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FEGATO:

Radioterapia stereotassica

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CLINICAL ASPECTS

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- Metastatic disease to the liver is a common life-threatening complication encountered by cancer patients. Among patients who die of cancer, **30–70% have liver metastasis at autopsy**

- **Most common primary sites** are lung, breast, colon-rectum and uterus

- **Synchronous or metachronous**

Hugh et al, Aust NZ J Surg 1997

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Living with Liver Cancer

Liver Cancer
treatment information

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- Majority of liver metastases initially **clinically silent** and symptoms present at a late stage

- Imaging techniques, like CT scan or MRI, can detect liver metastases earlier in **asymptomatic patients** with advanced stages

- A subset of patients who present with **solitary or limited number of liver lesions** show improved survival after **surgical excision**

Sharma et al, Journal of HBP Surgery 2008

Hugh et al, Aust NZ J Surg 1997

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treatment information

Surgery

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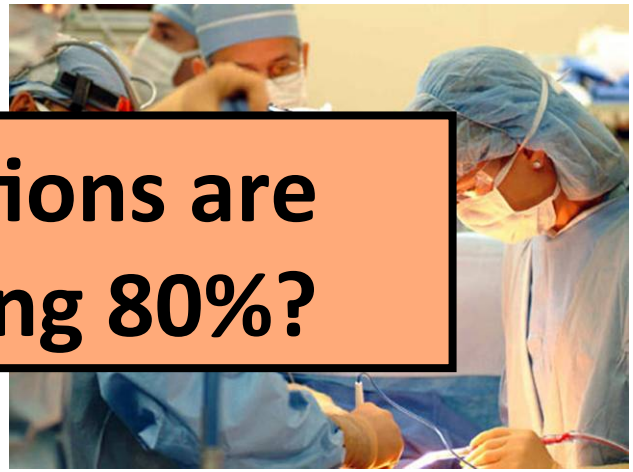
- Patients with resected **metastatic colorectal cancer have 5-year survival rates of 25–60%**

- **Surgery has a positive impact on survival**

What kind of ablative options are available for the remaining 80%?

- Surgery is technically difficult and **only 20% of metastatic colorectal cancer patients are candidates for surgical resection**



Fong Y. et al. (1995) CA Cancer J.Clin.

Simmonds P.C. et al. (2006) Br.J.Cancer

Local therapeutic approches

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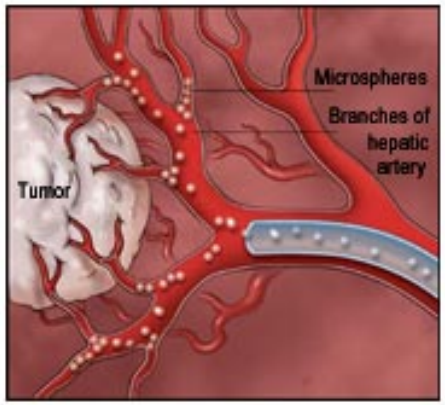
• **In selected patients** with a limited number of hepatic metastases who are not surgical candidates, **a variety of ablative techniques have been developed.**

• The most prominent in use are radiofrequency ablation (**RF**), transarterial chemoembolization (**TACE),** percutaneous ethanol injection (**PEI**).

• Although much less invasive than surgery, all of them have some grade of **invasiveness and serious limitations (large lesions, portohepatic region).**



Microspheres injected during chemoembolization
"lock in" chemotherapy

Meij et al, World Journal of Surgical Oncology 2005

Kemeny N. et al, Oncology 2006

SISTEMIC APPROACH

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- For the majority of patients, **chemotherapy** represents the only viable treatment option

- The introduction of new chemotherapeutic agents and **targeted therapies** has resulted in a dramatic **improvement in outcome** for patients with **colorectal cancer**

- Unfortunately, these results are not seen for most other malignancies, and **liver metastasis remains a difficult therapeutic challenge**

Kemeny N, Oncology 2006

MULTIDISCIPLINARY

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MEDICAL ONCOLOGIST

RADIOLOGIST

PATIENT

SURGEON

NURSES

RADIATION ONCOLOGIST

PATIENT BASED APPROACH

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REPORT

AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY (ASTRO) AND AMERICAN COLLEGE OF RADIOLOGY (ACR) PRACTICE GUIDELINE FOR THE PERFORMANCE OF STEREOTACTIC BODY RADIATION THERAPY

• Stereotactic body radiation therapy (SBRT) is an external beam radiation therapy method used to very precisely deliver a **high dose of radiation** to an extracranial target within the body, using either a single dose or a small number of fractions.

• Specialized treatment planning results in high target dose and **steep dose gradients** beyond the target.

• The ability to deliver a **single or a few fractions of high-dose ionizing radiation** with **high targeting accuracy** and rapid dose falloff gradients encompassing tumors within a patient provides the basis for the development of SBRT.

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REPORT

AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY (ASTRO) AND AMERICAN COLLEGE OF RADIOLOGY (ACR) PRACTICE GUIDELINE FOR THE PERFORMANCE OF STEREOTACTIC BODY RADIATION THERAPY

- SBRT can be applied using **non invasive** or minimally invasive stereotactic localization and radiation delivery techniques.

- It requires significantly **improved delivery precision** over that required for conventional radiotherapy.

- Maneuvers to either **limit or compensate for target movement** during treatment planning and delivery are often useful and may be required.

- The quality of a stereotactic body radiation therapy program depends on the **coordinated interactions of a team of skilled health care professionals**.

SBRT: inoperable early stages NSCLC

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REVIEWS

Stereotactic body radiation therapy: a novel treatment modality

Simon S. Lo, Achilles J. Fakiris, Eric L. Chang, Nina A. Mayr, Jian Z. Wang, Lech Papiez, Bin S. Teh, Ronald C. McGarry, Higinia R. Cardenes and Robert D. Timmerman

Nat. Rev. Clin. Oncol. **7**, 44–54 (2010); published online 8 December 2009; doi:10.1038/nrclinonc.2009.188

Table 1 | Results of SBRT trials in early stage non-small cell lung cancer

Study	Trial type	Disease stage	Number of patients	Radiation dose	Follow-up period (months)	Outcomes
McGarry *et al.* (2005)[27]	Prospective (phase I)	Medically inoperable stage I	47	24–72 Gy in 3 fractions at 80%	27.4 for T1 19.1 for T2	LC: 78.7%
Fakiris *et al.* (2009)[28]	Prospective (phase II)	Medically inoperable stage I	70	T1 tumors: 60 Gy in 3 fractions at 80% T2 tumors: 66 Gy in 3 fractions at 80%	50.2	LC: 88.1% at 3 years OS: 42.7% at 3 years CSS: 81.7% at 3 years
Nagata *et al.* (2005)[30]	Prospective (phase I–II)	IA and IB	45	48 Gy in 4 fractions at isocenter	30 for T1 tumors 22 for T2 tumors	LC: 98% (crude) OS: 92% and 83% at 1 and 3 years, respectively DFS: 80% and 72% at 1 and 3 years, respectively
Baumann *et al.* (2009)[31]	Prospective (phase II)	Medically inoperable stage I	57	45 Gy in 3 fractions at 67%	35	LC: 92% at 3 years OS: 86%, 65% and 60% at 1, 2 and 3 years, respectively CSS: 93%, 88% and 88% at 1, 2 and 3 years, respectively PFS: 52% at 3 years

Abbreviations: CSS, cancer-specific survival; DFS, disease-free survival; LC, local control; OS, overall survival; PFS, progression-free survival; SBRT, stereotactic body radiation therapy.

SBRT: operable early stages NSCLC

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CLINICAL INVESTIGATION

STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR OPERABLE STAGE I NON–SMALL-CELL LUNG CANCER: CAN SBRT BE COMPARABLE TO SURGERY?

HIROSHI ONISHI, M.D.,* HIROKI SHIRATO, M.D.,† YASUSHI NAGATA, M.D.,‡ MASAHIRO HIRAOKA, M.D.,§

- Between 1995 and 2004, a total of **87 patients with Stage I NSCLC** (median age, 74 years; T1N0M0, n = 65; T2N0M0, n = 22) **who were medically operable but refused surgery were treated using SBRT alone**

- Total dose was **45–72.5 Gy at the isocenter, administered in 3–10 fractions**. Median calculated BED was 116 Gy (range, 100–141 Gy).

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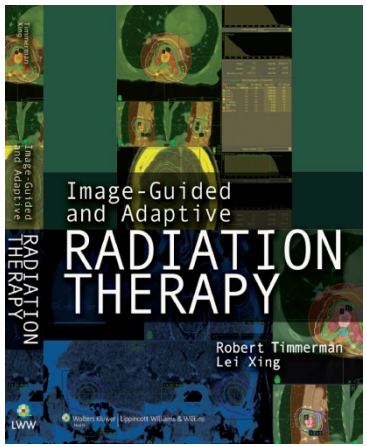
- Cumulative **local control rates for T1 and T2 tumors at 5 years after SBRT** we[illegible] **ge** IA [illegible]
- P[illegible]
- The survival rate for **SBRT is potentially comparable to that of surgery**

Could SBRT be an alternative to surgery in selected patients?



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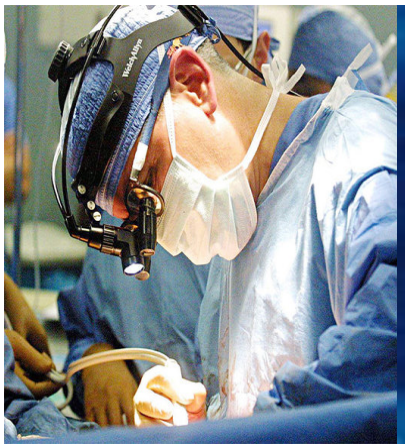

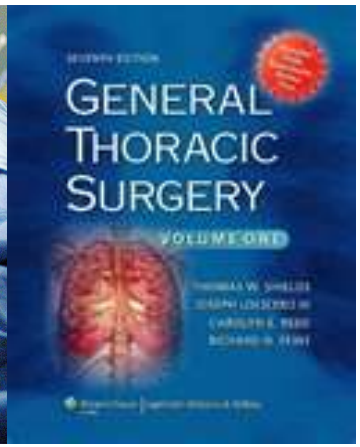

SBRT FOR LIVER METASTASES

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• The major **dose-limiting** concern in the use of SBRT for liver tumors is the risk of radiation-induced liver disease (**RILD**)

• **RILD is a clinical syndrome** characterized by anicteric hepatomegaly, ascites, elevated liver enzymes (particularly alkaline phosphatase) occuring 2 weeks to 4 months after radiotherapy

Tai et al, IJROBP 2009 - Sawrie et al, Cancer Control 2010

HEPATIC TOXICITY

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CLINICAL INVESTIGATION

STEREOTACTIC BODY RADIOTHERAPY FOR PATIENTS WITH UNRESECTABLE PRIMARY HEPATOCELLULAR CARCINOMA: DOSE-VOLUMETRIC PARAMETERS PREDICTING THE HEPATIC COMPLICATION

Seok Hyun Son, M.D.,* Byung Ock Choi, M.D.,* Mi Ryeong Ryu, M.D.,* Young Nam Kang, Ph.D.,* Ji Sun Jang, M.S.,* Si Hyun Bae, M.D.,† Seung Kew Yoon, M.D.,† Ihl Bohng Choi, M.D.,‡ Ki Mun Kang, M.D.,§ and Hong Seok Jang, M.D.*

From the Departments of *Radiation Oncology and †Internal Medicine, College of Medicine, the Catholic University of Korea, Seoul, Korea; ‡Cyberknife Center of Gimpo Wooridul Spine Hospital, Seoul, Korea; §Department of Radiation Oncology, College of Medicine, Gyeongsang National University, Jinju, Korea

- Liver obeys the **parallel architecture model of radiobiology**, so the risk of RILD is generally proportional to the **mean dose** of radiation delivered to normal liver tissue

- It should be possible to safely treat small hepatic lesions with high doses of radiation by **using SBRT**, with adequate dose constraints for normal liver (**minimum volume of 700mL should receive a total dose less than 15 Gy)**

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Table 3. Prospective Trials of Stereotactic Body Radiation Therapy for Hepatic Metastases

Study	No. of Lesions	Fractionation	Median Follow-Up	Actuarial Local Control	
				Time	%
Herfarth et al[6]	55	1 × 14 Gy to 1 × 26 Gy	6 months	18 months	67
Hoyer et al[24]	141*	3 × 15 Gy	4.3 years	2 years	79
Milano et al[21]	293†	10 × 5 Gy	41 months‡	2 years	67
Mendez-Romero et al[25]	45	3 × 12.5 Gy§	13 months	2 years	82
Rusthoven et al (this study)	49	3 × 20 Gy	16 months	2 years	92

*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.

Rusthoven et al, JCO 2009

- The primary end point was in field local control defined as no growth of the treated lesion in patients with at least 6 months of FU imaging post- SBRT
- The secondary end points were toxicity (CTCAE3), progression-free survival and overall survival

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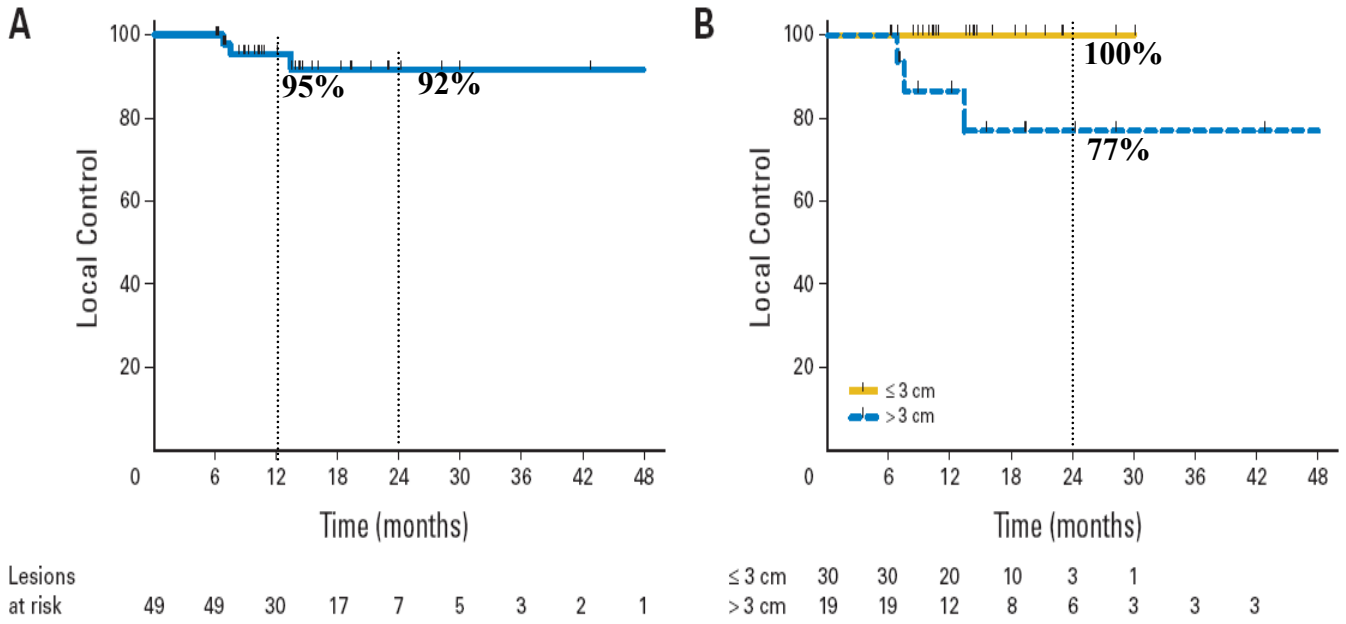
VOLUME 27 · NUMBER 10 · APRIL 1 2009

JOURNAL OF CLINICAL ONCOLOGY

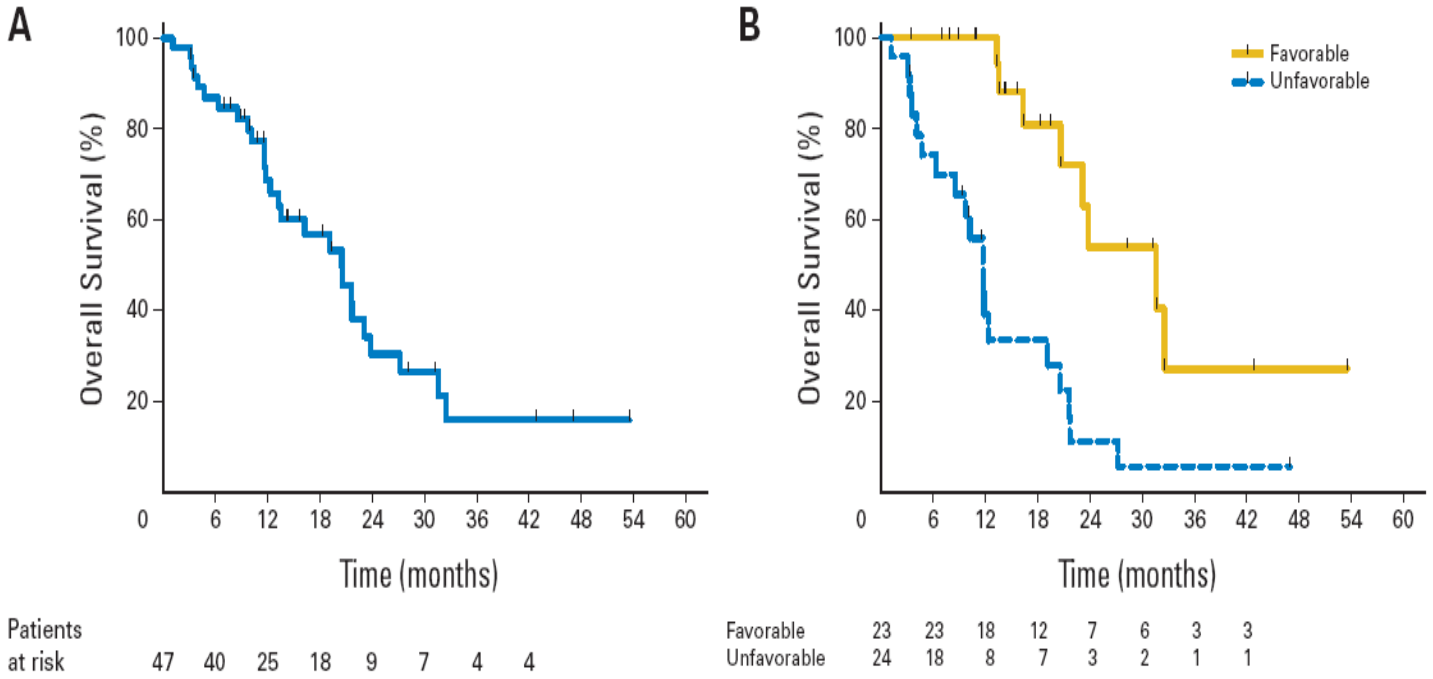
ORIGINAL REPORT

Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases

Kyle E. Rusthoven, Brian D. Kavanagh, Higinia Cardenes, Volker W. Stieber, Stuart H. Burri, Steven J. Feigenberg, Mark A. Chidel, Thomas J. Pugh, Wilbur Franklin, Madeleine Kane, Laurie E. Gaspar, and Tracey E. Schefter



Actuarial local control for (A) all lesions and (B) lesions according to maximal tumor diameter.



Actuarial survival for (A) all patients and (B) patients according to primary site.

• Primary tumors of the lung, ovary, and non colorectal gastrointestinal malignancies (ie, unfavorable primary sites) were associated with worse survival

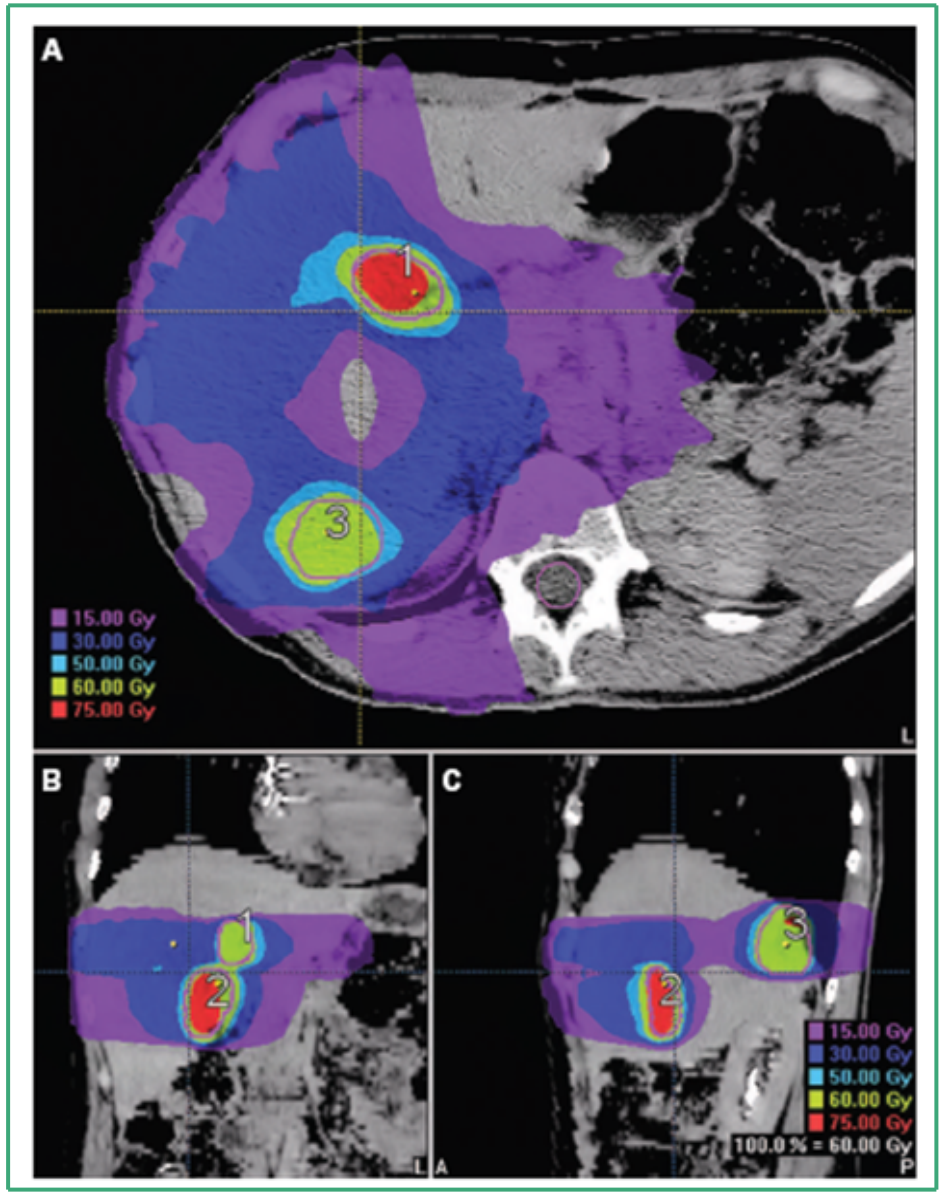


Fig 1. Stereotactic body radiation therapy plan for a patient with three metastases from ovarian cancer. The right superior-medial (lesion 1) and right inferior-medial (2) lesions were treated within a single isocenter. The right posterior-lateral lesion (3) was treated by using a separate isocenter. Prescription dose was 60 Gy in three fractions. Image A is an axial image that shows right posterior-lateral and right superior-medial lesions. Image B is a coronal image that shows the right superior-medial and right inferior-medial lesions. Image C is a sagittal image that shows a coplanar view of the right posterior-lateral and right inferior-medial lesions.

Rusthoven et al, JCO 2009

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Stereotactic Body Radiotherapy for Colorectal Liver Metastases

2011

A Pooled Analysis

Daniel T. Chang, MD[1]; Anand Swaminath, MD[2]; Margaret Kozak, BA[1]; Julie Weintraub, MD[3]; Albert C. Koong, MD, PhD[1]; John Kim, MD[2]; Rob Dinniwell, MD[2]; James Brierley, MD[2]; Brian D. Kavanagh, MD, MPh[3]; Laura A. Dawson, MD[2]; and Tracey E. Schefter, MD[3]

Patients with **colorectal liver metastases** from 3 institutions were included if they had **1 to 4 lesions**, **received 1 to 6 fractions** of stereotactic body radiotherapy, and had radiologic imaging 3 months post-treatment.

Sixty-five patients with 102 lesions treated from August 2003 to May 2009 were retrospectively analyzed. Forty-seven (72%) patients had ≥1 **chemotherapy regimen before stereotactic body radiotherapy**, and 27 (42%) patients had ≥ 2 regimens.

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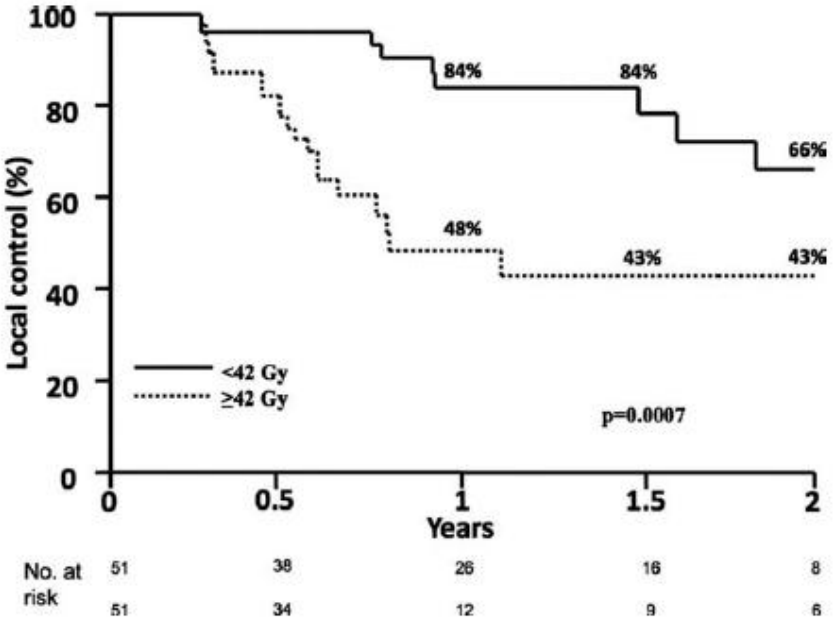

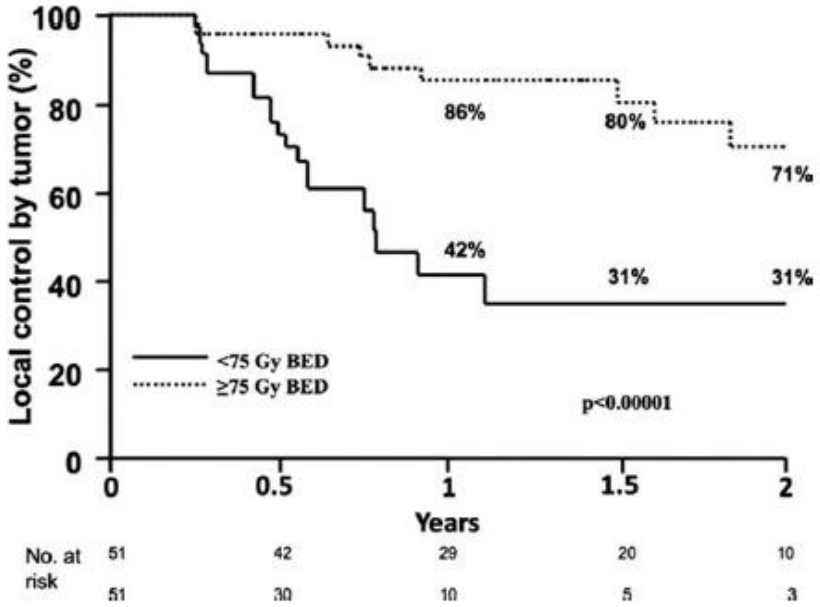

The median dose was 42 gray (Gy; range, 22-60 Gy). When evaluated separately by multivariate analysis, **total dose** (P ¼ .0015), **dose/fraction** (P ¼ .003), and **BED** (P ¼ .004) all **correlated with local control by lesion.**

For a 3-fraction regimen of stereotactic body radiotherapy, a **prescription dose of ≥ 48 Gy should be considered**, if normal tissue constraints allow.

Liver SBRT: our prospective study

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Is Stereotactic Body Radiation Therapy an Attractive Option for Unresectable Liver Metastases? A Preliminary Report From a Phase 2 Trial

Marta Scorsetti, MD,* Stefano Arcangeli, MD,* Angelo Tozzi, MD,* Tiziana Comito, MD,* Filippo Alongi, MD,* Pierina Navarria, MD,* Pietro Mancosu, MSc,* Giacomo Reggiori, MSc,* Antonella Fogliata, MSc,† Guido Torzilli, MD,† Stefano Tomatis, MSc,* and Luca Cozzi, PhD†

END POINTS:

PRIMARY: in-field local control

SECONDARY: toxicity and overall survival

INCLUSION CRITERIA:

- Inoperable or medically unsuitable for resection
- Maximum tumor diameter < 6cm
- ≤ 3 discrete lesions
- Performance status 0-2
- Good compliance to treatment

Liver SBRT: prescription dose

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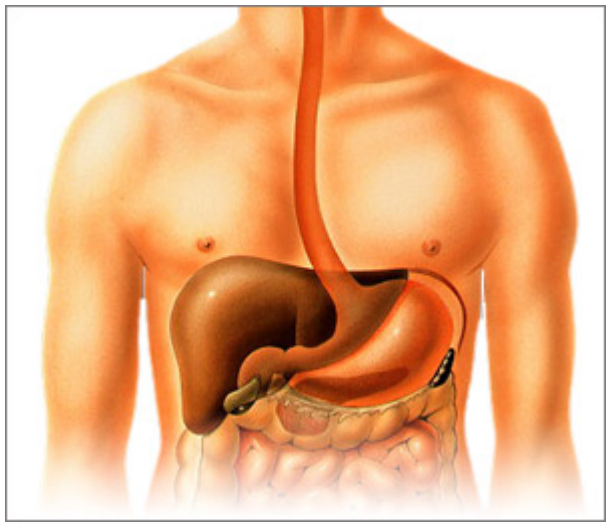
	Dose/fraction	Number fractions	Total Dose
Standard dose	25Gy	3	75 Gy
Dose reduction 10%	22.5 Gy	3	67.5 Gy
Dose reduction 20%	20. 63 Gy	3	61.89 Gy
Dose reduction 30%	18.75 Gy	3	56.25 Gy



Liver SBRT: dose constraints

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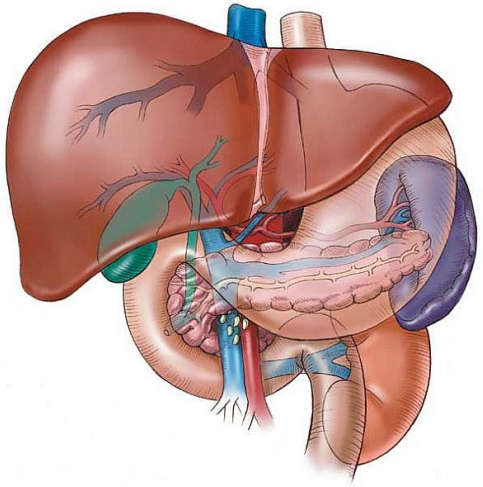
ORGAN	Dose-Volume Limits	Other Conditions
Healthy liver (defined as total liver volume minus cumulative GTV)	> 700 cc at < 15 Gy in 3 F	The volume of healthy liver > 1000 cc
Spinal cord	< 18 Gy in 3 F	
Kidneys (R+L)	V15 Gy < 35%	
Stomach, duodenum, small intestine	< 21 Gy in 3 F (also for minimum volumes)	Patients with GTV < 8 mm from the heart, stomach, duodenum and small intestine to be excluded
Heart	<30 Gy in 3 F	
Rib	D30cm3 <30Gy	



HUMANITAS EXPERIENCE 2010-2011
RapidArc - TrueBeam FFF

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Patients characteristics	Value
No. of patients	**61**
Age (y)	65 (range 39 – 87)
Sex (male:female)	26:35
Baseline KPS	> 90
Prior liver-directed therapy	21% (12 pts)
Primary site	29 Colon 19 Breast 5 Gyn 8 Other sites
Extrahepatic disease	34% (21 pts)

HUMANITAS EXPERIENCE 2010-2011
RapidArc - TrueBeam FFF

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Dose prescription	Lesions
Full dose 75 Gy	**62 (82 %)**
90%	**6 (8 %)**
80%	**4 (5 %)**
70%	**4 (5 %)**

Treatment charateristics	Value
No. of lesions	**76**
Diameter ≤ 3cm	45 (60%)
Diameter > 3cm	31 (40%)
No. of lesions per patient	1 for 48 pts (79%) 2 for 11 pts (18%) 3 for 2 pts (3%)

HUMANITAS EXPERIENCE: Local Control

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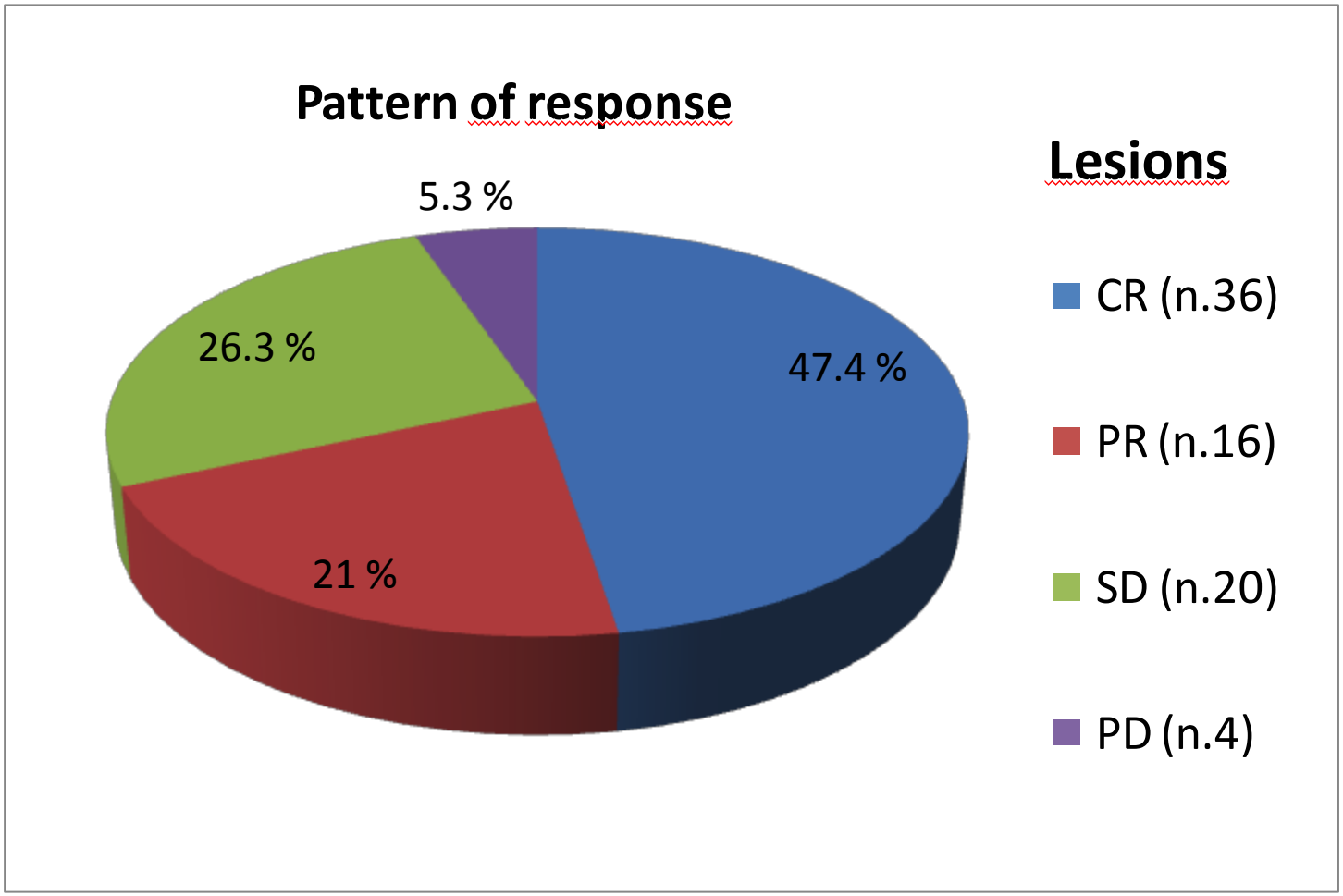
Median FU 12 months



HUMANITAS EXPERIENCE: Local Control

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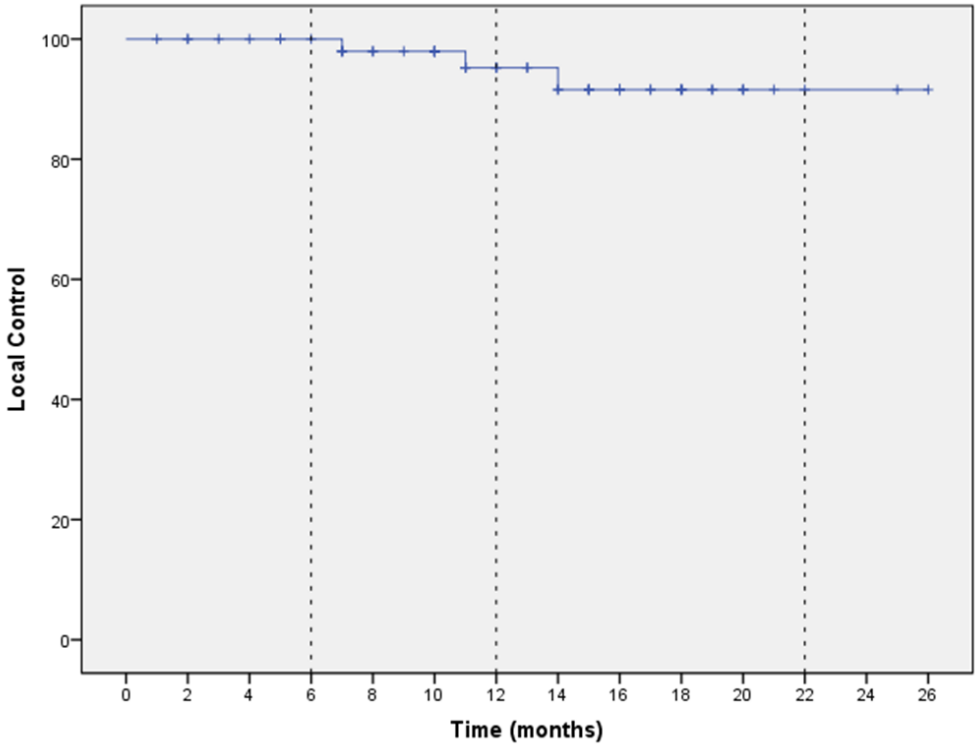
Median FU 12 months

Actuarial Local Control:

- **6 months=100%**
- **12 months=94%**
- **22 months =91%**



A subgroup analysis for lesions with diameter ≤ 3 cm compared with those > 3 cm revealed no statistical differences in local control rates (p=0.90)

HUMANITAS EXPERIENCE:
Overall Survival

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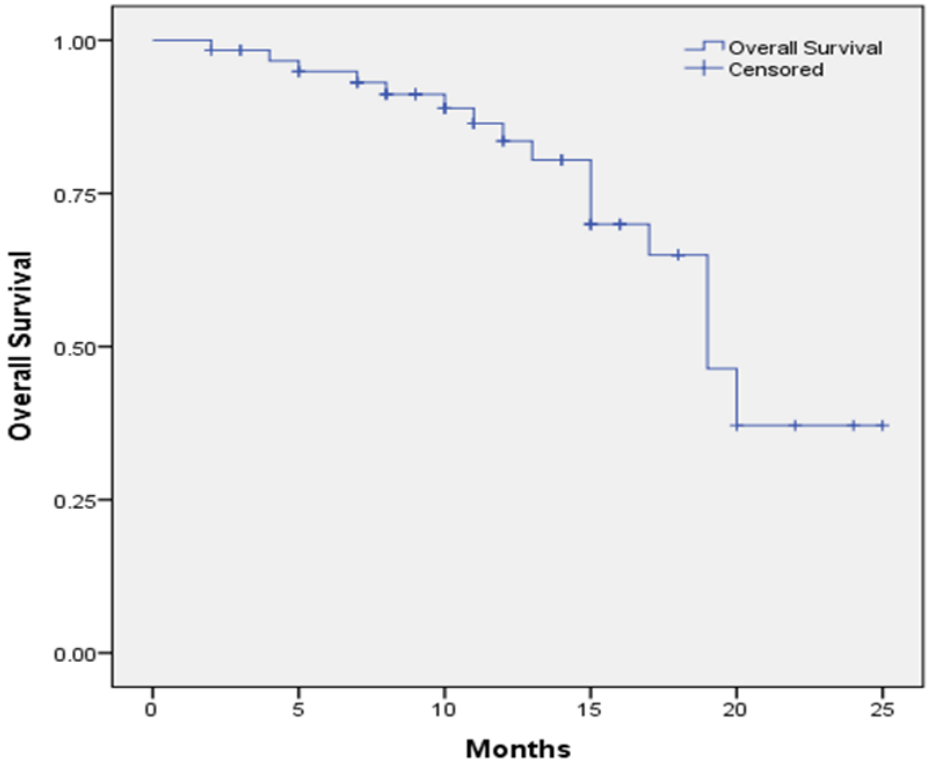
Actuarial OS

- **12 months= 84%**
- **18 months= 65%**



Median OS rate was 19 months

HUMANITAS EXPERIENCE:
Toxicity

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ACUTE TOXICITY:
- **G2 toxicity (vomiting, skin erythema and pain) 4%**
- **G2 transient transaminase increase 26%**
- **No G3-G4 or G5 toxicity observed**

LATE TOXICITY:
One case of G3 chronic chest wall pain

NO RILD

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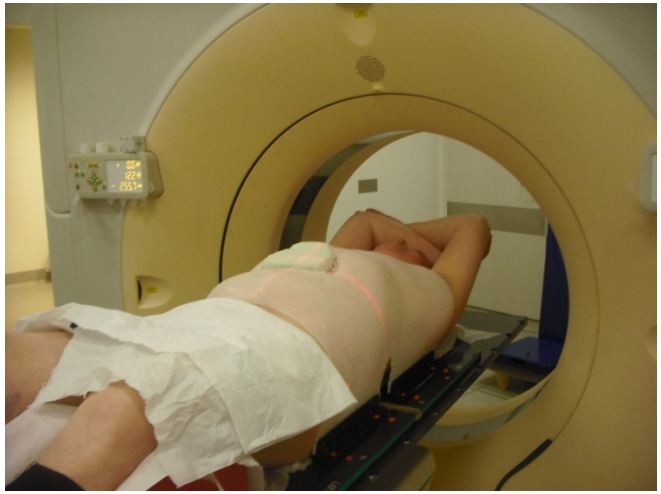

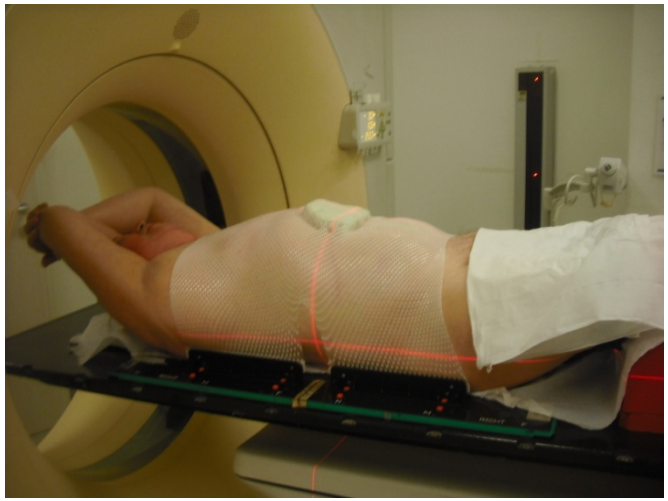

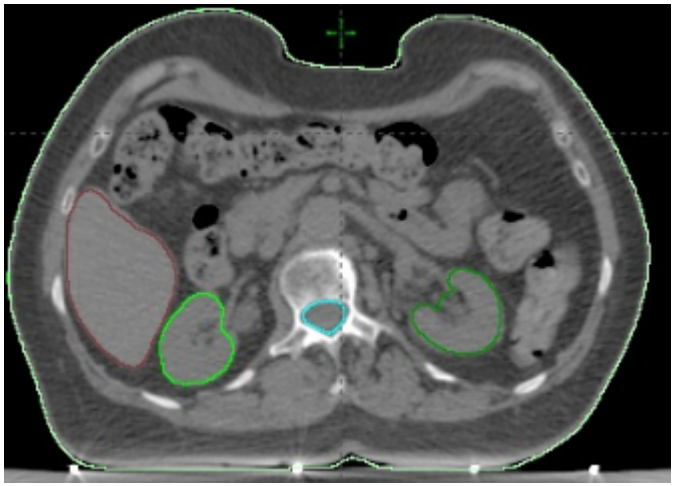

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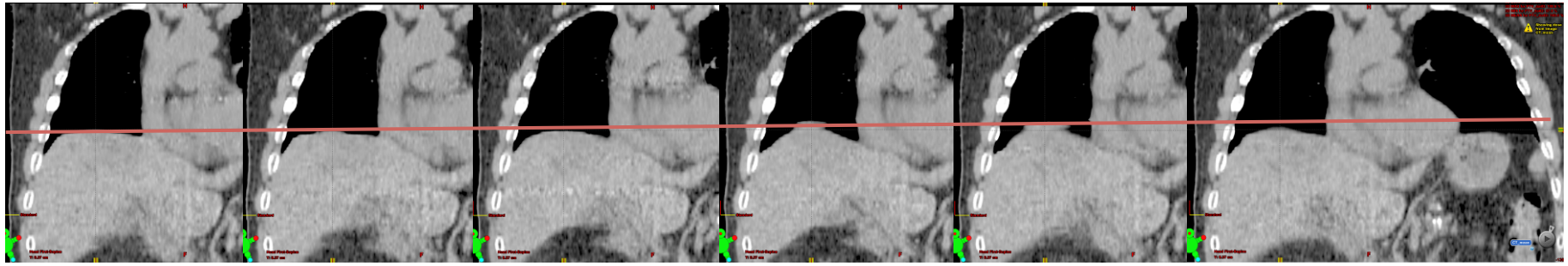

Min

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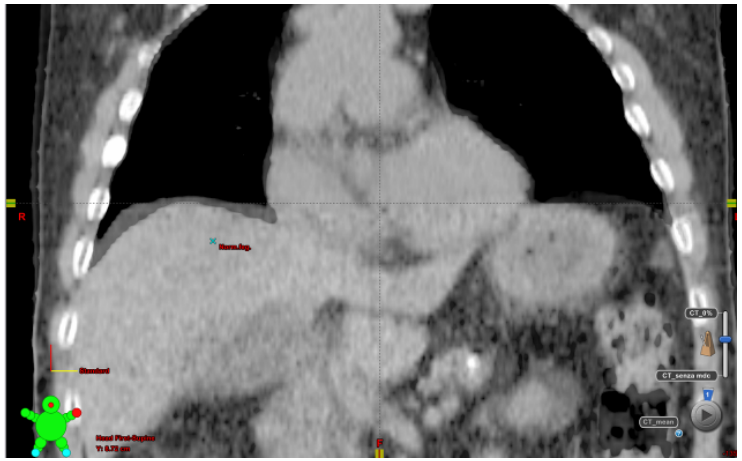

4D-CT min

4D-CT max

4D-CT

Case et al, Int J Rad Onc Biol Phys 2010

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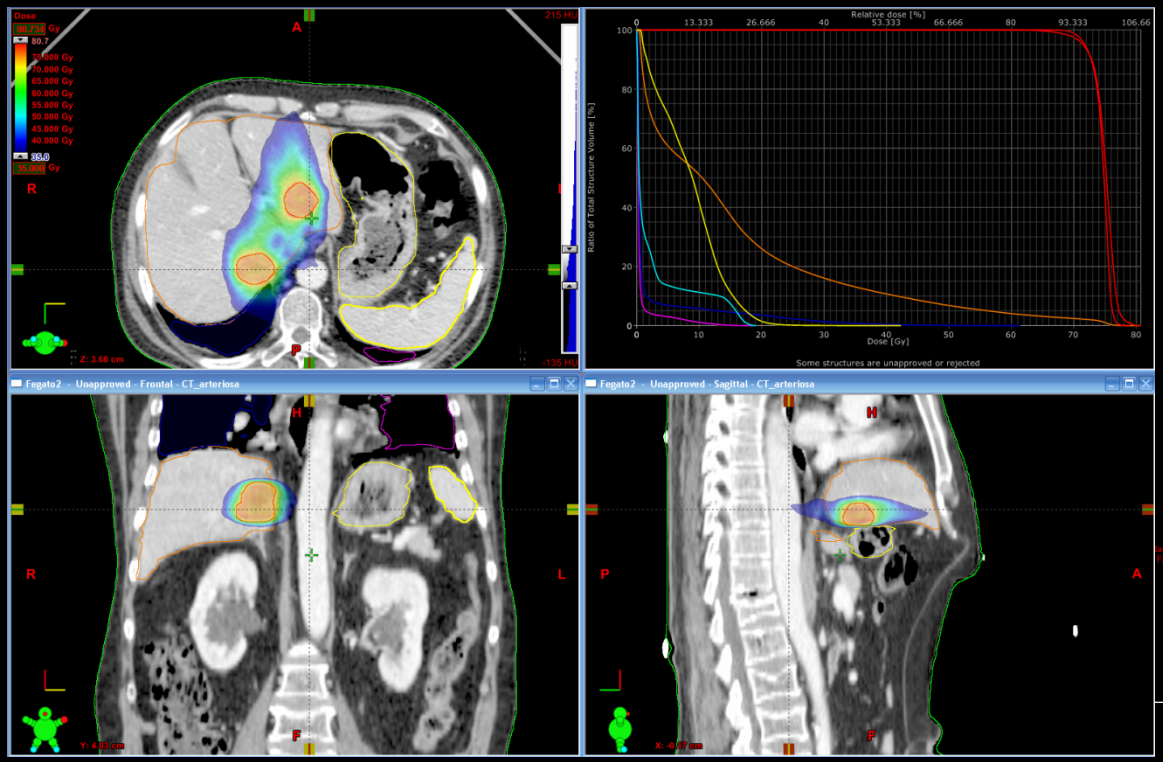
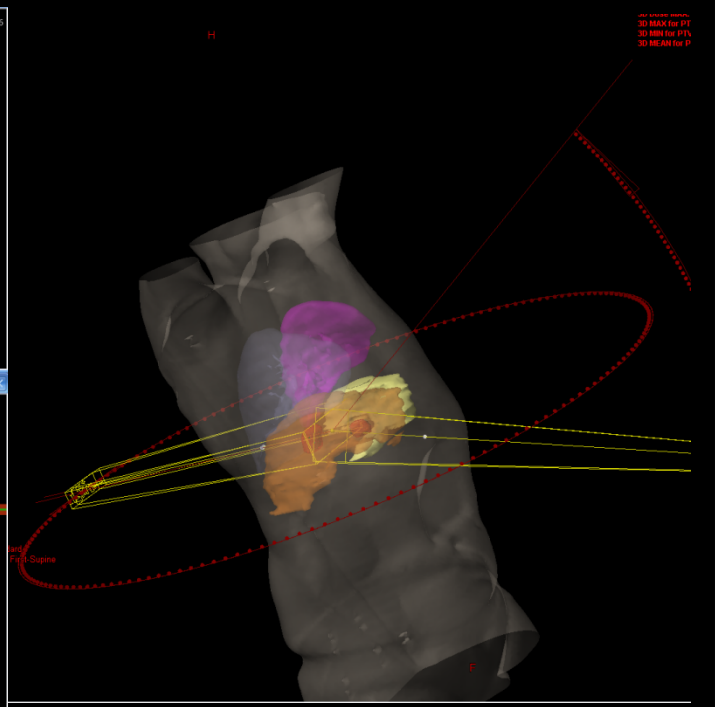
SBRT liver: 25Gy x 3; 10FFF; DR 2400





PTV1&PTV2: V95%=99.5%
Spinal cord: Max dose=17.3 Gy
Stomach: Max=21.0Gy, Mean=9.5 Gy
Liver: Mean=15.5 Gy, D15Gyfree=2811cc

1 isocentre, 3 arcs
Jaw tracking

MU:3216+3527+563
BOT: 174s(80+82+14s)

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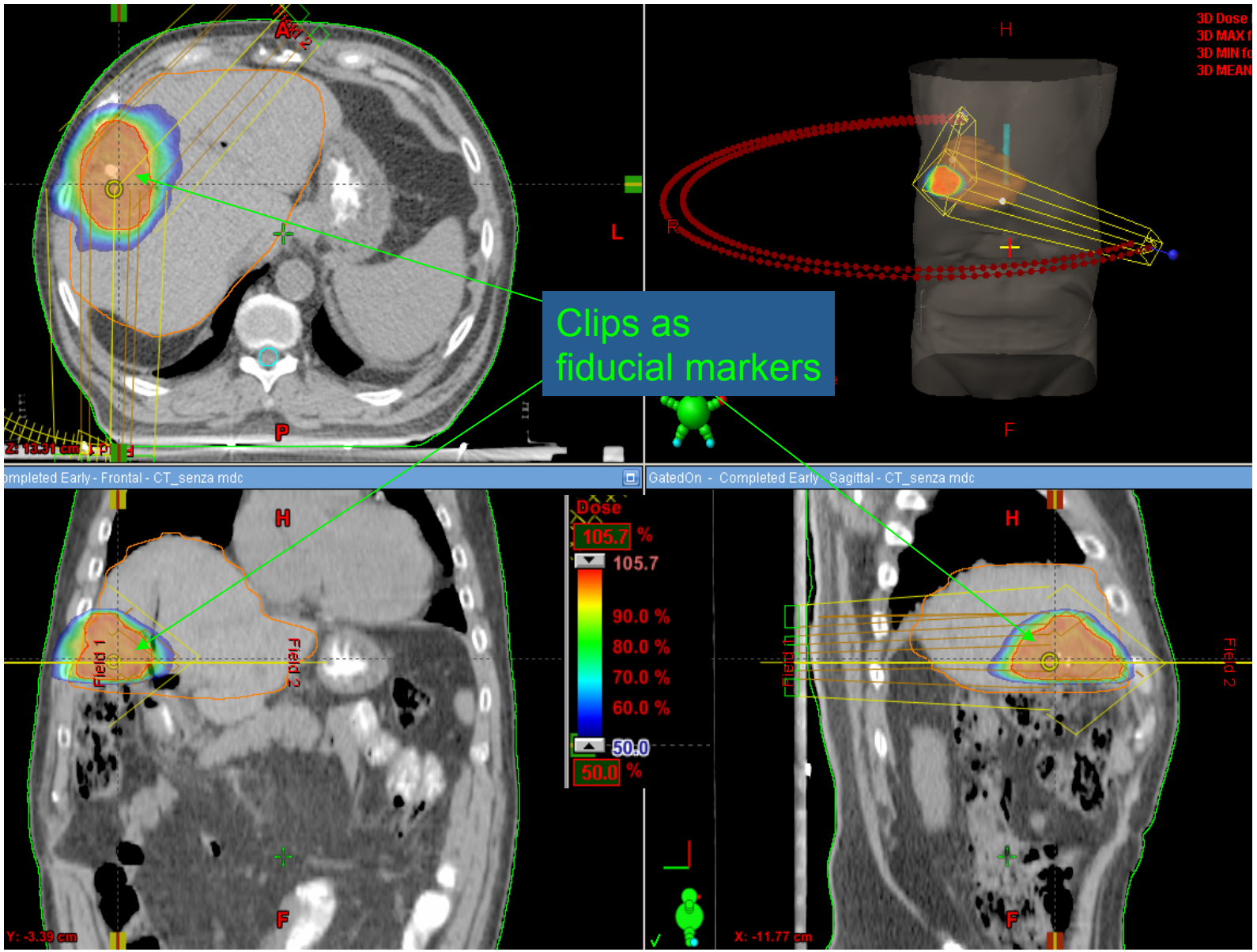
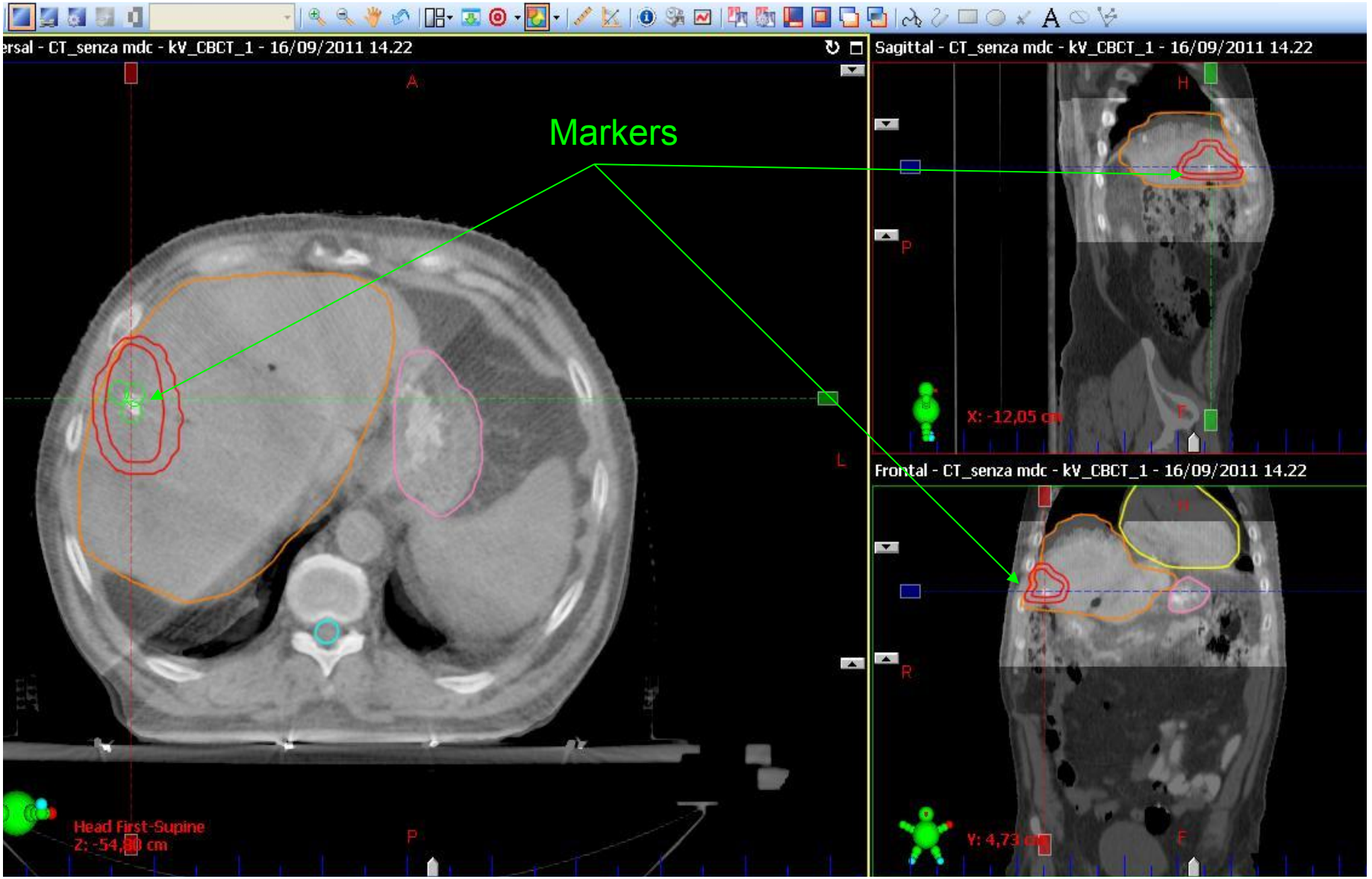


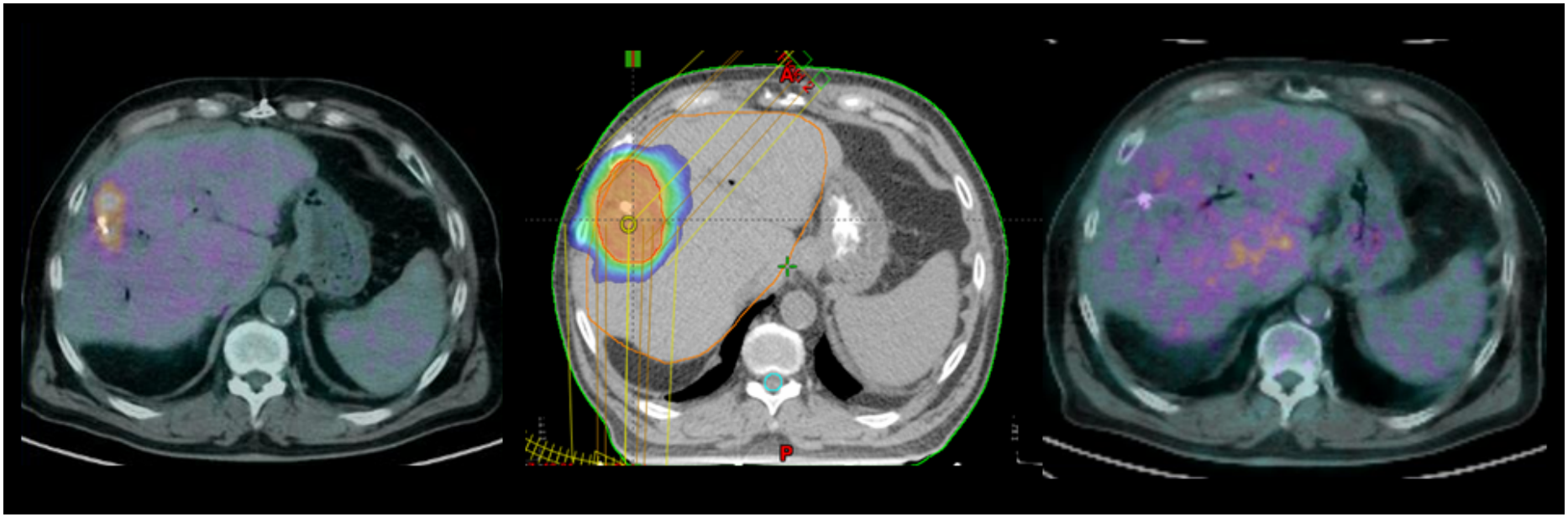
HUMANITAS
CANCER CENTER



HUMANITAS EXPERIENCE

HUMANITAS CANCER CENTER

Patient treated with SBRT for local relapse after hepatic surgery for colorectal metastasis



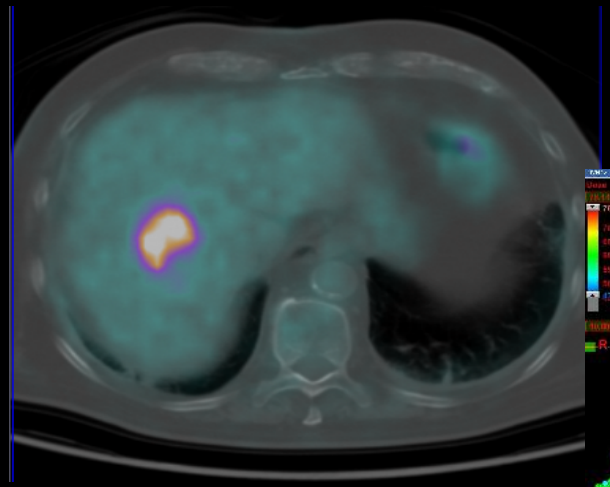
PET –CT pre-treatment, CEA 72

PET –CT post-treatment CEA 2.2

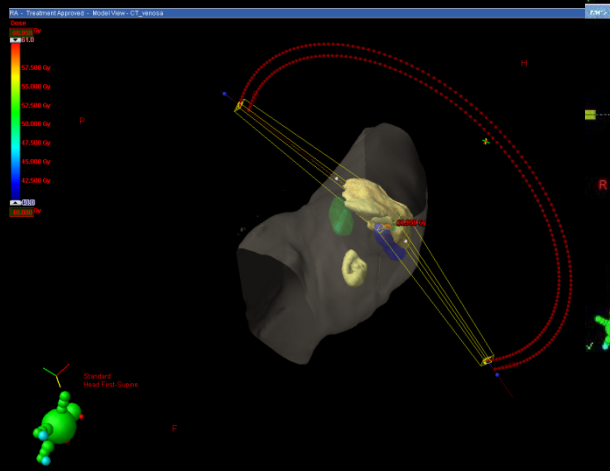
HUMANITAS
CANCER CENTER

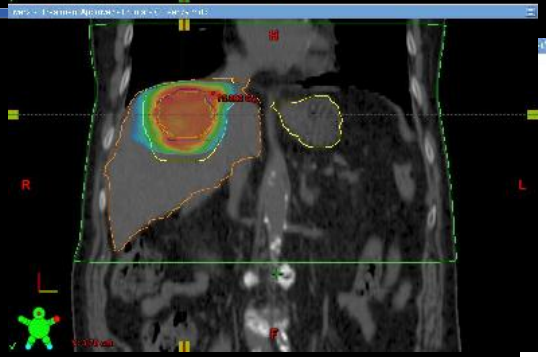
FU: SBRT 25Gy x 3; **10FFF**; DR 2400.

PET before SBRT



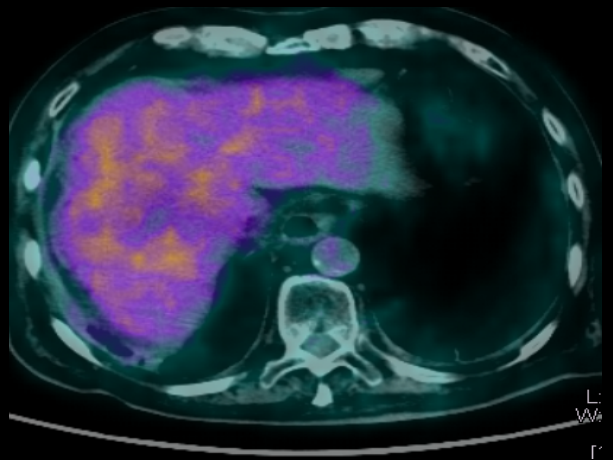
RapidArc
1isocentre
2 arcs
Jaw tracking

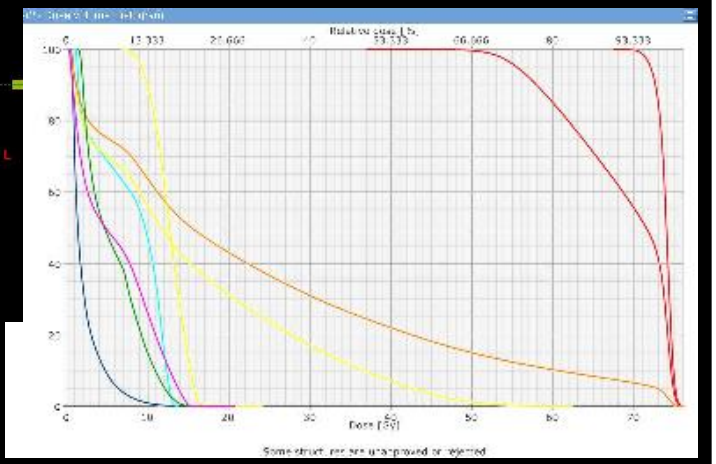




MU: 2953+2955
BOT: 150 sec

PET after 6 months





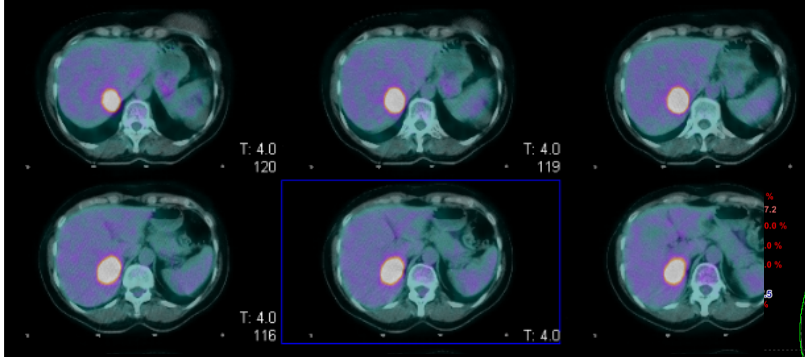
HUMANITAS
CANCER CENTER

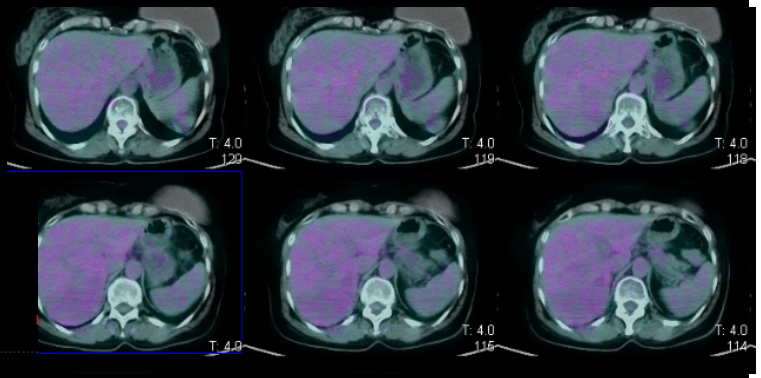
FU: SBRT 25Gy x 3; **10FFF**; DR 2400.

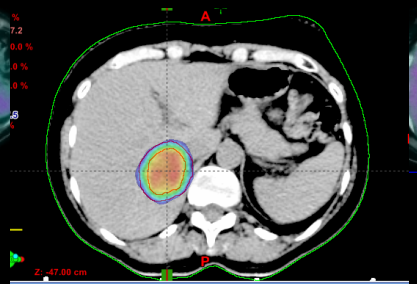
PET before SBRT

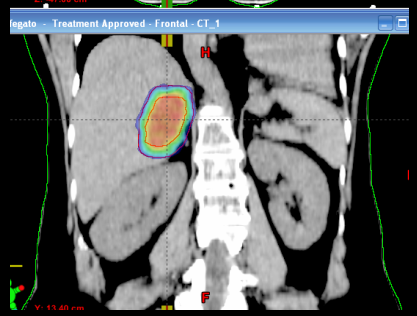
PET after 6 months

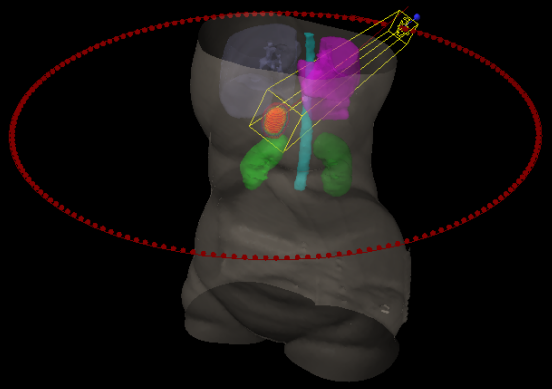
RapidArc
1 isocentre
1 arc
Jaw tracking

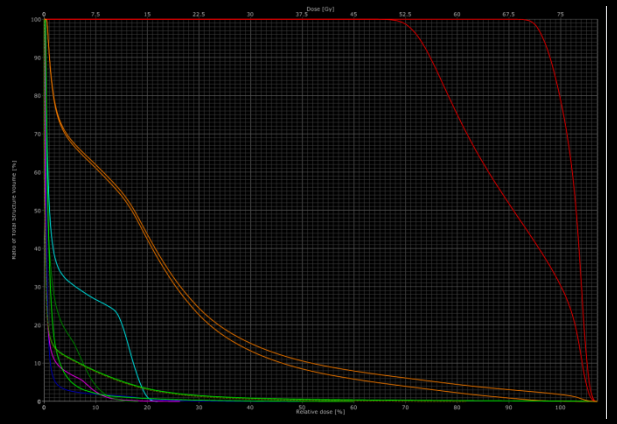






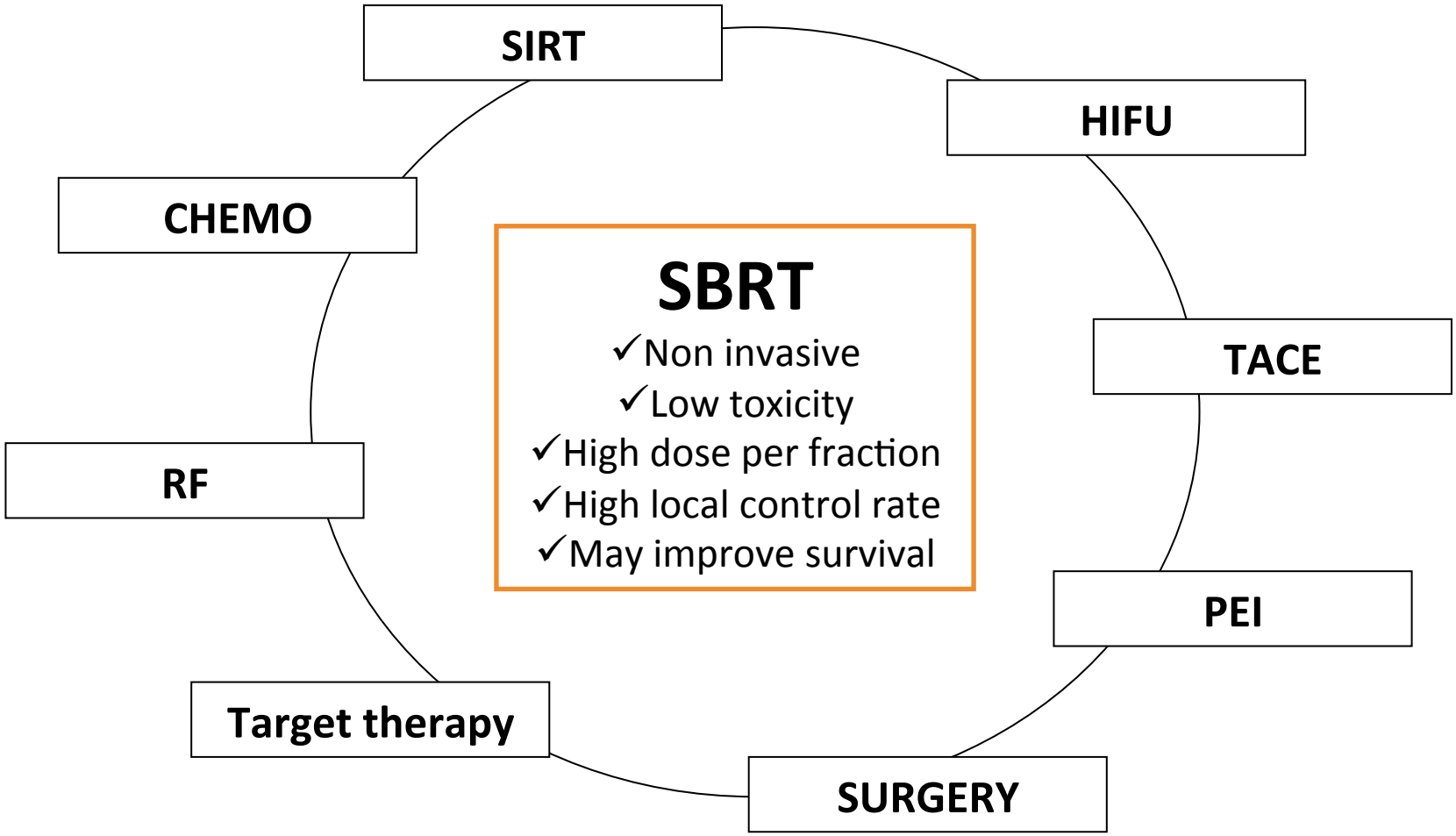






MU:5103
BOT:130s

HUMANITAS
CANCER CENTER



PATIENT BASED APPROACH

HUMANITAS
CANCER CENTER