# ARRO Case

# Unresectable Intrahepatic Cholangiocarcinoma

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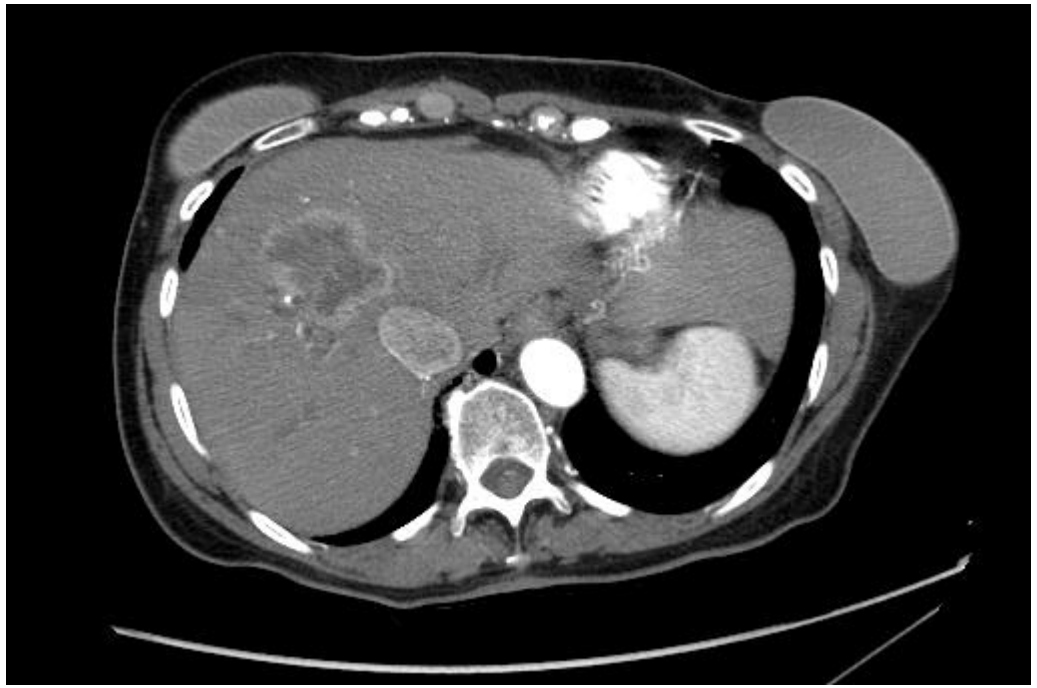
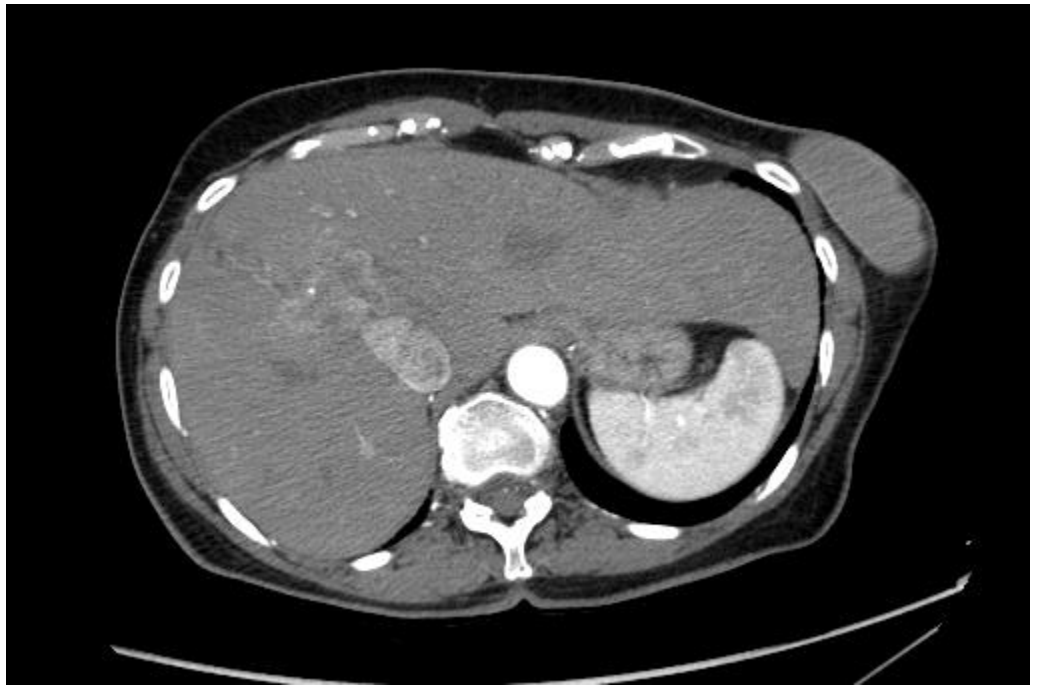
# Patient #1 History

- 79-year-old female with h/o bilateral breast cancer, undergoing surveillance PET/CT when an incidental hypermetabolic central liver mass was identified.
- Biopsy revealed CK7+CK20-, ER/PR- adenocarcinoma concerning for cholangiocarcinoma

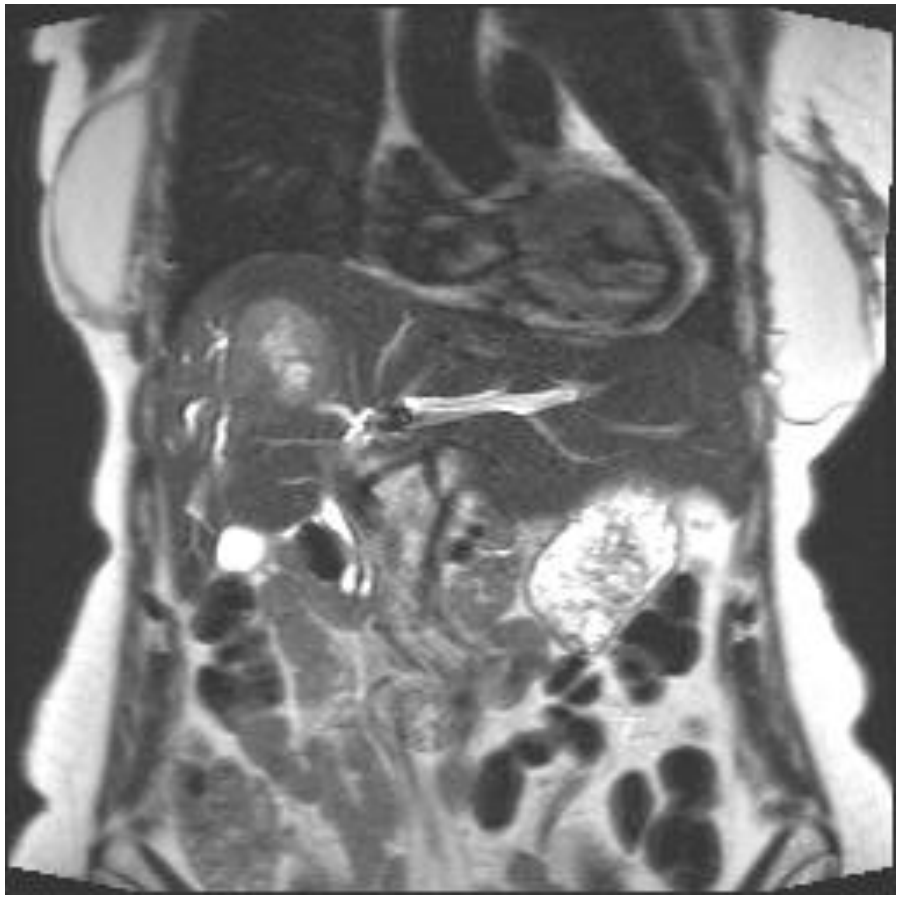
# Initial CT Abdomen

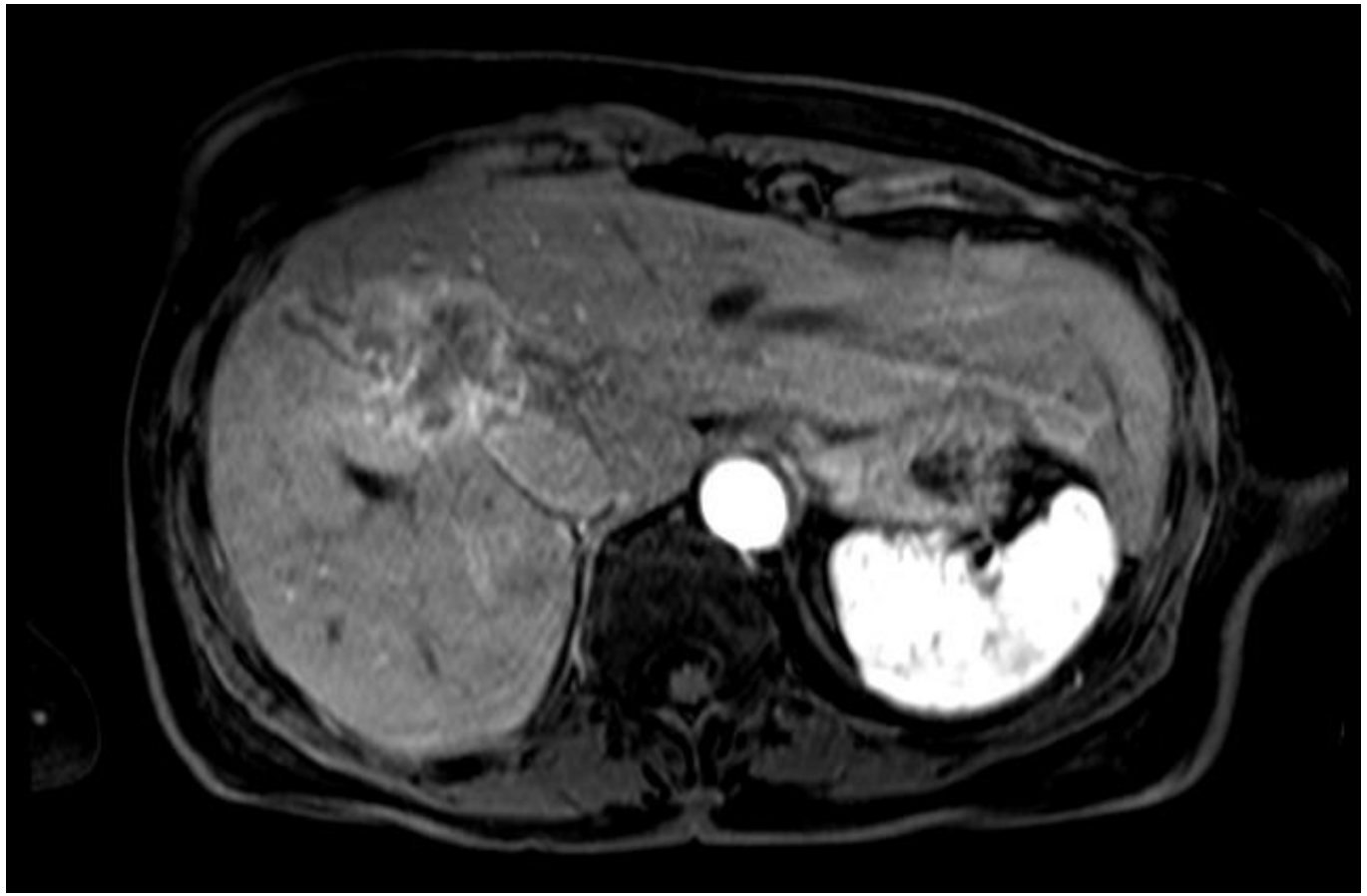




Cholangiocarcinoma centrally located in the plane of the middle hepatic vein with extension into the right and left liver, extension to the hilum of the liver. Anatomy of the biliary tree is poorly assess, involvement of the bifurcation is suspected. The tumor is inseparable from the portal bifurcation without definite involvement of the left portal vein. Left hepatic artery is not involved.

# Initial MRI Abdomen



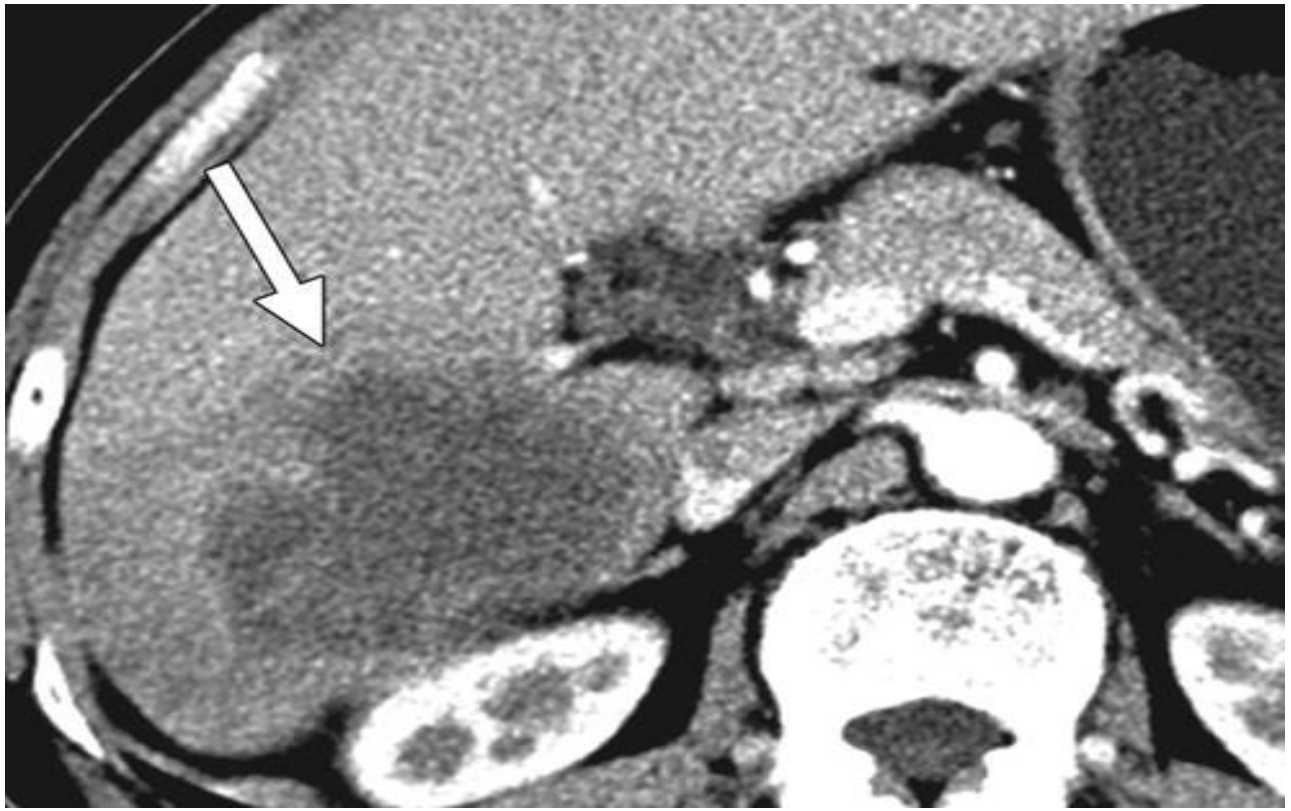


Lesion in segment 4A of liver, measures 4.9 x 4 cm
which previously measured 4.2 x 3.6 cm

# Imaging for Cholangiocarcinoma

- **Multiphase contrast-enhanced CT (arterial, portal venous and delayed phase):** Assists in detection of biliary ductal dilatation, vascular encasement and nodal involvement.
  - **HCC** more likely to demonstrate arterial enhancement than **Cholangio**.
  - **Cholangio** more often demonstrates fibrous stroma on delayed phase
- **Non-contrast CT phases:** can differentiate intraductal biliary stones causing dilatation vs enhancing intraductal mass.
- **MRI (inc. MRCP, T1 and T2 pulse, DWI and multiphase contrast-enhancement):** Can more accurately detect spread of tumor along bile ducts.
  - Degree of diffusion restriction on DWI is prognostic (Lee et al, 2016)

# 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

# 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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# NCCN Guidelines Version 2.2016
# Intrahepatic Cholangiocarcinoma

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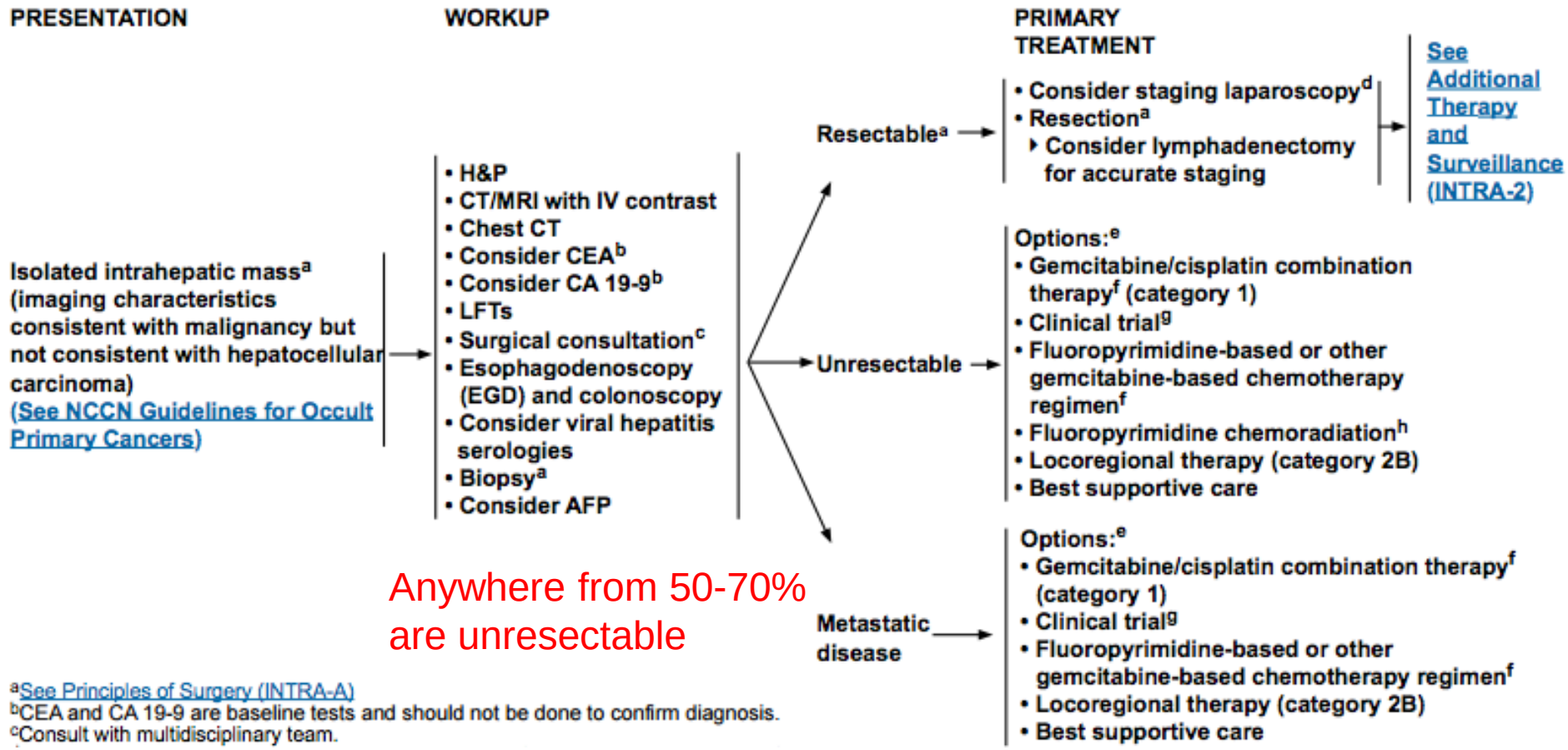
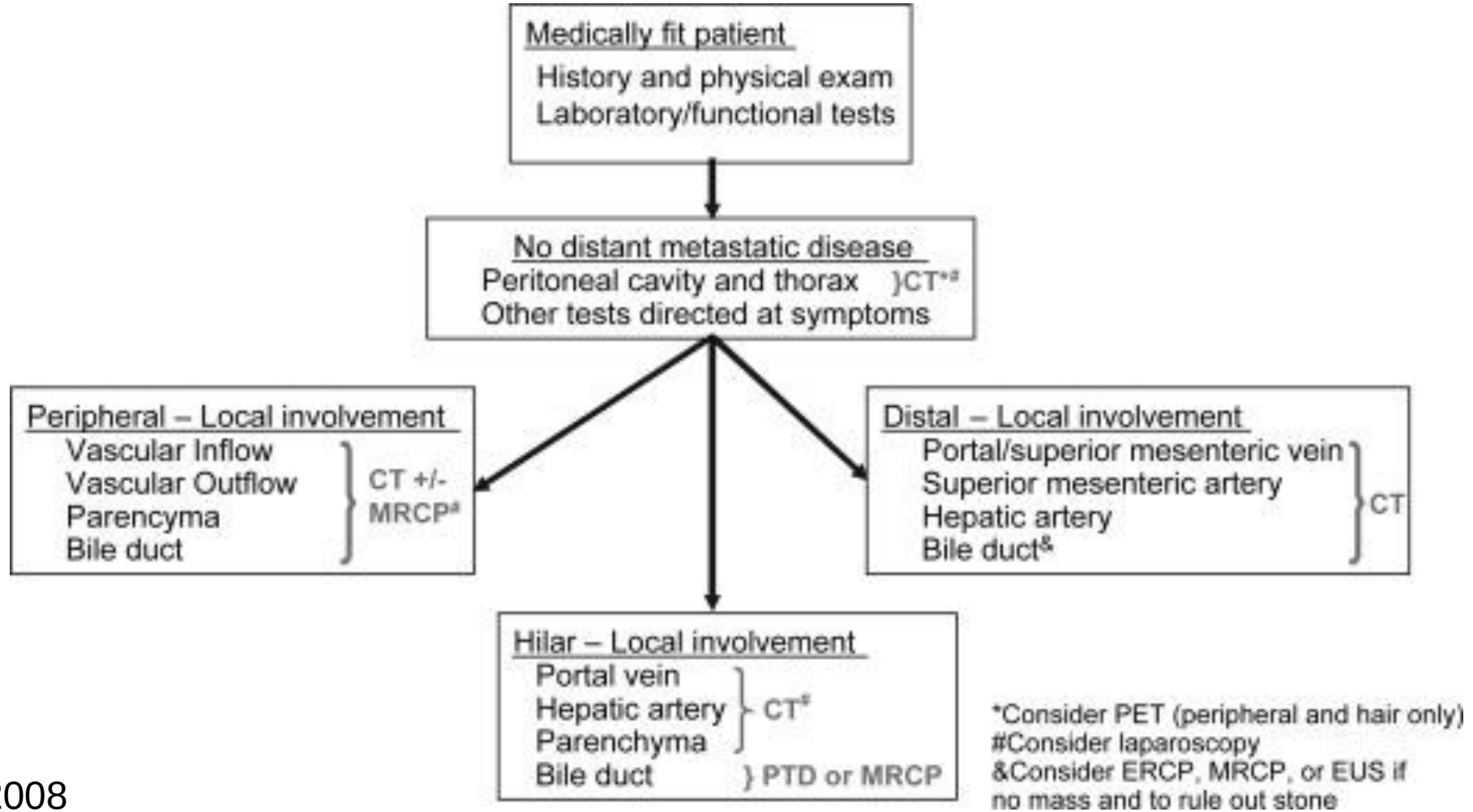



Anywhere from 50-70% are unresectable

[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.

# Resectability Determination

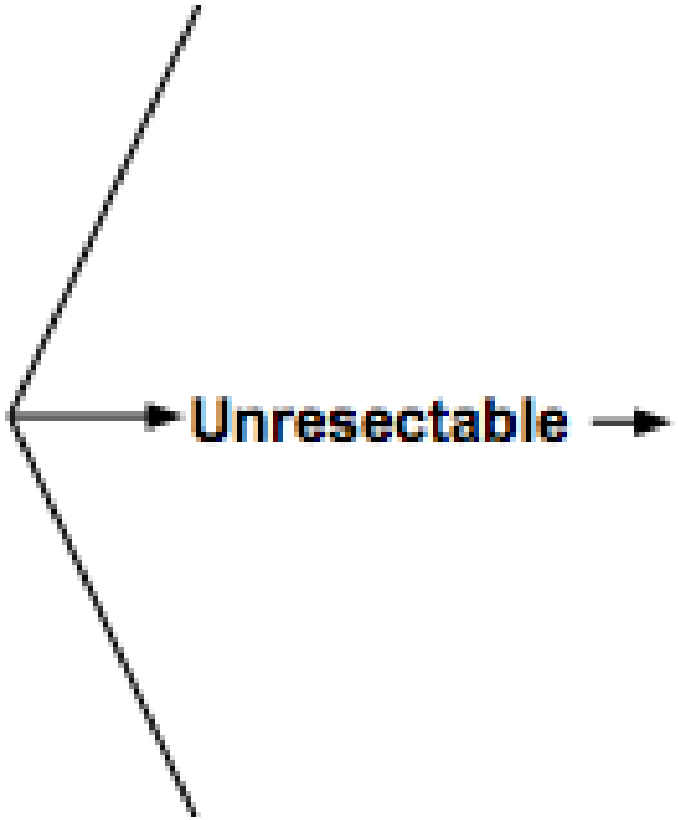



Schulick et al; 2008

# Surgical resection

- Patient was deemed potentially resectable and received chemotherapy consisting of gemcitabine and cisplatin.
- This was followed by re-imaging demonstrating stable disease, and an exploratory laparotomy with liver wedge biopsy.
- Resection was aborted due to intraoperative findings of satellite lesions.
- Intraoperative biopsy of satellite lesions confirmed cholangiocarcinoma

# Treatment Options



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

# Principles of Local Therapy (NCCN)

- **Ablation (radiofrequency, cryoablation, percutaneous alcohol injection, microwave):**
  - Tumors must be amenable to ablation (accessible, not near major vessels, vile ducts, diaphragm (dome of liver)
  - May be curative only in tumors <=3cm (Peng et al, 2012)
  - Probably not useful in tumors >5cm (Feng et al, 2012, Chen et al 2006, Yamakado et al 2008)
  - Should not be combine with adjuvant sorafenib (STORM trial; Bruix et al Lancet Onc 2015)
- **Arterial Directed Therapies (Transarterial embolization, transarterial chemoembolization w/ or w/o drug-eluting beads, Radioembolization with Y-90):**
  - Must have arterial blood supply that can be isolated without excessive normal tissue treatment
  - Bilirubin <3mg/dL (or 2mg/dL with Y-90) (Salem et al 2010, Ramsey et al 2002)
  - Contraindicated with main portal vein thrombosis and Child-Pugh Class C disease
  - Soragneib may be appropriate once bilirubin returns to baseline (Pawlik et al JCO 2011)

# Principles of Local Therapy (NCCN)

- **External Beam Radiation Therapy:**
  - Category 2B for those with unresectable disease OR medically inoperable
  - All tumors generally eligible for some form of radiation, regardless of size or location
  - SBRT may be alternative to ablation/embolization techniques in patients with 1-3 small tumors without unadressed extrahepatic disease (Hoffe et al 2010; Wahl et al 2016)
  - Hypofractionated dose-escalated radiation with either photons (Tao et al 2016; Yamashita et al 2017) or protons(Hong et al 2016; Bush et al 2016) may be appropriate

Jong, et al., *JCO* 2011

# Tao et al 2016

- Retrospective analysis of 79 consecutive patients treated at MDACC with ICC between 2002-2014.
- RT doses between 35Gy and 100Gy (median BED 80.5Gy)
- RT dose was single most important factor in OS; BED >80.5Gy resulted in 3-year OS of 73% vs 38% for <80.5Gy (p=0.017).
- No significant treatment-related toxicities

# Yamashita et al 2016

- Retrospective review of 362 patients with ICC who underwent either chemotherapy, radiation or resection as definitive treatment at MDACC between 2006-2015.
- Rates of non-liver failure related deaths were similar between resection (70%) and radiation (59%) and both higher than chemotherapy (28%)
- In the modern era, disease-free survival for radiation was 37% at 3 years.

# Hong et al 2016

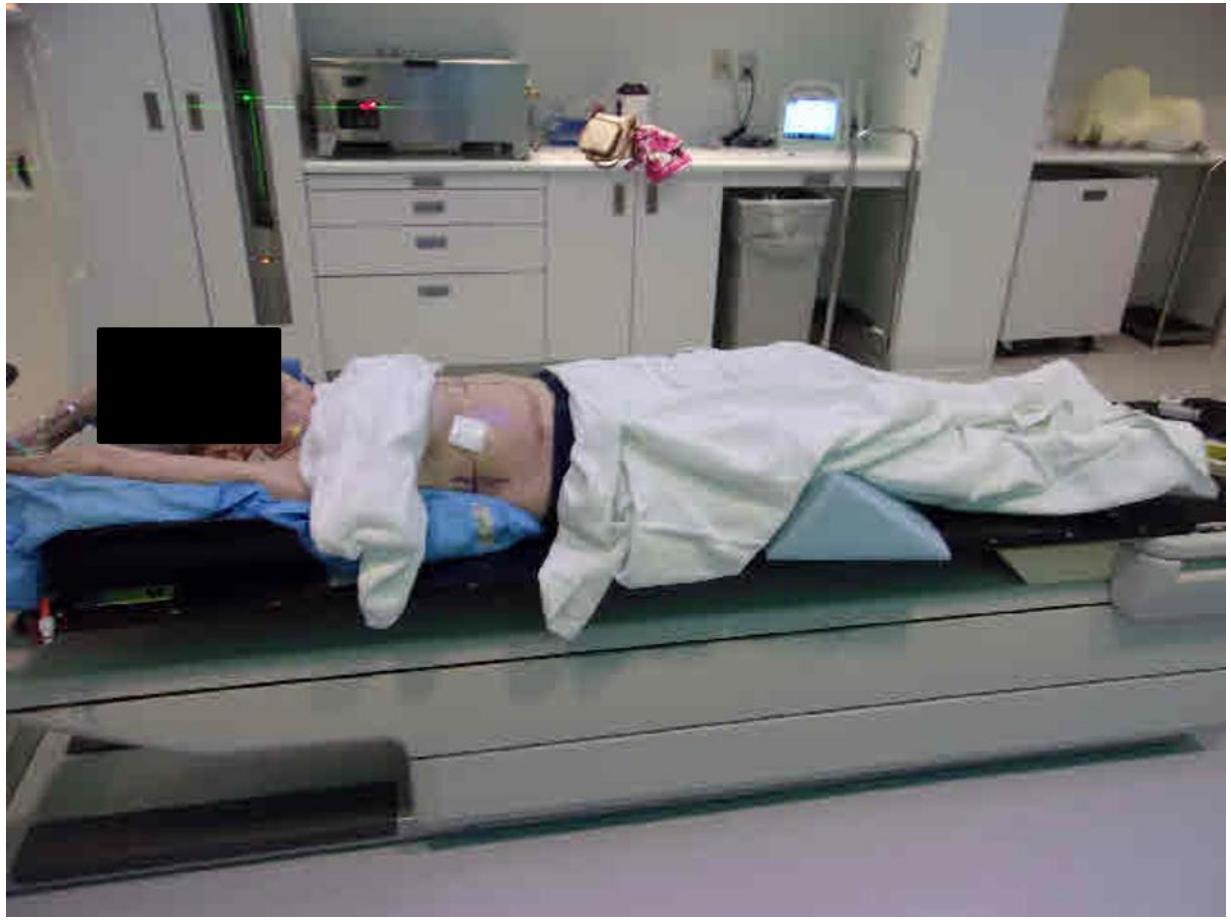
- Multi-institutional phase II study of 92 patients with biopsy-confirmed unresectable HCC or ICC
- Patients received 67.5Gy in 15 fractions using proton therapy
- 61.5% of ICC patients had prior therapy; Child-Pugh included A (79.5%) and B (15.7%)
- LC rate at 2 years was 94.1% for ICC and OS was 46.5% for ICC

# Can we dose escalate?

- How far is tumor from gastrointestinal mucosa? Would a 5mm expansion on gastrointestinal mucose still allow you to cover >50% of the tumor in the high dose region?
- How big is tumor and how is patient's overall liver function, and therefore how much normal liver will you cover with high dose? Remember, a small volume of normal liver can tolerate a high dose, but a high volume of normal liver cannot tolerate even a low dose
  - 700cc <24Gy; mean dose <24Gy for CP class A.
  - 700cc <20Gy; mean dose <20Gy for CP class B

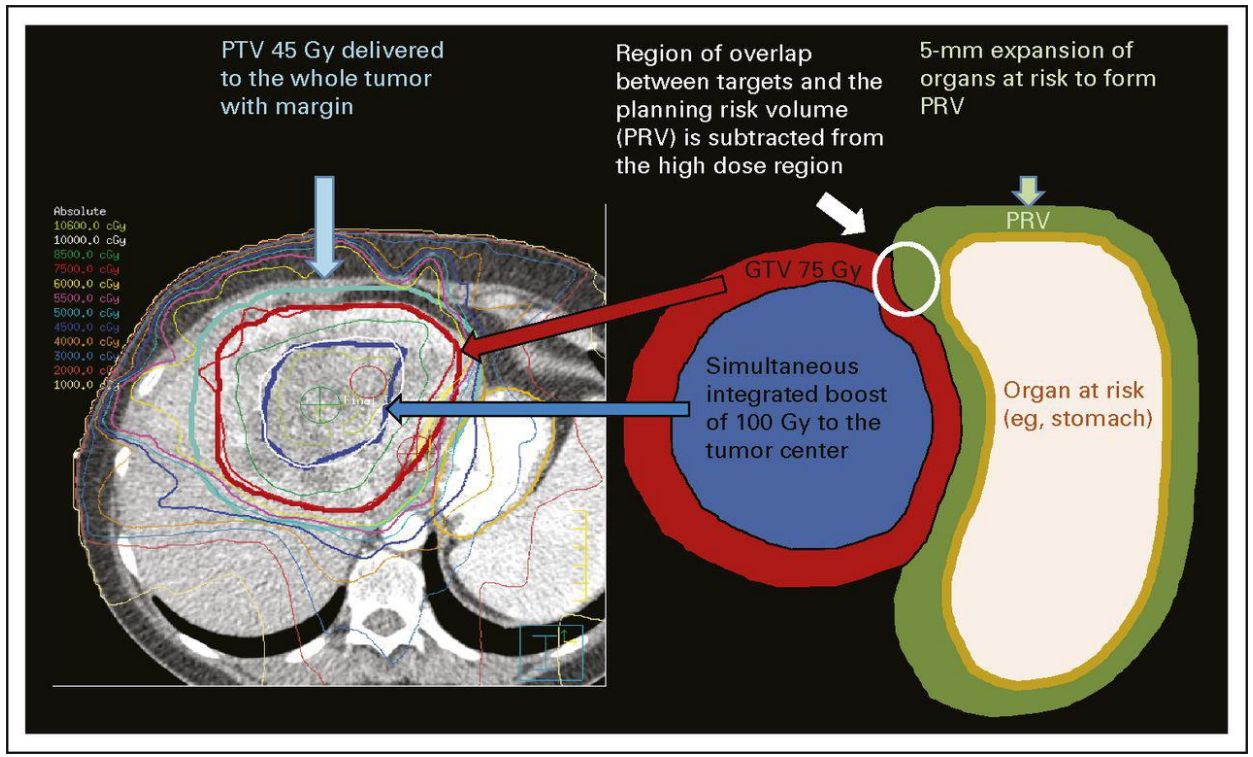
# Radiation Simulation

- Fiducials placed for daily imaging
- Upper Vaclock with arms overhead
- NPO 3 hours prior to simulation and treatment (to standardize duodenal and gastric filling)
- Multi-phase contrast-enhanced 4DCT simulation with 2-3mm slices; Free breathing scan and 3-5 Breath hold scans during contrast administration



# Contouring

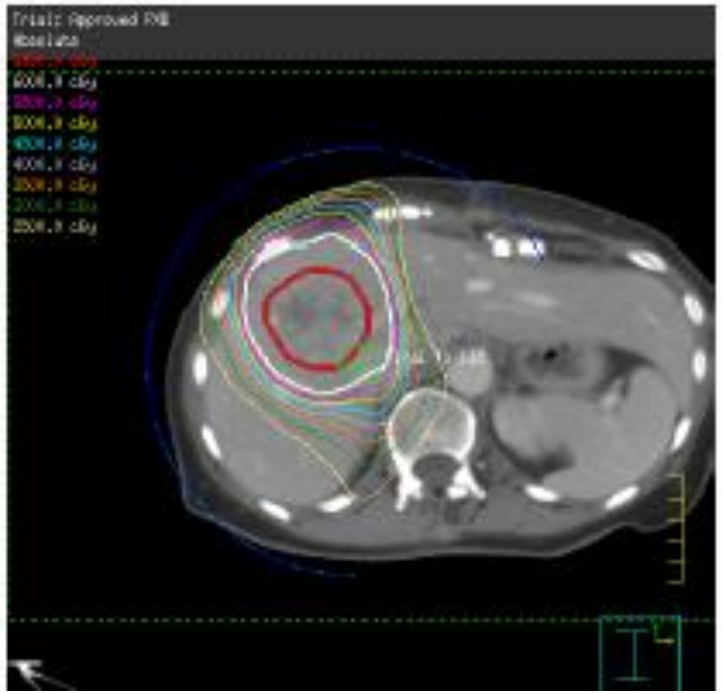
- Contour both target and normal structures on EACH breath hold scan; As you flip through scans, add but do NOT subtract from your volume. The goal is to cover everywhere the tumor or normal structures might be.
- If dose escalating, will contour avoidance structure (PRV) subtracted from high dose region (Right).

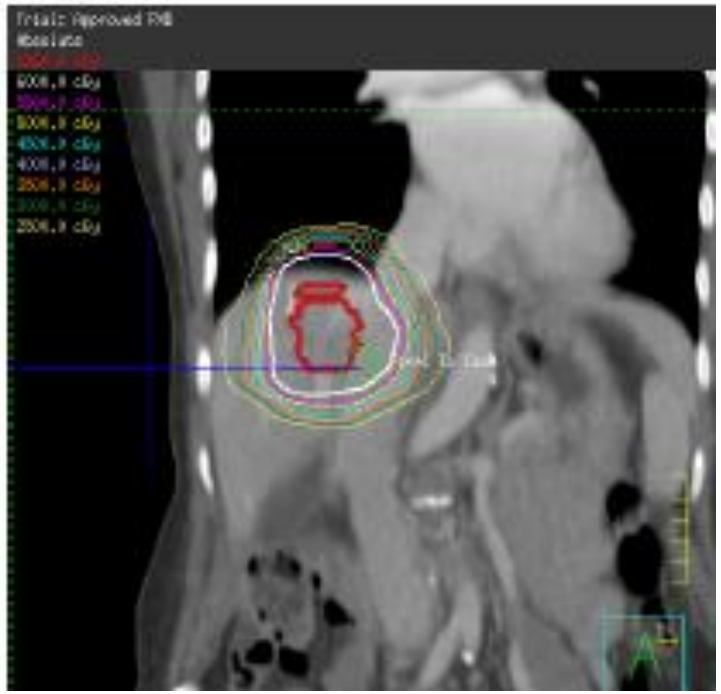



Tao et al; 2016

# Treatment Delivery

- Delivered 60Gy in 15 fractions using IMRT with 6-mV photons with daily kV (with fiducials) or daily in room CT imaging if available (without fiducials)
- Monitor labs and LFT’s weekly





# Dose Constraints

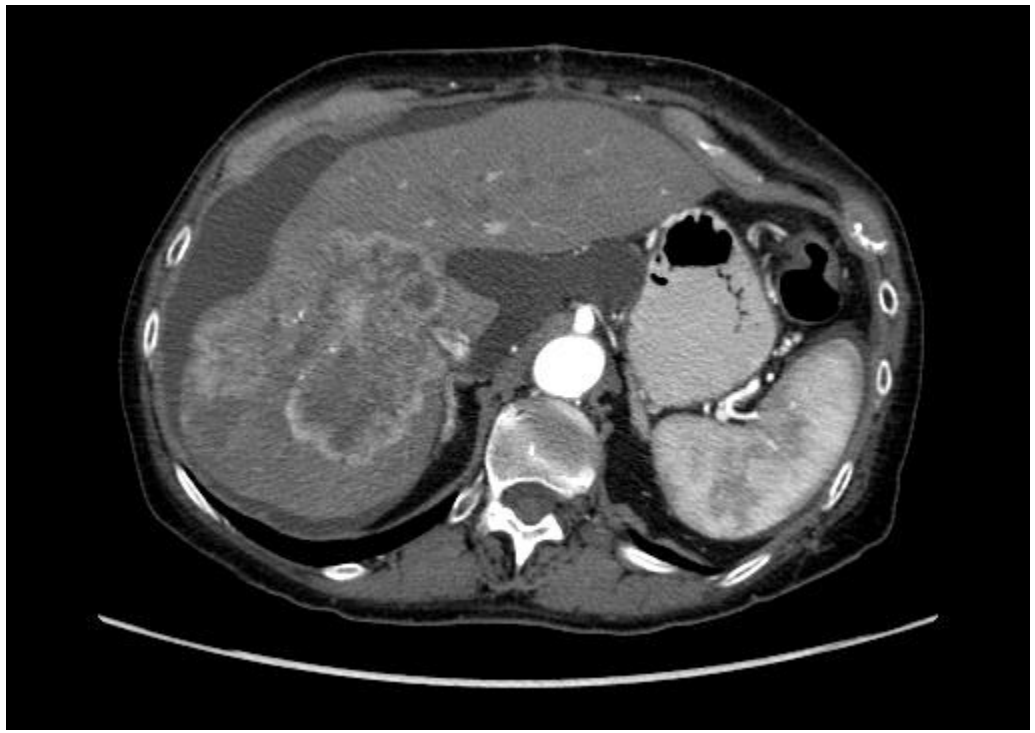
| Organ | Constraint |
|---|---|
| SpinalCord | Dmax < 30 Gy; Dmax < 45Gy |
| Heart | V40 Gy < 10% |
| Liver-GTV | 700cc <24 Gy; Mean <24 Gy |
| Kidneys | V20 < 33% for each |
| Stomach | Dmax < 45 Gy |
| Duodenum | Dmax < 45 Gy |
| Esophagus | Dmax < 45 Gy |
| Common/ Main Bile duct | Dmax < 70Gy |
| Chest Wall | V40 < 150cc |

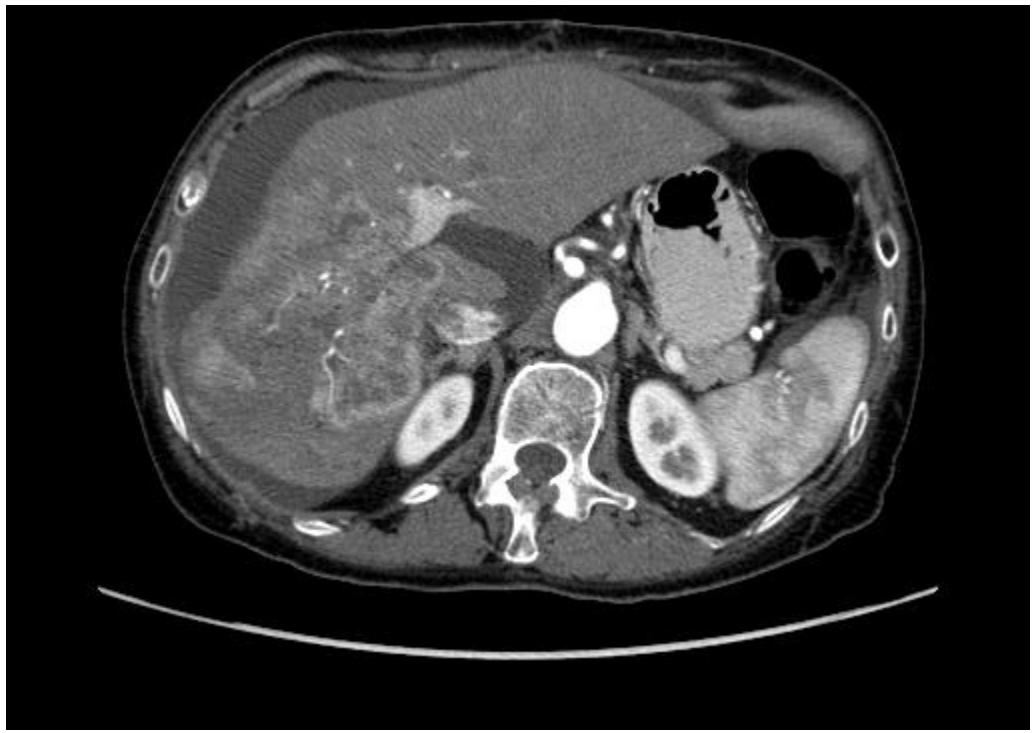
# Follow-up After Treatment

- Physical exam and imaging every 3-6 months for the first two years
- Patient is currently 3 months out from treatment and doing well

# Patient #2

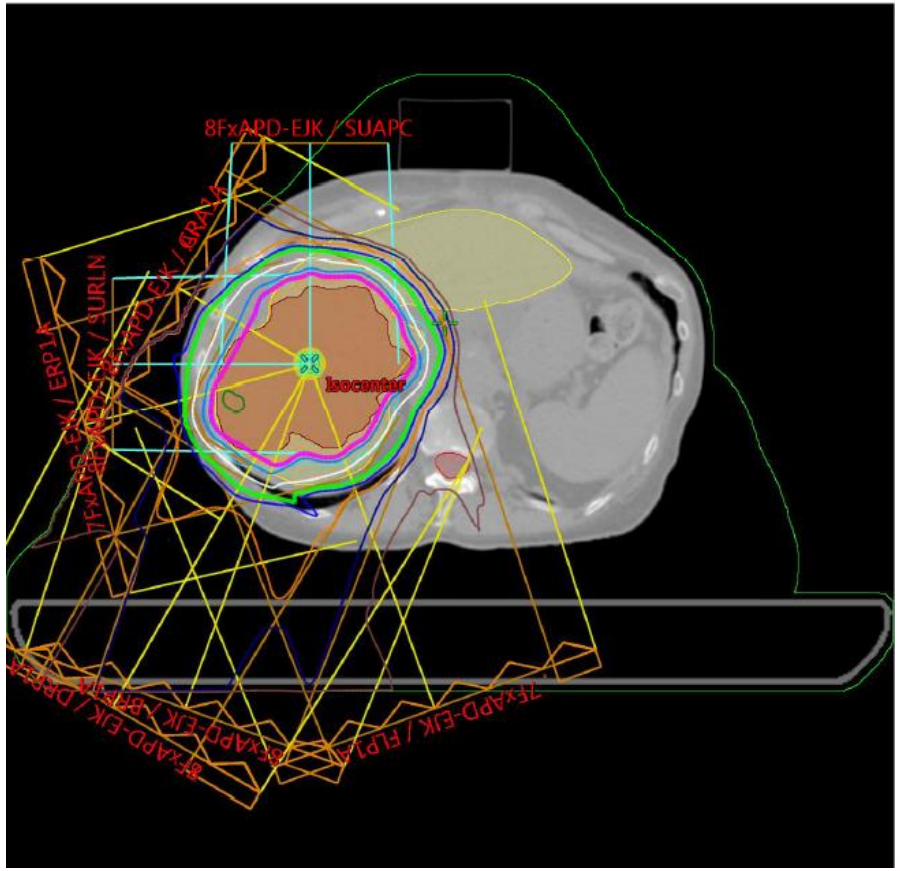
- T2N2M0 high grade intrahepatic cholangiocarcinoma measuring >10cm with invasion of hepatic and portal vein

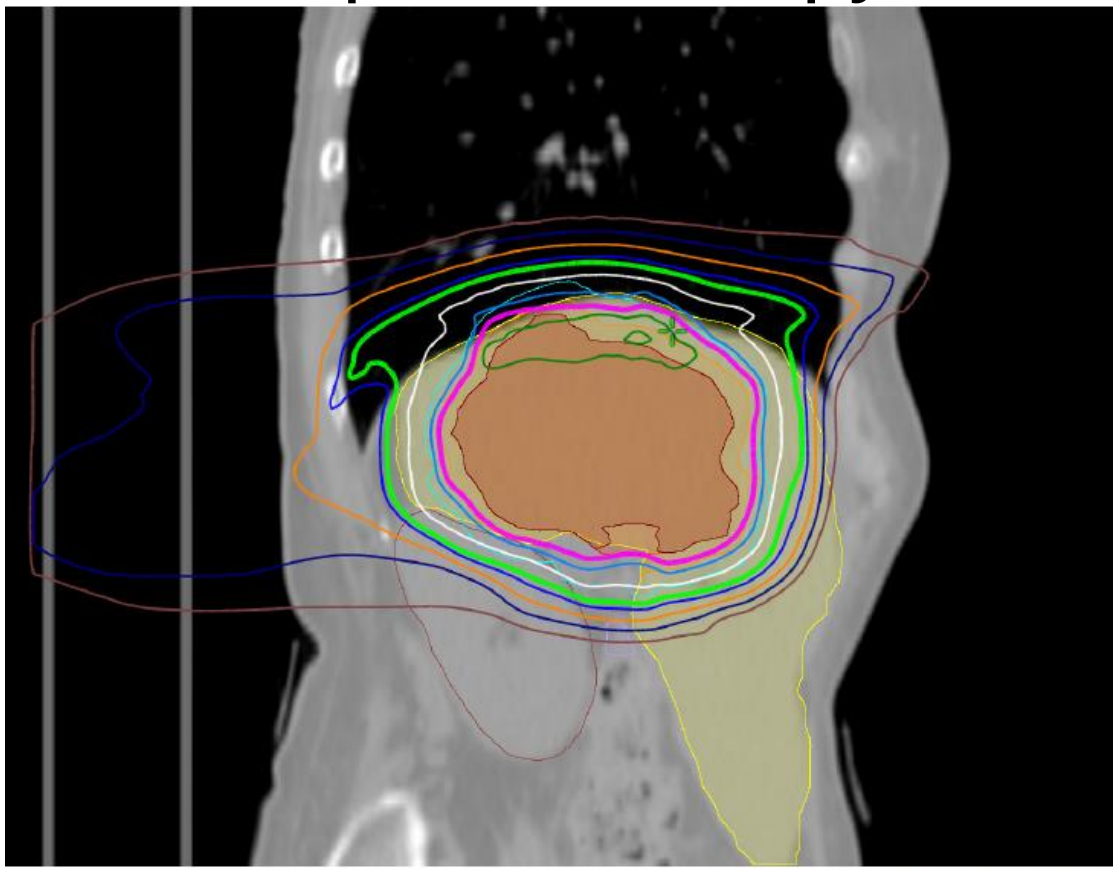




# Radiation Treatment

- 67.5Gy in 15 fractions delivered with proton therapy



# Follow up Imaging

- Large necrotic tumor replacing previous solid tumor
- Interval development of new liver abscesses drained with biliary catheter