Hepatocellular Carcinoma and SBRT

Author: Anna Lee, MD, MPH (PGY-3)

Faculty Advisor: David Schwartz, MD

Institution: SUNY Downstate Medical Center,

Dept of Veterans Affairs, New York Harbor Health System

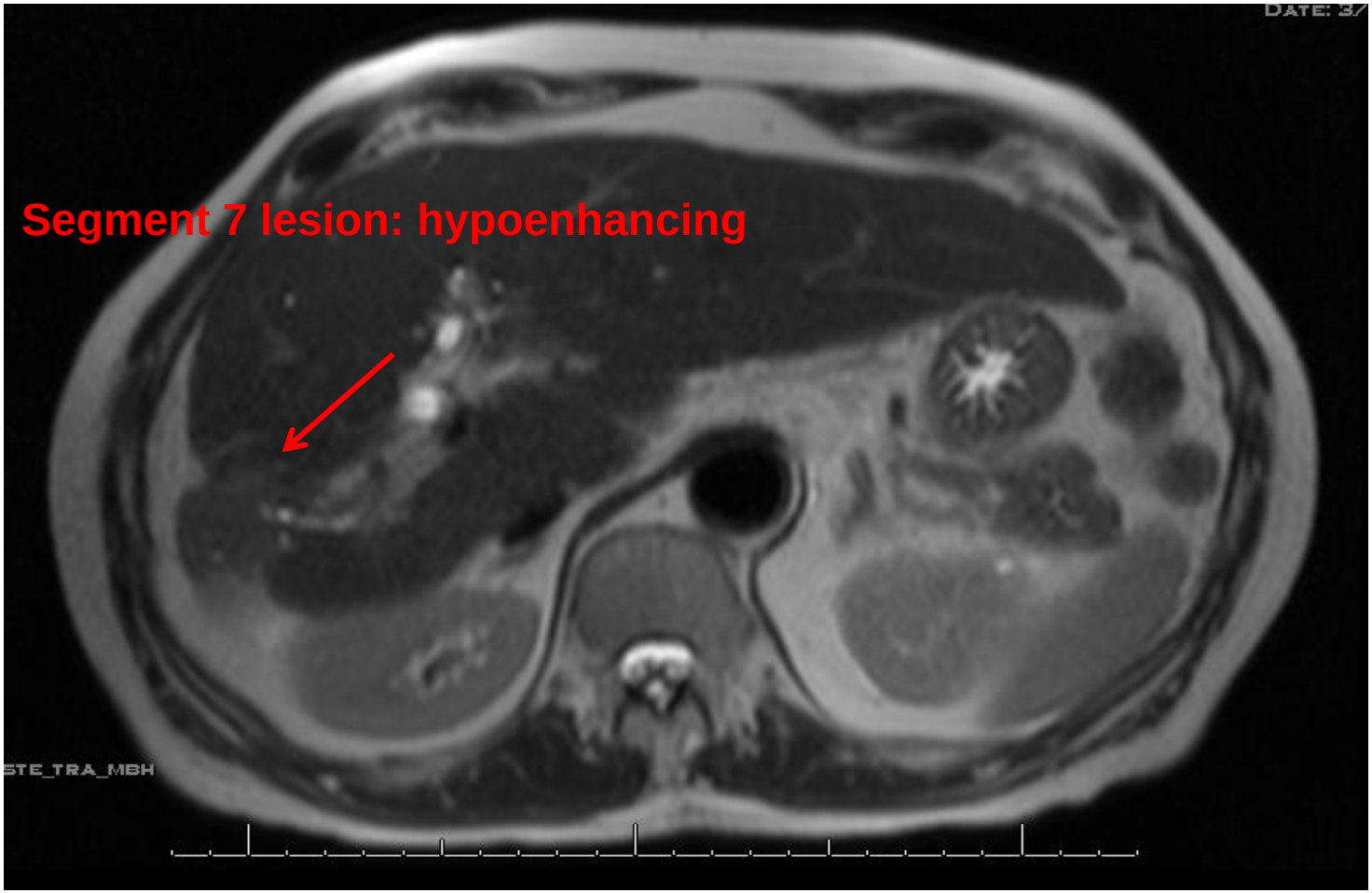
Initial Presentation

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

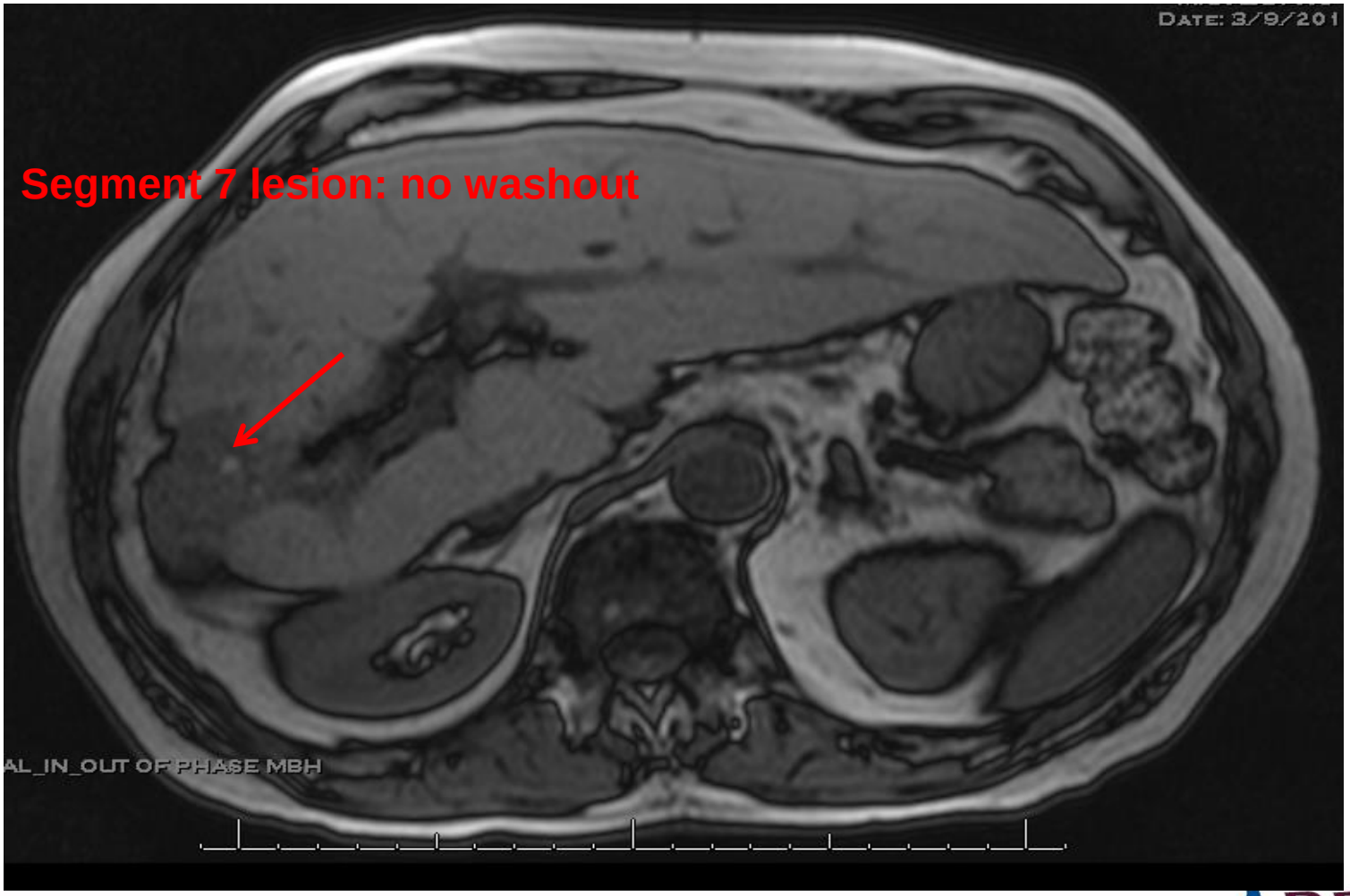
Labs

- 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



Pre-Tx MRI Abdomen Out of Phase



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

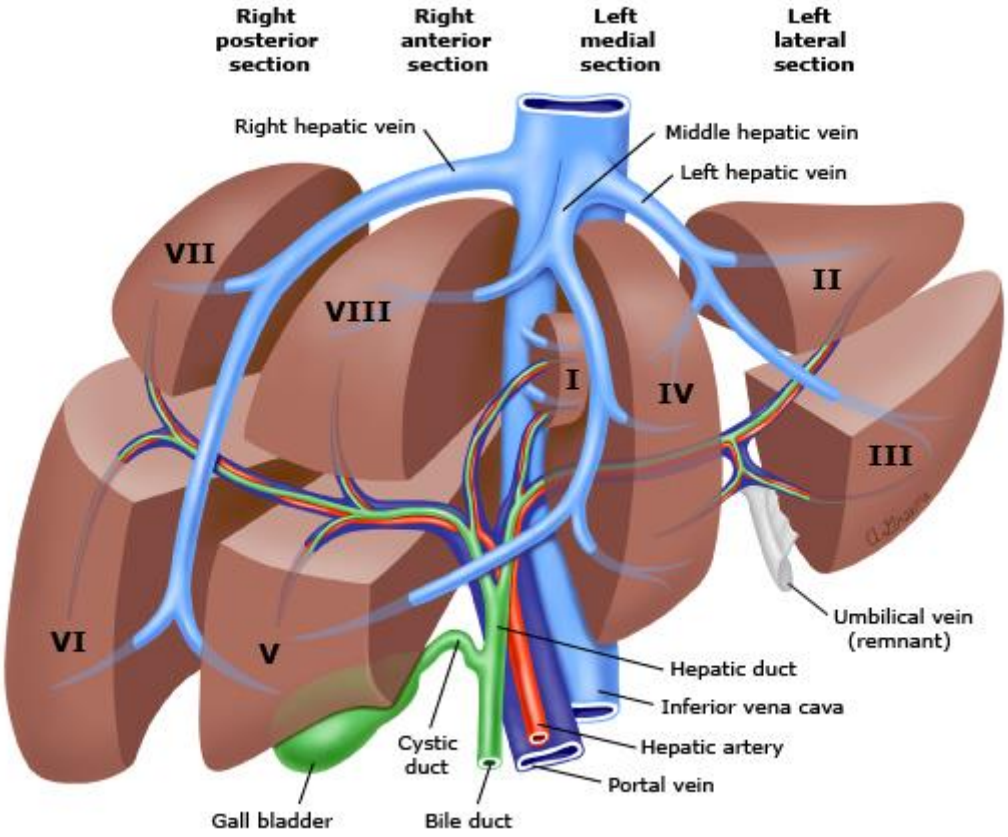
- Multifocal hepatocellular carcinoma (HCC)

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


Right posterior section
Right anterior section
Left medial section
Left lateral section
Right hepatic vein
Middle hepatic vein
Left hepatic vein
VII
VIII
II
I
IV
III
VI
V
Umbilical vein (remnant)
Hepatic duct
Inferior vena cava
Hepatic artery
Portal vein
Cystic duct
Gall bladder
Bile duct

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 6th 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 tarde, 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, HBcAb IgG

Initial Workup

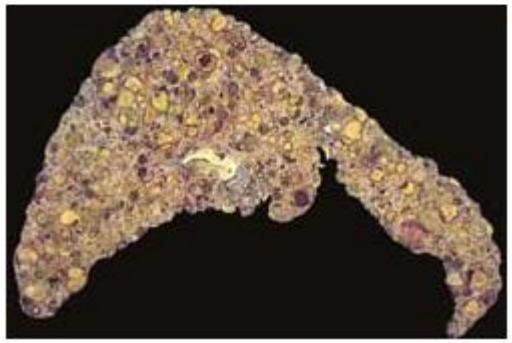
- Assessment of Liver Function
  - Serum levels of bilirubin, AST, ALT, ALP, PT, INR, albumin, PLT count, CBC, BUN, sCr (some of these are prognostic factors)
  - Child-Pugh score to assess hepatic functional reserve in patients with cirrhosis
    - Compensated (class A) vs. decompensated (classes B & 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)

Hepatocellular carcinoma; nodular type

Hepatocellular carcinoma; massive type



Hepatocellular carcinoma; diffuse type

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

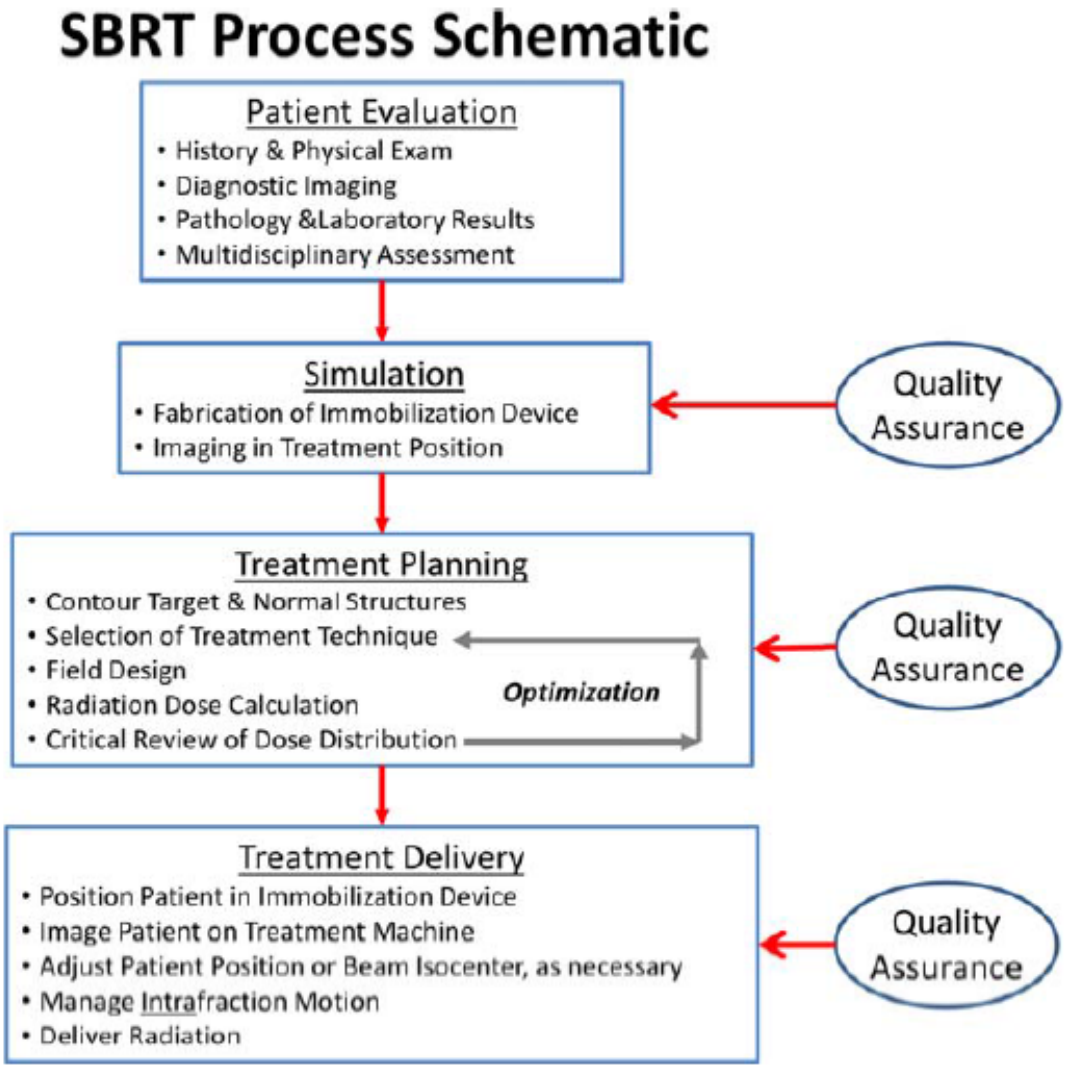


Figure 1. Schematic diagram shows the process flow for stereotactic body radiotherapy (SBRT). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

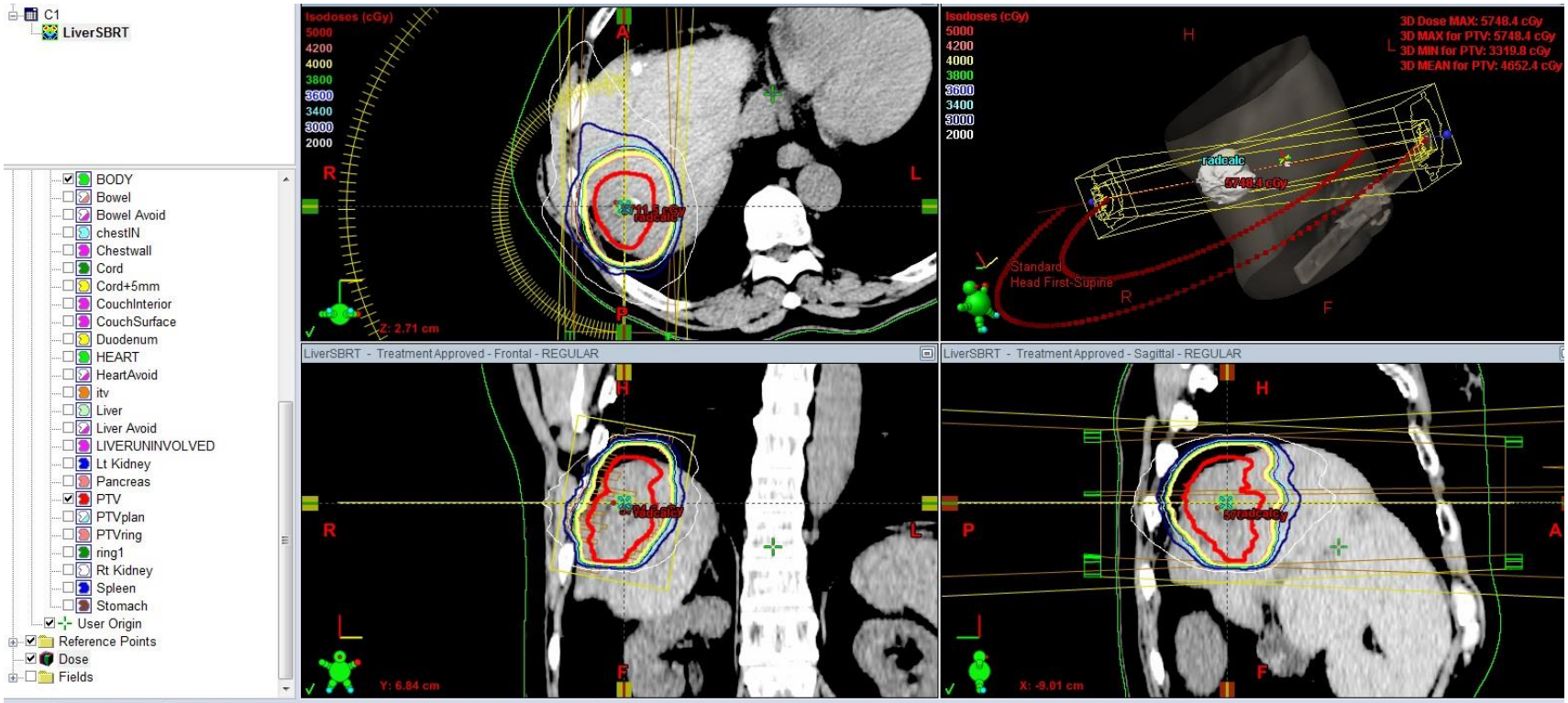
Respiratory Motion Management Techniques

- 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

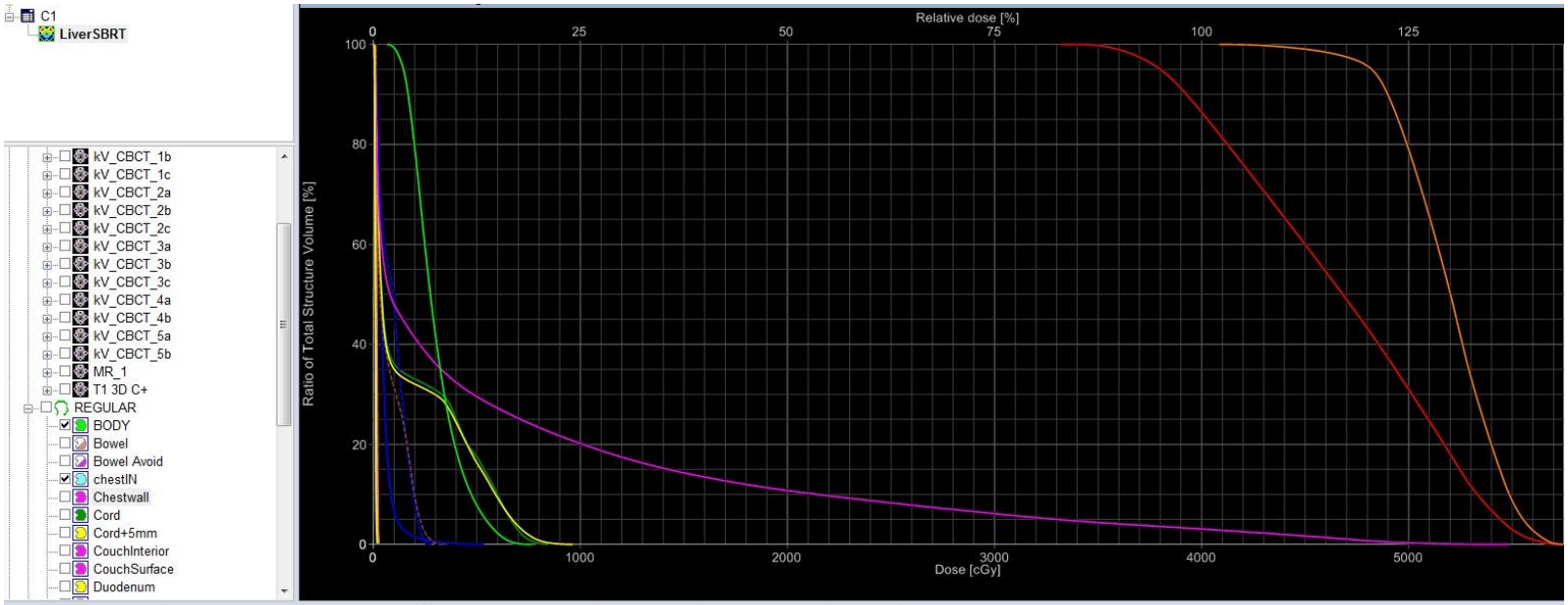
Plan



Fields | Dose Prescription | Field Alignments | Plan Objectives | Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

Group	Field ID	Technique	Machine/Energy	MLC	Field Weight	Scale	Gantry Rtn [deg]	Coll Rtn [deg]	Couch Rtn [deg]	Wedge	Field X [cm]	X1 [cm]	X2 [cm]	Field Y [cm]	Y1 [cm]	Y2 [cm]	X [cm]	Y [cm]	Z [cm]	SSD [cm]	MU	Ref. D [cGy]
☑	CBCT	STATIC-I	TrueBeamSN1535 - 10X-FFF		0.000	Varian IEC	0.0	0.0	0.0	None	10.0	+5.0	+5.0	10.0	+5.0	+5.0	-9.01	6.84	2.71	84.1		
☑	1CW	SRS ARC-I	TrueBeamSN1535 - 10X-FFF	VMAT	1.021	Varian IEC	181.0 CW 0.0	10.0	0.0	None	8.4	+4.2	+4.2	9.5	+4.8	+4.8	-9.01	6.84	2.71	93.4	805	
☑	CBCT Btwn	STATIC-I	TrueBeamSN1535 - 10X-FFF		0.000	Varian IEC	0.0	0.0	0.0	None	10.0	+5.0	+5.0	10.0	+5.0	+5.0	-9.01	6.84	2.71	84.1		
☑	2CCW	SRS ARC-I	TrueBeamSN1535 - 10X-FFF	VMAT	0.972	Varian IEC	0.0 CCW 181.0	350.0	0.0	None	8.7	+4.5	+4.2	9.5	+4.8	+4.8	-9.01	6.84	2.71	84.1	766	
☑	AP SETUP	STATIC-I	TrueBeamSN1535 - 10X-FFF		0.000	Varian IEC	0.0	0.0	0.0	None	10.0	+5.0	+5.0	10.0	+5.0	+5.0	-9.01	6.84	2.71	84.1		
☑	RT LAT SETUP	STATIC-I	TrueBeamSN1535 - 10X-FFF		0.000	Varian IEC	270.0	0.0	0.0	None	10.0	+5.0	+5.0	10.0	+5.0	+5.0	-9.01	6.84	2.71	93.8		
☑	AP OBI	STATIC-I	TrueBeamSN1535 - 10X-FFF		0.000	Varian IEC	0.0	0.0	0.0	None	10.0	+5.0	+5.0	10.0	+5.0	+5.0	-9.01	6.84	2.71	84.1		
☑	RT LAT OBI	STATIC-I	TrueBeamSN1535 - 10X-FFF		0.000	Varian IEC	270.0	0.0	0.0	None	10.0	+5.0	+5.0	10.0	+5.0	+5.0	-9.01	6.84	2.71	93.8		

Plan



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View	DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☐		Liver	Approved	LiverSBRT	C1						
☑		Rt Kidney	Approved	LiverSBRT	C1	157.1	100.0	100.0	3.2	28.5	10.9
☑		Lt Kidney	Approved	LiverSBRT	C1	157.1	100.0	100.0	11.5	536.1	48.6
☑		PTV	Approved	LiverSBRT	C1	175.1	100.0	100.0	3319.8	5748.4	4652.4
☑		Cord	Approved	LiverSBRT	C1	49.5	100.0	100.0	5.4	848.0	191.2
☑		Cord+5mm	Approved	LiverSBRT	C1	146.4	100.0	100.0	4.4	968.0	186.8
☑		Stomach	Approved	LiverSBRT	C1	103.7	100.0	100.0	9.6	335.7	76.3
☑		Spleen	Approved	LiverSBRT	C1	249.9	100.0	100.0	7.3	285.3	93.8
☑		Pancreas	Approved	LiverSBRT	C1	68.7	100.0	100.0	9.1	27.7	16.4
☑		LIVERUNINVOLVED	Approved	LiverSBRT	C1	2246.6	100.0	100.0	1.9	5491.2	624.5
☑		itv	Approved	LiverSBRT	C1	59.6	100.0	100.0	4086.2	5748.4	5189.8
☑		Duodenum	Approved	LiverSBRT	C1	68.2	100.0	100.0	4.4	20.1	9.6
☑		HEART	Approved	LiverSBRT	C1	591.5	100.0	100.0	65.4	772.5	299.3
☐		Chestwall	Approved	LiverSBRT	C1	250.1	100.0	100.0	0.0	4432.7	1993.9
☐		ring1	Approved	LiverSBRT	C1						
☐		chestIN	Approved	LiverSBRT	C1						
☐		PTVring	Approved	LiverSBRT	C1						

Dose Constraints

Organ	Volume	Dose (Gy)
Duodenum	Max point dose (0.03cc)	≤32
	<5cc	≤18
Small Bowel	Max point dose	<35
	<5cc	19.5
Liver Uninvolved	V(liver)-V21	>700cc
	Mean dose	<15

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 11.7months
- 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 17months, 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

- Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol.* 2013;31:1631-1639.
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- Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol.* 2009;27:1572-1578.
- Tse RV, Hawkins M, Lockwood G, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol.* 2008;26:657-664.
- Jacob R, Turley F, Redden DT, et al. Adjuvant stereotactic body radiotherapy following transarterial chemoembolization in patients with non-resectable hepatocellular carcinoma tumours of ≥3cm. HPB. 2015;17(2):140-9.

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