2014 AAPM SUMMER SCHOOL
University of Vermont • Burlington, VT • June 22–26, 2014
SRS/SBRT/SABR:
Safely and Accurately Delivering
High-Precision, Hypofractionated Treatments

Clinical Targets and Treatment Planning III
GI - Pancreas and Liver

Karyn A. Goodman, M.D., M.S.
Associate Attending Radiation Oncologist
Memorial Sloan-Kettering Cancer Center

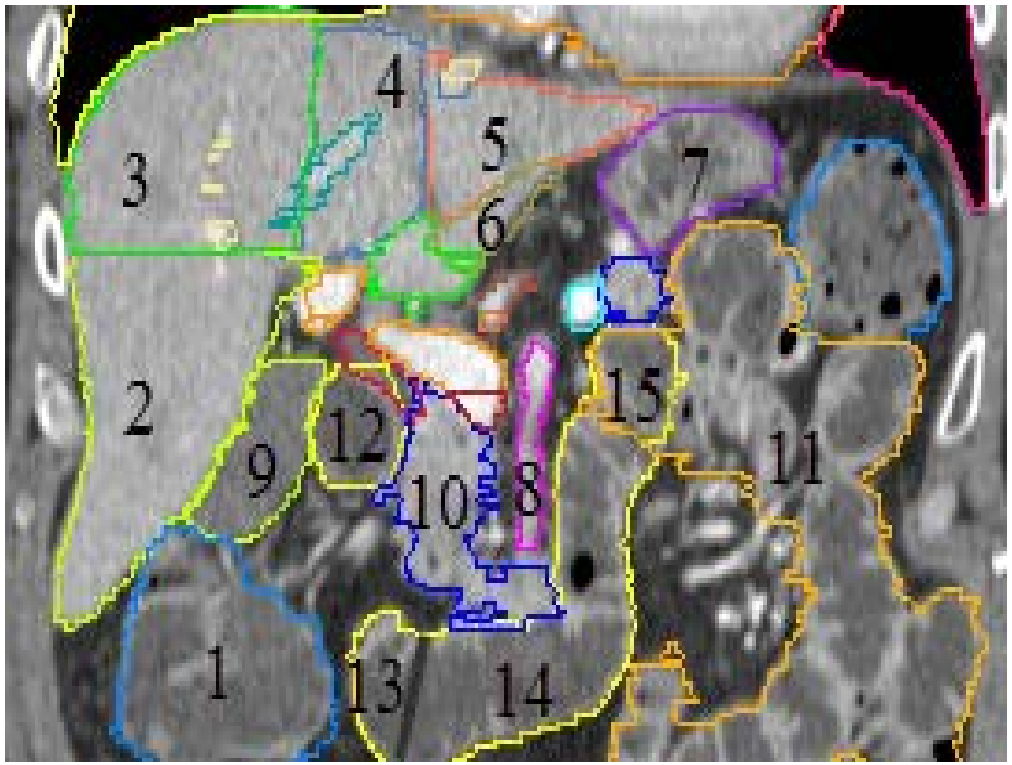
Learning Objectives

1. Achieve a basic understanding of abdominal anatomy
2. Appreciate the clinical outcomes of SBRT for liver and pancreas tumors
3. Evaluate the use of imaging, treatment planning, and treatment delivery techniques to account for respiratory motion
4. Review the normal tissue constraints for SBRT for abdominal tumors

Outline of Presentation

- Anatomy
  - Basic abdominal anatomy
- Rationale for SBRT for abdominal tumors
  - Emerging clinical data
- Simulation and Motion Management Techniques
  - Compression Belt
  - Respiratory Gating
- Treatment Planning
  - Dose constraints

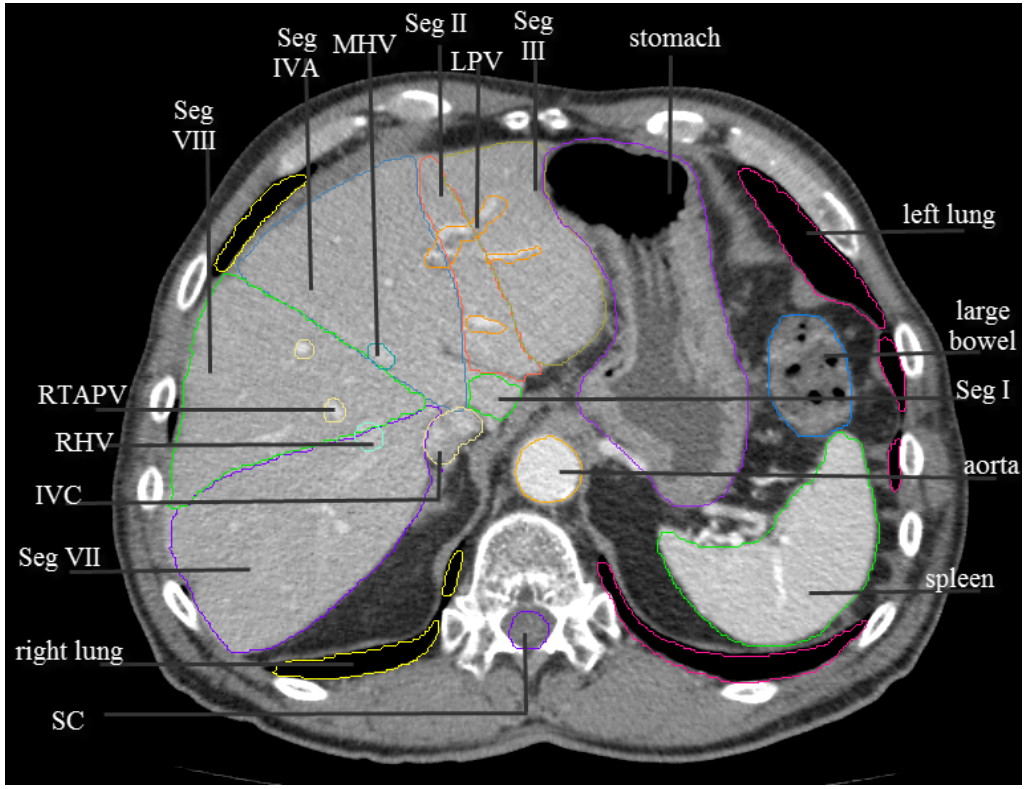
Abdominal Anatomy



- Highly radiosensitive organs
  - Small bowel
  - Stomach
  - Colon
  - Liver
  - Kidneys
  - Adrenals
  - Pancreas
  - Spleen
- Rich lymphatic supply
  - Para-aortic
  - Celiac
  - Superior mesenteric
  - Peri-gastric

Jabbour, et. al., PRO, 2014

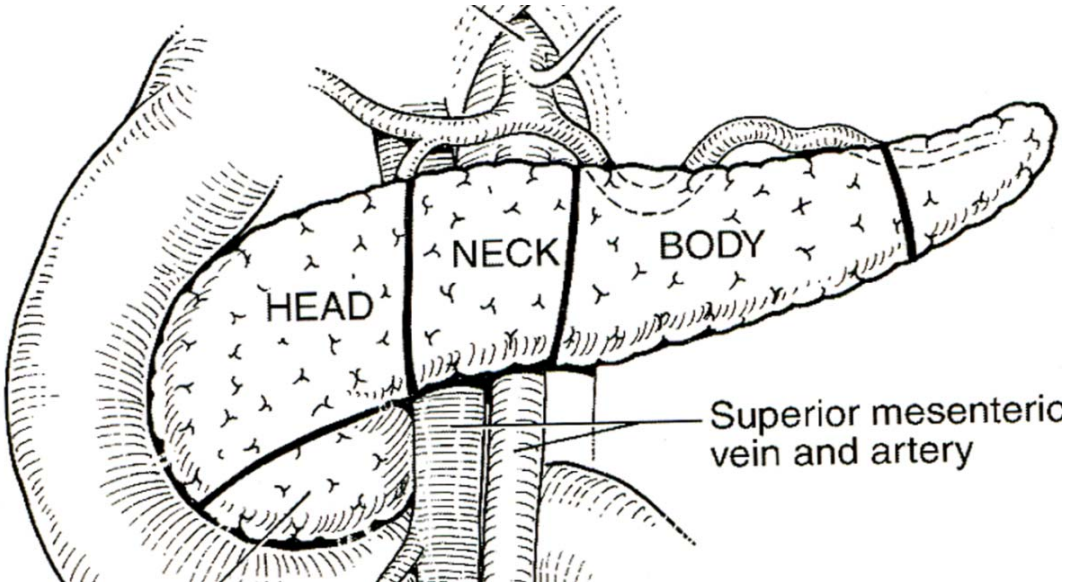
Hepatic Anatomy



- 2 Liver lobes
  - Right and left
- 8 Liver segments
  - Divided by hepatic vasculature
  - Determines extent of surgical resections
- Unique regenerative capacity
- Normal liver volume
  - Approx. 2100 cc
  - Need to maintain 1/3 of liver after resection (700cc)

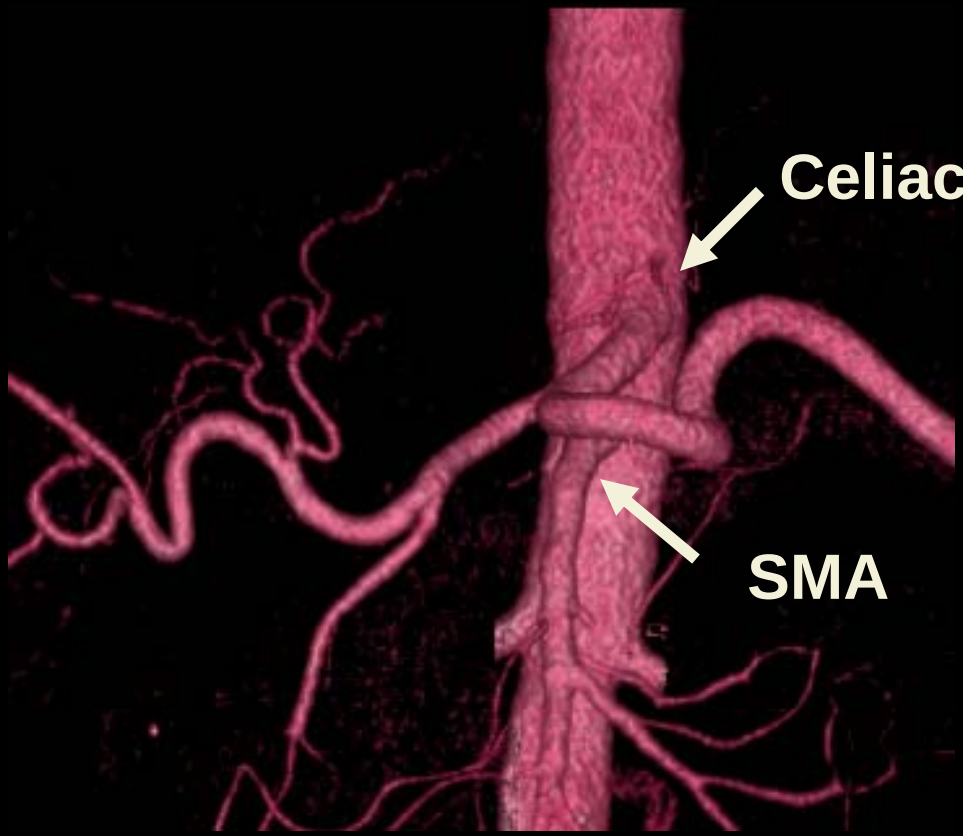
Jabbour, et. al., PRO, 2014

Pancreatic Anatomy

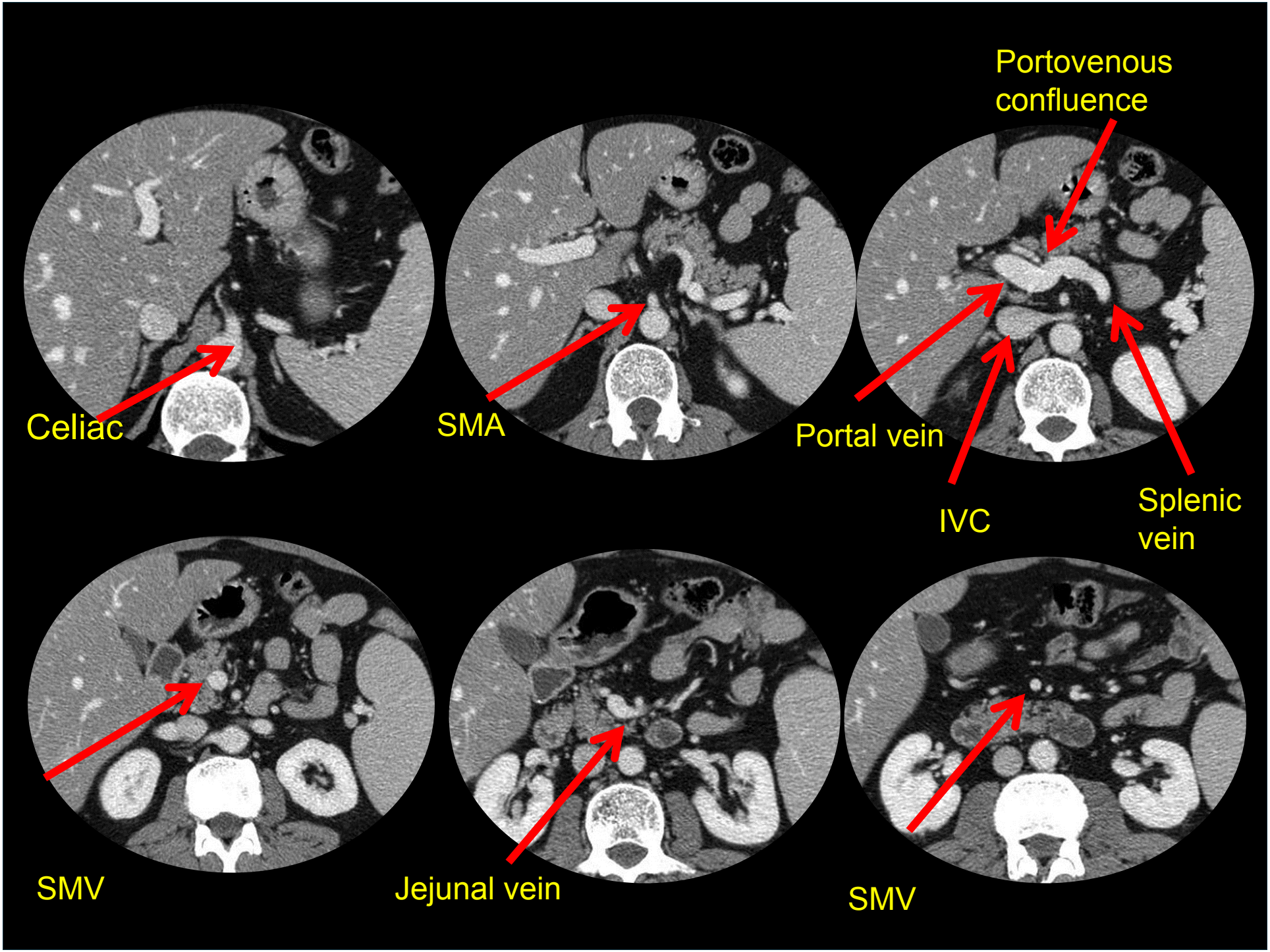


Surgery of the Liver and Biliary Tract. LH Blumgart, et al. 4th edition. W. B. Saunders. 2007

Classic Arterial Anatomy



Winston CB, et al. CT Angiography for Delineation of Celiac and SMA Arterial Variants in Patients Undergoing Hepatobiliary and Pancreatic Surgery. AJR. 2007.


Celiac
SMA
Portovenous confluence
Portal vein
IVC
Splenic vein
SMV
Jejunal vein
SMV

Which of the following is not an important vascular landmark in the abdomen?

1. Subclavian vein
2. Celiac artery
3. Portovenous confluence
4. Superior mesenteric vein
5. Inferior vena cava

Which of the following is not an important vascular landmark in the abdomen?

61% 1. Subclavian vein

3% 2. Celiac artery

2% 3. Portovenous confluence

2% 4. Superior mesenteric vein

32% 5. Inferior vena cava

Subclavian Vein

- The subclavian vein is in the thorax, it is not in the abdomen
- All of the other vessels are located in the abdomen

Outline of Presentation

- Anatomy
  - Basic abdominal anatomy
- Rationale for SBRT for abdominal tumors
  - Emerging clinical data
- Simulation and Motion Management Techniques
  - Compression Belt
  - Respiratory Gating
- Treatment Planning
  - Dose constraints

Radiotherapy for Liver Tumors

- Limited by low tolerance of liver to radiation
- Whole liver irradiation associated with risk of radiation-induced liver disease (RILD)

Clinical Syndrome

- Fatigue
- Elevated liver enzymes (Alk phos)
- Tender anicteric hepatomegaly
- Ascites

Pathologic Changes

- Hyperemia acutely
- Veno-occlusive disease
- Central venous congestion, sparing large veins
- Atrophy of adjacent hepatocytes

Excessive dose of radiation to the liver can cause radiation-induced liver disease (RILD) which is characterized by all of the following except:

1. Fatigue
2. Ascites
3. Neuropathy
4. Elevated Liver Enzymes
5. Hepatomegaly

Excessive dose of radiation to the liver can cause radiation-induced liver disease (RILD) which is characterized by all of the following except:

2%	1. Fatigue
7%	2. Ascites
82%	3. Neuropathy
3%	4. Elevated Liver Enzymes
7%	5. Hepatomegaly

Neuropathy

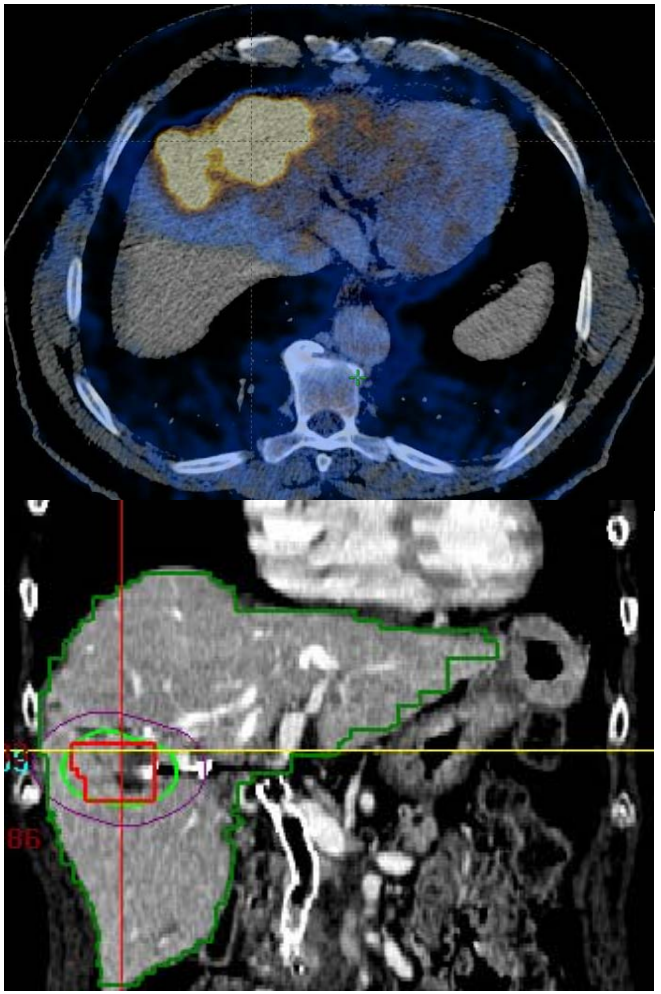
RILD Clinical Syndrome

- Fatigue
- Elevated liver enzymes (Alk phos)
- Tender anicteric hepatomegaly
- Ascites

- Neuropathy is not a classic finding of RILD

Radiotherapy for Liver Tumors

- Improved imaging and localizing techniques allow accurate targeting of focal hepatic lesions
- Deliver tumoricidal doses while sparing normal liver parenchyma
- Options to deliver RT more focally
  - 3DCRT
  - Intensity Modulated Radiotherapy
  - Stereotactic Body Radiotherapy



Unresectable Liver Metastases

- 150,000 cases of colorectal cancer diagnosed annually
- 50% of CRC patients will develop liver metastasis
- Surgery is gold standard for CRC liver metastases
  - 5-year survival approximately 50%
- Only 15% of CRC liver metastases are resectable
- Chemotherapy
  - 15 - 40 % Response Rate
  - First Line Chemo: 15-22 months survival
  - Historical 5-year survival <5%

First Liver SBRT Experience

- 50 patients treated to 75 lesions with SBRT for primary and metastatic liver tumors
- 15 to 45 Gy, 1-5 fractions
- Mean follow-up of 12 months
- 30% of tumors demonstrated growth arrest, 40% were reduced in size, and 32% disappeared by imaging studies
- 4 local failures (5.3%)
- Mean survival time was 13.4 months

Blomgren, et. al., J Radiosurgery, 1998

Single Fraction SBRT

- N = 60 unresectable liver tumors (37 pts)
- Dose escalation: 14-26 Gy, 80% isodose line surrounding PTV
- No RILD

# Patients	Dose	18 month LC
60	14-26 Gy	67%
5	14-16 Gy	0%
55	20-26 Gy	81%

Herfarth, et. al., JCO, 2001

Single Fraction SBRT

- Stanford Phase I Dose Escalation Study
- 2/04 – 2/08, 26 patients treated to 32 targets
- 40 identifiable lesions treated within targets
- 4 dose levels (18Gy, 22Gy, 26Gy, 30Gy)
- Mean treatment volume: 32.6cc (range 7.5 – 146.6 cc)
- 19 with hepatic metastases, 5 with IHCC, 2 with recurrent HCC

Goodman KA, et al., IJROBP, 2010

Single Fraction SBRT Toxicity

Dose Group (Gy)	No. Patients	Grade 1				Grade 2
		Nausea	Ab Pain	Fatigue	Fever	Duodenal Bleed*
18	3	0	0	0	0	1**
22	6	1	1	1	1	1
26	9	3	0	1	0	1
30	8	1	0	0	0	0
Total	22	5	1	2	1	3

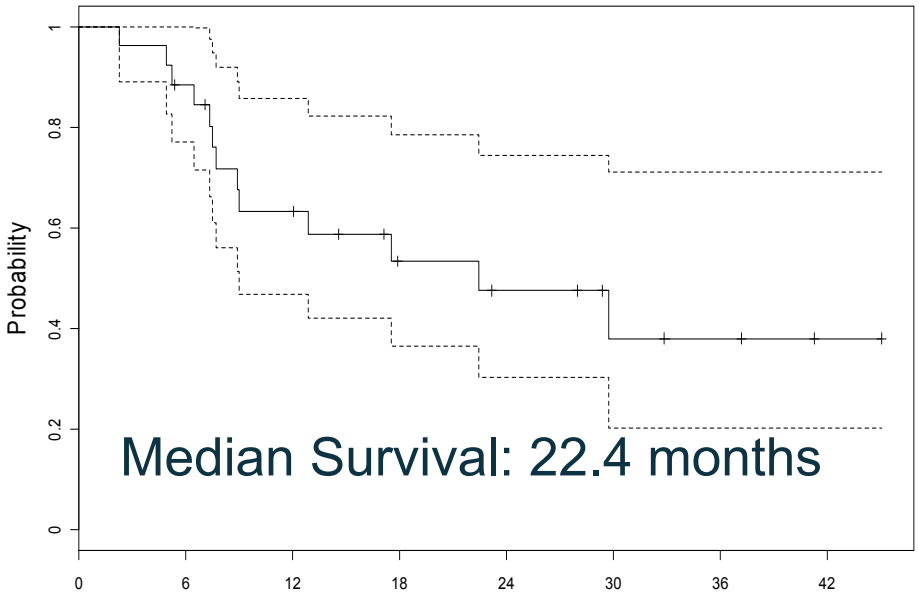
* All three of the patients who developed duodenal ulcers had been treated to sites in the porta hepatis

** This patient developed a duodenal ulcer after additional external beam irradiation to the porta hepatis for local failure

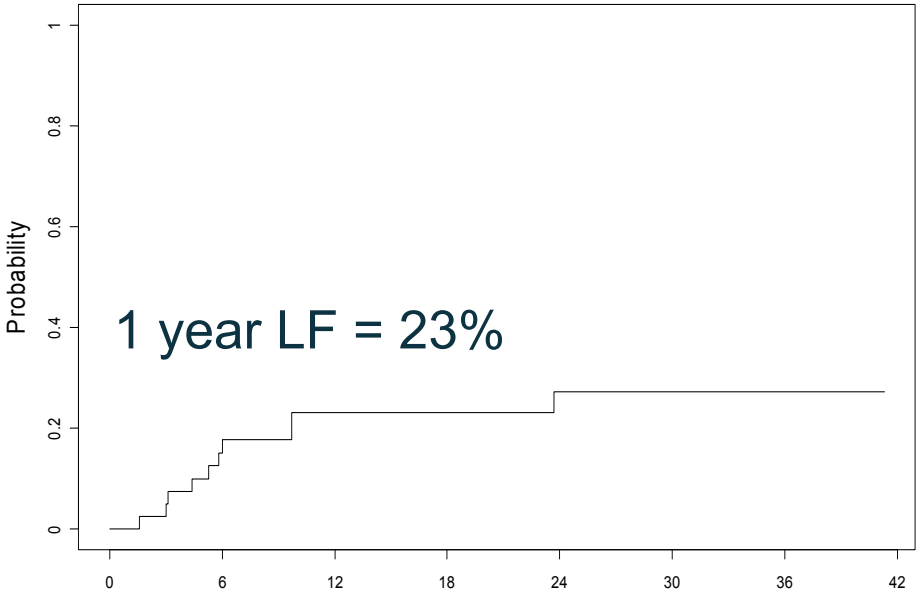
Goodman KA, et al., IJROBP, 2010

Single Fraction SBRT Outcomes

Median Follow-up = 14 mos



Overall Survival



Cumulative Incidence of LF

Goodman KA, *et al*., IJROBP, 2010

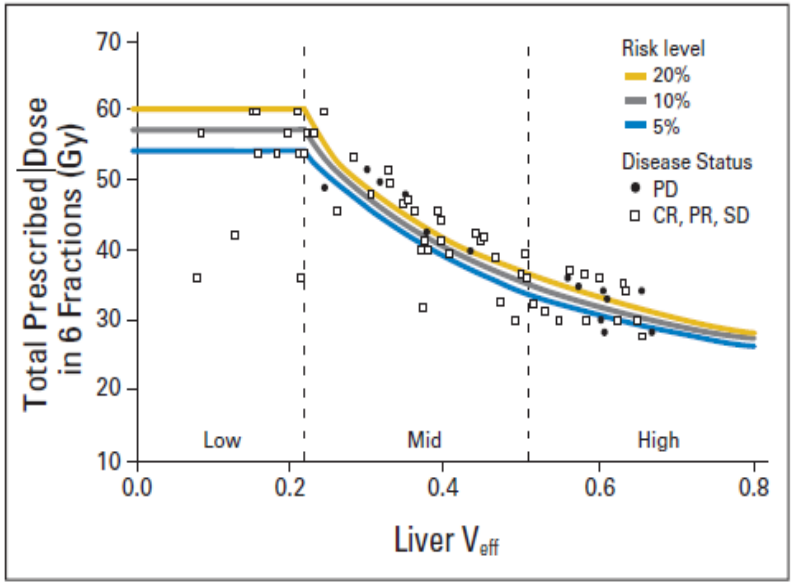
Hypofractionated SBRT

- Phase I/II Study
  - Dose escalation: 36 – 60 Gy in 3 fractions
- 47 patients with 56 lesions (1-3 lesions)
  - 13 pts received <60Gy, 36 received 60Gy
  - Median lesion volume: 15 cc
  - Respiratory gating
  - At least 700 cc had to receive < 15Gy
- Median follow-up: 16 mos
- 2 yr LC: 92% (100% for lesions ≤3cm)
- Grade 3+ toxicity: <2%

Rusthoven K, et. al., J Clin Oncol, 2009

Hypofractionated SBRT

- Phase I study of individualized 6 fraction SBRT for liver metastases in 68 pts
- Median SBRT dose: 41.8 Gy (27.7 to 60 Gy)
- Median tumor vol: 75 cc
- 1-year LC: 71%
- Minimal Toxicity
  - 2 grade 3 LFT changes
  - 6 acute grade 3 toxicities
  - No RILD



Lee M, et. al., J Clin Oncol, 2009

Hypofractionated SBRT

- Phase I/II Study UT Southwestern
  - 28 patients/136 tumors – 27 patients evaluable
  - Dose escalation to 60 Gy (5 fractions)
  - No Grade 3+ treatment-related toxicities

	Response rate	2 yr LC
30Gy (n=9)	30%	56%
50Gy (n=9)	50%	90%
60Gy (n=9)	90%	100%

Rule, et al, Ann Surg Oncol, 2011

Hypofractionated SBRT

- 61 patients with 76 liver metastases treated on Phase II trial of SBRT
- Objective: In-field local control, assess toxicity
- 75 Gy in 3 fractions to CTV
  - PTV covered by 67% - 50Gy in 3 fractions
  - Dose reduction of up to 30% in 14 patients
- No RILD, 1 Grade 3 chest wall pain
- 1 yr median f/u, 1 yr LC – 94%, 1 yr OS – 84%

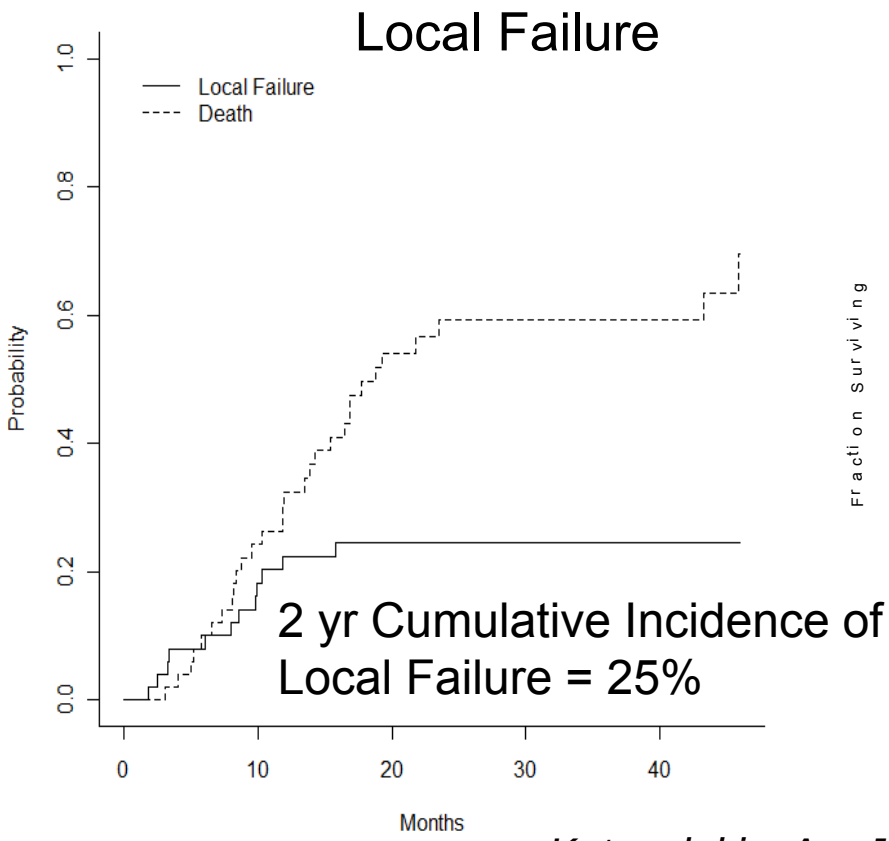
Scorsetti M, Int J Rad Oncol Biol Phys, 2013

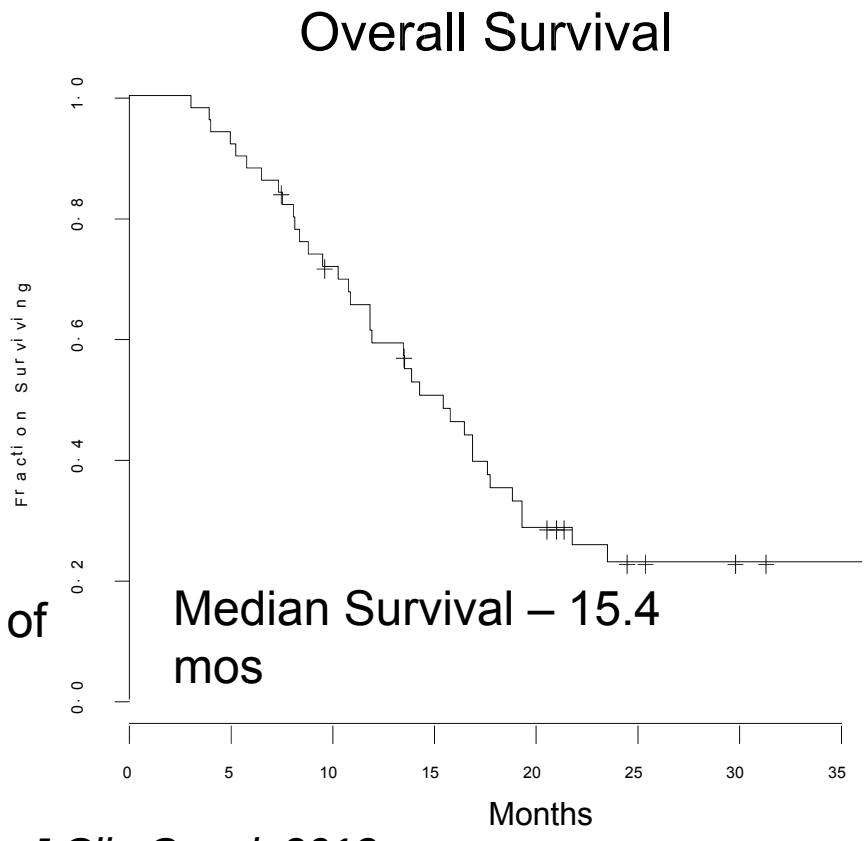
Pooled Analyses

- Chang, *et a*l. Cancer, 2011
  - 65 patients with 102 colorectal metastases
  - Multiple regimens pooled to estimate optimal local control
  - 46 – 52 Gy (3 fractions)
  - 90% 1 yr local control
- Berber, *et al*. HPB, 2013
  - 153 patients with 363 metastatic liver lesions
  - Mean RT dose of 37.5 Gy in 5 fractions
  - 62% 1 yr local control, 51% 1 yr overall survival

MSKCC Experience

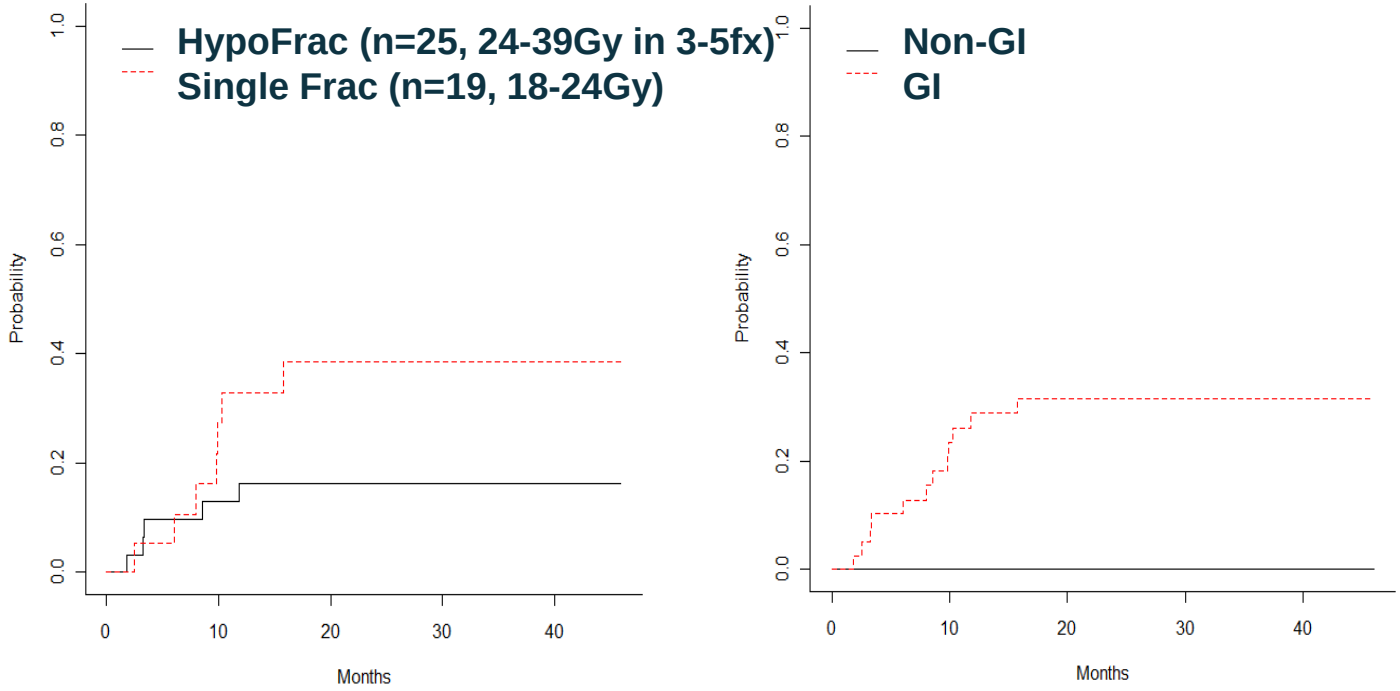
- 46 patients, 50 tumors (10 primary, 40 metastases) treated with SBRT from 3/04-3/11





Katsoulakis, Am J Clin Oncol, 2013

MSKCC Experience



- 3 Late Grade 3-4 GI toxicities, all in 24Gy single fraction and central lesions

Katsoulakis E, Am J Clin Oncol, 2013

SBRT RESULTS

Author/yr	Lesions	Dose-fractionation	Median follow-up (m)	Local control (%) 1, 2 years	Survival (%) 1, 2 years
Blomgren/'98	20	2-4x10-20Gy	Mean 9.6	95	Mean 17.8m
Herfarth/'01	102	1x20-26Gy	Mean 14.9	66, 60	76, 55
Fuss/'04	17	6x6Gy or 3x12Gy	6.5	94, NRC	80, NRC
Wulf/'01	51	3x12-12.5Gy or 1x26Gy 3x10Gy or 4x7Gy	15	100, 82 (high) 92, 66 (low)	72, 34
MéndezRomero/'06	34	3x10-12.5Gy	12.9	100, 86	85, 62
Hoyer/'06	141	3x10 Gy	52	NRP, 86	67, 38
Katz/'07	182	17.5 – 56 Gy in 2-10 fx		88%	
Rusthoven/'09	47	3 x 12-20Gy Dose escalation	16	95, 92	Median 17.6m
Lee/'09	68	Individualized dose 27.7-60Gy/ 6 fx	10.8	71, NRP	47% @18mo
Goodman/'10	19	18-30Gy single fx	17.3	77, NRP	62, 49
Rule/'11	136	5 x 6-10Gy Dose escalation	20	56/56 100/89 100/100	56 @ 2yr 67 @ 2yr 50 @ 2yr

Unresectable Hepatocellular Carcinoma

- Until recently, minimal role for RT
  - Perceived radioresistance of HCC
  - Underlying liver dysfunction increased risk of liver toxicity
- CT-based planning allowed more targeted RT
- Studies of 3DCRT in Asia and Univ. of Michigan demonstrated feasibility of dose escalated RT
- 1-year local control ranged from 50-80%

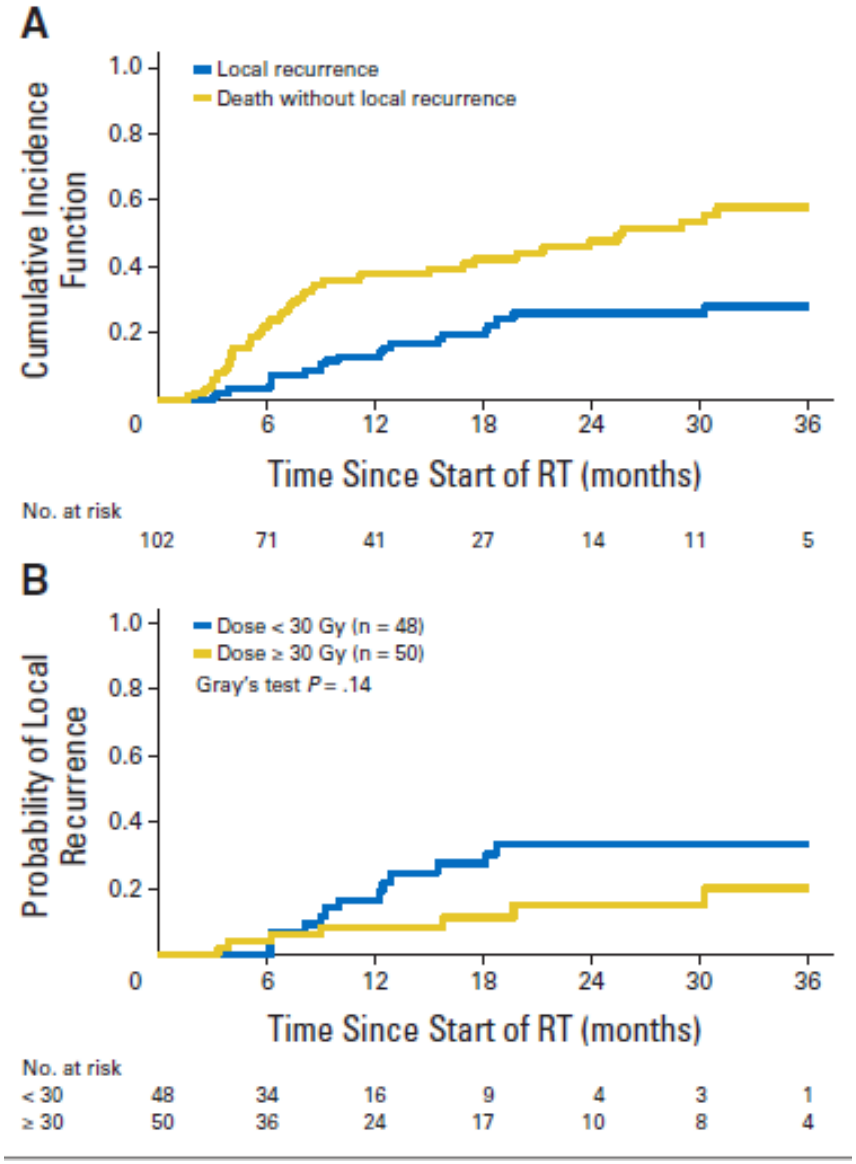
SBRT for Primary Liver Tumors

- 102 patients with locally advanced HCC enrolled on 2 prospective studies of SBRT
  - Childs A liver function
  - Tumor vascular thrombosis in 55%
- Prescribed a variable dose (24 – 54 Gy) over 6 fractions
- Median gross tumor volume was 117.0 cc (1.3 to 1,913.4 cc)
- Median follow-up was 31.4 months

Bujold A, et. al., J Clin Oncol, 2013

SBRT for Primary Liver Tumors

- 1 year LC was 87%
- Median OS was 17 mos
- Grade 3+ toxicity in 30%
- Possible Grade 5 in 7 patients (2 with TVT PD)
- Dose >30 Gy improves LC rates
- Even in this high-risk HCC population, SBRT associated with good LC



Phase I-II Trial of SBRT in Patients with HCC, Child-Pugh Class A and B

- Interim analysis of variables affecting toxicity and outcome

	CPC A	CPC B
Total Dose/# Fractions	4800cGy/3	4000cGy/5
2 yr LC	87%	85%
2 yr PFS	55%	28%
2 yr OS	81%	28%
Grade 3-4 Liver Toxicity	14%	33%

- Mean Tumor Volume = 33 cc
- For CPC B pts, volume effect on Grade III/IV liver toxicity
- SBRT for CPC A patients is feasible and safe
- SBRT for CPC B patients is still associated with significant toxicity in uncompensated liver and while SBRT results in LC, the overall outcome of this disease may not be addressed by local therapy

Lasley FD, ASTRO 2012

SBRT Trials for HCC

Author/yr	Lesions	Dose-fractionation	Median follow-up (m)	Local control (%) 1, 2 years	Survival (%) 1, 2 years
Mendez-Romero/ '06	5 CPC A, 2 CPC B, 1 w/o cirrhosis 11 lesions	5 Gy x 5 or 10-12.5 Gy x 3	12.9	75% at 22 mo	75%, 40%
Tse/'08	21 CPC A	36 Gy (24-54 Gy) in 6 fx	17.6	65% @ 1yr	48% @ 1yr
Cardenes/ '10	6 CPC A, 11 CPC B	12-16 Gy x 3, 8 Gy x 3	24	100%	75%, 60%
Lasley/'12	36 CPC A/ 21 CPC B	48Gy in 3 or 40Gy in 5 fx		87%/85% @ 2yr	81%/35% @ 2 yrs
Dawson/'13	102 CPC A	24Gy - 54Gy in 6	31	87% @ 1yr	Median Survival = 17 mo

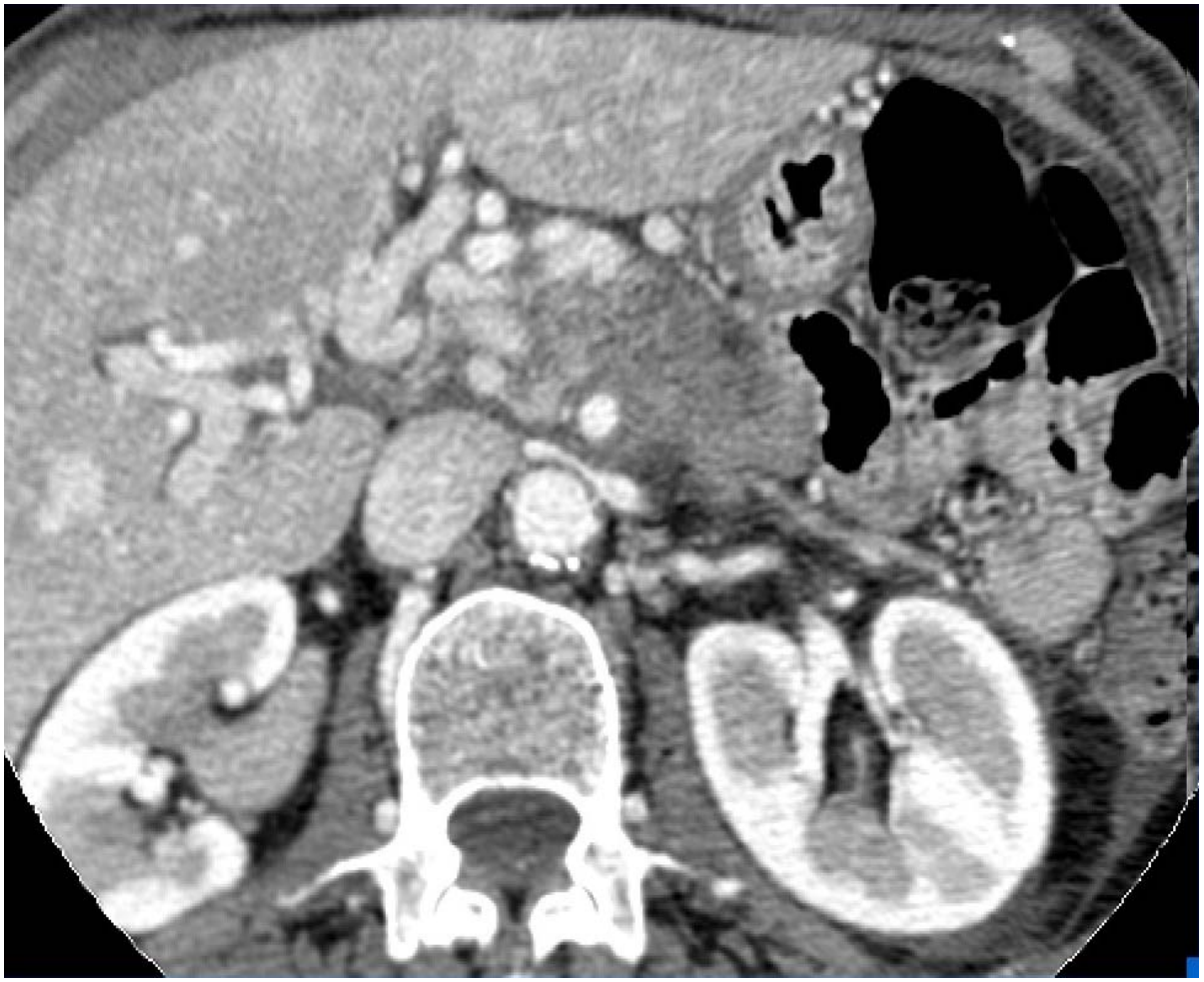
SBRT for Unresectable Intrahepatic and Hilar Cholangiocarcinoma

- Brachytherapy has been used as a boost to improve focal delivery of RT dose
- Availability of and expertise in biliary brachytherapy is limited
- SBRT is another option to deliver high, focal doses to the liver hilum and intrahepatic tumors

SBRT for Unresectable Intrahepatic and Hilar Cholangiocarcinoma

Author/yr	Lesions	Dose-fractionation	Median follow-up (m)	1 Year Local control (%)	Median Survival
Tse/'08	10 IHCC	32.5 in 6 fx	17.6	65%	15 mo
Kopek/'10	27 (26 hilar CC, 1 IHCC)	45 Gy in 3 fx	60 mo	84%	10.4 mo
Goodman/'10	5 IHCC	18-30Gy in 1 fx	17	77%	29 mo
Barney/ '12	10 pts, 12 lesions	55 Gy in 3-5 fx	14	100%	14 mo
Mahadevan/'12	20 pts/25 lesion	30 Gy in 3 fx		93%	17 mo

Unresectable Pancreatic Cancer



Pancreatic Cancer Epidemiology

- 45,000 pancreatic cancers diagnosed
- 38,500 deaths
- 4th leading cause of mortality from malignant disease
- Median Survival Times
  - Resectable, 18-22 months
  - Locally advanced, 12-15 months
  - Metastatic, 6-10 months

Siegel, *et al*, CA Cancer J Clin 2014

SBRT: Trials for Pancreas Cancer

Study	N	Prior EBRT	Regimen	Median OS Months	Toxicity
Koong, Phase I	15	2	15-25Gy /1 fx	11	33% G1-2 acute/NR
Koong, Phase II	16	16	45Gy/25 fx + 25Gy/1 fx	8.3	12% G3 acute/G2 late ulcers
Schellenburg,	16	0	25 Gy/1 fx	11.4	6% acute G3/ 13% late G3
Hoyer,		0	45 Gy/3 fx	5.7	18% severe GI toxicity
Mahadevan, 2010	36	0	24-36 Gy/3 fx	20.0	5% G3
Polistina, 2010	23	0	30 Gy/3 fx	10.6	No acute /late G2/3
Tozzi, 2013	30	0	45 Gy/6 fx	11.0	No acute /late G2/3
Gurka, 2013	11	0	25 Gy/5 fx	12.2	No acute /late G2/3
Herman, 2013	49	0	33 Gy/5 fx	13.9	8% late G3

Duodenal Doses

- Median time to duodenal toxicity: 6.2 mos
- 6- and 12-mo actuarial rates of toxicity: 11% and 29%

Variable*	Cutoff†	Incidence of Grade 2–4 duodenal toxicity (%)‡	Log-rank *p* value
V5			
	<25 cm^3	28	0.39
	≥25 cm^3	31	
V10			
	<16 cm^3	15	0.015
	≥16 cm^3	46	
V15			
	<9.1 cm^3	11	0.002
	≥9.1 cm^3	52	
V20			
	<3.3 cm^3	11	0.002
	≥3.3 cm^3	52	
V25			
	<0.21 cm^3	12	0.010
	≥0.21 cm^3	45	

* V5 refers to the volume of duodenum receiving 5 Gy.
† Cutoff refers to the median value.
‡ Actuarial incidence at 12 months.

Murphy J, *et al*., IJROBP, 2012

Phase II Multi-Institutional Study of Stereotactic Body Radiation Therapy for Unresectable Pancreatic Cancer

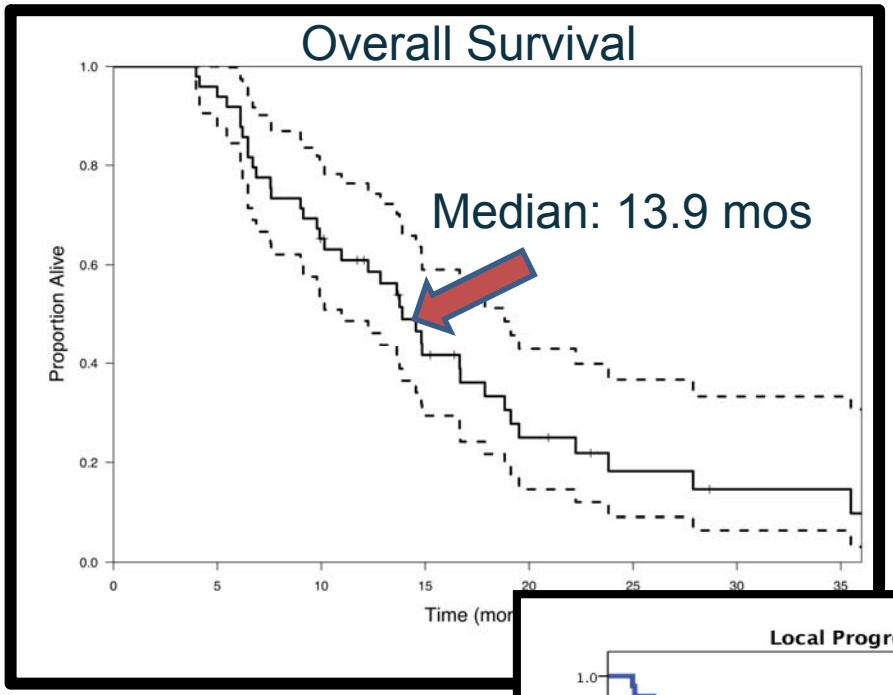
(Herman, Chang, Goodman, Koong PI's)

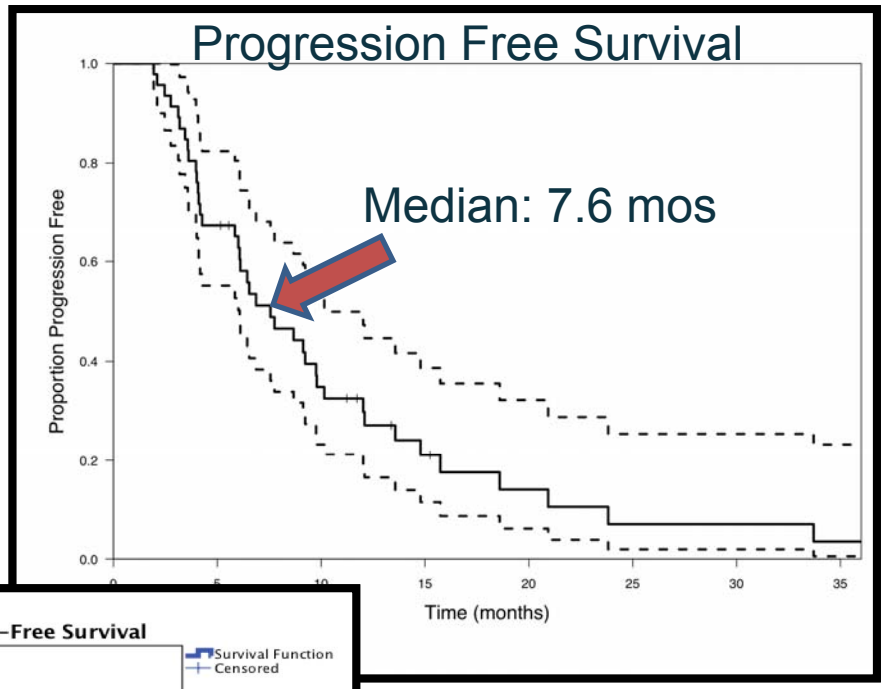
(GEM, up to 1 Cycle allowed)* → **1 week break** → **F-SBRT 6.6 Gy x 5 Mon-Fri** → **1 week break** → **GEM Chemotherapy (3 wks on, 1 wk off) Until toxicity or progression**

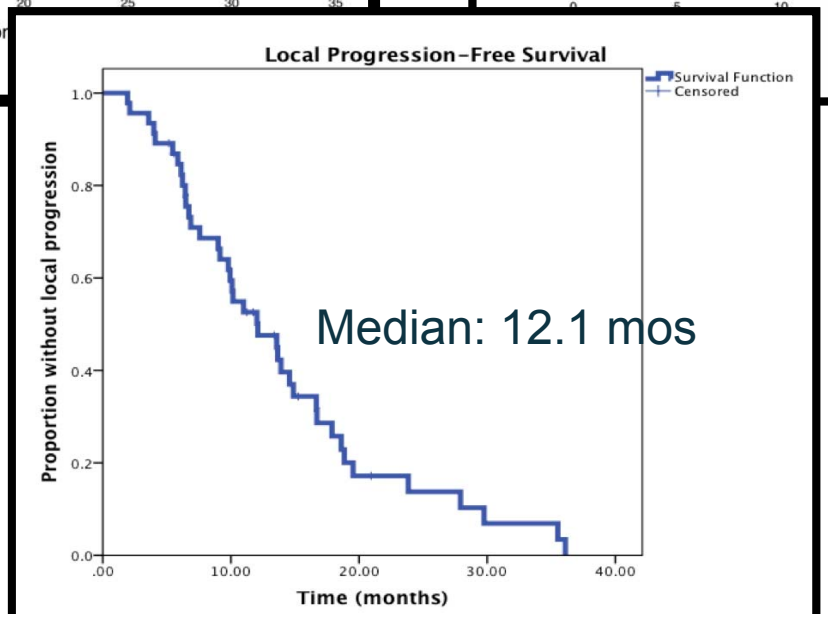
Primary endpoint: Late GI Toxicity > 4 months

Secondary: Tumor Progression Free Survival, pre-tx biopsy, PET/CT QOL, biomarkers.

Outcomes







Herman et al. J Clin Oncol, 2014 submitted

Toxicity and QOL

- Toxicity
  - Acute GI
    - Grade 1-2: **10%**
    - Grade ≥3: **0%**
  - Late GI
    - Grade ≥3: **8%**
      -GI bleed (2)

- Quality of Life (EORTC)
  - Mean global QOL
    - scores unchanged pre/post SBRT
  - Pancreas specific QOL
    - Improved ($p<0.05$)
      - pancreatic pain
      - body image

Herman et al. J Clin Oncol, 2014 submitted

For a 2 cm locally advanced tumor of the pancreatic head, the most severe dose limiting factor for 5 fraction SBRT would be:

1. Risk of radiation induced liver toxicity
2. Proximity to the right kidney
3. Proximity to the duodenum
4. Proximity to the chest wall
5. Proximity to the common bile duct

For a 2 cm locally advanced tumor of the pancreatic head, the most severe dose limiting factor for 5 fraction SBRT would be:

7%	1. Risk of radiation induced liver toxicity
3%	2. Proximity to the right kidney
84%	3. Proximity to the duodenum
2%	4. Proximity to the chest wall
4%	5. Proximity to the common bile duct

Proximity to the Duodenum

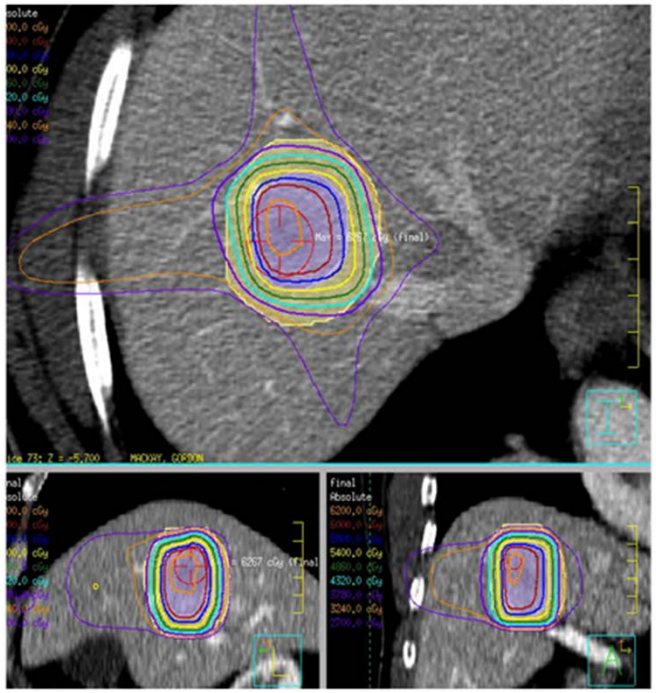
- The head of the pancreas is surrounded on 3 sides by the C-loop of the duodenum, thus, irradiating the pancreatic head mass would lead to partial irradiation of the duodenum.

Outline of Presentation

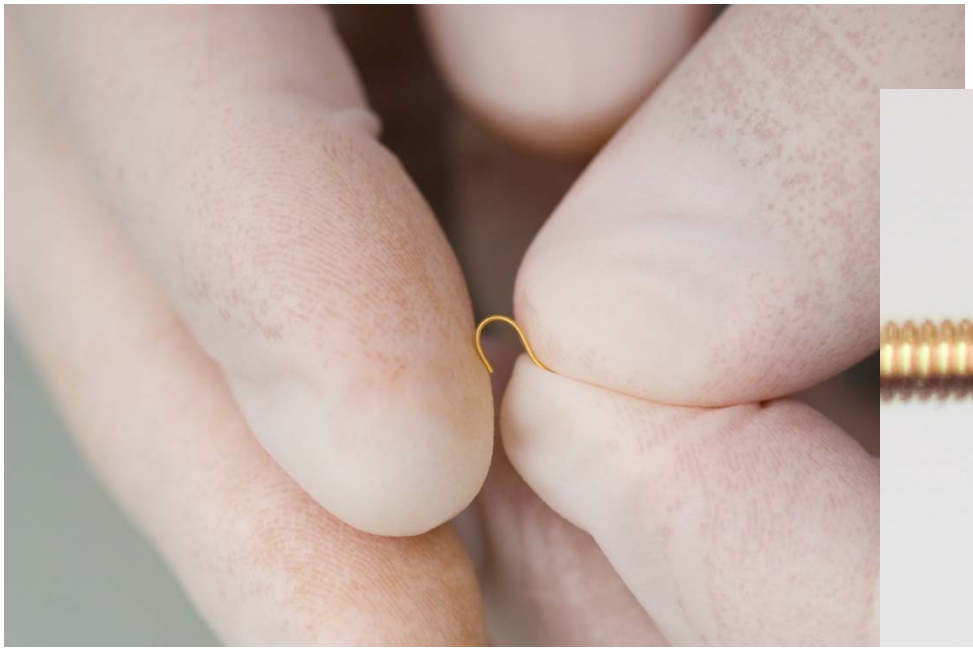
- Anatomy
  - Basic abdominal anatomy
- Rationale for SBRT for abdominal tumors
  - Emerging clinical data
- Simulation and Motion Management Techniques
  - Compression Belt
  - Respiratory Gating
- Treatment Planning
  - Dose constraints

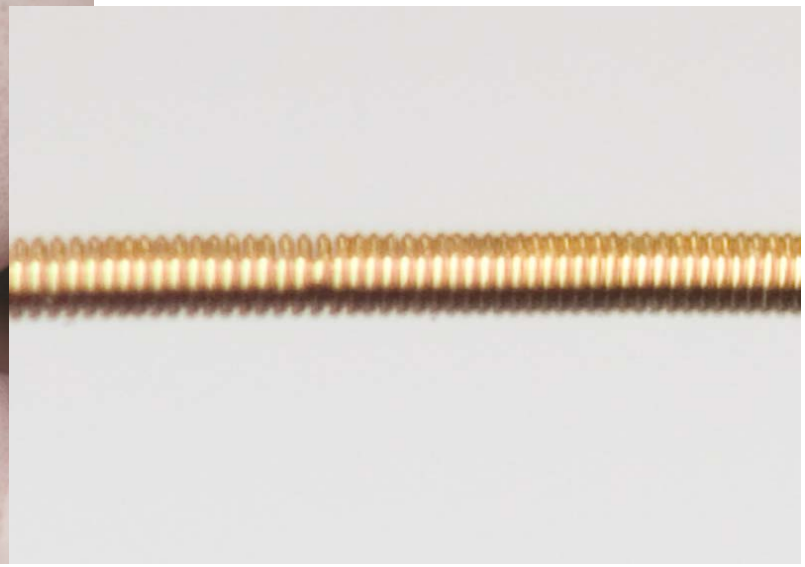
Challenges in Targeting Abdominal Tumors

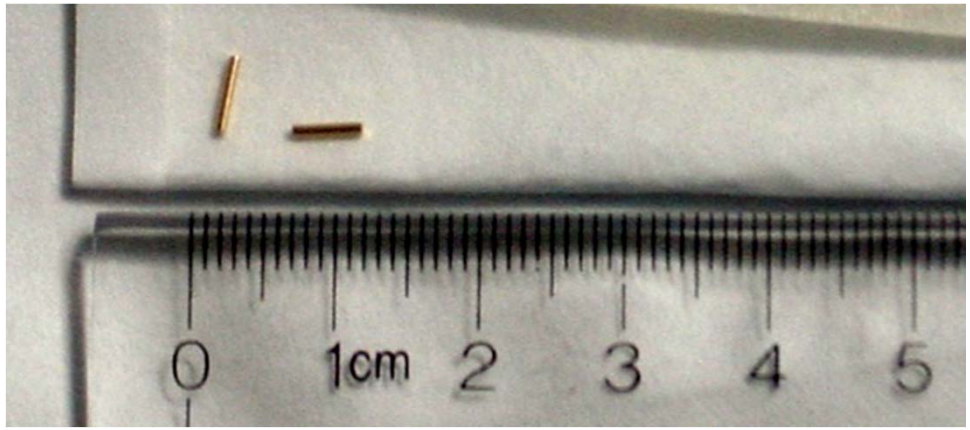
- Limited visualization of the target
- Organ deformation with respiration
- Changes in GI organ luminal filling
  - Critical structures (stomach) may change in shape and position between planning and treatment
- Interfraction target displacement with respect to bony anatomy



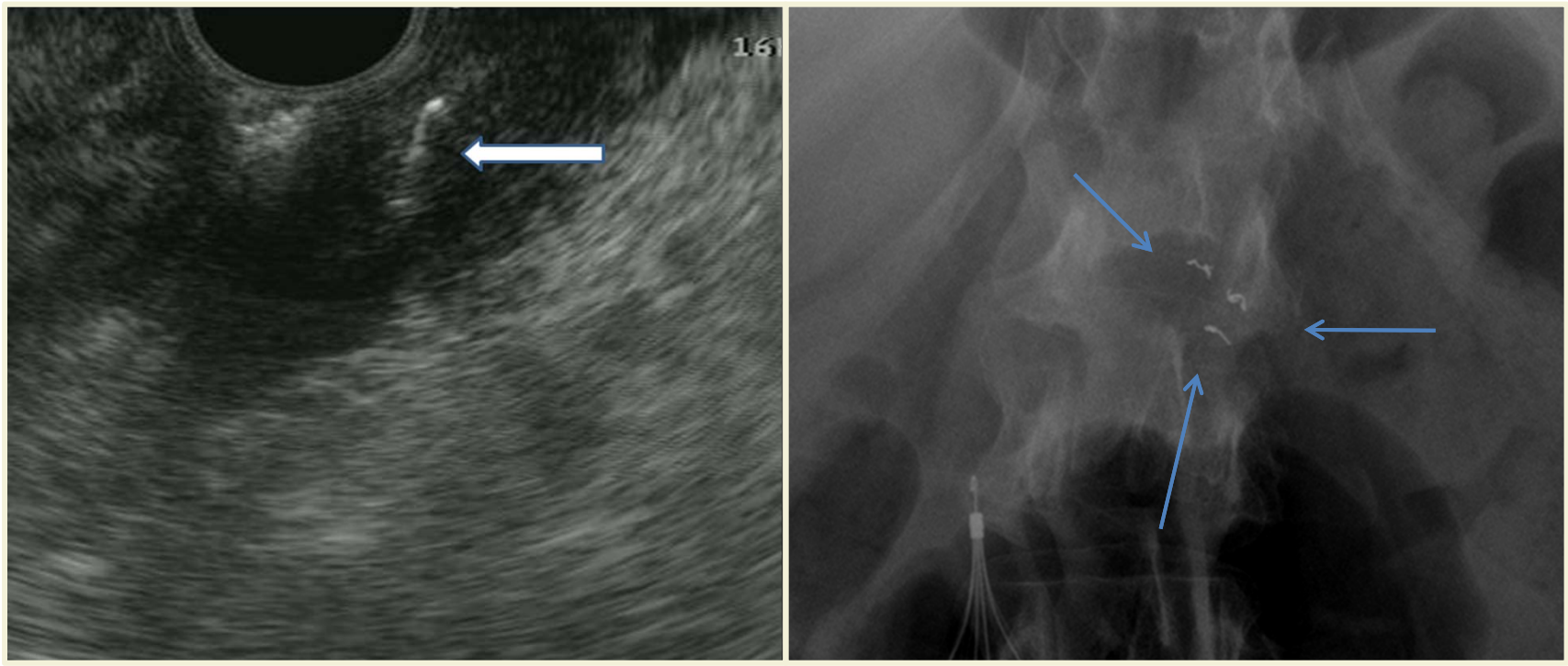
Fiducial Markers





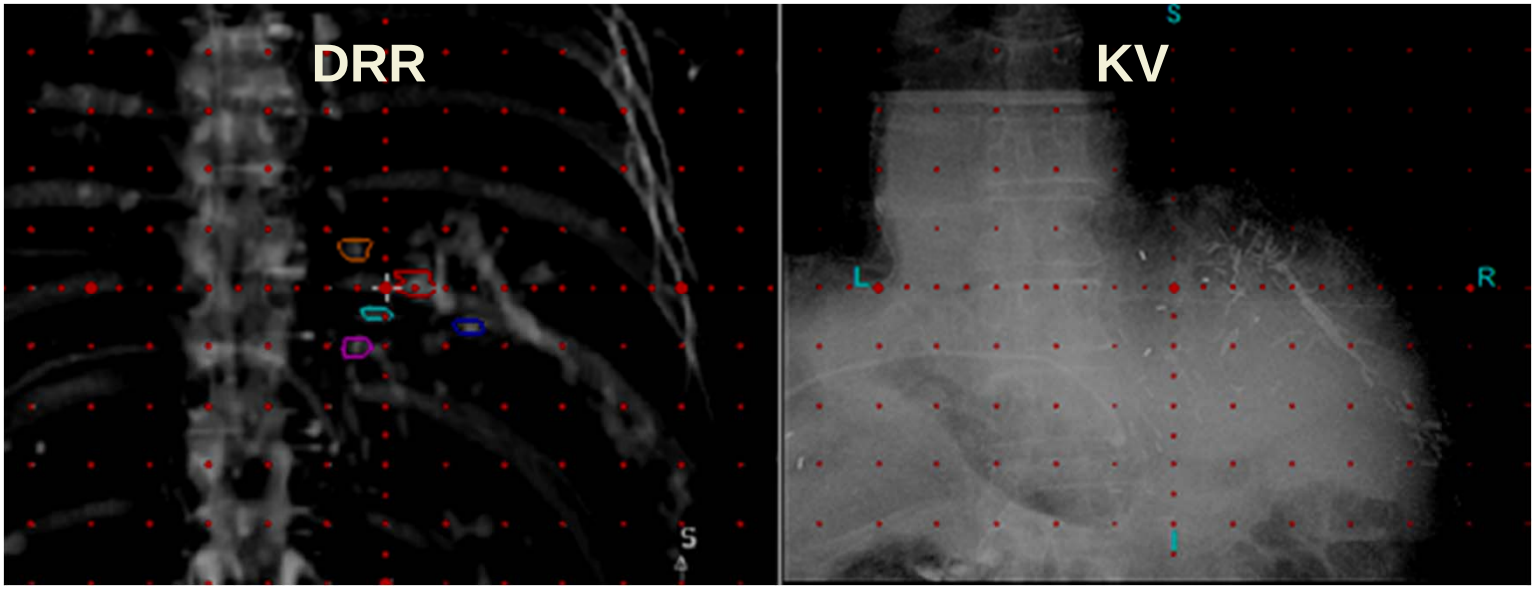


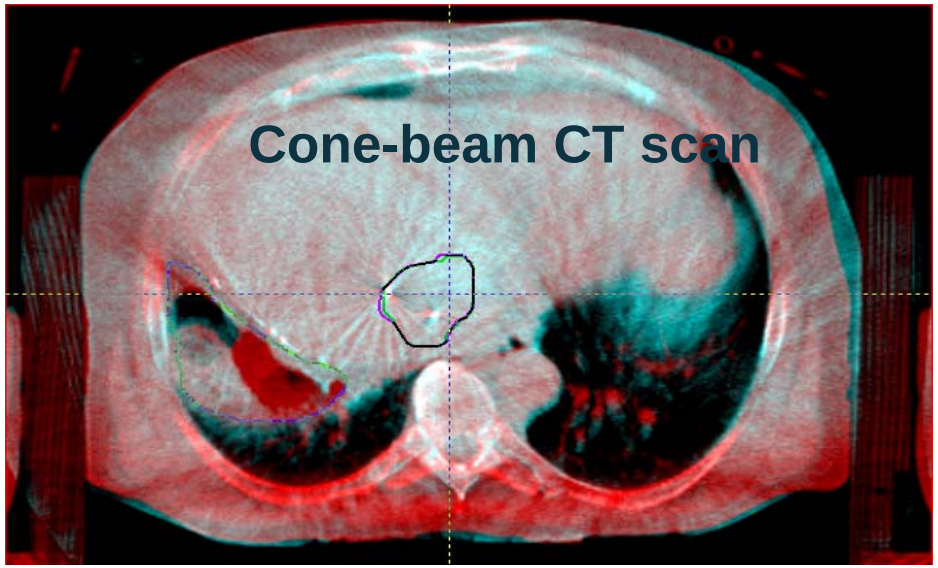
Fiducial Markers



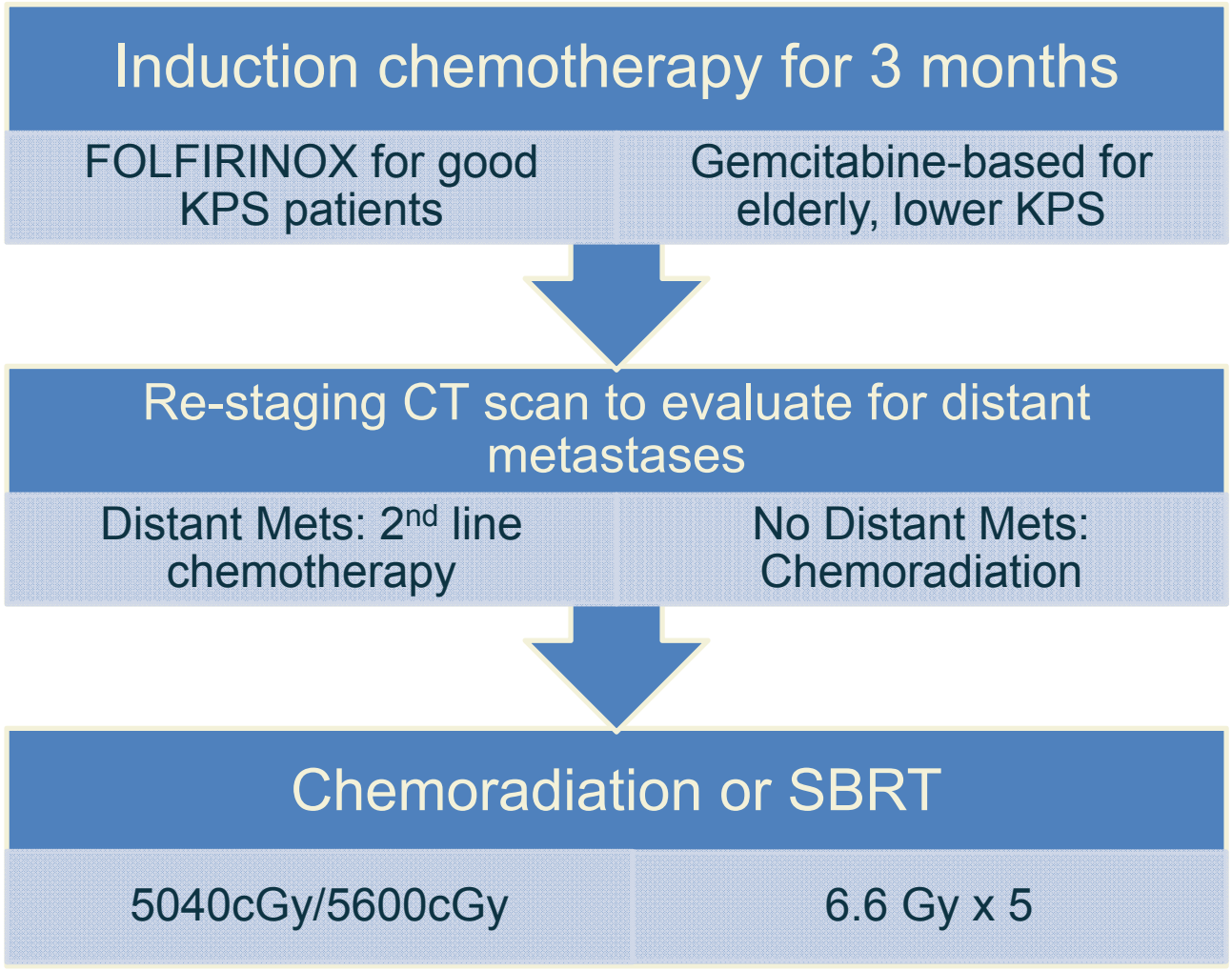
EUS-guided placement

Fiducial Markers: Daily Set-Up





Treatment Paradigm at MSKCC

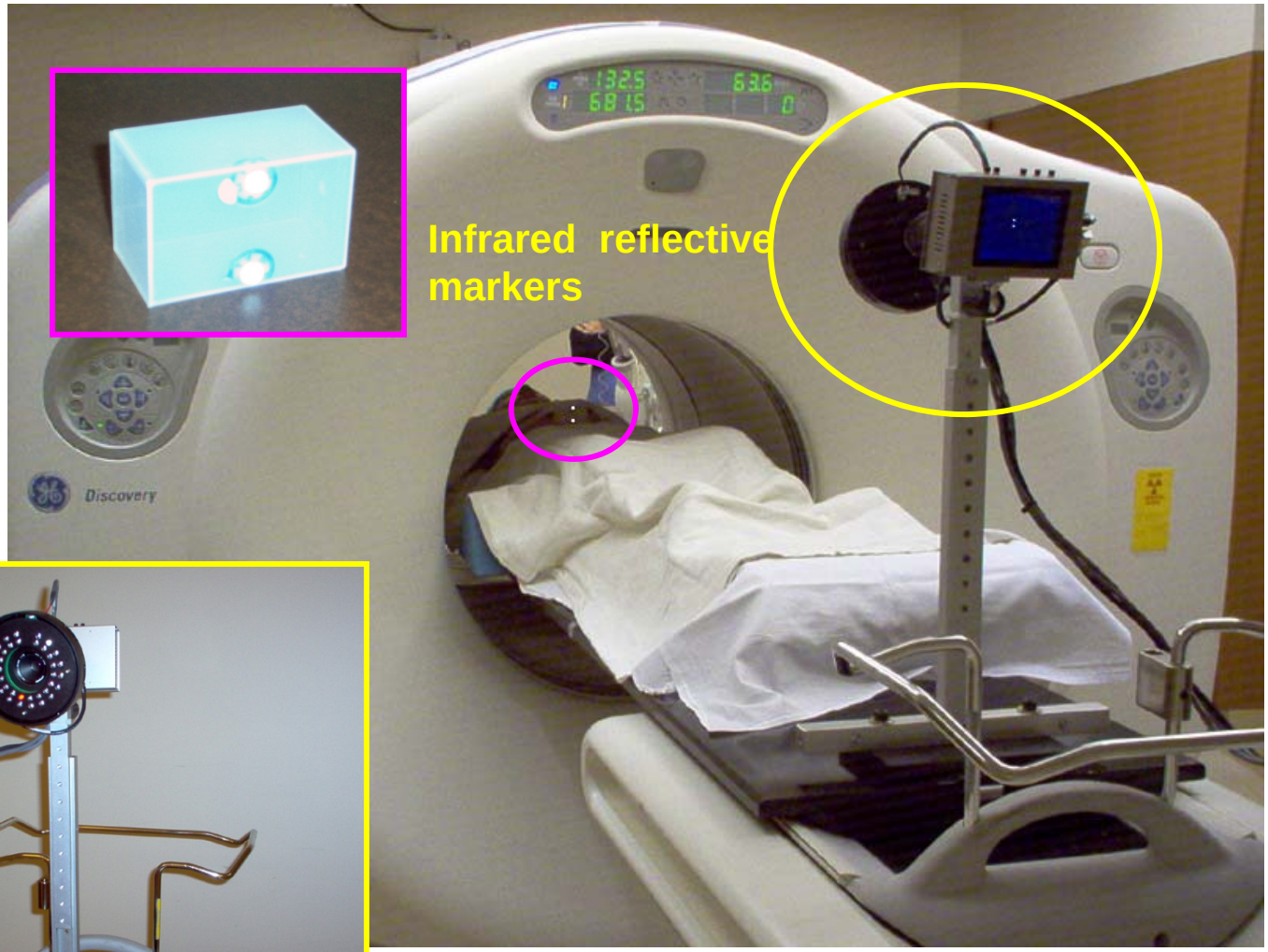


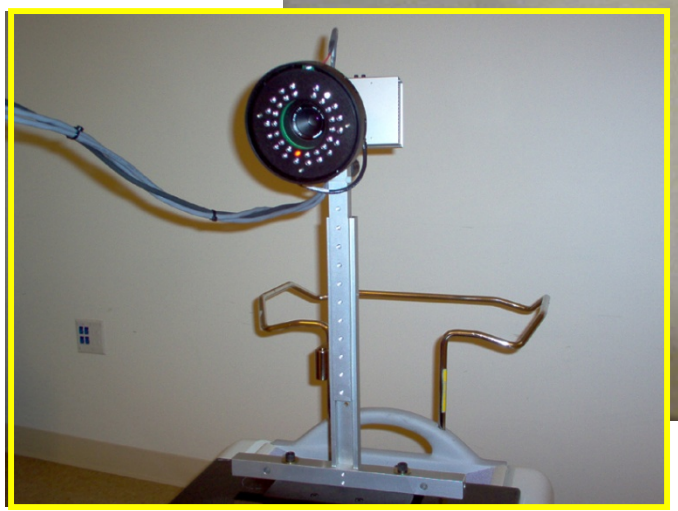
Simulation

- Supine, arms up immobilized in alpha cradle
- IV and PO contrast
- NPO 4 hours prior to simulation
  - Empty stomach for simulation and for daily treatment
- For respiratory gating patients
  - Scan during end-exhalation breath hold
  - 2.5 mm slice thickness
  - 4DCT with voice coaching
- For compression belt patients
  - Fluoro to determine pressure needed
  - PET/CT with compression applied

4-D PET/CT Simulation

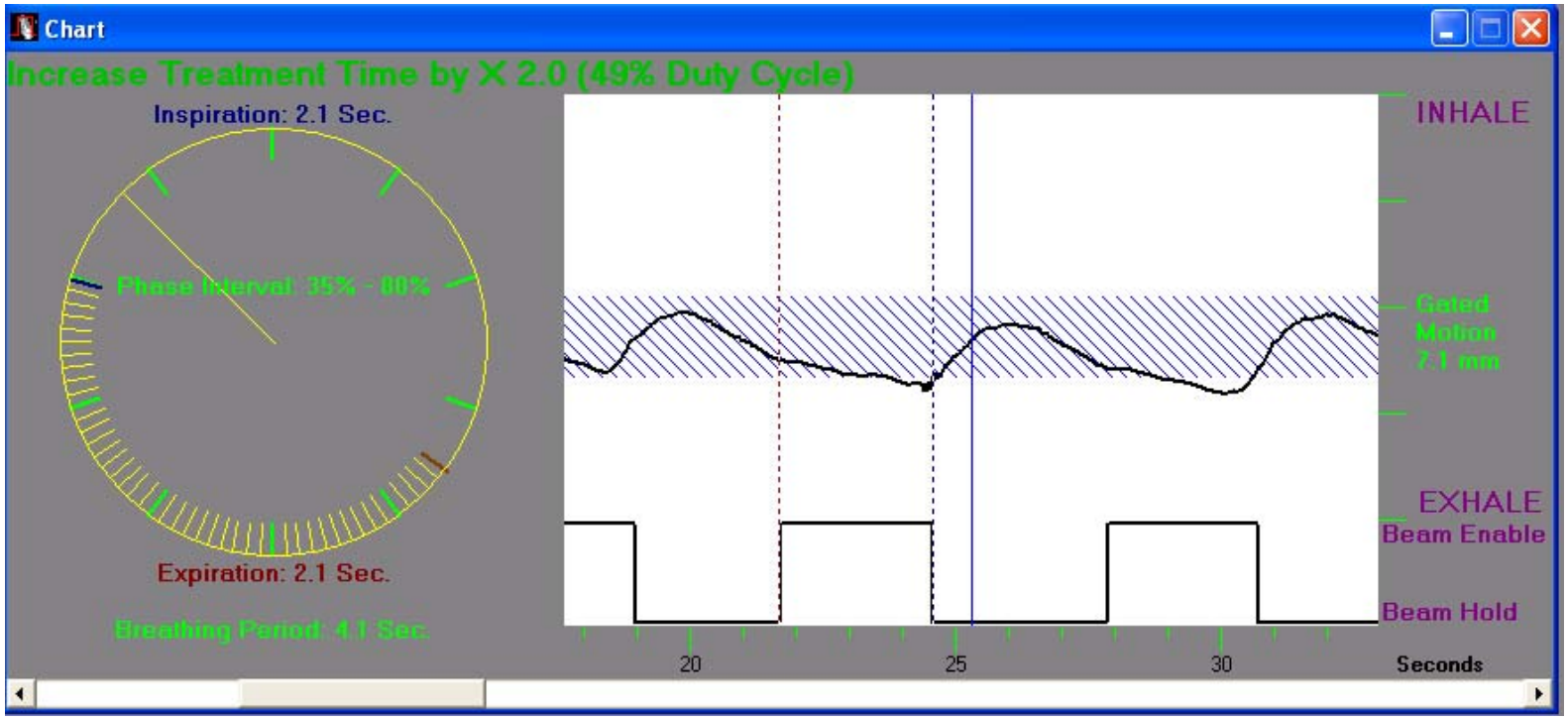
GE Discovery ST^8 PET/CT and Varian RPM





Infrared camera

Respiratory Cycle Tracing



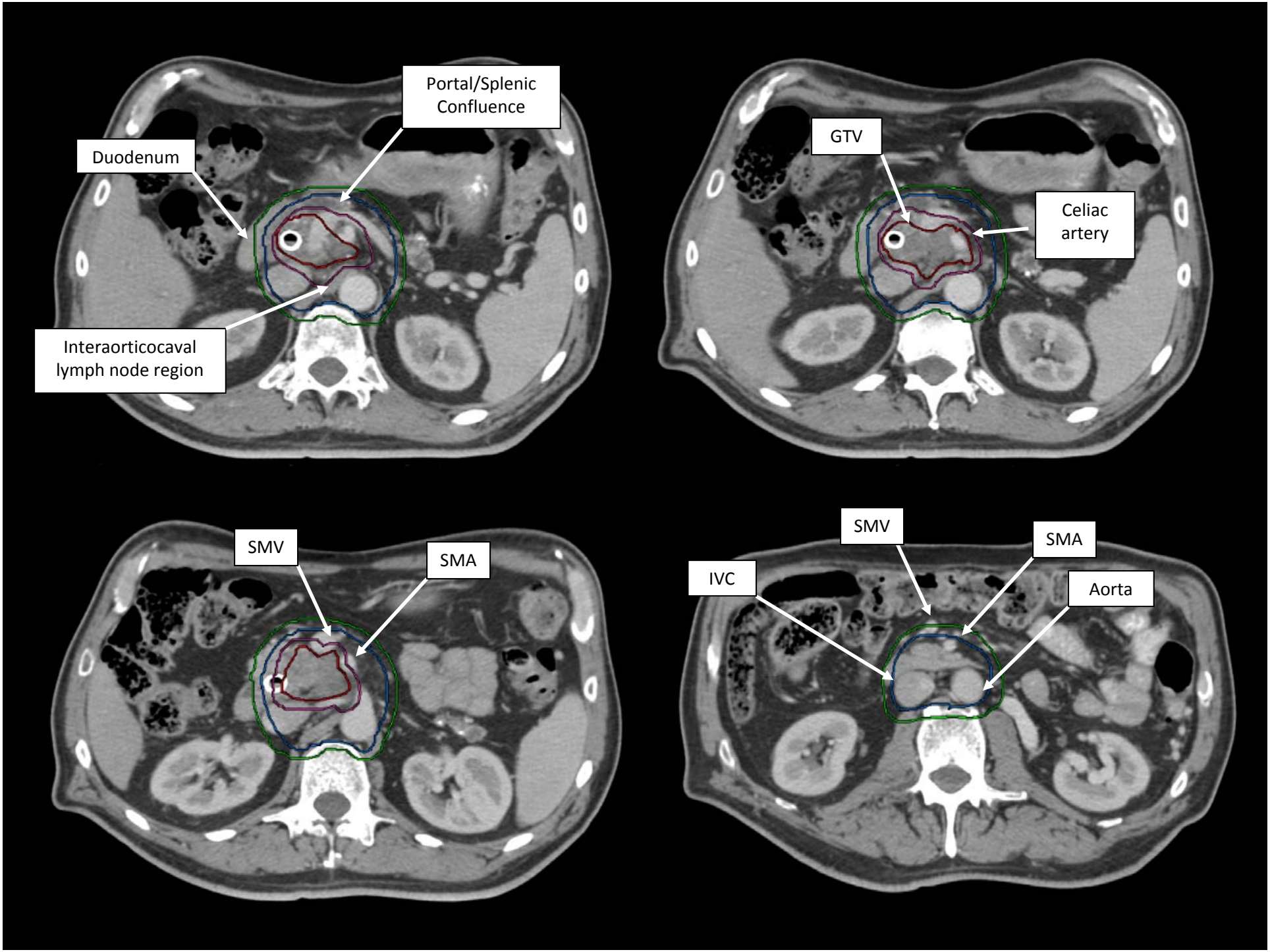
Target Delineation

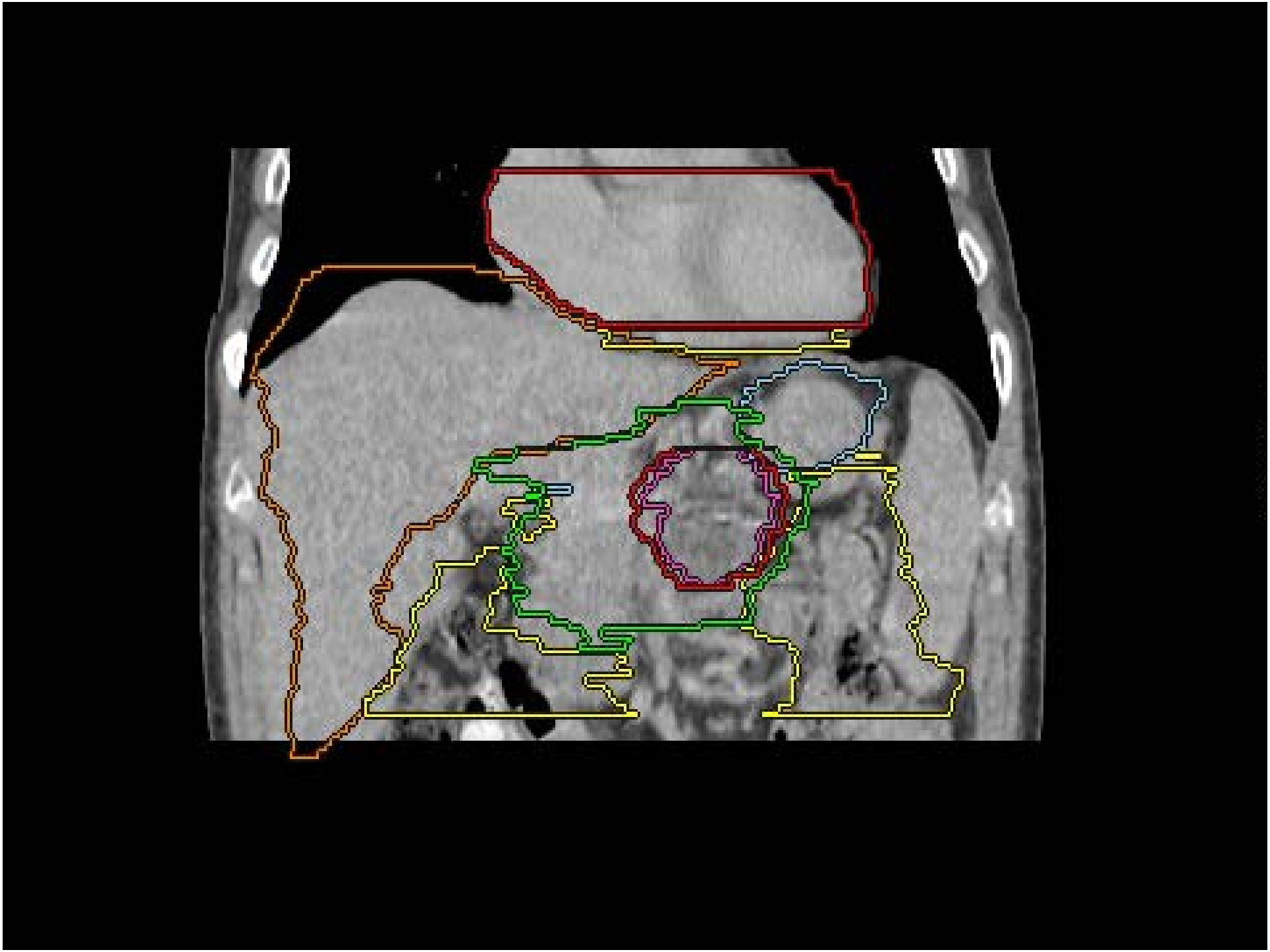
Nodal Regions

- Celiac nodes
- SMA nodes
- Peripancreatic
- Porta Hepatis
- PA/RP Lymph Nodes
- Splenic hilum (tail lesions)

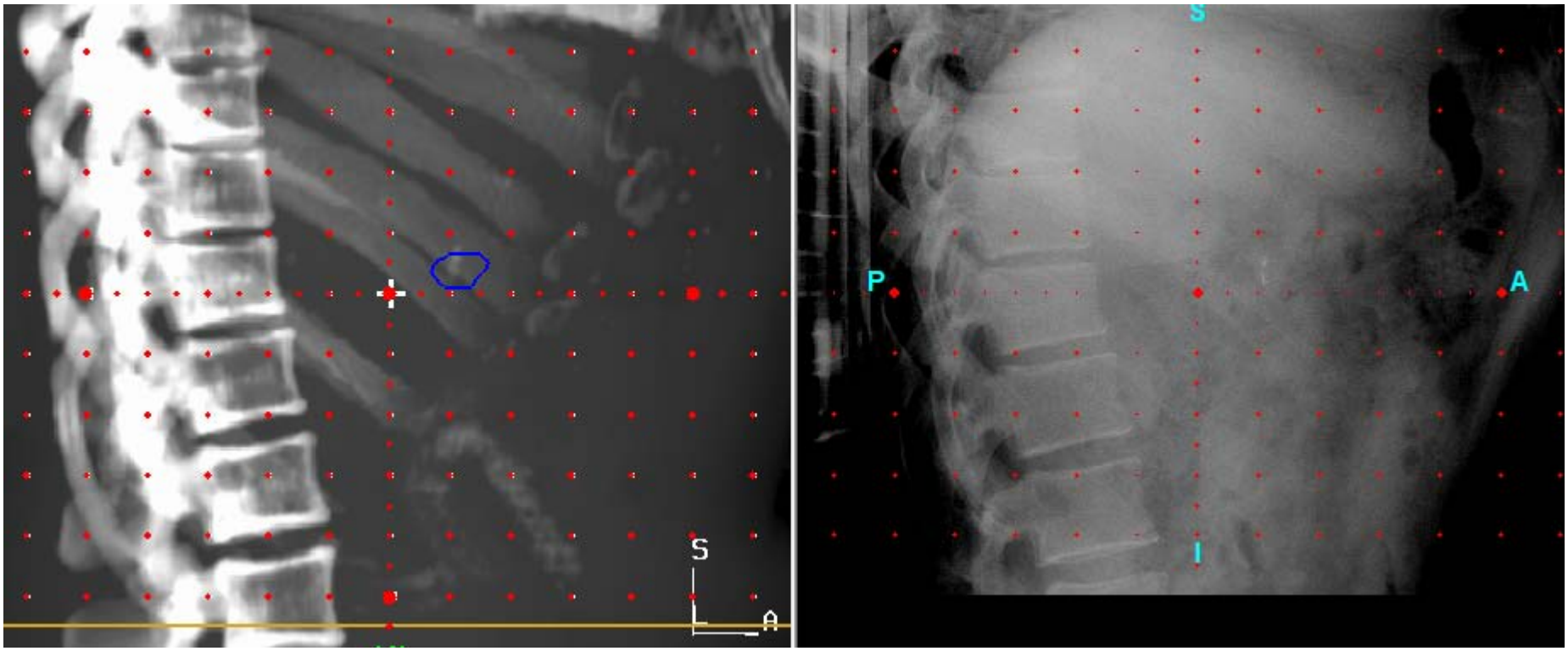
Normal Tissues

- Spinal Cord
- Stomach
- Duodenum
- Kidneys
- Liver
- Bowel
- Heart


Portal/Splenic Confluence
Duodenum
Interaorticocaval lymph node region
GTV
Celiac artery
SMV
SMA
SMV
SMA
IVC
Aorta



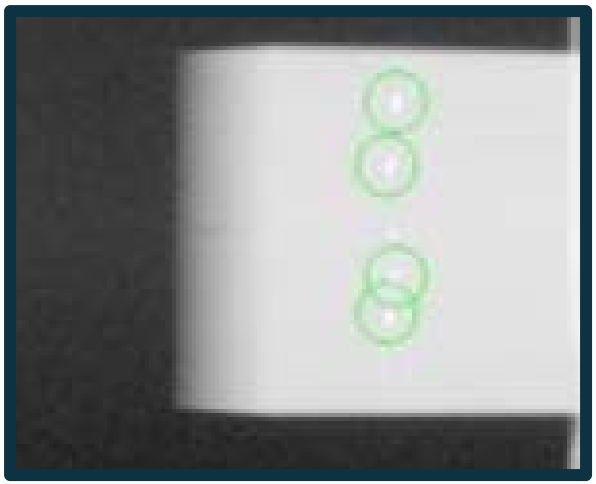
Daily KV Imaging

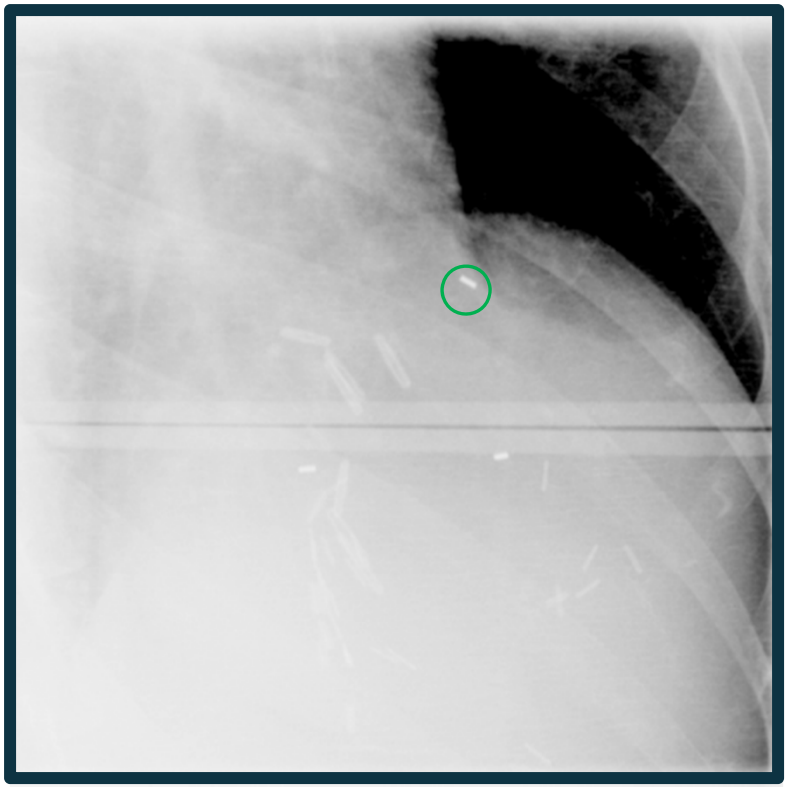


- Match on fiducials or stent
- KV's taken at beginning of gating interval

Intrafraction Imaging

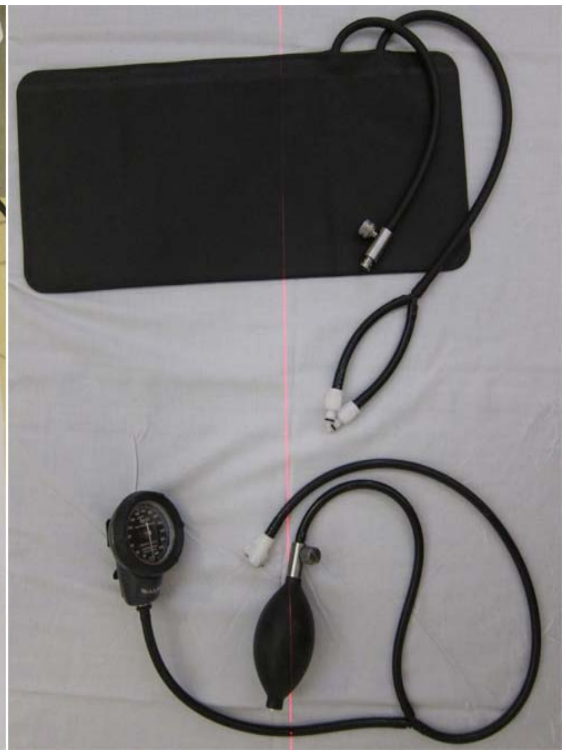
- IMRLite on Truebeam Linear Accelerator





Abdominal Compression

- Abdominal belt with inflatable bladder
- Inflation: 15-40 mmHg



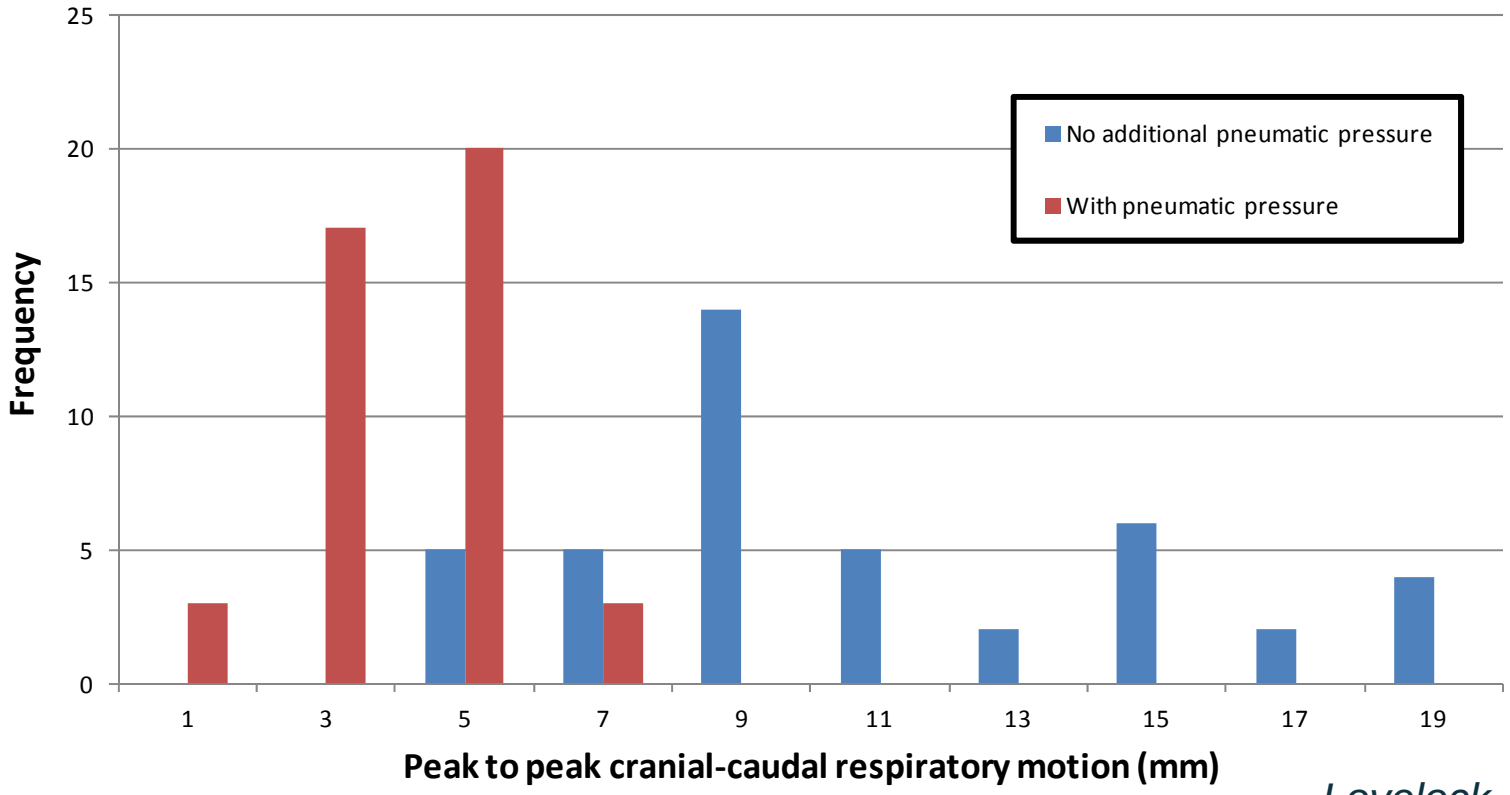
Abdominal Compression

- 44 patients treated with SBRT between 2004-2012 using abdominal compression belt
  - Liver (30), adrenal glands (6), pancreas (3) and lymph nodes (30)
- 2-3 radiopaque fiducial markers or clips
- Craniocaudal (CC) motion measured fluoroscopically with and without pneumatic pressure
- Objective: reduce CC motion ≤ 5 mm peak to peak

Lovelock, TCRT, 2014

Abdominal Compression

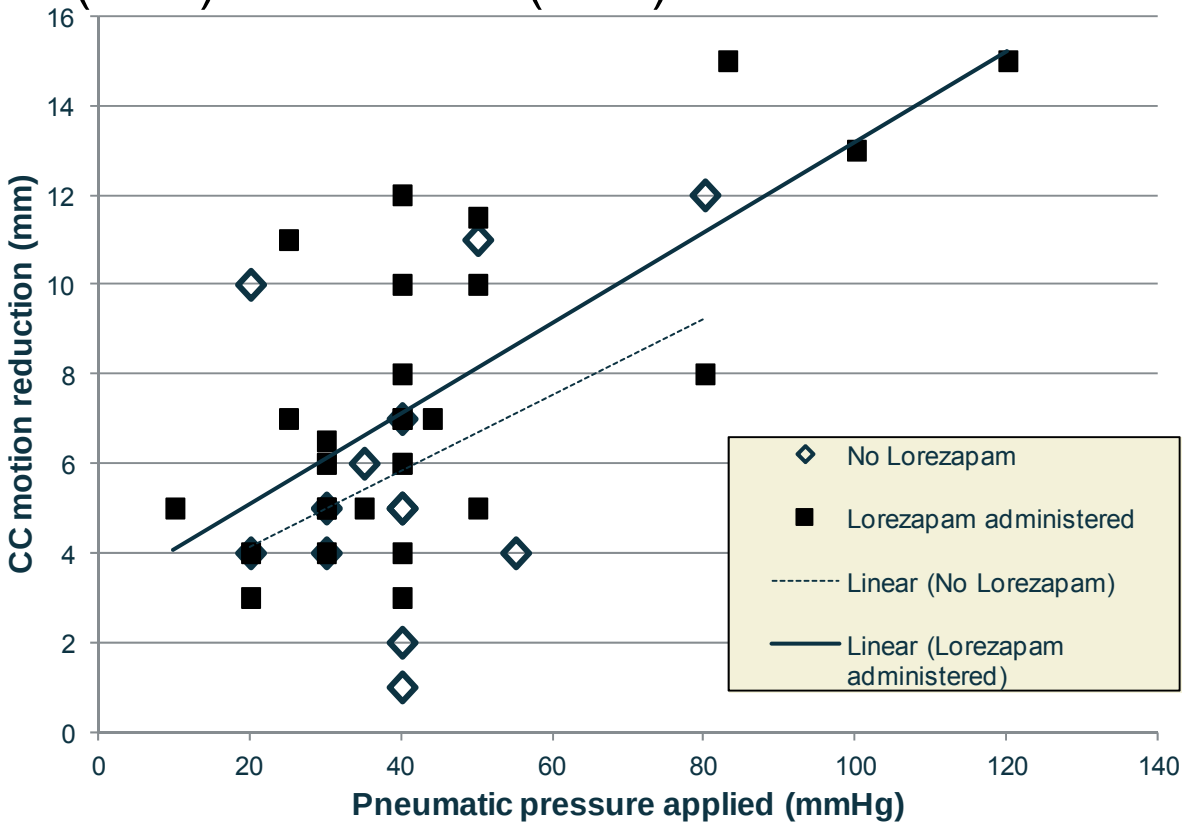
- Mean CC motion with no air pressure: 11.6 mm (range 5-20 mm)
- Mean CC motion with pressure applied: 4.4 mm (range 1-8 mm) (P-value < 0.001)



Lovelock, TCRT, 2014

Abdominal Compression

- Impact of Lorazepam use
  - Benzodiazepine anti-anxiety medication
  - Average motion reduction and % reduction of CC motion was 7.4 mm (61%) and 5.8 mm (55%) with and without Lorazepam



Motion Management Techniques

Respiratory Gating

- Cyclical delivery of RT
- Patient compliance with breathing instructions
- Requires fiducial marker and daily OBI
- Does not take into account non-respiratory motion
- Poor quality CBCT
- Standard fractionation RT

Abdominal Compression

- Continuous delivery of RT
- Patient tolerance of the compression belt
- Requires fiducial marker and daily OBI
- Does not take into account non-respiratory motion
- Less motion artifact in CBCT
- SBRT

Abdominal compression for motion management:

1. Requires a metal plate for compression
2. Causes artifact on daily CBCT
3. Is better tolerated with pre-tx Lorazepam
4. Is not a good option for diabetics
5. Does not reduce cranio-caudal motion <5mm

Abdominal compression for motion management:

5% 1. Requires a metal plate for compression

3% 2. Causes artifact on daily CBCT

83% 3. Is better tolerated with pre-treatment Ativan

3% 4. Is not a good option for diabetics

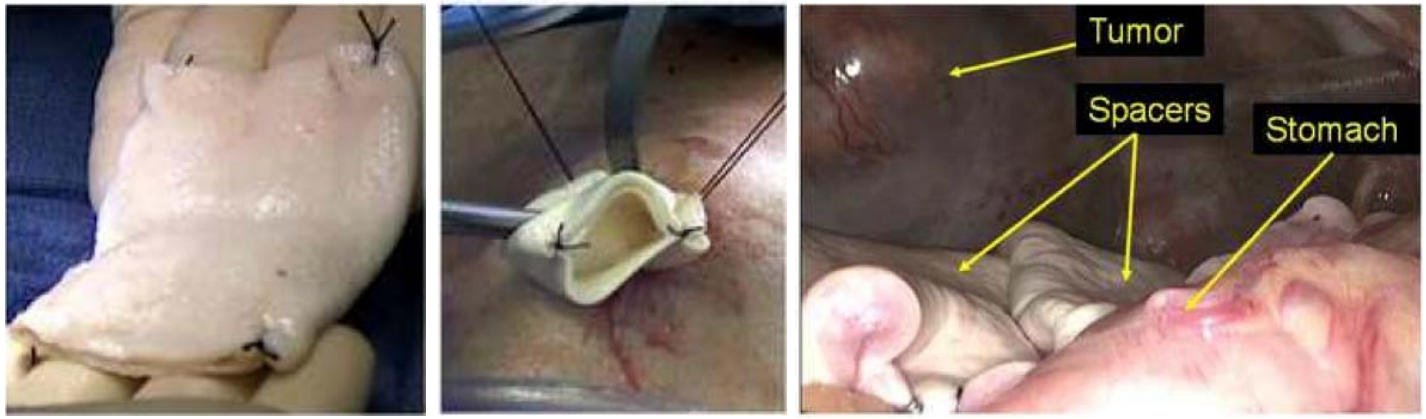
6% 5. Does not reduce cranio-caudal motion to <5mm

Abdominal Compression for Motion Management:

- Is better tolerated with Lorazepam
  - Approximately a 1 mm decrease in CC respiratory motion was observed for each 10 mmHg increase in pneumatic pressure in both groups. Use of Lorazepam resulted in a small additional improvement in motion reduction of approximately 1 mm per 10 mmHg increase in pressure

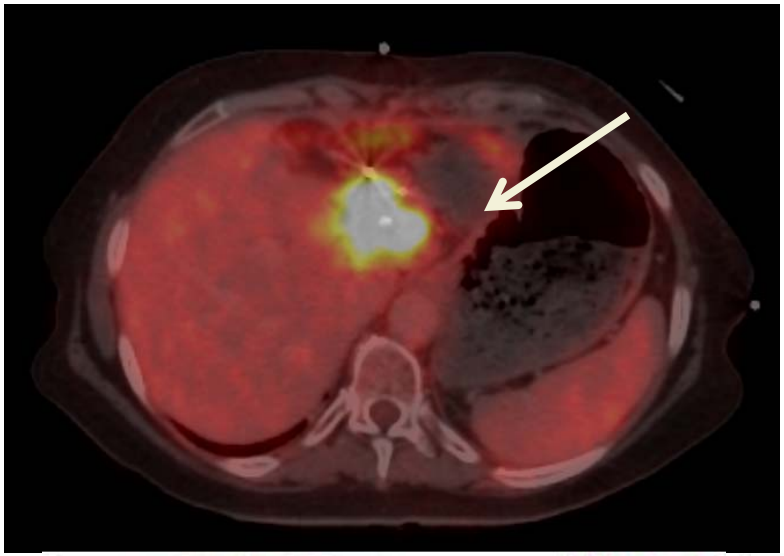
Permanent Spacers

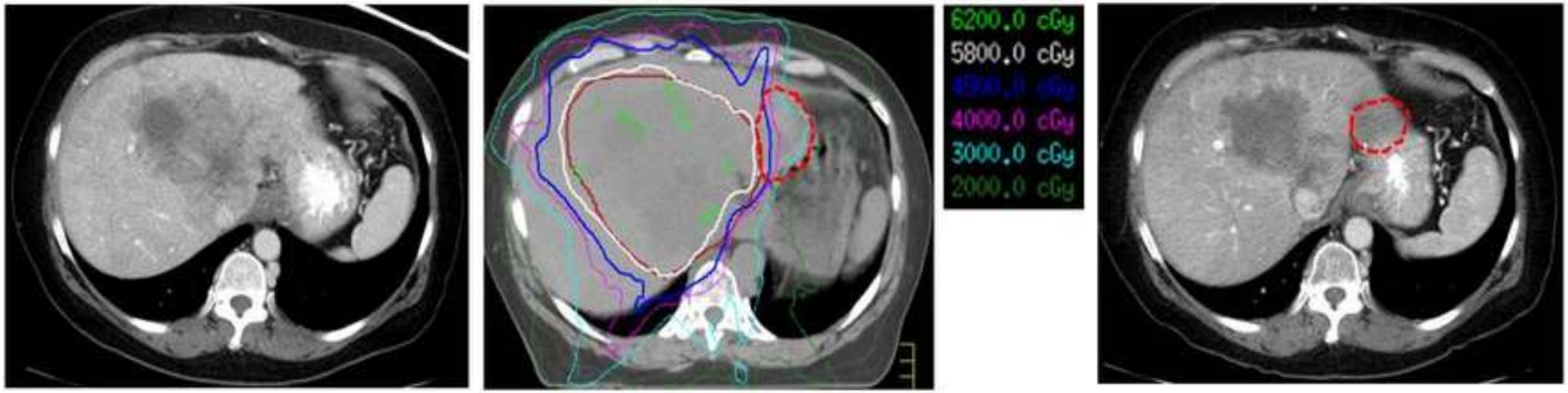
- Biological mesh spacer (Alloderm)
  - Cadaveric human skin treated to remove cells and preserve extracellular matrix
- 6 IHCC, 3 HCC, 5 liver metastases
- Mean Displacement:
  - Stomach 23 mm, duodenum 23 mm, small bowel 20 mm, colon 24 mm



Yoon S, *et al.* PRO, 2014

Permanent Spacer



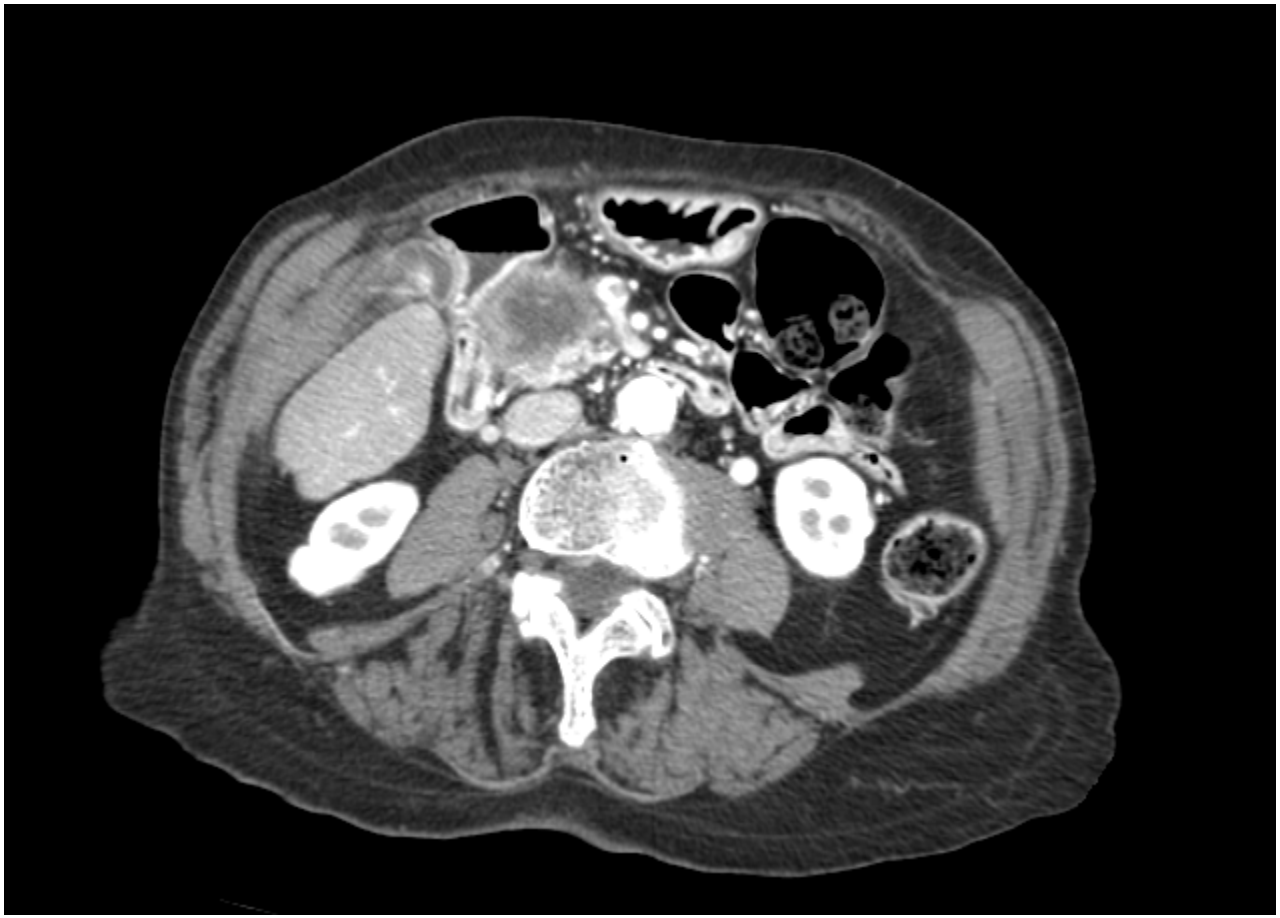


Median Dose: 54 Gy, 5-15 fractions (Protons/SBRT/IMRT)

Outline of Presentation

- Anatomy
  - Basic abdominal anatomy
- Rationale for SBRT for abdominal tumors
  - Emerging clinical data
- Simulation and Motion Management Techniques
  - Compression Belt
  - Respiratory Gating
- Treatment Planning
  - Dose constraints

Challenge for Treatment Planning

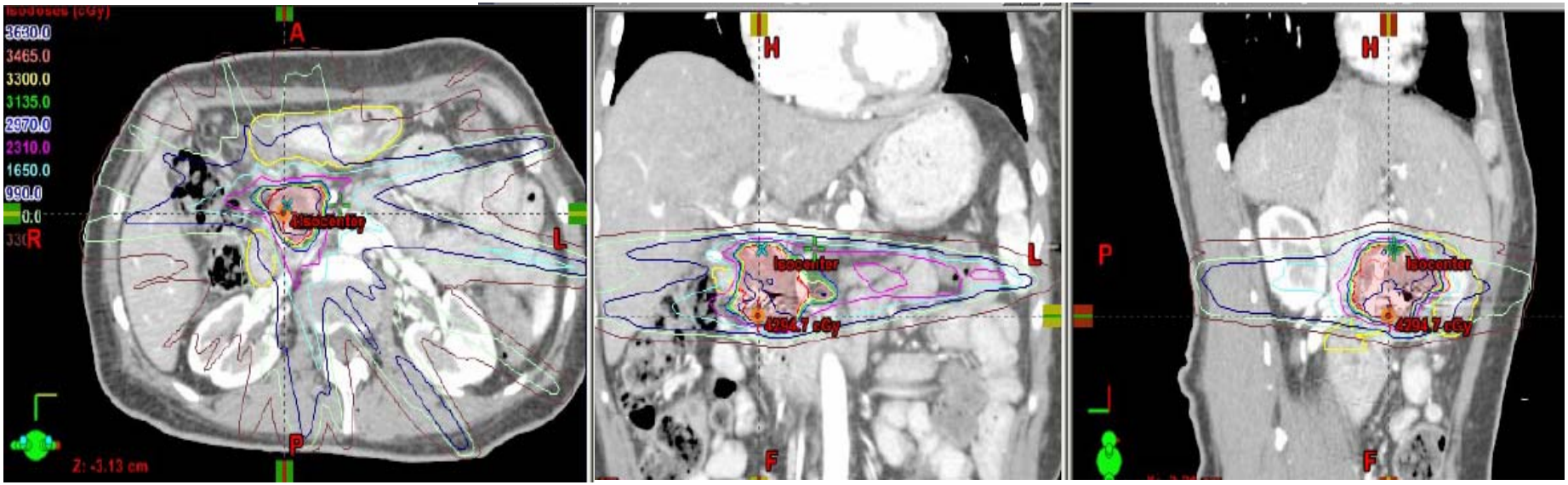


SBRT Dose Constraints

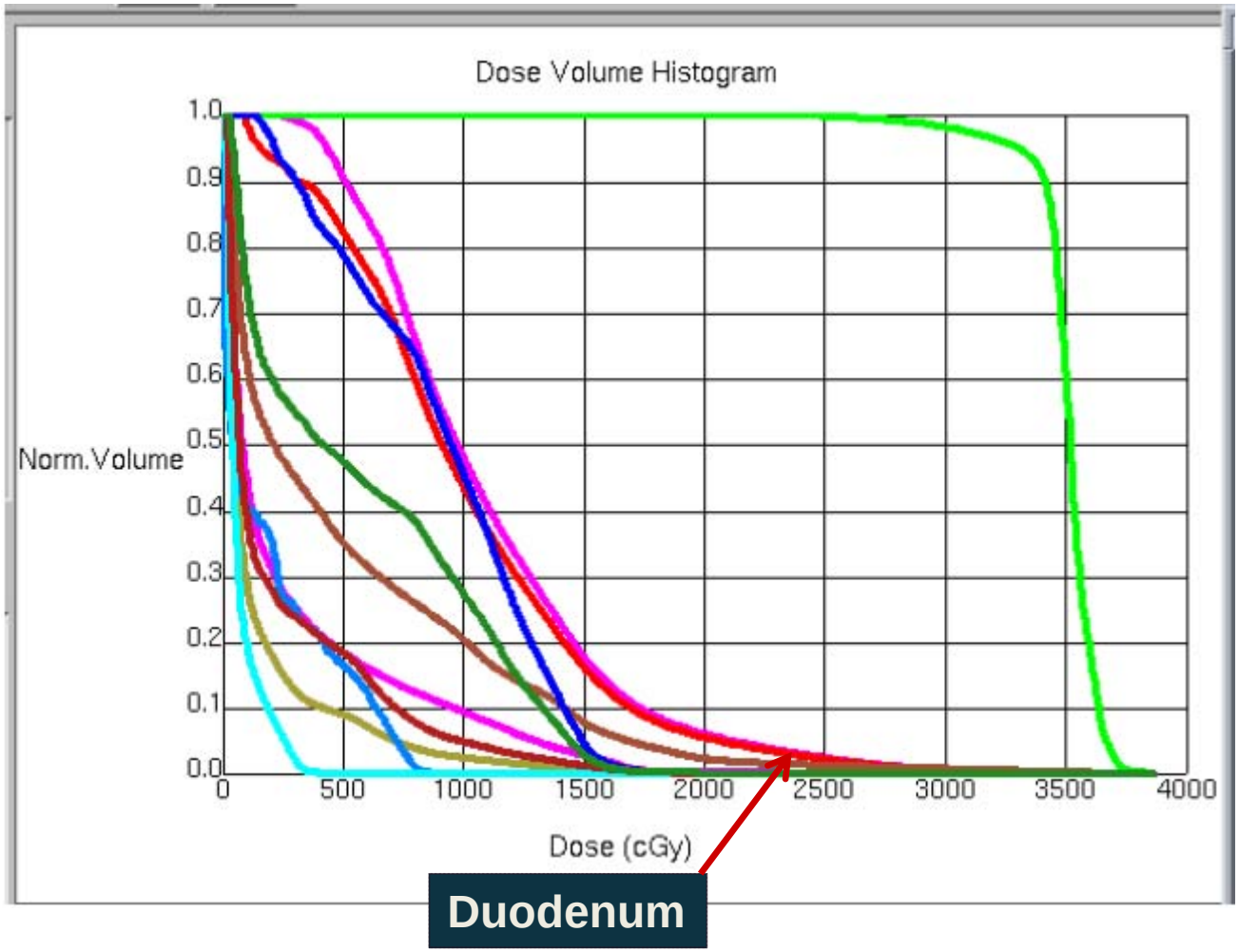
NORMAL TISSUE DOSE CONSTRAINTS	
Organ at Risk (OAR)	Constraints
Liver	V12 < 50%
Kidney	V12 < 25% (both kidneys combined)
Cord	V8 < 1cc
Stomach	V33 < 1cc, V20 < 3cc, V15 <9cc, V12 <50%
Duodenum	V33 < 1cc, V20 < 3cc, V15 <9cc, V12 <50%
Bowel (not duodenum)	V20 < 5cc (bowel is contoured 2cm superior and inferior to PTV)

SBRT Dosimetry

- Able to meet protocol dose constraints



RT Plan: DVH


Dose Volume Histogram
Norm.Volume
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
500
1000
1500
2000
2500
3000
3500
4000
Dose (cGy)
Duodenum

Liver Tolerance

- 204 pts treated with liver RT (hyperfrac) for primary or metastatic liver lesions at U. Michigan analyzed
- Lyman NTCP model applied to predict RILD
  - Large volume effect
  - Strong correlation of RILD and mean liver dose
- Mean liver doses associated with a 5% risk of classic RILD in 2 Gy per fraction:
  - Primary liver cancer: 28 Gy
  - Metastatic liver disease: 32 Gy

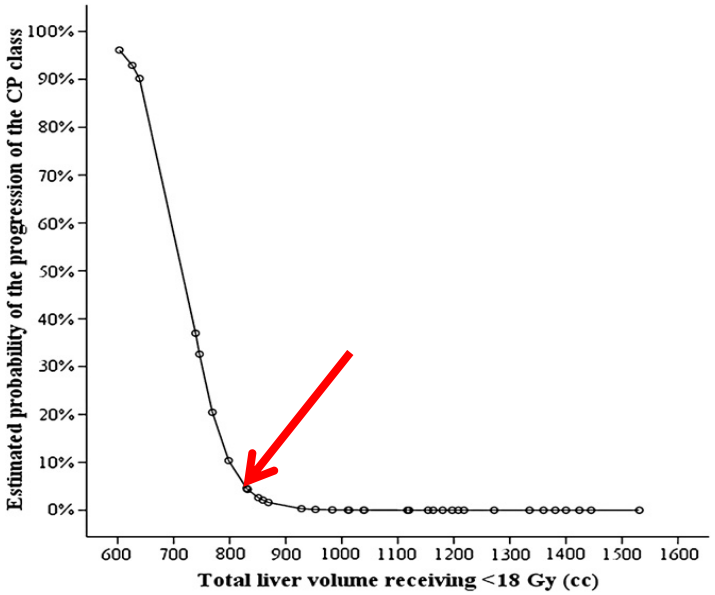
Dawson LA, IJROBP, 2002

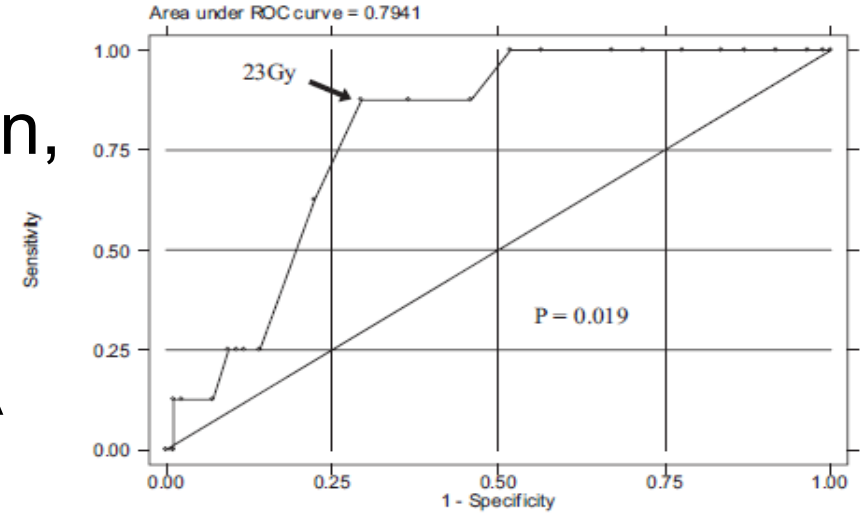
Liver Tolerance to Hypofractionation

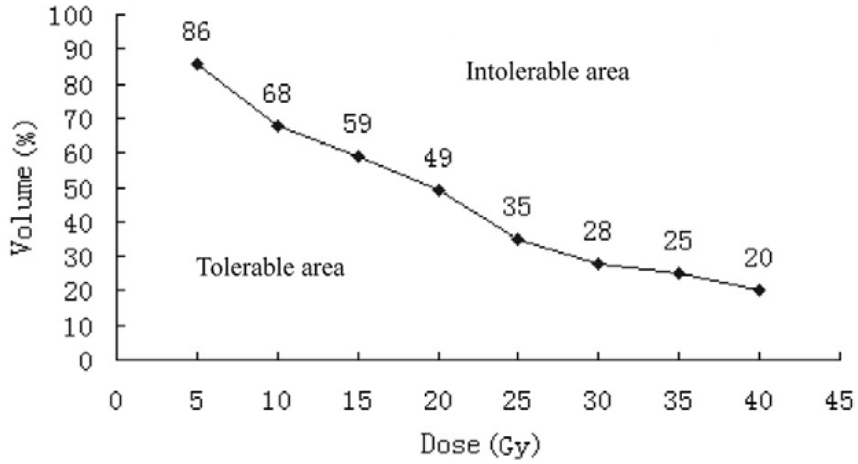
- U. Colorado SBRT Phase I trial
  - Used 700cc < 15Gy in 3 fractions
  - No reported RILD
  - None had underlying liver dysfunction
- PMH Phase 1/2 Trials of SBRT for primary liver tumors
  - Used Veff <80% (median 44%)
  - Median mean liver dose:
  - No RILD
  - Included Child-Pugh A patients

Liver Tolerance to Hypofractionation

- TD5/5 for RILD with hypofraction (4-8 Gy/fraction, median dose 54 Gy):
  - 23 Gy for hepatocellular carcinoma with Child-Pugh A cirrhosis







Jiang GL, IJROBP, 2006; Son SH, IJROBP, 2010

Liver Dose Constraints

Palliative whole-liver doses

Liver metastases
- ≤ 30 Gy, in 2 Gy per fraction
- 21 Gy in seven fractions (39)

Primary liver cancers
- ≤ 28 Gy, in 2 Gy per fraction
- 21 Gy in seven fractions (40)

Therapeutic partial liver RT (standard fractionation)

Mean normal liver dose (liver minus gross tumor volume)
- < 28 Gy in 2-Gy fractions for primary liver cancer
- < 32 Gy in 2-Gy fractions for liver metastases

Nonuniform liver recommendations (SBRT, three to six fractions)

Mean normal liver dose (liver minus gross tumor volume)
- < 13 Gy for primary liver cancer, in three fractions
- < 18 Gy for primary liver cancer, in six fractions
- < 15 Gy for liver metastases, in three fractions
- < 20 Gy for liver metastases, in six fractions
- < 6 Gy for primary liver cancer, Child-Pugh B, in 4–6 Gy per fraction (for classic or nonclassic RILD)

Critical volume model-based
- ≥ 700 mL of normal liver receives ≤ 15 Gy in three to five fractions

Pan CC, IJROBP, 2010

The risk of Radiation Induced Liver Disease (RILD) at 3 months is highest following SBRT in:

1. HCC, 700 cc liver receives15Gy/3 fx
2. Liver metastasis, 700 cc receives15Gy/3 fx
3. HCC, mean liver dose 13 Gy/6 fractions
4. Biliary tumor, mean liver dose 18Gy/6 fx
5. Liver metastasis, mean liver dose 18 Gy/6 fx

The risk of Radiation Induced Liver Disease (RILD) at 3 months is highest following SBRT in:

38% 1. HCC, 700 cc liver receives15Gy/3 fx

18% 2. Liver metastasis, 700 cc receives15Gy/3 fx

15% 3. HCC, mean liver dose 13 Gy/6 fractions

5% 4. Biliary tumor, mean liver dose 18Gy/6 fx

23% 5. Liver metastasis, mean liver dose 18 Gy/6 fx

HCC, 700 cc liver receives15Gy/3 fx

- Poor underlying liver function increases risk of RILD
- 700cc limited to 15 Gy is based on SBRT for liver metastases

Conclusions: SBRT for Pancreas Tumors

- Pancreatic SBRT with 3-5 fractions results in favorable OS compared to conventional regimens
- Minimal grade ≥2 acute/late toxicity and improved quality of life
- Combining SBRT with more aggressive systemic therapy (FOLFIRINOX) may improve survival by controlling distant disease
- Need biomarkers to select which patients will benefit from SBRT

Conclusions: SBRT for Liver Tumors

- Safe: high doses well tolerated in patients with normal underlying liver function
- Effective: Recent prospective studies of more focal RT for liver tumors suggest that higher doses associated with good local control
- Caution: SBRT may not be appropriate in patients with underlying liver dysfunction

Conclusions

- Newer techniques using functional imaging may help to identify functional regions that can be better spared to minimize normal tissue injury
- Prospective trials are necessary:
  - To define dose/fractionation schemes of SBRT
  - To evaluate SBRT in combination with radiosensitizers, VEGF inhibitors, hypoxic cell sensitizers

Thank you