SYSTEMATIC REVIEW

Bridging therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis on intention-to-treat outcomes

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Abstract

Introduction: Locoregional therapies are commonly used as bridging strategies to decrease the drop-out of patients with hepatocellular carcinoma (HCC) awaiting liver transplantation (LT). The present paper aims to assess the outcomes of bridging therapies in patients with HCC considered for LT according to an intention-to-treat (ITT) survival analysis.

Material and methods: Medline and Web of Science databases were searched for reports published before May 2021. Papers assessing adult patients with HCC considered for LT and reporting ITT survival outcomes were included. Two reviewers independently identified, extracted the data, and evaluated the papers according to Newcastle-Ottawa criteria. Outcomes analyzed were: drop-out rate; time on the waiting list; 1-, 3-, and 5-year survival after LT and based on an ITT analysis.

Results: The search identified 3106 records; six papers (1043 patients) met the inclusion criteria. Patients with HCC, listed for LT and submitted to bridging therapies presented a longer waiting time before LT (MD 3.77, 95% CI 2.07-5.48) in comparison with the non-interventional group. However, they presented a raised post LT after 1-year (OR 2.00, 95% CI 1.18-3.41), 3-years (OR 1.47, 95% CI 1.01-2.15), and 5-years (OR 1.50, 95% CI 1.06-2.13) survival.

Conclusion: Patients submitted to bridging procedures, despite having a longer interval on the waiting list, presented better post-LT survival outcomes. Bridging therapies for selected patients at low risk of post-procedural complications and long expected intervals on the waiting list should be encouraged. However, further clinical trials should confirm the survival benefit of bridging therapies in patients with HCC listed for LT.

KEYWORDS bridging, downstaging, hepatocellular carcinoma, liver transplantation, locoregional therapies
1 | INTRODUCTION

Liver transplantation (LT) is the best curative treatment for patients with cirrhosis and HCC as it can both remove the tumor and treat the liver cirrhosis liver.1,2 Favorable long-term oncological outcomes after LT as a curative treatment for HCC are attributed to selective listing criteria based on morphological and biological criteria.3–8 Additionally, once the patient is on the waiting list, several strategies have been proposed in order to decrease the number of drop-outs, especially in regions with shortage of donor organs and long waiting time before LT.9–11 It has been reported that the risk of drop-out, especially for those tumors >3 cm that are left untreated, is about 12% at 6 months and between 15%-30% at 6 months, with the tumor progression being the main cause of drop-out.12–15 Strategies aiming to minimize waitlist drop-out due to tumor progression are denominated bridging therapy. They include mostly LRT applied to patients with HCC meeting listing criteria and awaiting LT, aiming to maintain the tumor burden within the criteria, thus reducing the risk of drop-out.

However, the selection of appropriate candidates for LRT is paramount as they are not exempt from the risk of complications, exacerbating the underlying liver disease and/or portal hypertension.16,17 For this reason, bridging therapies are usually recommended when there is a long-expected waiting time before LT.18 Nevertheless, these recommendations are based on low-quality evidence, as there are no randomized controlled trials (RCTs) available on this issue.19 As a matter of fact, RCTs are challenging to conduct due to logistical and ethical reasons. Additionally, the vast majority of the available evidence, including some recently published systematic reviews,20 comes from the analysis of post-transplant outcomes of treated and untreated patients. However, these analyses were based on the comparison of a study and a control group that often present substantial differences in tumor burden, wait-list period, and drop-out rate. Therefore, these studies are prone to attrition bias as they do not consider the entire burden of patients on the waiting list that would only be assessed by intention-to-treat analysis. In conclusion, whether bridging therapies are associated with favorable long-term oncological outcomes and whether they should be considered a routine approach in clinical practice is still a debatable matter.

This review intends to synthesize the existing evidence about the effectiveness of bridging therapies, aiming to evaluate outcomes from ITT analysis of patients with HCC on the waiting list submitted to bridging versus those with non-interventional therapies.

2 | METHODS

2.1 | Search strategy

The search was undertaken according to the PRISMA guidelines.21 Two researchers systematically searched Medline, EMBASE, and the Cochrane Library for reports published before the 16th of May 2021, not limited to the English language, using a combined text and MeSH search strategy. The search terms for the literature review were divided into two groups. The first group contained the keywords downstaging, bridging, catheter ablation, chemoembolization, TACE, transarterial radioembolization, TARE, radiosurgery, radiofrequency ablation, RFA, microwave ablation, MWA, embolization, ethanol injection, PEI, high-intensity focused ultrasound ablation, high-intensity focused ultrasound, HIFU, stereotactic body radiation therapy, stereotactic radiation, SBRT, and radiotherapy. The second group contained the keywords hepatocellular carcinoma, HCC, and liver cancer. The search terms were structured by combining one word from each group in such a way that all possible combinations were employed. References from relevant papers were also included in order to constitute the initial pool of articles.

2.2 | Study selection

In order to assess the outcomes of bridging therapies for patients with HCC awaiting LT, the review included studies that enrolled adults with cirrhosis listed for LT, treated with bridging therapies before LT and reporting outcomes based on ITT analysis. Full-text published studies meeting the following criteria were included: (a) patients aged 18 years or older; (b) observational prospective and retrospective or randomized clinical trial; (c) patients with liver cirrhosis and HCC listed for LT; (d) survival outcomes reported according to an ITT protocol. When precise survival outcomes were not clearly reported, data were extrapolated from the Kaplan-Mayer survival curves. Experimental studies on animal models, case reports, short case series with fewer than 10 patients, reviews, editorials, and comments were excluded. When duplicate reports from the same study were identified, only the most recent publication or the one with the longest follow-up period was included. The full text of each article was assessed if it could not be excluded by the initial review.

2.3 | Data extraction

Two researchers (MDM and MM) assessed the abstracts of the selected studies to determine their eligibility. Treatment options included: (a) patients with HCC within the listing
criteria undergoing bridging LRT before LT; (b) patients with HCC within the listing criteria undergoing LT in absence of bridging therapies. The extracted data included country of study; design; number of participants; age; listing criteria; bridging selection criteria; drop-out rate; time from listing to transplant; perioperative mortality and morbidities for patients undergoing LT; post-LT recurrence, 1-, 3-, and 5-year survival from LT; 1-, 3-, and 5-year survival based on ITT analysis. Disagreements over data extraction were resolved by consensus between the two authors.

2.4 | Evaluation of studies and statistical analysis

Two researchers (MDM and MM) independently evaluated the included studies for quality assessment: observational studies were evaluated according to the Newcastle-Ottawa Criteria. The data were analyzed using the statistical software Review Manager 5.4 and presented as medians and proportions along with a corresponding minimum-maximum range. Differences in dichotomous variables were calculated using the odds ratio (OR) and respective 95% confidence intervals (CI); for continuous variables, the mean difference (MD) was calculated with a 95% CI. A random-effects model was used to take into account the heterogeneity of the estimates. Values were considered statistically significant when \( P \) was less than .05. The overlapping of CI was used to visually assess the heterogeneity. Heterogeneity was statistically explored with the chi-square test, with significance set to a \( P \)-value of .10, and the quantity of heterogeneity was measured with the \( I^2 \) statistic. The quality of evidence was estimated using the GRADE methodology, which takes into account the risk of bias, inconsistency (heterogeneity), directness of evidence, imprecision, and publication bias.

3 | RESULTS

3.1 | Literature review

The initial search identified 3106 records; 2978 were excluded due to study characteristics and/or methodology. The full-text articles of 128 papers were retrieved and assessed. Finally, six papers (1043 patients) were included in the analysis (Figure 1), assessing the results of patients

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**FIGURE 1** Flow chart of included studies.
listed for LT and submitted to bridging versus those with no bridging therapies. The reasons for exclusion were methodological issues and lack of outcomes from ITT analysis.

### 3.2 Study and patients’ characteristics

No RCT was found and one of the included papers was considered as at high risk of bias (Table S1). Mean age ranged from 53 to 58 years; other patient and disease characteristics in the included studies are shown in Table 1. LRT included transarterial embolization (TAE), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), thermal ablation, and a sequential combination of these strategies. Patients submitted to bridging procedures did not present major postoperative complications; minor complications ranged from 2.3% to 8.3%. As shown in Table 1, patients submitted to bridging procedures tended to present less advanced cirrhosis with an inferior percentage of Child-Pugh B and C patients in comparison with those who were not treated before the LT.

### 3.3 Patient selection for liver transplantation and bridging therapies

Except from one paper, that based the selection criteria on the University of California San Francisco (UCSF) criteria, all the others used the Milan Criteria (MC) for listing patients for LT. No specific bridging protocols or prespecified selection criteria for bridging therapies were found. DuBay et al. stated that bridging therapy was recommended to patients who were expected to have a transplant wait time more than 3 months; wait time was estimated based upon the patient’s position on the transplant waiting list and availability of living liver donor. Overall, patients submitted to bridging therapies presented a greater tumor burden and less advanced cirrhotic disease.

### 3.4 Should patients with HCC within the listing criteria undergo a bridging therapy? (ITT outcomes of bridging therapies vs non-interventional strategy) (Table 2)

#### 3.4.1 Waiting list drop-out outcomes and interval on the waiting list

Six studies (1043 patients) reported on drop-out due to any cause, five on drop-out due to progression. Drop-out rate ranged from 2.9% to 33.8% in the bridging group, while it ranged from 8.6% to 24.1% in the non-interventional group. No differences in drop-out rate were observed (Figure 2).

Five studies (778 patients) demonstrated that patients submitted to bridging therapies presented a longer waiting time on the waiting list before LT (MD 3.77, 95% CI 2.07-5.48) (Figure 3).

#### 3.4.2 HCC recurrence after LT

Two studies (267 patients) reported post-LT recurrence. Drop-out rate ranged from 1.3% to 4.8% in the bridging group, while it ranged from 2.2% to 5.7% in the non-interventional group. No differences in post-LT recurrence rate were observed (Figure 4).

#### 3.4.3 Post-LT survival outcomes

Four studies (659 patients) reported post-LT 1-, 3-, and 5-year survival. Patients submitted to bridging therapies presented a raised 1-year (OR 2.00, 95% CI 1.18-3.41), 3-year (OR 1.47, 95% CI 1.01-2.15), and 5-year (OR 1.50, 95% CI 1.06-2.13) survival post LT (Figure 5).

#### 3.4.4 Survival outcomes based on ITT analysis

Three studies (522 patients) reported on 1- and 5-year survival outcomes based on an ITT analysis, while two reported on 3-year survival. No differences in 1-, 3-, or 5-year survival based on an ITT analysis between the two groups were observed (Figure 6).

### 4 DISCUSSION

Several studies have postulated the benefit of bridging therapies in patients selected with liver cirrhosis and HCC before LT. However, current recommendations are mostly based on low-quality studies: observational, retrospective, with small sample size, short follow-up, and reporting exclusively on post-LT outcomes. Therefore, the real benefit of bridging therapies as a routine approach in patients with HCC listed for LT is still under discussion. To our knowledge, this is the first meta-analysis assessing outcomes of bridging therapies of patients listed for LT according to an ITT analysis. The present study demonstrated that patients with liver cirrhosis and HCC, listed for LT and submitted to bridging procedures, despite having a longer interval on the waiting list, presented for improved post-LT survival outcomes.
| Study ID    | Country | N  | Study group | Bridging procedure | N  | Patients’ characteristics                        | Control group | N  | Patients’ characteristics                        | Follow-up (months) |
|------------|---------|----|-------------|-------------------|----|-------------------------------------------------|---------------|----|-------------------------------------------------|-------------------|
| Branco 2009 | Spain   | 97 | Bridging    | PEI               | 62 | Child B (54.8%)  
Child C (9.6%)  
Post-bridging complications (no major  
– 2.3% minor) | Observation  | 35 | Child B (37.1%)  
Child C (11.4%) | 23.5 |
| DuBay 2011  | Canada  | 170| Bridging    | RFA               | 77 | Median MELD 14 (7-26)  
Post-bridging complications (no major  
– 2.5% minor) | Observation  | 93 | Median MELD 15 (6-25) |  |
| Frangakis 2011 | USA | 87 | Bridging    | TACE              | 35 | Child B (22.5%)  
Child C (57.1%)  
Mean MELD 21 (±3) | Observation  | 52 | Child B (9.5%)  
Child C (69.2%)  
Mean MELD 20 (±4) | 45.0 |
| Habibollahi 2018 | USA | 359| Bridging    | Various           | 200| Child B (2.3%)  
Mean MELD 10.6 (±4.3) | Observation  | 159| Child B (25.2%)  
Mean MELD 12.4 (±6.1) | 78.0 |
| Tan 2018    | Singapure | 65 | Bridging    | TACE              | 36 | Child B (22.2%)  
Child C (5.6%) | Observation  | 29 | Child B (41.4%)  
Child C (24.1%) |  |
| Xing 2017   | USA     | 265| Bridging    | Various           | 155| Child B (36.1%)  
Child C (7.1%)  
Post-bridging complications (no major  
– 8.3% minor) | Observation  | 110| Child B (38.1%)  
Child C (8.1%) |  |

Abbreviations: PEI, Percutaneous Ethanol Injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.
The indication of bridging therapies to patients with liver cirrhosis and HCC, listed for LT, is a controversial topic. There are multiple theoretical advantages of bridging therapies in patients on the waiting list while awaiting LT. First, they could reduce the rate of drop-out due to tumor progression while on the waiting list. Second, they could decrease the risk of post-OLT recurrences by reducing the tumor burden. Finally, they could play a role in identifying candidates with poor tumor biology who may not be ideal candidates for LT. Agopian et al assessed a large multicentric cohort of 3601 patients, showing that tumor response to bridging LRT could serve as a surrogate for underlying tumor biology and prioritize LT candidates, but it does not improve post-LT survival in patients who fail to achieve complete pathological response. Similarly, Di Norcia et al analyzed the United States Multicenter HCC Transplant Consortium (UMHTC) and showed that patients with HCC, listed for LT that presented a complete pathological response to LRT had a significantly lower cumulative incidences of HCC.

**Table 2** Summary of evidence

| Outcomes                                      | Studies | Patients | OR (95% CI) | I² | GRADE |
|-----------------------------------------------|---------|----------|-------------|----|-------|
| Drop-out due to all causes                    | 6       | 1043     | 1.42 (0.93-2.16) | 30%| □□□□ Low |
| Drop-out due to tumor progression             | 6       | 1043     | 1.41 (0.63-3.17) | 50%| □□□□ Low |
| Time from initial assessment to LT            | 5       | 778      | 3.77 (2.07-5.48) | 0% | □□□□ Low |
| Recurrence Rate                               | 2       | 267      | 0.74 (0.17-3.21) | 0% | □□□□ Very low |
| Post-LT 1 year-survival                       | 4       | 659      | 2.00 (1.18-3.41) | 0% | □□□□ Very low |
| Post-LT 3 years-survival                      | 4       | 659      | 1.47 (1.01-2.15) | 0% | □□□□ Very low |
| Post-LT 5 years-survival                      | 4       | 659      | 1.50 (1.06-2.13) | 10%| □□□□ Very low |
| ITT 1 year-survival                           | 3       | 522      | 1.25 (0.82-1.92) | 0% | □□□□ Very low |
| ITT 3 years-survival                          | 2       | 257      | 1.06 (0.63-1.78) | 0% | □□□□ Very low |
| ITT 5 years-survival                          | 3       | 522      | 0.67 (0.40-1.12) | 11%| □□□□ Very low |

Abbreviation: LT, Liver transplantation.

*MD (95% CI).*
FIGURE 3  Forrest plot on time to liver transplantation.

FIGURE 4  Forrest plot on recurrence rate.

FIGURE 5  Forrest plot post-LT survival: (A) 1-year overall survival; (B) 3-years overall survival; (C) 5-years overall survival.
recurrence at 1-, 3, and 5-years post-LT, compared with those without complete response. Therefore, response to bridging therapies, in combination morphological and biological criteria could possibly replace conventional criteria for defining transplantability.  

However, these arguments are still debatable as bridging therapies are still associated with a risk of exacerbating underlying liver disease and portal hypertension.  

Garwood et al demonstrated that a poor hepatic reserve increases the risk of irreversible hepatotoxicity, reporting reversible and irreversible hepatotoxicity rates of 11% and 9%, respectively, in a cohort of 251 patients with HCC and concurrent synthetic hepatic dysfunction after TACE.  

For these reasons, EASL and AASLD guidelines indicate bridging therapies in appropriate candidates when the there is a long expected transplant waiting time. A recent systematic review by Butcher et al on 8242 patients showed that subjects treated with TACE despite presenting worse prognostic features compared to non-TACE patients (in terms of tumor diameter and longer time on the waiting list) had similar survival and postoperative outcomes to non-TACE patients. These findings support the EASL and AASLD guidelines stating that neoadjuvant TACE can be used for patients with longer expected waiting list times (specifically >6 months according to the EASL guidelines). However, in the clinical practice, due to unpredictable waiting times and fear of tumor progression, the vast majority of patients receive some form of LRT while awaiting transplant. Whether this approach is justified or not is still a matter of debate. 

The analysis of baseline characteristics of patients included in the present systematic review suggests that patients selected for bridging presented less advanced cirrhosis and a more aggressive tumor biology. Overall, post-procedural complications did not seem to determine a higher drop-out rate in the bridging group with no major complication reported after the bridging and an incidence of minor complications between 2.3% and 8.3%. Despite the longer interval on the waiting list, patients submitted to downstaging presented improved post-LT survival. Hence, these findings support the utilization of LRT as a bridging strategy in selected patients with HCC, at low risk of post-procedural complications, and long expected intervals on the waiting list. However, the more advanced liver cirrhosis could be an important confounding responsible of the decreased post-LT survival outcome of the non-interventional patients.
group. As included studies in the present review had a retrospective design, thus prone to selection bias, it appears likely that there is still lack of equipoise on the survival benefit of bridging therapies as a routine approach in patients with HCC considered for LT. Therefore, well-designed randomized clinical trial comparing homogenous groups of patients should confirm the survival benefit of bridging therapies, according to an ITT analysis. Additionally, future research should investigate benefit and drawbacks of specific bridging strategies according to tumor burden and characteristic as well as the severity of the liver cirrhosis.

The reported outcomes of the present review should be considered and interpreted within the context of its inherent limitations. As mentioned above, there was a certain degree of heterogeneity in the LRT applied and the selection criteria for LRT as a bridging therapy. It must also be considered that the vast majority of the studies included in this research had retrospective non-randomized designs, which are inevitably subject to bias. Additionally, we did not assess the influence of tumor response to LRT on long-term oncological outcomes. However, to the best of our knowledge, this review represents the only systematic review and meta-analysis aiming to summarize outcomes of bridging LRT assessing the entire burden of patients listed for LT and not only those submitted to the surgical procedure.

5 | CONCLUSIONS

This analysis demonstrated that patients with liver cirrhosis and HCC, listed for LT and submitted to bridging procedures, despite having a longer interval on the waiting list, presented improved post-LT survival outcomes. Therefore, bridging therapies for patients at low risk of post-procedural complications and long expected intervals on the waiting list should be endorsed. Given the characteristics of the included papers, the bridging group was likely to include patients with more aggressive tumor biology but less advanced liver cirrhosis. Therefore, RCTs, performed according to an ITT principle, should confirm the survival benefit of bridging therapies as a routine approach in patients with HCC listed for LT. Additionally, future research should investigate the benefits and drawbacks of specific bridging strategies according to tumor burden and characteristic as well as the severity of the liver cirrhosis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

*How to cite this article:* Di Martino M, Ferraro D, Pisaniello D, Arenga G, Falaschi F, Terrone A, et al. Bridging therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis on intention-to-treat outcomes. J Hepatobiliary Pancreat Sci. 2023;30:429–438. [https://doi.org/10.1002/jhp.1248](https://doi.org/10.1002/jhp.1248)