular HCC) is higher nowadays due to the introduction of effective systemic treatments[46]. Again, this innovative concept of 'converse therapeutic hierarchy' is not considered in the 2022 BCLC algorithm, where only a left-to-right treatment stage migration to systemic therapies is allowed.

For all these reasons, the correct expert recommendation for answering the initial PICO cannot be the exclusion of LR as a therapeutic option for these HCC patients, as done in the last BCLC paper[4]. Conversely, the recommendation should be that in early oligo-nodular HCC patients with a resectable tumour, LR should be suggested instead of RFA or TACE.

Additional large comparative cohort studies specifically enrolling BCLC-A patients with oligo-nodular HCC are urgently needed to strengthen this recommendation in terms of certainty of evidence.

Author contributions

Pierluigi Romano (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing—original draft, Writing—review & editing), Marco Busti (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing—original draft, Writing—review & editing), Ilaria Billato (Methodology, Software, Visualization, Writing—original draft), Francesco D'Amico (Conceptualization, Supervision, Writing—review & editing), Giovanni Marchegiani (Supervision, Writing—review & editing), Filippo Pelizzaro (Writing—review & editing), Alessandro Vitale (Conceptualization, Data curation, Formal analysis, Project administration, Supervision, Validation, Writing—review & editing) and Umberto Cillo (Conceptualization, Project administration, Supervision, Validation).

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

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