ARRO Case
Resected Intrahepatic Cholangiocarcinoma

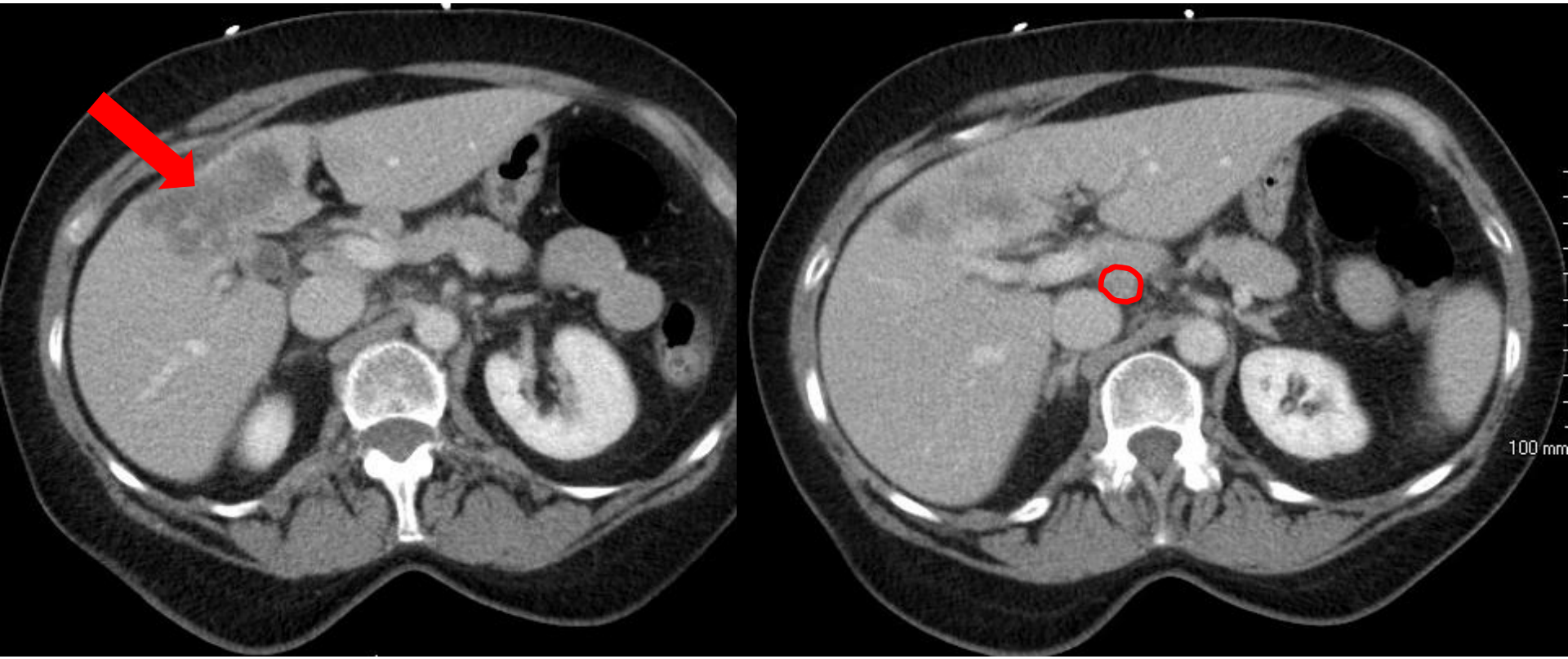
Stephen Rosenberg, MD (PGY-4)
Adam Burr, MD, PhD (PGY-2)
Faculty Advisor: Michael Bassetti, MD, PhD
Department of Human Oncology, University of Wisconsin

History

- 67-year-old woman noted acute onset of right upper quadrant abdominal pain associated with nausea and non-bilious and non-bloody emesis. This was associated with 30 lb weight loss, fatigue, and loss of appetite over a few months.

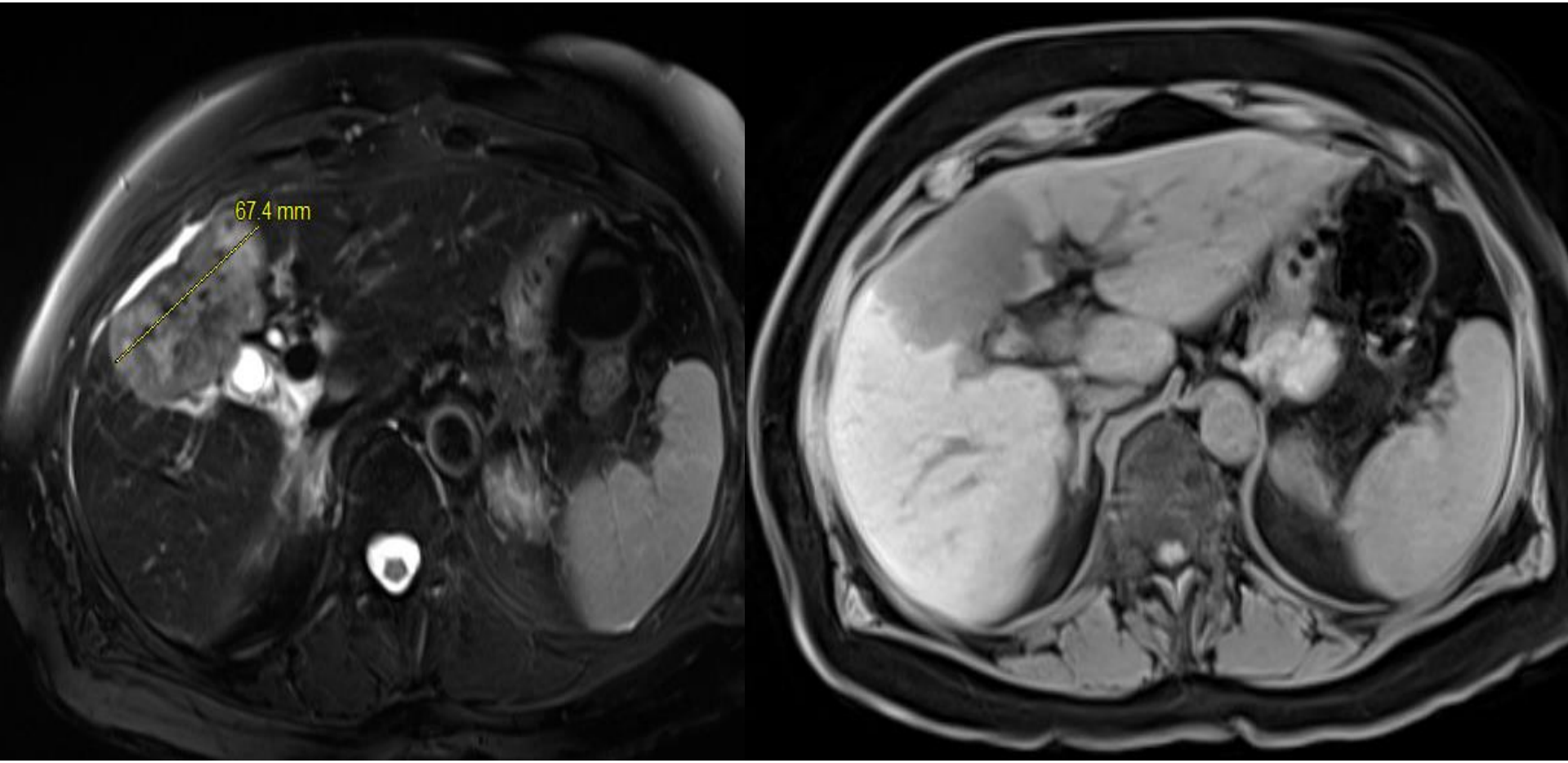
- She was sent for an abdominal ultrasound that showed a 4-5 cm hypoechoic lobulated mass in the liver adjacent to the gallbladder. There was no definitive biliary dilatation. CT of the abdomen and pelvis and an MRI abdomen was ordered.

CT Abdomen and Pelvis



Ill-defined hypodense lesion measuring 3 x 6.1 x 4.5 cm involving segments 4B and 5. A small portion of segment 4A was involved, with associated liver capsular contraction. There was also noted to be 1 enlarged necrotic portocaval lymph node.

MRI Imaging



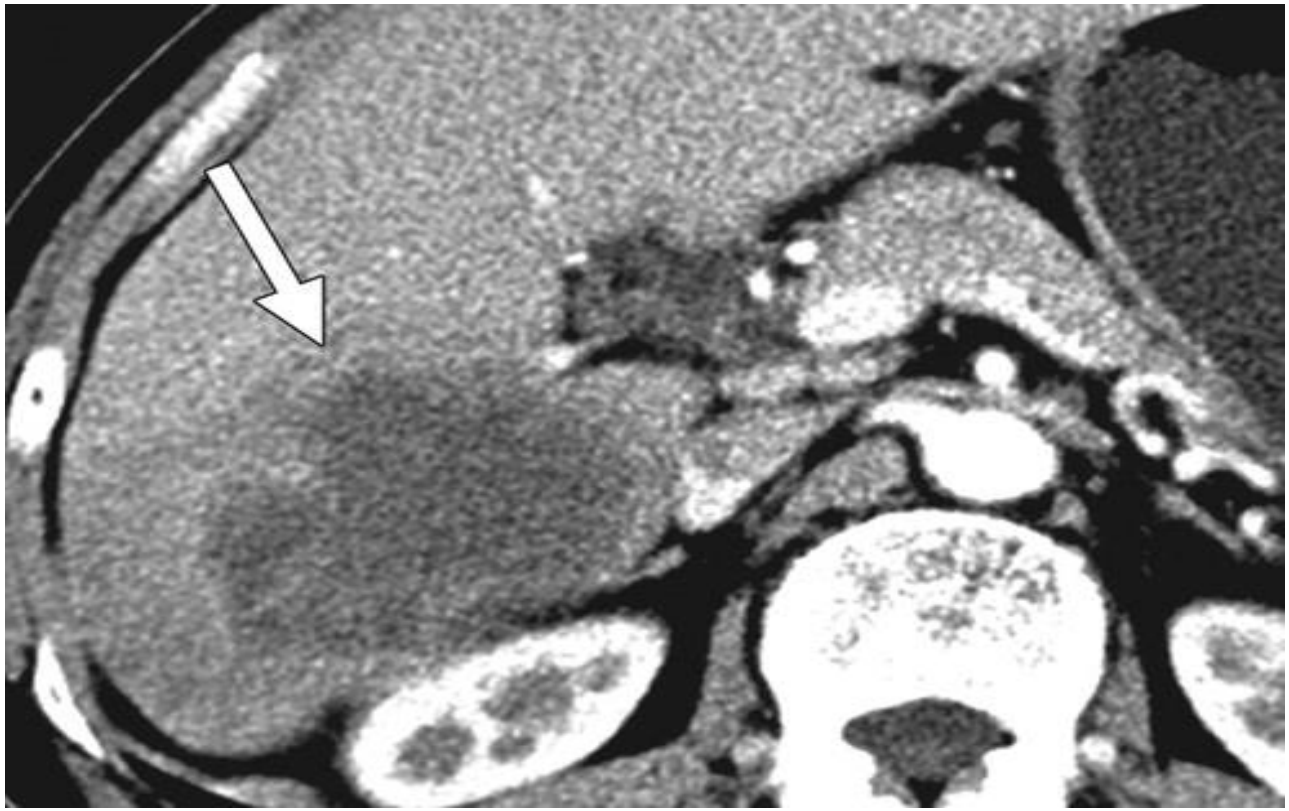
On MRI the tumor measured 6.9 x 4.2 x 5.2 cm, most likely thought to be cholangiocarcinoma.

Differential Diagnosis

- Hepatocellular Carcinoma (HCC)
- Intrahepatic Cholangiocarcinoma
- Metastatic Disease
- Gallbladder Carcinoma

Imaging Key Point: On multiphase CT scan HCC often enhances on the arterial phase while the intrahepatic cholangiocarcinoma has a delayed enhancement.

Arterial Enhancement



Arterial phase CT scan shows a tumor with ragged rim enhancement at the periphery (arrow) consistent with ICC.

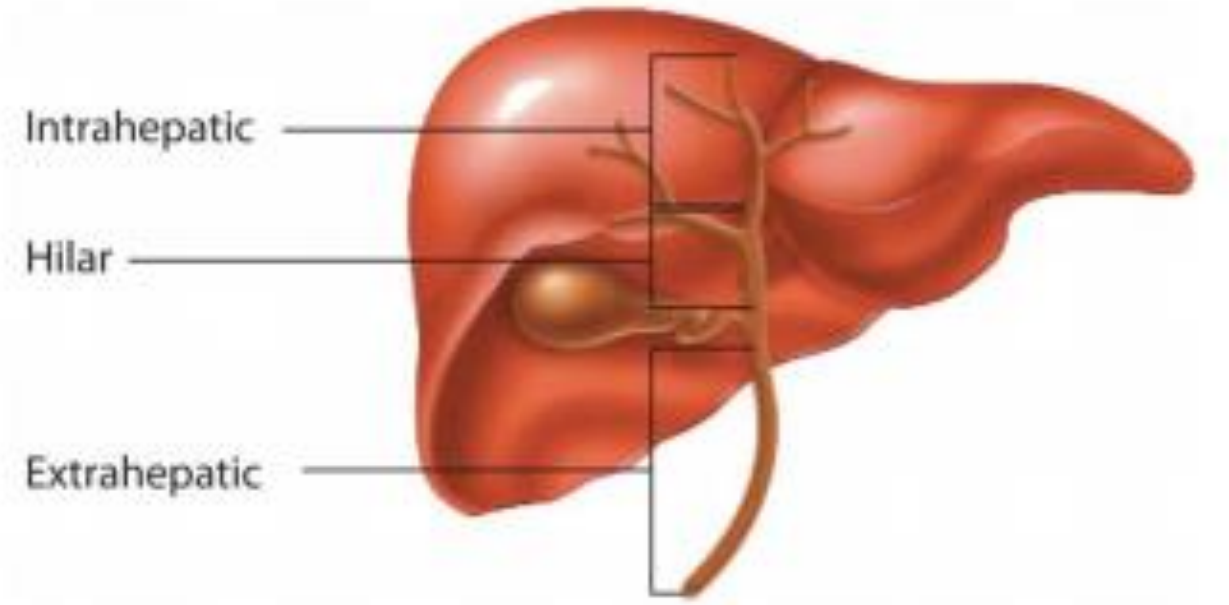
Chung Y.E., *et al. Radiographics,* 2009

Incidence & Risk Factors

- ~10,000 cases of cholangiocarcinoma & gall bladder cancers a year
- ~3,500 deaths a year
- Cholangiocarcinoma is broken down by site:
  - 10% intrahepatic
  - 60% perihilar
  - 30% extrahepatic
- **ICC is the 2nd most common primary hepatic malignancy following HCC**

Shaib, *et al. Gastroenterology,* 2005

Location of Cholangiocarcinoma



Patel T, *et al. Nat Clin Pract Gastroenterol Hepat* , 2006

Risk Factors

- Risk Factors (causes of biliary or hepatic inflammation):
  - Primary Sclerosing Cholangitis and IBD
  - Choledochal cysts
  - Liver flukes (Southeast Asia)
  - Cirrhosis (OR = 29, SEER analysis)
  - Alcoholic liver disease (OR = 7.4, SEER analysis)
  - Hepatitis C (OR = 6.1, SEER analysis)
  - HIV (OR = 5.9, SEER analysis)

Shaib*, et al. Gastroenterology,* 2005

Presentation & Natural History

- Patients present with malaise, nausea, abdominal pain, and jaundice.
- Intrahepatic CC has 20-30% risk of LN metastases (less than extrahepatic or hilar)
- Lymph node drainage: pericholedochal, portal vein, common hepatic artery, pancreaticoduodenal, celiac/SMA

Intrahepatic CC Staging

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Staging

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Table 3
American Joint Committee on Cancer (AJCC)
TNM Staging for Intrahepatic Bile Duct Tumors (7th ed., 2010)

Primary Tumor (T)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ* (intraductal tumor)
T1 Solitary tumor without vascular invasion
T2a Solitary tumor with vascular invasion
T2b Multiple tumors, with or without vascular invasion
T3 Tumor perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion
T4 Tumor with periductal invasion

Regional Lymph Nodes (N)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis present

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis present

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVA	T4	N0	M0
	Any T	N1	M0
Stage IVB	Any T	Any N	M1

Histologic Grade (G)
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

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Intrahepatic Cholangiocarcinoma

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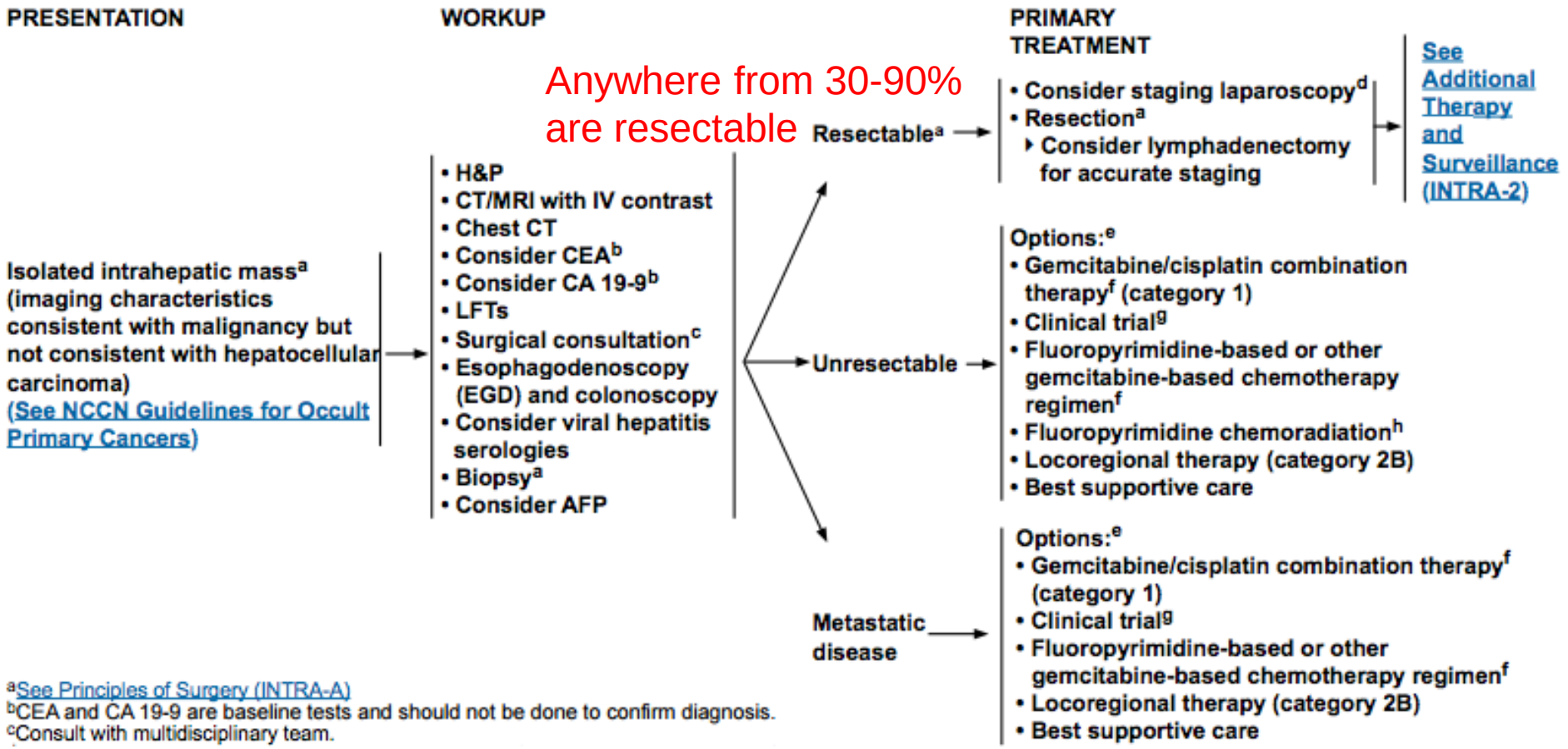
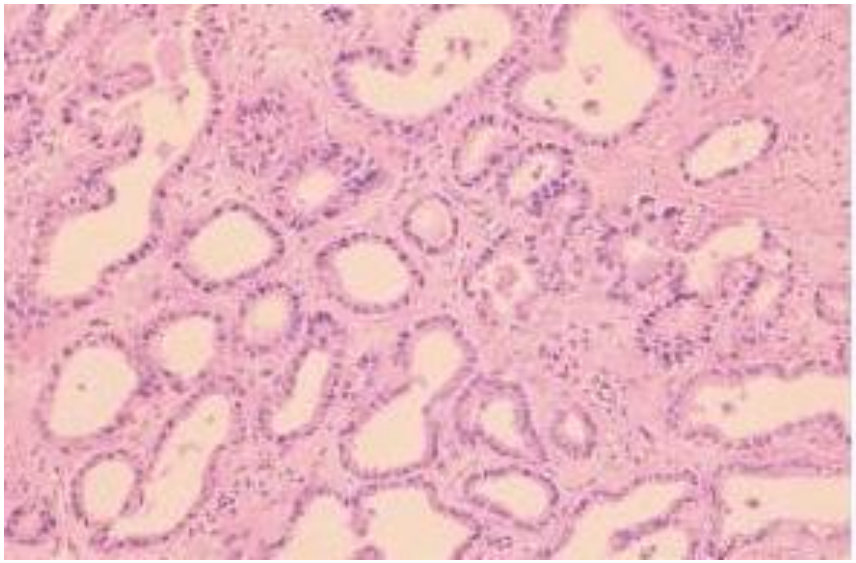
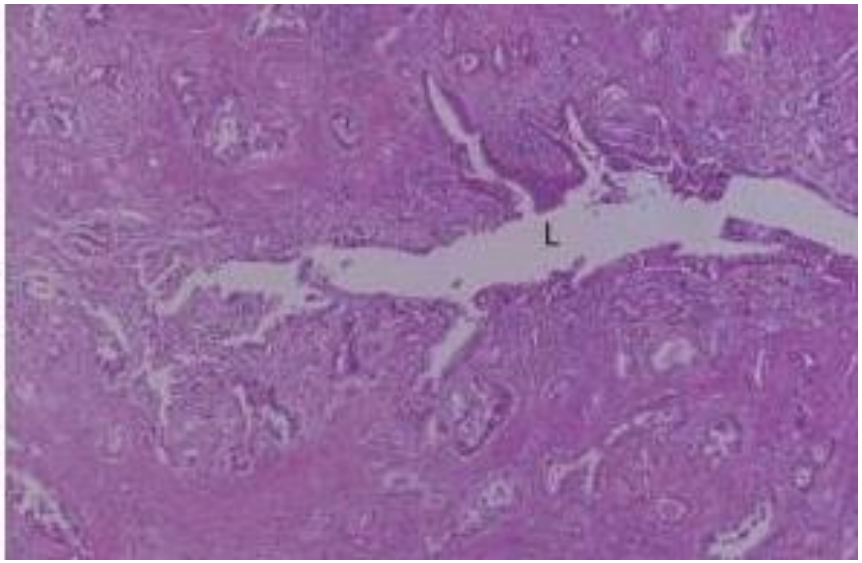


[a] See Principles of Surgery (INTRA-A)
[b] CEA and CA 19-9 are baseline tests and should not be done to confirm diagnosis.
[c] Consult with multidisciplinary team.

Biopsy & Pathology





- Most often adenocarcinoma but other rare histologies occur (mucinous, clear cell, sarcomatous)
- Typical appearance of adenocarcinoma consistent with cholangiocarcinoma. (L: bile duct lumen)
- Biopsy of her mass was an adenocarcinoma consistent with cholangiocarcinoma

Nakanuma, et al., *World Journal Hepat* 2010

Surgical resection

- She underwent an exploratory laparotomy and extended right hepatectomy with celiac and portal lymphadenectomy.

- In recent large series, only 50% of surgeries included LN dissection.

- Most common surgery was hemihepatectomy (42.1%) followed by extended hemihepatectomy (31%).

- 81% R0 resection rate in large multi-institutional series.

Jong, et al., *JCO* 2011

Surgical Pathology

- 6.5 x 6.3 x 3.8 cm, moderately differentiated adenocarcinoma
- Negative margins
- 1/1 common hepatic LNs involved and 2/2 portal lymph nodes involved
- Final diagnosis is Stage IVA (pT2a pN1c M0) intrahepatic cholangiocarcinoma.

Prognostic factors

- 449 patients analyzed in recent surgical series.
- Tumor size **NOT** associated with prognosis (mean =6.5cm)
- 5 year OS was 30-35%.
- Vascular invasion, tumor number, **positive margin and LN involvement were all associated with worse OS.**
- **Estimated 20-30% risk of LN involvement.**

Jong, et al., *JCO* 2011

Would this patient benefit from adjuvant treatment?

ORIGINAL ARTICLE

Intrahepatic Cholangiocarcinoma: expert consensus statement

Sharon M. Weber[1], Dario Ribero[2], Eileen M. O'Reilly[3], Norihiro Kokudo[4], Masaru Miyazaki[5] & Timothy M. Pawlik[6]

[1]Department of Surgery, University of Wisconsin, Madison, WI, USA, [2]Department of General Surgery and Surgical Oncology, Mauriziano 'Umberto I' Hospital, Turin, Italy, [3]Department of Medical Oncology, Memorial Sloan–Kettering Cancer Center, New York, NY, USA, [4]Hepato-Biliary-Pancreatic Surgery Division, Artificial Organ and Liver Transplantation Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan, [5]Department of Surgery, Chiba University Graduate School of Medicine, Chiba, Japan, and [6]Department of Surgery, Johns Hopkins Hospital, Baltimore, MD, USA

- No adequate prospective randomized Phase III trials for recommendations on adjuvant therapy.
- No known benefit of adjuvant therapy in margin and node negative patients but with high risk features (positive LVSI, multi-centric tumors, large tumors) should enroll on clinical trial
- Margin-positive or LN positive, systemic therapy with gemcitabine, 5FU, or chemoXRT should be considered

VOLUME 33 · NUMBER 24 · AUGUST 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

SWOG S0809: A Phase II Intergroup Trial of Adjuvant Capecitabine and Gemcitabine Followed by Radiotherapy and Concurrent Capecitabine in Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma

Edgar Ben-Josef, Katherine A. Guthrie, Anthony B. El-Khoueiry, Christopher L. Corless, Mark M. Zalupski, Andrew M. Lowy, Charles R. Thomas Jr, Steven R. Alberts, Laura A. Dawson, Kenneth C. Micetich, Melanie B. Thomas, Abby B. Siegel, and Charles D. Blanke

- No direct prospective Phase II/III data to guide adjuvant treatment.
- Our institution extrapolates SWOG 0809 to guide treatment of ICCs.
- N=79 patients, 2 year survival 65% and median OS 35 months (Well tolerated and better than historical controls)

SWOG S0809

- pT2-T4 or N+ or positive margin resected extrahepatic CC or gallbladder carcinoma
- 45 Gy to LNs in 25 fractions (retropancreaticoduodenal, celiac, and portal)
- 54 – 59.4 Gy delivered with 3D planning (28 fractions)
- 52.5 - 55 Gy delivered via IMRT (25 fractions)

Surgery → **4c gemcitabine and capecitabine** → **Concurrent radiation And capecitabine**

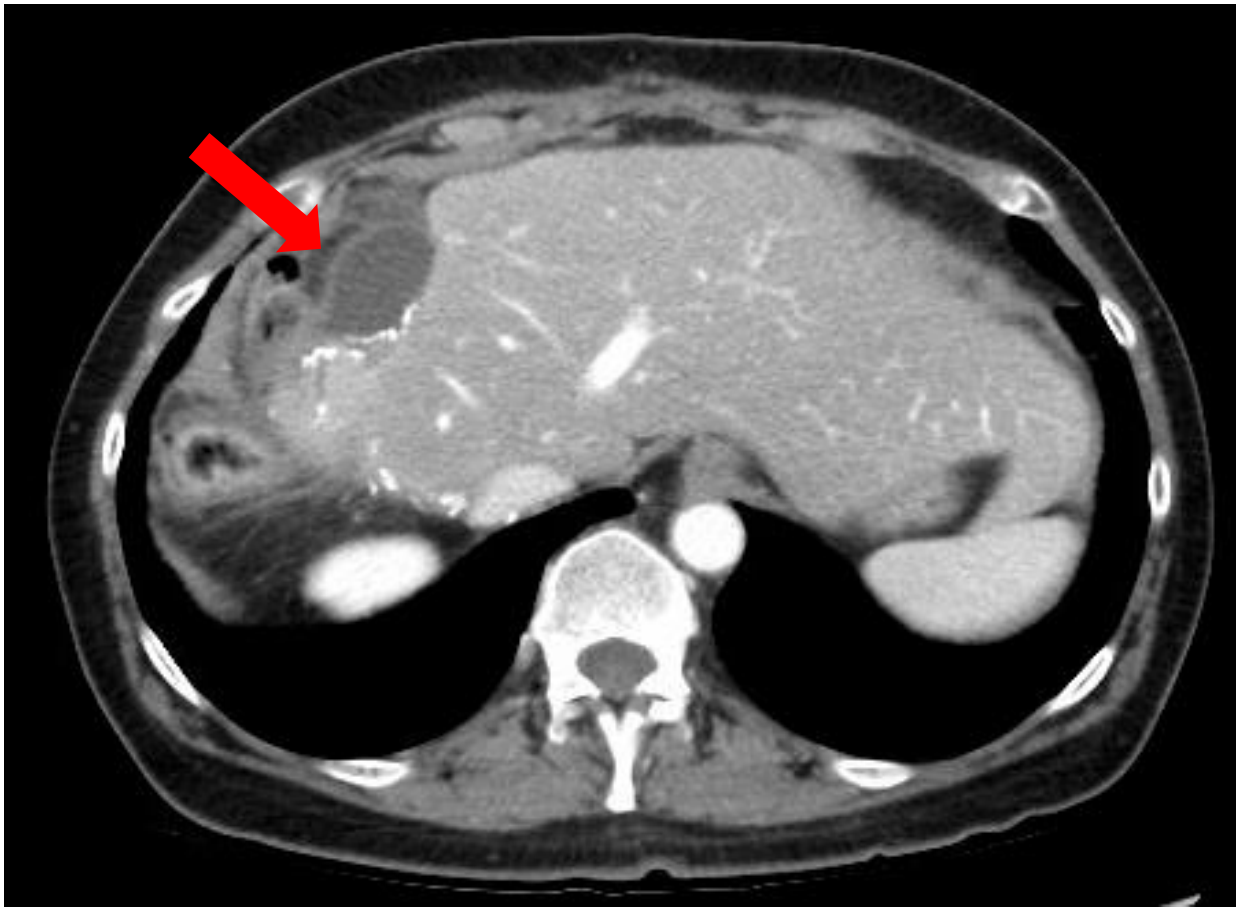
Ben-Josef, *JCO*, 2016

Meta-analysis of Adjuvant Therapy

- Recent meta-analysis of 20 studies with 6,712 patients were analyzed. Gall bladder and biliary tumors were included.
- No benefit of adjuvant treatment to unselected patients (OR=0.74 p=0.06).
- Lymph node positive disease (OR 0.49, p=0.004) or R1 resection (OR 0.36 p=0.002) benefit from AT.
- Chemotherapy or chemoradiation has a benefit over RT alone (p=0.02)

Horgan, et. Al, *JCO*, 2012

Post-Surgical CT



No evidence of disease. Potential hematoma at resection margin.

Adjuvant Chemotherapy

As a result of LN involvement, she underwent 4 cycles of adjuvant gemcitabine and capecitabine.

She tolerated chemotherapy well and is now presenting to the Radiation Oncology Clinic to discuss the need for radiation.

History Continued

PMH/PSH: Hypothyroidism, Osteopenia, Laparoscopy and Partial Hepatectomy

Medications: Capecitabine, Gemcitabine, Colace, Levothyroxine

Allergies: Hydromorphone, Naproxen

Family History: Her mother had a history of malignancy not known by patient. She reports she had an aunt with questionable bone cancer.

Social History: She is a nonsmoker and reports social alcohol use in the past. She is married with 4 children.

ROS: Fatigue throughout the past few months. She is down 30-40 lbs over a 6-7 month period. She has mild right upper quadrant discomfort. She denies nausea/vomiting, melena, hematochezia, fevers/chills, chest pain, shortness of breath, or other changes.

NCCN Guidelines Version 2.2016
Intrahepatic Cholangiocarcinoma

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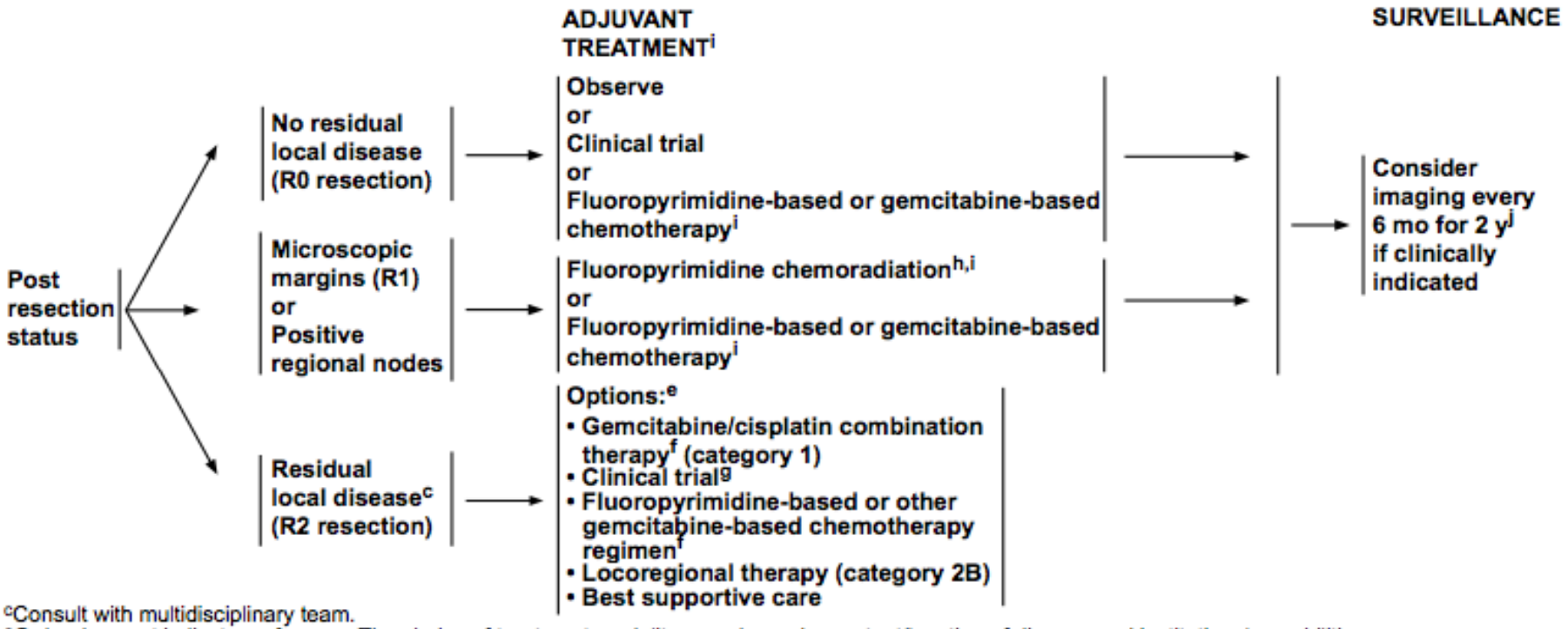

[c]Consult with multidisciplinary team.

[e]Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilities.

[f]A phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic billiary tract cancer. (Valle JW, Wasan HS, Palmer DD, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Eng J Med 2010;362:1273-1281.) Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/oxaliplatin, gemcitabine/capecitabine, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin, and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting. (Hezel AF and Zhu AX. Systemic therapy for biliary tract cancers. Oncologist 2008;13:415-423).

[g]Systemic or intra-arterial chemotherapy may be used in a clinical trial or at experienced centers.

[h]There are limited clinical trial data to define a standard regimen or definitive benefit. Participation in clinical trials is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11:941-954)

[i]Adjuvant chemotherapy or chemoradiation has been associated with survival benefit, in patients with biliary tract cancers, especially in patients with lymph node-positive disease. (Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systemic review and meta-analysis. J Clin Oncol 2012;30:1934-1940). However, this meta-analysis included only a few patients with intrahepatic cholangiocarcinoma. There are no randomized phase III clinical trial data to support a standard adjuvant regimen. Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/cisplatin, gemcitabine/oxaliplatin, gemcitabine/capecitabine, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin, and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting. (Hezel AF and Zhu AX. Systemic therapy for biliary tract cancers.Oncologist 2008;13:415-423).

[j]There are no data to support aggressive surveillance. There should be a patient/physician discussion regarding appropriate follow-up schedules/imaging.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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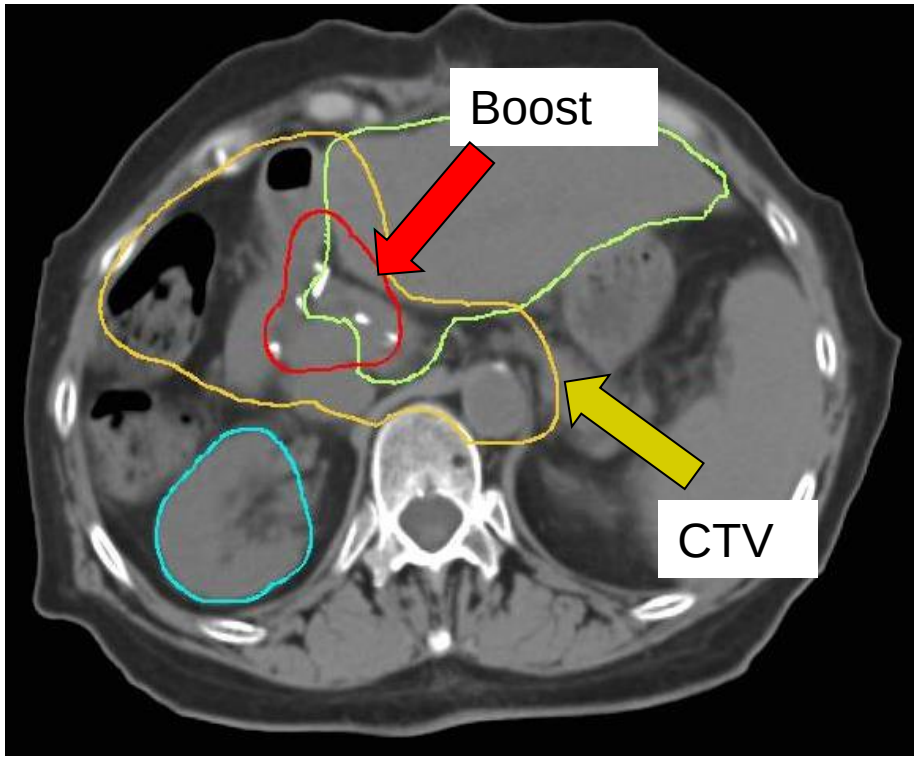
Radiation Treatment Planning

- LN Basin and Surgical Tumor Bed: CTV
- LN Basin:
  - pN0: pericholedochal lymph nodes only with negative lymph node dissection
  - pN+: porta hepatis, hepatic artery, pancreaticoduodenal, celiac, and SMA

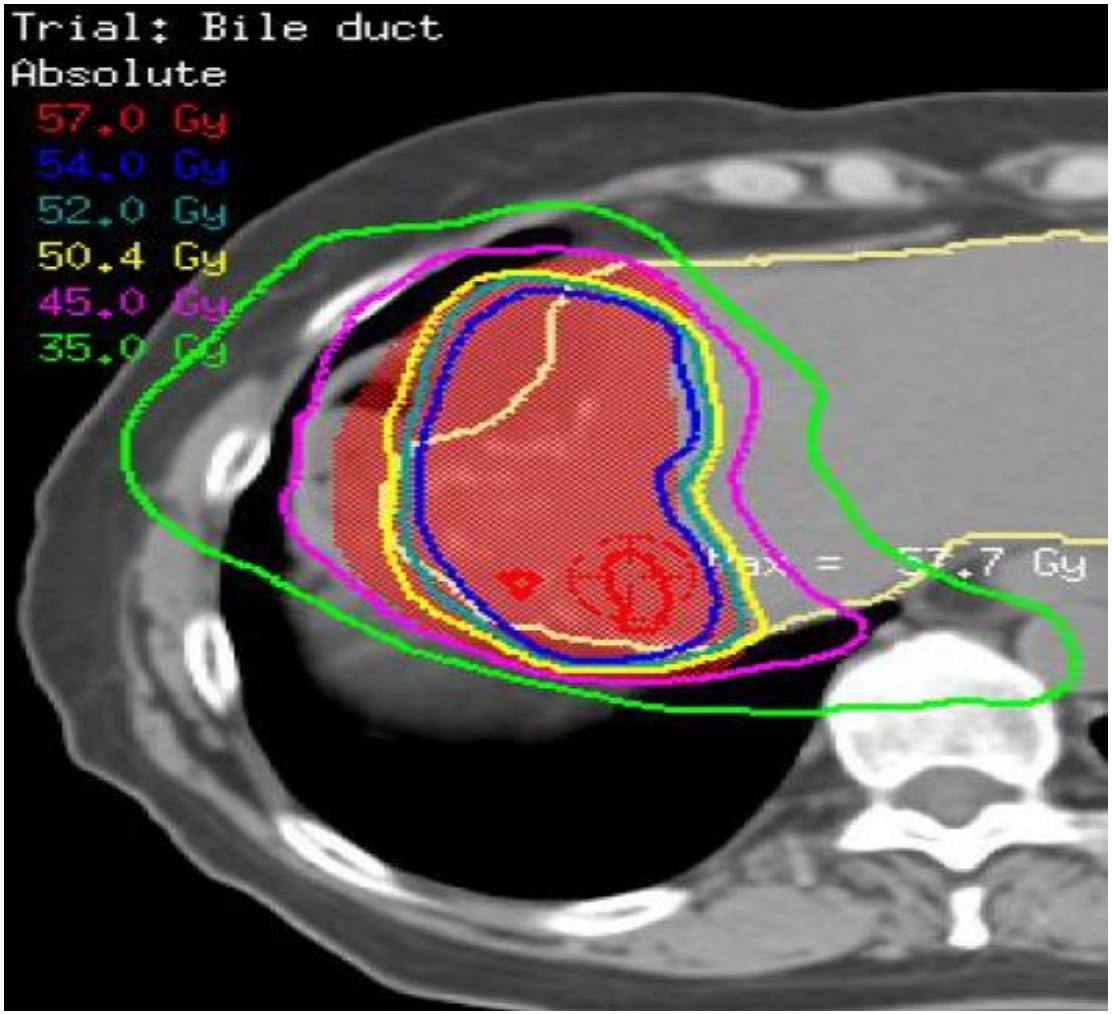


- CTV to 45 Gy at 1.8 Gy/fx
- Boost 5-15 Gy to surgical bed
- Concurrent Capecitabine

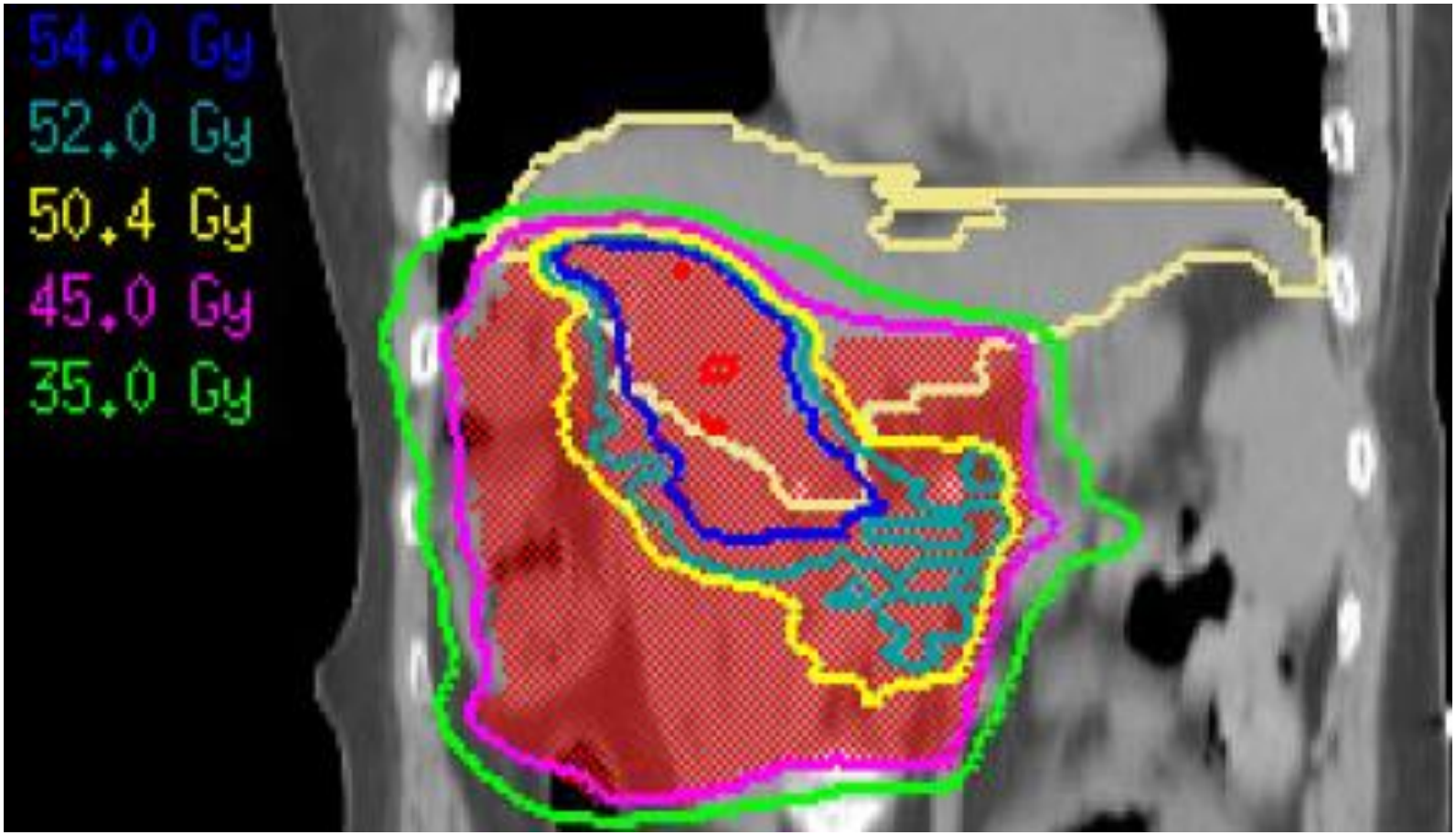
Simulation

- Arms up with body-fix
- 2 mm slices
- Free breathing CT and 4-D CT to assess motion
- Contrast optional to help delineate vessels depending on coverage needed

Radiation Treatment Plan



Radiation Treatment Plan



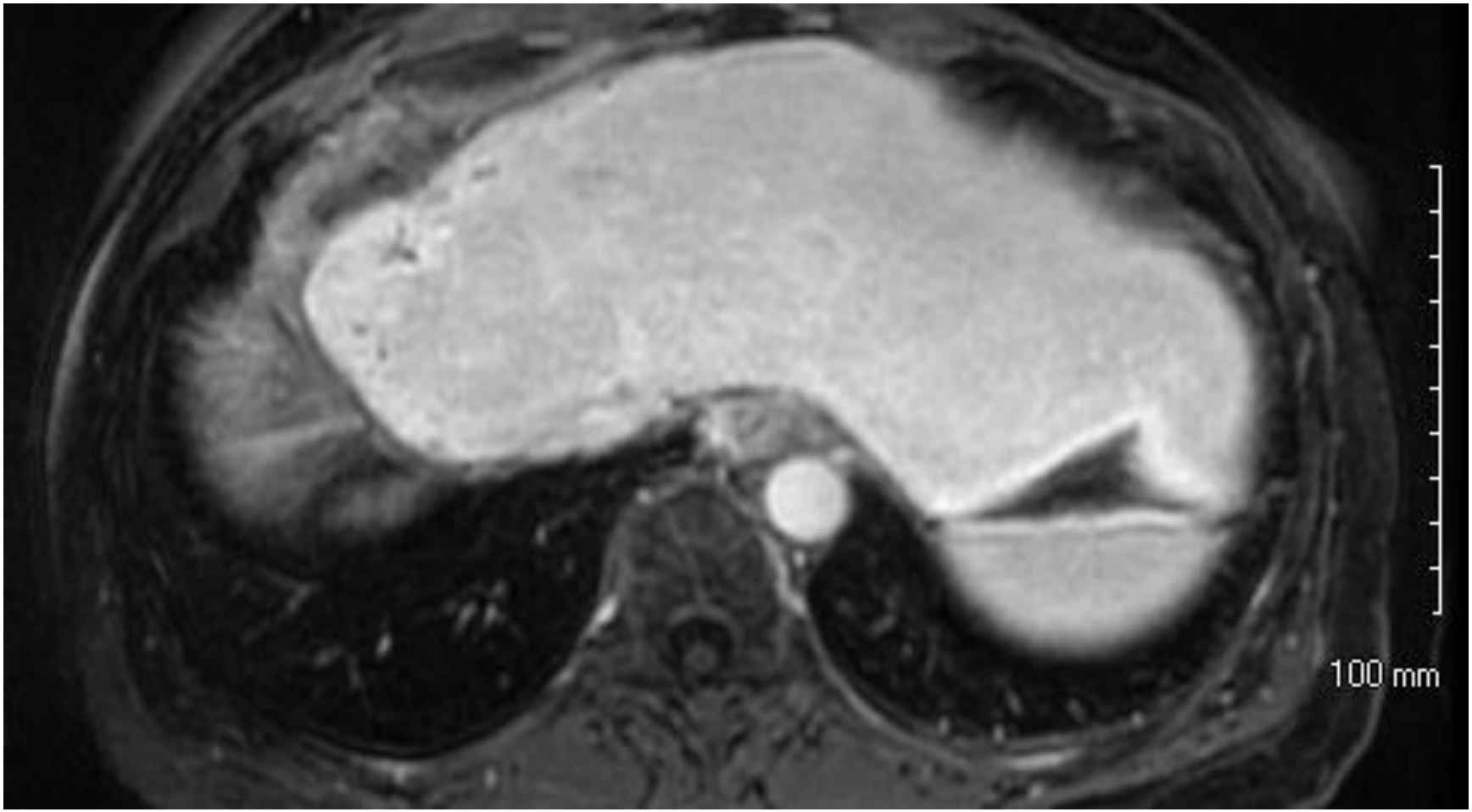
Dose Constraints

Organ	Constraint
SpinalCord	V45 Gy < 0.1 cc
SpinalCord_PRV_05	V50 Gy < 0.1 cc
CaudaEquina	V37.5 Gy < 0.1 cc
CaudaEquina_PRV_05	V50 Gy < 0.1 cc
Heart	V40 Gy < 60%
	V45 Gy <40%
	V60 Gy < 20%
	Dmean < 30 Gy
Esophagus	V60 Gy ≤ 20%
	V50 Gy ≤ 30%
	Dmean ≤ 30 Gy
	V105% RxPTV < 0.1 cc
Esophagus_PRV_05	V60 Gy ≤ 0.1 cc
Stomach	V54 Gy ≤ 0.1 cc
BowelBag	V55 Gy ≤ 0.1 cc
Skin	V50 Gy ≤ 0.1 cc
Liver-PTV	Mean<25
Kidney	Mean<15
	V20<30%

Follow-up After Treatment

- Physical exam and imaging every 6 months for the first two years

Follow-up



No evidence of disease 10 months after treatment

Unresectable Disease

VOLUME 34 · NUMBER 3 · JANUARY 20, 2016

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Ablative Radiotherapy Doses Lead to a Substantial Prolongation of Survival in Patients With Inoperable Intrahepatic Cholangiocarcinoma: A Retrospective Dose Response Analysis

Randa Tao, Sunil Krishnan, Priya R. Bhosale, Milind M. Javle, Thomas A. Aloia, Rachna T. Shroff, Ahmed O. Kaseb, Andrew J. Bishop, Cameron W. Swanick, Eugene J. Koay, Howard D. Thames, Theodore S. Hong, Prajnan Das, and Christopher H. Crane

- In unresectable intrahepatic cholangiocarcinoma achieving BED >80.5 significant benefit in local control and overall survival (3 year OS 73% vs. 38%)
- Historical median survival for unresectable cholangiocarcinoma <1 year
- Common regimen: 67.5 Gy in 15 fractions or 75 Gy in 25 fractions
- Being further tested in clinical trials

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

- In locally advanced or metastatic biliary tract cancers
- Phase 2 study cisplatin+gemcitabine vs. gemcitabine
- N=410 patients, median follow-up 8.2 months:
- 11.7 vs. 8.1 median OS ($p<0.001$)
- Median PFS 8.0 vs. 5.0 months ($p<0.001$)
- Similar adverse events (more neutropenia in cisplatin-gem group)

Summary

- Intrahepatic CC Rare
- Anywhere from 30-90% are resectable
- Limited prospective data
- Potential indications for adjuvant therapy include R1 resections or positive lymph nodes
- Extrapolation of SWOG0809 for post-operative treatment
- Hypofractionation (3-4.5 Gy/fx) for unresectable disease