International Journal of Multiphysics
Volume 18, No. 3, 2024
ISSN: 1750-9548

An Overview on Downstaging and Bridging Treatments for Liver Transplant Patients with Hepatocellular Carcinoma

Salama Mohamed Shabban[1], Jihan Ahmed Shawky[1], Yehia Zakaria Atwa[2], Mohamed Abd Elwahab Ali[3], Mostafa Tharwat Mostafa Mohamed[1*]

[1]Department of Hepatology, gastroenterology and infectious diseases, Faculty of Medicine, Zagazig University, Egypt

[2]Department of General Surgery, Faculty of Medicine, Zagazig University, Egypt

[3]Department of General Surgery, Faculty of Medicine, Mansoura University, Egypt

***Corresponding author:** Mostafa Tharwat Mostafa Mohamed

Email: drmutefa@gmail.com

Abstract:

Several therapeutic procedures have been proposed as bridging treatments for patients with hepatocellular carcinoma (HCC) awaiting liver transplantation (LT). The most used treatments include transarterial chemoembolization and radiofrequency ablation. Surgical resection has also been successfully used as a bridging procedure, and LT should be considered a rescue treatment in patients with previous HCC resection who experience tumor recurrence or post-treatment severe decompensation of liver function.

Keywords: Downstaging, Bridging, Liver Transplant, Hepatocellular Carcinoma.

Introduction:

Bridging therapy for liver transplant candidates on the waiting list with LRT aiming to decrease the tumor progression and lowering the dropout rate ,Patients with HCCs on the waiting list for LT are often delisted due to tumor progression beyond the accepted criteria for LT **(1).**

When the tumor burden meets the Milan criteria at the time of the first referral, this approach is called bridging toward LT**(2).**

One of the limitations of expansion of the limits in tumor size/ number alone is that it does not account for the effects of local regional therapy (LRT), which has been widely used to control tumor growth as a bridge to LT, particularly if the waiting time is prolonged **(3).**

More than 50% of all patients listed for liver transplant in the United States with a diagnosis of HCC received bridging therapy **(4).**

The use of LRT is now considered standard practice for waitlisted patients either as a bridge to transplantation or for tumor downstaging **(5).**

TACE is a commonly used bridging therapy, which was shown to achieve complete tumor necrosis in 30–50% of the patients **(6).** higher tumor necrosis rate could be achieved by the use of doxorubicin eluting bead TACE (DEB-TACE)**(7).**

Percutaneous RFA is another popular bridging therapy for HCC patients on waiting list; its efficacy depends on the size of tumor **(8).** However, poor liver function and presence of ascites limit its use in cirrhotic patients **(9).**

Emerging methods of bridging therapy includes transarterial radioembolization using Yttrium-90 and external radiotherapy ,Both of them were shown to have high tumor necrosis and safety profile making them ideal alternatives for HCC which respond poorly or contraindicated to conventional bridging treatments **(10).**

Currently no one type of LRT over another for bridging therapy. The choice of locoregional modality should be based on tumor size, location, and center expertise **(11).**

Downstaging therapy for liver transplant

Tumor downstaging, defined as a reduction in tumor burden using LRT to meet acceptable criteria for LT , Down-staging is an attractive alternative to simply expanding the tumor size limits since response to down-staging treatment may also serve as a prognostic marker and a tool to select a subgroup of patients with more favorable tumor biology who will likely do well after LT **(12).**

All patients beyond transplant criteria, without extra-hepatic disease or macrovascular invasion, should be considered for downstaging as long as potentially eligible for transplantation, as the original HCC state has not demonstrated to significantly hamper post-transplant survival **(11).**

There are several advantages to downstaging HCC prior to or as a bridge to transplantation. First, the ability to successfully downstage a patient may impart insight into an individual's tumor biology and improve the selection process, therefore, potentially translating into superior posttransplant survival **(13).** On the other hand, patients with HCC who do not respond to downstaging efforts may in fact be declaring the aggressive biologic behavior of the HCC they harbor, perhaps indicating that recurrence post transplantation is likely **(14).**

First reported in 2005, the University of California, San Francisco (UCSF) proposed downstaging inclusion criteria, which is defined as one lesion >5 cm and ≤8 cm, two or three lesions each ≤5 cm, or four to five lesions each ≤3 cm with a total tumor diameter ≤8 cm, demonstrating a 5-year post-LT survival after successful downstaging of 78%, which was similar to a control group of patients with HCC always within Milan criteria before transplantation (81%)**(15).**

Multicenter study in UNOS Region-5 demonstrated an excellent 5-year post transplantation survival of 80% using the UCSF downstaging protocol **(14).**

The UNOS/OPTN adopted the UCSF downstaging protocol in 2017 (UNOS-DS), and patients meeting UNOS-DS that are successfully downstaged are eligible for automatic approval for MELD exception **(16).**

The ‘ablate and wait’ period after down-staging therapy is an essential component of the whole policy; by providing this ‘test of time’ which usually last for 6 months for evaluating tumor response to LRT and changes in AFP prior to LT **(17).**

No single locoregional or systemic therapy has been unequivocally associated with higher pre-transplant downstaging efficacy. The downstaging strategy should be tailored to each patient and a multimodal, sequential approach is recommended when downstaging is not achieved with a single treatment option **(18).**

Failure of tumor downstaging after multimodal treatment is associated with poor post-transplant outcomes, and therefore listing of such patients is not recommended**(19).**

Systemic therapy for HCC downstaging includes tyrosine kinase inhibitors (TKIs) and immunotherapies, Due to their mechanism of action in molecular pathways involving tissue regeneration and repair, TKIs inhibit wound healing**(20).**

Because this may confer a higher risk of complications for patients undergoing liver transplant, The extent of the efficacy and safety of TKIs pretransplant is largely unknown given the lack of large trials, and their true utility as a downstaging therapy has yet to be fully answered **(21).**

in the last decade, immune checkpoint inhibitors (ICIs) are expected to increase for a broader group of patients with HCC**(22).**

To date, there are several case reports as well as two case series describing the use of immunotherapy for downstaging in patients who subsequently received LT**(23).**Duration of treatment, which included multiple different agents ranged from 6weeks to 2 years, with washout periods ranging from1 day to 253 days with early graft failure due to suspected refractory rejection, with histology demonstrating massive hepatic necrosis and dense lymphocytic infiltrate, with the remainder having a satisfactory recovery post-LT, including two patients reported to have mild rejection **(24).**

Recently published reviews identified 42 days203 and 90 days204 before the transplant as the safest washout period for rejection-free survival, The 3-months washout was also suggested in a multicenter US study. Thus, the limited available data to date consists of case reports and case series, and prospective data are needed to further illustrate the risks and benefits of immunotherapy for HCC downstaging, as well as the optimal washout period to prevent refractory immunologic graft loss **(25).**

Many of the current downstaging trials have focused on combination therapies and the effect of LRTs (typically TACE or TARE) in various combination with systemic chemotherapies. No published study has provided evidence of superiority of any combination therapy over another; however, the highest rates of downstaging success have been seen with multimodal therapy**(26).**

Table (1) : Overview of Locoregional Therapies

Therapy	Mechanism	Primary Application	Complications	Advantages	Limitations
cTACE	Embolic ischemia augmented by emulsified chemotherapy	• Larger (>3 cm) tumors • Tumors <3 cm not amenable to resection/ablation	PES Liver failure GI ulcers Liver abscess Renal dysfunction	Studied extensively can be repeated	More systemic toxicity than DEB-TACE. Technical variability and non-standardized protocols Cannot be used with PVT
DEB-TACE	Embolic ischemia augmented by chemotherapeutic drug eluting beads	• Larger (>3 cm) tumors • Tumors <3 cm not amenable to resection/ablation	Similar to cTACE	More controlled and sustained drug delivery than cTACE	More costly than cTACE. Cannot be used with PVT
TARE	Radiation induced cell death from Y-90 microspheres, minimal embolic effect	• Larger (>3 cm) tumors • Tumors <3 cm not amenable to resection/ablation	RILD Radiation induced pneumonitis Biliary stricturing Enteritis	Safe in PVT Slower TTP than TACE Outpatient procedure	Requires pre treatment mapping angiography More costly than TACE Requires higher level of Expertise
Thermal Ablation (RFA)	High frequency alternating currents induce thermal injury and necrosis	• Smaller (<3 cm) tumors, • ≤3 nodules Improved outcomes	Thermal injury to adjacent organs. Liver capsule rupture.	Similar outcomes as surgical resection for tumors <3 cm (curative)	Heat sink effect. Limited efficacy in tumors >3 cm

		combined with TACE for tumors 3-5 cm	Risk of peritoneal seeding treating peripheral tumors	Excellent safety profile	
SBRT	Multiple nonparallel radiation beams delivered in highdose radiation fractions	• Larger (>3 cm) tumors • Tumors <3 cm not amenable to resection/ablation	Few: nausea, vomiting, GI ulcers (rare)	Alternative BT for patients with decompensated liver disease that are not LT candidates or failed other LRTs. Can treat lesions near adjacent organs, unlike ablation No heat sink effect Spares liver from RILD unlike TARE	Few comparative studies with other LRT

References:

1. **D. Kollmann, N. Selzner and M. Selzner(2017):**Bridging to liver transplantation in HCC patients.Langenbeck's archives of surgery,402(863-871.
2. **Q. Lai, A. Vitale, S. Iesari, A. Finkenstedt, G. Mennini, S. Onali, M. Hoppe-Lotichius, T. M. Manzia, D. Nicolini and A. W. Avolio(2019):**The Intention-to-Treat Effect of Bridging Treatments in the Setting of Milan Criteria–In Patients Waiting for Liver Transplantation.Liver Transplantation,25(7),1023-1033.
3. **P. R. Galle, A. Forner, J. M. Llovet, V. Mazzaferro, F. Piscaglia, J.-L. Raoul, P. Schirmacher and V. Vilgrain(2018):**EASL clinical practice guidelines: management of hepatocellular carcinoma.Journal of hepatology,69(1),182-236.
4. **A. Hill, F. Olumba and W. Chapman(2024):**Transplantation for Hepatocellular Carcinoma.Surgical Clinics,104(1),103-111.
5. **A. Arvind, K. S. El Dahan, R. Malhotra, D. Daher, N. E. Rich, M. S. Patel, L. B. VanWagner, S. R. Lieber, T. G. Cotter and J. Louissaint(2024):**Association between bridging therapy and posttransplant outcomes in patients with HCC within Milan criteria: A systematic review and meta-analysis.Liver Transplantation,30(6),595-606.
6. **E. Tsochatzis, M. Garcovich, L. Marelli, V. Papastergiou, E. Fatourou, M. L. Rodriguez-Peralvarez, G. Germani, N. Davies, D. Yu and T. V. Luong(2013):**Transarterial embolization as neo-adjuvant therapy pretransplantation in patients with hepatocellular carcinoma.Liver International,33(6),944-949.
7. **D. Dorcaratto, V. Udupa, N. M. Hogan, D. P. Brophy, J. W. McCann, D. Maguire, J. Geoghegan, C. P. Cantwell and E. Hoti(2017):**Does neoadjuvant doxorubicin drug-eluting bead transarterial chemoembolization improve survival in patients undergoing liver transplant for hepatocellular carcinoma?Diagnostic and Interventional Radiology,23(6),441.
8. **M. W. Lee, S. S. Raman, N. H. Asvadi, S. Siripongsakun, R. M. Hicks, J. Chen, A. Worakitsitisatorn, J. McWilliams, M. J. Tong and R. S. Finn(2017):**Radiofrequency ablation of hepatocellular carcinoma as bridge therapy to liver transplantation: A 10-year intention-to-treat analysis.Hepatology,65(6),1979-1990.
9. **W. Y. Lau and E. C. Lai(2009):**The current role of radiofrequency ablation in the management of hepatocellular carcinoma: a systematic review.Annals of surgery,249(1),20-25.

10. **G. M. Ettorre and A. Laurenzi(2020):**Other "bridge" therapies for liver transplantation: RFA, TACE, and TARE.Liver Transplantation and Hepatobiliary Surgery: Interplay of Technical and Theoretical Aspects,183-191.
11. **M. P. A. W. Claasen, D. Sneiders, Y. S. Rakké, R. Adam, S. Bhoori, U. Cillo, C. Fondevila, M. Reig, G. Sapisochin and P. Tabrizian(2023):**European Society of Organ Transplantation (ESOT) Consensus Report on Downstaging, Bridging and Immunotherapy in Liver Transplantation for Hepatocellular Carcinoma.Transplant International,36(11648.
12. **T. M. Manzia, Q. Lai, S. Iesari, M. T. P. Perera, M. Komuta, A. Carvalheiro, T. Shah, R. Angelico, C. Quaranta and D. Nicolini(2018):**Impact of remnant vital tissue after locoregional treatment and liver transplant in hepatocellular cancer patients, a multicentre cohort study.Transplant International,31(9),988-998.
13. **L.-y. Wang and S.-s. Zheng(2018):**Advances in predicting the prognosis of hepatocellular carcinoma recipients after liver transplantation.Journal of Zhejiang University. Science. B,19(7),497.
14. **N. Mehta, J. Guy, C. T. Frenette, J. L. Dodge, R. W. Osorio, W. B. Minteer, J. P. Roberts and F. Y. Yao(2018):**Excellent outcomes of liver transplantation following down-staging of hepatocellular carcinoma to within Milan criteria: a multicenter study.Clinical Gastroenterology and Hepatology,16(6),955-964.
15. **F. Y. Yao, N. Mehta, J. Flemming, J. Dodge, B. Hameed, O. Fix, R. Hirose, N. Fidelman, R. K. Kerlan Jr and J. P. Roberts(2015):**Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria.Hepatology,61(6),1968-1977.
16. **A. S. Kierans, V. Chernyak, M. Mendiratta-Lala, C. B. Sirlin, E. M. Hecht and K. J. Fowler(2022):**The Organ Procurement and Transplantation Network hepatocellular carcinoma classification: Alignment with Liver Imaging Reporting and Data System, current gaps, and future direction.Liver Transplantation,
17. **K. W. Ma and T. T. Cheung(2017):**When to consider liver transplantation in hepatocellular carcinoma patients?Hepatic Oncology,4(1),15-24.
18. **N. H. Tran, S. Muñoz, S. Thompson, C. L. Hallemeier and J. Bruix(2022):**Hepatocellular carcinoma downstaging for liver transplantation in the era of systemic combined therapy with anti-VEGF/TKI and immunotherapy.Hepatology,76(4),1203-1218.
19. **P. Tabrizian, M. L. Holzner, N. Mehta, K. Halazun, V. G. Agopian, F. Yao, R. W. Busuttil, J. Roberts, J. C. Emond and B. Samstein(2022):**Ten-year outcomes of liver transplant and downstaging for hepatocellular carcinoma.JAMA surgery,157(9),779-788.
20. **K. Bryce and E. A. Tsochatzis(2017):**Downstaging for hepatocellular cancer: harm or benefit?Translational Gastroenterology and Hepatology,2(106.
21. **M. Biolato, T. Galasso, G. Marrone, L. Miele and A. Grieco(2021):**Upper limits of downstaging for hepatocellular carcinoma in liver transplantation.Cancers,13(24),6337.
22. **P. Tabrizian, S. S. Florman and M. E. Schwartz(2021):**PD-1 inhibitor as bridge therapy to liver transplantation?American Journal of Transplantation,21(5),1979-1980.
23. **Q. Gao, I. J. Anwar, N. Abraham and A. S. Barbas(2021):**Liver transplantation for hepatocellular carcinoma after downstaging or bridging therapy with immune checkpoint inhibitors.Cancers,13(24),6307.
24. **G. T. Schnickel, K. Fabbri, M. Hosseini, M. Misel, J. Berumen, J. Parekh, K. Mekeel, Y. Dehghan, Y. Kono and V. Ajmera(2022):**Liver transplantation for hepatocellular carcinoma following checkpoint inhibitor therapy with nivolumab.American Journal of Transplantation,22(6),1699-1704.
25. **V. Mazzaferro, Chun, Y. S., Poon, R. T., Schwartz, M. E., Yao, F. Y., Marsh, J. W., ... & Lee, S. G. (2008).** Liver transplantation for hepatocellular carcinoma. Annals of surgical oncology, 15, 1001-1007.
26. **L. Matevish, M. S. Patel and P. A. Vagefi(2024):**Downstaging techniques for hepatocellular carcinoma in candidates awaiting liver transplantation.Surgical Clinics,104(1),145-162.