ARRO Case
Resected Intrahepatic Cholangiocarcinoma

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

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 2\textsuperscript{nd} most common primary hepatic malignancy following HCC

Shaib, et al. Gastroenterology, 2005
Location of Cholangiocarcinoma

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

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

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Anatomic Stage/Prognostic Groups</th>
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</thead>
<tbody>
<tr>
<td>TX</td>
<td>Stage 0</td>
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<tr>
<td>T0</td>
<td>Stage I</td>
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<tr>
<td>T1</td>
<td>Stage II</td>
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<td>T2a</td>
<td>Stage III</td>
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<tr>
<td>T2b</td>
<td>Stage IVA</td>
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**Histologic Grade (G)**
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated
- G4: Undifferentiated

**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
Anywhere from 30-90% are resectable
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 = 6.5 cm)
- 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?
• 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
• 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
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.
Intrahepatic Cholangiocarcinoma

ADJUVANT TREATMENT

No residual local disease (R0 resection)
- Observe
- or Clinical trial
- or Fluoropyrimidine-based or gemcitabine-based chemotherapy

Microscopic margins (R1) or Positive regional nodes
- Fluoropyrimidine chemoradiation
- or Fluoropyrimidine-based or gemcitabine-based chemotherapy

Residual local disease (R2 resection)
- Options:
  - Gemcitabine/cisplatin combination therapy (category 1)
  - Clinical trial
  - Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen
  - Locoregional therapy (category 2B)
  - Best supportive care

SURVEILLANCE

Consider imaging every 6 mo for 2 yrs if clinically indicated

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.
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

<table>
<thead>
<tr>
<th>Organ</th>
<th>Constraint</th>
</tr>
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<tbody>
<tr>
<td>SpinalCord</td>
<td>V45 Gy &lt; 0.1 cc</td>
</tr>
<tr>
<td>SpinalCord_PRV_05</td>
<td>V50 Gy &lt; 0.1 cc</td>
</tr>
<tr>
<td>CaudaEquina</td>
<td>V37.5 Gy &lt; 0.1 cc</td>
</tr>
<tr>
<td>CaudaEquina_PRV_05</td>
<td>V50 Gy &lt; 0.1 cc</td>
</tr>
<tr>
<td>Heart</td>
<td>V40 Gy &lt; 60%</td>
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<tr>
<td></td>
<td>V45 Gy &lt; 40%</td>
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<tr>
<td></td>
<td>V60 Gy &lt; 20%</td>
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<tr>
<td></td>
<td>Dmean &lt; 30 Gy</td>
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<tr>
<td>Esophagus</td>
<td>V60 Gy ≤ 20%</td>
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<td></td>
<td>V50 Gy ≤ 30%</td>
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<tr>
<td></td>
<td>Dmean ≤ 30 Gy</td>
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<tr>
<td></td>
<td>V105% RxPTV &lt; 0.1 cc</td>
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<tr>
<td>Esophagus_PRV_05</td>
<td>V60 Gy ≤ 0.1 cc</td>
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<tr>
<td>Stomach</td>
<td>V54 Gy ≤ 0.1 cc</td>
</tr>
<tr>
<td>BowelBag</td>
<td>V55 Gy ≤ 0.1 cc</td>
</tr>
<tr>
<td>Skin</td>
<td>V50 Gy ≤ 0.1 cc</td>
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<tr>
<td>Liver-PTV</td>
<td>Mean&lt;25</td>
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<tr>
<td>Kidney</td>
<td>Mean&lt;15</td>
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<td>V20&lt;30%</td>
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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
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
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