Downstaging, Bridging and Immunotherapy in liver transplantation

PICO 1: Should all eligible patients be transplanted after successful downstaging?

Population: HCC patients with successful downstaging (=reaching transplant criteria)
Intervention: Listing in view of transplantation
Comparators: No transplantation
Outcome: Intend-to-treat survival
Paper type: RCT
Author: S. Bhoori /Co-author: C. Toso

STATEMENT: All HCC patients achieving a successful downstaging to pre-defined transplantable criteria should be considered for liver transplantation as the benefit in terms of both RFS and OS of this approach is significantly higher than any other non-transplant strategy.

Level of evidence: high
Level of recommendation: strong

PICO 2: Should all patients outside transplant criteria (all comers) be considered for downstaging?

Population: HCC patients with successful downstaging (=reaching transplant criteria)
Intervention: Patients originally "just" outside transplant criteria
Comparators: Patients originally "far" outside transplant criteria
Outcome: Intend-to-treat survival
Author: C. Toso /Co-author: S. Bhoori

STATEMENT: All patients beyond transplant criteria, without extra-hepatic disease, and otherwise candidate for transplantation should be considered for downstaging, as the original HCC state has no demonstrated impact on post-transplant survival.

However, the higher the burden of disease (based on morphology and/or biology), the less likely to achieve successful downstaging.

Level of evidence: low
Level of recommendation: strong

PICO 3: Should patients with complete response of HCC macrovascular invasion be considered for liver transplantation?

Population: Liver transplant recipients with complete response of HCC macrovascular invasion
Intervention: Listing in view of transplantation
Comparators: No transplantation
Outcome: Intend-to-treat survival
Author: G. Sapisochin/Co-author: M. Reig

STATEMENT: Several observational studies without comparator have suggested that liver transplantation for patients with macrovascular invasion can be done safely. However, overall and recurrence-free survival is variable among different studies. In general, the recurrence rate is high.

Level of evidence: low
Level of recommendation: weak

UNMET NEED: Future studies should focus on loco-regional or systemic treatment, and some sustained (~6 months) response prior to transplantation.

PICO 4: Does bridging decrease waitlist drop-out?

Population: Liver transplant candidates with HCC
Intervention: Bridging (all types)
Comparator: No bridging
Outcome: Waitlist drop-out (including both list exclusion/mortality)
Author: M. Claasen/Co-author: T. Fondevila

PREMISE There is no evidence in the current literature suggesting that bridging therapy over no bridging therapy would reduce waitlist dropout in patients listed with a tumor burden within Milan criteria, within UCSF criteria, or within ETC criteria.

STATEMENT: Despite the low evidence, in view of disease control, waiting list dynamics, and regional factors, we recommend that bridging therapy be continued in the usual way by multidisciplinary consultation. Only if a short waiting period to transplant is plausible (estimated at 6 months), consideration can be given to waiving this.

Level of evidence: low
Level of recommendation: strong

PICO 5: Does bridging improve post-transplant survival?

Population: Liver transplant candidates with HCC
Intervention: Bridging (all types)
Comparator: No bridging
Outcome: Post-transplant overall survival
Author: M. Claasen/Co-author: T. Fondevila

STATEMENT: There are some studies that suggest a positive effect of bridging therapy on long-term post-transplant survival.
Level of evidence: moderate
Level of recommendation: strong

PICO 6: Does the type of response to bridging have an impact on survival?

Population: Liver transplant candidates with HCC
Intervention: Complete radiological or pathological response
Comparators: No response (excluding progression)
Outcome: Post-transplant survival
Author: S. Bhoori /Co-author: C. Toso

STATEMENT a: Patients on the waiting list with an HCC within conventional criteria, should undergo locoregional bridging treatments with the aim of achieving a complete response (better if pathological) which is suggested to decrease the rate of post-transplantation tumour recurrence and improve post-transplant survival.
STATEMENT b: At this time point there is no radiological imaging able to predict complete pathological response.

Level of evidence: low
Level of recommendation: strong

PICO 7: What is the best bridging/downstaging strategy?

Population: Patients with HCC
Intervention: ablation
Comparators: TACE, SBRT, resection, SIRT
Outcome: Clinical response rate
Paper type: RCT
Author: D. Sneiders, B. Rakke/Co-author: R. Adam

Lesion number	Lesion size	BCLC	Milan	Statements
=< 3	≤ 3cm	A,0	Within Milan	1. **RFA or MWA is the preferred first line therapy and are equally effective in obtaining short-term tumour control.** Level of evidence: Moderate Level of recommendation: strong 2. **Intention to treat with combined ablation therapy and TACE does not impact short term tumour control.** Level of evidence: Low to Very low Level of recommendation: weak
1	3-5cm	A	Within Milan	1. **When feasible, liver resection, preferably by laparoscopic route and segmental extension, should be considered** Level of evidence: moderate Level of recommendation: weak 2. **When technically feasible RFA or MWA are the preferred second-line therapies**

				and are equally effective in obtaining short-term tumour control. When ablation is not obtained or not expected to be obtained, TACE is the preferred therapy. Level of evidence: Moderate Level of recommendation: weak 3. **Intention to treat with combined RFA/MWA and TACE may result in superior short term tumour control compared to TACE or RFA alone and can be used on indication.** Level of evidence: Very low Level of recommendation: weak 4. **Alternatives to TACE or RFA/MWA, including radio-embolization or SIRT, SBRT, proton-beam radiation therapy or brachytherapy have shown non-inferior or improved short term tumour control in preliminary trials and should preferably be used in a research setting.** Level of evidence: Very low Level of recommendation: weak
1	≥ 5	A	Outside Milan	1. **Liver resection, if feasible and indicated, is associated to the higher probability to obtain a complete response on the single HCC** Level of evidence: low Level of recommendation: weak 2. **Downstaging therapy with TACE is preferred over bland embolization or chemo infusion alone.** Level of evidence: Moderate Level of recommendation: weak 3. **Intention to treat with combined RFA/MWA and TACE may result in superior short term tumour control than TACE alone and can be used on indication.** Level of evidence: Very low Level of recommendation: weak 5. **Alternatives to TACE, including radio-embolization or SIRT, SBRT, proton-beam radiation therapy or brachytherapy have shown non-inferior or slightly improved short term tumour control in preliminary trials and should preferably be used in a research setting.** Level of evidence: Very low
> 1	≥ 5	B	Outside Milan	

				Level of recommendation: weak

PICO 8: Are patients on immunotherapy prior to liver transplantation at higher risk of rejection?

Population: Patients with HCC treated by immunotherapy prior to transplantation
Comparators: Patients with HCC not treated by immunotherapy prior to transplantation
Outcome: Rejection rate
Author: P. Tabrizian/Co-author: U. Cillo

PREMISE Data consists of a heterogenous cohort based on few case reports and short series.
STATEMENT: Liver transplantation in patients previously treated with immune checkpoint inhibitors has shown encouraging results despite a potential risk of rejection.

Level of evidence: low
Level of recommendation: weak

UNMET NEED: Patient selection for immune checkpoint inhibitors, and minimal washout period between the last drug dose and transplantation, are unmet clinical needs that require investigation.

PICO 9: What is the best way to assess response to immunotherapy?

Population: Patients with HCC treated with immunotherapy
Gold-standard: CT
Comparators: MRI
Outcome: Predictor of pathological response (% of necrotic tumor area)
Secondary outcome: Progression-free survival
Author: P. Tabrizian/Co-author: U. Cillo

STATEMENT: Contrast enhanced MRI has been shown to assess tumour necrosis in response to therapy and could be used in conjunction with RECIST 1.1 to quantify the total change in viable tumour following therapy

Level of evidence: moderate
Level of recommendation: weak

UNMET NEED: Improved imaging techniques are needed to define response ahead of pathologic assessments and oncologic outcomes.

PICO 10: What is the best way to assess response to immunotherapy?

Population: Patients with HCC
Intervention: Combined immunotherapy and LRT
Comparators: LRT
Outcome: Side effects
Secondary outcome: Intend-to-treat survival
Author: M. Reig/Co-author: G. Sapisochin

STATEMENT: Despite the limited information available the combined treatment with immunotherapy and loco-regional therapy (LRT) seems safe. There is no data in the context of pre- or post- liver transplantation

Level of evidence: low
Level of recommendation: weak

UNMET NEED: Further investigations are needed to explore the safety and long-term oncologic outcomes in the pre- and post-transplant setting.