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Bridging locoregional treatment prior to liver transplantation for cirrhotic patients with hepatocellular carcinoma within the Milan criteria: a systematic review and meta-analysis

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Abstract

Background We performed a meta-analysis to assess the benefit of bridging locoregional treatment (LRT) before liver transplantation for cirrhotic patients with hepatocellular carcinoma (HCC) already within the Milan criteria at diagnosis.

Methods We included original studies with HCC cases within the Milan criteria at diagnosis, comparing patients with and without bridging LRT before liver transplantation.

Results Twenty-six retrospective original studies were included. Out of the 9068 patients within the Milan criteria, 6435 (71%) received bridging LRT and 2633 (29%) did not. The most frequent LRTs were transarterial chemoembolization, radiofrequency ablation, and microwave ablation. Most of the patient and tumor characteristics were similar between the 2 groups. Maximum tumor diameter on scans was slightly larger in the LRT arm (mean difference: 0.36 cm, 95% confidence interval [CI] 0.11-0.61; I^2=79%). The LRT group also had multifocal disease slightly more frequently (risk ratio [RR] 1.21, 95%CI 1.04-1.41; I^2=0%) and disease extent outside the Milan criteria (RR 1.3, 95%CI 1.03-1.66; I^2=0%) on pathological examination of explanted livers. There was no difference between the 2 arms in the waiting time for transplant, dropout rates, disease-free survival at 1, 3, 5 years after transplant, or overall survival at 3 and 5 years after transplant. However, cases with LRT had better overall survival at 1 year after transplant (hazard ratio 0.54, 95%CI 0.35-0.86; I^2=0%).

Conclusions The precise benefit of bridging LRT for cirrhotic patients with HCC within the Milan criteria at diagnosis is unclear. There may be an advantage regarding short-term overall survival after liver transplantation.

Keywords Hepatocellular carcinoma, liver cirrhosis, liver transplantation, locoregional treatment, bridging

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide and the presence of liver cirrhosis is a well-recognised risk factor [1]. There is a variety of different treatment options for HCC, including liver resection, liver transplantation, locoregional treatment (LRT), and systemic treatment. The choice of therapy or a combination of therapies for a cirrhotic patient with HCC is based on tumor extent, extrahepatic spread, macrovascular invasion, preserved liver function, as well as performance status [2]. Although liver transplantation can achieve the longest survival for cirrhotic patients with HCC [3], the high recurrence rates and short survival frequently seen after the early attempts made it clear that a threshold in tumor burden had to be set [4].

Mazzaferro *et al* were the first to propose a list of criteria for cirrhotic patients with HCC in 1996, which became

known as the Milan criteria and were considered the gold standard. They reported that, by accepting only patients with a single tumor up to 5 cm, or 2-3 tumors up to 3 cm each, and without gross vascular invasion or extrahepatic disease, they had achieved an overall survival rate of 75%, and a recurrence-free survival rate of 83% at 4 years after transplantation [5]. Several studies have reported similar survival rates between cases exceeding the Milan criteria at diagnosis, but successfully downstaged after LRT, and cases within the Milan criteria at diagnosis [6-8]. However, it is unclear whether there is a need to treat cirrhotic patients with HCC, already within the Milan criteria at diagnosis, with LRT as a bridge to liver transplantation to avoid disease progression while they are on the waiting list.

Our aim was to perform a meta-analysis of the studies comparing HCC cases with and without bridging LRT prior to liver transplantation, to assess the clinical benefit of bridging LRT for the cirrhotic patients already within the Milan criteria at the time of diagnosis.

Materials and methods

Search strategy

We conducted a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, as revised in 2020 [9]. On June 30, 2022, we searched the databases PubMed/Medline, Scopus and Google Scholar for articles published up to that date, using the search terms "liver transplant", "hepatocellular carcinoma", "percutaneous", "ablation", "ethanol injection", "transarterial", "embolization", "chemoembolization", "radioembolization", "stereotactic", "radiotherapy", "locoregional treatment", and "bridging therapy", combined with the Boolean operators AND/OR.

Inclusion and exclusion criteria

We included only original articles referring to patients with HCC who underwent liver transplantation and whose disease extent was within the Milan criteria at the time of diagnosis. Studies had to include a comparison between patients with and without bridging LRT prior to liver transplantation. We excluded congress abstracts, editorials, comments, reviews, case reports, animal studies, non-comparative studies, studies that just compared different types of bridging LRT in liver transplant recipients, without comparison with treatment-naive cases, and comparative studies that included cases outside the Milan criteria at the time of diagnosis and had no separate analysis for cases within the Milan criteria.

Review and analysis

We extracted the following data about the patients within the Milan criteria at the time of diagnosis: number, sex, age, cause of liver cirrhosis, model for end-stage liver disease (MELD) score, Child-Pugh score, pre-treatment with α-fetoprotein (AFP), type of LRT, donor type (living or deceased), waiting time between listing and transplant, number of tumors and maximum tumor diameter according to radiological findings, radiological response for the cases with bridging LRT, number of tumors, maximum tumor diameter, tumor grade and cases outside the Milan criteria according to pathological examination of the explanted liver, pathological response for the cases with bridging LRT (tumor viability after LRT in the explanted liver), dropout cases (progression outside criteria before being able to be transplanted), postoperative morbidity and mortality, disease-free survival after liver transplantation, and overall survival after liver transplantation. The primary endpoints of our meta-analysis were the dropout rates from the waiting list, disease-free survival after liver transplantation, and overall survival after liver transplantation, in cases with bridging LRT and those without. The secondary endpoints of our meta-analysis were assessing the type and frequency of LRT modalities, as well as the radiological and complete pathological response after bridging LRT.

Statistical analysis

Risk ratio (RR) was calculated for qualitative variables, mean difference (MD) for quantitative variables, and hazard ratio (HR) for survival. Given the expected heterogeneity among the included studies, the random effects model was selected for all comparisons. Comparisons between qualitative or quantitative variables were performed using the inverse variance method. Comparisons regarding survival were performed using the generic inverse variance method. Statistical heterogeneity was assessed using Higgin's I^2 statistic. The equations proposed by Hozo *et al* [10] and Wan *et al* [11] were applied for the estimation of mean values and/or standard deviations (SD) when they were not reported. The equations proposed by Parmar *et al* [12] were applied for the calculation of log HR and/or its standard error (SE) when they were not reported. The level of statistical significance was defined as a $P<0.05$. The methodological index for non-randomized studies (MINORS) was used for the quality assessment of the included studies. This is a validated tool for assessing the methodological quality of non-randomized studies. As far as comparative studies are concerned, it includes 12 items, each of them scored between 0 and 2, thus providing a final score ranging between 0 and 24 for each study [13]. The quality of evidence for the main outcomes (dropout rate, disease-free survival, overall survival) was evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach [14]. Meta-analysis was performed using the Review Manager software Version 5.3.

Results

Search outcomes

Out of the 3094 articles identified during the initial search, 26 original studies met the inclusion criteria for our meta-analysis, as described in the review flowchart (Fig. 1). All the included studies were retrospective [6,15-39]. Fourteen originated from the USA [19,20,22-26,28,31,32,34,36,38,39], 4 from Korea [6,17,30,35], 3 from Germany [15,27,29], 1 from France [37], 1 from Austria [18], 1 from Canada [33], 1 from Saudi Arabia [21], and 1 was multinational [16]. There were 10,154 patients in total in the included studies, of whom 7186 (70.8%) underwent bridging LRT before liver transplantation, whereas 2968 (29.2%) proceeded to liver transplantation without previous bridging LRT. Of the 10,154 total patients, 9068 (89.3%) were within the Milan criteria at the time of diagnosis, according to radiological findings; of these 6435 (71%) received bridging LRT whereas 2633 (29%) did not [6,15-39]. The included studies were considered as methodologically adequate according to the MINORS scale, with scores ranging from 15 to 22 and an average score of 18.1. Table 1 summarizes the study characteristics.

Types of bridging LRT

Twenty of the 26 included studies (76.9%) used more than 1 type of LRT. Transarterial chemoembolization (TACE), either alone or in combination with another treatment, was used in 3400 out of the 4777 patients for whom data about the exact type of bridging LRT (71.2%) were available, making it the most implemented form of LRT. The second most frequent bridging LRT was thermal ablation, in the form of radiofrequency ablation (RFA) or microwave ablation (MWA), which was used in 1398 of the 4777 patients (29.3%), either alone or in combination with another treatment. Other types of LRT, either alone or in combination, were used much less frequently: transarterial embolization (TAE) in 39/4777 (0.8%), transarterial radioembolization (TARE) in 163/4777 (3.4%), percutaneous ethanol injection (PEI) in 79/4777 (1.7%), and others [17-20,22-25,28-37,39]. A detailed description of the various LRT types in each study is included in Table 1.

Patient characteristics

There was no statistically significant difference between patients who underwent bridging LRT and those who did not in terms of sex (LRT: male: 3686/4741 [77.7%], no LRT: male: 1425/1812 [78.6%]; RR 0.99, 95%CI 0.96 to 1.02, P=0.65; I^2=0%, P=0.97) or age (MD 0.44 years, 95%CI -0.94 to 1.81, P=0.53), although there was high heterogeneity among the included studies as regards age (I^2=82%, P<0.001) [16,17,19,20,22,28,30,32-36]. Regarding the underlying etiology of the liver cirrhosis, there was

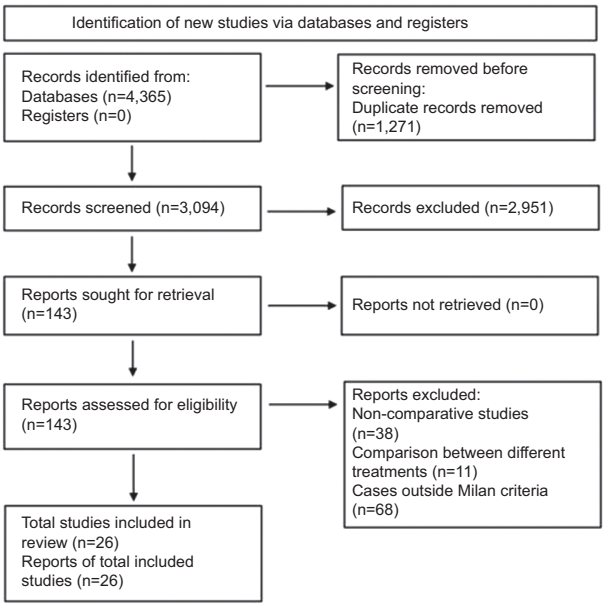

Figure 1 Review flowchart

no actual difference in the rates of hepatitis C between the 2 arms (LRT: 2702/4584 [58.9%], no LRT: 963/1648 [58.4%]; RR 1.02, 95%CI 0.98 to 1.05, P=0.32; I^2=0%, P=0.64) [16,18-20,22,23,28,30-33,35,36,39]. The same was true for rates of hepatitis B (LRT: 787/4708 [16.7%], no LRT: 294/1765 (16.7%); RR 1.07, 95%CI 0.95 to 1.22, P=0.27), although there was some degree of heterogeneity among studies (I^2=46%, P=0.03) [16-20,22,23,28,30,32-36,39]. On the other hand, the rate of alcohol-related cirrhosis was lower in the group with bridging LRT (LRT: 660/4520 (14.6%), no LRT: 261/1568 (16.6%); RR 0.8, 95%CI 0.67 to 0.95, P=0.01; I^2=17%, P=0.29) [16,18-20,22,23,28,30,32,33,35].

Although the higher rate of Child-Pugh A cirrhosis in the bridging LRT arm did not reach statistical significance (LRT: 191/385 [49.6%], no LRT: 105/265 [39.6%]; RR 1.51, 95%CI 0.94 to 2.42, P=0.09) [17,22,30,32], the MELD score was somewhat lower in this group (MD -1.71, 95%CI -3.18 to -0.23, P=0.02) [16,17,20,22,28,30,32-36]. However, there was significant heterogeneity among the included studies concerning Child-Pugh grade (I^2=77%, P=0.004) [17,22,30,32] and MELD score (I^2=92%, P<0.001) [16,17,20,22,28,30,32-36]. Pre-transplant AFP was similar between the 2 groups when all the included studies with relevant information were considered (MD 12.1 ng/mL, 95%CI -14.9 to 39.1, P=0.38), but the findings differed significantly among them (I^2=98%, P<0.001) [16,17,20,30,32-35]. Waiting time from listing to transplant was similar between the 2 arms (MD -1.68 months, 95%CI -5.76 to 2.39, P=0.42), although there was high interstudy heterogeneity (I^2=99%, P<0.001) [16,19,22,25,28,31-34,36]. Finally, the distribution of deceased donors did not differ significantly between cases with and without bridging LRT (LRT: 261/429 [60.8%], no LRT: 270/370 [73%]; RR 1, 95%CI 0.98 to 1.03, P=0.79; I^2=0%, P=0.43) [17,24,29,30,33-35].

Table 1 Study characteristics

Author, year [ref.]	Country	Time period	LRT (n)	No LRT (n)	LRT – patients within Milan criteria (n)	No LRT – patients within Milan criteria (n)	Types of LRT	MINORS score
Lee *et al*, 2020 [6]	Korea	2005-2015	688	208	441	177	TACE, RFA, other	18
Bauschke *et al*, 2020 [15]	Germany	1996-2017	87	79	37	33	TACE, RFA, TKI	20
Lai *et al*, 2019 [16]	Austria, Belgium, Croatia, Germany, Italy, UK	2001-2015	901	182	901	182	TACE, RFA, PEI	19
Kim *et al*, 2018 [17]	Korea	2005-2011	124	73	124	73	TACE, RFA	17
Gyori *et al*, 2017 [18]	Austria	2004-2011	120	26	80	22	TACE, RFA, PEI	18
Kallini *et al*, 2018 [19]	USA	2003-2013	175	159	175	159	TACE, RFA	15
Agopian *et al*, 2017 [20]	USA	2002-2013	2,854	747	2,854	747	TACE, TARE, RFA/ MWA, PEI, other	18
Al Sebayel *et al*, 2017 [21]	Saudi Arabia	2001-2016	69	89	30	81	TACE, TARE	16
Xing *et al*, 2017 [22]	USA	1998-2013	155	110	155	110	TACE, TARE, RFA	20
Beal *et al*, 2016 [23]	USA	2008-2015	43	20	43	20	TACE, RFA, MWA	19
Sheth *et al*, 2015 [24]	USA	2004-2012	147	30	147	30	TACE, RFA, MWA, other	19
Macdonald *et al*, 2015 [25]	USA	2004-2009	802	272	802	272	TACE, RFA, other	19
Kim *et al*, 2013 [26]	USA	2002-2008	157	65	112	61	TACE, RFA, other	16
Kornberg *et al*, 2013 [27]	Germany	1996-2008	59	34	37	20	TACE, RFA	18
Sourianarayanane *et al*, 2012 [28]	USA	2002-2009	93	132	93	132	TACE, TARE, TAE, RFA	20
Seehofer *et al*, 2012 [29]	Germany	1989-2008	71	106	38	79	TACE	16
Kim *et al*, 2012 [30]	Korea	2002-2008	71	30	71	30	TACE, RFA, PEI, other	19
Cabrera *et al*, 2012 [31]	USA	1996-2005	33	47	33	47	TAE	20
Frangakis *et al*, 2011 [32]	USA	2001-2008	35	52	35	52	TACE	17
DuBay *et al*, 2011 [33]	Canada	1999-2007	77	93	77	93	RFA	22
Lao *et al*, 2009 [34]	USA	2001-2006	33	91	33	91	TACE, RFA, PEI	18
Kim *et al*, 2006 [35]	Korea	1996-2004	36	21	36	21	TACE	17
Porrett *et al*, 2006 [36]	USA	2002-2004	31	33	31	33	TACE, TARE, RFA, PEI	18
Dacaens *et al*, 2005 [37]	France	1985-1998	100	100	66	66	TACE	20
Yao *et al*, 2005 [38]	USA	1988-2002	103	65	56	34	TACE, RFA, PEI, other	16
Maluf *et al*, 2003 [39]	USA	1997-2001	11	10	11	10	TACE, RFA, PEI	16

LRT, locoregional treatment; MINORS, methodological index for non-randomized studies; MWA, microwave ablation; N/A, not available; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TAE, transarterial embolization; TACE, transarterial chemo-embolization; TARE, transarterial radio-embolization

Tumor characteristics

As far as pre-transplant radiological findings are concerned, there was no significant difference in the percentage of cases with multifocal tumors between the 2 groups (LRT: 294/726 [40.5%], no LRT: 262/728 [36%]; RR 1.18, 95%CI 0.92 to 1.52; P=0.19), although there was significant interstudy heterogeneity (I^2=65%, P=0.002) [17,19,22,28,31,32,34-36,39]. Moreover, the number of tumors on scans was similar between cases with and without bridging LRT (MD 0.12, 95%CI -0.05 to 0.29, P=0.18; I^2=56%, P=0.06) [16,28,30,32,35]. However, maximum tumor diameter, as identified by pre-transplant scans, was slightly larger in the LRT arm (MD 0.36 cm, 95%CI 0.11 to 0.61; P=0.004), although there was high heterogeneity among the included studies (I^2=79%, P<0.001) [16,17,28,30,34,35].

Regarding pathological findings in the explanted livers, transplants with bridging LRT had a slightly, but statistically significantly higher percentage of multifocal disease (LRT: 425/918 [46.3%], no LRT: 142/355 [40%]; RR 1.21, 95%CI 1.04 to 1.41, P=0.02; I^2=0%, P=0.96) [16,28,35,36], as well as a slightly, but again statistically significantly greater number of tumors (MD 0.22, 95%CI 0.03 to 0.41, P=0.02) than transplants without bridging LRT, even though there was some interstudy heterogeneity concerning the latter (I^2=57%, P=0.04) [16,20,23,28,30,35]. Nevertheless, the maximum tumor diameter in the explanted livers was similar in both groups when all the included studies with relevant information were taken into account (MD 0.12 cm, 95%CI -0.14 to 0.39; P=0.37), even though there was high heterogeneity among the included studies (I^2=78%, P=0.001) [16,20,28,30,35]. Furthermore, the percentage of high-grade tumors was similar between the 2 arms (LRT: 342/3,838 [8.9%], no LRT: 130/1,096 [11.9%]; RR 0.83, 95%CI 0.61 to 1.13, P=0.24; I^2=23%, P=0.25) [16,20,23,30,33,35,36]. On the other hand, the percentage of cases outside the Milan criteria based on the pathological examination of the explanted livers was slightly higher in the LRT arm (LRT: 242/973 [24.9%], no LRT: 81/407 [19.9%]; RR 1.3, 95%CI 1.03 to 1.66, P=0.03; I^2=0%, P=0.99] [16,28,30,33].

Response to locoregional treatment, dropout rates, and post-transplant survival

Unfortunately, only 3 studies reported the radiological response to bridging LRT. Radiological complete response was seen in 333 of 1125 cases (29.6%) [16,24,33]. In addition, 8 studies reported a pathological response to bridging LRT. Pathological complete response was detected in 834 of 3876 cases (21.5%) [16,18,20,23,28,35,36,39]. There was no statistically significant difference in dropout rates from the waiting list between cases with bridging LRT and those without, when all the included studies with relevant information were considered (LRT: 282/1395 [20.2%], no LRT: 75/489 [15.3%]; RR 1.22, 95%CI 0.7 to 2.12, P=0.48]. However, the heterogeneity among the included studies was high (I^2=79%, P<0.001) [16,18,22,24,32,33] (Fig. 2).

There was no difference between the 2 approaches in terms of disease-free survival at 1 (HR 0.66, 95%CI 0.2 to 2.14, P=0.49; I^2=95%, P<0.001) [6,17,20,28,30,38], 3 (HR 1.06, 95%CI 0.8 to 1.41, P=0.69; I^2=28%, P=0.21) [6,17,20,28,30,35,36] or 5 years (HR 0.94, 95%CI 0.63 to 1.4, P=0.75; I^2=58%, P=0.02) after liver transplantation [6,20,26-30,35,38], but the interstudy heterogeneity was significant at 1 and 5 years after liver transplantation (Fig. 3) [6,17,20,26-30,35,38]. In contrast, the LRT arm had a lower risk of death from any cause at 1 year after liver transplantation, thus an advantage regarding 1-year overall survival over the non-LRT arm (HR 0.54, 95%CI 0.35 to 0.86, P=0.009; I^2=0%, P=0.57) [6,18,22,28,35]. Nonetheless, overall survival was similar between the 2 groups at 3 (HR 1.07, 95%CI 0.73 to 1.55, P=0.73; I^2=0%, P=0.85) [6,18,28,35,36] and 5 years (HR 0.94, 95%CI 0.66 to 1.34, P=0.74; I^2=59%, P=0.01) after liver transplantation, although the interstudy heterogeneity was significant at 5 years after liver transplantation (Fig. 4) [6,15,18,21,22,26,28,29,35,37] (Fig. 4). Outcomes regarding dropout rates and post-transplant survival are summarized in Table 2.

Discussion

There are various types of LRT for HCC. They fall into 3 major categories: namely, percutaneous techniques,

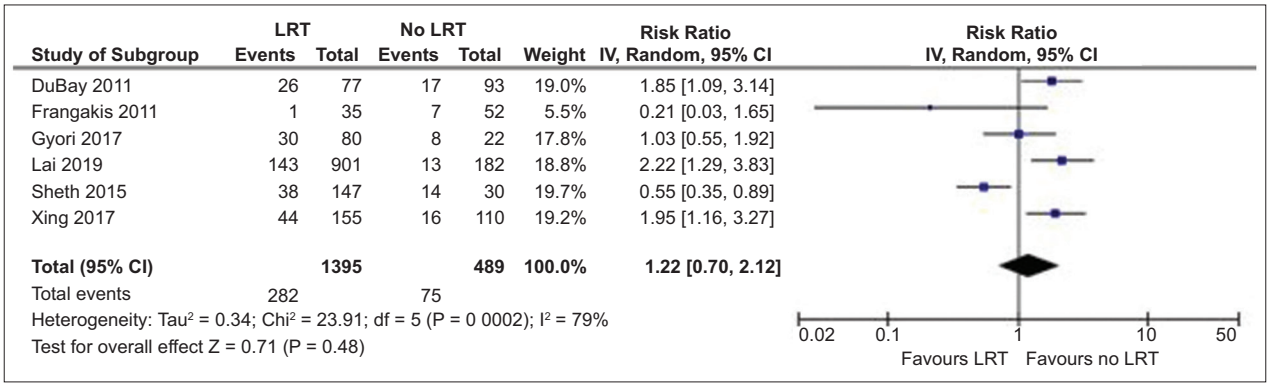

Figure 2 Dropout from waiting list
LRT, locoregional treatment; CI, confidence interval

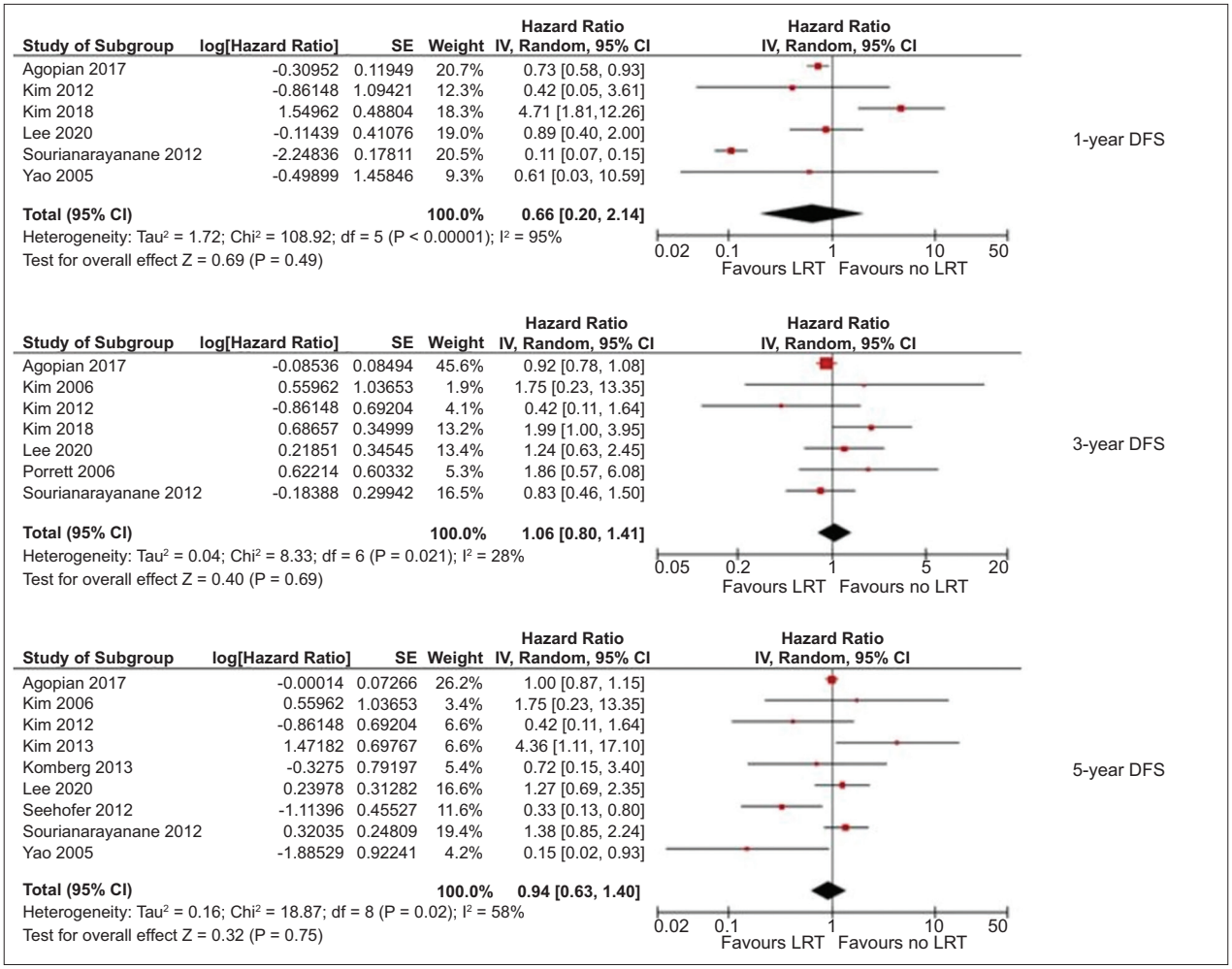

Figure 3 Disease-free survival (DFS) after liver transplantation
LRT, locoregional treatment; CI, confidence interval

Table 2 Comparison of dropout rates and post-transplant survival between cases with and without locoregional treatment

Outcome	Number of participants (studies)	Quality of evidence (GRADE)	Relative effect (95%CI)
Dropout	1884 (6 studies)	MODERATE Due to inconsistency	RR 1.22, 95%CI 0.7 to 2.12
1-year disease-free survival	4832 (6 studies)	MODERATE Due to inconsistency	HR 0.66, 95%CI 0.2 to 2.14
3-year disease-free survival	4863 (7 studies)	HIGH	HR 1.06, 95%CI 0.8 to 1.41
5-year disease-free survival	5039 (9 studies)	MODERATE Due to inconsistency	HR 0.94, 95%CI 0.63 to 1.4
1-year overall survival	1267 (5 studies)	HIGH	HR 0.54, 95%CI 0.35 to 0.86
3-year overall survival	1066 (5 studies)	HIGH	HR 1.07, 95%CI 0.73 to 1.55
5-year overall survival	1870 (10 studies)	MODERATE Due to inconsistency	HR 0.94, 95%CI 0.66 to 1.34

HR, hazard ratio; RR, risk ratio; CI, confidence interval

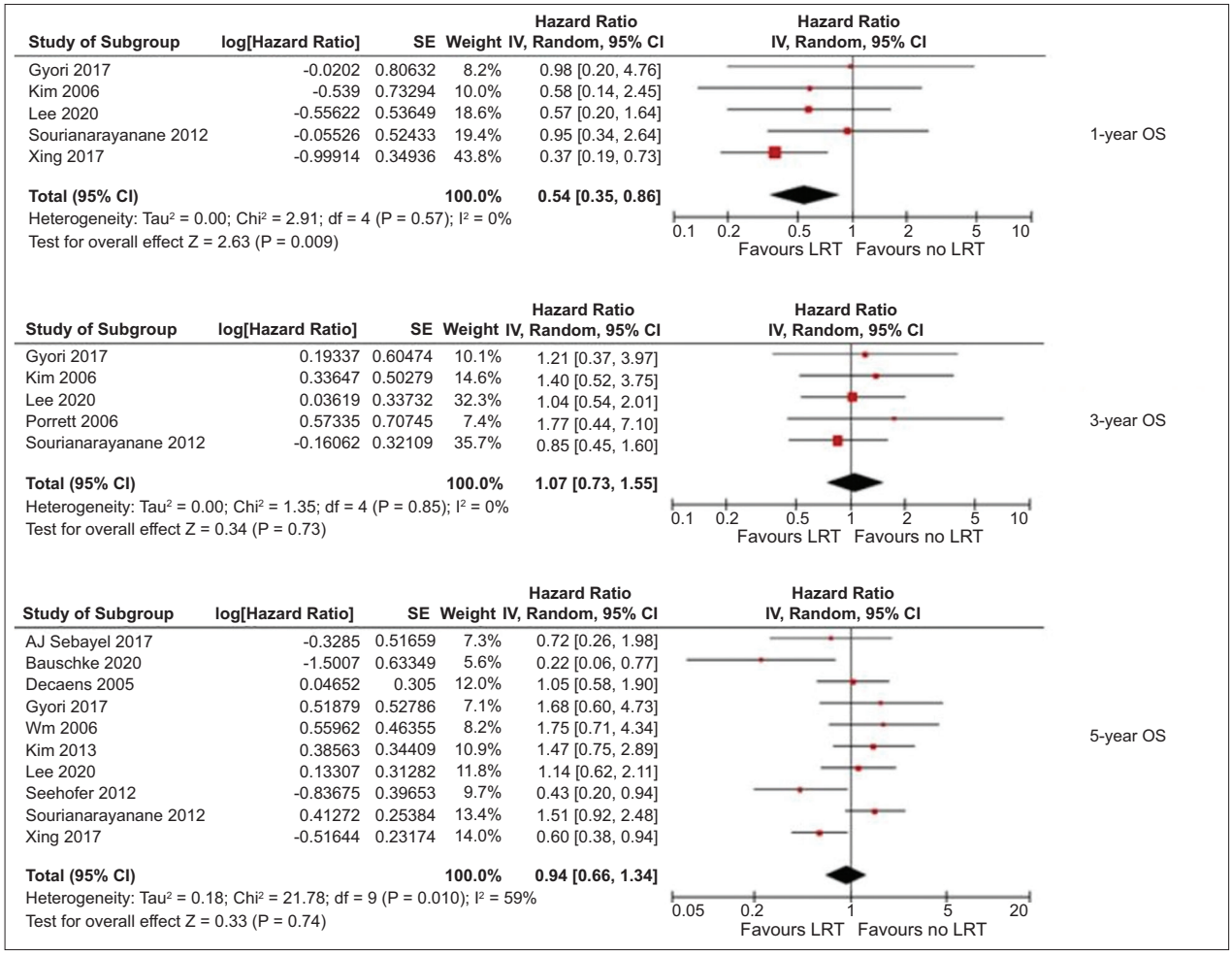

Figure 4 Overall survival (OS) after liver transplantation
LRT, locoregional treatment; CI, confidence interval

transarterial techniques, and stereotactic body radiation therapy (SBRT). Percutaneous techniques are generally applied in cases of up to 3 tumors and up to 3 cm each, but preserved liver function (Child-Pugh A) and absence of untreatable coagulopathy are necessary. These include RFA, MWA and PEI, with RFA being the most frequently used [40-43]. However, RFA is contraindicated if the lesions are too close to main biliary ducts, stomach or bowel, in which cases PEI can be applied [40,41]. There is also a heat-sink effect if a lesion is too close to a major blood vessel. MWA can also be applied to slightly bigger lesions and is less sensitive to the heat sink effect than RFA [40-43]. The use of PEI has been greatly reduced over the years, because RFA is more effective [40,41]. Transarterial techniques are generally applied in cases with multiple and/or larger tumors, but preserved liver function (Child-Pugh A), absence of untreatable coagulopathy, and absence of portal vein thrombosis are necessary. These include TAE, TACE and TARE, with TACE being the most frequently used. TAE consists of embolization of the arterial branches feeding the tumors; it has mostly been replaced by TACE, which involves transarterial injection of a cytotoxic agent (usually doxorubicin) and an ethiodized oil emulsion. A newer form of TACE involves embolization with drug-eluting beads. TARE is a new technique that uses ^{90}Y microspheres to embolize the tumors, resulting in beta particle emission and tumor necrosis [40-43]. Finally, SBRT is applied in patients not suitable candidates for either percutaneous or transarterial treatment, such as those with severely impaired liver function (Child-Pugh B or C) or portal vein thrombosis [40,43].

LRTs have been utilised in the context of downstaging therapy for cirrhotic patients whose HCC is outside the listing criteria initially, so that they may eventually meet the listing criteria for liver transplantation. First of all, around 40-60% cirrhotic patients with HCC outside the Milan criteria at the time of diagnosis will eventually manage to downstage their disease and meet the Milan criteria after having undergone LRT [44-46]. There is no agreement in the literature as to whether cases that are successfully downstaged to the Milan criteria can achieve a post-transplantation survival rate comparable to those who meet the Milan criteria at diagnosis, with some studies reporting similar survival between the 2 groups [6,7], while other studies reporting shorter survival for the LRT group [45,47]. Nevertheless, recent studies have shown that outcomes depend on the exact disease extent

before the downstaging treatment. In particular, cases that are beyond the Milan criteria at diagnosis but within the downstaging criteria of the University of California at San Francisco (UCSF-DS) (1 lesion >5 cm and ≤8 cm, or 2-3 lesions with at least 1 >3 cm and ≤5 cm, or 4 to 5 lesions with none >3 cm and total tumor diameter ≤8 cm) [8] can achieve similar post-transplant survival to those within the Milan criteria at diagnosis, if they are successfully downstaged [46]. On the other hand, cases that are beyond the UCSF-DS criteria at diagnosis have post-transplantation survival inferior to those within the Milan criteria at diagnosis, even if they are successfully downstaged [46].

In addition, LRTs have been used as bridging therapy to liver transplantation for cirrhotic patients who have HCC within the Milan criteria at diagnosis, to prevent disease progression and dropout while they are on the waiting list. Data from non-comparative studies have shown dropout rates around 25-40% without bridging therapy, but around 10-20% with bridging therapy, for patients who spent 6-12 months on the waiting list. Things are less clear when the waiting time for a liver transplantation is less than 6 months [4]. Even though there are several studies including information about both bridged and non-bridged cases, very few comparative studies have included a large number of patients, and these have shown no significant difference in terms of disease-free or overall survival between cases with and without LRT who were within the Milan criteria at the time of diagnosis [6,20].

According to the findings of our meta-analysis, the most frequently used LRT is TACE, followed by RFA and MWA. A radiological complete response can be expected in around 30% of the treated cases and a pathological complete response can be achieved in just above 20% of the treated cases. It seems that the administration of bridging LRT to cirrhotic patients who have HCC within the Milan criteria does not materially reduce the risk of dropout while on the waiting list, nor the risk of disease recurrence after the liver transplantation. There is a lower risk of death within the first year after the liver transplantation for those who have received bridging LRT, but this benefit is subsequently attenuated, and there is no difference regarding overall survival at 3 or 5 years after the liver transplantation between the bridged and non-bridged cases.

Nonetheless, our findings should be interpreted with caution for several reasons. Firstly, all the included studies were retrospective and non-randomized. There was no prospective randomised trial comparing bridged and non-bridged cirrhotic patients with HCC within the Milan criteria at diagnosis. There was also great heterogeneity among studies concerning the exact types of LRT used, with more than 1 type of LRT being used in 20 of the 26 included studies. Unfortunately, for most of these studies no separate analysis for each different type, or the various combinations of treatments, was available. Thus, we cannot comment on the effect of each separate LRT when it is used as bridging treatment to liver transplantation. Furthermore, even though there was no significant difference between the 2 arms as far as the waiting time for transplantation is concerned, patients who received bridging therapy had slightly larger tumors on scans at diagnosis. This could indicate a potential selection bias in the included studies that could also explain the slightly higher number of tumors and the disease burden being slightly more often outside the Milan criteria on histopathological examination of the explanted livers after bridging therapy. In addition, this difference in tumor burden may account for the similar outcomes between the 2 arms, and may even indicate a superiority for the bridging LRT.

In conclusion, the precise benefit of bridging LRT for cirrhotic patients who have HCC within the Milan criteria at the time of diagnosis is unclear. There is perhaps an advantage regarding the short-term overall survival after liver transplantation. However, it is not clear how long the waiting time for transplantation needs to be so that a benefit in reducing the dropout risk and/or prolonging the post-transplantation survival becomes apparent. There is a need for well-designed prospective randomized trials to answer these questions.

Summary Box

What is already known:

- Locoregional treatments (LRTs) are applied in patients with liver cirrhosis and hepatocellular carcinoma (HCC) who are to be treated via liver transplantation, either to keep the HCC within the listing criteria as a bridge to liver transplantation, or to downstage the HCC within listing criteria and render them eligible transplant candidates
- Several studies have reported similar survival rates between cases exceeding the Milan criteria at diagnosis, but successfully downstaged after LRT, and cases within the Milan criteria at diagnosis
- It is unclear whether, in cirrhotic patients with HCC already within the Milan criteria at diagnosis, there is a need to treat them with LRT as a bridge to liver transplantation, to avoid disease progression while they are on the waiting list

What the new findings are:

- In cirrhotic patients with HCC already within the Milan criteria at diagnosis, there was no difference between cases with bridging LRT and cases without in terms of dropout rates, disease-free survival at 1, 3, 5 years after transplant, or overall survival at 3 and 5 years after transplant
- Cases with bridging LRT had better overall survival at 1 year after transplantation than those without
- It is not clear how long the waiting time for transplantation needs to be so that a benefit in reducing the dropout risk and/or prolonging the post-transplantation survival becomes apparent

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