Hepatocellular Carcinoma and SBRT

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Initial Presentation

• 69M with PMH of HTN, HIV (on HAART), HCV cirrhosis (genotype 1a) who presents with RUQ pain
Labs

- Hepatitis panel
- Direct Bilirubin 0.2, ALT 30, ALP 129
- INR 1.06, PTT 29.9, BUN 11, albumin 4.8, sCr 1.0
- CBC 8.7/13.3/38.9/226
- AFP 1492.9 (H)
  - Gp normally produced during gestation by the fetal liver and yolk sac—does not correlate well with size, stage, or px. Also elevated in gastric cancer and chronic liver disease. >500 concern for HCC
Pre-Tx MRI Abdomen T2

Segment 7 lesion: hypoenhancing
Pre-Tx MRI Abdomen Out of Phase

Segment 7 lesion: no washout
Diagnosis without Biopsy

• A classic appearance on one of the following imaging modalities
  – Ultrasound
  – CT
  – MRI
  – Angiography

• Elevated AFP

• Our patient did not meet imaging criteria so a biopsy was done
Workup

• CT Chest 03/23/2016
  – Negative

• Core Biopsy Hepatic Lobe Lesion 2011
  – Hepatocellular carcinoma, moderately differentiated
Diagnosis

• Multifocal hepatocellular carcinoma (HCC)
Liver Tumor Board

- Cirrhosis: yes
- Etiology of cirrhosis: HCV
- EGD: yes
- Varices: no
- Ascites: no
- Encephalopathy: no
- Portal HTN: no
- Child-Pugh Score: A
- MELD score: 7

Consensus:
Unresectable due to multifocal disease.
Lesion of interest was too large for ablation.
Proceed with TACE -> SBRT
Anatomy
Risk Factors & Epidemiology

• Most common hepatobiliary malignancy
• Develops from liver parenchymal disease
• Males are 3 times more likely to develop than females
• Peaks in the 6\textsuperscript{th} decade of life
Risk Factors & Epidemiology

• Viral infections
  – Chronic HBV is leading cause in Asia (East > SE) and Africa (middle > East > West)
  – HCV is leading cause in Europe, Japan and North America
  – In U.S., retrospective study of patients at liver transplantation centers found 50% with HCV and 15% with HBV
Risk Factors & Epidemiology

• Nonviral infections: alcoholic cirrhosis, inherited errors of metabolism (hereditary hemochromatosis, porphyria cutanea tarda, alpha1-AT deficiency, Wilson’s disease, stage IV primary biliary cirrhosis, environmental exposure to aflatoxin, growing evidence for sequelae of non-alcoholic fatty liver disease (i.e. NASH))

• Common sites of metastasis include lung, abdominal LN, peritoneum and bone
Screening

• AASLD panel recommends periodic screening with ultrasound and AFP testing every 6-12 months for patients at risk for HCC followed by additional imaging (at least a 3-phase CT scan or MRI) for those with rising serum AFP or following identification of a liver mass nodule on ultrasound
Clinical Presentation

• Usually asymptomatic
• Nonspecific symptoms including
  – jaundice, anorexia, weight loss, malaise, upper abdominal pain, hepatomegaly and ascites
Diagnosis: Imaging

• Imaging per NCCN
  – Lesions are classically characterized by intense arterial uptake or enhancement followed by contrast washout or hypointensity in the delayed venous phase
  – Diagnostic studies include 4-phase helical CT, 4-phase dynamic contrast-enhanced MRI or contrast-enhanced ultrasound
  – 4-phase refers to phases of scanning: unenhanced phase, arterial phase, portal venous phase, venous phase after a delay
  – PET-CT is not adequate
LI-RADS

• LI-RADS features that favor HCC Diagnosis
  – Early arterial enhancement with early "washout."
  – Mild-moderate T2 hyperintensity
  – Capsule (rim enhancement on delayed post contrast imaging)
  – Mosaic architecture
  – "Restricted" diffusion
  – Fat deposition disproportionate to that in surrounding liver
  – Iron sparing in iron-overloaded liver
Diagnosis: Biopsy

• Biopsy
  – Not always necessary in the case of liver nodules greater than 1cm in size, the finding of 2 classic enhancements on either one of the recommended imaging modalities (3-phase contrast-enhanced CT or MRI) is sufficient
  – Core needle biopsy (preferred) or FNAB is recommended when 0 or 1 classic arterial enhancement is observed by the recommended imaging method
  – Growing mass with negative biopsy does not rule out HCC
Initial Workup

• Determine etiology of liver disease and assess presence of comorbidity, imaging to detect metastatic disease, evaluation of hepatic function (and whether portal HTN is present)

• Confirm viral load for patients who test positive for HCV antibodies, HBsAg, HBeAb IgG
Initial Workup

• Assessment of Liver Function
  – Serum levels of bilirubin, AST, ALT, ALP, PT, INR, albumin, PLT count, CBC, BUN, sCr (some of these are prognostic factors)
  – Child-Pugh score to assess hepatic functional reserve in patients with cirrhosis
    • Compensated (class A) vs. decompensated (classes B & C)
  – MELD also evaluates hepatic reserve without the clinical assessments of ascites and encephalopathy
Pathology

- 3 morphologic types of HCC:
  - nodular (a/w cirrhosis, characterized by well-circumscribed nodules)
  - massive (a/w noncirrhotic liver)
  - diffuse (many small indistinct tumor nodules throughout the liver)
Staging

• In general, patients are stratified into 4 categories:
  – Potentially resectable or transplantable, operable by performance status or comorbidity
  – Unresectable disease
  – Inoperable by performance status or comorbidity with local disease only
  – Metastatic disease

• 3 other staging systems aside from AJCC are Barcelona Clinic Liver Cancer (BCLC), Cancer of the Liver Italian Program (CLIP), and Japanese Integrated Staging (JIP) score
NCCN Guidelines Summary

- Resect if feasible
- If not: ablation or TACE (SBRT is cat 2B)
  - Reasons patients are poor candidates for surgery/ablation/TACE
    - Poor surgical status, tumors next to major vessels for ablation (heat sink), no accessible vascular path to the tumor
- UNOS criteria for transplant: one tumor <5cm or 2-3 tumors <3cm each, no vascular involvement, N0M0
- Avoid Y90 if bili>2mg/dL or CP class C
Figure 1. Schematic diagram shows the process flow for stereotactic body radiotherapy (SBRT). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
Respiratory Motion Management Techniques

• Motion encompassing methods- 4DCT, multiple breath hold CT, slow CT, fluoroscopy
• Breath hold methods- ABC (active breath holding)
• Direct immobilization- abdominal compression
• Target tracking - internal fiducial markers (recommended), Calypso, cyberknife, dynamic MLC
• Respiratory gating
SBRT

• Prescription
  – 4000cGy to the PTV and 5000cGy to the ITV at 800cGy/fx

• Technique
  – Gated sim with contrast
  – GTV: all visible disease on CT
  – ITV: all visible disease at all parts of breathing cycles
  – PTV: 5-10mm around ITV depending on normal liver volumes left and tolerances
Plan
Plan

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## Dose Constraints

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Evidence for SBRT

• Traditionally was 50+Gy (2Gy/ fx) with 3D or IMRT

• Tse 2008 at Princess Margaret
  – 41 patients; median 36Gy in 6 fx; median OS 11.7 months

• Rusthoven 2009
  – Definitive alternative for limited disease (1-3 hepatic lesions and max individual tumor diameter < 6cm)
  – 60Gy in 3 fx; 2-yr LC 92%, OS 30%
Evidence for SBRT

• Dawson 2012
  – Phase I study suggests sorafenib increases RT toxicity

• Bujold 2013
  – Definitive alternative for locally advanced disease
  – 102 pts; median 36/6; OS 17 months, LC 87%, grade 3+ toxicity 30%

• Also used for palliation and bridge to transplant
Evidence for post-TACE SBRT

- Retrospective study at University of AL (Jacob et al. 2015)
- 161 patients treated with ≥ 3cm HCC
  - 124 patients TACE alone
  - 37 patients TACE + SBRT
- LR 25.8% TACE vs. 10.8% TACE+SBRT (p=0.04)
- Median OS 20mo TACE vs. 33mo TACE+SBRT (p=0.02)
Current Protocol (RTOG 1112)

• Randomized phase III study of sorafenib vs. SBRT+sorafenib in HCC

• Primary objective
  – To determine if SBRT improves overall survival in HCC patients treated with sorafenib

• Patient Population
  – Unsuitable for resection or transplant or RFA
  – Unsuitable for TACE or refractory to TACE
  – BCLC Intermediate (B) or Advanced (C)
References


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