Cancer of the Liver and Bile Duct

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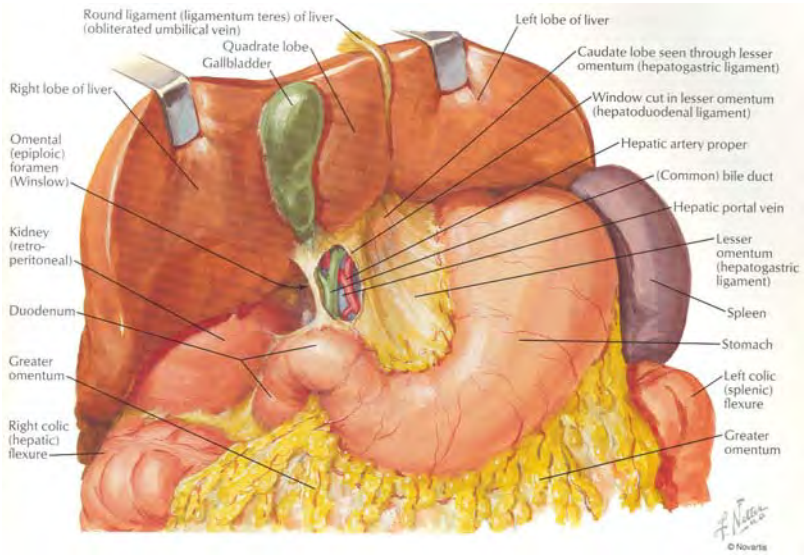
Disclosures

- No financial disclosures
- I am a surgeon

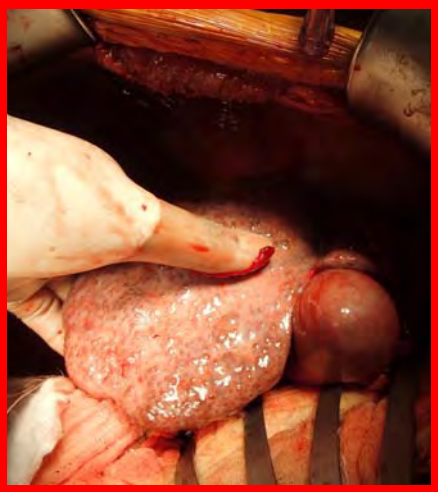


Cancer of the Liver and Bile Duct

- Hepatocellular carcinoma (HCC)
- Cholangiocarcinoma
- Gallbladder cancer

HCC

- Increasing incidence
- Risk factors
  - Cirrhosis
    - Hepatitis B and C
    - Alcohol
    - Hemochromatosis
    - NAFLD
    - Primary biliary cirrhosis
  - Hepatitis B
- Tumor marker alfa-fetoprotein (AFP)



Estimated Number* of New Cancer Cases and Deaths by Sex, US, 2014

	Estimated New Cases			Estimated Deaths		
	Both Sexes	Male	Female	Both Sexes	Male	Female
All Sites	1,665,540	855,220	810,320	585,720	310,010	275,710
Oral cavity & pharynx	42,440	30,220	12,220	8,390	5,730	2,660
Tongue	13,590	9,720	3,870	2,150	1,450	700
Mouth	11,920	7,150	4,770	2,070	1,130	940
Pharynx	14,410	11,550	2,860	2,540	1,900	640
Other oral cavity	2,520	1,800	720	1,630	1,250	380
Digestive system	289,610	162,730	126,880	147,260	84,970	62,290
Esophagus	18,170	14,660	3,510	15,450	12,450	3,000
Stomach	22,220	13,730	8,490	10,990	6,720	4,270
Small intestine	9,160	4,880	4,280	1,210	640	570
Colon[1]					26,270	24,040
Rectum	40,000	23,380	16,620			
Anus, anal canal, & anorectum	7,210	2,660	4,550	950	370	580
Liver & intrahepatic bile duct	33,190	24,600	8,590	23,000	15,870	7,130
Gallbladder & other biliary	10,650	4,960	5,690	3,630	1,610	2,020
Pancreas	46,420	23,530	22,890	39,590	20,170	19,420
Other digestive organs	5,760	1,880	3,880	2,130	870	
Respiratory system					90,280	73,380
Larynx	12,630	10,000	2,630	3,610	2,870	740
Lung & bronchus	224,210	116,000	108,210	159,260	86,930	72,330
Other respiratory organs	5,710	4,000	1,710	790	480	310
Bones & joints	3,020	1,680	1,340	1,460	830	630
Soft tissue (including heart)	12,020	6,550	5,470	4,740	2,550	2,190
Skin (excluding basal & squamous)	81,220	46,630	34,590	12,980	8,840	4,140
Melanoma-skin	76,100	43,890	32,210	9,710	6,470	3,240
Other nonepithelial skin	5,120	2,740	2,380	3,270	2,370	900
Breast	235,030	2,360	232,670	40,430	430	40,000
Genital system	338,450	243,460	94,990	58,970	30,180	28,790
Uterine cervix	12,360		12,360	4,020		4,020
Uterine corpus	52,630		52,630	8,590		8,590

http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf

treatment.

- Treatments are available that can eliminate the virus from the body and prevent liver damage, cirrhosis, and even liver cancer.

CDC recommends that anyone born from 1945 through 1965 get tested for Hepatitis C.

past. Still, many baby boomers do not know how or when they were infected.

What should baby boomers know about Hepatitis C?

Hepatitis C is a serious liver disease that results from infection with the Hepatitis C virus. Some people who get infected with Hepatitis C are able to clear, or get rid of, the virus, but most people who get infected develop a chronic, or lifelong, infection. Over time, chronic Hepatitis C can cause serious health problems including liver damage, cirrhosis, liver cancer and even death. In fact, Hepatitis C is a leading cause of liver cancer and the leading cause of liver transplants.

People with Hepatitis C:

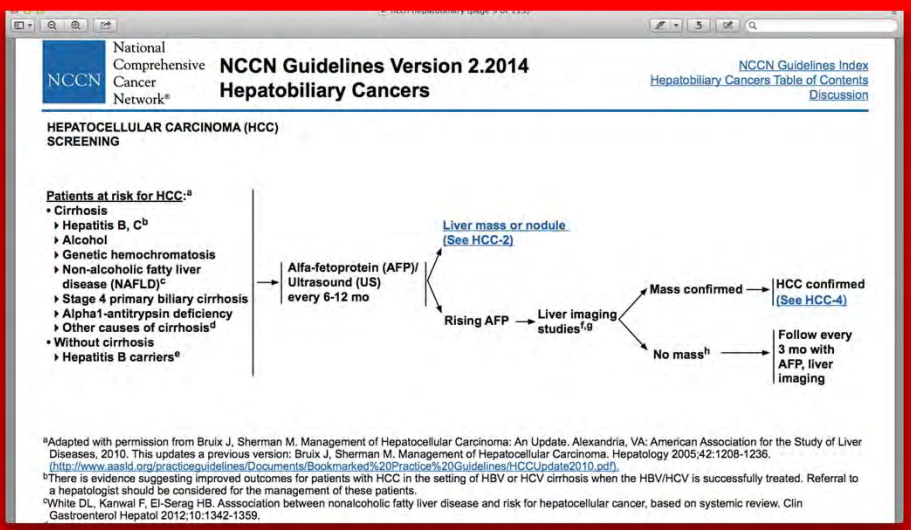
- Often have no symptoms
- Can live with an infection for decades without feeling sick
- Can be successfully treated with medications

Continued on next page

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

HCC

- Increasing incidence
- Risk factors
  - Cirrhosis
    - Hepatitis B and C
    - Alcohol
    - Hemochromatosis
    - NAFLD
    - Primary biliary cirrhosis
  - Hepatitis B
- Tumor marker alfa-fetoprotein (AFP)



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Hepatobiliary Cancers

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HEPATOCELLULAR CARCINOMA (HCC) SCREENING

Patients at risk for HCC:[a]
- **Cirrhosis**
  - **Hepatitis B, C**[b]
  - **Alcohol**
  - **Genetic hemochromatosis**
  - **Non-alcoholic fatty liver disease (NAFLD)**[c]
  - **Stage 4 primary biliary cirrhosis**
  - **Alpha1-antitrypsin deficiency**
  - **Other causes of cirrhosis**[d]
- **Without cirrhosis**
  - **Hepatitis B carriers**[e]

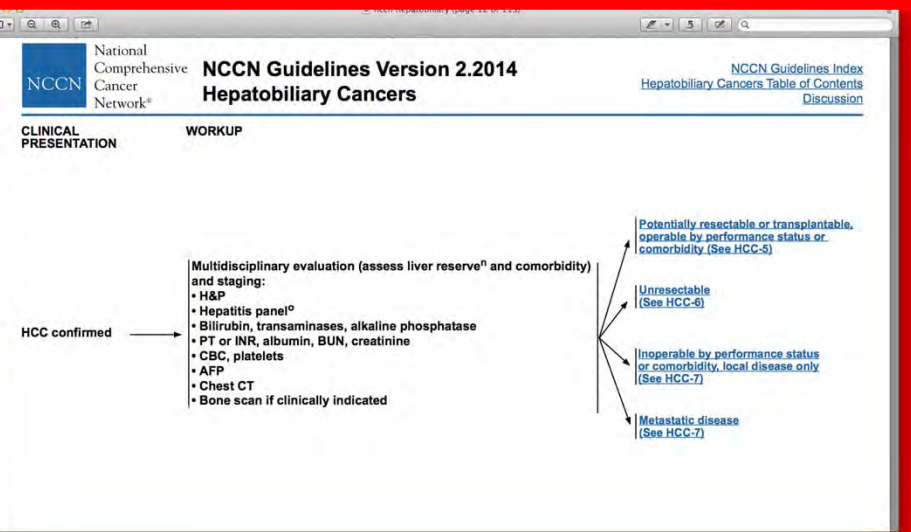
→ **Alfa-fetoprotein (AFP)/ Ultrasound (US) every 6-12 mo**

- **Liver mass or nodule (See HCC-2)**
- **Rising AFP** → **Liver imaging studies**[f,g]
  - **Mass confirmed** → **HCC confirmed (See HCC-4)**
  - **No mass**[h] → **Follow every 3 mo with AFP, liver imaging**

[a]Adapted with permission from Bruix J, Sherman M. Management of Hepatocellular Carcinoma: An Update. Alexandria, VA: American Association for the Study of Liver Diseases, 2010. This updates a previous version: Bruix J, Sherman M. Management of Hepatocellular Carcinoma. Hepatology 2005;42:1208-1236. (http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf).

[b]There is evidence suggesting improved outcomes for patients with HCC in the setting of HBV or HCV cirrhosis when the HBV/HCV is successfully treated. Referral to a hepatologist should be considered for the management of these patients.

[c]White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systemic review. Clin Gastroenterol Hepatol 2012;10:1342-1359.



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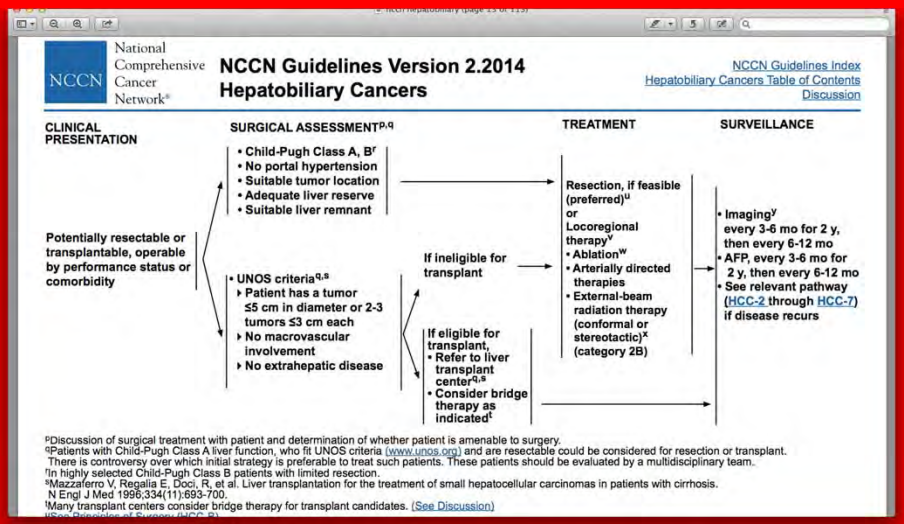
CLINICAL PRESENTATION	WORKUP

HCC confirmed →

Multidisciplinary evaluation (assess liver reserve[n] **and comorbidity) and staging:**
- **H&P**
- **Hepatitis panel**[o]
- **Bilirubin, transaminases, alkaline phosphatase**
- **PT or INR, albumin, BUN, creatinine**
- **CBC, platelets**
- **AFP**
- **Chest CT**
- **Bone scan if clinically indicated**

→
- **Potentially resectable or transplantable, operable by performance status or comorbidity (See HCC-5)**
- **Unresectable (See HCC-6)**
- **Inoperable by performance status or comorbidity, local disease only (See HCC-7)**
- **Metastatic disease (See HCC-7)**



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CLINICAL PRESENTATION

SURGICAL ASSESSMENT[P,Q]

TREATMENT

SURVEILLANCE

Potentially resectable or transplantable, operable by performance status or comorbidity

- Child-Pugh Class A, B[r]
- No portal hypertension
- Suitable tumor location
- Adequate liver reserve
- Suitable liver remnant

→ Resection, if feasible (preferred)[U] or Locoregional therapy[V]
- Ablation[W]
- Arterially directed therapies
- External-beam radiation therapy (conformal or stereotactic)[X] (category 2B)

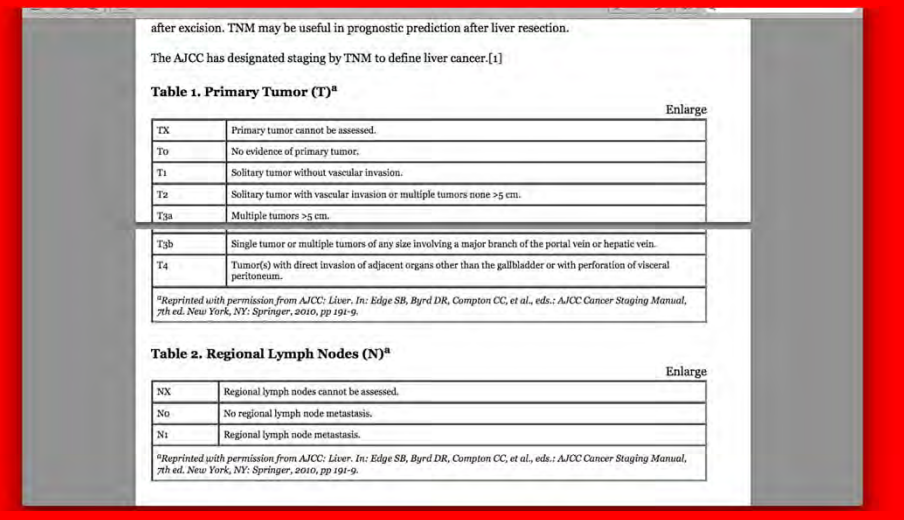
→ If ineligible for transplant

- UNOS criteria[Q,S]
  - Patient has a tumor ≤5 cm in diameter or 2-3 tumors ≤3 cm each
  - No macrovascular involvement
  - No extrahepatic disease

→ If eligible for transplant,
- Refer to liver transplant center[Q,S]
- Consider bridge therapy as indicated[t]

→
- Imaging[Y] every 3-6 mo for 2 y, then every 6-12 mo
- AFP, every 3-6 mo for 2 y, then every 6-12 mo
- See relevant pathway (HCC-2 through HCC-7) if disease recurs

[P]Discussion of surgical treatment with patient and determination of whether patient is amenable to surgery.
[Q]Patients with Child-Pugh Class A liver function, who fit UNOS criteria (www.unos.org) and are resectable could be considered for resection or transplant. There is controversy over which initial strategy is preferable to treat such patients. These patients should be evaluated by a multidisciplinary team.
[r]In highly selected Child-Pugh Class B patients with limited resection.
[S]Mazzaferro V, Regalia E, Doci, R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334(11):693-700.
[t]Many transplant centers consider bridge therapy for transplant candidates. (See Discussion)



after excision. TNM may be useful in prognostic prediction after liver resection.

The AJCC has designated staging by TNM to define liver cancer.[1]

Table 1. Primary Tumor (T)[a]

Enlarge

TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
T1	Solitary tumor without vascular invasion.
T2	Solitary tumor with vascular invasion or multiple tumors none >5 cm.
T3a	Multiple tumors >5 cm.
T3b	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein.
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum.

[a]Reprinted with permission from AJCC: Liver. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual, 7th ed. New York, NY: Springer, 2010, pp 191-9.

Table 2. Regional Lymph Nodes (N)[a]

Enlarge

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Regional lymph node metastasis.

[a]Reprinted with permission from AJCC: Liver. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual, 7th ed. New York, NY: Springer, 2010, pp 191-9.

http://www.cancer.gov/cancertopics/pdq/treatment/adult-primary-liver/HealthProfessional/page3

Nodules found on images of cirrhotic livers are classified according to *Table 9-5*. Use the largest dimension of each tumor to report the size of Hepatocellular Carcinoma (HCC) lesions. Nodules less than 1 cm are indeterminate and cannot be considered for additional priority.

Table 9-5: Classification System for Nodules Seen on Imaging of Cirrhotic Livers

Class	Description
0	Incomplete or technically inadequate study
5A	Must meet *all* of the following: 1. Single nodule ≥ 1 cm and < 2 cm. The maximum diameter of lesions should be measured on late arterial or portal phase images. 2. Increased contrast enhancement on late arterial phase (relative to hepatic parenchyma). 3. Washout during the later contrast phases and peripheral rim enhancement (capsule/pseudocapsule) on delayed phase *or* a biopsy. (A pre-listing biopsy is not mandatory.)
5A-g (growth)	Must meet *all* of the following: 1. Single nodule ≥ 1 cm and < 2 cm. The maximum diameter of lesions should be measured on late arterial or portal phase images. 2. Increased contrast enhancement on late arterial phase (relative to hepatic parenchyma). 3. Growth (maximum diameter increase) by 50% or more documented on serial MRI or CT obtained ≤ 6 months apart. Growth criteria do not apply to ablated lesions.
5B	Must meet *all* of the following:

How our team works ….

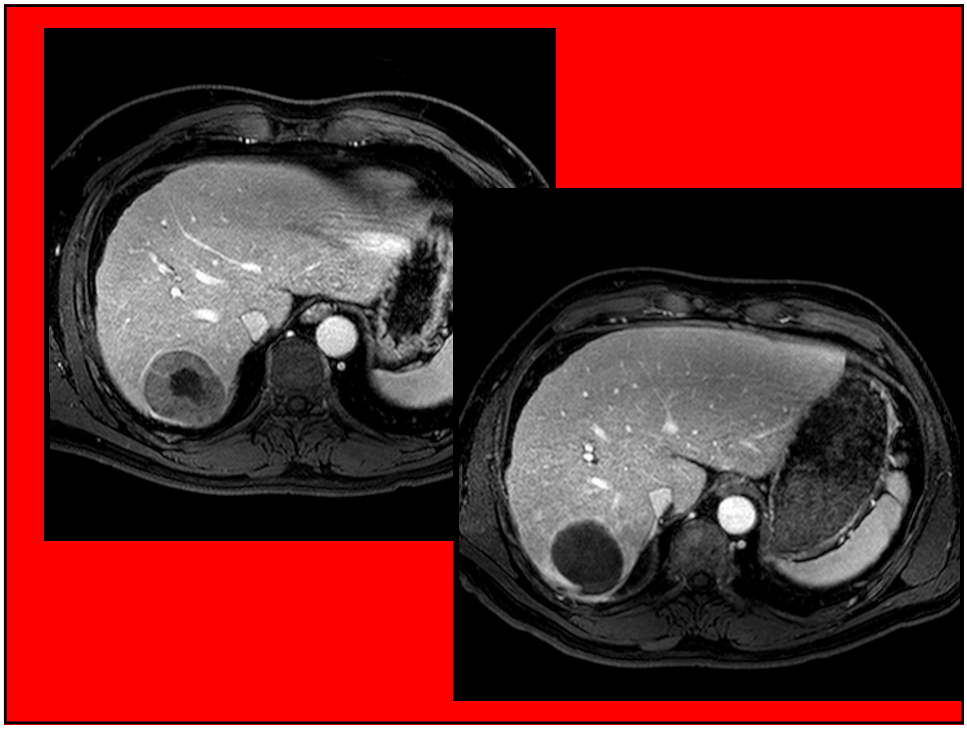
"HCC Meeting"

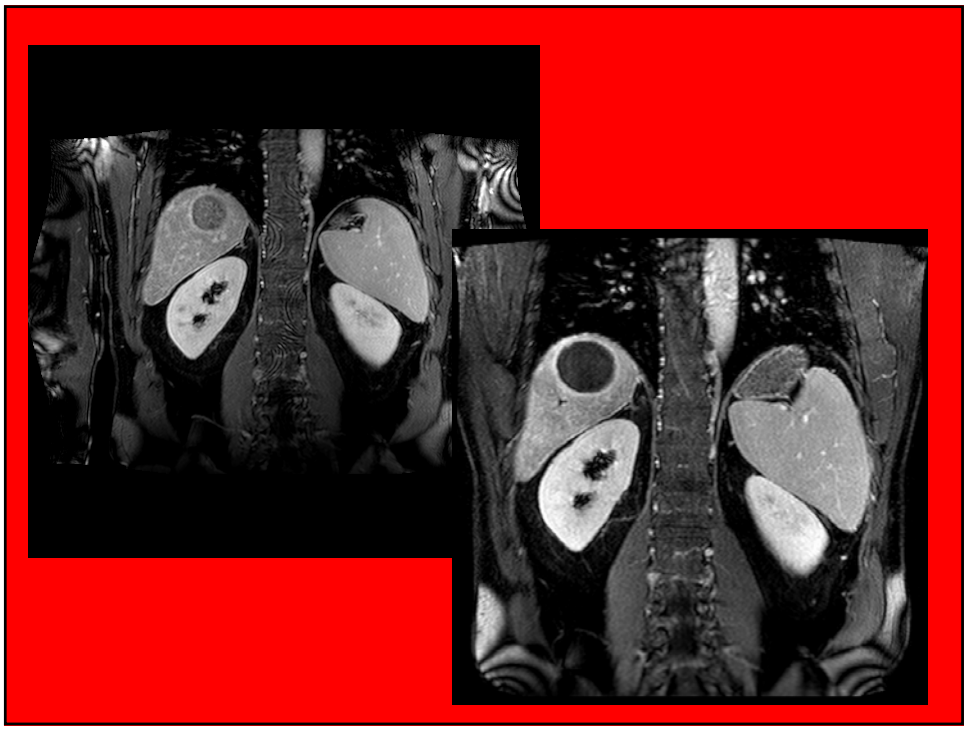
- Dr. R (leader of the meeting - hepatologist)
  - "Mr. H has cirrhosis and a 5.3cm lesion on imaging AFP is 26.4"
- Dr. O (radiologist)
  - " MRI from 2 weeks ago that shows a 5.3 cm lesion in segment 7 that is bright on T2 and has washout – meets radiographic criteria for HCC – OPTN 5"
- Dr. V (surgeon)
  - "does the patient have evidence of portal hypertension?"

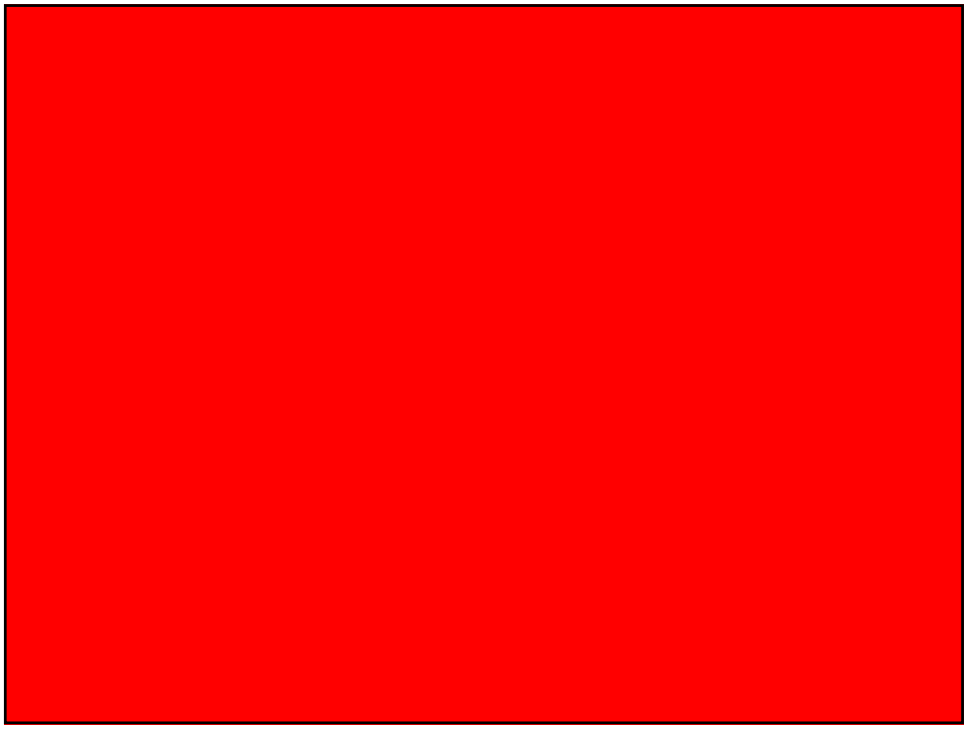
- Dr. O (radiologist)
  - "there are some varices, but no ascites"
- Dr. R (meeting leader – hepatologist)
  - "he is a Child's A cirrhotic but has hepatitis C and a right lobe mass"
- Dr. S (Interventional radiologist)
  - This lesion could be treated with locoregional therapy, I think it is a little big for cryoablation, but this is also a possibility"

- Dr. L (surgeon)
  - "for this lesion, the best long term therapy would be transplant – if he is a candidate"
- Dr. S (Interventional radiologist)
  - "we could treat the lesion while he is being evaluated and waiting for transplant"

- Dr S (hepatologist)
  - "This patient should be evaluated for liver transplant and given all of his options so that he can make a decision. I have seen this patient and I think he would make an excellent transplant candidate."
- SE (Nurse coordinator)
  - "He has been scheduled for transplant evaluation – should we go ahead and set him up for a consultation with Interventional Radiology?
- Dr. R (leader of the meeting - hepatologist)
  - "Yes. Any other thoughts?"







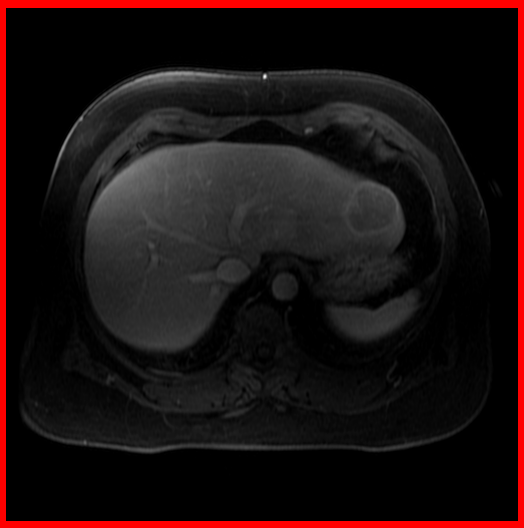
"HCC Meeting"

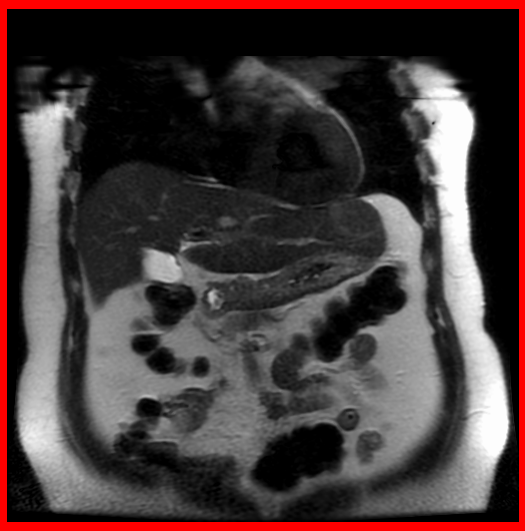
- Dr. R (leader of the meeting - hepatologist)
  - "Mr. H has HCV and a 3.5cm lesion on imaging AFP is 26.4. He has had a biopsy from an outside hospital and it is read as well differentiated HCC"
- Dr. O (radiologist)
  - " MRI from 2 weeks ago shows a 3.5 cm lesion in segment 2 that is bright on T2 and has washout – meets radiographic criteria for HCC – OPTN 5"
- Dr. R (Pathologist)
  - "We reviewed the outside biopsy and agree with the diagnosis of well-differentiated HCC"

- Dr. V (surgeon)
  - "does the patient have evidence of portal hypertension?"
- Dr. O (radiologist)
  - "There is minimal evidence of varices and no ascites. The liver looks abnormal but not frankly cirrhotic"
- Dr. R (leader of the meeting - hepatologist)
  - "reports from the outside gastroenterologist and oncologist indicate that the patient does not have encephalopathy and good quality of life. He does have brittle diabetes, obesity and some cardiac disease"

- Dr. S (Interventional Radiologist)
  - "This would be amenable to chemoembilization. I'm not so sure about cryoablation due to the proximity to the stomach"
- Dr. G (surgeon)
  - "it looks like it could be resected with minimal impact on residual liver volume – with a left lateral segmentectomy"
- Dr. S. (Hepatologist)
  - "Given his age and diabetes he may tolerate a resection better than a transplant and this would give him a decent disease free survival despite his hepatitis C"

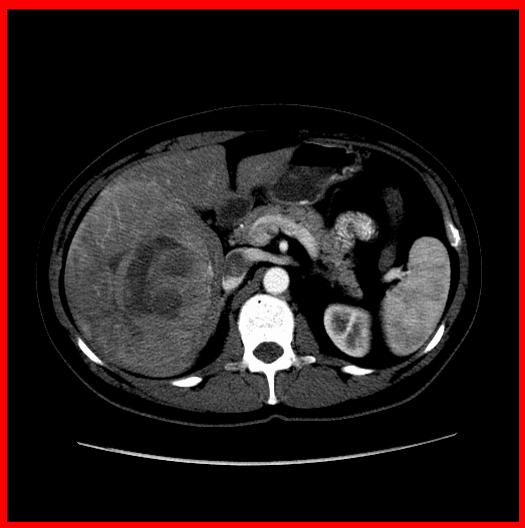
- Dr. R (leader of the meeting - hepatologist)
  - "the outside reports indicate that he is active but has very brittle diabetes"
- SE (nurse coordinator)
  - "so we should set him up for a surgical consultation and if the surgeon thinks that resection is not reasonable, we can always have him come for transplant evaluation"
- Dr. R (leader of the meeting - hepatologist)
  - "Sounds like a good plan. Any other thoughts?"

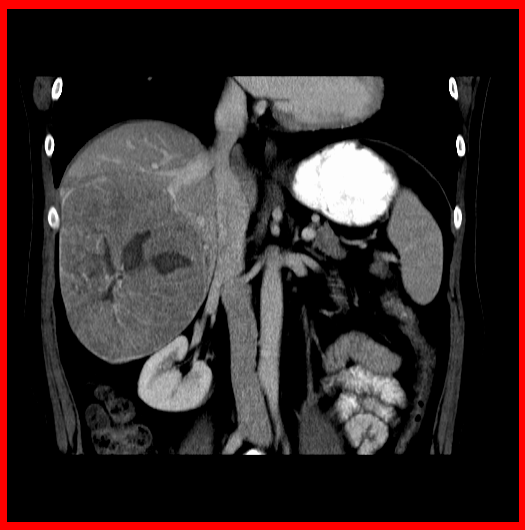




Another case

- 49 year old man with abdominal fullness for several months
- Ultrasound to look for gallbladder pathology
- Mass seen in liver

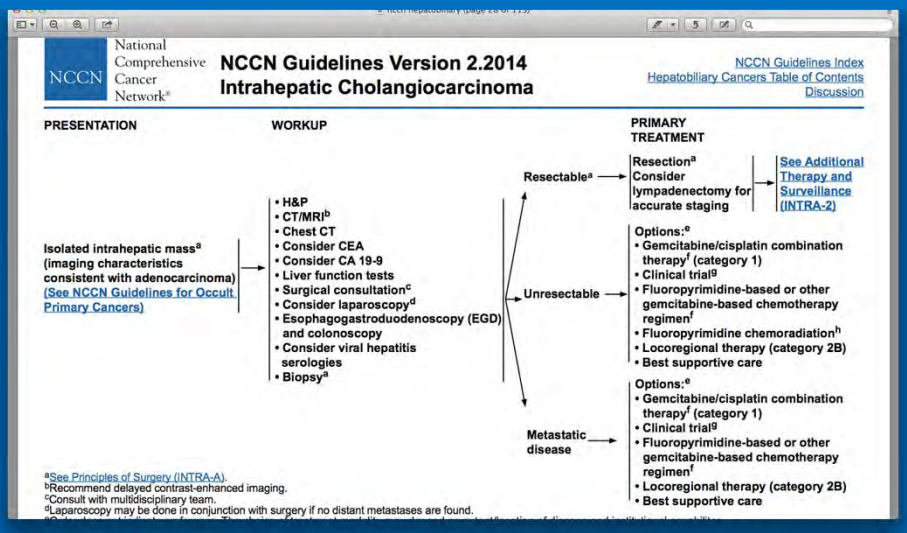




Cholangiocarcinoma

- Intrahepatic
- Extrahepatic
- Risk factors
  - Primary sclerosing cholangitis
  - Choledochal cyst
- No routine screening except in patients with PSC
- Tumor marker CA19-9

Intrahepatic cholangiocarcinoma



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Intrahepatic Cholangiocarcinoma

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PRESENTATION

Isolated intrahepatic mass[a] (imaging characteristics consistent with adenocarcinoma)
(See NCCN Guidelines for Occult Primary Cancers)

WORKUP

- H&P
- CT/MRI[b]
- Chest CT
- Consider CEA
- Consider CA 19-9
- Liver function tests
- Surgical consultation[c]
- Consider laparoscopy[d]
- Esophagogastroduodenoscopy (EGD) and colonoscopy
- Consider viral hepatitis serologies
- Biopsy[a]

PRIMARY TREATMENT

Resectable[a] → Resection[a] Consider lympadenectomy for accurate staging → See Additional Therapy and Surveillance (INTRA-2)

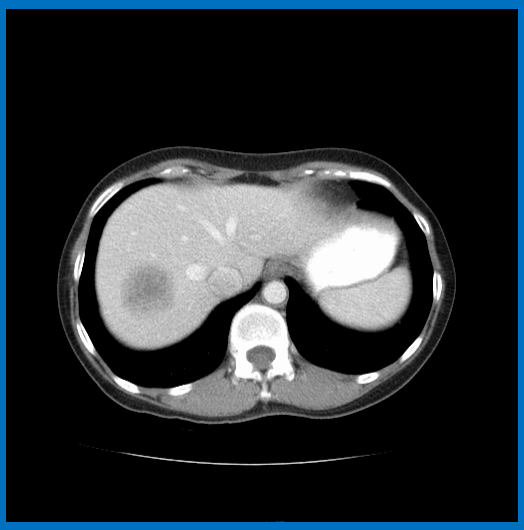
Unresectable → Options:[e]
- Gemcitabine/cisplatin combination therapy[f] (category 1)
- Clinical trial[g]
- Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen[f]
- Fluoropyrimidine chemoradiation[h]
- Locoregional therapy (category 2B)
- Best supportive care

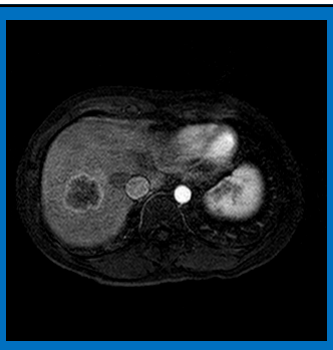
Metastatic disease → Options:[e]
- Gemcitabine/cisplatin combination therapy[f] (category 1)
- Clinical trial[g]
- Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen[f]
- Locoregional therapy (category 2B)
- Best supportive care

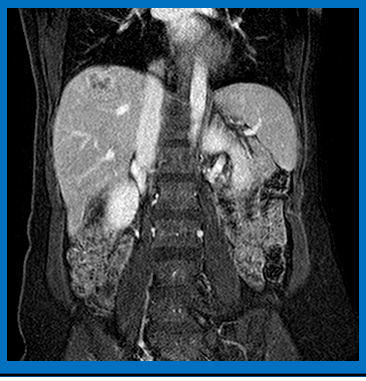
[a]See Principles of Surgery (INTRA-A).
[b]Recommend delayed contrast-enhanced imaging.
[c]Consult with multidisciplinary team.
[d]Laparoscopy may be done in conjunction with surgery if no distant metastases are found.

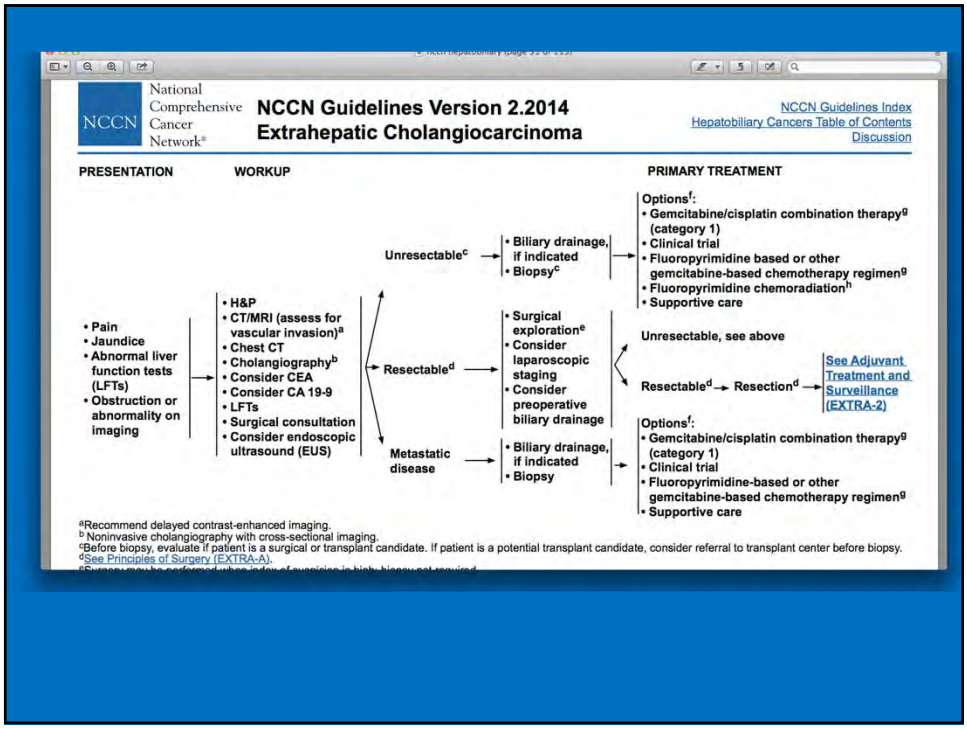
Case

- 68 year old woman with vague abdominal symptoms. Had previously been worked up for ovarian pathology and was having a follow up ultrasound
- Mass seen in the right lobe of the liver
- Further imaging suspicious for malignancy
- Biopsy showed adenocarcinoma









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Extrahepatic Cholangiocarcinoma

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PRESENTATION

- Pain
- Jaundice
- Abnormal liver function tests (LFTs)
- Obstruction or abnormality on imaging

WORKUP

- H&P
- CT/MRI (assess for vascular invasion)[a]
- Chest CT
- Cholangiography[b]
- Consider CEA
- Consider CA 19-9
- LFTs
- Surgical consultation
- Consider endoscopic ultrasound (EUS)

Unresectable[c] → Biliary drainage, if indicated; Biopsy[c] → **PRIMARY TREATMENT**

Options[f]:
- Gemcitabine/cisplatin combination therapy[g] (category 1)
- Clinical trial
- Fluoropyrimidine based or other gemcitabine-based chemotherapy regimen[g]
- Fluoropyrimidine chemoradiation[h]
- Supportive care

Resectable[d] → Surgical exploration[e]; Consider laparoscopic staging; Consider preoperative biliary drainage

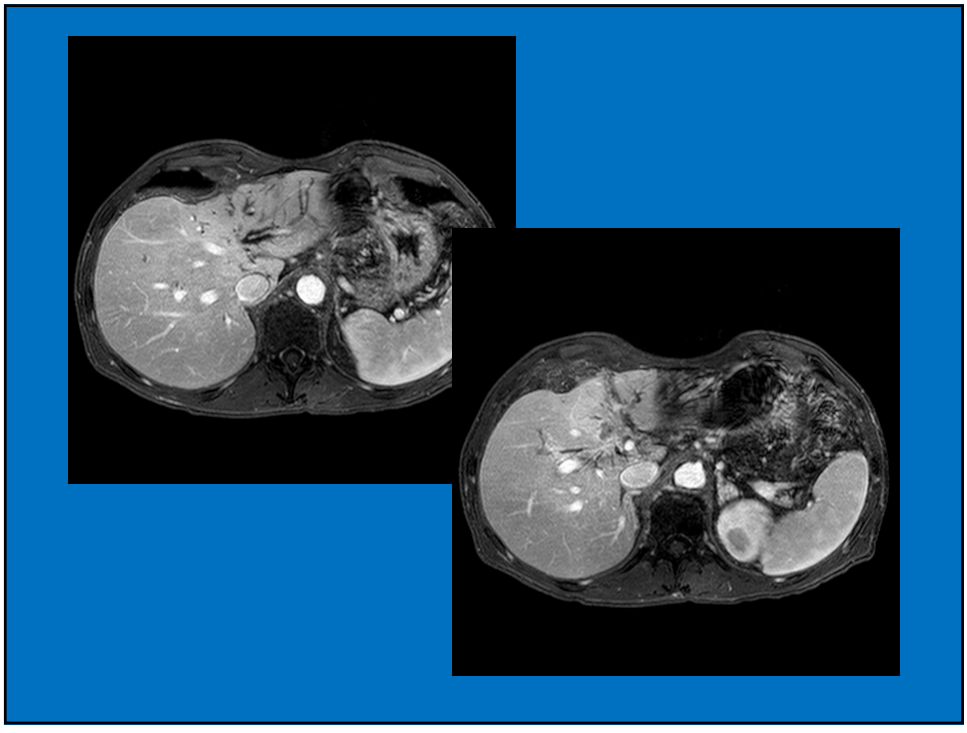
Unresectable, see above

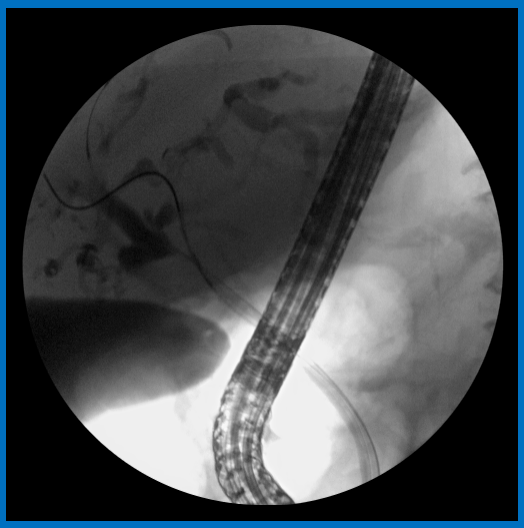
Resectable[d] → Resection[d] → See Adjuvant Treatment and Surveillance (EXTRA-2)

Metastatic disease → Biliary drainage, if indicated; Biopsy → **PRIMARY TREATMENT**

Options[f]:
- Gemcitabine/cisplatin combination therapy[g] (category 1)
- Clinical trial
- Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen[g]
- Supportive care

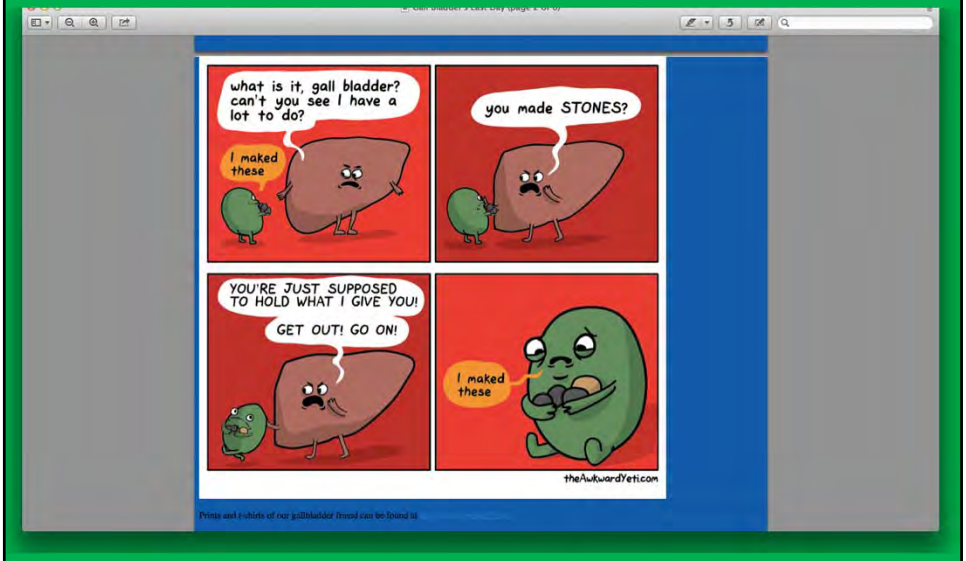
[a]Recommend delayed contrast-enhanced imaging.
[b] Noninvasive cholangiography with cross-sectional imaging.
[c]Before biopsy, evaluate if patient is a surgical or transplant candidate. If patient is a potential transplant candidate, consider referral to transplant center before biopsy.
[d]See Principles of Surgery (EXTRA-A).



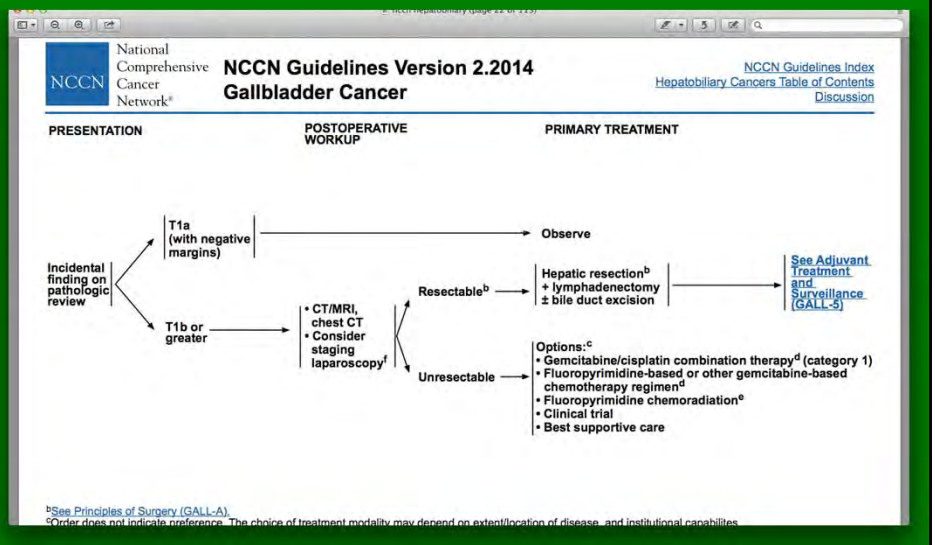


Gallbladder cancer

- Very rare
- Porcelain gallbladder
- Incidental finding on cholecystectomy for another reason



http://theawkwardyeti.com/gall-bladders-day/



Patient

- 69 year old woman from rural Nebraska
- Cholecystectomy for symptomatic cholelithiasis
- Pathology showed cancer
- Primary care physician called and we saw here here and used team approach to design a treatment

- GALLBLADDER, EXCISION:
  - INVASIVE, MODERATE TO POORLY DIFFERENTIATED ADENOCARCINOMA.
  - FOCAL LYMPHOVASCULAR INVASION BY TUMOR IDENTIFIED.
  - MAXIMUM GROSS DIMENTION OF TUMOR IS 2.8 CM.
  - TUMOR INVADES THROUGH MUSCULARIS PROPRIA INTO PERIMUSCULAR CONNECTIVE TISSUE BUT WITHOUT INVOLVEMENT OF THE SEROSAL SERVICE.
  - CYSTIC DUCT LYMPH NODE IS NEGATIVE FOR TUMOR (0/1).
  - CARCINOMA IS ARISING IN THE BACKGROUND OF CHOLELITHIASIS AND CHRONIC CHOLECYSTITIS WITH AREAS OF HIGH-GRADE DYSPLASIA, PSEUDOPYLORIC METAPLASIA AND INTESTINAL METAPLASIA.
  - ACUTE CHOLECYSTITIS SUPERIMPOSED ON THE BACKGROUND OF CHRONIC CHOLECYSTITIS.

- Final Diagnosis:
A. LIVER, BIOPSY:
- HEPATIC PARENCHYMA WITH FOCAL FIBROSIS.
- NEGATIVE FOR MALIGNANCY.

B. BILE DUCT, PROXIMAL, EXCISION:
- NEGATIVE FOR MALIGNANCY.

C. FALCIFORM LIGAMENT, EXCISION:
- BENIGN FIBROUS TISSUE WITH FOCAL ACUTE INFLAMMATION.
- NEGATIVE FOR MALIGNANCY.

D. LYMPH NODE, RIGHT HILAR, EXCISION:
- ONE LYMPH NODE NEGATIVE FOR METASTATIC CARCINOMA (0/1).

E. COMMON BILE DUCT, DISTAL MARGIN, EXCISION:
- NEGATIVE FOR MALIGNANCY.

F. LIVER, DUODENUM, AND COMMON BILE DUCT, PARTIAL HEPATECTOMY AND EXCISION:
- FOCUS OF MODERATELY DIFFERENTIATED ADENOCARCINOMA, LIVER (0.3 MM) (SEE COMMENT)
- GALLBLADDER FOSSA WITH 1 MM FOCUS OF ADENOCARCINOMA.
- PRIOR SURGICAL SITE CHANGES.
- DUODENUM WITHOUT SIGNIFICANT HISTOPATHOLOGIC ABNORMALITY.
- COMMON BILE DUCT WITHOUT SIGNIFICANT HISTOPATHOLOGIC ABNORMALITY.

Conclusion

- HCC
  - Screening for patients with risk factors
  - Multi-disciplinary approach essential
- Cholangiocarcinoma
  - Patients with PSC are really only population that should be screened
  - Resection best approach if possible
- Gallbladder cancer
  - RARE
  - Patients with incidentally found tumors should be seen by multidisciplinary team for treatment