



**HUMANITAS**  
CANCER CENTER

**STUDIO DI FASE II SULL'UTILIZZO  
DELLA RADIOTERAPIA  
STEREOTASSICA IN PAZIENTI CON  
METASTASI EPATICHE INOPERABILI  
DA TUMORE DEL COLON-RETTO**

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# Background

- In colorectal cancer 30% to 70% of patients will develop liver metastases, often isolated or associated with limited metastatic foci of disease.
- **Surgical resection** of CRC liver metastases improves overall survival
  - median OS of 40-53 months
- Only 10-60% of patients were suitable to surgical resection
- **Radiofrequency ablation (RFA)** is the most valid alternative to surgery:
  - local control rates of 90-98%
  - median overall survival of 25 months
- RFA limits:
  - lesions higher than 3 cm of diameter
  - lesions located in proximity of major blood vessels, main biliary tract, gallbladder or just beneath the diaphragm

# Liver metastases treatment: is there an alternative?

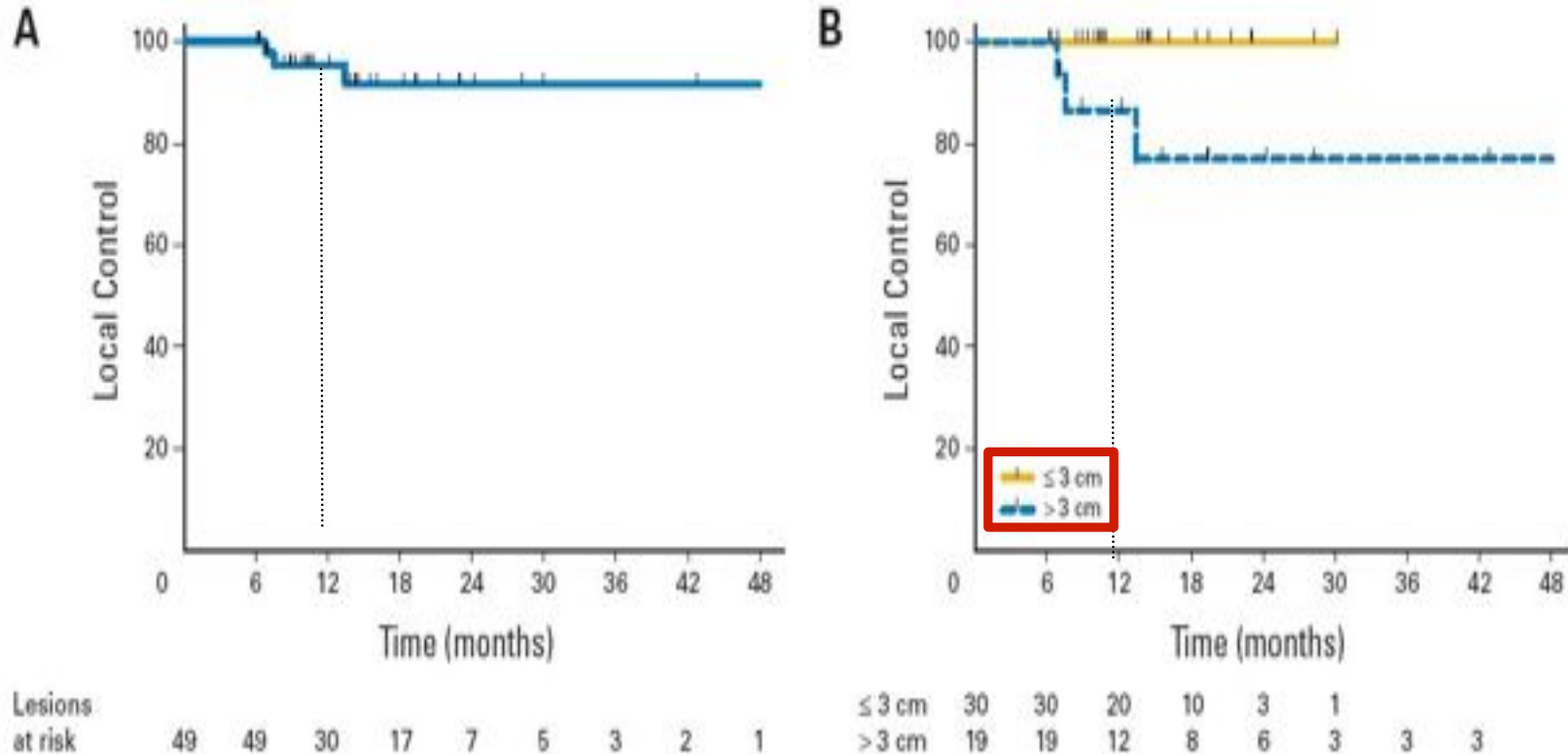
**Table 1** Prospective clinical trials in the literature studying stereotactic ablative radiotherapy in liver metastases and their results

Ref.	Design	No of patients	Tumor size	SABR dose	Toxicity	Outcomes
Scorsetti <i>et al</i> <sup>[15]</sup>	Phase II (preliminary report)	61 (76 tumors)	1.8-134.3 cm <sup>3</sup> (mean 18.6 cm <sup>3</sup> )	75 Gy in 3 fractions	No case of RILD. Twenty-six percent had grade 2 transaminase increase (normalized in 3 mo). Grade 2 fatigue in 65% patients, one grade 3 chest wall pain which regressed within 1 year.	1-yr LC94, 22-mo LC 90.6%
Goodman <i>et al</i> <sup>[16]</sup>	Phase I (HCC and liver mets)	26 (19 liver mets)	0.8-146.6 mL (median, 32.6 mL)	Dose escalation, 18-30 Gy (1 fr)	No dose-limiting toxicity 4 cases of Grade 2 late toxicity (2 GI, 2 soft tissue/rib)	1-yr local failure, 3% 2-yr OS, 49% (mets only)
Ambrosino <i>et al</i> <sup>[17]</sup>	Prospective cohort	27	20-165 mL (median, 69 mL)	25-60 Gy (3 fr)	No serious toxicity	Crude LC rate 74%
Lee <i>et al</i> <sup>[18]</sup>	Phase I - II	68	1.2-3090 mL (median, 75.9 mL)	Individualized dose, 27.7-60 Gy (6 fr)	No RILD, 10% Grade 3/4 acute toxicity No Grade 3/4 late toxicity	1-yr LC, 71% Median survival, 17.6 mo
Rusthoven <i>et al</i> <sup>[19]</sup>	Phase I - II	47	0.75-97.98 mL (median, 14.93 mL)	Dose escalation, 36-60 Gy (3 fr)	No RILD, Late Grade 3/4 < 2%	1-yr LC, 95% 2-yr LC, 92% Median survival, 20.5 mo
Hoyer <i>et al</i> <sup>[20]</sup>	Phase II (CRC oligomets)	64 (44 liver mets)	1-8.8 cm (median, 3.5 cm)	45 Gy (3 fr)	One liver failure, two severe late GI Toxicities	2-yr LC, 79% (by tumor) and 64% (by patient)
Méndez Romero <i>et al</i> <sup>[20]</sup>	Phase I - II (HCC and mets)	25 (17 liver mets)	1.1-322 mL (median, 22.2 mL)	30-37.5 Gy (3 fr)	Two Grade 3 liver toxicities	2-yr LC, 86% 2-yr OS, 62%
Herfarth <i>et al</i> <sup>[21]</sup>	Phase I - II	35	1-132 mL (median, 10 mL)	Dose escalation, 14-26 Gy (1 fr)	No significant toxicity reported	1-yr LC, 71% 18-mo LC, 67% 1-yr OS, 72%

Nair *et al*, WJR 2014

## Correlation between dose prescription and tumor size

**60 Gy /3 fr**



**For lesion diameter > 3cm, a prescription dose of >60 Gy should be considered.**

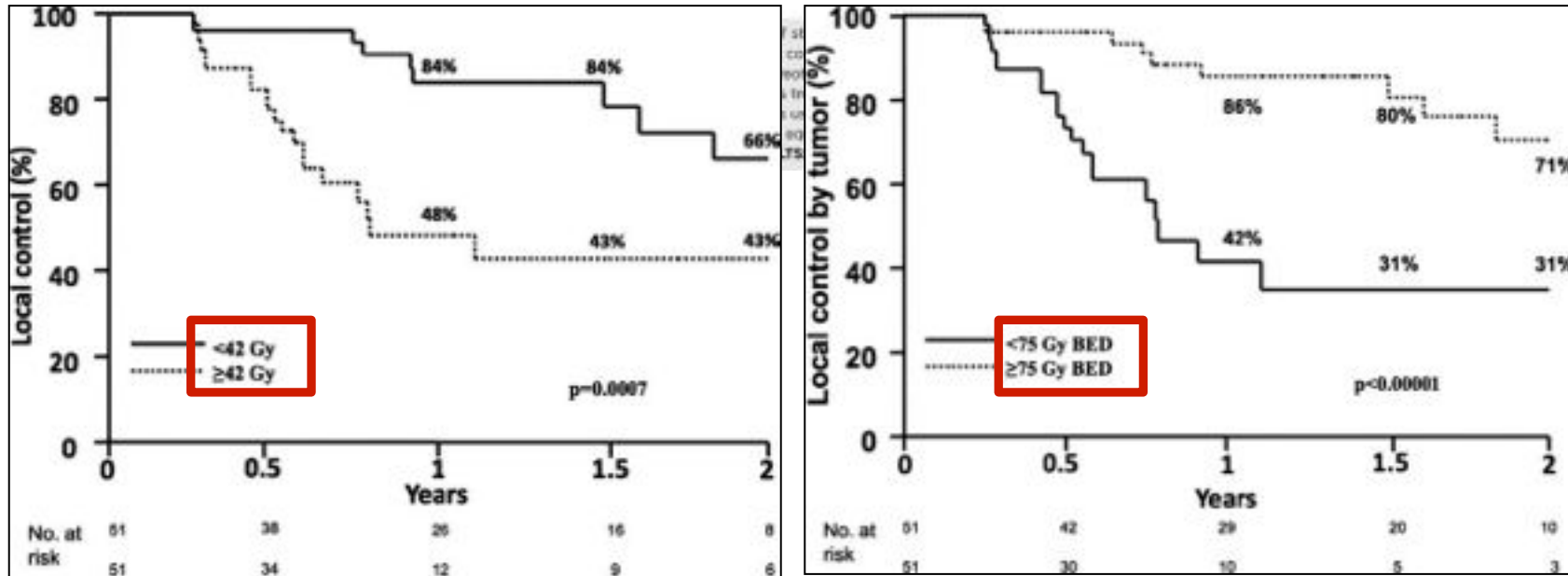


Original Article

# Stereotactic Body Radiotherapy for Colorectal Liver Metastases

A Pooled Analysis

## Correlation between dose prescription and local control

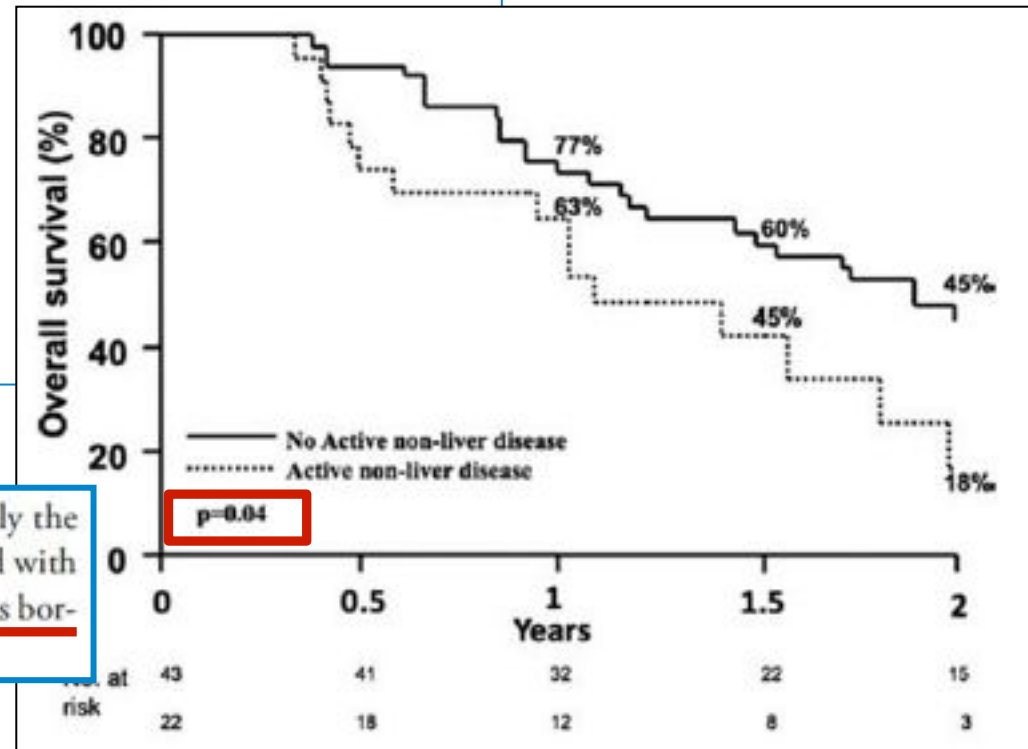


for 1-year local control >90% is 46 to 52 Gy in 3 fractions. **CONCLUSIONS:** Liver stereotactic body radiotherapy is well tolerated and effective for colorectal liver metastases. The strong correlation between local control and OS supports controlling hepatic disease even for heavily pretreated patients. For a 3-fraction regimen of stereotactic body radiotherapy, a prescription dose of ≥48 Gy should be considered, if normal tissue constraints allow. *Cancer*



## Correlation between dose prescription and OS

Factor	Local Control		Factor	Overall Survival
	By Lesion	By Patient		
Total dose	.0015	.034	Active nonliver disease	.046
No. of prior chemotherapy regimens	.63	.84	<b>Local failure</b>	<b>.06</b>
Age	.13	.42	Total No. of chemotherapy regimens	.64
No. of days of SBRT	.75	.88	No. of lesions (1 vs 2-4)	.5
GTV	.94	.42 <sup>a</sup>	GTV	.14 <sup>a</sup>
Dose per fraction	.003	.18		
No. of prior chemotherapy regimens	.6	.81		
Age	.28	.42		
No. of days of SBRT	.11	.37		
GTV	.74	.68		
BED	.004	.09		
No. of prior chemotherapy regimens	.42	.58		
Age	.35	.71		
No. of days of SBRT	.2	.5		
GTV	.86	.53		



OS ( $P = .09$ ). On multivariate analysis for OS, only the absence of active extrahepatic disease was associated with improved OS ( $P = .046$ ). However, local control was borderline significant for OS ( $P = .06$ ).



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

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 Guido Torzilli, MD,<sup>‡</sup> Stefano Tomatis, MSc,\* and Luca Cozzi, PhD<sup>‡</sup>

**Table 1** Baseline patient and treatment characteristics

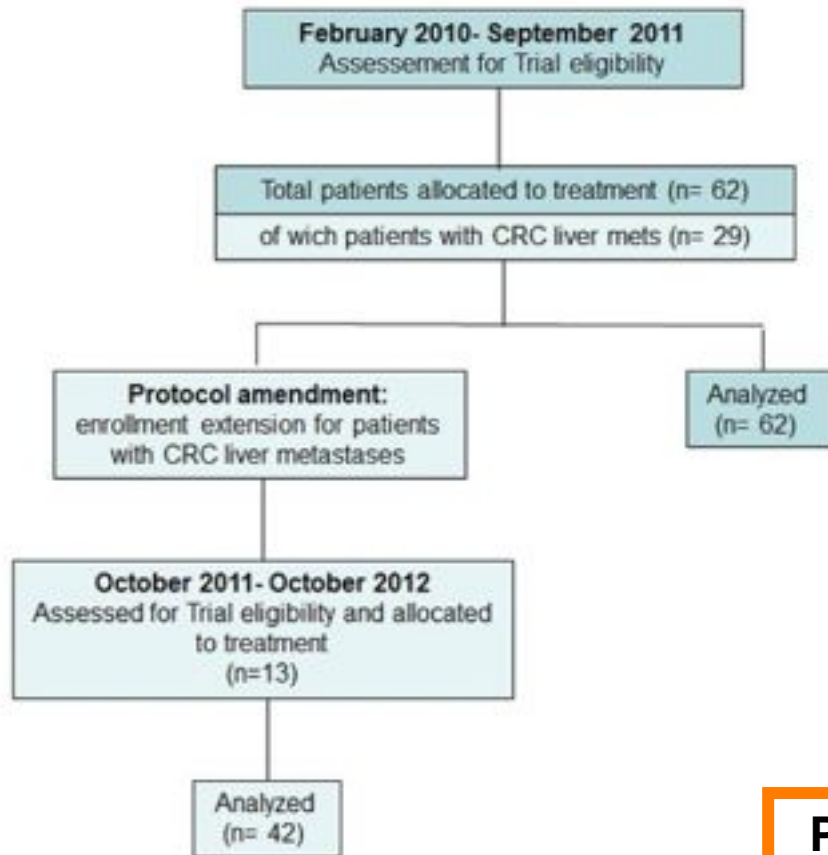
Characteristic	n	%
No. of patients	61	
Male	28	42.6
Female	35	57.4
Median age, y	65	-
Range	39-87	
No. of liver lesions		
1	48	78.7
2	11	18.0
3	2	3.3
Primary		
Colorectal	29	47.5
Breast	11	18.0
Gynecological	7	11.5
Other	14	22.9
Time since diagnosis, mo		
≤12	35	57.4
>12	26	42.6
No. of prior systemic treatment regimens		
0	10	16.4
1	15	24.6
2	13	21.3
3	14	22.9
≥4	9	14.7
Presence of stable extrahepatic disease		
Yes	21	34.4
No	40	65.6
Prior liver-directed therapy		
Yes	28	45.9
Surgery	21	75
RFA	2	7
Both	5	19
No	33	54.1

Treatment	No. of lesions	%
Lesion diameter (mm)		
≤30 mm	45	59.2
>30 mm	31	40.8
CTV volume (cm <sup>3</sup> )		
Mean ± SD	18.6 ± 22.7	
Range	1.8-134.3	
PTV volume (cm <sup>3</sup> )		
Mean	54.9 ± 41.998	
Range	7.7-209.4	
Dose prescription (per lesion)		
Full dose (75 Gy)	62	82
90% (67.5 Gy)	6	8
80% (60 Gy)	4	5
70% (52.5 Gy)	4	5

*Abbreviations:* CTV = clinical target volume; PTV = planning target volume; RFA = radiofrequency ablation.

## Final results of a phase II trial for stereotactic body radiation therapy for patients with inoperable liver metastases from colorectal cancer

Marta Scorsetti · Tiziana Comito · Angelo Tozzi · Pierina Navarria · Antonella Fogliata · Elena Clerici · Pietro Mancosu · Giacomo Reggiori · Lorenza Rimassa · Guido Torzilli · Stefano Tomatis · Armando Santoro · Luca Cozzi



### **END POINTS:**

Primary: in-field local control  
Secondary: toxicity and overall survival

### **INCLUSION CRITERIA:**

- Unresectable CRC liver metastases
- Maximum tumor diameter < 6cm
- ≤ 3 discrete lesions
- Performance status 0-2
- Good compliance to treatment

**Prescription dose was 75Gy in 3 fractions**

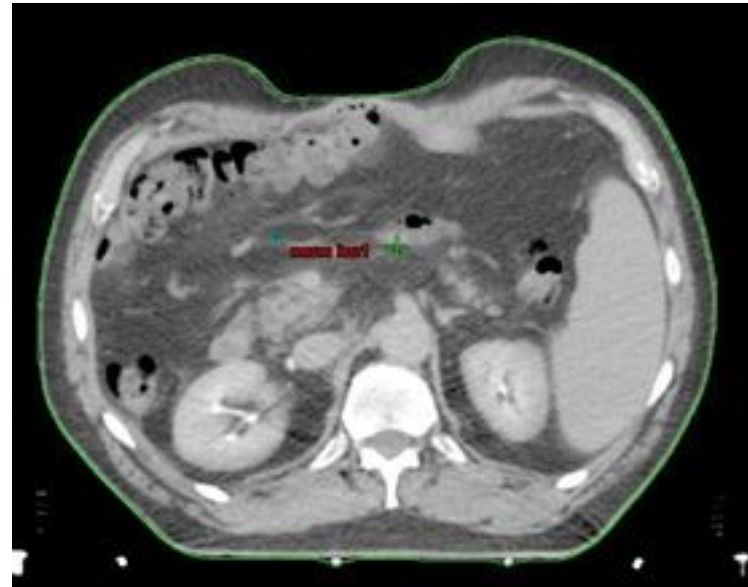
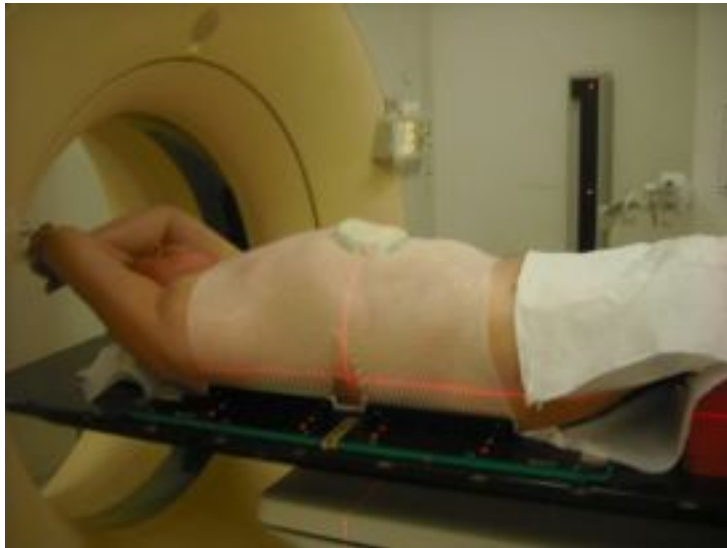


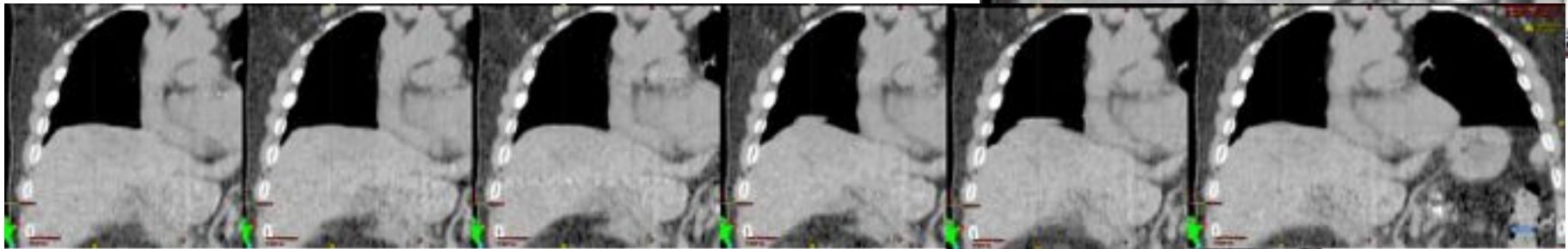
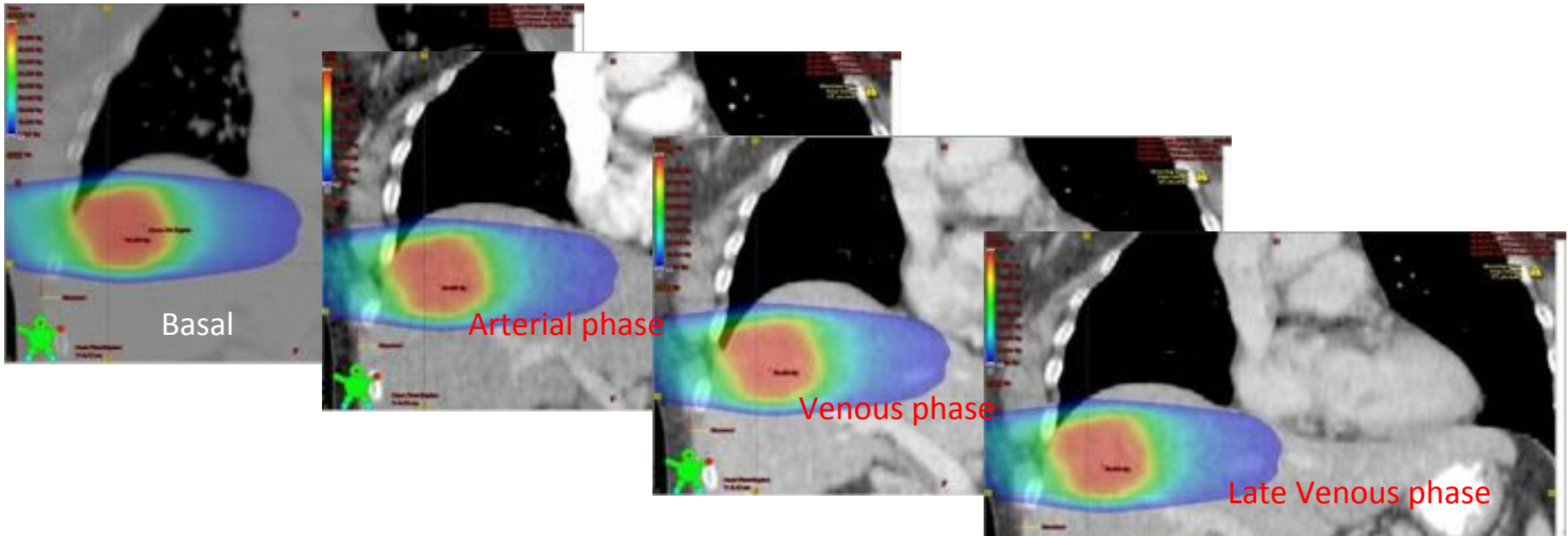
Patients	number
	42
Mean age (range)y	67 (43–87)
Sex (M:F)	36:6
Primary	
Colon	30 (71%)
Rectum	12 (29%)
TNM Primary Classification	
T1	2 (5%)
T2	9 (21)
T3	28 (67%)
T4	3(7%)
N0	21 (50%)
N1-2	21 (50%)
M1	17 (40%)
Only liver	15 (88%)
Liver and lung	2 (12%)
Timing of liver metastases	
Synchronous (DFI ≤ 12 months)	20 (47.6%)
Metachronous (DFI > 12 months)	22 (52.4%)
Previous local treatments	
Surgery	17 (40%)
RFA or other	4 (9.5%)
Systemic treatments	
Pre-SBRT chemotherapy	42 (100%)
Post-SBRT chemotherapy	6 (14%)
Time of SBRT since diagnosis	
<12 mo	3 (7 %)
>12 mo	39 (93%)

February 2010- October 2012

**Median FUP 24 months  
(4-48 months)**

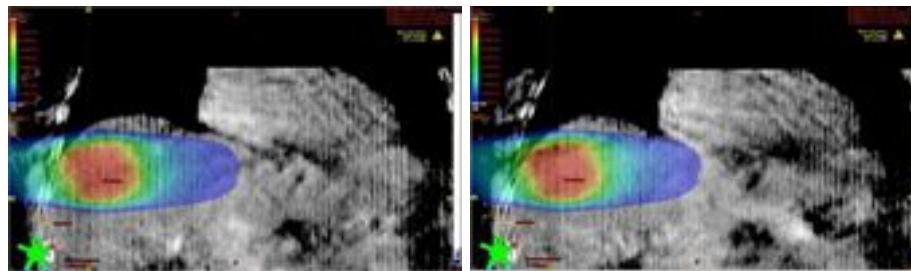
Number of lesions treated	52
Number of lesions for patients	
1	34 (81%)
2	5 (12%)
3	3(7%)
Size of lesions	
< 3 cm	28 (55%)
> 3 cm	24 (45%)
Mean volume (range) [cm <sup>3</sup> ]	
CTV	18.6 ± 22.03 (1.8-134.3)
PTV	54.90 ± 41.90 (7.7-909.10)



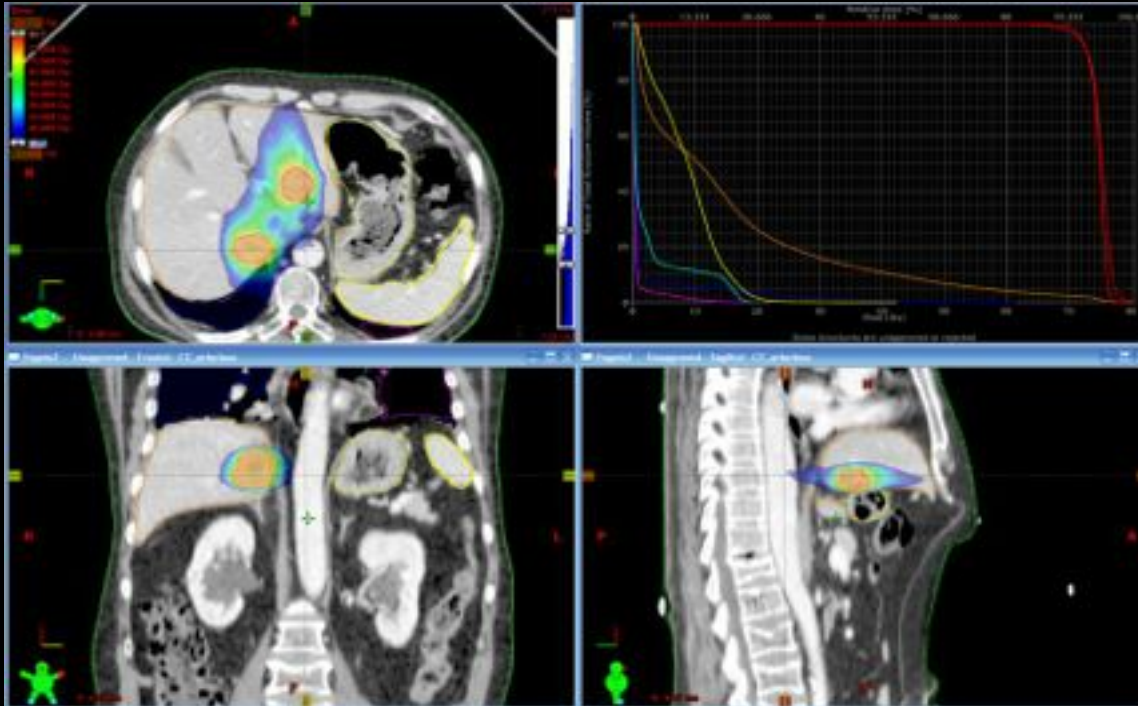


CB\_CT Day I

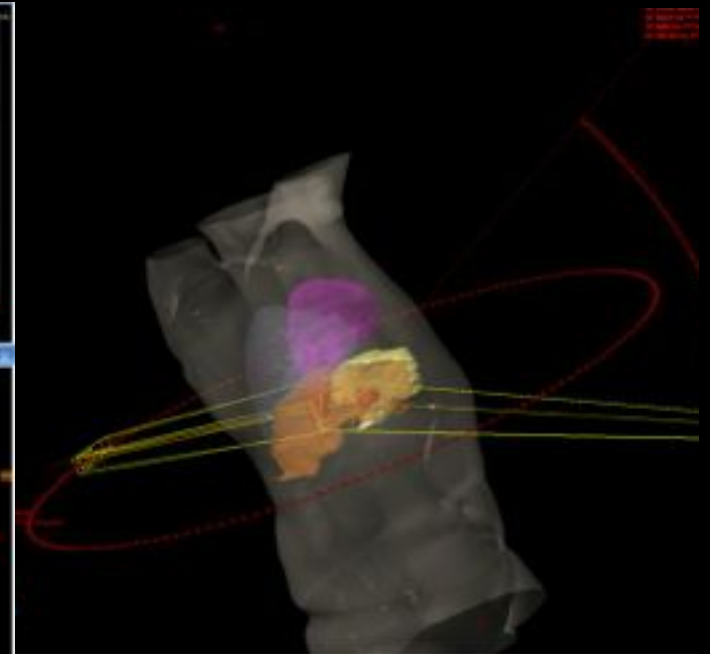
CB\_CT Day III



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

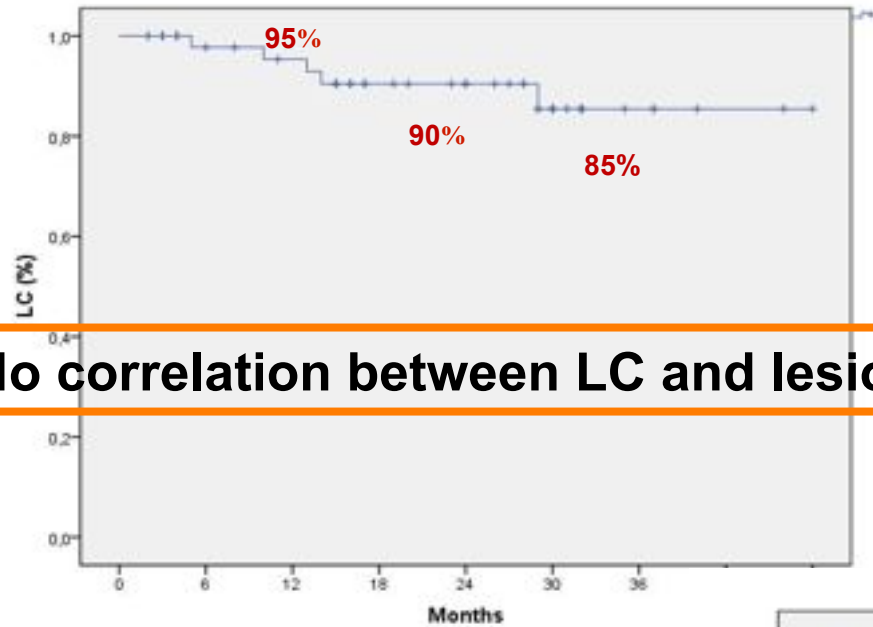


PTV1&PTV2: V95%=99.5%  
Spinal cord: Max dose=17.3 Gy  
Stomach: Max=21.0Gy, Mean=9.5 Gy  
Liver: Mean=15.5 Gy, D15Gyfree=2811cc



1 isocentre, 3 arcs  
Jaw tracking

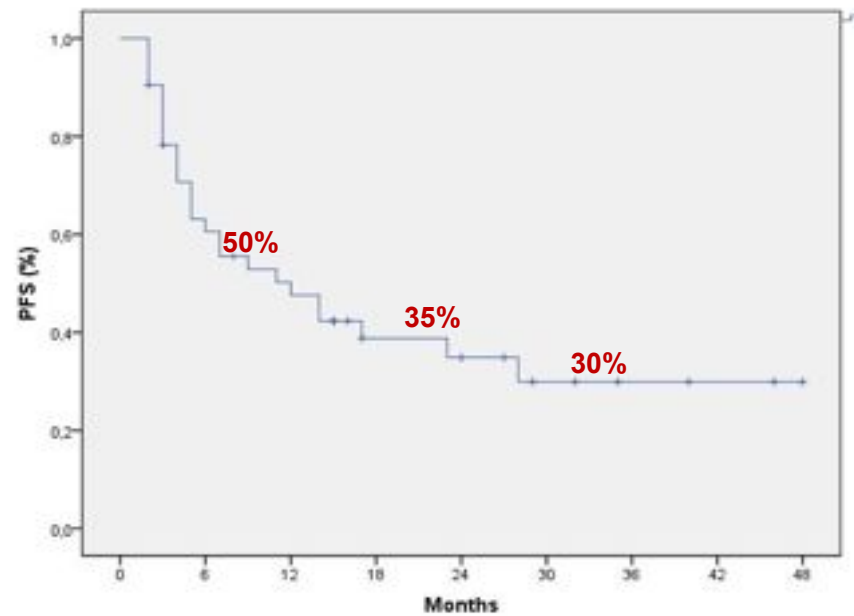
MU:3216+3527+563  
BOT: 174s(80+82+14s)



**1 - year LC = 95%**  
**2 - years LC = 90%**  
**3 - years LC = 85%**

**No correlation between LC and lesion size**

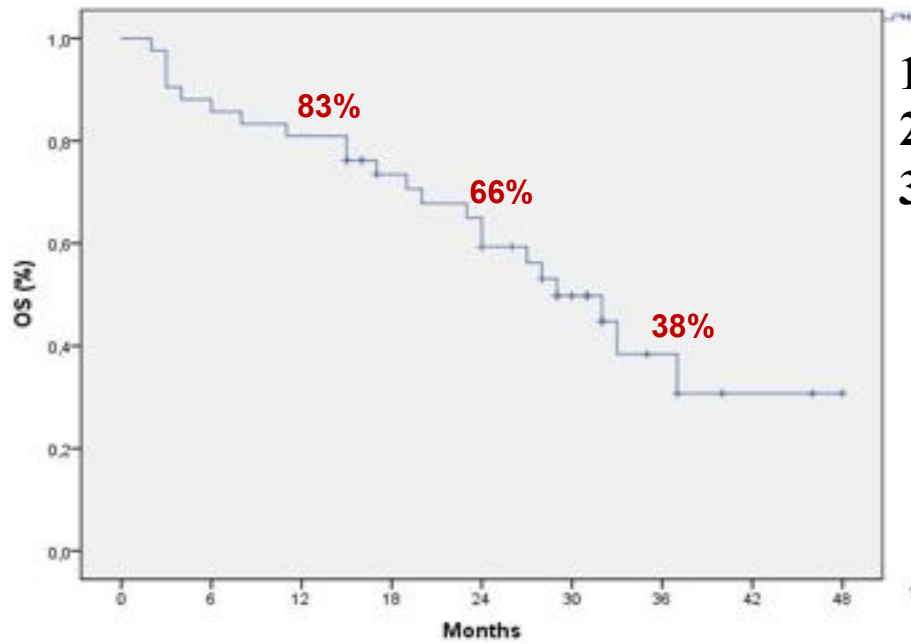
**Median PFS = 12 months**



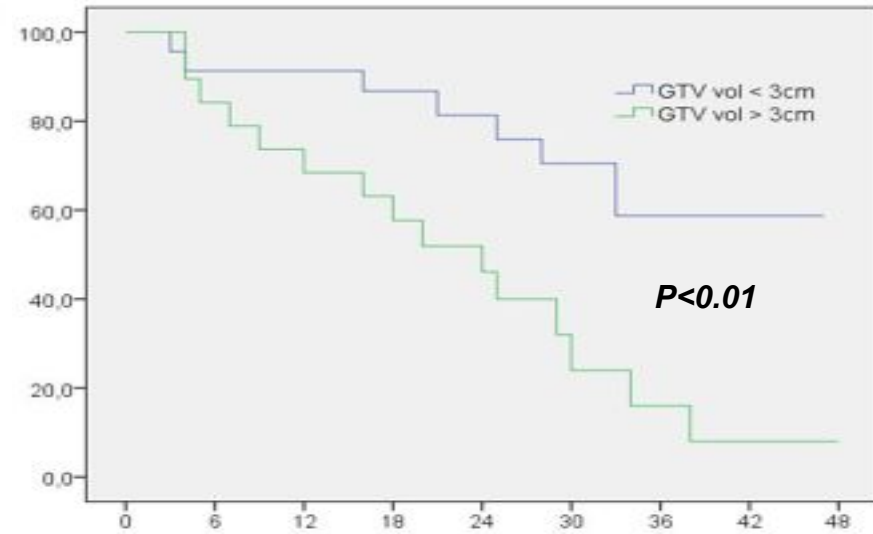
**1 - year PFS = 50 %**  
**2 - years PFS = 35%**  
**3 - years PFS = 30%**



**Median OS = 29 months**



**1 - year OS = 83%**  
**2 - years OS = 66%**  
**3 - years OS = 38%**



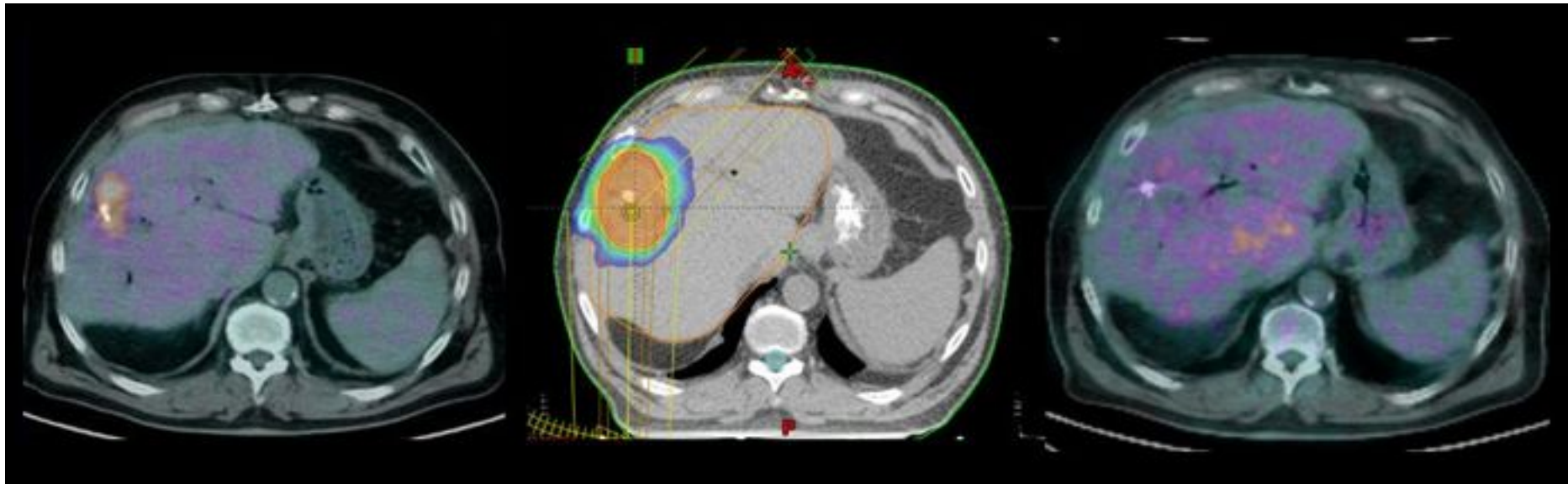
**ACUTE and LATE TOXICITY:**

**No G3-G4 or G5 toxicity observed**

**No RILD**

- **55%) G2 fatigue**
- **25%G2 transient hepatic transaminase increase (normalized within the 3 months after SBRT)**
- **12% G2 nausea (Five patients with treated lesions in II and III hepatic segments)**

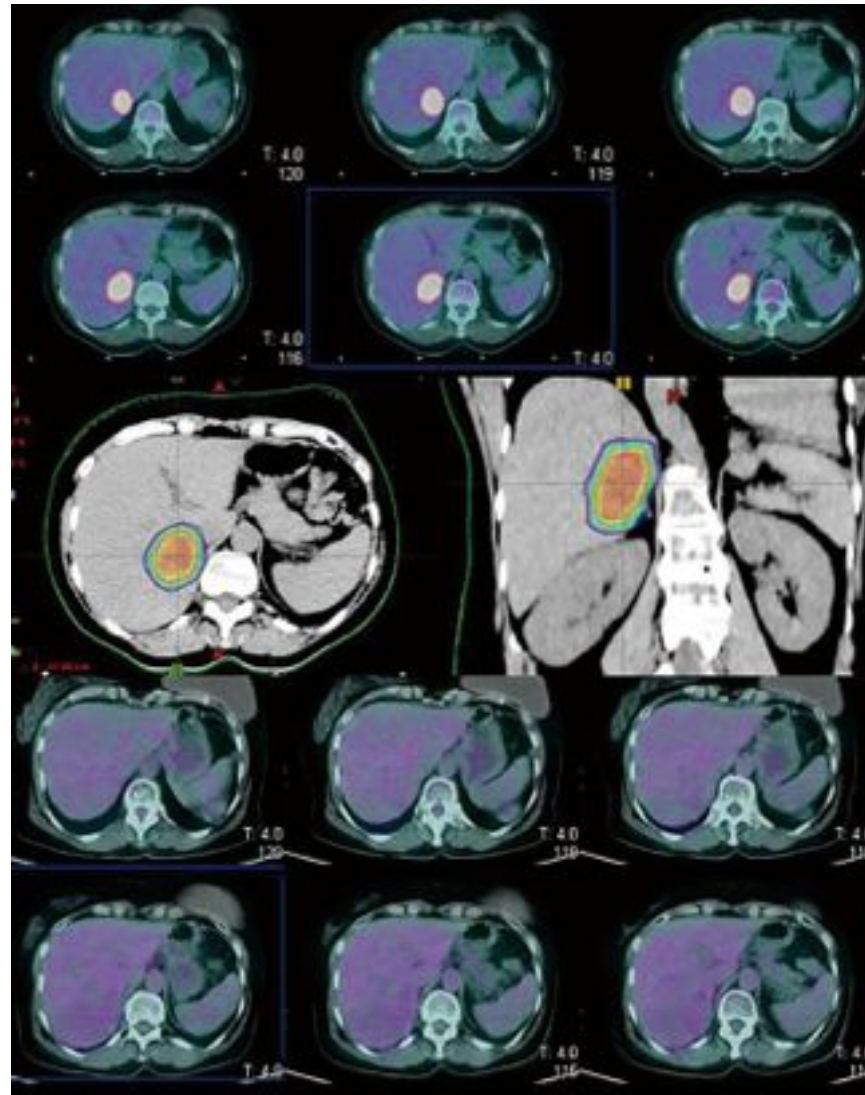
**Patient treated with SBRT for local relapse after hepatic surgery for colorectal metastasis**



**PET –CT pre-treatment,  
CEA 72**

**PET –CT post-treatment  
CEA 2.2**

## Patient treated with SBRT for inoperable colorectal liver metastasis



# Conclusions

## Current evidence of SBRT in CRC liver metastases:

**Feasibility:** Non invasive and low toxicity

**Efficacy:** Acceptable local control rate

**Table 2**

**Selection criteria for SBRT**

Selection criteria	Patients categories		
	Suitable	Cautionary	Unsuitable
Lesion number	<3	4	>4
Lesion diameter (cm)	1-3	>3 and ≤6	>6
Distance from OARs (mm)	>8	5-8	<5
Liver function	Child A	Child B	Child C
Free liver volume (cc)	>1,000	<1,000 and ≥700	<700

SBRT, stereotactic body radiation therapy; OARs, organs at risk.

## Future directions:

1. Selection of patients with favourable prognosis to evaluate the impact on survival
2. Comparative RCTs with other local procedures (SR and RF)
3. Association with chemo\target therapy

Scorsetti M, Clerici E, Comito T. Stereotactic body radiation therapy for liver metastases. J Gastrointest Oncol. Jun 2014.



# Thank you!

**“We can not solve our problems with the same level of  
thinking that created them”**

**A. Einstein**