Where Does IO Stand in the NCCN Guidelines: HCC

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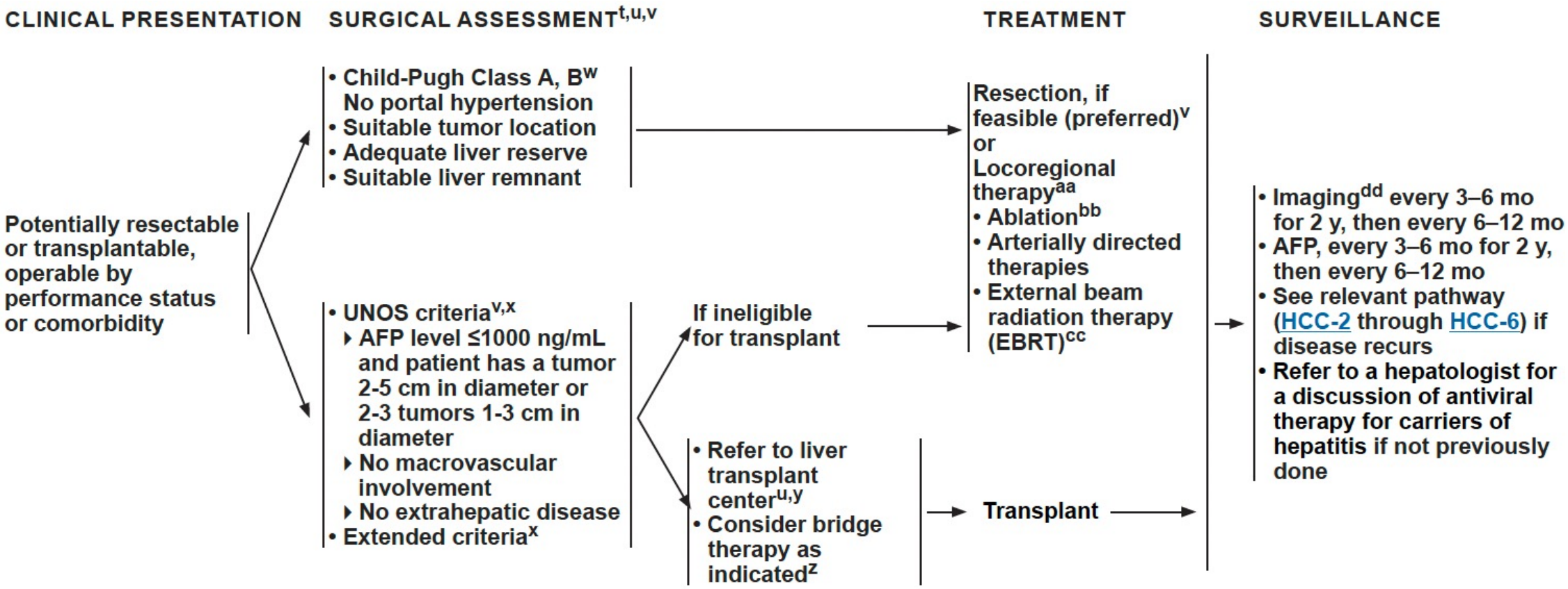
Objectives

- Review 2021 NCCN Guideline for HCC
- IO therapies
  - Potentially resectable or transplantable (Bridging/Downstaging)
  - Unresectable
- EBRT/SBRT

National Comprehensive Cancer Network®

- 31 leading American cancer centers
- Yearly updated guidelines
- 60 cancers
- **Free membership**
- Many tumor boards refer to them when deciding on treatment for patients

Potentially Resectable/Transplantable HCC



Potentially Resectable HCC

- CP A or B
- No portal hypertension
- Tumor amenable to surgical resection → Surgical resection (**preferred**)

PRINCIPLES OF LOCOREGIONAL THERAPY

I. General Principles

- All patients with HCC should be evaluated for potential curative therapies (resection, transplantation, and for small lesions, ablative strategies). Locoregional therapy should be considered in patients who are not candidates for surgical curative treatments, or as a part of a strategy to bridge patients for other curative therapies. These are broadly categorized into ablation, arterially directed therapies, and radiotherapy.

II. Treatment Information

A. Ablation (radiofrequency, cryoablation, percutaneous alcohol injection, microwave):

- All tumors should be amenable to ablation such that the tumor and, in the case of thermal ablation, a margin of normal tissue is treated. A margin is not expected following percutaneous ethanol injection.
- Tumors should be in a location accessible for percutaneous/laparoscopic/open approaches for ablation.
- Caution should be exercised when ablating lesions near major vessels, major bile ducts, diaphragm, and other intra-abdominal organs.
- Ablation alone may be curative in treating tumors ≤3 cm. In well-selected patients with small properly located tumors, ablation should be considered as definitive treatment in the context of a multidisciplinary review. Lesions 3 to 5 cm may be treated to prolong survival using arterially directed therapies, or with combination of an arterially directed therapy and ablation as long as tumor location is accessible for ablation.[1-3]
- Unresectable/inoperable lesions >5 cm should be considered for treatment using arterially directed therapy, systemic therapy, or EBRT.[4-6]
- Sorafenib should not be used as adjuvant therapy post-ablation.[7]

B. Arterially Directed Therapies:

- All tumors irrespective of location may be amenable to arterially directed therapies provided that the arterial blood supply to the tumor may be isolated without excessive non-target treatment.
- Arterially directed therapies include bland transarterial embolization (TAE),[4,5,8,9] chemoembolization (transarterial chemoembolization [TACE][10] and TACE with drug-eluting beads [DEB-TACE][4,11]), and radioembolization (RE) with yttrium-90 (Y-90) microspheres.[12,13]
- All arterially directed therapies are relatively contraindicated in patients with bilirubin >3 mg/dL unless segmental treatment can be performed.[14] RE with Y-90 microspheres has an increased risk of radiation-induced liver disease in patients with bilirubin >2 mg/dL.[13]
  - With RE, delivery of ≥205 Gy to the tumor may be associated with increased overall survival.[18]
- Arterially directed therapies in highly selected patients have been shown to be safe in the presence of limited tumor invasion of the portal vein.
  - Randomized controlled trials have shown that Y-90 is not superior to sorafenib for treating advanced HCC. RE may be appropriate in some patients with advanced HCC,[19,20] specifically patients with segmental or lobar portal vein, rather than main portal vein thrombosis.[22]
- Sorafenib may be appropriate following arterially directed therapies in patients with adequate liver function once bilirubin returns to baseline if there is evidence of residual/recurrent tumor not amenable to additional local therapies. The safety and efficacy of the use of sorafenib concomitantly with arterially directed therapies has not been associated with significant benefit in three randomized trials; other randomized phase III trials are ongoing to investigate other systemic therapies including immunotherapy in combination with arterial therapies.[15-17,22]

Potentially Resectable HCC

Ablation

- RFA, MWA, Cryo, percutaneous EtOH
- **"In-well selected patients with small, properly located tumors, ablation should be considered as definitive treatment in the context of multidisciplinary review."**
- ≤3 cm, location amenable to ablation
- 3-5 cm (**combination** of ablation and arterially directed therapy)
- >5cm (**ablation NOT recommended**)
- Sorafenib should NOT be used as adjuvant post-ablation

OLT

- **Meets UNOS criteria**
  - AFP < 1000 ng/ml
  - Single tumor: 2-5 cm
  - 2-3 tumors: 1-3 cm
  - No macrovascular involvement
  - No extrahepatic Dz
- **Refer to transplant center**
- **Consider bridging or downstaging**

Bridging

- **Meta-analysis[1]: bridge therapy did NOT increase post transplant mortality, survival or recurrence vs. transplant alone**
- Some single institution studies have shown improved outcome
- **No RCT**
- Use of bridge Rx increasing
  - Especially in areas with long wait times for OLT

1. Kulik et al. *Hepatology.* 2018.

Downstaging

- **For tumor burden beyond accepted transplant criteria w/ the goal of future transplant**
- Meta-analysis[1]: **Downstaging improved 1 and 5 year OS post OLT vs. OLT alone**
- Systematic review[2]: 48% success rate to transplant eligibility in 950 pts
- Phase IIb/III[3]: downstaging with locoregional rx, surgery or systemic therapy prior to transplant vs. observation
  - 5-year OS: 78% vs. 31%

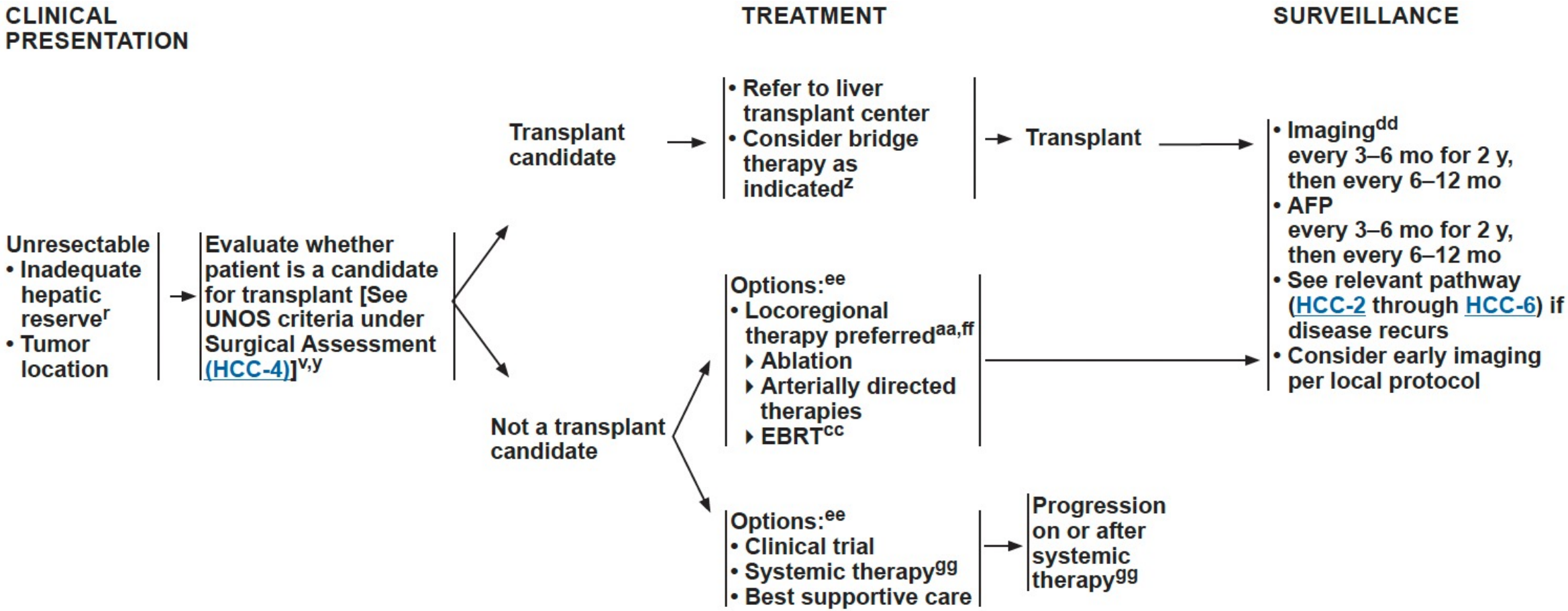
1. Kulik et al. *Hepatology.* 2018.
2. Parikh et al. Liver Transpl. 2015
3. Mazzaferro et al. Lancet Oncol. 2020

Bridging/downstaging therapies for HCC

- **Bridging**
  - **Recommendation: Neutral**
    - **Further information needed**

- **Downstaging**
  - **If successful: Transplant should be offered**
  - **Recommendation: Neutral**
    - **Further information needed**

Unresctable HCC



Arterially Directed Therapies for HCC

- Bland embo (TAE) , C-TACE, DEB-TACE, Y90
- **Y90: ≥205 Gy to tumor**
- Y90: may be appropriate for pts w/ segmental and lobar PVT
  - **Not main PVT**
- Sorafenib may be appropriate following arterially directed therapies
  - Adequate liver function
  - Residual or recurrent dz not amenable to further LRT

Recommendations Re Arterially Directed Therapy

- All tumors, irrespective of location in the liver
- Bilirubin <3 mg/dL (unless segmental)
  - <2 mg/dL (Y90)
- CP A or B
  - **No CP C except in bridging to OLT**
- Acceptable performance status (ECOG <=2)
- No significant extrahepatic disease

What about EBRT or SBRT?

- **“Should be considered as an alternative to ablation and/or embolization techniques when these therapies have failed or are contraindicated”**
- Palliative setting for symptom control and prevention of complications from metastatic disease (bone and brain)
- Encourages prospective trials to determine role of SBRT in pts with unresectable locally advanced disease

Take Home Points

- NCCN Guideline: Thorough up-to-date literature review
- Heavily rely on Interventional Oncology therapies
- Neutral recommendation re bridging/downstaging with IO therapies

Take Home Points

- Ablation can be considered curative in lieu of surgery in select patient
  - Need more data to prove Rad Seg as alternate viable option

- Arterially directed therapies for all unresectable HCC if appropriate liver function and performance status

- EBRT or SBRT **only if** arterially directed therapies not possible or failed

Thank You

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