

Medical Therapies for HCC: An Oncologist's Algorithm

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Disclosures

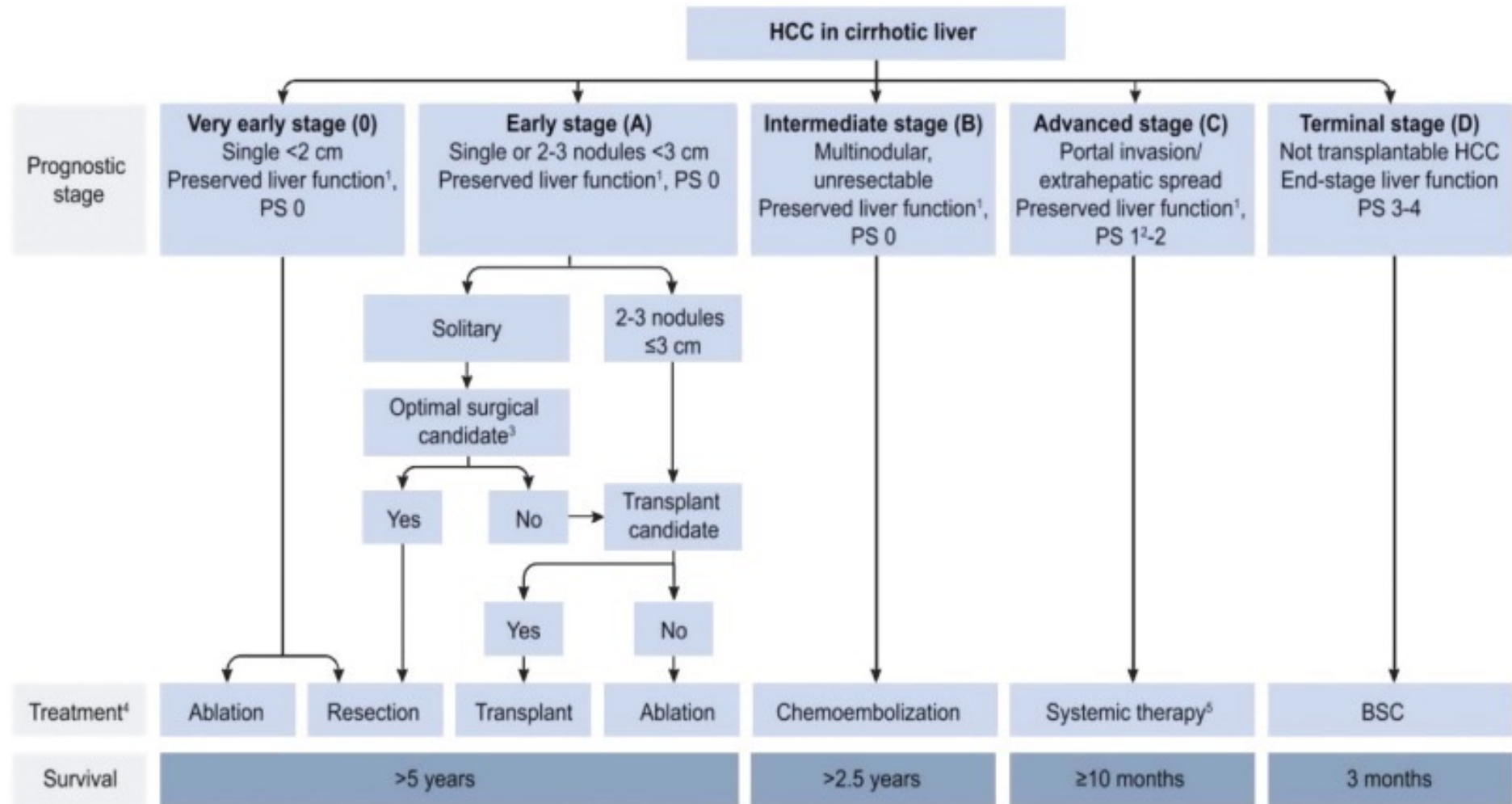
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Hepatocellular Carcinoma

- Sorafenib (Nexavar) was the only FDA-approved therapy for more than a decade.
- Immunotherapy, tyrosine kinase inhibitors (TKIs), and monoclonal antibodies targeting VEGF have now all received FDA approval.
- Treatment of HCC is guided by Child-Pugh score and Barcelona Clinic Liver Cancer (BCLC) staging system.
- Benefit of systemic therapy is primarily limited to patients with Child-Pugh score A5 or A6.

Barcelona Clinic Liver Cancer



NCCN Guidelines



National
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NCCN Guidelines Version 5.2021 Hepatocellular Carcinoma

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First-Line Systemic Therapy

Preferred Regimens

- Atezolizumab + bevacizumab (Child-Pugh Class A only) (category 1)^{a,b,c,1}

Other Recommended Regimens

- Sorafenib (Child-Pugh Class A) [category 1] or B7)^{d,e,2,3}
- Lenvatinib (Child-Pugh Class A only)^{4,5} (category 1)

Useful in Certain Circumstances

- Nivolumab^{b,6} (if ineligible for tyrosine kinase inhibitors [TKIs] or other anti-angiogenic agents) (Child-Pugh Class A or B) (category 2B)
- FOLFOX (category 2B)^f

Subsequent-Line Therapy^g if Disease Progression^h

Options

- Regorafenib (Child-Pugh Class A only) (category 1)^{i,7}
- Cabozantinib (Child-Pugh Class A only) (category 1)^{i,8}
- Ramucirumab (AFP ≥400 ng/mL only) (category 1)^{i,9}
- Lenvatinib (Child-Pugh Class A only)
- Sorafenib (Child-Pugh Class A or B7)^{d,e}

Other Recommended Regimens

- Nivolumab + ipilimumab (Child-Pugh Class A only)^{b,i,13}
- Pembrolizumab (Child-Pugh Class A only)^{b,j,k,14} (category 2B)

Useful in Certain Circumstances

- Nivolumab (Child-Pugh Class B only)^{b,j,10-12} (category 2B)
- Dostarlimab-gxly^{b,j,l,15,16} for MSI-H/dMMR tumors (category 2B)

First Line Therapies

Drug	Comparator	Line of Therapy	Phase	Trial	Primary Endpoint	Secondary Endpoint	Approval Year
Sorafenib	Placebo	First	3	SHARP	mOS of 10.7m vs 7.9m	TTP 5.5m vs 2.8m	2007
Lenvatinib	Sorafenib	First	3	REFLECT	mOS 13.6m vs 12.3m	mPFS 7.4m vs 3.7m ORR 24.1% vs 9.2%	2018
Atezolizumab/Bevacizumab	Sorafenib	First	3	IMbrave-150	mOS 19.2 vs 13.4m	mPFS 6.9m vs 4.3m	2020
Nivolumab	Sorafenib	First	3	CheckMate-459	mOS (no benefit)		N/A

Subsequent Therapies

Drug	Comparator	Line of Therapy	Phase	Trial	Primary Endpoint	Secondary Endpoint	Approval Year
Regorafenib	Placebo	Second	3	RESORCE	mOS 10.6m vs 7.8m	mPFS 3.1m vs 1.5m	2017
Cabozantinib	Placebo	Second/Third	3	CELESTIAL	mOS 10.2m vs 8m	5.2m vs 1.9m	2019
Ramucirumab	Placebo	Second	3	REACH-2	mOS 8.5m vs 7.3m	mPFS 2.8m vs 1.6m	2019
Pembrolizumab	Placebo	Second	II	KEYNOTE-224	ORR 16%	DOR >6m in 94%	2018
Nivolumab*	Sorafenib	Second	1/2	CheckMate-040	ORR 14%	mDOR 16.6m	2017
Ipilimumab/Nivolumab	Placebo	Second	3	CheckMate-040	ORR 33%	DOR 4.6 to 30.5m	2020

Ongoing Trials

Drug	Comparator	Line of Therapy	Phase	Trial	Primary Endpoint	Secondary Endpoint	Read Out
Lenvatinib/Pembrolizumab	Lenvatinib	First	III	LEAP-002	mOS/mPFS	ORR 45% DOR/DCR/TTP	2021
Durvalumab/Tremelimumab	Sorafenib	First	III	HIMALAYA	mOS 18.73m	ORR 24% DOR - NR	2021
Ipilimumab/Nivolumab	Sorafenib/Lenvatinib	First	III	CheckMate 9DW	mOS		?
Cabozantinib/Atezolizumab	Sorafenib	First	III	COSMIC-312	mOS - mPFS +	mPFS for Cabo	2022
TACE/Nivolumab	N/A	Stage B	II	IMMUTACE	ORR 55%	mPFS, TTP, OS, DOR	?
Pembrolizumab	Placebo	Second	III	KEYNOTE-394	mOS	mPFS	2021

Challenges In Clinical Practice

- Local vs Systemic approaches for unresectable/nonmetastatic (Up-to-7 criteria) – Lenvatinib
- Combining locoregional therapies/systemic treatment
- Atezolizumab/Bevacizumab as first-line therapy
 - Active varices/high risk of bleeding
 - Child-Pugh B
 - Autoimmune disease/Transplantation
- 2nd line - lenvatinib, sorafenib, cabozantinib
- 3rd line - regorafenib, cabozantinib, or ramucirumab

Sequencing of Therapy

- CELESTIAL trial included patients who had gotten IO therapy
- Regorafenib if Sorafenib was efficacious and well-tolerated
- Ipilimumab plus nivolumab has shown activity but remains untested in patients treated with prior checkpoint inhibitors.
- Ramucirumab efficacy remains unclear in patients who failed bevacizumab in the first line.

Future Direction

- Benefit with systemic therapy is limited to patients with good performance status with Child-Pugh score 7 or lower, excluding a vast proportion of patients.
- We should compare newer systemic options with locoregional therapy for patients with high-risk disease.
- Neoadjuvant/Adjuvant setting.
- Urgent need to develop biomarkers that can help in selecting patients for different treatment options.

Thank You