Overview of liver neoplasms – Ahmad AlHurani

Liver neoplasms are divided into;

1. Primary liver neoplasms (Less common), they are tumors that originate from the liver, and include the following:

Benign liver neoplasms

1) Hemangioma – most common benign tumor of the liver, aka "Cavernous hemangioma"

- Can be single or multiple, variable in size; (Giant when > 6cm)
- Composed of vascular spaces (Often filled with thrombus)
- Mostly asymptomatic, might present as RUQ pain, heaviness, early satiety, as complications
- Diagnosis: US, CT, MRI, Angiography, Isotopic scan. Needle biopsy is contraindicated! Risk of fatal hemorrhage.
- Management: Observation, resection, embolization.

2) Hepatocellular adenoma

- Rare, heavily related to female hormonal therapy (OCPs, hormone replacement therapy, anabolic steroids), so the usual patient of HCA is a young female (20-40), however, it can happen in males.
- Mostly asymptomatic, but often detected during work-up of abdominal pain.
- It's epithelial in origin, usually solitary in the right lobe.
- Its lesions are hyper vascular, thus big lesion can be complicated as hemorrhage or rupture ~ especially during pregnancy.
- Another important characteristic is that HCA is pre-malignant; it can degenerate to ca.
- Diagnosis: US, CT, MRI, needle biopsy and histopathology.
- Management: stop hormonal therapy, resection.

3) Follicular nodular hyperplasia

- It's a result from congenital arteriovenous malformation (AVM).
- Presents as central fibrosis (scar).
- Affects both sexes.
- Diagnosis: US, CT, MRI, Needle biopsy (rarely needed).
- Management: Observation, surgery is only indicated if diagnosis is unclear.

Malignant liver neoplasms

1) Hepatocellular carcinoma (HCC) – most common primary malignant liver tumor, (*incidence up to 20/100k)*

Epidemiology

- Its incidence is geographically variable, being **high** in: **South East Asia, Japan and Tropical Africa**, and low in the west (But increasing their due to the increase in steatohepatitis which is a risk factor, rest of them are discussed below).
- It affects **males more commonly** than females (4-9 times more common).
- Age of diagnosis: ~25-35 years in Africa, ~50 years in Southeast Asia, ~60 years in the west and middle east.
- 5th most common cancer worldwide, 3rd most common cause of cancer death.

Etiologies, risk factors and implicated causes:

- HCC is usually a consequence of chronic liver diseases thus high risk patients are regularly screened for HCC
- Etiologies and risk factors of HCC include:

1. Hepatitis B, C

HBV treatment and vaccination reduced the incidence of HCC, HCC incidence is higher in regions where HBV and HCV are endemic.

2. Cirrhosis regardless of the etiology ~ NASH, Alcoholic etc.

3. Wilson's disease
4. Hemochromatosis
5. Aflatoxin
A toxin (Carcinogen) produced by the fungus aspergillus, in developed countries they screen food for this toxin unlike the developing countries thus it may contaminate locally grown corn, soybeans and peanuts.
6. Others: α-1 antitrypsin deficiency, DM, Hepatocellular Adenoma (A pre-malignant benign tumor), *Blood group B*

Implicated causes
1. Vinyl chloride (paints)
2. Thorotrast (contrast material used previously)
3. Smoking
4. Parasites
5. Organochloride pesticides
6. OCPs & Androgens
7. Plant alkaloids.

Pathology and clinical presentation

- Often **asymptomatic**, that's why it is key to regularly screen high risk patients, **LFT is usually abnormal** but in a non-specific pattern (as we said, HCC patients already have liver disease thus a baseline abnormal LFT = LFT may not help you), **Hepatomegaly** and eventually if the tumor is large enough it can cause **liver failure** with obstructive jaundice and ascites.

- HCC often spreads to: (BUT it's often not metastatic, that's why liver transplantation is an option)
1) Lymphatic spread, thus when resecting HCC, we do "porta hepatis lymphadenectomy".
2) Intrahepatic spread; one big lesion in the liver and around it few smaller nodules called "Satellite nodules" is typical of HCC .
3) Spread to portal vein is characteristic of HCC as it invades and grows inside it.
4) Transperitoneal; not rare, always look for peritoneal seeding and implantation.
5) distant metastases (Blood stream spread); Lung, bone, brain, adrenals etc.
- If symptomatic, patient may complain of RUQ pain, weight loss, palpable mass, anorexia, nausea and lethargy.
- HCC might rarely present as decompensation in either a known cirrhotic patient or an unrecognized cirrhosis.
- HCC might rarely also present as Budd Chiari syndrome (Classic triad; abdominal pain, ascites, hepatomegaly), haemobilia or a paraneoplastic syndrome such as:
1) Hypoglycemia: might be seen with 1) large tumors due to high metabolic rate, or because rarely, 2) tumor produces insulin-like growth factor II and 3) tumor can grow large enough to damage hepatocytes that there aren't enough hepatocyte available to perform gluconeogenesis during fasting.
2) Hypercalcemia: Parathyroid hormone-related protein (PTHrP)
3) Erythrocytosis: HCC can secrete erythropoietin leading to paraneoplastic erythrocytosis.
- Even more rarely, a patient might present with hemoperitoneum due to rupture, leading to hypovolemic shock.

Grading and variants

Graded into: Well/moderately/poorly differentiated, and it's important to note that there is no relation between degree of differentiation and prognosis!

Grossly, either: different slides have different classification systems 🙁

1) Hanging type (Pedunculated)
   Pushing type; well demarcated and contains fibrous capsule
   Infiltrative
   Small type
   Multinodular type

2) Nodular, Massive, Diffuse
3) Okuda 1984 system: Expanding, Spreading, Multifocal, Indeterminate, Fibrolamellar variant
Fibrolamellar variant of HCC is a subcategory of the classical HCC that's different in these points:
1- It happens in **younger patients**.
2- Happens **on top of a healthy non-cirrhotic normal liver**.
3- The **size of the tumor at time of discovery is huge** and you should do your best to resect it as the first option (remember, the underlying liver is healthy!). Also, it's usually **Encapsulated**
4- The tumor marker which is usually elevated in HCC (Alpha fetal protein) is **normal in fibrolamellar variant HCC**.
On the molecular level, we have distinct variants other than fibrolamellar part;
-Mixed hepatocellular-cholangiocellular variant
-Clear cell variant
-Pleomorphic / giant cell variant
-Childhood variant

Diagnosis-Labs

Alpha fetal protein (AFP)
- It's secreted by HCC, can be elevated in chronic liver disease which limits its accuracy, but what you can do is monitor the baseline level and if there's a rise in the AFP level that can be suspicious for the development of HCC on top of CLD.
- AFP is specific ONLY if elevated more than 400 ng/dl.
- AFP is not always raised in classical HCC, 30% of classical HCC have negative AFP.
- AFP is normal in fibrolamellar variant as we previously stated.
- HBsAg and HCV Antibodies help in the diagnosis, discussed below.

Diagnosis-Imaging

- You can use **Triphasic CT scan** (Finding: Early arterial phase enhancement and delayed venous washout), MRI, Ultrasound, PET scan (for distant mets)
- CLD patients are often screened through imaging

Diagnosis-Definitive

The definitive diagnosis is done after performing a biopsy (true-cut needle biopsy and not FNA), but that's invasive thus we need to know when to perform a biopsy!
- If patient's imaging shows a mass/lesion in the liver, cirrhotic, has positive HBV/HCV markers, raised AFP this is HCC, **no need to take a biopsy**.
- If patient's imaging shows a mass/lesion in the liver, normal AFP, negative HBV/HCV markers, no predisposing factors, **we need to take a biopsy**.
- If patient's imaging shows a mass/lesion in the liver, with portal vein thrombosis, this is HCC, **no need to take a biopsy**

Prognosis

- Overall prognosis is poor with a median survival after diagnosis is 6-20 months, reaches years if treated.
- With cirrhosis, even worse prognosis (3-6 months after diagnosis) if not treated.
- With transplantation, 80% survive more than 5 years if transplantation was done according to its indications.
- If resected with no cirrhosis: CURED

Assessment of the functional liver reserves:

1) CHILD-PUGH's classification:
-Jaundice, Ascites, Encephalopathy (1 factor)
-Albumin < 3g/dl, bilirubin > 30mg/dl (1 factor)
-Prothrombin time (PT) of 2 – 5 seconds (1 factor)
- Prothrombin time (PT) > 5 seconds (2 factors)

0 factors → CHILD-PUGH's A – rare mortality from related surgery (resection)
1 or 2 factors → CHILD-PUGH's B – up to 10-15% mortality from related surgery (resection)
> 2 factors → CHILD-PUGH's C – you should NOT do related surgery (resection) (100% mortality)

2) Indocynine Green retention
We inject this dye intra-venously and blood sample at different times (T0, T15, T20, T30 etc.)
Blood sampling at different times yields liver retention of the dye, the more the retention, the better is the liver reserve!

3) Model of end liver disease (MELD) score: (For ages <12 years we use pediatric version PELD)
-Age -Bilirubin -Na Lever -INR -Creatinine
Score is normally less than 12, and more than 12 is cirrhotic liver (score is between 6 and 40)

4) Morphologic method using CT volumetry (Calculates total volume of the liver, and how much of that remains after surgical resection) and Laparoscopic assessment (To exclude mets).

Management-Curative

- Resection is only feasible and is curative when there's **no cirrhosis** or patient is **(CHILD-PUGH A/B 1 factor** or **MELD<12) cirrhosis** or **fibrolamellar variant.**
- Transplantation (preferred from cadaveric donor) has a criteria:
1) Single lesion < 5 cm
2) Three lesions each < 3 cm

Management-Palliative

HCC is poorly responsive to chemotherapy or radiation, but we have other palliative ways to improve prognosis:

1) Trans-arterial-chemo-embolization (TACE): Emulsion of Lipiodol (radio-opaque material), chemotherapeutic agent (such as Adriamycin and cisplatin), and embolizing material. All nowadays come in single ready package called "Beeds". MOA is blocking the feeding artery of the tumor by clot formation, destroys up to 80% of the tumor but cannot kill 100% of it. Usually used as a bridge for surgery or transplantation or repeated to improve prognosis in non-resectable/non-transplantable patients!

2) Radiofrequency (RF): Heat application (~ 70deg Celsius) targeted on the tumor either and is done intraoperatively or using percutaneous probes. Not useful for lesions greater than 5cm (because it's then easier to hit a biliary duct or a vessel while trying to target the bigger tumor) thus usually done as a bridge to surgery and has reasonable complications.

3) Cryosurgery: Freeze application targeted on tumor, less effective than RF, thus usually done as a bridge to surgery and has reasonable complications.

4) Percutaneous ethanol injection (PEI): Injection of ethanol (100% alcohol), Not useful for lesions greater than 5cm, used when other options are not available, and the maximum dose is 5cc per session.

5) External beam radiation (EBT) Targeted on the tumor cells

6) Sorafenib, kinase inhibitor, not a chemotherapeutic agent, only mentioned

7) Systemic chemotherapy

2) Cholangiocarcinoma

- 2nd most common primary liver cancer.
- Arises from biliary epithelium.
- Cholangiocarcinoma affecting the liver is not the most common site for cholangiocarcinoma (It is m/c extrahepatic).
- Risk factors include
1) Primary sclerosing cholangitis

2) Oriental cholangio-hepatitis; an endemic disease in Southeast Asia, is characterized by recurrent attacks of abdominal pain, fever, and jaundice. Pathologically, the intra- and extrahepatic ducts are dilated and contain soft, pigmented stone and pus, it's caused by a parasite infection.
- Usually **diagnosed late** (By a biopsy) until there's biliary obstruction and jaundice, thus **poor prognosis**.
- Resection is the ideal treatment.

3) Hepatoblastoma

- Affects infants and children.
- Arises from immature liver cells.
- Two types: Epithelial type, mixed epithelial and mesenchymal type.
- Coexist with other syndromes; Trisomy 18, 21 and Familial adenomatous polyposis.
- Can metastasize.
- Diagnosis: Palpable abdominal mass, > 500ng/dl AFP levels, biopsy
- Treatment:
1) Neoadjuvant chemotherapy
2) Surgical resection
3) Liver transplantation
- Prognosis:
If responsive to neoadjuvant chemo and was followed by resection/transplantation, survival is close to 100%
If metastasized, poor prognosis.

2. Secondary liver tumors- (Much more common than primary liver tumors)

- The liver is a **common site of distant metastasis** originating from different neoplasms including gastrointestinal (pancreatic, stomach, colorectal-most common), lung, breast cancers, melanoma (eye, skin), renal and gynecological system.
Also primary liver tumors such as cholangiocellular carcinomas (CCC), cancers of the bile ducts, may disseminate into the liver.
- The **reason for the high frequency of liver metastases** has multiple reasons including:
1) The liver's vast blood supply, which originates from portal and systemic systems.
2) The fenestrations of the hepatic sinusoidal endothelium may facilitate penetration of malignant cells into the hepatic parenchyma.
3) Humoral factors that promote cell growth and cellular factors, such as adhesion molecules, favor metastatic spread to the liver.
4) The liver's geographic proximity to other intra-abdominal organs may allow malignant infiltration by direct extension including kidneys, colon, adrenals and inferior part of the right lung.
- Previously, oncologists were so pessimistic about the appearance of hepatic metastases that "no treatment" was often the recommendation. Advancing technology and improved surgical techniques changed this.
- **Patient selection is the most important aspect of surgical therapy for metastatic disease in the liver** and clinical follow-up of resected patients has identified those most and least likely to benefit. Therefore, realistic expectations and honest patient education are important aspects of treatment.

Clinical presentation

- Clinical presentation or liver metastases is **subtle** and often **variable** depending primarily on the primary tumor, and the extent of liver metastases.
- **Mostly asymptomatic** and discovered incidentally during staging of the primary tumor. But with very extensive disease affecting that liver, patient might present with RUQ pain and heaviness, ascites, and if the lesions are compressing the biliary tree; jaundice or pruritus.
- Symptoms of carcinoid syndrome (primary tumor symptoms).
- On physical exam, findings include hepatomegaly, ascites caused by hepatic venous obstruction or peritoneal carcinomatosis, a friction rub over hepatic metastasis.

Biochemical laboratory tests

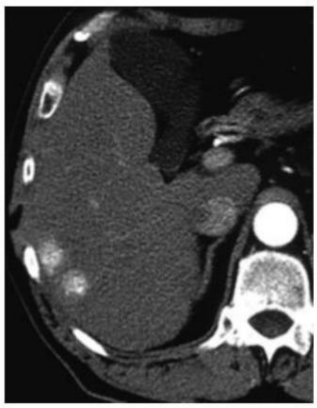
- Doctor believes that no blood test can be used to tell that a patient has liver metastasis, as the laboratory tests that are available for liver function assessment are not very sensitive. Thus, the dependance on imaging techniques.
- CEA remains the most sensitive test for metastatic colon cancer (Especially when very elevated), but even this test can be normal in the presence of liver metastasis, especially with minimal hepatic disease. (Carcinoembryonic antigen)

Imaging techniques

- The best modality to detect liver metastasis.
-The choice among the various techniques, and the sequence with which they are used, should be guided primarily by the clinical indication, taking into account the primary type and the different possible treatments, which also depend on the general status of clinical history of the patient.
- Dedicated liver imaging is not needed in patients diagnosed with disseminated, inoperable disease.
- Imaging techniques used include:

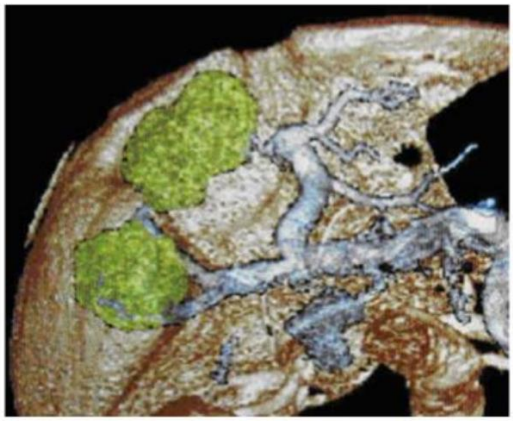
1) Ultrasonography – Cheap, quick, non-invasive and done bed side. But is operator dependent! And the size of the tumor has to be pretty big (relative to other techniques) in order to be detected.
Types:
- Transabdominal ultrasonography – usually used, operator puts ultrasound gel on the abdomen before, yields better results in thinner patients.
- Contrast-enhanced US – we give IV contrast that'll enhance liver lesions on ultrasound, used for equivocal masses on transabdominal ultrasonography.
- Endoscopic ultrasound – an ultrasound probe is equipped with the endoscope, yields great results especially for esophageal or gastric cancer, and as we're talking about metastasis, its very useful for detection of periesophageal or porta-hepatis lymph nodes enlargement, also detects smaller lesions unlike transabdominal ultrasonography as its closer and bypasses abdominal wall and bowel gasses.
- Intraoperative ultrasound – most sensitive for our topic, directly applied probe either laparoscopically or during open surgery, detects 5-10% of missed lesions.

2) Computed tomography (CT) – *hyperdense = white ~ normal bone, hypodense = black ~ normal liver.*
- Either with or without contrast. (Triphasic contrast images are better of course)



Computed tomography of hypervascular liver metastases from a renal primary tumor at the arterial phase.

We can see the normally hypodense liver, with 2 hyperdense lesions = liver metastasis.



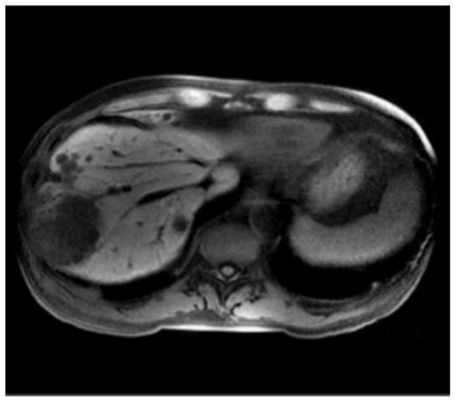
Computed tomography 3-D reconstruction before surgical showing liver metastases

- Every type of tumor radiologically differs;
colorectal metastasis = **hypo**dense lesions even at the arterial phase
neuroendocrine tumors = **hyper**dense lesions at the arterial phase

3) Magnetic resonance imaging (MRI)
- Much more sensitive than CT, as it can pick up even **sub-centimetric lesions.**
- In cases of fatty liver / post-chemotherapy (which similarly causes steatosis), **CT scan is not sensitive** and MRI is used.
- Also, when there's contraindication to contrast ~ kidney failure, allergy to contrast. Or not to expose young patients to radiation.
- Dynamic, breath-hold MR imaging with a gadolinium-based contrast material is considered to be **the most sensitive MRI technique** for detection of hepatic metastases.

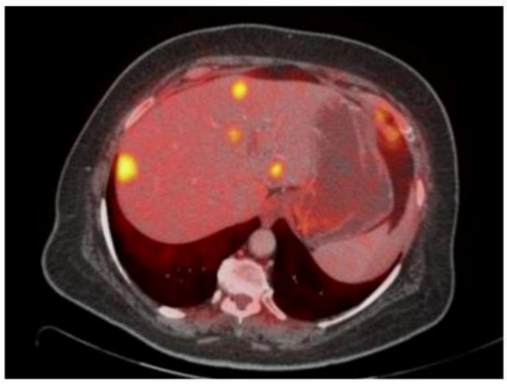
4) Positron emission tomography (PET scan)
- Detects glucose metabolic activity in all cells.
- Relies on the fact that malignant cells depend mainly on glucose for metabolism.
- We use glucose with either a radioactive material or fluorine isotope, when it's injected into the body, malignant cells will uptake this modified glucose **more than normal cells** (all cells will be highlighted but malignant cells will be heavily highlighted.
- Similar to octreotide scan of endocrine tumors
- 18F-Fluorodeoxyglucose 18FDG, the most commonly used marker in PET imaging, is an analogue of glucose in which a carbon atom is replaced by a radioactive fluorine isotope.
- Combined PET/CT scans allow the precise localization of the abnormal areas of uptake.

MRI



. Liver metastases after Mn DPPD or mangafodipir injection.

PET/CT combined scan



PET/CT Cancer pancreas with liver metastases (http://www.radrounds.com/photo/petct- -2context).

Histopathology

- The histologic appearances of metastatic deposits in the liver may resemble those of the primary tumors. Because the metastatic cell population may not be representative of the primary tumor, it can be difficult to determine the site of origin based on the histologic appearance of the metastases alone.
- So we do US/CT guided true-cut biopsy and the histopathologist will tell us the type of primary tumor if we were lucky enough to have well-differentiated tissue. Otherwise, with poorly differentiated tissues, they'll have a hard time, until they use immune-histochemical studies!
- The initial light-microscopic findings can be used to categorize the tissue into one of three groups: 1. poorly differentiated carcinoma or adenocarcinoma.2. well-differentiated adenocarcinoma.3. squamous carcinoma

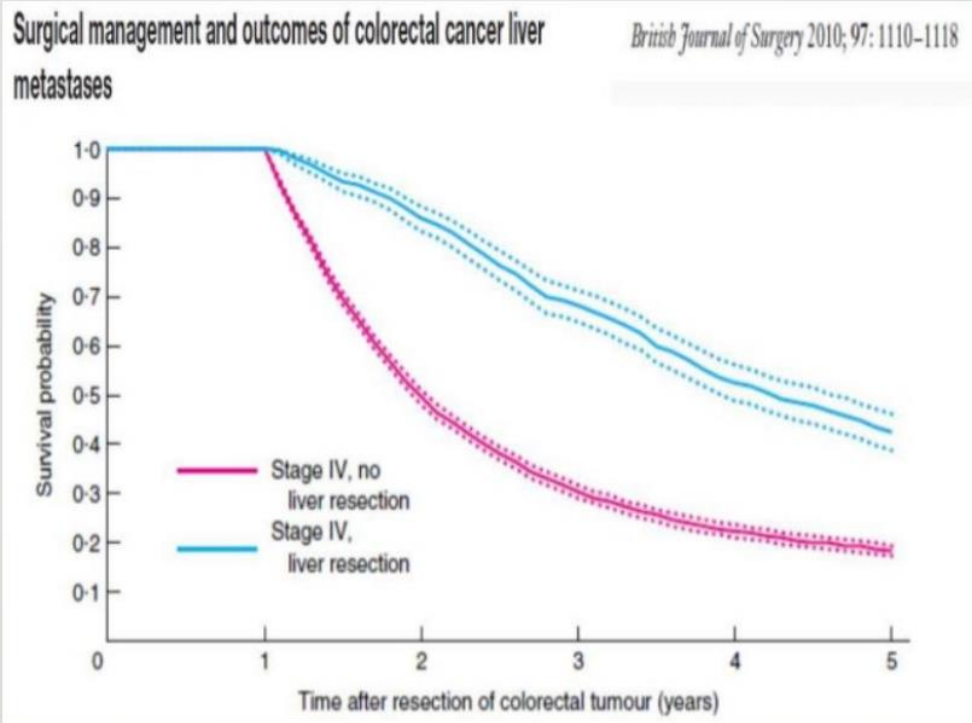
Do not memorize.

Tumor	Antigens
Colonic adenocarcinoma	CEA
Pancreatic carcinoma	CEA, pancreatic carcinoma-associated antigen
Lung carcinoma	CEA, cytokeratin, neuron-specific enolase
Breast carcinoma	CEA, milk-fat globulin, hCG
Thyroid carcinoma	Thyroglobulin
Prostate carcinoma	Prostate-specific acid phosphatase, PSA
Melanoma	S-100, vimentin, neuron-specific enolase
Carcinoid	Chromogranin, neuron-specific enolase
Lymphoma and leukemia	CLA
Sarcoma	
Smooth muscle	Type IV collagen, vimentin, desmin
Skeletal muscle	Myoglobin, vimentin, desmin
Neurogenic	S-100, myelin basic protein
Cartilage	S-100, vimentin
Bone	Vimentin
Germ cell tumors	α-fetoprotien, α1-antitrypsin
Trophoblastic tumors	hCG, α-Fetoprotein

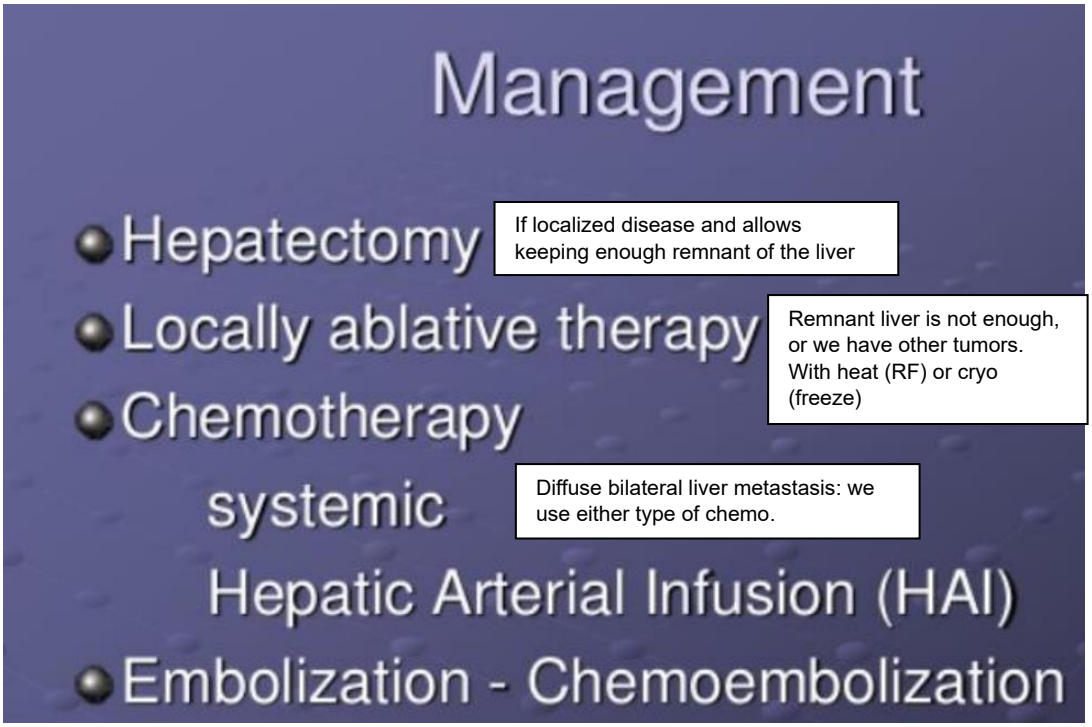
Immunohistochemical antigens for the identification of primary tumors.

Colorectal liver metastasis (CRLM)

- Colorectal cancer (CRC) is one of the most common cancers in the world, ranking third in terms of incidence (10.2% of all cancer cases worldwide) and second most common cause of cancer mortality (9.2% of all cancer mortality) in the world. Over 1.8 million new CRC cases and 881,000 deaths are estimated to occur in 2018, accounting for about 1 in 10 cancer cases and deaths.
- We noticed that CRLM patients that underwent surgery have an overall survival is much better than unresected patients.



- And for the previous reason, we should try and cure any patient with CRLM by resection of distant metastatic lesion in the liver, lung or any site (As long as it is resectable = which is the case if we have enough liver remnant after resection (25% of healthy liver remnant is enough, we need 40% remnant if patient received chemo or has a fatty liver)



- Hepatic arterial infusion (HAI) allows for injection of high dose chemo with very minimal side effects, similar to catheterization, we go from the celiac artery to the common hepatic artery and then right/left depending on the tumor location (And we do that from the segmental arteries).

- Chemotherapy is either:
Neoadjuvant: Given prior to surgery to either down stage or shrink the tumor in order to allow for resection.
Adjuvant: Given post-surgery
Palliative: Given to stabilize the size of tumor and avoid complications, so if the tumor was in the eye, we stabilize its size not to cause ulceration, rupture of the eyeball or cosmetic reasons etc. and if it was behind IVC as an example, to prevent its compression thus avoiding edema, ascites etc.

Past Papers :-

Best of luck <3