Liver Radiation: Review of Pertinent Anatomy and Physiology, Functional Imaging, and Potential Future Direction

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S.L.I.F.T.

(Sorry, Liver. It's Tuesday.)
Introduction

- Liver radiation can be complex, but we can offer a safe treatment if delivered appropriately
- The patients we treat with radiation have cancer in their liver, but they often also often have a poorly functioning liver on top of that
  - Hepatocellular carcinoma (HCC) arises primarily in pts with cirrhosis
  - Even in patients with secondary liver malignancies (i.e. metastatic colon cancer) without cirrhosis, often heavily pre-treated
Introduction

• The most commonly used methods for assessing the severity of cirrhosis are Child-Turcotte-Pugh (CTP) and Modified End-Stage Liver Disease (MELD) scores

• Although not widely used, indocyanine green (ICG) retention measurement is the gold standard for assessing liver function
  – ICG is a fluorescent dye which is injected and is only excreted by the liver
  – If the liver is functioning poorly, ICG will be left in the bloodstream and patients have higher ICG retention at 15 minutes (ICG15)

• These methods provide a global assessment of liver function, but do not allow visualization of the regional variations in liver function which can exist
Introduction

• Functional imaging may be utilized to visualize this regional variation
  – Different techniques have been validated by correlation with ICG15 (in large part by work in the Department of Radiation Oncology at University of Michigan)

• Utilizing functional imaging as a "roadmap" for RT planning may improve the therapeutic ratio and allow better prediction of toxicity
Outline

- Liver anatomy and physiology
  - What does the liver do?
- Review different types of liver malignancy
  - Focus on radiation in hepatocellular carcinoma and liver metastasis
- Methods of grading liver disease severity
- Discuss different functional imaging techniques
- Highlight Functional Liver Image Guided Hepatic Therapy (FLIGHT) as a technique to maximize functional hepatic reserve
  - This is a current prospective protocol which recently opened at IU
Brief Review of Anatomy
Liver Anatomy

- Located in right upper quadrant
- Dual blood supply
  - ~80% of the blood flow is from the portal vein which comes from digestive tract (poorly oxygenated)
  - ~20% is from the hepatic artery (oxygenated)
Liver Segmental Anatomy

- 8 functionally independent segments based on largely on venous anatomy
- Each segment has its own branch of the portal triad: hepatic artery, portal vein, and bile duct
- Numbered clockwise if looking anteriorly
- Classic parallel tissue radiobiologically

Drawing depicting the functional segments of the liver (Couinaud’s segments). Segments I to IV make up the left lobe and segments V to VIII constitute the right lobe.
Liver Segmental Anatomy

- Important in surgical planning
- In a healthy liver, up to 75-80% of the liver can be resected (>25% future remnant)
- In a cirrhotic liver, only 40-60% can be resected (>40% future remnant)
- Portal vein embolization (PVE) can stimulate hyperplasia of the remnant liver if initial future liver remnant (FLR) is inadequate
Brief Review of Physiology and Pathology
What does the liver do?

• Process and store nutrients
  – Nutrients from digestive tract drain to liver via portal vein and are processed and stored

• Aid in digestion and excretion of waste
  – Hepatocytes produces bile which gets stored in gallbladder and eventually is ejected to emulsify fats / fat soluble vitamins and aid in digestion
  – Excreting bilirubin (a breakdown product of red blood cell hemoglobin)
  – Removing metabolic waste products, hormones, drugs, and toxins (i.e. alcohol)

• Produce proteins
  – Synthesizing plasma proteins, albumin, and clotting factors
Causes of Liver Dysfunction

- **Causes**
  - Chronic viral hepatitis (hepatitis B, C): HCV predominates in US
  - Alcoholic liver disease
  - Nonalcoholic fatty liver disease
  - Hemochromatosis (deposition of iron)
  - *Other causes: autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, medications (methotrexate, isoniazid), Wilson disease, alpha-1 antitrypsin deficiency, polycystic liver disease, veno-occlusive disease, etc*

- **Cirrhosis** is a late stage of hepatic fibrosis which for the most part is irreversible unless treated in its early stages
  - Typically diagnosed by liver biopsy only although can be diagnosed clinically
Complications of Cirrhosis

- Things we may see on physical exam *(bold indicates decompensation)*
  - **Ascites** – hypoalbuminemia and portal HTN
  - **Hepatic encephalopathy** – ammonia
  - Jaundice or dark urine – bilirubin
  - Palmar erythema, spider angiomata, gynecomastia – estrogen
  - Pruritus or itching – cholestasis (bile acids)
  - **Spontaneous bacterial peritonitis**
Complications of cirrhosis

- Things that we monitor patients for (bold indicates decompensation)
  - **Hepatocellular carcinoma**: screened by ultrasound and AFP q6months
  - **Esophageal variceal bleeding**: scoped for potential therapeutic intervention via banding or cauterization
  - Hepatorenal syndrome
  - Hepatopulmonary syndrome
Types of Liver Malignancies

• Primary
  – Hepatocellular carcinoma (HCC): cancer of the hepatocytes
  – Cholangiocarcinoma (Intrahepatic, Extrahepatic, or hilar): cancer of the bile ducts
  – Others (rare): Angiosarcoma and epithelioid hemangioendothelioma (cancers of the blood vessels), hepatoblastoma (most often children <2 yo), mixed tumors

• Secondary (much more common than primary liver tumors)
  – Metastases from other primaries (colon, breast, lung)
    • We may treat these in setting of oligometastatic disease (limited sites of metastases); most commonly colorectal cancer
Classification of Cirrhosis
# Child-Turcotte-Pugh (CTP) Class

- CTP A (5-6), B (7-9), C (10-15)

## Child-Pugh classification of severity of cirrhosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt;2 mg/dL (&lt;34.2 micromol/L)</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt;3.5 g/dL (35 g/L)</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td></td>
</tr>
<tr>
<td>Seconds over control</td>
<td>&lt;4</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
</tbody>
</table>

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh class A (well-compensated disease); 7 to 9 is class B (significant functional compromise); and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100 and 85 percent; class B: 80 and 60 percent; and class C: 45 and 35 percent.

INR: international normalized ratio.
Child-Turcotte-Pugh (CTP) Class

- Predicts postoperative mortality and survival without intervention
- Has been the classification used in vast majority of radiation trials
  - Risk of toxicity increases with increasing CTP score in certain series
  - Indiana University Phase I/II trial for HCC was the trial suggesting patients with CTP ≥B8 should not be routinely offered SBRT unless listed for transplant (Andolino 2011)
    - 4/8 pts with CTP ≥B8 had progressive liver dysfunction whereas only 12% of pts with CTP ≤B7 had increase of >1 grade in hematologic/hepatic toxicity from baseline

<table>
<thead>
<tr>
<th>CTP Class</th>
<th>Postoperative Mortality (Mansour 1997)</th>
<th>1 year Survival (Infante-Rivard 1987)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10%</td>
<td>100%</td>
</tr>
<tr>
<td>B</td>
<td>30%</td>
<td>80%</td>
</tr>
<tr>
<td>C</td>
<td>82%</td>
<td>45%</td>
</tr>
</tbody>
</table>
Modified End-Stage Liver Disease (MELD)

- Bilirubin, INR, Creatinine (online calculators)
  - Multiple variations have been attempted (MELDNa)
- Adopted by the United Network for Organ Sharing (UNOS) in 2002
  - “Sickest first” policy; time spent on transplant list as tie-breaker (MELD ≥ 25 updated q7days)
  - Patients with HCC who undergo transplant were not found to have inferior survival
    - Depending on disease extent points can be added to the MELD score after 6 months of diagnosis of HCC if certain criteria are met (standard exceptions)
**Albumin-Bilirubin (ALBI) Score**

- Online calculator
- Developed model on 1,313 Japanese patients and validated this in pts from different geographic regions and in different clinical scenarios
- Performed as well as CTP, but ALBI allowed prognosis in CTP A patients to be differentiated

*Cirrhosis is a competing cause of mortality*
I'm not an alcoholic. They go to meetings.

I'm a drunk. We go to parties.
Primary Liver Malignancy

Hepatocellular Carcinoma
Staging and Treatment
Hepatocellular Carcinoma Diagnosis

- One of the few cancers that is most commonly diagnosed noninvasively without biopsy by characteristic imaging findings
- Arterial hyperenhancement with progressive washout on portal venous and delayed phases
Hepatocellular Carcinoma (HCC) Staging

- TNM has been validated in surgical cohort with 5 yr OS for:
  - Stage I – 55%
  - Stage II – 37%
  - Stage III – 16%
- Other prognostic systems have been proposed for those with more advanced disease: CLIP

**TNM staging for hepatocellular cancer**

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Primary tumor without vascular invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Solitary tumor with vascular invasion or multiple tumors none more than 3 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>Multiple tumors more than 3 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with involvement of visceral peritoneum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Distant metastasis (M)**

- M0: No distant metastasis
- M1: Distant metastasis

**Fibrosis score (F)**

- F0: Fibrosis score 0–4 (none to moderate fibrosis)
- F1: Fibrosis score 5–8 (severe fibrosis or cirrhosis)

**Anatomic stage/prognostic groups**

- Stage I: T1 N0 M0
- Stage II: T2 N0 M0
- Stage IIIA: T3a N0 M0
- Stage IIIB: T3b N0 M0
- Stage IIIC: T4 N0 M0
- Stage IVa: Any T N1 M0
- Stage IVb: Any T N2 M0

**CLIP (Cancer of the Liver Italian Program) scoring system for hepatocellular cancer**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh stage</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
</tr>
<tr>
<td>Tumor morphology</td>
<td></td>
</tr>
<tr>
<td>Uninodular and extension ≤50%</td>
<td>0</td>
</tr>
<tr>
<td>Multinodular and extension ≤50%</td>
<td>1</td>
</tr>
<tr>
<td>Massive or extension &gt;50%</td>
<td>2</td>
</tr>
<tr>
<td>Alpha-fetoprotein</td>
<td></td>
</tr>
<tr>
<td>&lt;400</td>
<td>0</td>
</tr>
<tr>
<td>≥400</td>
<td>1</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>

The Cancer of the Liver Italian Program (CLIP) score has been used to predict survival in patients with hepatocellular carcinoma. The total score is derived by adding each of the subscores. In one study, median survival was 36, 22, 9, 7, and 3 months for patients in CLIP categories 0, 1, 2, 3, and 4 to 6, respectively.

HCC Treatment Overview

- Treatment options for liver malignancies depend on extent of tumor and the patient’s hepatic reserve; in general surgery preferred if able
- Surgical
  - Transplant (gets rid of cirrhosis) - 5 yr OS 70%, relapse rates <15%
  - Resection - 5 yr OS of ~40-50%
HCC Treatment Overview

• Nonsurgical
  – Ablation: Radiofrequency ablation (RFA), Microwave ablation, cryoablation, percutaneous ethanol injection (PEI)
  – Stereotactic Body Radiation Therapy (SBRT) or conformal RT
  – Catheter-based techniques: TransArterial ChemoEmbolization (TACE), radioembolization with yttrium-90, bland embolization
  – Chemotherapy/Systemic therapy: sorafenib, although others being investigated (i.e. immunotherapy)
HCC Treatment Overview

- Treatment decisions discussed in multidisciplinary tumor board
  - Surgery, Radiation oncology, Medical oncology, Interventional radiology, Gastroenterology/Transplant, Radiology
- Expert consensus guidelines vary regarding role of EBRT
  - NCCN guidelines have EBRT (conformal or stereotactic) as option for unresectable HCC
  - The EASL-EORTC 2012 guidelines follow the BCLC staging system for treatment allocation; EBRT is considered investigational
Liver Radiation
Introduction

• Historically RT hasn’t been used because of risk radiation induced liver disease (RILD)
• Classic RILD: anicteric hepatomegaly with transaminitis and elevated ALP
  – Risk of RILD in pts with CTP A cirrhosis (Pan 2010):
    • Mean liver dose of 28 Gy in 2 Gy/fx  5%
    • Mean liver dose of 36 Gy in 2 Gy/fx  50%
• Classic RILD is uncommon in modern radiation therapy series
  – Advances in treatment planning: 3DCRT, IMRT, SBRT, protons
  – Motion management
  – Image guided radiation therapy (IGRT)
Liver Radiation: From Whole Liver to Stereotactic Body Radiation Therapy (SBRT)

- In 2002, the multiinstitutional phase I/II study evaluating SBRT in liver metastases opened (Rusthoven et al 2009)
  - Dosimetric constraints for the “safe” hepatic reserve were extrapolated from (1) surgical data on required future liver remnant and (2) whole liver data
- For whole liver RT 30 Gy in 1.5 Gy/fx or 21 Gy in 3 Gy/fx were found to be safe regimens with BED of 45 Gy³ and 42 Gy³, respectively, for liver metastases (RTOG 84-05 & 76-05)
- Average liver volume 2000 cc, therefore need at least 500 cc (or 700 cc conservatively) to receive <~40 Gy³ which for a 3-fraction regimen is 15 Gy
- 700 cc <15 Gy
Liver Radiation: From Whole Liver to Stereotactic Body Radiation Therapy (SBRT)

- Phase I dose escalation trial from 36 Gy to 60 Gy in 3 fractions for the phase II component
- 3 fraction constraints for this trial (majority pts without liver disease):
  - Uninvolved liver (liver-GTV) >700 mL <15 Gy
  - Spinal cord max 6 Gy/fx (18 Gy)
  - Stomach/small intesting 10 Gy/fx (30 Gy)
  - Total kidney volume <35% >15 Gy
- 2 year local control rate 92%
- 2% grade ≥3 toxicity
  - One grade 3 skin toxicity in area where skin dose was 48 Gy
Phase I/II trial for HCC SBRT at IU opened in 2004, reported in 2011 (Andolino/Cardenes)

- CTP A dose escalation 36 to 48 Gy in 3 fx
- CTP B dose escalation 36 to 42 Gy in 3 fx however dose limiting toxicity was met so phase II dose was 40 Gy in 5 fx
- 2 yr local control 90%, 20% of pts had decline in CTP class
  - 24/60 (40%) pts were CTP B; of those 9 (37.5%) were CTP \( \geq B8 \)

**SBRT HCC Treatment Timeline**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Pts</th>
<th>CP Class</th>
<th>Tumor Size cm med (range)</th>
<th>PVT</th>
<th>Dose (Gy) GyE</th>
<th>No. Fx</th>
<th>Local Control</th>
<th>Survival</th>
<th>Grade 2+ Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 year</td>
<td>2 year</td>
<td>3 year</td>
</tr>
<tr>
<td>Sahuki</td>
<td>185</td>
<td>A 96%, B</td>
<td>2.7 (0.8-5)</td>
<td>NR</td>
<td>30-40</td>
<td>5</td>
<td>90%</td>
<td>91%</td>
<td>85%</td>
</tr>
<tr>
<td>Jang</td>
<td>108</td>
<td>A, B</td>
<td>1 cm-7 cm</td>
<td>NR</td>
<td>51 (39-66)</td>
<td>3</td>
<td>87%</td>
<td>87%</td>
<td>65%</td>
</tr>
<tr>
<td>Yoon</td>
<td>93</td>
<td>A 76%, B</td>
<td>1 cm-6 cm</td>
<td>0%</td>
<td>43 (35-60)</td>
<td>3.4</td>
<td>93%</td>
<td>92%</td>
<td>56%</td>
</tr>
<tr>
<td>Bibault</td>
<td>75</td>
<td>A, B</td>
<td>3 cm-4.4 cm</td>
<td>NR</td>
<td>43 (24-43)</td>
<td>3</td>
<td>90%</td>
<td>90%</td>
<td>79%</td>
</tr>
<tr>
<td>Honda</td>
<td>30</td>
<td>A, B</td>
<td>1 cm-3 cm</td>
<td>0%</td>
<td>48-60</td>
<td>4-8</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Huang</td>
<td>36</td>
<td>A, B, C</td>
<td>1.1-12.3 cm</td>
<td>NR</td>
<td>37 (25-48)</td>
<td>4-5</td>
<td>93%</td>
<td>93%</td>
<td>64%</td>
</tr>
<tr>
<td>Andolino</td>
<td>60</td>
<td>A 60%, B</td>
<td>3.1 (1-3.5)</td>
<td>NR</td>
<td>44 (24-48)</td>
<td>3-5</td>
<td>90%</td>
<td>90%</td>
<td>97%</td>
</tr>
<tr>
<td>Kwon</td>
<td>42</td>
<td>A 96%, B</td>
<td>3.0 mL-8 mL</td>
<td>0%</td>
<td>30-39</td>
<td>3</td>
<td>72%</td>
<td>68%</td>
<td>59%</td>
</tr>
</tbody>
</table>

*CP Class, Child-Pugh class; Fx, fractions; NR, not reported; Pts, Patients; PVT, portal vein thrombosis.*
EBRT HCC Treatment

- The role for protons are being investigated
  - Benefit: reduction in integral dose to reduce toxicity
  - Promising results have been reported especially considering patient population (2009-2011)
Liver Radiation for HCC

- Potential fractionation
  - RTOG 1112 50 Gy in 5 fx; adjusted based on mean liver dose
  - IU Phase I/II Trial
    CTP A: 48 Gy in 3 fx
    CTP B: 40 Gy in 5 fx
- RTOG 1112
  - *Important trial as this is first randomized trial comparing the addition of SBRT to an established modality with a survival benefit
HCC: SBRT vs. RFA

- Retrospective analysis from the University of Michigan suggests SBRT appears to have better local control with tumors >2 cm (Wahl D 2016)
HCC: SBRT vs. Surgery vs. Others

- Retrospective analysis of 1121 pts from Indiana University from 2000-2016 suggests similar outcomes with SBRT to surgery (Kong FM ASCO 2017)
  - Surgery=379, SBRT=116, CEBRT=43, Other tx=217, no treatment 366

![Survival Curve](image)

<table>
<thead>
<tr>
<th>Local Therapy</th>
<th>Median Survival (months)</th>
<th>3-year survival</th>
<th>5-year survival</th>
<th>HR* Median (95%CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBRT</td>
<td>50 (32-66)</td>
<td>53% (44%, 65%)</td>
<td>44% (34%, 57%)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Surgery</td>
<td>75 (57-94)</td>
<td>63% (58%, 69%)</td>
<td>54% (50%, 61%)</td>
<td>0.87 (0.64-1.19)</td>
<td>0.39</td>
</tr>
<tr>
<td>CEBRT</td>
<td>22 (13-31)</td>
<td>41% (27%, 60%)</td>
<td>29% (16%, 54%)</td>
<td>1.78 (1.12-2.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Other Local Tx</td>
<td>15 (13-20)</td>
<td>26% (20%, 34%)</td>
<td>22% (17%, 31%)</td>
<td>2.21 (1.6-3.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
I wish I could trade my heart in for another liver. Then I could drink more and care less.
Liver Stereotactic Body Radiation Therapy (SBRT) Technique
Simulation

- Patient positioning
  - Elekta body frame or Pro-Loc stereotactic body frames for immobilization

- Motion management
  - Abdominal compression to limit diaphragmatic excursion to <1 cm as assessed by fluoro
  - Active breathing control
  - Fiducials most often not used but would be nice

- Triple-phase CT simulation
  - Simulation images of diagnostic quality for target delineation

- 4D-CT
Planning

• Target and OAR delineation
  – *Appropriate image fusion is critical
  – GTV based on CT/MRI arterial/venous/delayed phases +/- PET/CT (rare)
  – ITV as able to be delineated on 4D CT
  – PTV 0.5 cm radially / 1 cm longitudinal although customized to individual patient motion

• Beam arrangement
  – 8-12 non-coplanar beams
  – No parallel opposed fields
Treatment Delivery and Monitoring

- Experienced therapists are important in the delivery process
- Often limited to matching to liver contour as tumors often not visible on CBCT and most often without fiducials

Planning Concerns: Using CBCT

Before Registration

After Registration
Functional Imaging

Visualizing Regional Variations in Liver Function to Guide Radiation
Functional Imaging and Radiation Therapy

• Not a new concept
• First proposed in early 1993, most work in lung cancer with perfusion scans
Functional Imaging of the Liver:
Hepatobiliary Iminidiacetic Acid (HIDA) Scans

- HIDA scans utilize $^{99}$Tc-mebrofenin which mimics the body’s processing of bilirubin
- The rate of liver uptake over time correlates well with the indocyanine-green (ICG) retention
Predictive Models for Regional Hepatic Function Based on 99mTc-IDA SPECT and Local Radiation Dose for Physiologic Adaptive Radiation Therapy

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Received Jan 6, 2013, and in revised form Apr 3, 2013. Accepted for publication Apr 4, 2013

• First study looking at functional changes as assessed by HIDA scans before, during, and after liver radiation
• Validated HIDA to ICG
• Established a dose-response relationship
• Demonstrated prediction of post-RT functional liver was improved by scanning after 50-60% of treatment (potential for adaptive therapy)
Other Functional Imaging Techniques

- CT Perfusion [Cao et al IJROBP 2008]
  - Developed dose-response relationship
  - Defined lower limit for portal venous perfusion representing functional liver
  - The dose that made an area non-functional for each patient ranged from 42.4 to 67.8 Gy, indicating significant individual variations in radiosensitivity
  - Perfusion is not static; low dose areas can re-perfuse

Fig. 1. Scatter plots of regional portal vein perfusion (FP) (mL/(100g min)) 1 month after the completion of radiotherapy (RT) vs. local dose (cGy) accumulated at the end of RT in 2 patients (open circles). The solid lines plot linear regression fits. The dashed lines represent the portal vein perfusion values before radiotherapy. Note that the portal vein perfusion values before radiotherapy are smaller than the intercepts of linear regression, suggesting that whereas high dose causes a decrease in perfusion, low dose can result in an increase.
Other Functional Imaging Techniques

- MR Perfusion [Cao et al IJROBP 2013]
  - Developed dose-response relationship
  - Demonstrated regional changes in perfusion occurred at doses >17 Gy
  - Pre-treatment and mid-treatment perfusion scans were able to be used to predict 1 month post-treatment scans
  - Perfusion is not static; low dose areas can re-perfuse

Fig. 3. Color-coded portal venous perfusion images overlaid on computerized treatment planning CT pre-RT (left) and 1 month post-RT (middle) in patient 10 (top) and 12 (bottom). For each patient, the images pre- and post-RT are windowed identically and color bars on the left side indicate perfusion in units per ml/100 g/min. Hyperperfusion pre-RT and hypoperfusion post-RT were observed in patient no. 10, associated with improvement in overall liver function post-RT. Reprofusion in the left lobe post-RT was observed in patient no. 12. Perfusion dose response functions of the 2 patients are plotted in the panels at right. Isodose curves = 10, 20, 30, 40, 50, and 55 Gy for red, green, blue, cyan, pink, and yellow, respectively.
Indiana University HIDA Experience

- 32 pts with HCC had baseline SPECT-HIDA prior to intervention (SBRT=17, catheter-based therapy=5, surgery=4, no therapy=6)
- In SBRT pts, those without toxicity (n=7) had a higher HIDA values than those with toxicity (n=6)

<table>
<thead>
<tr>
<th>SBRT pts</th>
<th>HIDA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without toxicity</td>
<td>Global HIDA</td>
<td>0.025</td>
</tr>
<tr>
<td>With toxicity</td>
<td>3.6%/min/BSA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.2%/min/BSA</td>
<td></td>
</tr>
<tr>
<td>Mean FRC HIDA**</td>
<td></td>
<td>0.022</td>
</tr>
<tr>
<td>Without toxicity</td>
<td>2.8%/min/BSA</td>
<td></td>
</tr>
<tr>
<td>With toxicity</td>
<td>1.8%/min/BSA</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All pts</th>
<th>Mean Global HIDA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTP A</td>
<td>3.6%/min/BSA</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CTP B</td>
<td>1.8%/min/BSA</td>
<td></td>
</tr>
<tr>
<td>MELD ≤9</td>
<td>3.7%/min/BSA</td>
<td>0.001</td>
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<tr>
<td>MELD ≥10</td>
<td>2.0%/min/BSA</td>
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</tbody>
</table>

*Toxicity defined as increase in MELD ≥3 at 3 months
**FRC HIDA defined as amount of function <15 Gy
Functional Liver Image-Guided Hepatic Therapy (FLIGHT) Planning

A Technique to Maximize Functional Hepatic Reserve
Indiana University HIDA Experience

• 10 of the 17 SBRT pts have been replanned using FLIGHT planning
• Target coverage was maintained
• Resulting dose to each relative functional liver structure was examined and compared
• Doses to organs at risk (OARs), conformity index (CI), and gradient index (GI) were evaluated

Contours of relative functional liver based on HIDA SPECT scan. Liver function is represented by the following contours: low (orange), low-intermediate (blue), high-intermediate (green), and high (magenta).

Variation in the location and volume of the high functioning liver for Patient D (left) and Patient E (right). GTV and PTV are shown in red and cyan contours, respectively.
Indiana University HIDA Experience

- FLIGHT plans reduced the mean dose to the high functioning liver (50-100% max) by a median of 3.0 Gy (range 0.7-4.6 Gy)
  - 31.4% mean reduction compared to standard planning
- Maintained conformality and gradient indices

Comparison of Conformality and Gradient Indices for FLIGHT and standard SBRT plans

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>FLIGHT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conformity Index (CI)</td>
<td>1.04</td>
<td>1.02</td>
<td>0.64</td>
</tr>
<tr>
<td>Gradient Index (GI)</td>
<td>3.73</td>
<td>3.50</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Beam arrangement of (A) standard SBRT plan, and (B) FLIGHT plan. High functioning liver (75-100% max) is shown in magenta.
Functional Imaging and Liver Radiation

- FLIGHT SBRT allows for field design and plan optimization individualized to a patient’s baseline regional liver function to maximize hepatic functional reserve
- Recently opened prospective trial at IU to assess functional changes at baseline, during, and after radiation utilizing this approach
Conclusions

• Patients we treat with radiation
  • Have significant variation in their underlying liver function
  • Can have multiple drivers of mortality other than of their liver cancer in setting of cirrhosis
• There are multiple therapeutic interventions which have been shown to be efficacious in the management of liver malignancies
  • EBRT has a growing role given the improvements in technology which have led to improved local control with reduced toxicity
• FLIGHT planning may help to maximize an individual patient’s functional hepatic reserve
QUESTIONS?
Support

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  Mark Tann, MD

Radiation Oncology
  Susannah G. Ellsworth, MD
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  Richard Zellars, MD
  Colin Huang, PhD
  Hong Zhang, BS
  Yukie Furukawa, BS, RT(T)

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