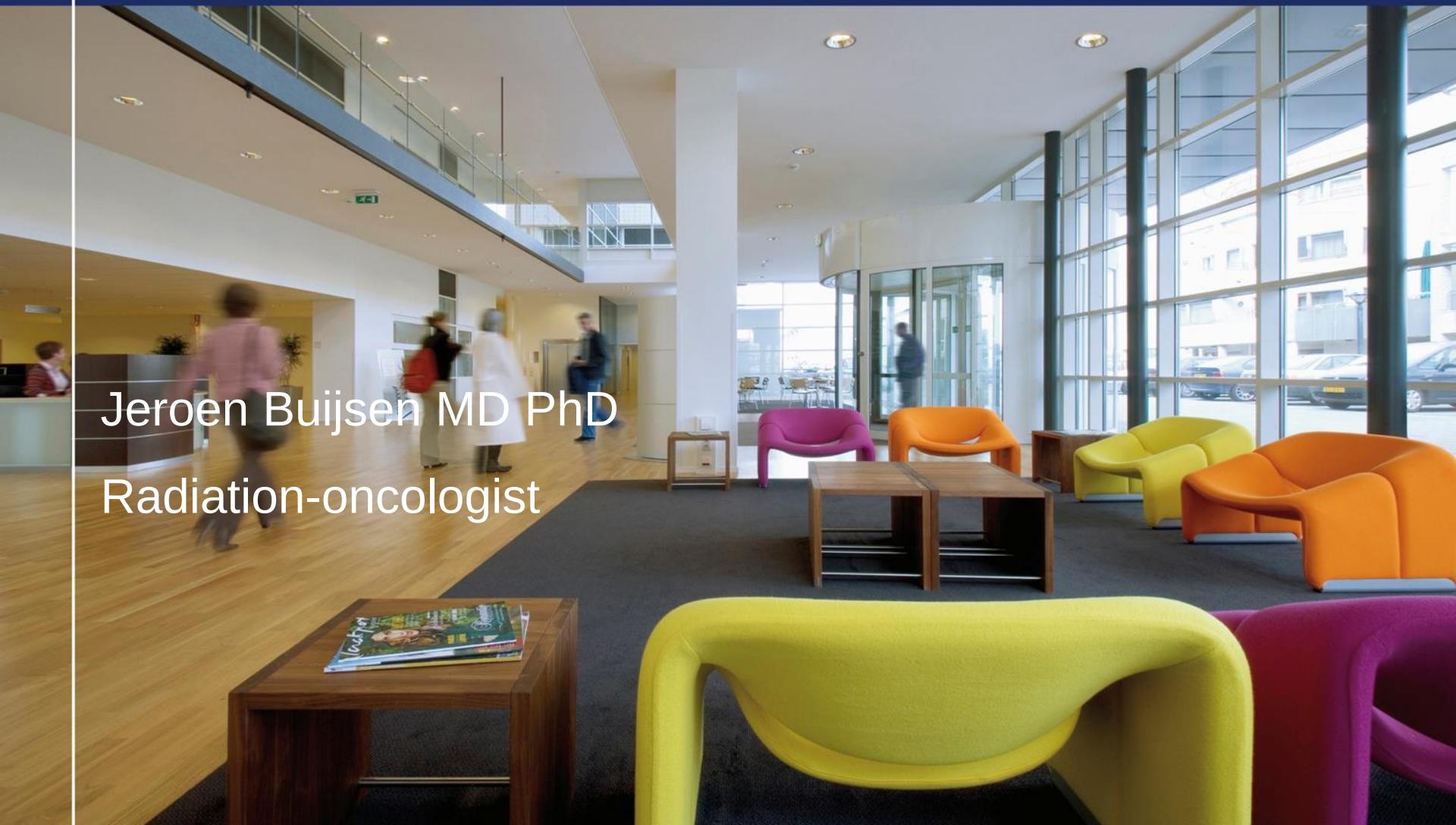
Stereotactic radiotherapy for liver tumors

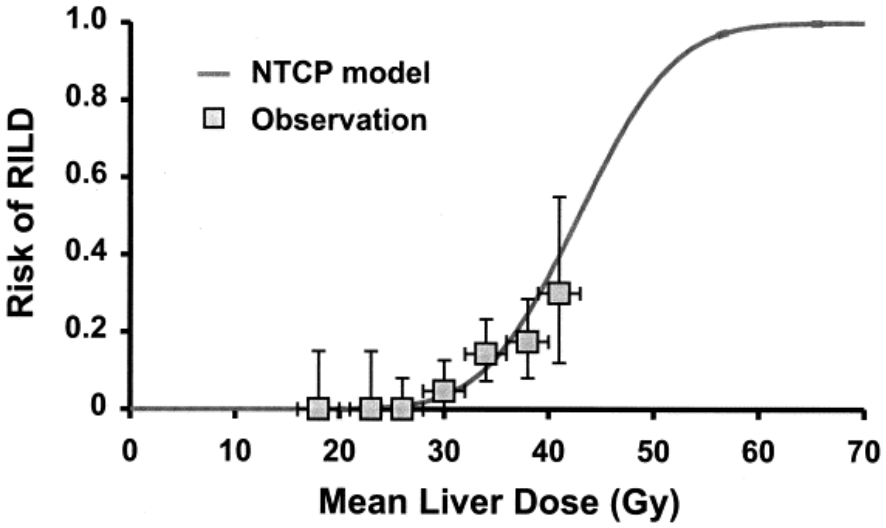


Jeroen Buijsen MD PhD

Radiation-oncologist

Historical background

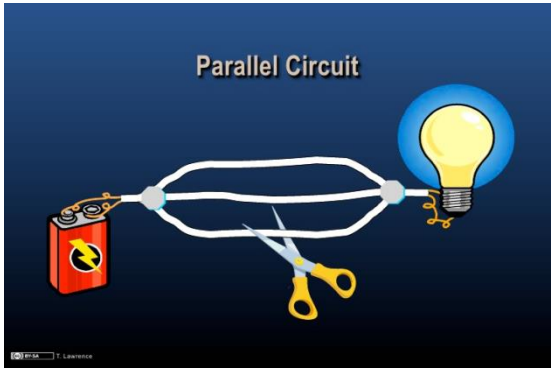
- Historically limited role of radiotherapy
- Liver tissue is sensitive to radiation
- Radiation induced liver disease (RILD)
- Technical inability to get a curative dose to the tumour without damaging the liver

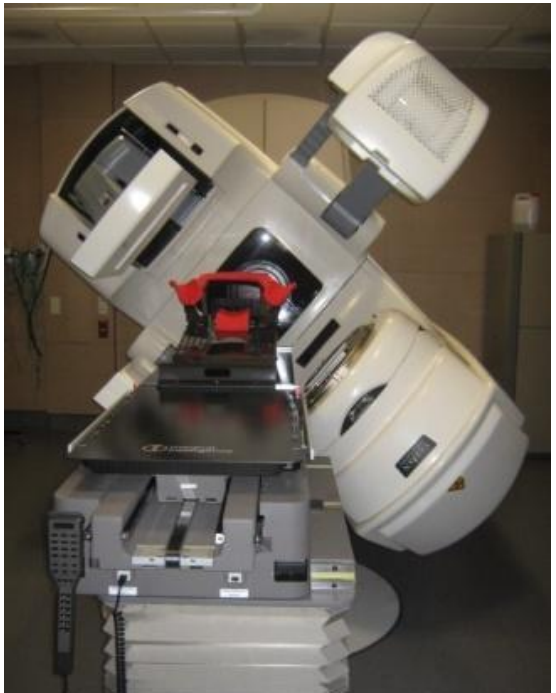


But… radiotherapy is not what it used to be!

Radiation of liver tumours can be safe

- Liver is a parallel organ
- High doses to limited volumes are safe
- Significant improvement in image guidance and conformal RT delivery





“Stereotactic” radiotherapy

- Originates from neuro-oncology
- Very precise irradiation of a small volume using an external coordinate system

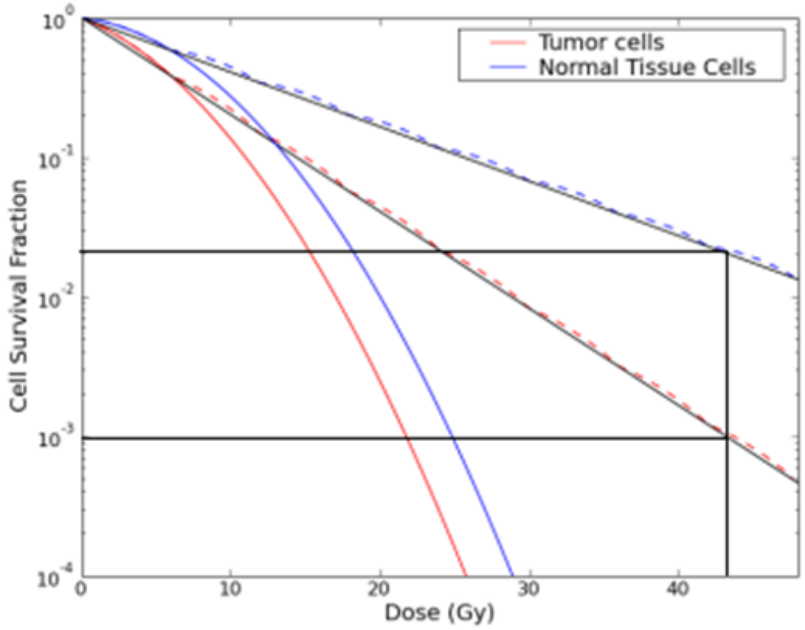
“Stereotactic” radiotherapy

- Originates from neuro-oncology
- Very precise irradiation of a small volume using an external coordinate system

- SBRT or SABR
- Highly focussed
- High dose per fraction
- Special immobilisation
- High quality imaging

SBRT: (Extreme) hypofractionation

A little bit of radiobiology…



3 x 20 ≠ 20 x 3

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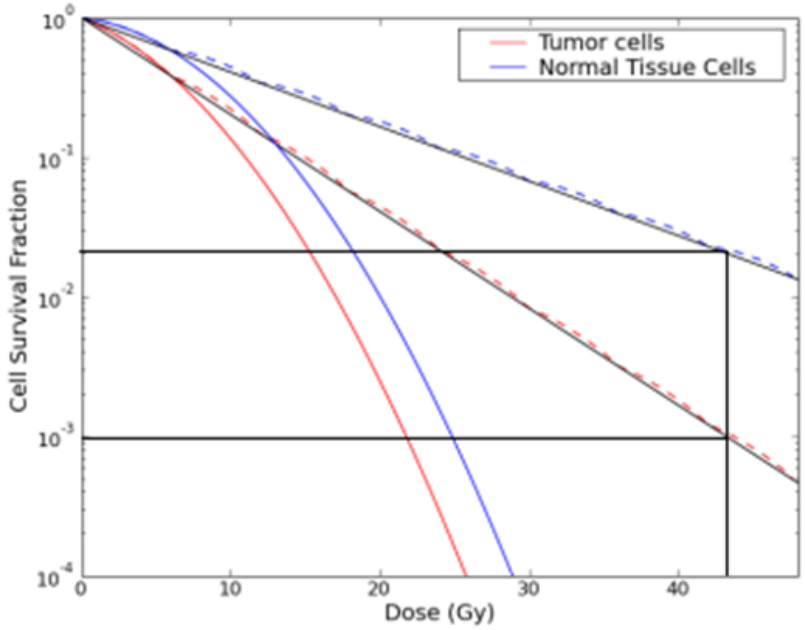
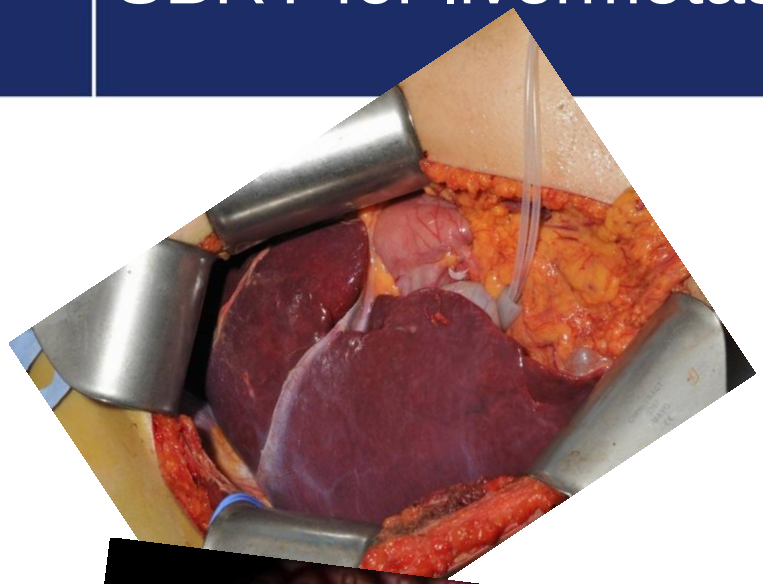
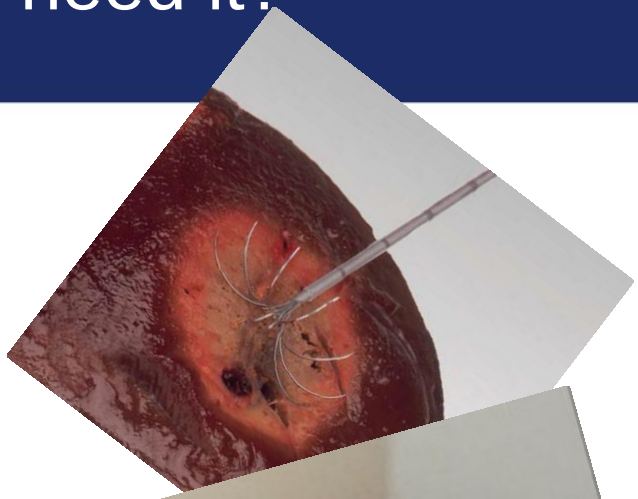


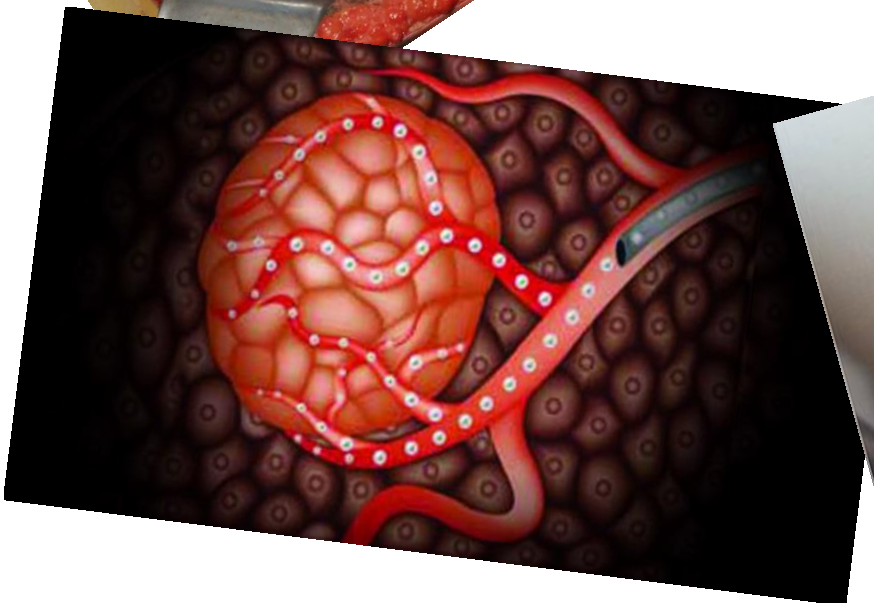
3 x 20 ≠ 20 x 3

150 ≠ 65 EQD2

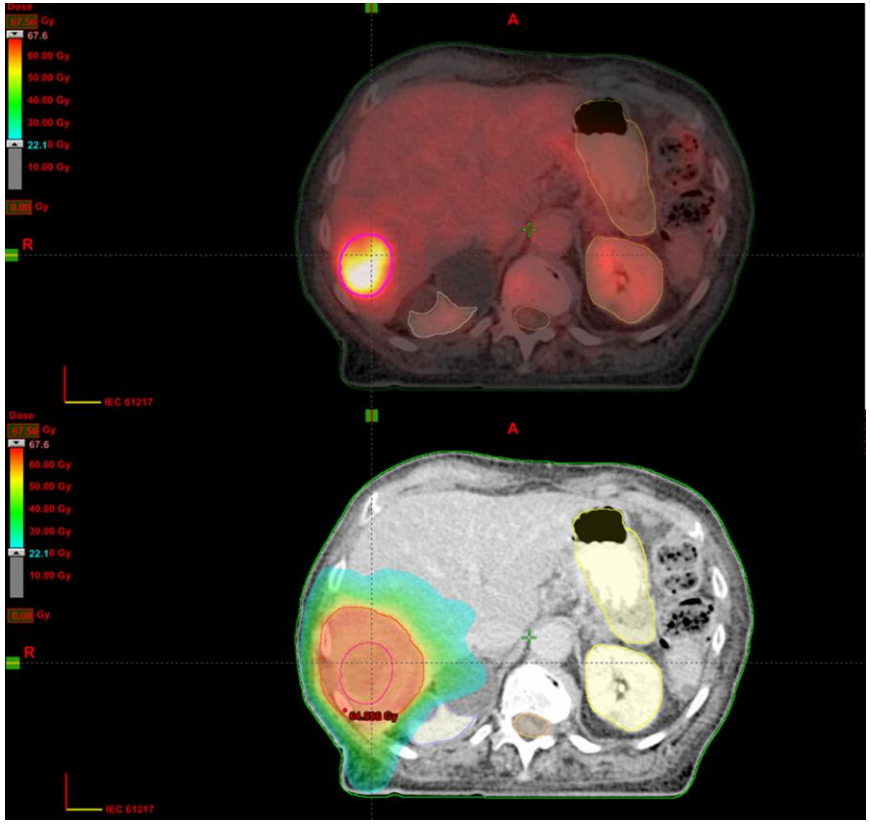
SBRT for livermetastases…do we need it?







SBRT for livermetastases… for which patient?

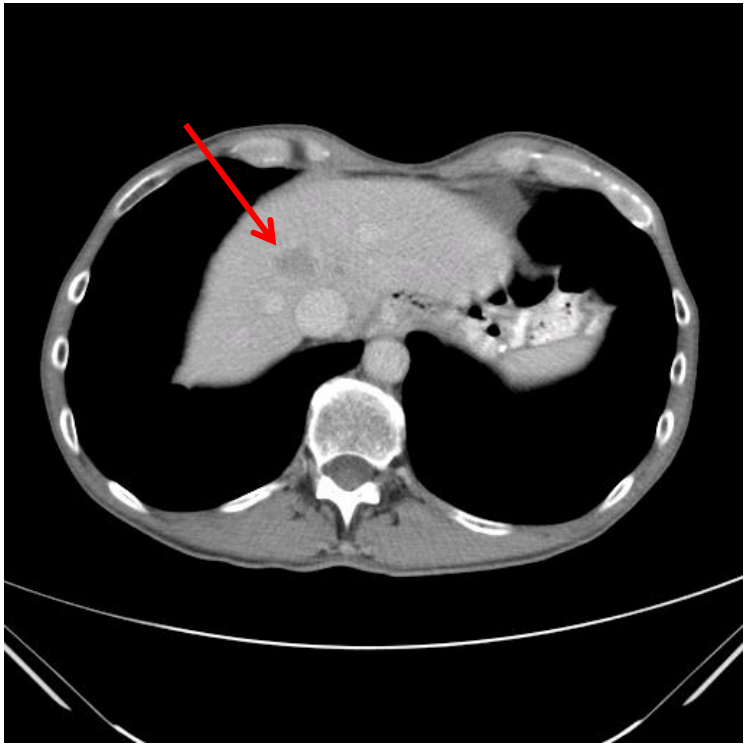


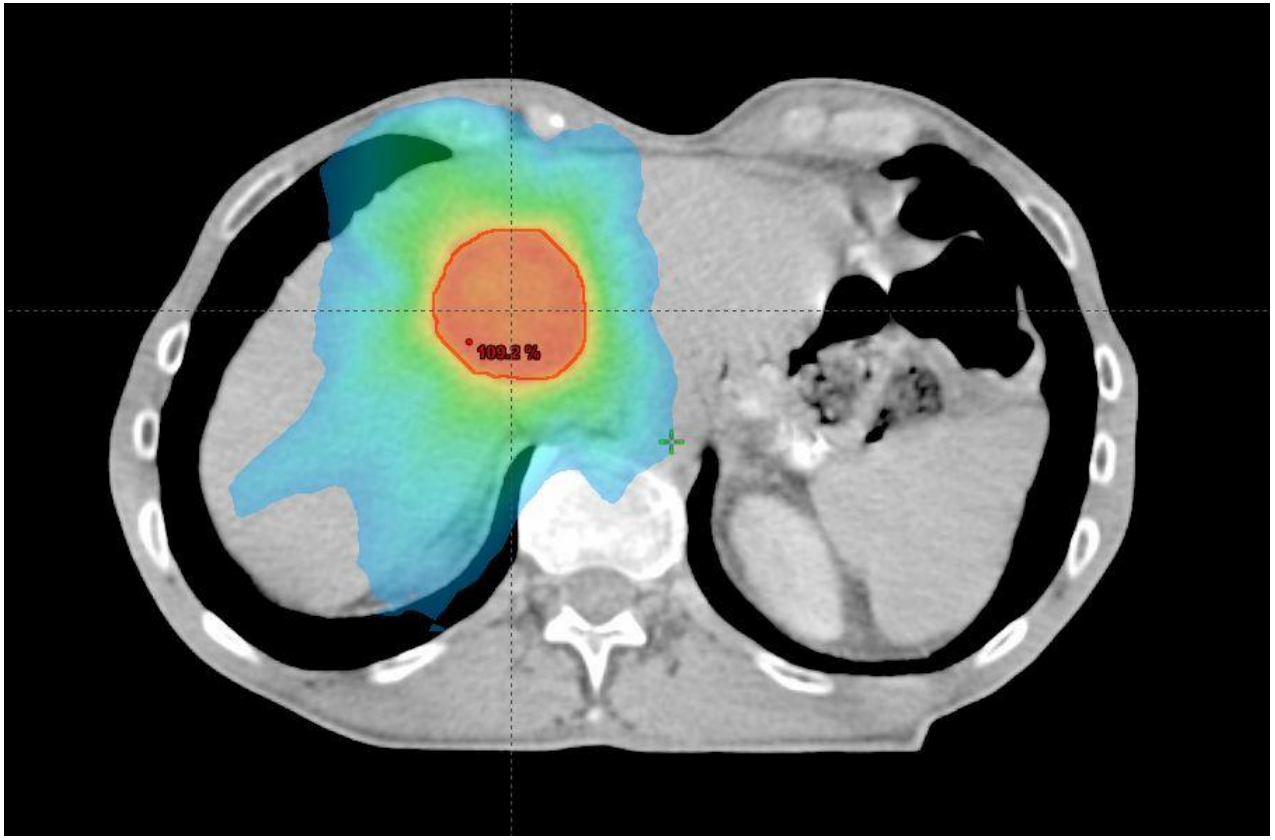
- High risk patient not fit to undergo surgery
- Uncertain tumorbiology
- Technical “irresectable”
- Alternative strategy if a large resection is needed for a small deep lying lesion

Patient case

Mr M, 66 years

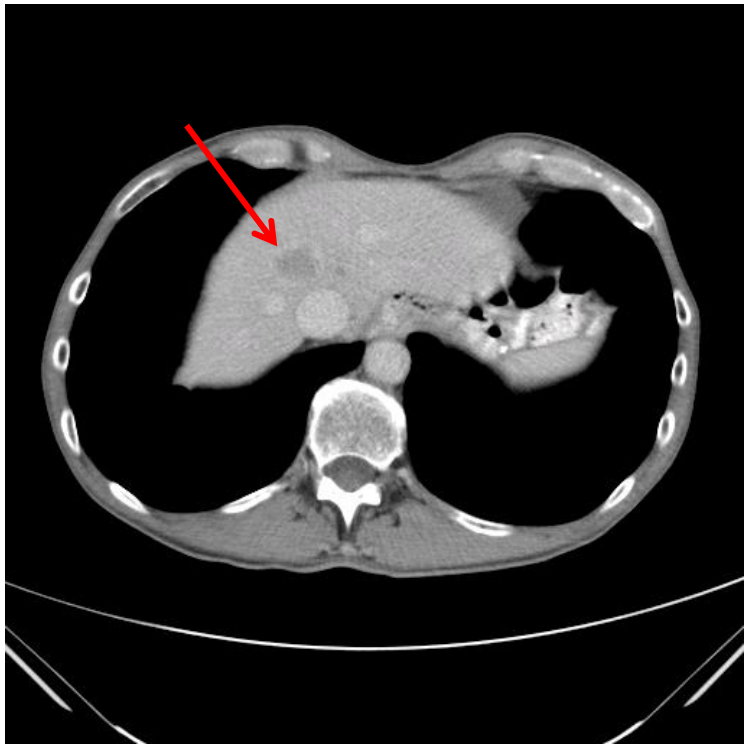
7-2010	Adenocarcinoma of the stomach, treated with peri-operative chemotherapy (ECC) in Critics study Total gastrectomy: ypT3N2M0
7-2012	CT-abdomen: new hypodense lesion in segment 8, 2.7 cm



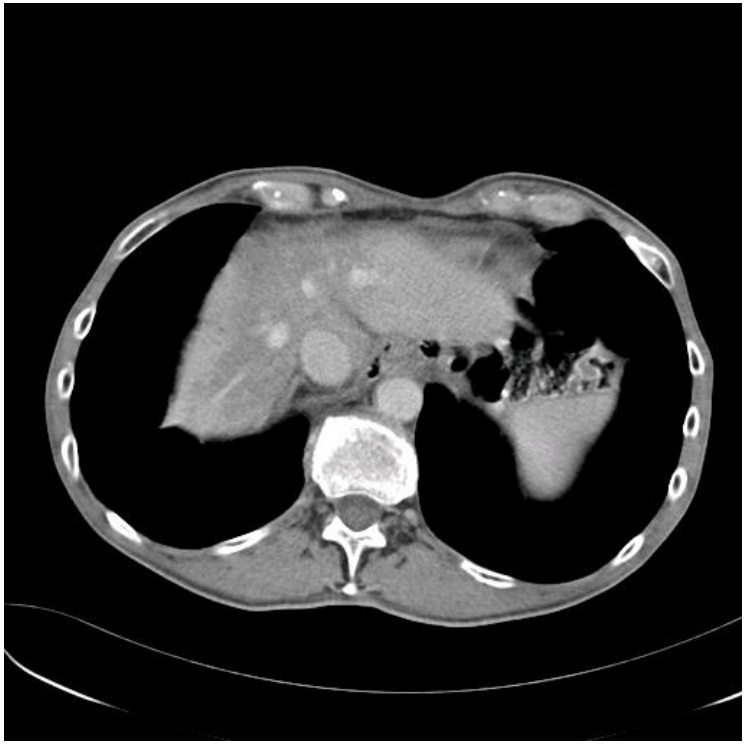


8-2012: 3x20 Gy

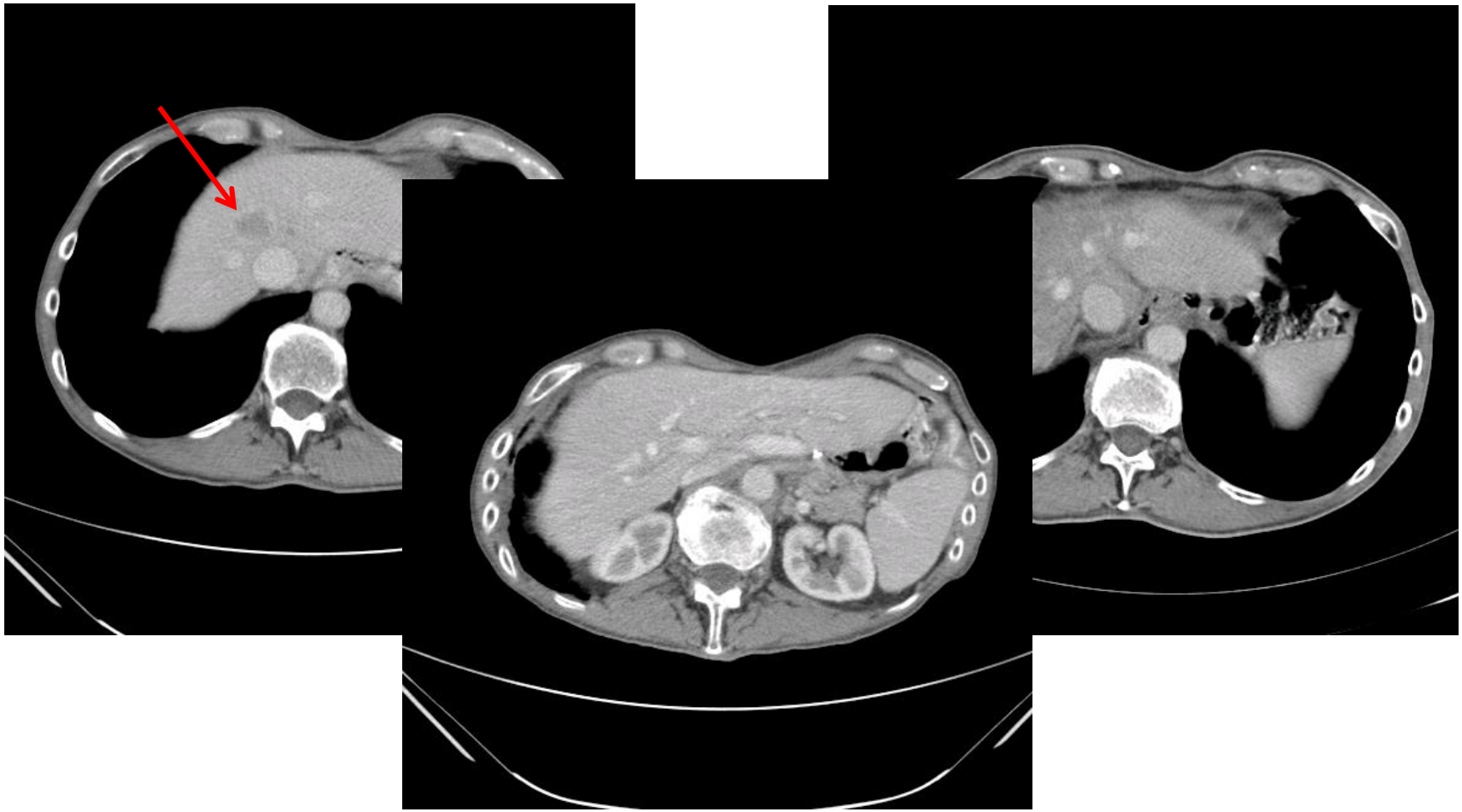
Well tolerated, fatigue for several weeks



7-2012



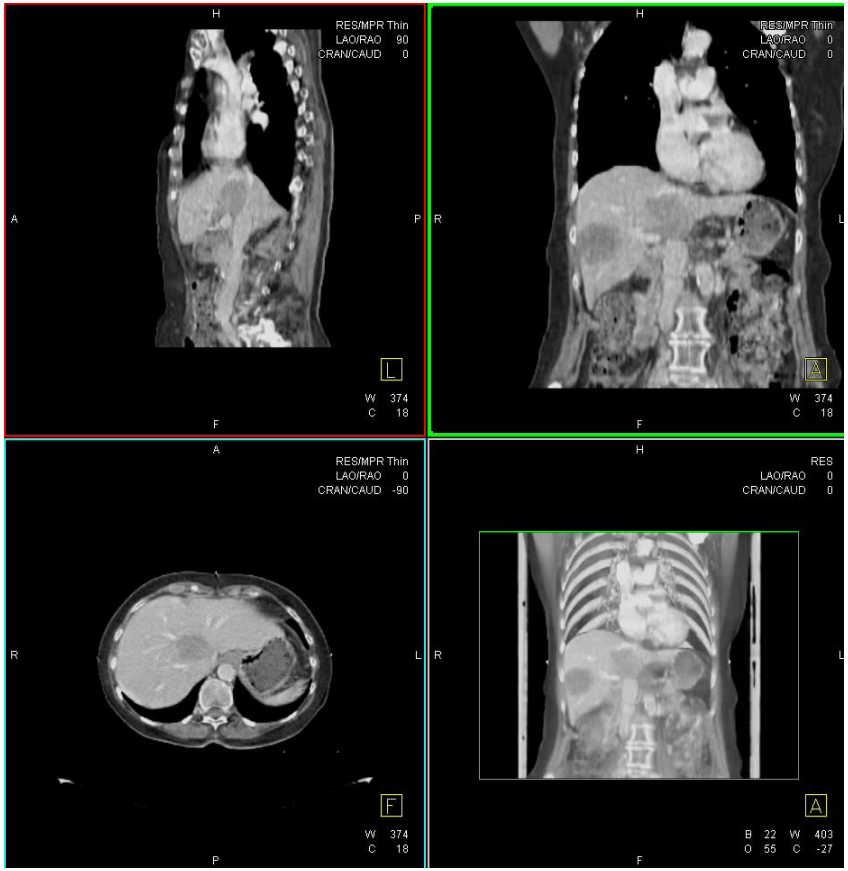
1-2013



11-2015

Treatment preparation

- PET-CT and 4D-CT with IV contrast
- CT is reconstructed in 10 phases of the respiration cycle
- Tumor delineation on each respiration phase
- Margin for setup variation



Treatment planning

- Dose per fraction and number of fractions can be varied
- Depends on location of the tumor in relation to surrounding organs at risk

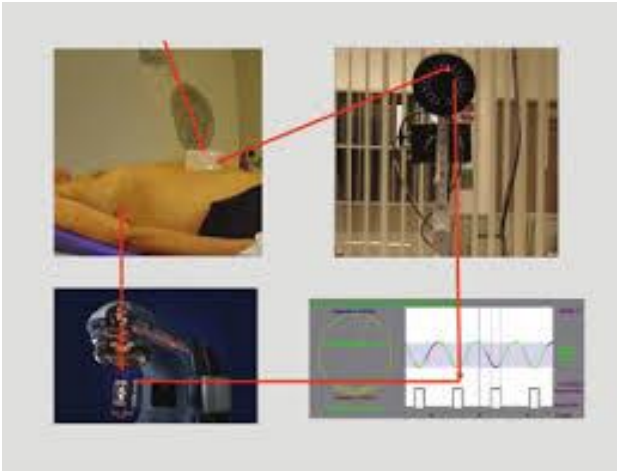
OAR	Constraints
Non-tumor liver	V(=<15 Gy) >= 700 cc
Spinal cord	Dmax =< 18 Gy
Kidneys	Both kidneys : V(=>=≥15Gy) =< 35% Right kidney : V(>=15Gy) =< 67%
Esophagus	Dmax ≤ 27 Gy
Stomach, duodenum, small bowel	Dmax = 30Gy V(22.5Gy) =< 5ml
Heart	Dmax =< 30 Gy

Challenges in targeting liver tumors

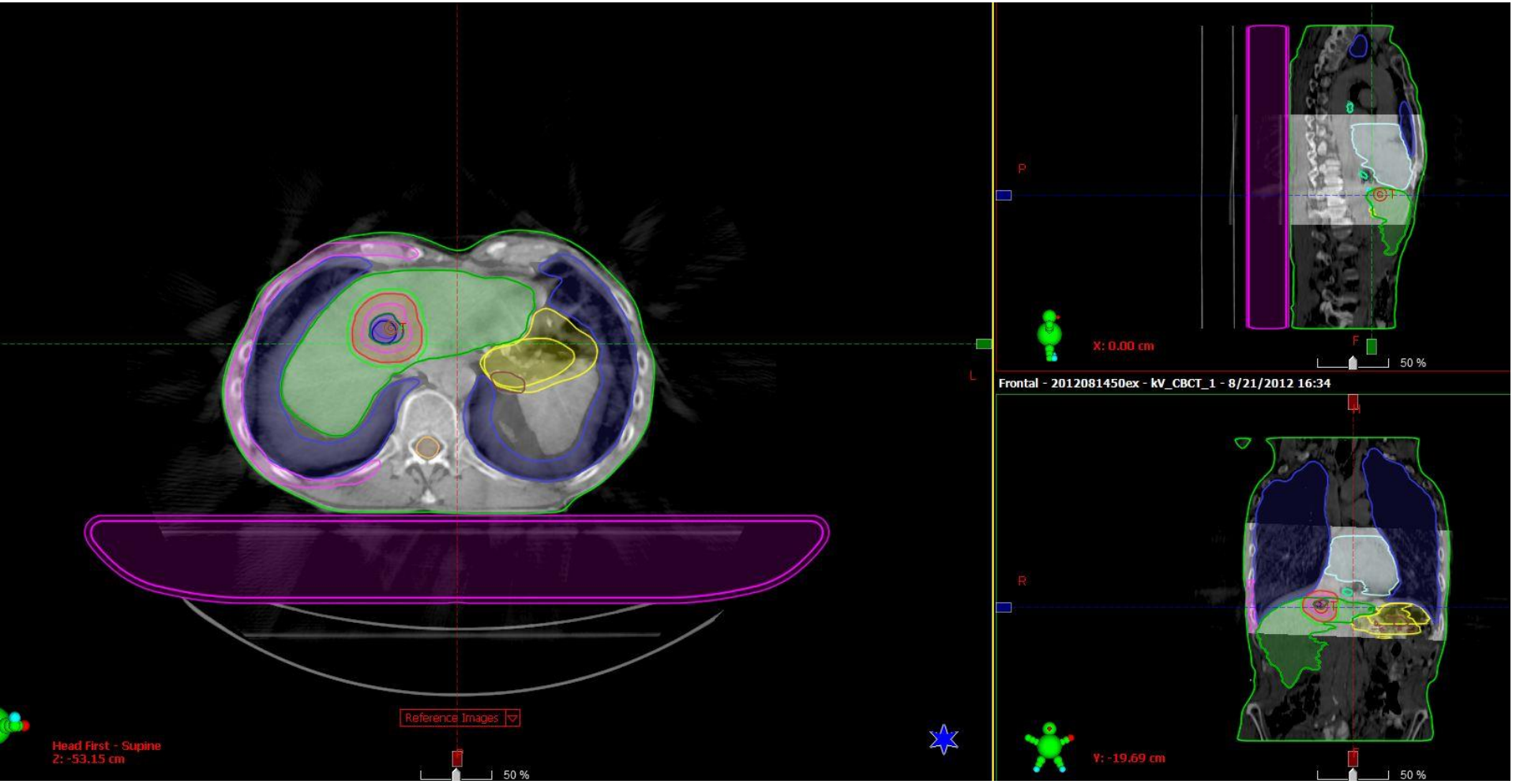
- Limited visualization of the target
- Liver deformation with respiration
- Changes in GI organ luminal filling
  - Critical structures (stomach) may change in shape and position between planning and treatment
- Interfraction target displacement with respect to bony anatomy

Ways to address motion

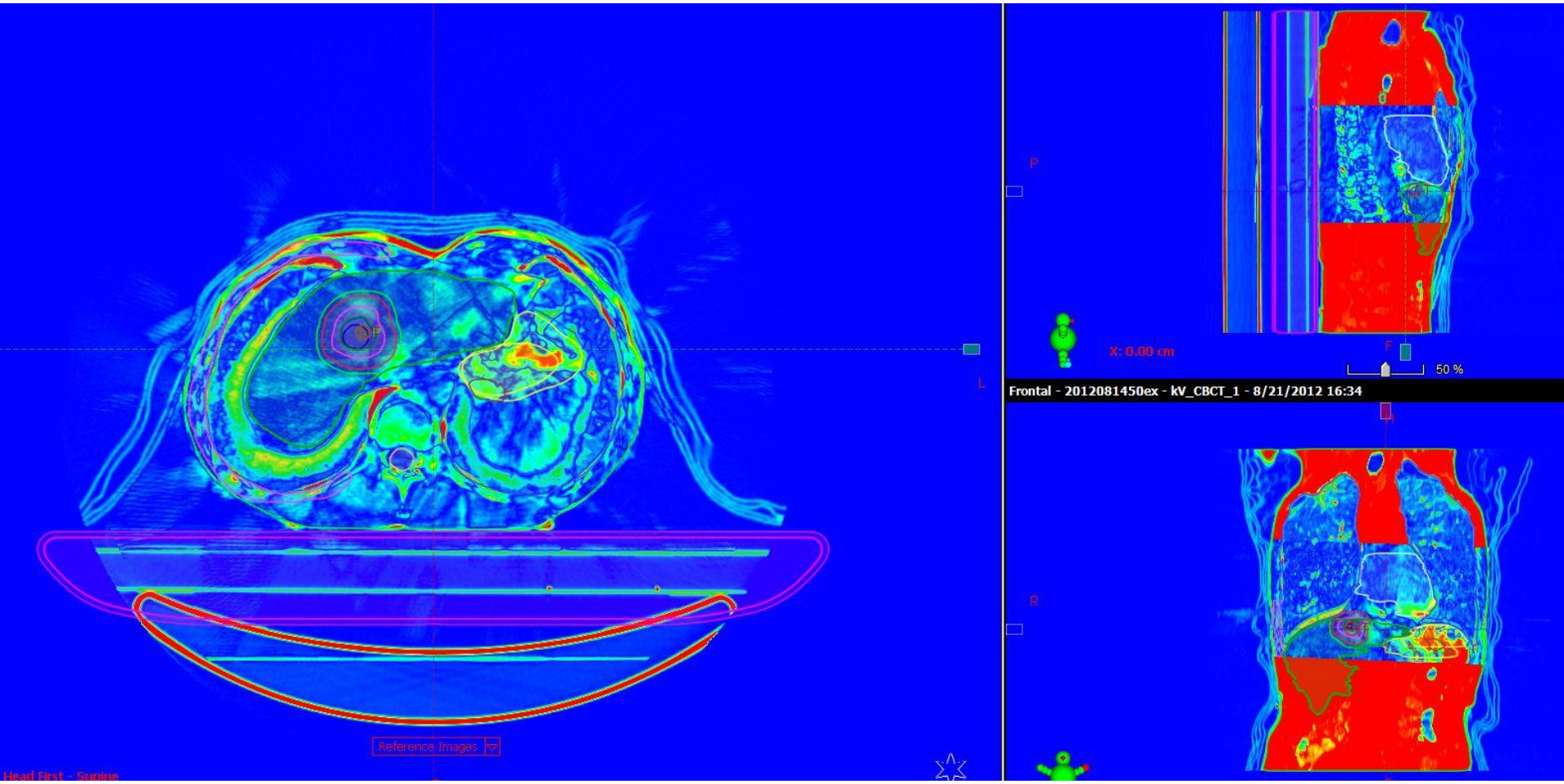
- Image guidance
- Limit motion
- Quantify actual motion
- Track motion
- Treat at certain phases of respiration



Conebeam CT


Reference Images
Head First - Supine
Z: -53.15 cm
50 %
X: 0.00 cm
50 %
Frontal - 2012081450ex - kV_CBCT_1 - 8/21/2012 16:34
Y: -19.69 cm
50 %

Conebeam CT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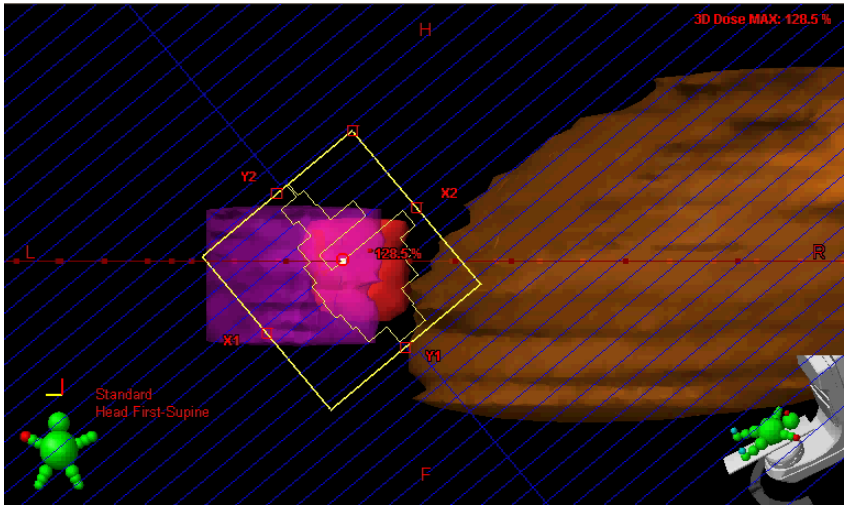
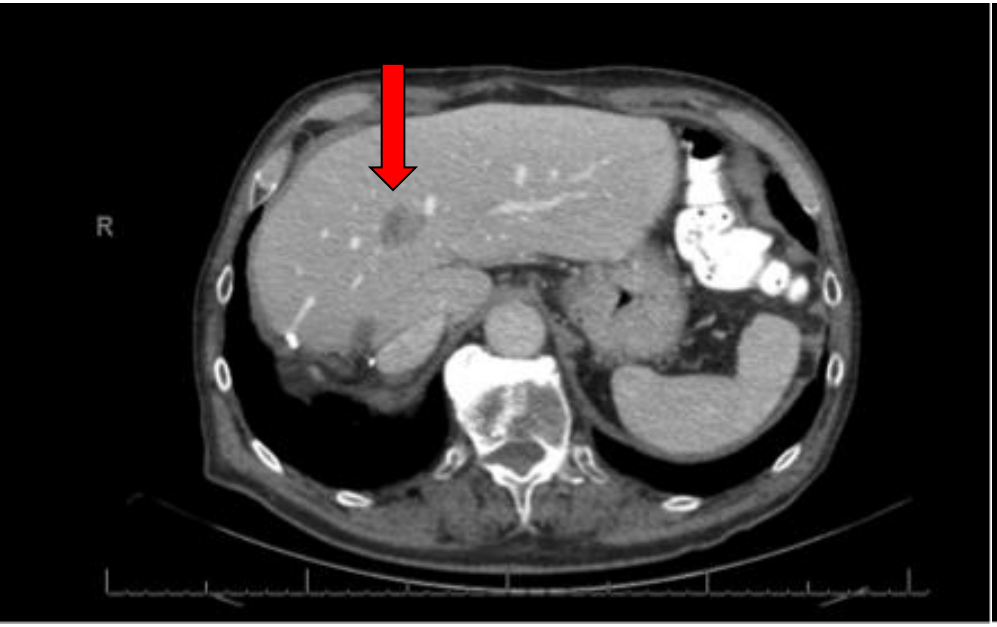
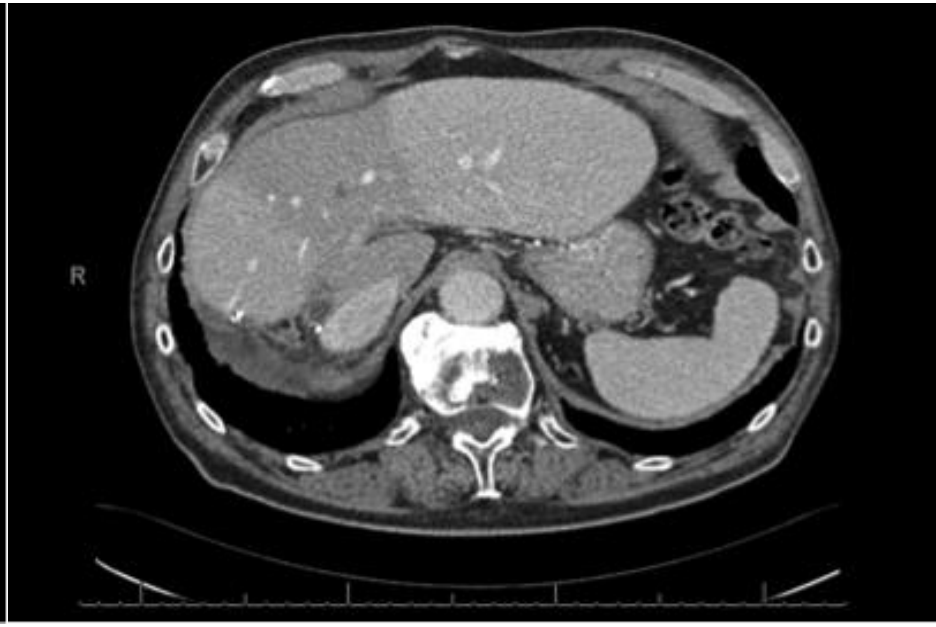
Radiation treatment



- In Maastro: VMAT=volumetric modulated arc therapye
- kV conebeam CT before eacht fraction
- Total treatment time (including match procedure) 15-20 min

Follow-up





Results of SBRT for liver tumors

- No randomized trials between surgery-SBRT or RFA-SBRT
- Only indirect comparisons

Results of SBRT for liver metastases

Reference	Design	No. patients	Tumour volume	Primary site	Radiotherapy dose	Prescription isodose line	Delivery platform	Toxicity	Outcome
[37]	Phase I–II	35	1–132 ml (median 10)	NR	14–26 Gy (1 fraction) Dose escalation	80%	Linac	No serious toxicity	1 year LC 71% 18 month LC 67% 1 year OS 72%
[38]	Phase I–II (HCC and metastases)	25 (17 liver)	1.1–322 ml (median 22.2)	CRC (14) Lung (1) Breast (1) Carcinoid (1)	30–37.5 Gy (3 fractions)	65%	Linac	2 grade 3 liver toxicities	2 year LC 86% 2 year OS 62%
[39]	Phase II (CRC oligometastases)	64 (44 liver metastases)	1–8.8 cm (median 3.5 cm)	CRC (44)	45 Gy (3 fractions)	67%	Linac	1 liver failure 2 severe late GI toxicities	2 year LC 79% 1 year LC 95% months
[40]	Phase I–II	68	1.2–3090 ml (median 75.9)	CRC (40) Breast (12) Gallbladder (4) Lung (2) Anal canal (2) Melanoma (2) Other (6)	Individualised dose 27.7–60 Gy (6 fractions)	Periphery of PTV	Linac	No RILD 10% grade 3/4 acute toxicity No grade 3/4 late toxicity	1 year LC 71% Median survival 17.6 months
[41]	Prospective cohort	27	20–165 (median 69)	CRC (11) Other (16)	25–60 Gy (3 fractions)	80%	CyberKnife	No serious toxicity	Crude LC rate 74%
[42]	Phase I–II	47	0.75–97.98 ml (median 14.93)	CRC (15) Lung (10) Breast (4) Ovarian (3) Oesophageal (3) HCC (2) Other (10)	Dose escalation 36–60 Gy (3 fractions)	80–90%	Linac	No RILD Late grade 3/4 toxicity <2%	1 year LC 95% 2 year LC 92% Median survival 20.5 months
[43]	Phase I (HCC and liver metastases)	26 (19 liver metastases)	0.8–146.6 ml (median 32.6 ml)	CRC (6) Pancreatic (3) Gastric (2) Ovarian (2) Other (6)	Dose escalation 18–30 Gy (1 fraction)	Isodose covering PTV	Linac and CyberKnife	No dose limiting toxicity 4 cases of grade 2 late toxicity (2 GI, 2 soft tissue/rib)	1 year local failure 23% 2 year OS 49%
[44]	Prospective phase 2	61	CTV 1.8–134 cm^3 (mean 18.6)	CRC (29) Breast (11) Gynaecological (7) Other (14)	52.5–75 Gy (3 fraction)	Prescribed as mean dose to PTV	Linac (RapidArc)	1 case late grade 3 toxicity	1 year LC 94%, 1 year OS 84%

CRC, colorectal; NR, not reported; LC, local control; OS, overall survival; HCC, hepatocellular carcinoma; RILD, radiation-induced liver disease; GI, gastrointestinal; PTV, planning target volume; CTV, clinical target volume.

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LC 71 – 94 %

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Toxicity of SBRT for liver metastases

- Most series: low rates of grade 3-4 toxicity
- RILD generally <1%
- Gastrointestinal complications
- Thoracic wall pain and rib fractures

Factors influencing local control rates

- Lesion size
- Biological effective dose
- Histology

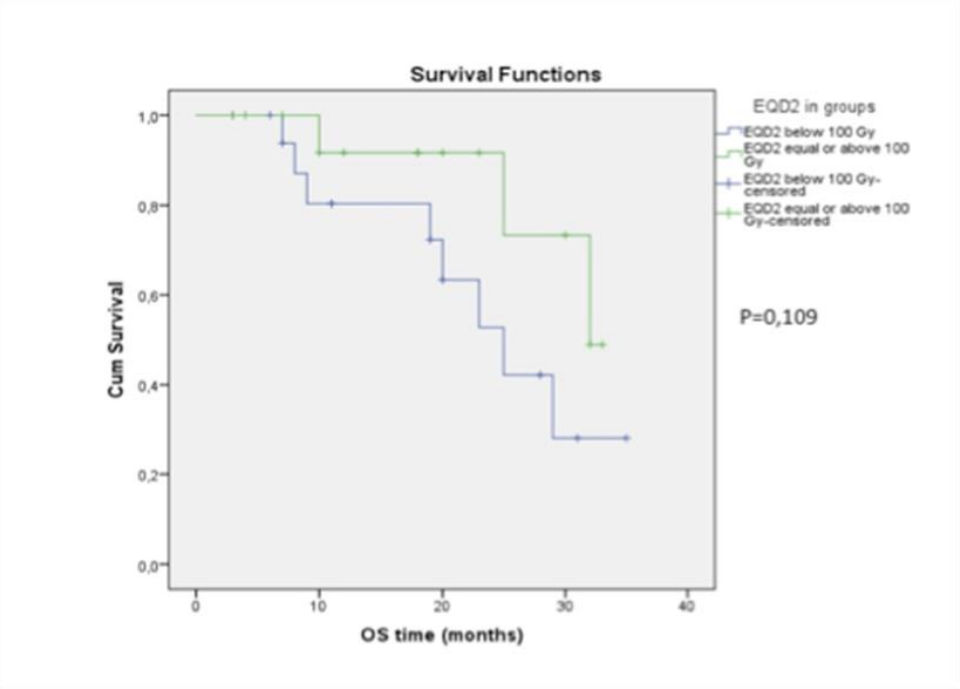
Maastricht results

Characteristic	Value (%)
Total number of patients	33
Total number of lesions	39
Age (years)	
•Mean	68
•Range	46−81
Gender	
•Female	15 (45.5)
•Male	18 (54.5)
Number of lesions	
•1	28 (84.8)
•2	4 (12.1)
•3	1 (3.0)
Primary tumor site	
•Colorectal	17 (51.5)
•Non-colorectal	11 (33.3)
•Hepatocellular	5 (15.2)
Involved liver segment	
•2	1 (2.6)
•3	2 (5.1)
•4	6 (15.4)
•6	5 (12.8)
•7	5 (12.8)
•8	20 (51.3)
Extrahepatic disease	
•No	26 (78.8)
•Yes	7 (21.2)
Chemotherapy	
•Yes	11 (33.0)
•No	22 (67.0)
EQD2	
•Below 100 Gy	17 (51.5)
•Equal or above 100 Gy	16 (48.5)
PTV volume (ml)	
•Minimum	22.9
•Maximum	758.3
•Mean	170.1
Dosimetric value of the liver	
•Mean dose (Gy)	14
•Mean volume healthy liver (ml)	1562.9

Van de Voorde et al EJSO 2015

Results Maastro

- CT-based regression:
  - 73% partial remission
  - 27% complete remission
- Progression pattern mainly distant
- Overall survival
  - 1y: 85,4%
  - 2y: 68,8%
  - Median: 29 months
- EQD2 ≥ 100 Gy
  - Higher LC
  - Longer median survival
- Smaller PTV



Toxicity

Acute Toxicity

- Fatigue (n=11)
- Grade 1 nausea (n=8)
- Diarrhea (n=2)
- Grade 1 erythema (n=1)

Late toxicity

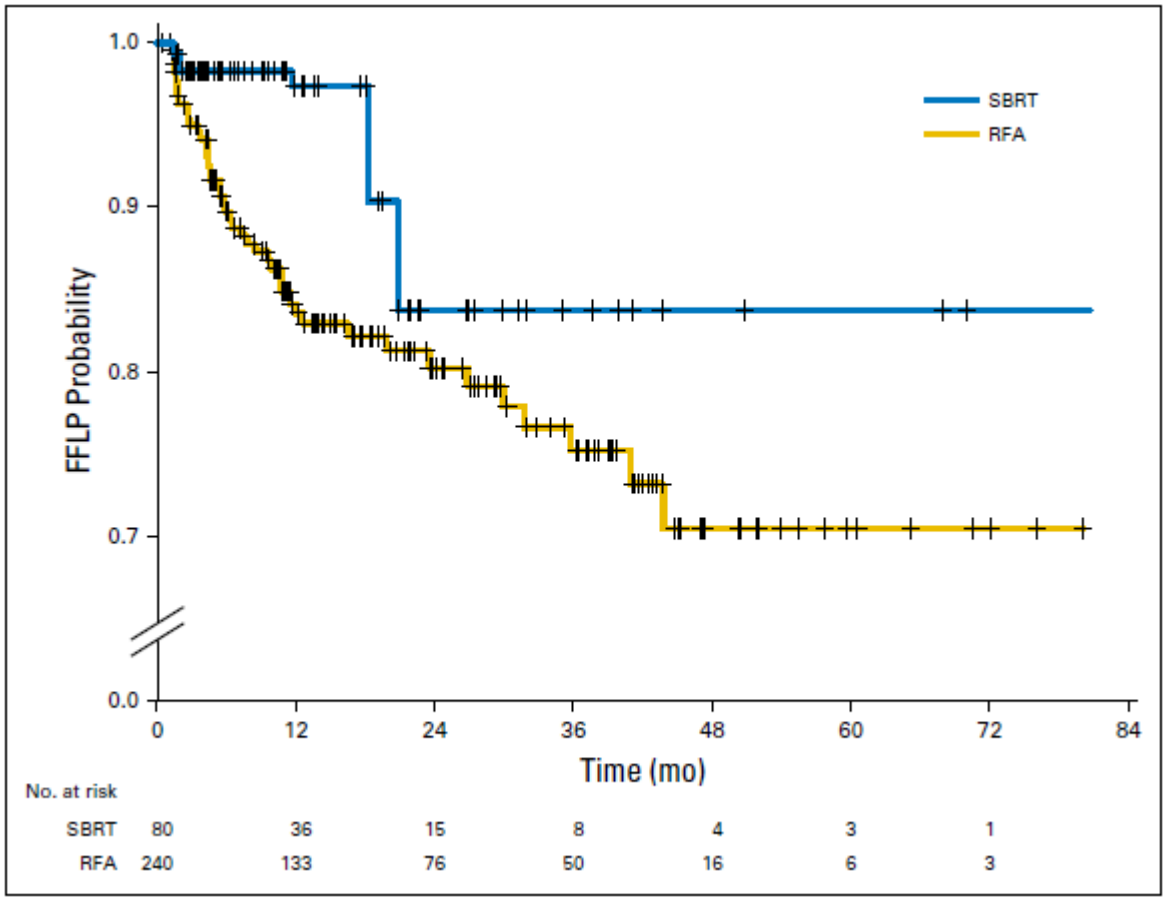
- Radiation pneumonitis (n=1)
- No RILD

SBRT vs RFA

- Retrospective study at U. Michigan (2004-2012)
- Primary and metastatic liver lesions
- RFA
  - 161 pts, 249 liver lesions
  - General anesthesia, u/s guidance
  - Median FU 51 mo
- SBRT
  - 63 pts, 83 liver lesions
  - 30-60 Gy in 3-5 fractions
  - Median FU 27 mo

Wahl JCO 2015

SBRT vs RFA



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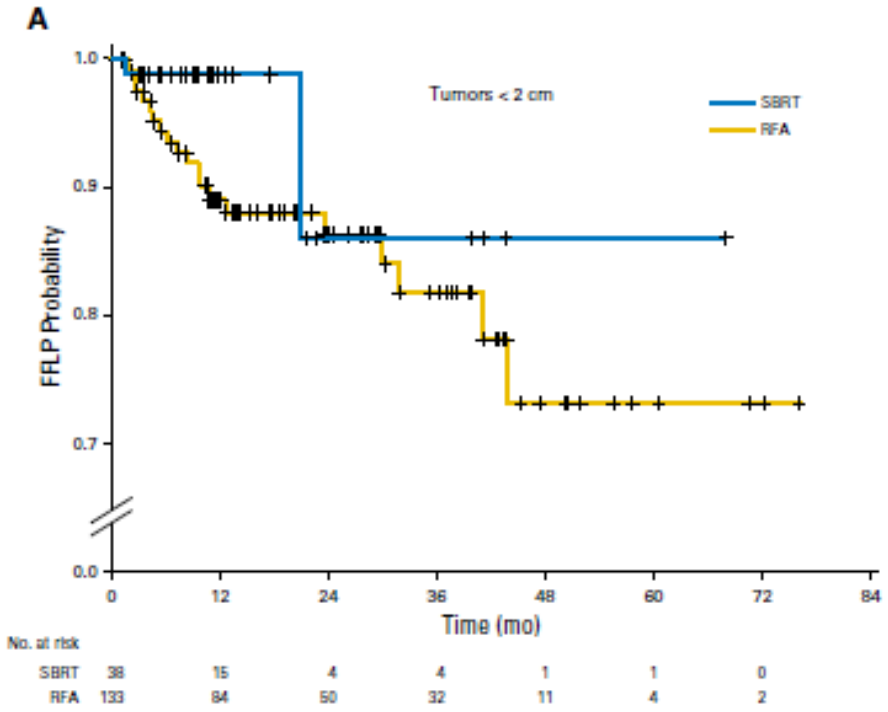
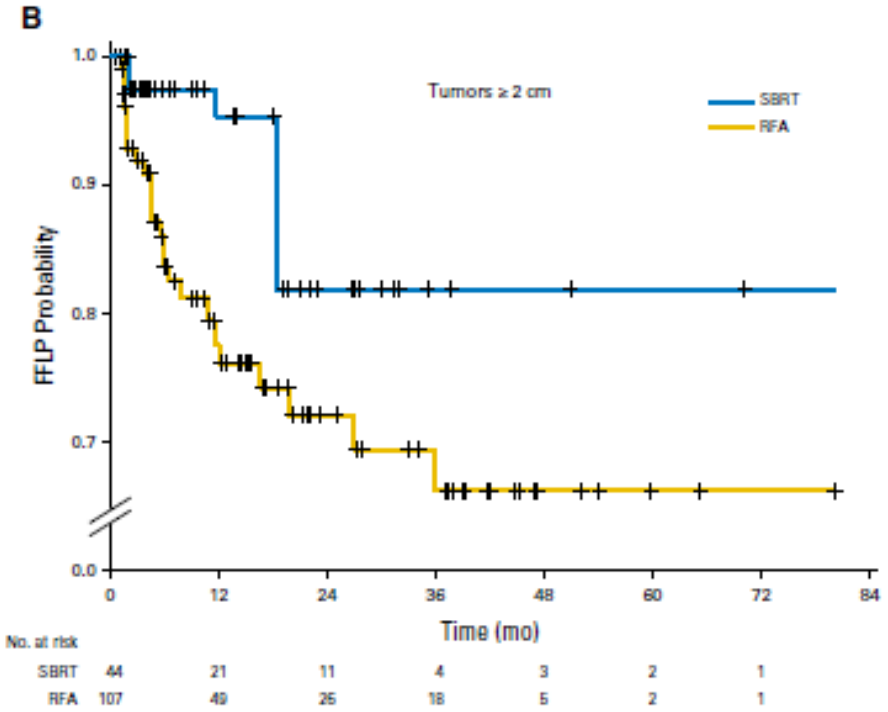
SBRT vs RFA: size dependent





Wahl JCO 2015

Complications (≥ grade 3)

- SBRT (5%)
  - RILD (CP-B liver)
  - GI bleeding
  - Worsening ascites
- RFA (11%)
  - Pneumothorax (n=1)
  - Sepsis (n=2)
  - Duodenum perforation (n=1)
  - Colon perforation (n=1)
  - Bleeding (n=3)

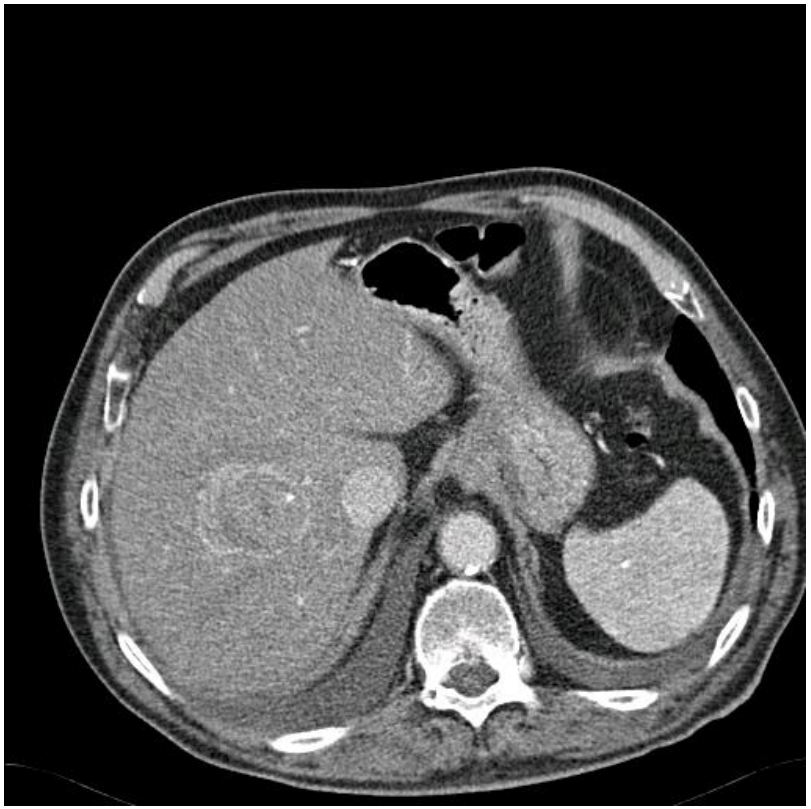
Wahl JCO 2015

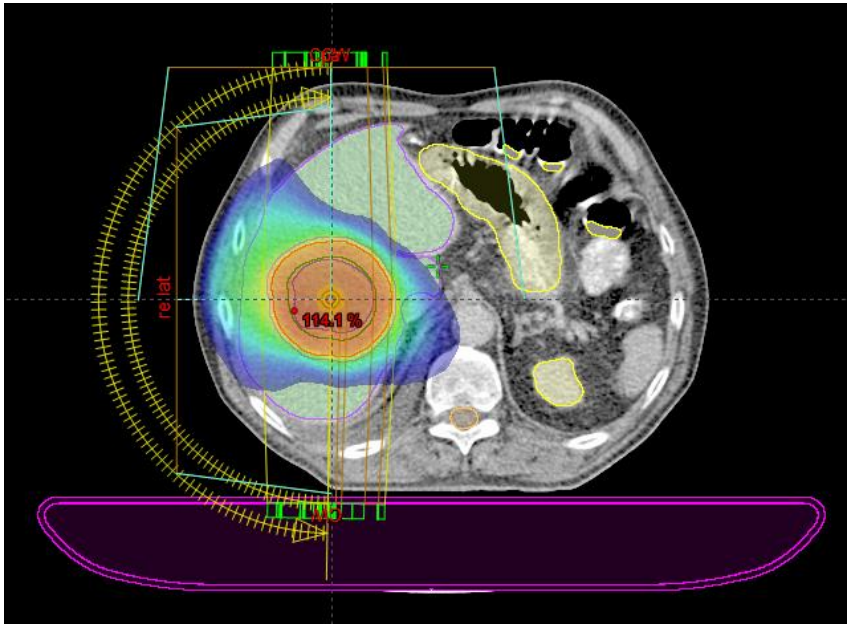
Patient case 2

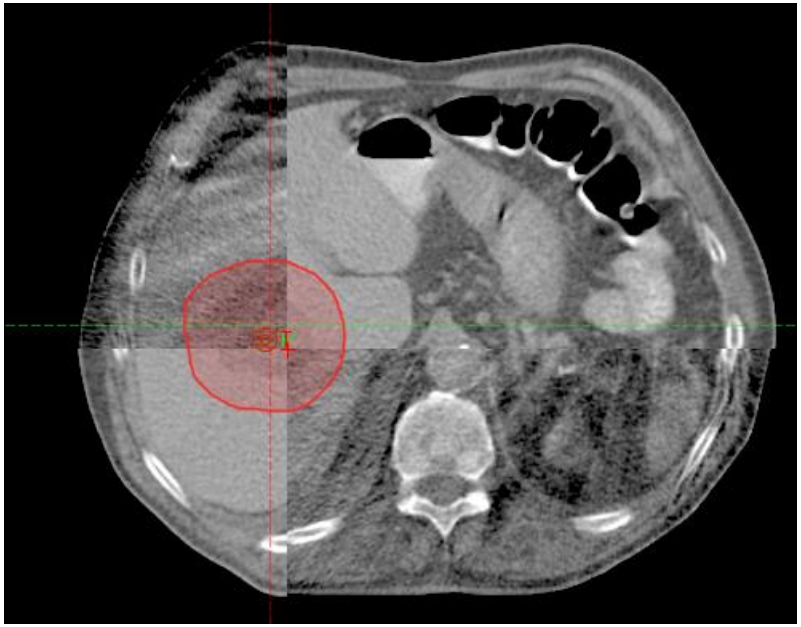
- Mr W, 79 years
- Medical history:
  - Diabetes
  - Heart failure
  - Polyneuropathy
  - Hypokinetic rigid syndrome
- Presented with hematemesis, caused by gastric ulcer

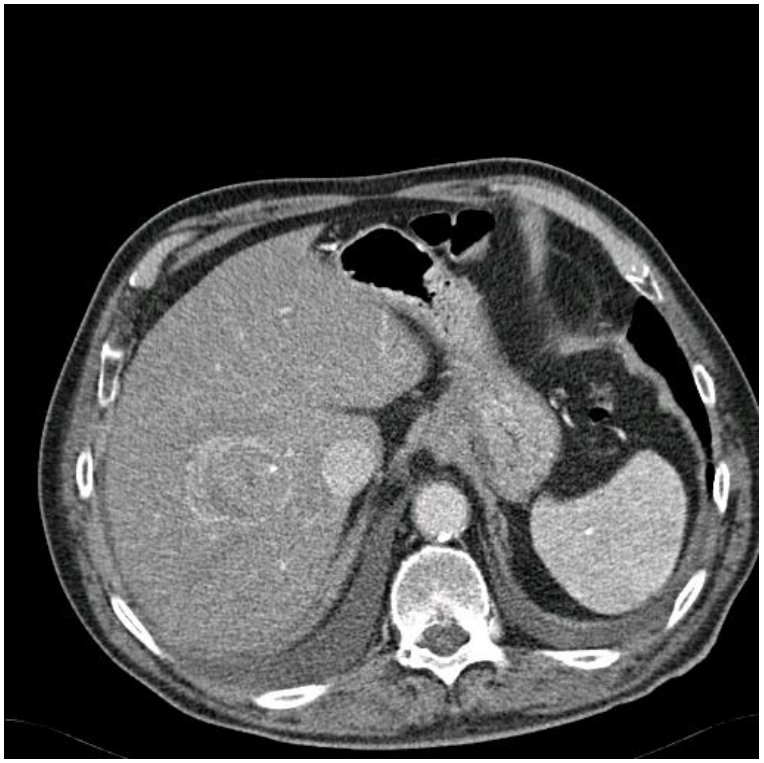
Patient case 2

- CT-abdomen (7-2015): lesion in segment 7/8, 4.8 cm, some arterial contrast enhancement and wash out. Suspicion of an HCC in a non-cirrhotic liver.
- Biopsy: hepatocellular carcinoma moderately differentiated
- MDT: stereotactic radiotherapy

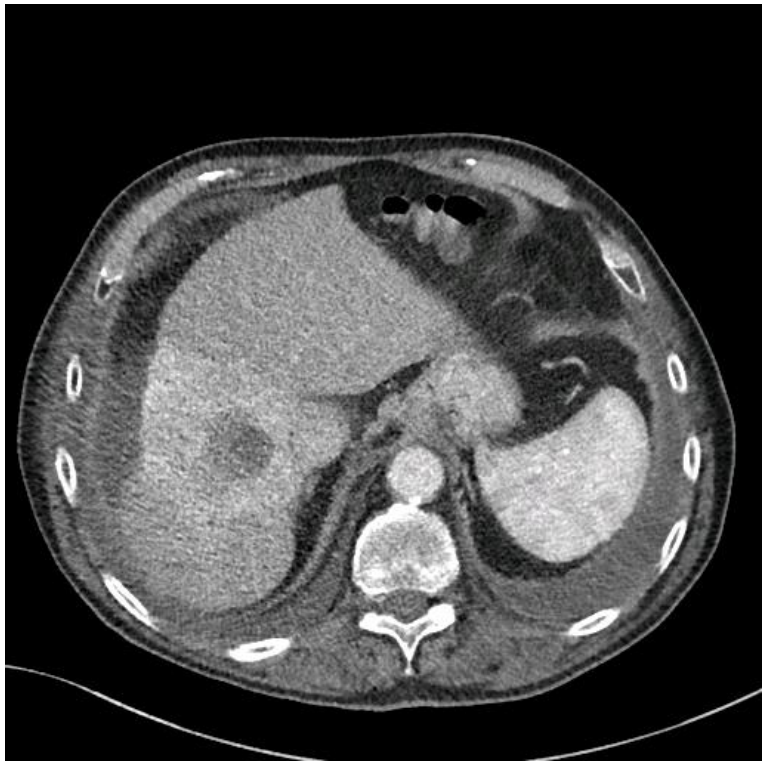



re:lat
114.1 %

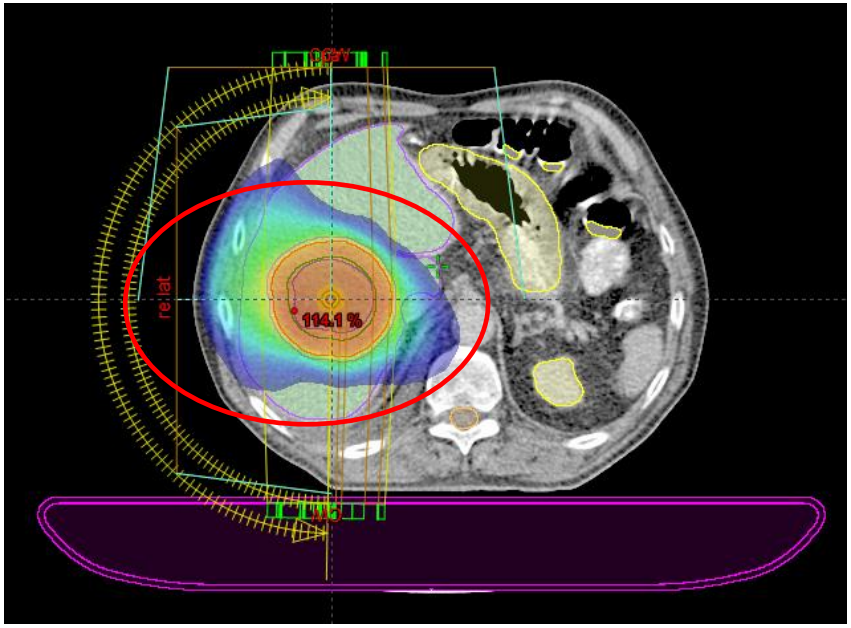


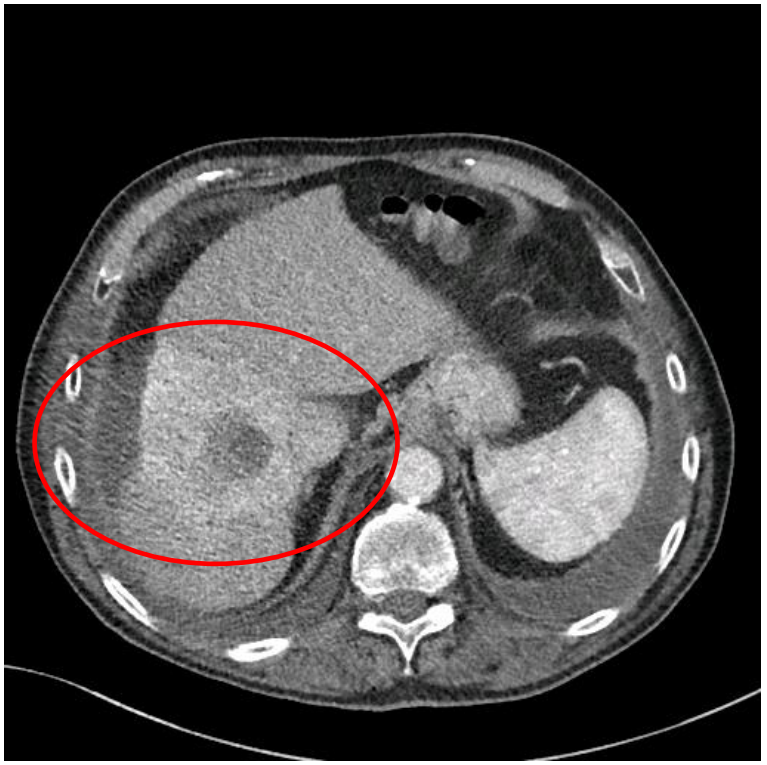


7-2015



9 months after SBRT





9 months after SBRT

Conclusions

- SBRT can be a safe alternative for surgery in patients with solitary or limited liver metastases or a primary liver tumor in selected patients
- Local control rates after SBRT for liver lesions are 70-90%
- Randomised trials comparing surgery-RFA-SBRT are lacking
- The follow-up of liver lesions treated with SBRT should be done in close collaboration between radiologist and radiation oncologist