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Therapies for Patients With Hepatocellular Carcinoma Awaiting Liver Transplantation: A Systematic Review and Meta-analysis

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Patients with hepatocellular carcinoma (HCC) who are listed for liver transplantation (LT) are often treated while on the waiting list with locoregional therapy (LRT), which is aimed at either preventing progression of HCC or reducing the measurable disease burden of HCC in order to receive increased allocation priority. We aimed to synthesize evidence regarding the effectiveness of LRT in the management of patients with HCC who were on the LT waitlist. We conducted a comprehensive search of multiple databases from 1996 to April 25, 2016, for studies that enrolled adults with cirrhosis awaiting LT and treated with bridging or down-staging therapies before LT. Therapies included transcatheter arterial chemoembolization, transarterial radioembolization, ablation, and radiotherapy. We included both comparative and noncomparative studies. There were no randomized controlled trials identified. For adults with T1 HCC and waiting for LT, there were only two nonrandomized comparative studies, both with a high risk of bias, which reported the outcome of interest. In one series, the rate of dropout from all causes at 6 months in T1 HCC patients who underwent LRT was 5.3%, while in the other series of T1 HCC patients who did not receive LRT, the dropout rate at median follow-up of 2.4 years and the progression rate to T2 HCC were 30% and 88%, respectively. For adults with T2 HCC awaiting LT, transplant with any bridging therapy showed a nonsignificant reduction in the risk of waitlist dropout due to progression (relative risk [RR], 0.32; 95% confidence interval [CI], 0.06-1.85; I^2 = 0%) and of waitlist dropout from all causes (RR, 0.38; 95% CI, 0.060-2.370; I^2 = 85.7%) compared to no therapy based on three comparative studies. The quality of evidence is very low due to high risk of bias, imprecision, and inconsistency. There were five comparative studies which reported on posttransplant survival rates and 10 comparative studies which reported on posttransplant recurrence, and there was no significant difference seen in either of these endpoints. For adults initially with stage T3 HCC who received LRT, there were three studies reporting on transplant with any downstaging therapy versus no downstaging, and this showed a significant increase in 1-year (two studies, RR, 1.11; 95% CI, 1.01-1.23) and 5-year (1 study, RR, 1.17; 95% CI, 1.03-1.32) post-LT survival rates for patients who received LRT. The quality of evidence is very low due to serious risk of bias and imprecision. *Conclusion:* In patients with HCC listed for LT, the use of LRT is associated with a nonsignificant trend toward improved waitlist and posttransplant outcomes, though there is a high risk of selection bias in the available evidence. (HEPATOLOGY 2018;67:381-400).

Hepatocellular carcinoma (HCC) is a growing indication for liver transplantation (LT) due to the rising incidence of HCC and recognition that transplantation offers the best chance for long-term survival for patients with unresectable HCC. Transplant offers the benefit of removal of the cancer as well as the harboring risk of *de novo* HCC in a cirrhotic liver. Patients with early HCC, defined by the Milan criteria (one lesion ≤5 cm or three lesions all <3 cm without evidence of extrahepatic spread or vascular invasion) have overall survival rates comparable to those without HCC. A priority for LT is

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HCC, hepatocellular carcinoma; LRT, locoregional therapy; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; OLT, orthotopic LT; RCT, randomized controlled trial; RFA, radio frequency ablation; RR, relative risk; TACE, transcatheter arterial chemoembolization; TARE, transarterial radioembolization.

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granted to those with HCC fulfilling the Milan criteria in order to allow transplant in a timely fashion prior to progression of HCC that would eliminate LT as a therapeutic option, given the increased risk of recurrent HCC after LT for patients with more advanced HCC. Patients who develop tumor progression beyond the Milan criteria while awaiting LT become ineligible for an HCC Model for End-Stage Liver Disease (MELD) upgrade, which equates to dropout and subsequent death due to progression of HCC. Strategies to minimize waitlist dropout due to tumor progression include locoregional therapy (LRT). The selection of appropriate candidates for LRT is paramount to diminish the risk of exacerbating underlying liver disease and hence the development of worsening synthetic function and/or complications of portal hypertension.

A consensus statement for LT for HCC has recommended LRT if the anticipated waiting time for an organ to become available exceeds 6 months.[1] However, due to unpredictable waiting times and fear of tumor progression, the vast majority of patients receive some form of LRT while awaiting transplant. Various types of LRT have been employed; however, transarterial chemoembolization (TACE) is the most common. The choice of which LRT to use is influenced by tumor size/number, location, liver function, and individual center experience. Level-one data to confirm the benefit of this approach are lacking and not anticipated in the future. We conducted this systematic review and meta-analysis to synthesize the existing evidence about the effectiveness of LRT as a strategy to prevent HCC progression for patients with HCC who are waiting for LT or as a down-staging strategy for patients with HCC beyond the Milan criteria who are being considered for LT.

Materials and Methods

We followed *a priori* the protocol developed by HCC guideline and systematic review committees of the American Association for the Study of Liver Diseases. We reported this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements.[2]

ELIGIBILITY CRITERIA

The American Association for the Study of Liver Diseases committees identified and developed three key questions (Table 1). We included studies that enrolled adults with cirrhosis awaiting LT and treated with bridging or down-staging therapies before transplant. Therapies included TACE, transarterial radioembolization (TARE), ablation, and radiotherapy. We included both comparative and noncomparative studies with no language restrictions. We excluded studies with patients enrolled before 1996, case reports, cohorts with fewer than 5 patients, reviews, letters, errata, commentaries, and studies published only as abstracts.

SEARCH STRATEGY

A comprehensive search of several databases from each database inception to April 25, 2016, in any

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TABLE 1. Population, Intervention, Comparison, and Outcomes of the Proposed Questions

Question No.	Population	Intervention Versus Comparison	Outcomes
1	Adults with cirrhosis awaiting LT and T1 HCC	Observation versus any therapy (TACE, TARE, ablation, or radiotherapy)	Waitlist dropout due to progression beyond transplant criteria, post-LT survival, recurrence
2	Adults with cirrhosis awaiting LT and T2 HCC	Transplant alone versus transplant with any bridging therapy (TACE, TARE, ablation, or radiotherapy)	Waitlist dropout due to progression beyond transplant criteria, post-LT survival, recurrence
3	Adults with cirrhosis awaiting LT and beyond Milan (T3) HCC	Transplant without down-staging versus transplant following down-staging to within Milan (T2)	Waitlist dropout due to progression beyond transplant criteria, post-LT survival, recurrence

language was conducted. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigators. Supporting Table S1 describes the detailed search strategy.

STUDY SELECTION

Using an online reference management system (DistillerSR; Evidence Partners, Inc.), two reviewers independently screened the titles and abstracts for potential eligibility. The full text of the included abstracts was retrieved and screened in duplicate. Disagreements were harmonized by consensus and, if not possible, by consensus through arbitration by a third reviewer.

DATA EXTRACTION

For each study, data extraction was done in duplicate using a standardized form. We extracted the following variables from each study: study characteristics (first author's last name, year of publication, country, study design), patient baseline characteristics (number of patients, age, inclusion criteria for transplant, pretransplant staging, MELD score, number of hepatic lesions, Child-Pugh score, size of hepatic lesions, alpha-fetoprotein [AFP] levels, duration of follow-up, waitlist time for transplant), type of LRT, and outcomes of interest. We extracted the following outcomes from each study: waitlist dropout rate due to progression and/or any cause, post-LT mortality and survival rates, and post-LT recurrence and recurrence-free survival rates.

METHODOLOGICAL QUALITY AND RISK OF BIAS ASSESSMENT

We used the modified Newcastle-Ottawa Scale to assess the risk of bias in observational studies. Two reviewers independently assessed the risk of bias in each study. Selected items focused on the representativeness of the study population, comparability of cohorts, adequate assessment of outcome, sufficient length of follow-up to allow outcomes to arise, adequacy of follow-up, and source of study funding. Quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methods.

STATISTICAL ANALYSIS

For comparative studies, we calculated relative risks (RRs) and 95% confidence intervals (CIs) using binomial distribution. We then pooled the log-transformed risk ratios using the DerSimonian and Laird random-effect models, with the heterogeneity estimated from the Mantel-Haenszel model. For noncomparative studies, we calculated event rates of outcome (the proportion of patients who developed outcomes of interest), and we estimated 95% CIs with the Jeffreys method. We pooled log-transformed event rates with DerSimonian and Laird random-effect models. To measure heterogeneity across the included studies, we used the I^2 statistic, where $I^2 > 50\%$ suggests high heterogeneity. All statistical analyses were conducted using Stata version 13 (StataCorp, College Station, TX).

Results

The initial search resulted in 4,022 citations, of which 483 full-text articles were reviewed. We included a total of 63 studies. Figure 1 shows the study selection process. Detailed baseline characteristics of the studies are described in Supporting Table S2.

QUESTION 1: SHOULD ADULTS WITH CIRRHOSIS AWAITING LT AND HCC (T1) UNDERGO LRT VERSUS OBSERVATION?

There were not any studies that directly compared LRT versus observation for patients on the LT waiting list. Two noncomparative cohorts[3,4] enrolled patients with cirrhosis and T1 HCC and reported the outcome of interest. Baseline characteristics are described in Supporting Table S2. The two studies were at high risk of bias (Supporting Table S3). In the first study, the rate of dropout from all causes at 6 months in T1 HCC patients who underwent LRT was 5.3%.[3] In the second study, assessing T1 HCC patients who did not receive LRT,[4] the dropout rate at a median follow-up of 2.4 years and the progression rate to T2 HCC were 15.2% and 88%, respectively. A summary of outcomes is reported in Table 2.

QUESTION 2: SHOULD ADULTS WITH CIRRHOSIS AWAITING LT AND HCC (T2) UNDERGO TRANSPLANT ALONE VERSUS TRANSPLANT WITH BRIDGING THERAPY?

Analysis of Comparative Studies

Eighteen comparative studies[5-22] reported outcomes of interest. Baseline characteristics of included studies are described in Supporting Table S2. Risk of bias for the 18 comparative studies was considered moderate to high. Most of the studies (95%) provided adequate assessment of outcome, 83% had an acceptable length of follow-up, and 66% had comparable cohorts. However, selection of cohorts, adequacy of follow-up, and source of funding were either at high risk of bias or not reported in most of the studies (Fig. 2A). Details of risk of bias assessment are presented in Supporting Table S3.

WAITLIST DROPOUT OUTCOMES

Two studies[7,10] enrolled 257 patients and reported waitlist dropout due to progression, and three studies[5,7,10] enrolled 382 patients and reported dropout due to any cause. Compared to transplant alone (Fig. 3), transplant with any bridging therapy showed a nonsignificant reduction in the risk of waitlist dropout due to progression (RR, 0.32; 95% CI, 0.06-1.85; I^2 = 0%) and waitlist dropout from all causes (RR, 0.38; 95% CI, 0.060-2.370; I^2 = 85.7%). The quality of evidence is very low due to high risk of bias, imprecision, and inconsistency.

MORTALITY OUTCOMES

Five studies[6,7,9,18,20] enrolled 531 patients and reported mortality rates, three studies[11,13,20] reported 1-year post-LT survival rate, five studies[8,11,13,18,20] reported 3-year post-LT survival rate, and five studies[11,13,15,20,21] reported 5-year post-LT survival rate. Compared to transplant alone (Fig. 4), transplant with any bridging therapy showed a nonsignificant change in posttransplantation mortality and survival rates.

RECURRENCE OUTCOMES

Ten studies[6-9,13,15-18,20] enrolled 889 patients and reported post-LT recurrence rates; two studies[14,20] reported 1-year and 3-year post-LT recurrence-free survival rates; and three studies[12,14,20] reported 5-year post-LT recurrence-free survival rates. No significant difference was noted between both groups in recurrence rate and recurrence-free survival rate (Fig. 5).

SUBGROUP ANALYSIS

We conducted a subgroup analysis based on the type of LRT. A summary of evidence for outcomes of transplant with bridging therapy versus transplant alone for all bridging therapies and subgrouped based on the type of LRT is presented in Table 3.

Sensitivity analysis was done to exclude cohorts conducted outside the United States and cohorts enrolled patients before 2002. Nine studies[6,7,9,10,15,18,20-22] were conducted in the United States and showed no change in results (Supporting Figs. S1-S3). Three cohorts[15,18,20] were conducted in the United States and enrolled patients at or after 2002; no change in results was noticed. A summary of evidence for the sensitivity analysis is presented in Supporting Table S4.

Analysis of Noncomparative Studies

Thirty-one noncomparative studies[3,4,23-51] enrolled HCC patients within Milan criteria and reported outcomes for transplant with any bridging therapies. Risk of bias of the noncomparative studies (Fig. 2B) was considered high. Most of the studies (97%) provided adequate assessment of outcome, and 93% had an acceptable length of follow-up. However, selection and comparability of cohorts, adequacy of follow-up, and source of funding were

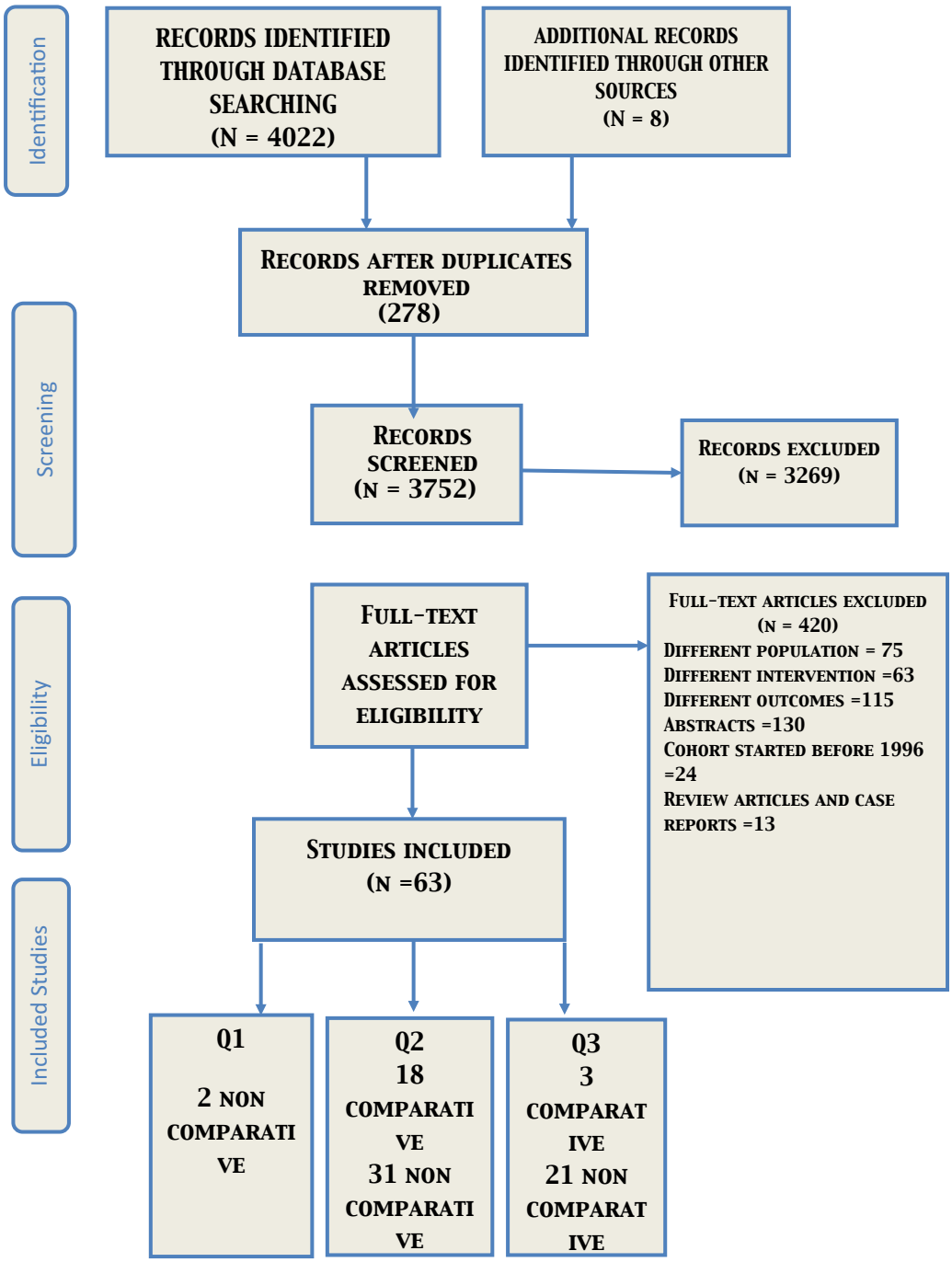

FIG. 1. The process of study selection.

either at high risk of bias or not reported in most of the studies.

WAITLIST DROPOUT RATES

Fifteen studies[3,4,23,25,29,32,33,35,37,38,41-44,50] reported dropout rates due to all causes, and nine studies[23,25,26,29,35,38,42-44] reported dropout rates due to progression. Dropout rates due to all causes and due to progression were 0.19 (95% CI, 0.15-0.24) and 0.11 (95% CI, 0.07-0.17), respectively.

MORTALITY OUTCOMES

Ten studies[23,26,28,33,34,36,37,43,46,49] reported post-LT mortality rate, and 11 studies[23,24,27-29,31,33,37,41,48,49]

TABLE 2. Dropout Rates in Adults With Cirrhosis Awaiting LT and HCC (T1)

Reference	Intervention	Patients (n)	Outcome	Follow-up	Proportion (95% CI)
Huo et al.[3]	PAI, PEI, RFA, TACE	94	Dropout from all causes	6 months	0.05 (0.01-0.1)
Mehta et al.[4]	Observation	114	Dropout from all causes	2.4 years	0.30 (0.20-0.32)
		114	Progression to T2	(IQR, 1.4-4.4 years)	0.88 (0.82-0.94)

Abbreviations: IQR, interquartile range; PAI, percutaneous acetic acid injection; PEI, percutaneous ethanol injection.

reported post-LT survival rates. Post-LT all-cause mortality rate was 0.17 (95% CI, 0.11-0.25). Post-LT survival rates at 1, 3, and 5 years were 0.94 (95% CI, 0.91-0.97), 0.86 (95% CI 0.82-0.9), and 0.78 (95% CI, 0.67-0.90), respectively.

RECURRENCE OUTCOMES

Fifteen studies[23,28,31,33,34,36,37,39,40,43,45-47,49,51] reported post-LT recurrence rate, and six studies[22,29,30,40,47,48] reported post-LT recurrence-free survival rates. The rate of post-LT recurrence was 0.14 (95% CI, 0.1-0.21). Post-LT recurrence-free survival rates at 1, 3, and 5 years were 0.88 (95% CI, 0.82-0.94), 0.82 (95% CI, 0.73-0.93), and 0.77 (95% CI, 0.61-0.98), respectively.

Table 4 shows event rates of outcomes reported for transplant with bridging therapies in adults with cirrhosis awaiting LT and T2 HCC. Supporting Table S5 shows subgroup analysis based on the type of LRT and studies conducted in the United States only.

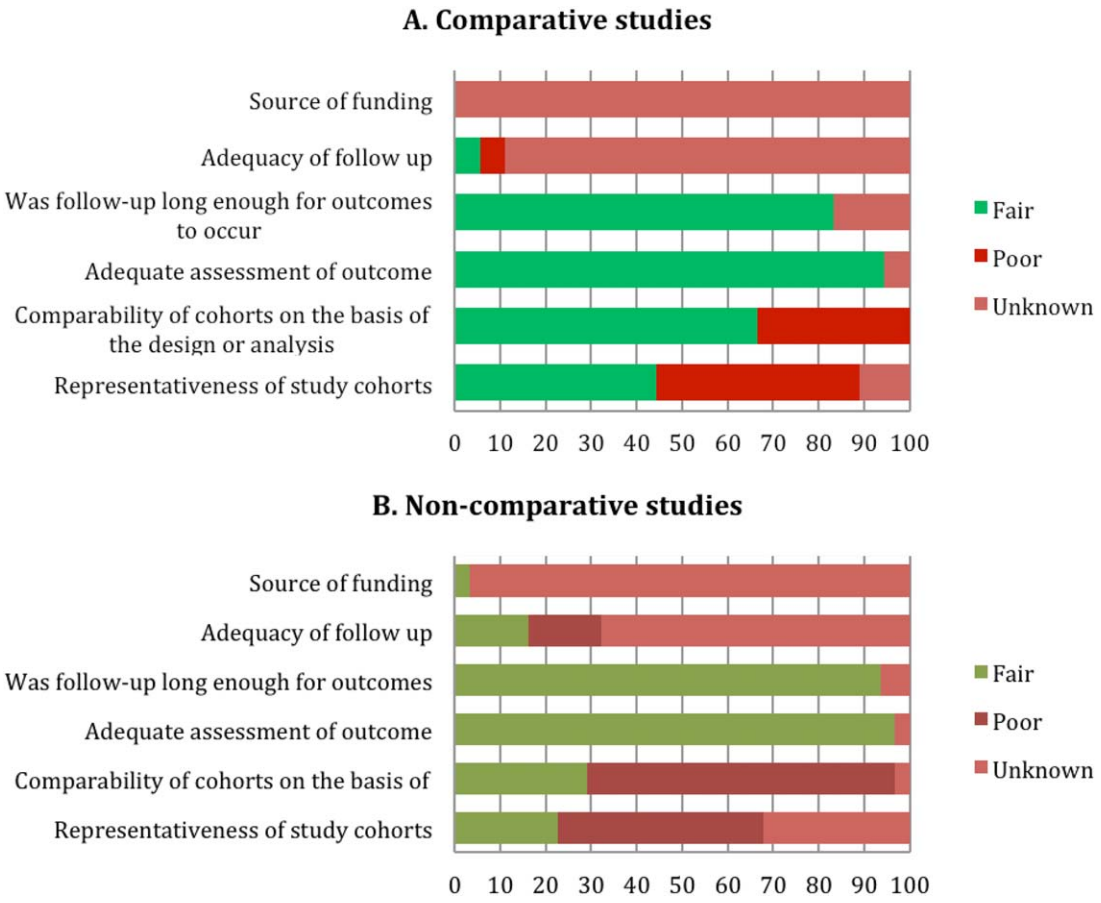

FIG. 2. Methodological quality of the studies that enrolled adults with cirrhosis awaiting LT and HCC (T2).

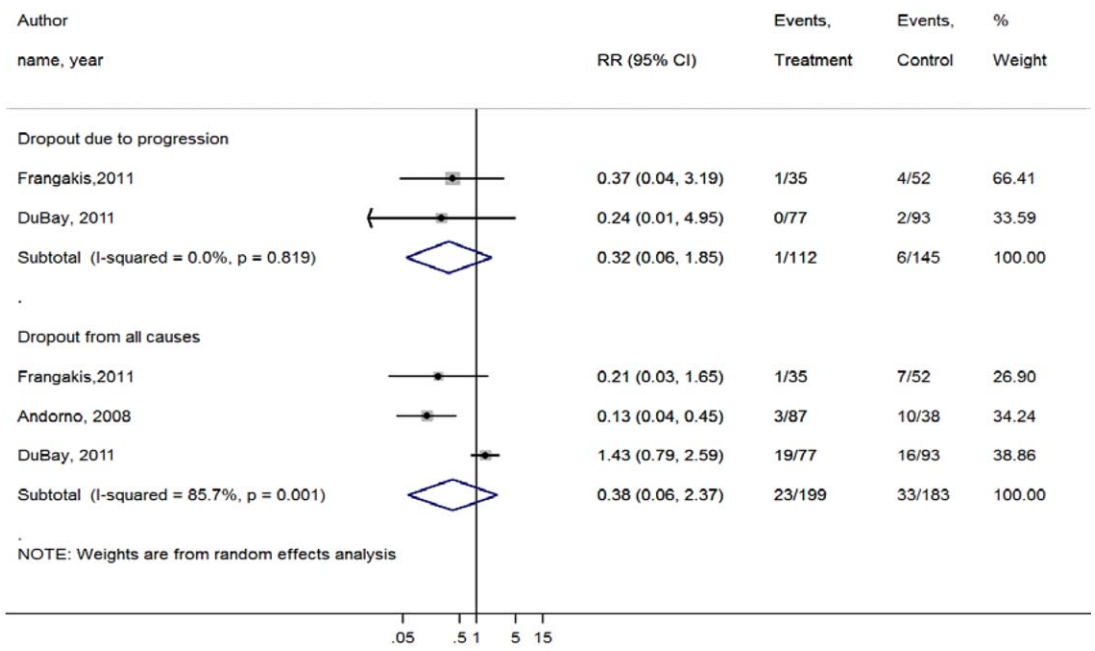

FIG. 3. Dropout rate (bridging therapies versus no therapy) for adults with cirrhosis awaiting LT and HCC (T2). Andorno et al.,[5] DuBay et al.,[7] and Frangakis et al.[10]

Q3: SHOULD ADULTS WITH CIRRHOSIS AND HCC BEYOND MILAN CRITERIA (T3) BE TRANSPLANTED FOLLOWING DOWN-STAGING TO WITHIN MILAN CRITERIA (T2)?

Analysis of Comparative Studies

Three studies[12,52,53] enrolled HCC patients and compared any T3 patients treated with transplant and down-staging therapy versus T2 patients treated with transplant alone. Baseline characteristics of the three studies are described in Supporting Table S2. The risk of bias (Table 3) in the studies was moderate as two studies reported fair comparability of the studies, adequate assessment of the follow-up, and an acceptable length of follow-up. No studies reported waitlist dropout rates as outcomes.

Compared to transplant alone for T2 (Fig. 6), transplant with any down-staging therapy showed significant increases in 1-year (two studies,[51,52] RR, 1.11; 95% CI, 1.01-1.23) and 5-year (one study,[53] RR, 1.17; 95% CI, 1.03-1.32) post-LT survival rates. The quality of evidence is very low due to serious risk of bias and imprecision.

No significant difference was noted for 3-year post-LT survival rate and 1-year and 5-year post-LT recurrence-free survival rates (Fig. 6). Sensitivity analysis was conducted to limit the analysis to one study[52] conducted in the United States and reported 1-year and 3-year post-LT survival rates. No significant difference was noted between the two groups. Table 5 shows a summary of evidence for T3 patients treated with down-stating plus transplantation versus T2 patients treated with transplant alone in adults with cirrhosis awaiting LT and HCC beyond Milan criteria (T3).

Analysis of Noncomparative Studies

Twenty-one studies[28,29,31-33,39,42,48,53-65] enrolled 2,698 HCC patients beyond Milan criteria and reported outcomes for transplant with down-staging therapy only. Baseline characteristics are reported in Supporting Table S2. Risk of bias assessment (Fig. 7) of the included noncomparative studies was considered moderate to high. Most of the studies (91%) provided adequate assessment of outcome, and all of the studies provided an acceptable length of follow-up. However, selection of the studies, comparability of cohorts, adequacy of follow-up, and source of funding were either

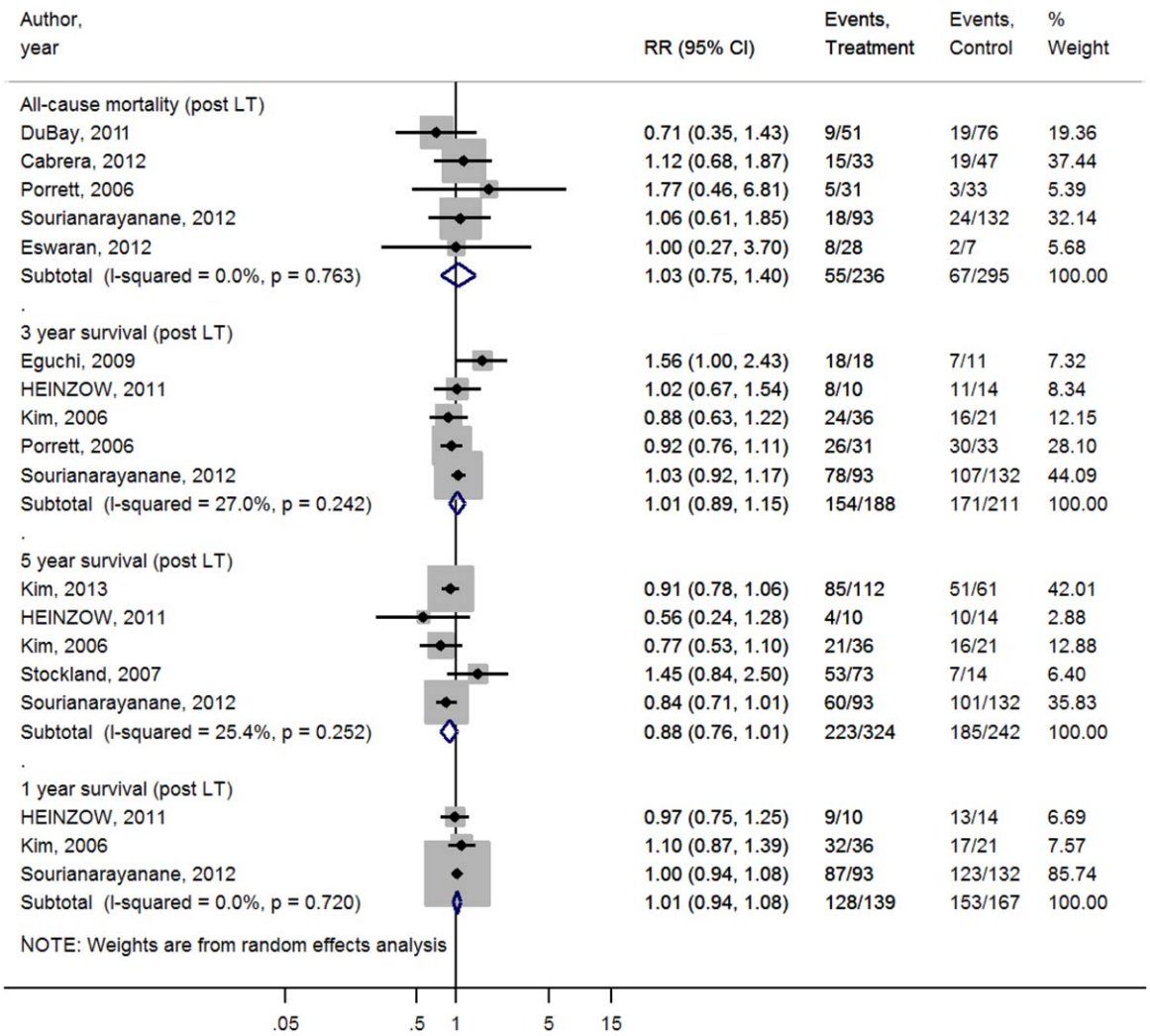

FIG. 4. Mortality and survival rates (transplant with bridging therapies versus transplant alone) for adults with cirrhosis awaiting LT and HCC (T2). Cabrera et al.,[6] DuBay et al.,[7] Eguchi et al.,[8] Eswaran et al.,[9] Heinzow et al.,[11] Kim et al.,[13,15] Porrett et al.,[18] Sourianarayanane et al.,[20] Stockland et al.[21]

at high risk of bias or not reported in most of the studies.

WAITLIST DROPOUT RATES

Seven studies[29,32,42,59,60,63,65] reported dropout rates due to all causes, and six studies[28,41,58,59,62,64] reported dropout rates due to progression. Dropout rates due to all causes and due to progression were 0.41 (95% CI, 0.32-0.53) and 0.53 (95% CI, 0.43-0.65), respectively.

MORTALITY OUTCOMES

Seven studies[33,54-56,60,63,64] reported post-LT mortality rates, and 10 studies[27,28,30,47,52,55,59,60,63,64] reported post-LT survival rates. The post-LT all-cause mortality rate was 0.31 (95% CI, 0.20-0.49). Post-LT survival rates at 1, 3, and 5 years were 0.94 (95% CI, 0.91-0.97), 0.86 (95% CI, 0.77-0.96), and 0.78 (95% CI, 0.71-0.84), respectively.

RECURRENCE OUTCOMES

Twelve studies[28,33,54-57,59-62,64,65] reported post-LT recurrence rates, and 14 studies[28,31,39,42,48,53,56,58,60-65] reported post-LT recurrence-free survival rates. The rate of post-LT recurrence was 0.20 (95% CI, 0.15-0.28). Post-LT recurrence-free survival rates at 1, 3, and 5 years were 0.91 (95% CI, 0.88-0.94), 0.79 (95% CI, 0.73-0.85), and 0.8 (95% CI, 0.73-0.87), respectively.

Table 6 shows event rates of outcomes reported for transplant following down-staging in patient with

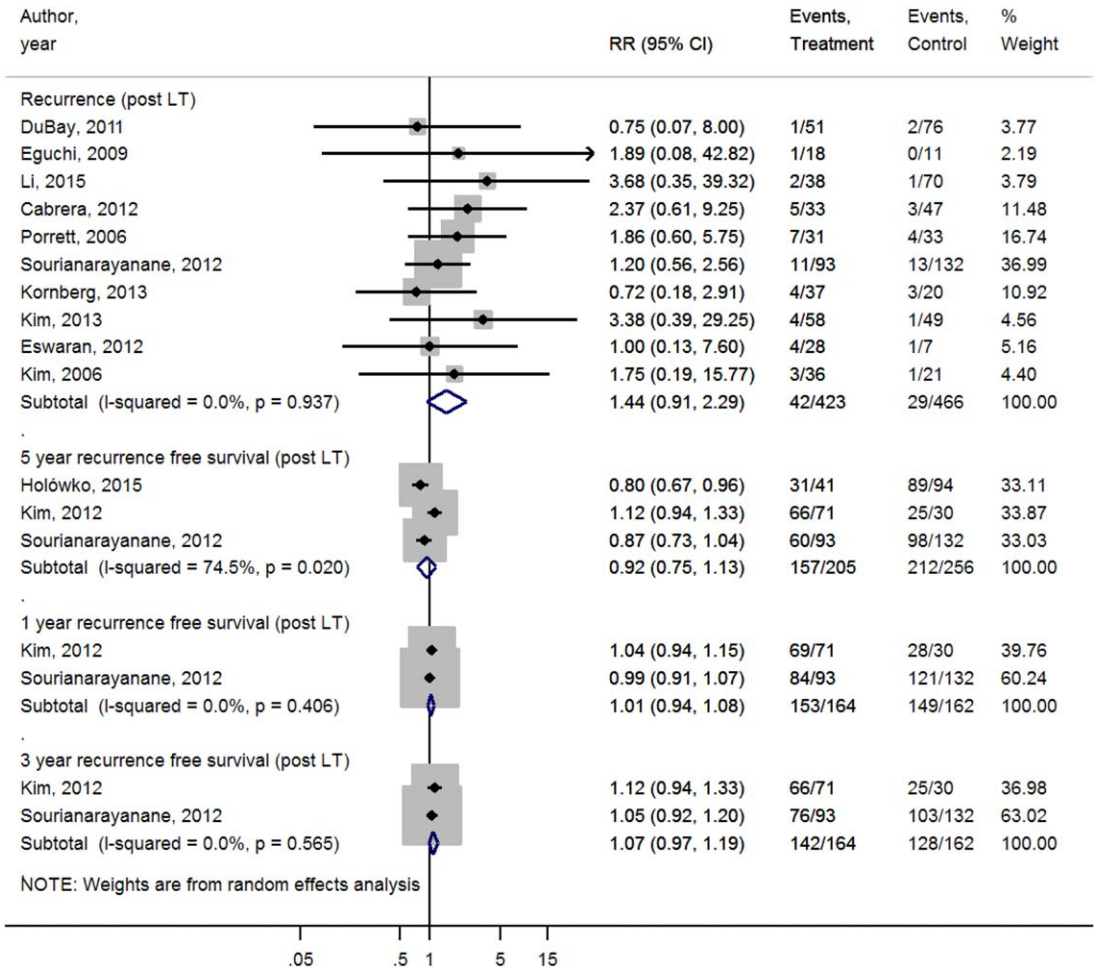

FIG. 5. Recurrence and recurrence-free survival rates (transplant with bridging therapies versus transplant alone) for adults with cirrhosis awaiting LT and HCC (T2). Cabrera et al.,[6] DuBay et al.,[7] Eguchi et al.,[8] Eswaran et al.,[9] Holowko et al.,[12] Kim et al.,[13-15] Kornberg et al.,[16] Li et al.,[17] Porrett et al.,[18] Sourianarayanane et al.[20]

cirrhosis awaiting LT and HCC beyond Milan criteria (T3). Supporting Table S6 shows subgroup analysis based on the type of LRT and studies conducted in the United States only.

Discussion

The American Association for the Study of Liver Diseases' methodology and writing committees for the HCC practice guidelines developed three key questions regarding the use of liver-directed therapy for HCC in patients in a pretransplant setting including T1 lesions, bridging, and down-staging to transplant. This entailed a detailed literature search to identify studies with a comparison group and data on relevant clinical outcomes. These data were then rated based on the quality of the evidence using the GRADE system. There were no randomized controlled trials (RCTs) addressing any of the posed questions, and the quality of the data overall was deemed very low.

T1 LESIONS

Shortly after the implementation of MELD, it was recognized that overprioritization to HCC was negatively impacting those without HCC. In addition, approximately 21% had no evidence of HCC on explant pathology, and this was most significantly related to having T1 stage on pretransplant imaging despite a lack of pretransplant LRT. This led to a reduction of initial MELD exception scores granted to patients with T2 HCC and elimination of the MELD

TABLE 3. Summary of Evidence for Transplant With Bridging Therapies Versus Transplant Alone in Adults With Cirrhosis Awaiting LT and HCC (T2)

	Outcomes	Cohorts (n)	RR (95% CI)	I^2 (%)	GRADE
All bridging therapies:	Dropout due to progression	2	0.321 (0.056-1.851)	0	⊕◯◯◯ Very low*,†
	Dropout from all causes	3	0.378 (0.060-2.370)	85.7	⊕◯◯◯ Very low*,‡
	All-cause mortality (post-LT)	5	1.028 (0.752-1.404)	0	⊕◯◯◯ Very low*,†
	Recurrence (post-LT)	10	1.445 (0.0911-2.29)	0	⊕◯◯◯ Very low*
	3-year survival (post-LT)	5	1.010 (0.890-1.147)	27	⊕◯◯◯ Very low*,†
	5-year survival (post-LT)	5	0.879 (0.762-1.014)	25	⊕◯◯◯ Very low*,†
	1-year survival (post-LT)	3	1.008 (0.945-1.076)	0	⊕◯◯◯ Very low*,†
	5-year recurrence-free survival (post-LT)	3	0.920 (0.75-1.127)	74.5	⊕◯◯◯ Very low*,‡
	1-year recurrence-free survival (post-LT)	2	1.007 (0.944-1.075)	0	⊕◯◯◯ Very low*,†
	3-year recurrence-free survival (post-LT)	2	1.072 (0.965-1.190)	0	⊕◯◯◯ Very low*,†
Subgroup analysis based on type of LRT					
TACE	Dropout due to progression	1	0.371 (0.043-3.185)	NA	⊕◯◯◯ Very low*,†
	Dropout from all causes	1	0.212 (0.027-1.650)	NA	⊕◯◯◯ Very low*,†
	All-cause mortality (post-LT)	1	1.000 (0.270-3.705)	NA	⊕◯◯◯ Very low*,†
	Recurrence (post-LT)	3	1.74 (0.49-6.15)	0	⊕◯◯◯ Very low*,†
	3-year survival (post-LT)	2	0.929 (0.717-1.203)	0	⊕◯◯◯ Very low*,†
	5-year survival (post-LT)	3	0.888 (0.534-1.475)	60.7	⊕◯◯◯ Very low*,‡
	1-year survival (post-LT)	2	1.036 (0.871-1.231)	0	⊕◯◯◯ Very low*,†
	5-year recurrence-free survival (post-LT)	1	0.799 (0.667-0.956)	NA	⊕◯◯◯ Very low*,†
TACE and RFA	Recurrence (post-LT)	1	0.72 (0.0.18-2.91)	NA	⊕◯◯◯ Very low*,†
TAE	All-cause mortality (post-LT)	1	1.124 (0.675-1.873)	NA	⊕◯◯◯ Very low*,†
	Recurrence (post-LT)	1	2.374 (0.609-9.252)	NA	⊕◯◯◯ Very low*,†
Multi- therapies	Dropout from all causes	1	0.131 (0.038-0.449)	NA	⊕◯◯◯ Very low*,†
	All-cause mortality (post-LT)	2	1.145 (0.688-1.907)	0	⊕◯◯◯ Very low*,†
	Recurrence (post-LT)	4	1.49 (0.826-2.7)	8.6	⊕◯◯◯ Very low*,†
	3-year survival (post-LT)	3	1.049 (0.868-1.268)	58.7	⊕◯◯◯ Very low*,†
	5-year survival (post-LT)	2	0.880 (0.784-0.988)	0	⊕◯◯◯ Very low*,†
	1-year survival (post-LT)	1	1.004 (0.936-1.077)	NA	⊕◯◯◯ Very low*,†
	1-year recurrence-free survival (post-LT)	2	1.007 (0.944-1.075)	0	⊕◯◯◯ Very low*,†
	3-year recurrence-free survival (post-LT)	2	1.072 (0.965-1.190)	0	⊕◯◯◯ Very low*,†
	5-year recurrence-free survival (post-LT)	2	0.986 (0.758-1.282)	77.4	⊕◯◯◯

TABLE 3. *Continued*

	Outcomes	Cohorts (n)	RR (95% CI)	I^2 (%)	GRADE
RFA	Dropout due to progression	1	0.241 (0.012-4.946)	NA	Very low*,‡ ⊕◯◯◯
	Dropout from all causes	1	1.434 (0.793-2.594)	NA	Very low*,† ⊕◯◯◯
	All-cause mortality (post-LT)	1	0.706 (0.347-1.435)	NA	Very low*,† ⊕◯◯◯
	Recurrence (post-LT)	1	0.745 (0.069-8.003)	NA	Very low*,† ⊕◯◯◯ Very low*,†

*Serious risk of bias.
†Imprecision.
‡Inconsistency.
Abbreviations: NA, not available; TAE, transarterial embolization.

upgrade for those with a solitary T1 lesion.[66] Thus, patients with unresectable T1 HCC on the LT waiting list have the option of observation until the lesion increases in size to stage T2 in order to receive additional waitlist priority or treatment of the lesion with LRT. Patients also have the option of living donor LT or receiving LT based on their calculated MELD score (applicable for patients with significantly decompensated liver disease). LRT at the time of diagnosis of T1 HCC versus observation with treatment only after meeting T2 criteria was examined in two noncomparative studies, one of which deferred treatment of T1 lesions and one of which treated all T1 lesions. Due to a lack of randomization, these studies are unable to definitively address the question of the impact on survival of early LRT in T1 lesions versus LRT + intent for transplantation only after tumor growth to >T1. For patients already listed for LT and thus, presumably, with another indication for LT, the evidence supports that observation until the tumor had reached T2 was not associated with excess waitlist dropout rates. The majority of studies on LRT as a primary treatment have been using radio frequency ablation (RFA), with results approaching what has been reported for resectable patients treated with resection, though not all lesions lend themselves to ablative procedures. In such cases there is not an RCT that has examined ablation versus intra-arterial therapies in very early HCC, and therefore the intent for a potential curative therapy outside of ablation is not known.

BRIDGING TO LT

Patients listed for LT due to HCC are at risk of dropout with competing risks of tumor progression and morbidity/mortality related to chronic liver disease. The intended goals of bridging to orthotopic LT (OLT) are to prevent dropout on the waiting list and decrease the risk of post-OLT HCC recurrence. LRT has been widely used as a strategy to minimize tumor growth while awaiting transplantation. There were 18 comparative studies that reported various outcomes, and a nonsignificant improvement with lower dropout rates was seen among patients treated with LRT compared to no therapy for both tumor progression (RR, 0.32; 95% CI, 0.06-1.85) and all causes of dropout (RR, 0.38; 95% CI, 0.060-2.370). Overall survival (1, 3, and 5 years) and HCC recurrence post-LT were not significantly impacted by LRT versus proceeding directly to transplantation. Neither the type of LRT nor the limitation of studies to the United States after the implementation of MELD impacted these results. However, given the lack of randomized studies, it is likely that patients selected for LRT are different from those not selected for LRT. Therefore, similar waitlist and post-LT outcomes could potentially mean that LRT patients with more advanced tumors, potentially more aggressive tumor biology, or longer waiting times did as well as those not receiving LRT who had fewer risk factors. With ever increasing waiting times, nearly all waitlisted patients in the United States are treated with LRT; and thus, randomized studies are not likely to be available to address this question.[67] Additionally, a large RCT is unlikely to be conducted to definitively address the superiority of one form of LRT over another in selected groups of patients with HCC due to variation in waiting times and other practice differences. Two pilot RCTs compared radioembolization to chemoembolization in unresectable HCC with progression-free survival as the primary endpoint.[68,69] While progression-free survival was similar between the two modalities, the study design dictated

TABLE 4. Event Rates for Outcomes Reported for Transplant With Bridging Therapies in Adults With Cirrhosis Awaiting LT and T2 HCC

Outcomes	Cohorts (n)	Event Rate (95% CI)	I^2 (%)
All bridging therapies			
Dropout due to progression	9	0.110 (0.073-0.165)	71.3
Dropout from all causes	18	0.191 (0.150-0.242)	82.5
All-cause mortality (post-LT)	10	0.165 (0.110-0.247)	51.1
Recurrence (post-LT)	15	0.139 (0.094-0.206)	62.3
1-year survival (post-LT)	8	0.940 (0.913-0.967)	0
2-year survival (post-LT)	5	0.918 (0.868-0.971)	0
3-year survival (post-LT)	5	0.856 (0.817-0.898)	0
5-year survival (post-LT)	6	0.779 (0.672-0.903)	82.3
1-year recurrence-free survival (post-LT)	5	0.877 (0.816-0.942)	34.1
3-year recurrence-free survival (post-LT)	3	0.821 (0.725-0.928)	54.6
5-year recurrence-free survival (post-LT)	5	0.772(0.608-0.979)	80.6
TACE			
Dropout from all causes	5	0.156 (0.082-0.297)	58.2
All-cause mortality (post-LT)	4	0.128 (0.073-0.224)	33.5
Recurrence (post-LT)	7	0.139 (0.104-0.187)	0
5-year recurrence-free survival (post-LT)	3	0.722 (0.613-0.850)	52.5
Dropout due to progression	2	0.109 (0.034-0.342)	57.2
3-year recurrence-free survival (post-LT)	2	0.457 (0.098-2.144)	75.5
1-year recurrence-free survival (post-LT)	3	0.843 (0.746-0.952)	42.6
2-year survival (post-LT)	1	0.927 (0.836-1.028)	NA
1-year survival (post-LT)	3	0.941 (0.900-0.984)	79
5-year survival (post-LT)	4	0.774 (0.656-0.912)	46.6
3-year survival (post-LT)	3	0.852 (0.730-0.994)	92.1
RFA			
Dropout from all causes	1	0.000 (0.000-0.000)	NA
All-cause mortality (post-LT)	1	0.080 (0.027-0.235)	NA
Recurrence (post-LT)	1	0.040 (0.008-0.212)	NA
1-year survival (post-LT)	1	0.960 (0.894-1.031)	NA
3-year survival (post-LT)	1	0.840 (0.734-0.961)	NA
TACE + RFA			
All-cause mortality (post-LT)	1	0.316 (0.149-0.670)	NA
Recurrence (post-LT)	2	0.000 (0.000-0.001)	88.3
2-year survival (post-LT)	1	0.737 (0.540-1.005)	NA
1-year survival (post-LT)	1	0.842 (0.666-1.065)	NA
TAE			
All-cause mortality (post-LT)	1	0.324 (0.190-0.551)	NA
Recurrence (post-LT)	1	0.118 (0.041-0.339)	NA
2-year survival (post-LT)	1	0.833 (0.500-1.388)	NA
1-year recurrence-free survival (post-LT)	1	0.833 (0.500-1.388)	NA
1-year survival (post-LT)	1	0.833 (0.500-1.388)	NA
Multiple therapies			
Dropout from all causes	7	0.192 (0.145-0.255)	84.6
All-cause mortality (post-LT)	1	0.055 (0.015-0.199)	NA
Recurrence (post-LT)	3	0.161 (0.078-0.332)	63.7
Dropout due to progression	4	0.167 (0.129-0.217)	31.4
3-year recurrence-free survival (post-LT)	1	0.810 (0.732-0.897)	NA
1-year recurrence-free survival (post-LT)	1	0.920 (0.863-0.981)	NA
1-year survival (post-LT)	1	0.940 (0.889-0.994)	NA
5-year survival (post-LT)	1	0.650 (0.558-0.757)	NA
3-year survival (post-LT)	1	0.840 (0.766-0.921)	NA

Abbreviation: TAE, transarterial embolization.

differences in the treatment schedule with radioembolization performed one time and chemoembolization repeated every 6 weeks until there was no radiographically viable tumor. A larger single-center RCT compared radioembolization to chemoembolization in unresectable, nonablatable HCC.[70] The primary endpoint, time to progression, was significantly prolonged among those treated with ^{90}Y, with no significant difference in the

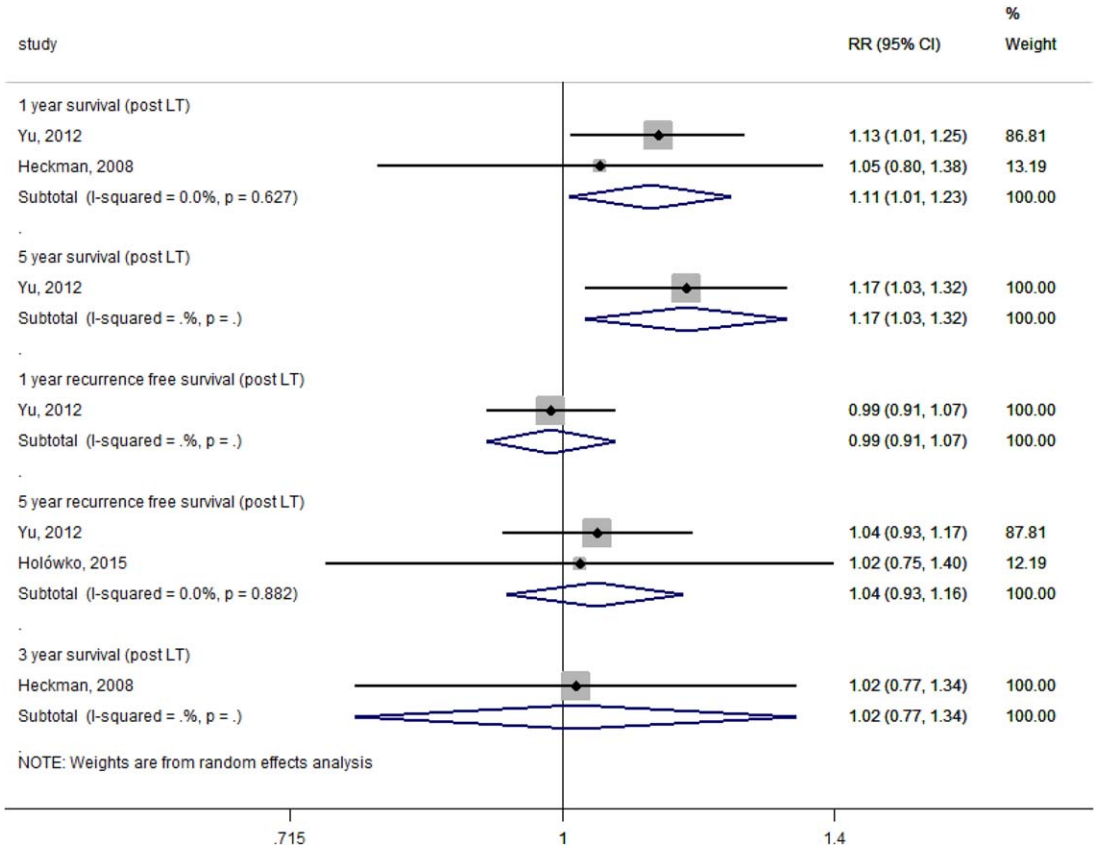

FIG. 6. Outcomes of transplant with down-staged therapy for adults with cirrhosis awaiting LT and HCC beyond Milan criteria (T3). Heckman et al.,[52] Holowko et al.,[12] Yu et al.[53]

TABLE 5. Summary of Evidence for Transplant With Down-Staged Therapy Versus Transplant Alone In Adults With Cirrhosis Awaiting LT and HCC Beyond Milan Criteria (T3)

Outcomes	Cohorts (n)	RR (95% CI)	I^2	GRADE
All bridging therapies				
1-year survival (post-LT)	2	1.11 (1.01-1.23)	0	⊕◯◯◯ Very low*†
5-year survival (post-LT)	1	1.17 (1.03-1.32)	NA	⊕◯◯◯ Very low*†
3-year survival (post-LT)	1	1.02 (0.77-1.34)	0	⊕◯◯◯ Very low*†
1-year recurrence-free survival (post-LT)	1	0.99 (0.91-1.07)	NA	⊕◯◯◯ Very low*†
5-year recurrence-free survival (post-LT)	2	1.04 (0.93-1.16)	0	⊕◯◯◯ Very low*†
All bridging therapies (US studies only)				
1-year survival (post-LT)	1	1.05 (0.80-1.38)	NA	⊕◯◯◯ Very low*†
3-year survival (post-LT)	1	1.02 (0.77-1.34)	NA	⊕◯◯◯ Very low*†

Abbreviation: NA, not available.

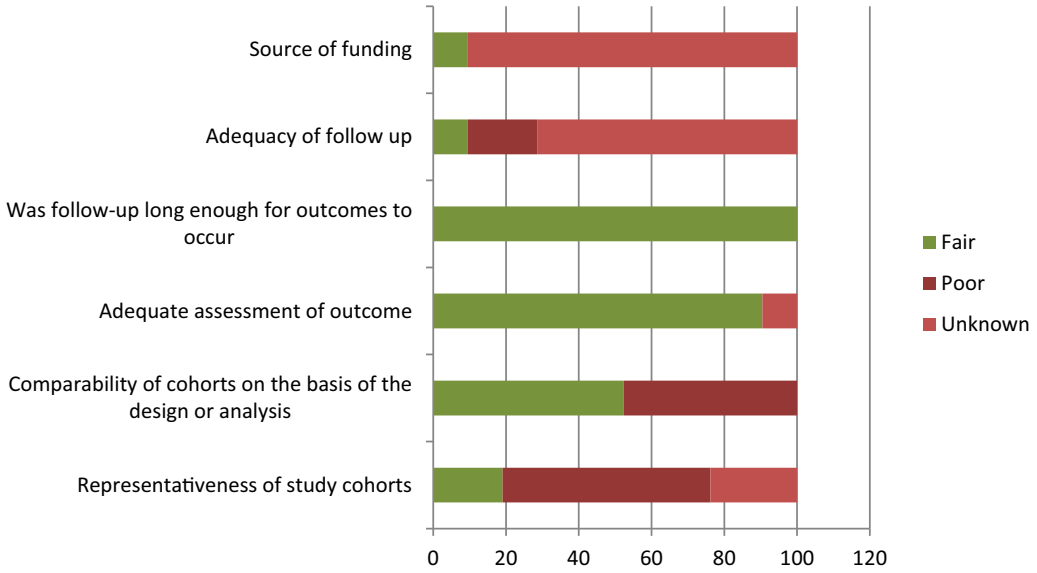

FIG. 7. Methodological quality of the noncomparative studies that enrolled adults with cirrhosis awaiting LT and HCC beyond Milan criteria (T3).

number of treatments between the two intra-arterial therapies (^{90}Y >26 months versus TACE 6.8 months; hazard ratio, 0.122; $P = 0.0012$) and no differences in observed survival censored to transplant (^{90}Y 18.6 months versus TACE 17.7 months; $P = 0.99$). This trial was closed early due to slow accrual; however, the conditional *post hoc* power using the results from the 45 patients enrolled in the study was 96.8%, suggesting that the likelihood of erroneously concluding that ^{90}Y provides significantly longer time to progression over TACE is 3.2%. Ideally, small single-center or multicenter trials comparing more novel strategies such as TARE or stereotactic body radiation therapy to more conventional therapies such as RFA or TACE would be completed in either patients with prolonged waiting time and T2 lesions or those who present with T3 lesions and are transplanted following down-staging, in order to further guide management of patients with unresectable HCC.

DOWN-STAGING

The optimal approach to patients with tumors beyond Milan criteria is controversial given the shortage of available organs for transplantation and the imprecision of identifying which patients with HCC are most likely to benefit from LT. While it is recognized that tumor biology is more complex than size and number alone, factors significantly associated with higher rates of HCC recurrence independent of tumor burden, such as the presence of microvascular invasion and/or poorly differentiated tumor grade, are generally not available pre-LT. Response to LRT may be a surrogate of tumor aggressiveness and has been reported to correlate with post-LT outcomes. Furthermore, a period of at least 3 months of a sustained radiographic response after a successful down-staging therapy has been advocated, to minimize risk of recurrence.[65] In addition to radiographic response to LRT, AFP closest to OLT has been demonstrated to be a predictor of post-OLT outcomes. Several studies have shown AFP to be an independent predictor of overall survival.[71,72] In a detailed analysis of the Organ Procurement and Transplantation Network data of explant pathology of patients transplanted for HCC, AFP (log) level was a pretransplant predictor for HCC recurrence with an odds ratio of 1.2 per increase in AFP ($P < 0.001$).[67] The premise of employing down-staging is to attempt to select appropriate candidate for transplant presenting with HCC outside the Milan criteria.

The initial question posed was whether patients with T3 disease should undergo down-staging prior to LT or proceed to transplant without need for down-staging. However, the significant limitations of receiving a deceased donor LT for patients with T3 HCC has led to a lack of available evidence and made this

TABLE 6. Event Rates of Outcomes Reported for Transplant Following Down-Staging in Patients With Cirrhosis Awaiting LT and HCC Beyond Milan Criteria (T3)

Outcomes	Cohorts (n)	Event Rate (95% CI)	I^2 (%)
All bridging therapies			
Dropout from all causes	8	0.413 (0.319-0.534)	94.6
Recurrence (post-LT)	14	0.204 (0.150-0.277)	25.6
All-cause mortality (post-LT)	7	0.313 (0.199-0.493)	62.5
5-year recurrence-free survival (post-LT)	8	0.800 (0.733-0.873)	53.2
Dropout due to progression	6	0.527 (0.426-0.653)	91.2
3-year recurrence-free survival (post-LT)	6	0.788 (0.732-0.849)	0
1-year recurrence-free survival (post-LT)	15	0.910 (0.880-0.941)	0
2-year recurrence-free survival (post-LT)	2	0.745 (0.610-0.909)	0
2-year survival (post-LT)	3	0.747 (0.628-0.888)	0
1-year survival (post-LT)	10	0.941 (0.912-0.970)	0
5-year survival (post-LT)	6	0.776 (0.713-0.844)	34
3-year survival (post-LT)	6	0.860 (0.773-0.956)	60.6
^{90}Y embolization			
Recurrence (post-LT)	2	0.000 (0.000-6679.281)	86.7
All-cause mortality (post-LT)	1	0.000 (0.000-0.001)	NA
1-year recurrence-free survival (post-LT)	1	0.889 (0.640-1.234)	NA
DEB-TACE			
Recurrence (post-LT)	1	0.286 (0.065-1.256)	NA
Dropout due to progression	1	0.353 (0.169-0.735)	NA
Dropout from all causes	2	0.246 (0.052-1.168)	91.2
PEI			
1-year survival (post-LT)	1	0.857 (0.557-1.318)	NA
1-year disease-free survival (post-LT)	1	1.000 (0.768-1.301)	NA
5-year survival (post-LT)	1	0.857 (0.421-0.996)	NA
5-year disease-free survival (post-LT)	1	1.000 (0.590-1.000)	NA
RFA			
1-year survival (post-LT)	1	0.958 (0.852-1.078)	NA
1-year disease-free survival (post-LT)	1	0.917 (0.787-1.067)	NA
5-year survival (post-LT)	1	0.708 (0.530-0.947)	NA
5-year disease-free survival (post-LT)	1	0.792 (0.625-1.003)	NA
TACE			
Recurrence (post-LT)	4	0.273 (0.170-0.440)	0
All-cause mortality (post-LT)	2	0.423 (0.217-0.826)	61.5
Dropout due to progression	1	0.029 (0.002-0.422)	NA
Dropout from all causes	2	0.152 (0.100-0.231)	0
1-year survival (post-LT)	3	0.947 (0.890-1.007)	0
5-year survival (post-LT)	3	0.843 (0.742-0.958)	37.7
1-year recurrence-free survival (post-LT)	4	0.920 (0.859-0.985)	0
3-year recurrence-free survival (post-LT)	1	0.758 (0.611-0.940)	NA
5-year recurrence-free survival (post-LT)	3	0.825 (0.724-0.940)	80.3
3-year survival (post-LT)	2	0.885 (0.675-1.159)	83
TACI			
Dropout due to progression	1	0.412 (0.216-0.785)	NA
2-year survival (post-LT)	1	0.800 (0.589-1.086)	NA
Dropout from all causes	1	0.412 (0.216-0.785)	NA
1-year survival (post-LT)	1	0.933 (0.771-1.130)	NA
3-year survival (post-LT)	1	0.800 (0.589-1.086)	NA
TACL			
Recurrence (post-LT)	1	0.297 (0.173-0.511)	NA
All-cause mortality (post-LT)	1	0.378 (0.241-0.593)	NA
Dropout due to progression	1	0.716 (0.620-0.828)	NA
2-year survival (post-LT)	1	0.703 (0.558-0.885)	NA
Dropout from all causes	1	0.679 (0.543-0.850)	NA
1-year survival (post-LT)	1	0.892 (0.782-1.017)	NA
5-year survival (post-LT)	1	0.541 (0.391-0.747)	NA

TABLE 6. *Continued*

Outcomes	Cohorts (n)	Event Rate (95% CI)	I^2 (%)
1-year recurrence-free survival (post-LT)	1	0.757 (0.618-0.927)	NA
5-year recurrence-free survival (post-LT)	1	0.676 (0.529-0.863)	NA
TAE			
2-year survival (post-LT)	1	0.833 (0.500-1.388)	NA
2-year recurrence-free survival (post-LT)	1	0.833 (0.500-1.388)	NA
1-year survival (post-LT)	1	1.000 (0.735-1.360)	NA
1-year recurrence-free survival (post-LT)	1	1.000 (0.735-1.360)	NA
Multiple therapies			
Recurrence (post-LT)	6	0.165 (0.118-0.230)	0
All-cause mortality (post-LT)	3	0.235 (0.157-0.352)	0
Dropout due to progression	2	0.277 (0.214-0.360)	0
Dropout from all causes	2	0.344 (0.275-0.429)	0
1-year survival (post-LT)	5	0.941 (0.905-0.978)	0
5-year survival (post-LT)	3	0.759 (0.689-0.836)	0
1-year recurrence-free survival (post-LT)	7	0.910 (0.873-0.949)	NA
3-year recurrence-free survival (post-LT)	5	0.792 (0.727-0.863)	12.2
5-year recurrence-free survival (post-LT)	5	0.770 (0.652-0.910)	69.9
5-year survival (post-LT)	3	0.844 (0.743-0.959)	54.2

Abbreviations: DEB, doxorubicin-eluting bead; NA, not available; PEI, percutaneous ethanol injection; TACI, transarterial chemoinfusion; TACL, transarterial chemolipiodolization; TAE, transarterial embolization.

question not clinically practical. Thus, we later modified the question to one much more clinically relevant: should patients with T3 HCC undergo LT after successful down-staging to T2 HCC?

There was significant heterogeneity among the three studies that looked at down-staging for T3 HCC compared to transplant for T3 HCC without down-staging in terms of the comparative group. Heckman et al. compared 12 patients who were successfully down-staged to a subset with >T2 without LRT due to indolent disease plus T2 patients in receipt of LRT.[52] The second study by Holowko and colleagues compared patients with and without pretransplant TACE who exceeded Milan on explant.[12] Lastly, a study from Asia comprised of predominantly living donor LT compared 51 patients exceeding the University of California–San Francisco criteria to 110 patients who were not down-staged, presumably within Milan, and proceeded directly to LT.[53] In these three studies, there was no significant difference in posttransplant outcomes among those submitted to down-staging prior to LT versus the comparative group.

A study that more precisely addresses the question of utility of transplant in those who have been successfully down-staged is a prospective trial by Yao et al.[65] Patients included in a down-staging protocol had a defined upper tumor limit (without evidence of vascular invasion or metastatic disease) which included one lesion up to 8 cm, two or three lesions each ≤5 cm with a total tumor diameter not exceeding 8 cm, or four or five lesions each ≤3 cm and not exceeding a total tumor diameter >8 cm. They reported outcomes among 118 patients exceeding the Milan criteria who underwent LRT in a down-staging protocol with the intent for LT and compared them to 488 patients with T2 disease on presentation, of whom 97% received LRT prior to transplant. Among the 64 patients in the down-staged group who underwent LT, overall survival and recurrence rates were comparable to the 488 T2 patients. This study also reported a dropout rate of 35% at a median of 8.2 months from enrollment into a down-staging protocol. Dropout was significantly higher among those in the down-staging group compared to those who were listed with T2 HCC ($P = 0.04$). AFP levels >1,000 ng/mL and Child-Pugh B/C were significantly associated with risk of dropout in the down-staging cohort. Other studies have provided a cautionary note with an anticipated higher rate of recurrence post-OLT the further the tumor burden is beyond the Milan criteria. The Metroticket devised the "up-to-seven" criteria based on the explant pathology including the size of the largest tumor nodules, number of tumor nodules, and presence or absence of microvascular invasion.[73] Among patients exceeding Milan who met the up-to-seven criteria without microvascular invasion, 5-year overall survival was excellent at 71.2%. Lower overall survival was noted in those meeting the expanded criteria with microvascular

invasion and in those beyond the up-to-seven criteria. The Metroticket project has now expanded to a calculator to predict post-OLT 5-year overall survival based on preoperative imaging (size of the largest viable tumor, number of viable tumors) and AFP level closest to OLT.[74]

LIMITATIONS

Despite a large number of publications addressing the role of LRT for HCC in the transplant setting, none were RCTs, most were single-center, and the overall quality of the data used to inform these questions was very low. Decisions regarding LRT are heavily influenced by the milieu of the demographic area, most notably the anticipated wait time. Moreover, there is significant heterogeneity in terms of selection of which LRT is performed at various stages of HCC (T1, T2, T3) based on institutional experience/preference as well as differences in the treatment dynamics of the individual forms of LRT.

FUTURE DIRECTIONS

The Milan criteria have consistently demonstrated 5-year overall survival of approximately 70% over the last two decades. Patients with tumors less than or greater than the Milan criteria will require additional data to determine the role/benefit of transplant and the impact on non-HCC patients awaiting LT. The efficacy of LRT for T1, particularly in the era of direct-acting agents for hepatitis C virus with anticipated decline in complications of portal hypertension, is needed to determine if the "not ablate and wait" approach should be abandoned in favor of allocation of these organs to patients with more advanced liver disease. While down-staging for selected candidates has shown promise with outcomes comparable to patients presenting with T2 tumors, others have rejected any upper tumor size or number as a restriction. The Toronto group has recently reported excellent outcomes regardless of tumor burden (restricted to the liver without vascular/biliary involvement and without metastasis outside the liver) using a biological assessment including tumor grade, performance status, and AFP levels.[75]

The ability to complete an RCT to determine any significant difference in overall survival afforded by a particular form of LRT, predominantly in those with less advanced disease, Barcelona Clinic Liver Cancer A/B is not feasible due to expected crossover to different treatments (sorafenib, regiorafenib), censorship at the time of transplant/resection, and obstacles to recruitment related to patient and referring physician preference for a specific therapy. Hence, performing a randomized clinical trial in Barcelona Clinic Liver Cancer A or B, considering all of the difficulties above, in such a way that a survival benefit can be isolated to the initial intervention, is not statistically possible without thousands of patients. Future RCTs aimed at evaluating the impact of therapies on HCC could be enriched by designing large multicenter trials and by referral to multidisciplinary tumor boards with the goal to engage potential eligible patients in a time-sensitive manner prior to stage migration and/or deterioration in liver function.

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