HEPATOCELLULAR CARCINOMA (HCC)

UPDATED MANAGEMENT

WHAT IS NEW?

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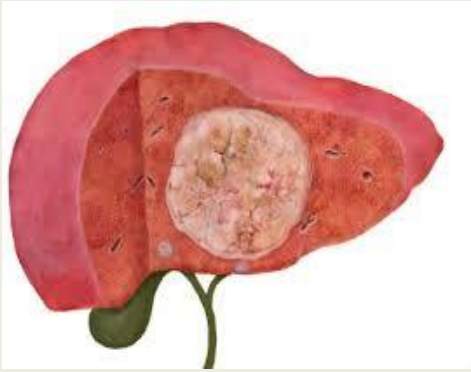
HCC



- According to WHO, HCC is the fifth most common tumor.
- Liver cancer is currently the second most common cause of cancer-related death worldwide.
- HCC accounts for more than 90% of liver cancers.
- There has been a marked increase in HCC related annual death rates during the past two decades.
- The majority of all cases of HCC worldwide found in the Asia–Pacific region.
- HCC represents a major public health problem in the Asia–Pacific region.

CAUSES OF HCC

In United States:

- Hepatitis C- 2-8% annual incidence.
- Hepatitis B- 0.5% annual incidence.
- Cirrhosis due to other causes-
  - Alcohol
  - NASH
  - Others

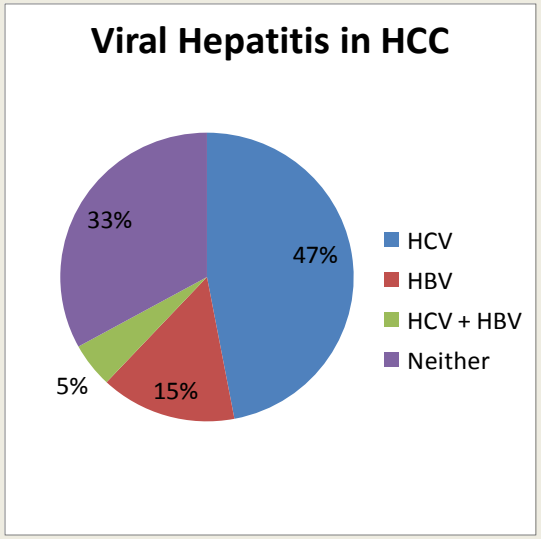
    Wilson's

    α1AT-def

    Haemochromatosis

    Biliary cirrhosis

    Autoimmune hepatitis)

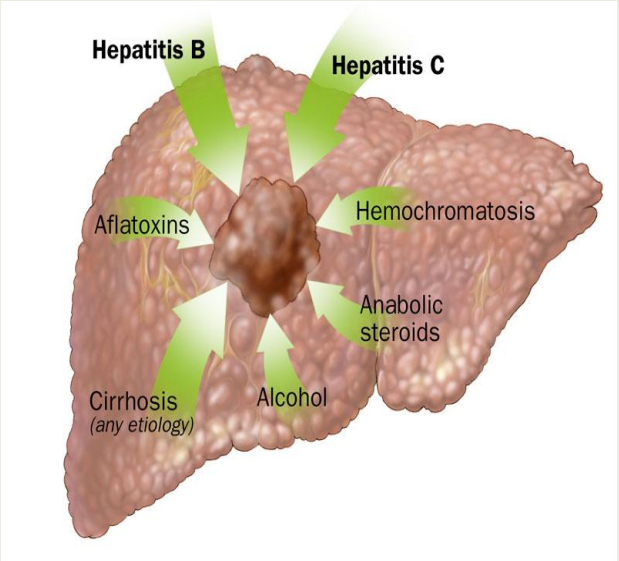


***Gastroenterology* 2004; 127: S27-234**

OTHER RISK FACTORS OF HCC

Other risk factors:

- Aflatoxins
- Thorotrast (X-ray contrast material)
- Vinyl Chloride
- Steroid Hormones
- Schistosomiasis,
- Liver flukes
- Iron
- Tobacco
- Diet



RISK FACTOR

Chronic hepatitis C:

1.5% of US population and cirrhosis in 20-30% of them.

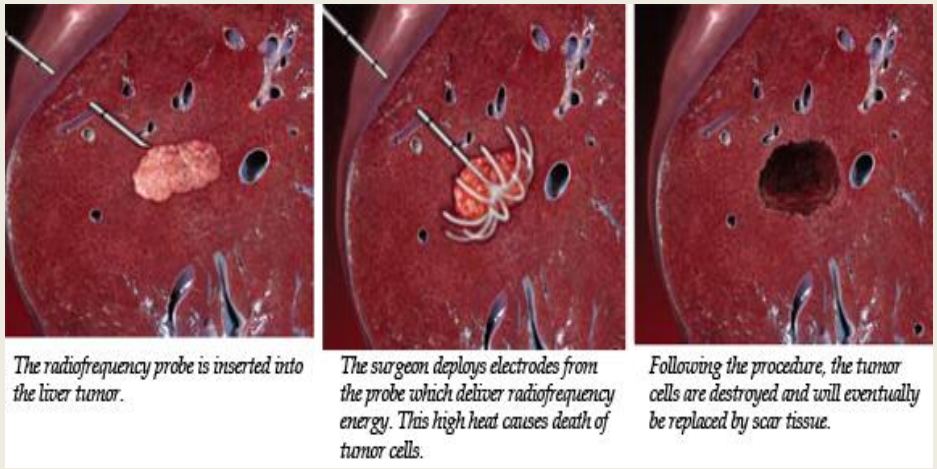
Risk of HCC:

- 20-30 x higher in those with HBV than normal
- 130 x higher in those with hepatitis B + C

Management of HCC

<u>Major treatment modalities of HCC</u>:

- ❑ **Surgical resection**
- ❑ **Liver transplantation**
- ❑ **Local ablation therapy**
  - ➢ Ethanol injection
  - ➢ Microwave ablation
  - ➢ Radiofrequency ablation



The radiofrequency probe is inserted into the liver tumor.

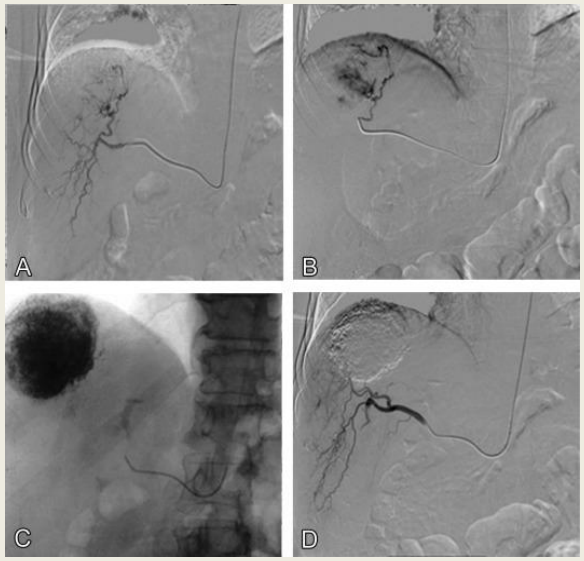
The surgeon deploys electrodes from the probe which deliver radiofrequency energy. This high heat causes death of tumor cells.

Following the procedure, the tumor cells are destroyed and will eventually be replaced by scar tissue.

Management of HCC

Major treatment modalities of HCC:

- **Transarterial therapies**



- Transarterial chemoembolization (TACE)
- Transarterial embolization
- Transarterial bland embolization
- Transarterial chemotherapy
- Transarterial radioembolization

- **Systemic treatment**

- Sorafenib
- Regorafenib
- Newer compounds (molecular targeted agents, immunotherpy)

Treatment for Early-Stage Resectable HCC

- Partial hepatectomy may be curative.
- Patient's overall liver function, tumor assessment, and liver anatomy must be taken into consideration.
- Resection is recommended:
  a. Patients who have preserved liver function
  b. Generally Child-Pugh class A (good operative risk)
  c. Without portal hypertension.
- Liver transplantation also offers patients a potential curative treatment option in early HCC.

Surgical Resection

- **Liver resection (LR**) is a first-line curative treatment for HCC among Child–Pugh A patients.

- Recent advances in surgical technique and postoperative management have made LR safe even for those with cirrhosis.

- **In the current most popular guidelines-**

  Surgery is restricted to patients in the very early or early stages of disease (BCLC score 0–A).

- **At present, the AASLD and EASL guidelines (following the BCLC recommendations**):

  a. Set narrower indication for LR.

  b. LR is only recommended for single nodule and Child–Pugh class A without evidence of portal hypertension.

Treatment for Unresectable HCC

- Liver transplantation should be offered to those

  - Single tumor ≤5 cm in diameter
  - 2-3 tumors each ≤3 cm in diameter
  - No macrovascular involvement
  - No extrahepatic disease

- Locoregional therapies

  - Ablation
  - Transarterial chemoembolization
  - Stereotactic body radiotherapy and external-body radiotherapy

Liver Transplantation (LT)

- LT is the only treatment that offers the real chance of a cure for both HCC and the underlying liver cirrhosis.
- LT provides the best curative treatment for all HCC patients from an oncologic point of view.
- 1st-line treatment for HCC among Child–Pugh class B and C patients, if the liver graft is available.
- In contrast to LR, there is no restriction for indication of LT (at least in terms of liver function).
- The indication of LT for HCC in terms of liver functional reserve is based on the MELD score with additional points in Western countries.
- LT can be offered for those with Child–Pugh class A as shown in the BCLC algorithm, if they satisfy the Milan criteria.

Local Ablation

- **Percutaneous ablation therapies** should be performed on patients with HCC-
  a. Generally for Child–Pugh class A or B patients with
  b. 3 or fewer tumors,
  c. 3 cm or less in diameter

- **RFA** is a first-line treatment in HCC 2 cm or smaller in Child–Pugh class A or B cirrhosis.

- Ablation is less invasive and less expensive.

- Patients with HCC have been markedly aging, minimally invasive therapies such as ablation would play a more important role.

- Highly cost-effective therapies such as ablation should have priority.

Transarterial Chemoembolization

- **TACE** is recommended as a 1st-line treatment of HCC:
  a. Patients with unresectable, large/multifocal HCCs
  b. Who do not have vascular invasion or extrahepatic spread.

- Selective or superselective TACE should be attempted in order to preserve non-tumorous liver parenchyma.

- TACE using **drug-eluting beads** has similar therapeutic efficacy with less systemic adverse events compared with conventional TACE.

Systemic Treatment for Unresectable & Advanced Metastatic HCC

- Patients with Child-Pugh score of A or B (moderate operative risk).

- Recommended systemic treatment such as the following:

  - Sorafenib
  - Regorafenib
  - Nivolumab

SORAFENIB

- **Sorafenib** is recommended as first-line treatment of advanced-stage patients or not suitable for locoregional therapy.

- Sorafenib (Nexavar) is a small molecule-
  a. Inhibits tumor-cell proliferation
  b. Inhibits tumor angiogenesis and
  c. Increases the rate of apoptosis in a wide range of tumor models.

- **'Sorafenib in Advanced Hepatocellular Carcinoma'-** Joseph et al, 2008 showed that-
  Sorafenib prolonged median survival and the time to progression by nearly 3 months in patients with advanced hepatocellular carcinoma.

Regorafenib

- **Regorafenib,** a novel multikinase inhibitor, was approved by the FDA for use in HCC patients previously treated with Sorafenib.

- **Regorafenib** has more potent inhibitory activities against multiple angiogenic pathways (VEGFR, PDGFR, TIE2, and FGFR) and oncogenic pathways (RET, KIT, c-RAF/RAF-1 and BRAF) than sorafenib.

Chemotherapy

According to National Comprehensive Cancer Network (NCCN), the following regimens have shown marginal activity in small clinical trials:

- Gemcitabine **plus** Oxaliplatin

  or

- Capecitabine **plus** Oxaliplatin

  or

- Capecitabine

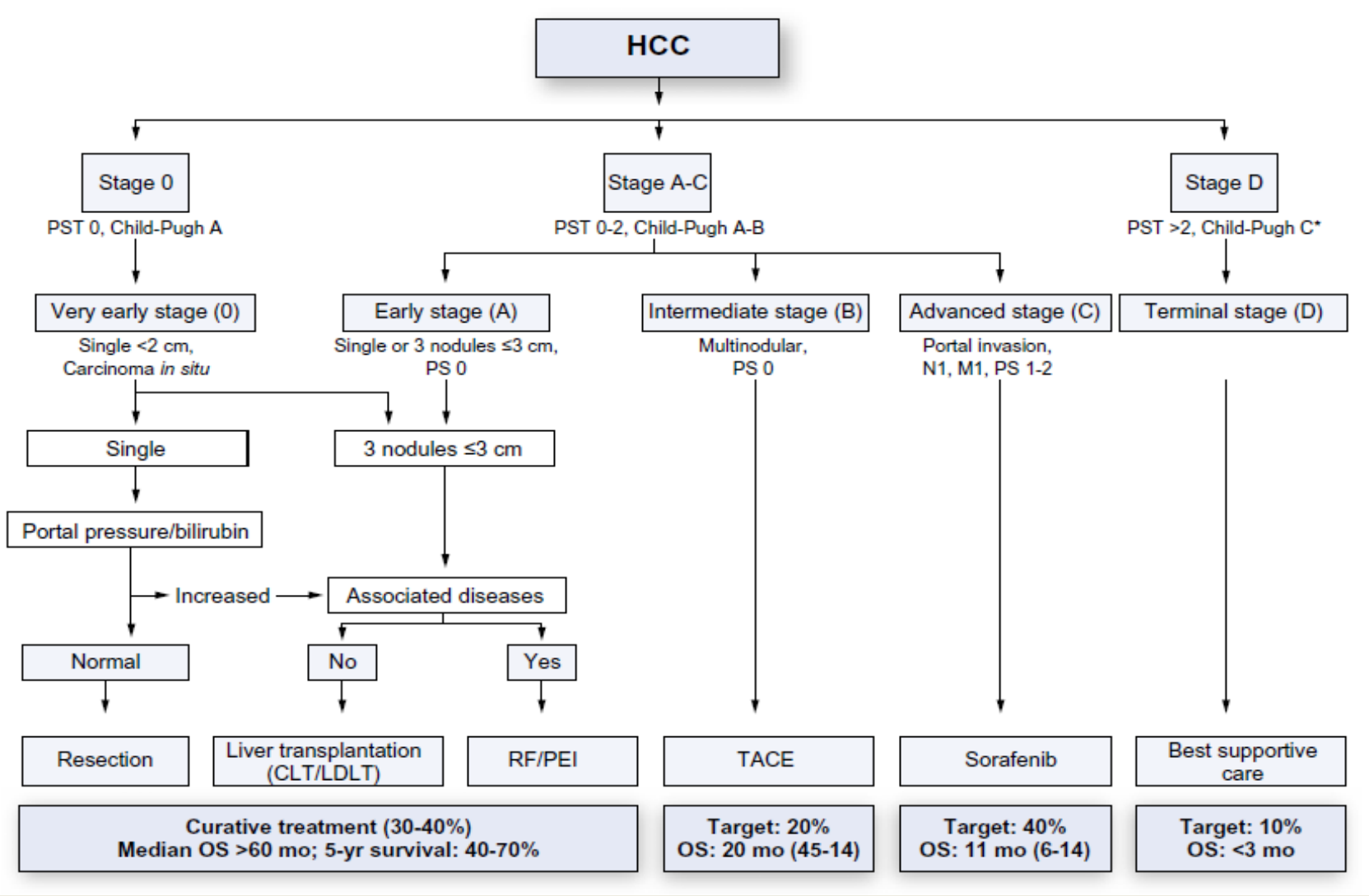
  or

- Doxorubicin

  or

- Gemcitabine **plus** Cisplatin

Management of HCC complicating Cirrhosis



New Compounds on the Horizon

- **Molecular targeted agents:**

  In addition to sorafenib and regorafenib, a variety of molecular targeted agents have been thoroughly
  investigated including
  Sunitinib
  Brivanib
  Linifanib
  Ramucirumab (angiogenesis inhibitors)
  Erlotinib (EGFR inhibitor)
  Everolimus (mTOR inhibitor)

- However, none have shown survival benefits in either first-line or second-line setting in phase III RCTs.

- The results of large randomized phase III trials for lenvatinib (first-line) and cabozantinib (secondline) will soon be available.

New Compounds on the Horizon

Immunotherapy:

- Immuno-oncology is an emerging area of drug development.
- Major breakthroughs have been achieved in agents targeting immune checkpoint proteins, such as cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed cell death-1 (PD-1).
- A significant proportion of patients with chronic HBV or HCV infection had reduction of viral load with study treatment.
- Recently, **Nivolumab** was approved by the FDA for patients with HCC who have been previously treated with Sorafenib.

Immunotherapy (Nivolumab)

- A trial of **Nivolumab** was conducted in 154 patients with HCC who had progressed on, or were intolerant of, sorafenib.

- The overall response rate was **14.3% (22 of 154 patients)**, with **3 patients (1.9%)** showing a complete response and **19 patients (12.3%)** a partial response.

- The manufacturer noted in a press release, the duration of the responses ranged from
  a. **3.2 to 38.2+ months**;
  b. **91%** of those patients had responses of 6 months or longer and
  c. **55%** had responses of 12 months or longer.

Ongoing clinical trials of immune checkpoint inhibitors for advanced HCC

Asia–Pacific clinical practice guidelines on the management of HCC: a 2017 update

	Drug	Phase	Design
1ST line	1. **Nivolumab** versus sorafenib	III	Randomized, open label
	2. **Nivolumab** plus **ipilimumab** (anti-CTLA-4) versus **nivolumab** versus sorafenib	II	Randomized, Open label
2ND line	1. **Nivoluma**b	Ib	Open label
	2. **Pembrolizumab** (anti-PD-1)	II	Open label
	3. **Pembrolizumab** versus placebo	III	Randomized, double blind, placebo Controlled
	4. **Nivolumab** plus **galunisertib** (GSK-b inhibitor)	II	Open label
	5. **Durvalumab** (anti-PD-L1) plus **tremelimumab** versus **durvalumab** versus **tremelimumab**	II	Randomized, open label
	6. **Durvalumab** plus **ramucirumab** (anti-VEGFR)	I	Open label
	7. **PDR001** (anti-PD-1) plus **capmatinib** (cMet inhibitor) versus PDR001	Ib/II	Open label

Conclusion

- The prognosis and treatment outcome of HCC is related with tumor staging, liver function and patient's physical status.
- To ensure the most effective treatment for HCC patients, a good patient selection for the right modality is essential.
- **Immuno-oncology** is an emerging area of drug development in the treatment of advanced HCC.
- The promising results of ongoing clinical trials of **immune checkpoint inhibitors** for advanced HCC indicate an important step toward a new paradigm of systemic therapy for advanced HCC.