

Place of SBRT (Stereotactic Body Radiation Therapy) in liver metastases.



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Disclosures

No relevant financial relationships to disclose

Rationale- Liver metastases

- **Liver metastases** from colorectal or other solid cancers : a large source of morbidity and mortality
- **Complete resection** for liver-confined CRC MTS results in a **5-year survival of 30 - 60%**
- **Most patients not suitable for surgery** (only 25%, 6% for hepatectomy), RFA and other ablative therapies.
- For this majority of patients, **the search for viable treatment options continues.**

Courtesy of Laura Dawson

Alternatives to surgery ?

- Surgical resection of limited metastatic disease in the liver is associated with **favorable outcome in well-selected patients**
- **→ Can Radiation (SBRT) be used to achieve equivalent results of surgery in unresectable pts?**
- SBRT, if demonstrated safe and similarly effective, would be advantageous over surgery, being entirely non invasive and also deliverable on an outpatient basis, with no requirement for anesthesia.

Simmonds PC, Pirrossi JN, Colquh J, et al. Br J Cancer. 2006; 94: 952-959
The International Registry of Lung Metastases. J Thorac Cardiovasc Surg. 1997; 115: 37-49.

RT and SBRT: why not earlier ?

- **RILD** : RT previously limited by the potential for radiation-induced liver disease (ascites-enzyme elevation), 3 months after low dose (30 Gy) whole-liver radiotherapy.
- **Liver motion**
- **IGRT** : Advances in radiation planning, motion management, allows higher, conformal doses of RT, improving the probability of tumor control with a low risk of toxicity.
- **SBRT** refers to the very precise delivery of high doses of RT, with small number of high fractions.

How to deliver RT safely

- **Appropriate patient selection**
 - Child-Pugh A > B >>> C
- **Technological advances**
 - I maging
 - RT Breathing motion management
 - RT Planning
 - RT I mage guidance
- **Ensure enough residual liver spared / RT**

Courtesy of Laura Dawson

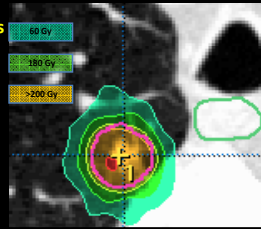
Stereotactic radiotherapy (SBRT)

High-precision image-guided RT characterized by:

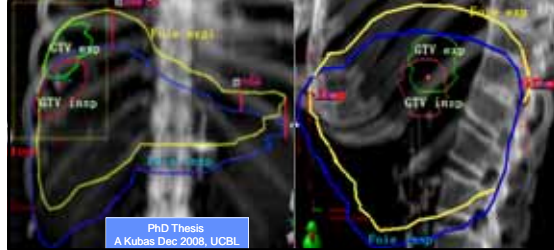
- 4D target definition (Integration of time, Tumor movements)
- Accurate patient positioning
- Multiple non-coplanar RT beams

allowing for:

- Steep dose-gradients
- Hypofractionation (3-8 Fx)
- High biological effective dose

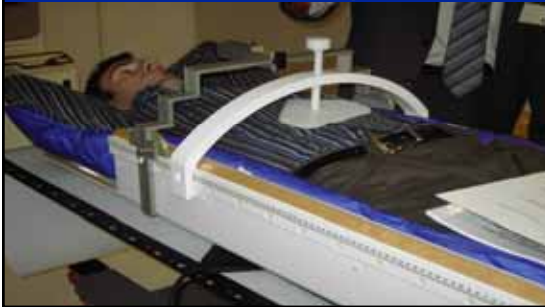


Movement	Minimum	Mean	Maximum	Deviation
Cranio-caudal	5 mm	19.7	35 mm	8.3
Lateral	2	4.5	10	2.3
Anteroposterior	0	8.9	22	6.5



PhD Thesis
A Kubas Dec 2008, UCBL

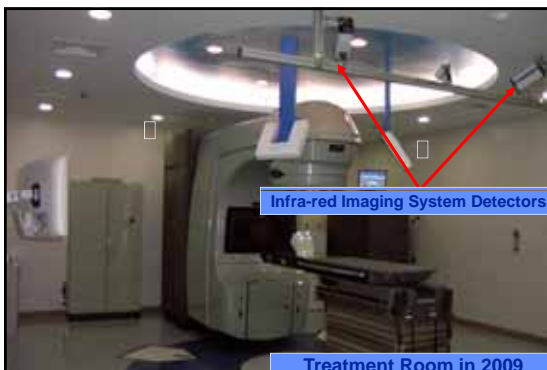
Immobilisation device tailored for each patient



Stereotactic RT for liver metastases



New therapeutic option,
new devices, new rules for radiation, new requirements, new debate.



Infra-red Imaging System Detectors

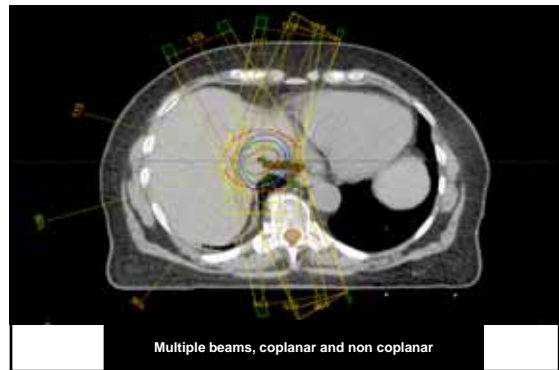
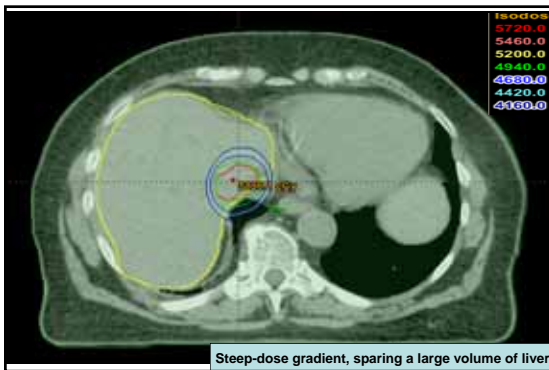
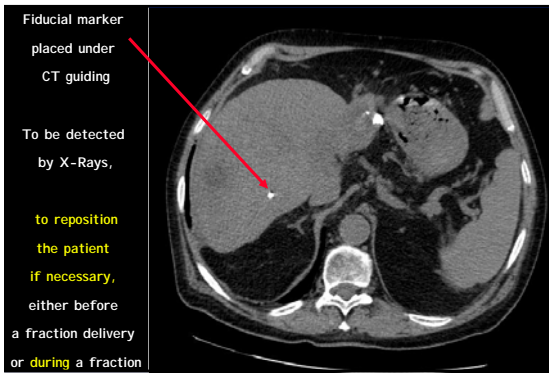
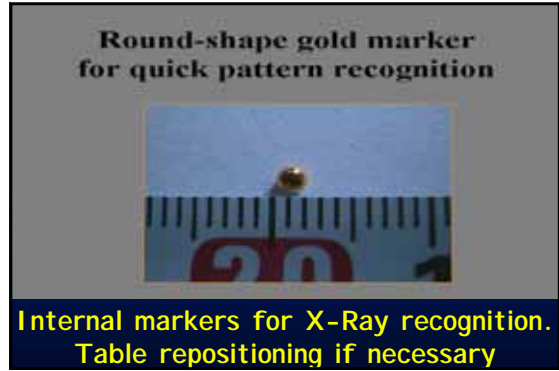
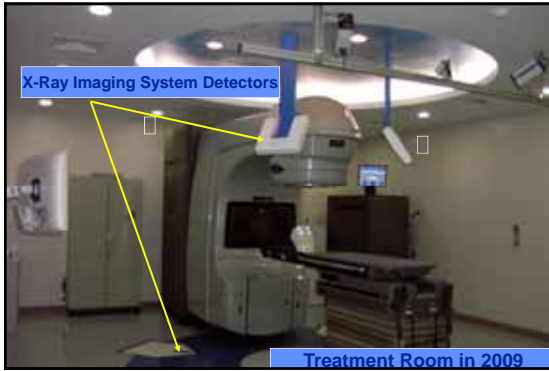
Treatment Room in 2009

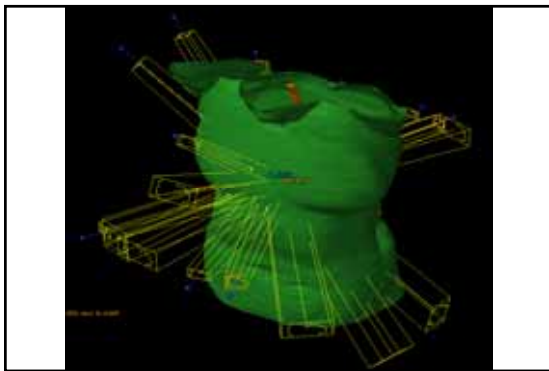
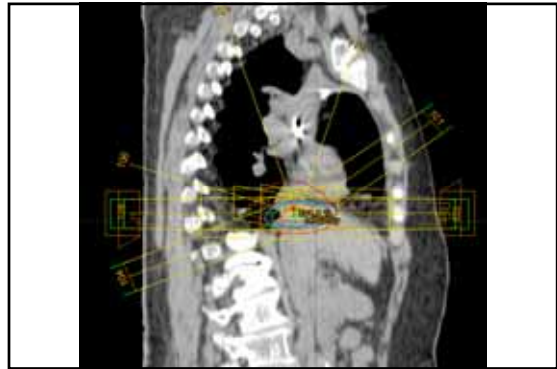
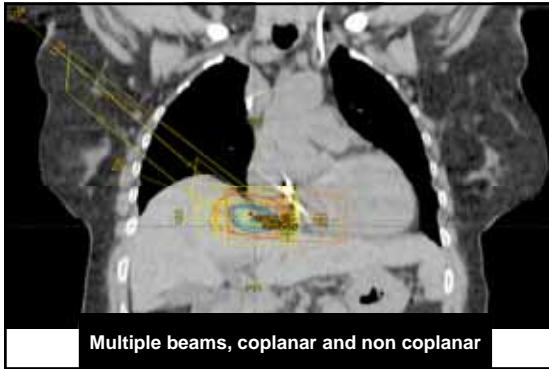
External markers



Skin Markers placed before treatment, localized by infrared beams.

Patient repositioning if necessary





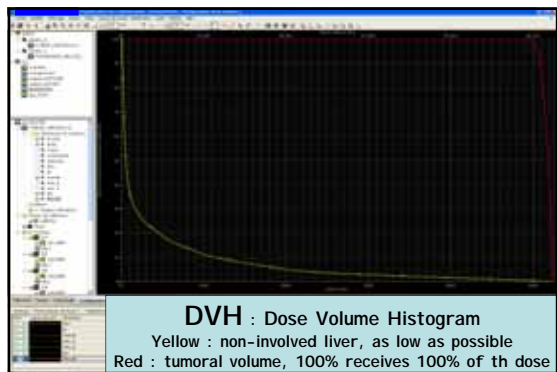
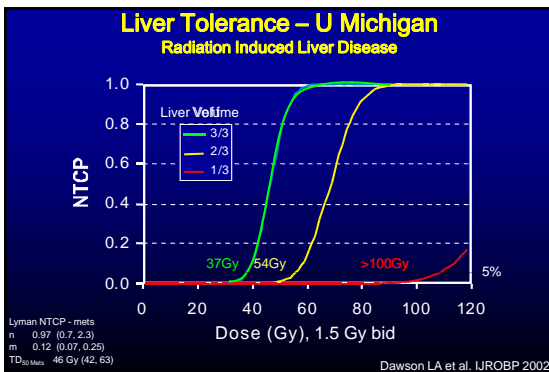
Tolerance: Hypofractionated RT

- Liver toxicity uncommon following hypofractionated RT or SBRT
- Most experience with liver hypofractionated RT - low liver volume irradiated low (< 30%)

➡ 'Safe' liver dose-volume constraints

- 6 fractions: mean liver dose < 20 Gy
- 3 fractions: >700 cc < 15 Gy
D30% < 21 Gy, D50% < 15 Gy
- 1 fraction: D30% < 12 Gy, D50% < 7 Gy

Dawson, Kavanagh, Wulf, Atca Oncologica 2006



SBRT for liver tumors : results

SBRT for liver tumors : An example of optimal development of a new technique

University of Michigan RT Strategy

Week 1 Week 2 Week 5 Week 6 Week 7
 MTWTFSS MTWTFSS MTWTFSS MTWTFSS MTWTFSS
 1.5 Gy bid
 HA FUdR 0.2 mg/kg/d

Phase I study, n = 128

- Concurrent hepatic arterial FUdR radiosensitizer
- Individualized prescription dose - based on volume of liver irradiated/ risk of RILD
- Maximum dose 90 Gy, 1.5 Gy/# bid**

McGinn C et al. J Clin Oncol. 1998

Toxicity: Michigan, n=123

- Grade 1/2 - 30%
- Grade 3/4 - 30%
- Grade 5 - 0.8%

- Most common severe complications:
 - Upper GI ulcer and bleeding 5%
 - Radiation induced liver disease 4%
 - Hepatic catheter-related 3%

Courtesy of Laura Dawson

University of Michigan: Phase I/II

N=128 unresectable colorectal liver metastases, HCC or cholangiocarcinoma

47 CRC mets
-med survival 17 mo

**RT dose:
median 61 Gy
(24-90 Gy)
1.5 Gy fractions
twice daily**

Overall Survival by Total Dose
 O Complete * Censored
 P=0.0008

Ben Josef E. et al, JCO, 2005

3 Fx-SBRT Phase I -Colorado

Group	N pts	Dose/Fx	Total Dose	Tox
1	3	12	36	
2	3	14	42	
3	3	16	48	G1 dermat
4	4	18	54	G1 pain
5	5	20	60	G1 dermat, pain, fatigue

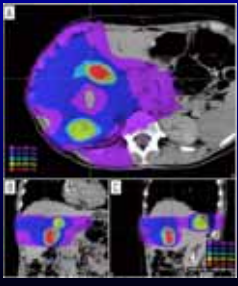
No dose-limiting toxicity

Results form the basis for a phase II of 60 Gy over 3 fx for liver metastases

Scheffer TE, Kavanagh BD, Timmerman R, LROBP 2005, 62: 1371-1378

Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases
 Rusthoven KE, Burri BD, Kavanagh BD, Higgins B, et al. JCO. 2009; 27:1579-1584

- **Eligibility, n=46**
 - 1-3 liver metastases
 - **Solid tumors < 6cm**
 - Liver and kidney function OK
 - Bilirubin < 3 mg/dL, alb > 2.5 g/dL
 - Liver enzymes < 3xULN
 - No ascites
 - No systemic therapy within 14 days pre- or post-SBRT
- **Dose escalation to 20 Gy x 3** (13 less than 20x3, 36 Phase II)
- Image guidance and breathing motion management
- Liver doses: > 700 cc had to receive < 15 Gy (equ 40 Gy)



Rusthoven, J Clin Oncol. 2009.

Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases
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- **1- and 2-year local control rate 95%; 92%**
- 2- year local control rate if **60 Gy** : 94%
- 2- year local control rate if < **3 cm**: **100%** / 77%

p<0.015
- Local progression in 3/49 pts
- MS 20 months **CRC :32 if CRC** **2-year LC 97%**
- 2-year survival rate 30%
- 1G3 (2%) soft tissue late toxicity

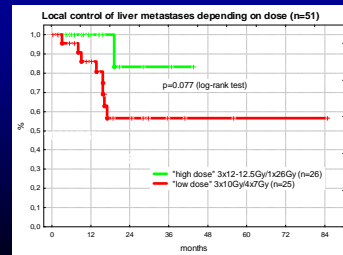
Phase II -Colorado

These results indicate that a SBRT dose of **at least 60 Gy in 3 fractions** can be safely administered to patients with 1 to 3 discrete liver metastases as long as **adequate prehepatic functions are present**, and as long as **700 mL of uninvolved normal liver receives less than 15 Gy total dose**.

Rusthoven KE, Kavanagh BD, Burri SH, JCO. 2009; 27:1579-1584

Würzburg SBRT : Dose Effect LINDENHOF SPITAL

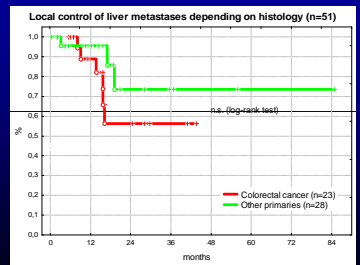
51 liver metastases
 23 colorectal
 Improved control with higher dose
 3 x 12 Gy vs. 3 X 10 Gy



Courtesy of Laura Dawson Wulf et al. Acta Oncol 2006

Würzburg SBRT : Dose Effect LINDENHOF SPITAL

51 liver metastases
 23 colorectal
 Reduced control of CRC vs. other



Wulf et al. Acta Oncol 2006

PMH Phase I Study - Metastases

- Conformal RT for unresectable liver cancer
 - **Individualized 'iso-toxic' dose (24 – 60 Gy in 6 #)**
 - Breath hold for liver immobilization
- Daily IGRT and repositioning
- **68 patients with metastases**
 - 40 CRC
 - 12 breast
 - 4 gall bladder
 - 12 other (lung, melanoma..)

} Refractory to or unsuitable for standard treatment
- Median GTV size 75 cc (2 – **3090 cc**) (other 8-54 !!)
- Median dose 41 Gy (28 – 60 Gy), in **6 fractions**
- Stratification on **V eff** (Effective liver volume irradiated)

Lee, Dawson JCO April 2009

PMH Phase I Study - Metastases

- Med follow-up 10.8 months, n=68
- Acute Toxicity**
 - Fatigue, gr 1 common
 - 3 Gastritis, gr ½
 - 3 gastritis gr 3
- Late Toxicity**
 - No liver toxicity
 - 1 intermittent pain (gr 2)
 - 1 rib fracture
 - 1 colitis (gr 2)
 - 1 duodenal bleed (gr 4), in presence of tumor
 - 1 small bowel obstruction (gr 5), in presence of tumor

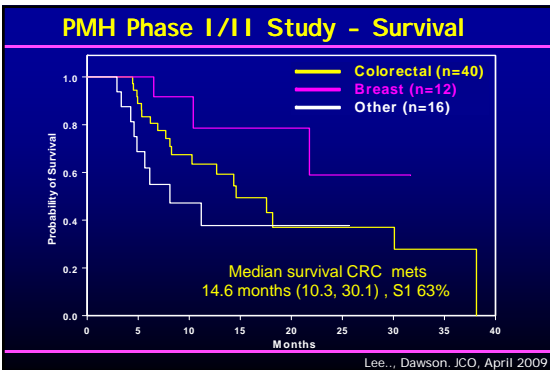
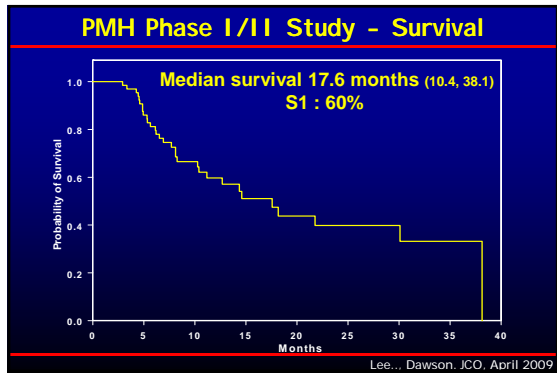
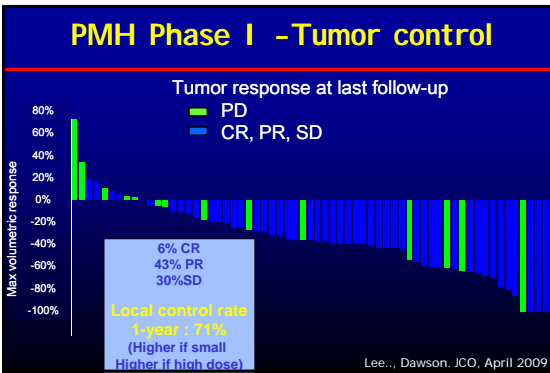
Lee..., Dawson, JCO, April 2009

Responses

54Gy Prescription Dose
45Gy IsoDose
30Gy IsoDose

Liver Metastasis Sustained Complete Response

© Courtesy of Lee and Dawson



Prospective trials of SBRT (hypo-fractionation) for liver metastases

Author/Institution	No. lesions	Fractions	Dose/frn, Gy	Med followup, mos	Timepoint	Actuarial LC
Herfarth (Heidelberg)	55	1	14-26	6	18m	67
Hoyer (Aarhus)	141*	3	15	4.3 ys	2yr	79
Milano (Rochester)	293**	10	5	41	2yr	67
Mendez-Romero (Rotterdam)	45	3	12.5	13	2yr	82
Wulf (Wurzburg)	51	1-4	7-26	15	2yr	82
Rusthoven (Colorado)	49	3	20	16	2yr	92
Dawson (Toronto)	140	6	24	11	1 yr	71

*Total number of colorectal cancer metastases: 44 liver metastases.
**Total number of lesions treated; 45% of patients were treated for hepatic metastases.
†In surviving patients.
‡Different fractionation (3-10 Gy or 5-5 Gy) used for patients with hepatocellular carcinoma or with lesions < 4 cm.

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*Total number of colorectal cancer metastases; 44 liver metastases.
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†16 surviving patients.
‡Different fractionation (3 10 Gy or 5 5 Gy) used for patients with hepatocellular carcinoma or with lesions > 4 cm.

Dose-Control relationship : Dose-effect

McCammon R, IJROBP, 2009; 73, 112-118

- 141 pts, 81 liver MTS (1-185 cc, median 9cc)

3-year local control rate

89.3% if 54-60 Gy
59% if 36-53.9 Gy **p<0.01**
8.1% if less than 36 Gy

Multivariate analysis :
Dose, Size only significant
Histology: no difference
Primary site : no diff
Primary/MTS : no diff

Author	Herfarth	Wulf	Kavanagh
BED	60	70.4	180
18 ms Local control rate	61%	66%	93%

Lung : Does biological dose matter ?

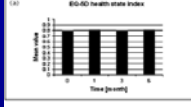
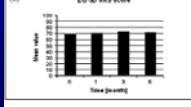
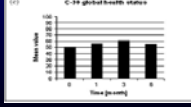
Total Dose	Reference	BED Gy10	NTD, Gy 2-Gy Fractions)	Estimated Progression-free Survival at 30 Mo. (Assuming No Hypoxia)
Conventional fractionation	—	(Fig. 1.1)	—	—
60 Gy, 30 fractions	—	60	60	35%
70 Gy, 35 fractions	—	84	73	34%
SBRT	—	(Fig. 1.2)	—	—
48 Gy, 4 fractions	(6)	106	62	34%
35 Gy, 3 fractions	(2)	113	64	36%
48 Gy, 3 fractions	(2)	125	104	39%
60 Gy, 3 fractions	(12)	132	110	>99%
80 Gy, 3 fractions	(3)	165	155	>99%
89 Gy, 3 fractions	(23)	223	191	>99%

BED, biologically equivalent dose; NTD, normalized total dose in 2 Gy fractions; SBRT, stereotactic body radiation therapy; NSCLC, non-small cell lung cancer; Tx, Tx; T4, T4; linear-quadratic.

Fowler et al. 2005

QOL - Netherlands

- N=28
- Med size 3 cm (0.5 – 7 cm)
- 10-12.5 Gy x 3
- EQ-5D, EQ-5D VAS & EORTC QLQ C-30
- Increased fatigue 1 month post RT
- Trend for improved QOL from baseline to 3 and 6 months**

Mendez, IJROBP, 2007

Effects on histology

Histological and volumetric changes in normal liver

After 3 fractions of 20 Gy

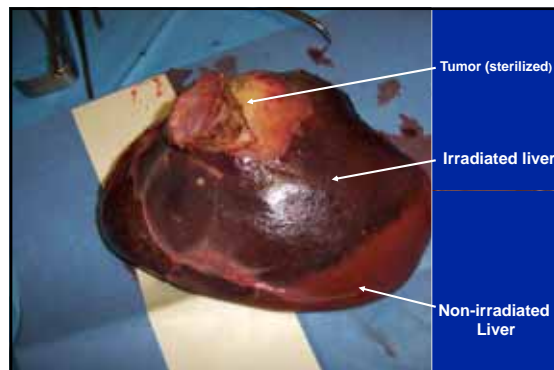
CT : **Hypoperfusion, congestion, variations in density** within time for the same phase (hypodensity within the 30 Gy Isodose, threshold dose))

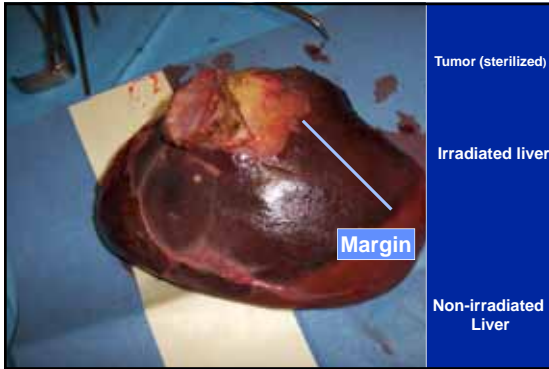
Decrease of the normal liver volume (median 18%) (V30 = predictor)

Paucicellular collagenized zone, liquefaction necrosis /More capillary rich zone (lymphocytes)

Radiation-induced Veno-occlusive disease

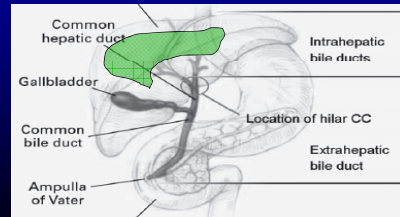
Bile ducts are spared (Important if the volume of normal liver is low, < 1000 cc)





Location: Lowest Risk to Higher Risk

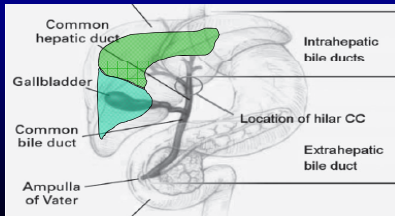
- Lowest risk: Away from stomach, bowel, caudate lobe, capsule, gall bladder



Courtesy of Laura Dawson

Location: Lowest Risk to Higher Risk

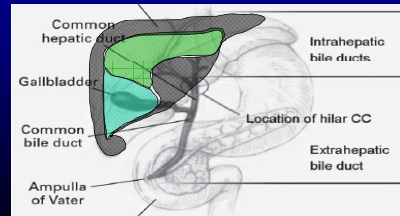
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Courtesy of Laura Dawson

Location: Lowest Risk to Higher Risk

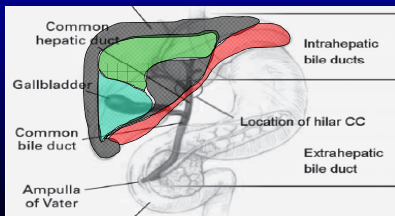
- Low risk: Away from stomach, bowel



Courtesy of Laura Dawson

Location: Lowest Risk to Higher Risk

- Risk of stomach and bowel toxicity: Near stomach and small bowel



Courtesy of Laura Dawson

We need a comparative index between DVH

How to compare the equivalence between 10 fractions of 6 Gy each, and 3 fractions of 20 Gy each ?

A reliable index of radiobiological dose equivalency will facilitate the dose-response relationship

BED? Biological Equivalent Dose

EUD? Equivalent Uniform Dose

TCP? Tumor Control Probability

Most Suitable Patients

- Liver confined disease
- **Not suitable for other local therapies**
- **No underlying cirrhosis or Hepatitis**
- > 700 cc uninvolved liver
- Non-diffuse, focal, metastases (< 5)
- **< 8 cm diameter metastases**
- Breathing motion < 5 mm
- Metastases not adjacent to stomach or small bowel

Courtesy of Dr. Daniel Dawson

More Challenging Patients

- Underlying cirrhosis or Hepatitis
 - Treat viral Hepatitis pre-RT
- < 700 cc uninvolved liver
- > 5 non focal metastases
- > 8 cm diameter metastases
- Breathing motion 5-30 mm
- Metastases near stomach or small bowel

Courtesy of Dr. Daniel Dawson

Ongoing RT Studies

- RTOG phase I study: 40-50 Gy in 10# (PI: Katz)
- Ph II studies of RT in CRC metastases
- Ph I studies of RT + biologic tx
- **Ph III study of SBRT (12 - 16Gy x 3) vs RFA for unresectable CRC liver mets < 4cm planned (PI: Hoyer, Denmark)**
- **Randomized Ph II study of soraf +/- SBRT for HCC (PI: Dawson, RTOG)**

HCC and RT : Response Rate, Local Control Rate

- 58% : RT alone or **TACE + RT** (Cheng, Taiwan)
- 61% : **RT + TACE** (Liu, Taiwan)
- 63% : **RT + TACE** (Seong, Korea)
- 60% : RT (RT **Thrombosis only**, Yamada, Japan)
- 68% : **RT + CT** (Dawson-Lawrence, USA)
- 78% 1-Y local control, **RT high dose** (Dawson, Canada)
- 78% 1-Y local control, **T<5 cm** (Mornex, France)
- 88% 5-Y local control, **protons** (Hashimoto, Japan)

Diversity of tumors and treatments

Conclusions

- **High dose conformal RT can be delivered safely to unresectable liver metastases (and HCC)**
- Results support the use of SBRT as an **effective, safe and non-invasive** therapeutic option.
- Sustained local control is possible

- Optimal integration of RT with **other therapies** unknown
- Multi-disciplinary team and Quality assurance required
- **Rationale for randomized trials**

