HUMANITAS
CANCER CENTER

Applicazione clinica: Fegato

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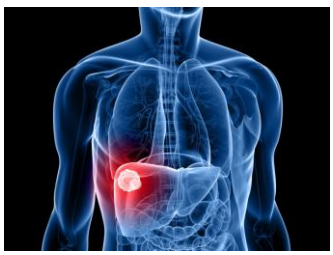
LIVER and SABR



Primary Tumor

Metastases

CLINICAL ASPECTS

• 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

CLINICAL ASPECTS

• 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

SURGERY

• 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**

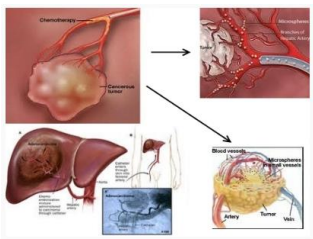
Fong Y. et al. (1995) CA Cancer J.Clin.
Simmonds P.C. et al. (2006) Br.J.Cancer

LOCAL THERAPEUTIC APPROCHES

• **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).**

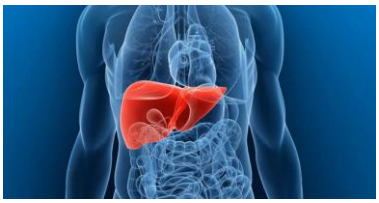


Meij et al, World Journal of Surgical Oncology 2005
Kemeny N. et al, Oncology 2006

Liver SBRT: Is it feasible?

• 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

Pan CC, Kavanagh BD, Dawson LA, Int J Radiat Oncol Biol Phys, 2010 (suppl)

Liver SBRT: dose-volumetric parameters

CLINICAL INVESTIGATION

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

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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)**

Liver SBRT: Is it effective?

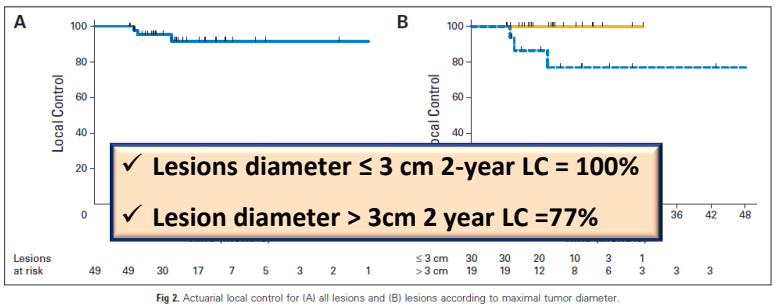


Fig 2. Actuarial local control for (A) all lesions and (B) lesions according to maximal tumor diameter.

Correlation between local control and diameter > 3cm

Rusthoven JCO 2009

Liver SBRT: Is it effective?

Stereotactic Body Radiotherapy for Colorectal Liver Metastases

A Pooled Analysis

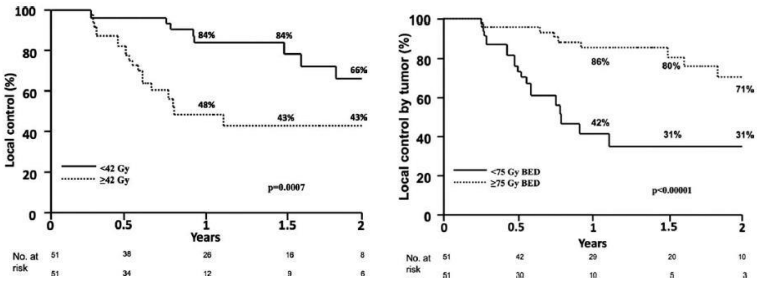
2011

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.

Liver SBRT: Is it effective?



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: Is it effective?

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 *et al*[15]	Phase II (preliminary report)	61 (76 tumors)	1.8-134.3 cm^3 (mean 18.6 cm^3)	75 Gy in 3 fractions	No case of RILD. Twenty-six percent had grade 2 transaminase increase (normalised 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 *et al*[16]	Phase 1 (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 *et al*[17]	Prospective cohort	27	20-165 mL (median, 69 mL)	25-60 Gy (3 fr)	No serious toxicity	Crude LC rate 74%
Lee *et al*[18]	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 *et al*[19]	Phase I - II	47	0.75-97.98 mL (median, 14.93 mL)	Dose escalation, 36-60 Gy (3 fr)	No RILD, Late Grade ¾ < 2%	1-yr LC, 95% 2-yr LC, 92% Median survival, 20.5 mo
Høyer *et al*[10]	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 *et al*[20]	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 *et al*[21]	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%

SABR: Stereotactic ablative radiotherapy; RILD: Radiation induced liver disease; CRC: Colorectal cancer; HCC: Hepatocellular carcinoma; GI: Gastrointestinal; LC: Local control.

Nair et al. World J Radiol 2014 February 28; 6(2): 18-25

LIVER METASTASES: ICH Experience

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

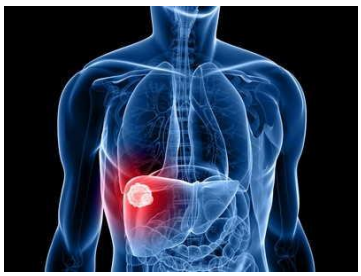
SECONDARY: toxicity and overall survival

INCLUSION CRITERIA:

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

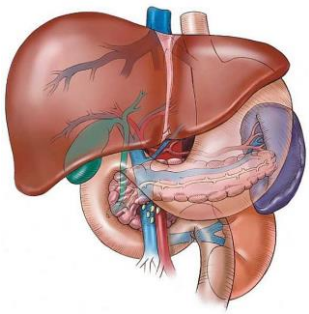
Liver SABR: prescription dose

	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 SABR: dose constraints

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	
Ribs	V30 Gy <30cc	



Patient characteristics

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	45% (28 pts)
Primary site	29 Colon 11 Breast 7 Gyn 14 Other sites
Extrahepatic disease	34% (21 pts)

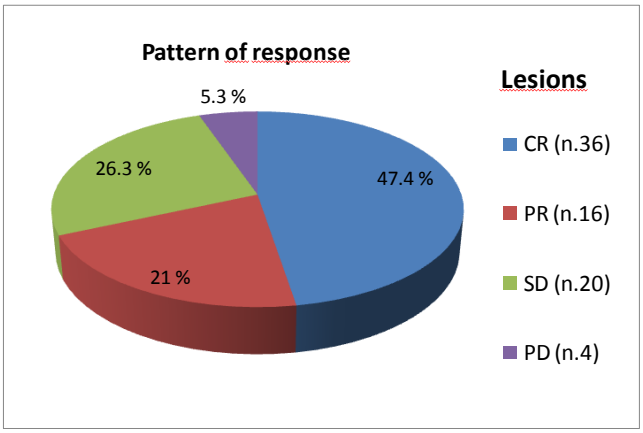
Treatment characteristics

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%)

Local Control

Median FU 12 months

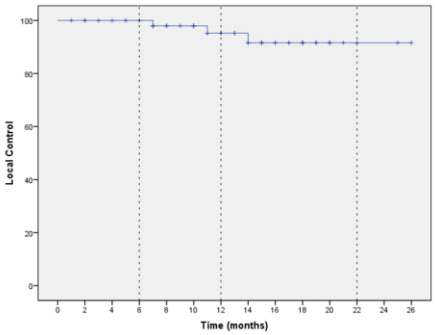


Local Control

Median FU 12 months

Actuarial Local Control:

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

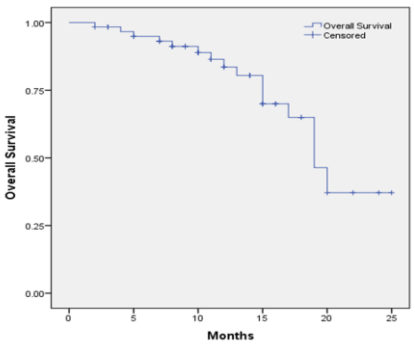


A subgroup analysis for lesions with diameter ≤ 3 cm compared with those > 3 cm revealed no statistical differences in local control rates (p=0.90)

Overall Survival

Actuarial OS

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



Median OS rate was 19 months

Toxicity

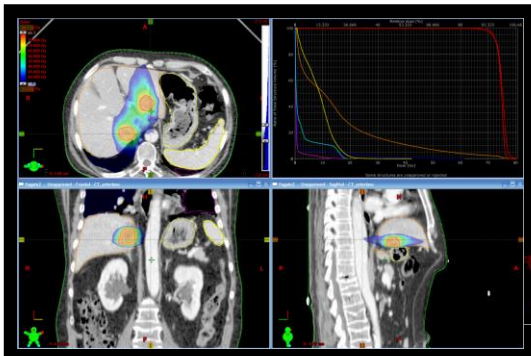
ACUTE TOXICITY:
- **G2 toxicity (vomiting, skin erythema and pain) 4%**
- **G2 transient transaminase increase 26%**
- **No G3-G4 or G5 toxicity observed**

LATE TOXICITY:
One case of G3 chronic chest wall pain

NO RILD

LIVER METASTASES

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

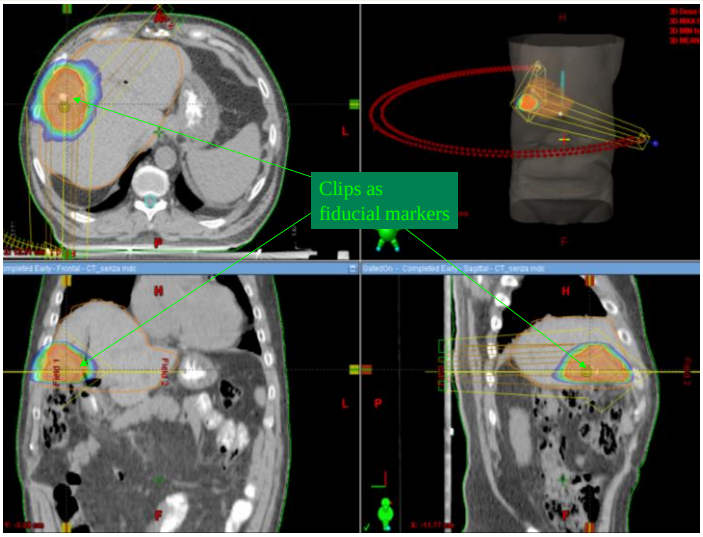


PTV1&PTV2: V95%=99.5%
Spinal cord: Max dose=17.3 Gy
Stomach: Max=21.0Gy, Mean=9.5 Gy
Liver: Mean=15.5 Gy,
D15Gyfree=2811cc

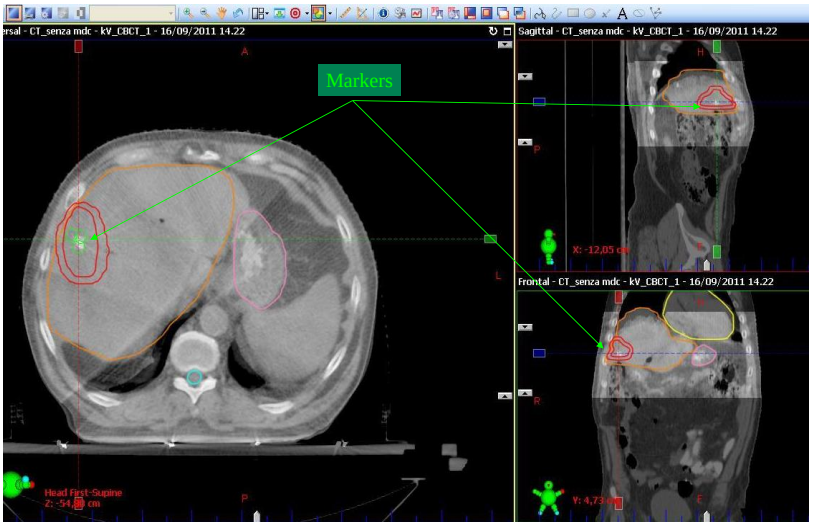
1 isocentre, 3 arcs
Jaw tracking

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

LIVER METASTASES

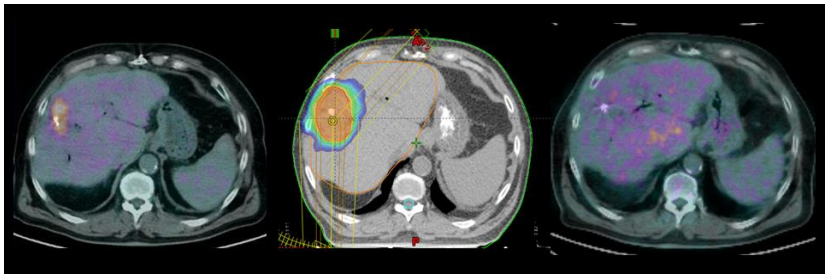


LIVER METASTASES



LIVER METASTASES

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

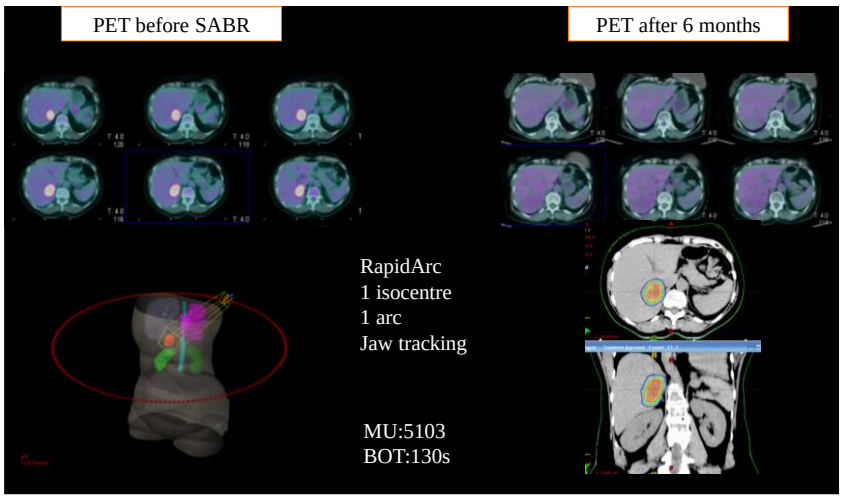


PET –CT pre-treatment, CEA 72

PET –CT post-treatment CEA 2.2

LIVER METASTASES

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

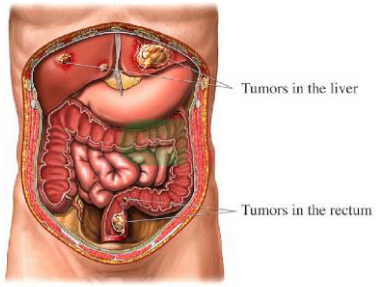


LIVER METS FROM COLORECTAL CANCER

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

Purpose To evaluate the feasibility and efficacy of stereotactic body radiation therapy (SBRT) in the treatment of colorectal liver metastases.



Patient and treatment characteristics

No. of Patients	**42**
Mean age (range)	67 (43-87)
Gender (M:F)	36:6
No. of treated lesions:	**52**
No. of liver lesions/pts:	
1	34 (81%)
2	5 (12%)
3	3 (7%)
Size of lesions	
≤ 3 cm	28 (55%)
> 3 cm	24 (45%)
Total Dose / Frs	**75Gy/3fr**

LIVER METS FROM COLORECTAL CANCER

Results Median follow-up was 24 (range 4–47) months. The progression in field was observed in 5 lesions. **Twenty four months actuarial local control (LC) rate was 91 %.**

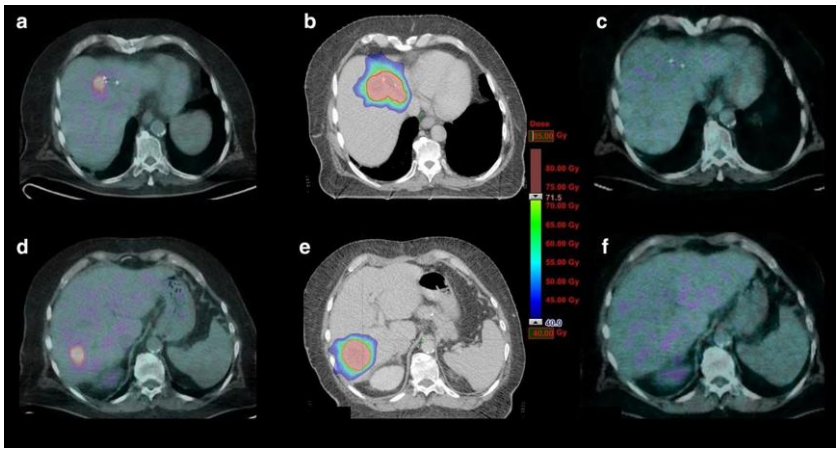
Median overall survival (OS) was 29.2 ± 3.7 months. **Actuarial OS rate at 24 months was 65%.**

Median progression free survival was 12.0 ± 4.2 months; 24 months actuarial rate was 35 %.

No patients experienced radiation-induced liver disease or grade ≥3 toxicity.

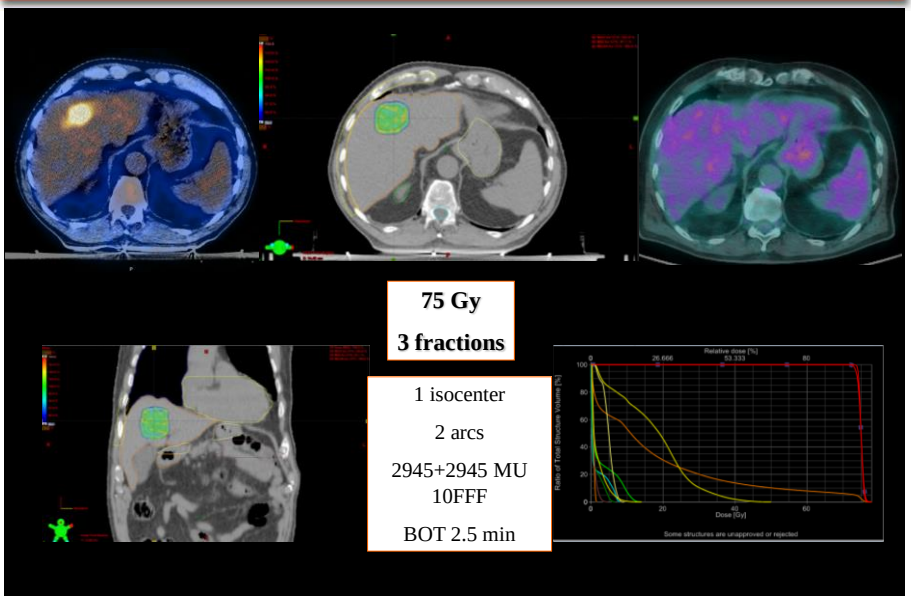
Conclusions SBRT represents a feasible alternative for the treatment of colorectal liver metastases not amenable to surgery or other ablative treatments in selected patients, showing optimal LC and promising survival rate.

Clinical Experience



Patient treated with SBRT for two liver colorectal metastases. **a–d** Positron emission tomography (PET) pre-treatment image showing the lesions, defined by metal surgical clips. **b–e** Visualization of dose distribution on the planning target volume. **c–f** PET-CT image at 3 months after radiation therapy, showing complete metabolic response

LIVER METS FROM COLORECTAL CANCER



Conclusions

Current evidence

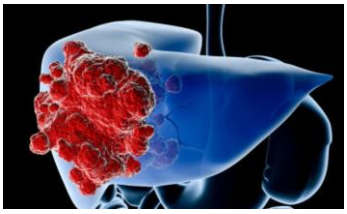
Feasibility: Non invasive and low toxicity

Efficacy: Optimal local control rate

Future directions:

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

LIVER and SABR



Primary Tumor

Metastases

HCC: Evidence in Radiation Therapy

Critical Review

Hepatocellular Carcinoma Radiation Therapy: Review of Evidence and Future Opportunities

Jonathan Klein, MD, and Laura A. Dawson, MD

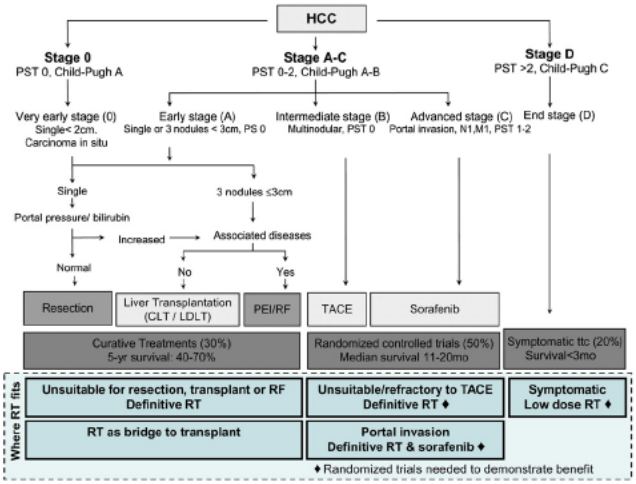
Department of Radiation Oncology, Princess Margaret Hospital/University of Toronto, Toronto, Ontario, Canada

HCC is a leading cause of **global cancer death**. **Curative therapy is not an option for most patients**, often because of underlying liver disease.

Experience in radiation therapy (RT) for HCC is **rapidly increasing**. Conformal RT can deliver tumoricidal doses to focal HCC with low rates of toxicity and sustained local control **in HCC unsuitable for other locoregional treatments**.

Stereotactic body RT and particle therapy have been used with **long-term control in early HCC or as a bridge to liver transplant**. RT has **also been effective** in treating HCC with **portal venous thrombosis**.

BCLC staging system



Jonathan Klein and Laura A. Dawson, Int J Rad Onc Biol Ph. 2012

BCLC Stages and Results of Radiotherapy

BCLC stage*	Okuda stage	Definition	Liver function/PST	Applications of radiation	Median survival
Very early stage (0)	0	Single <2 cm Carcinoma *in situ*	Child A/0	SBRT alone or TACE+SBRT	44.4[56]
Early stage (A)	1-2	Single to 3 nodules, <3 cm	Child A-B/0	TACE+RT	16-20[39,65]
Intermediate stage (B)	1-2	Multinodular	Child A-B/0	TACE+RT	
Advanced stage (C)	1-2	Portal invasion, N1, M1	Child A-B/1-2	CCRT→iA CTx	15.2-16.7[69,76]
Terminal stage (D)	3	Disseminated	Child C/>2	Palliative RT	2-5.1[80-82]

Lee et al.Gut and Liver, Vol. 6, No. 2, April 2012

SABR for HCC

Author, (reference) Design study.	Pts	CTPc	Dose (Gy/ fr)	FUP Median months	Actuarial local Control (%) 1-year	2-years	Actuarial overall survivall (%) 1-year	2-years	PFS months
Andolino, (1,4) *Phase I- II*	36	A	48Gy/3fr	27	-	90%	75%	67%	20,4
	24	B	40Gy/5fr 45Gy /6fr						
Dawson, (2) *Phase II*	102	A/B	24-54Gy/6fr	31.4	87%	-	55%	-	6
Iwata, (3) Phase II	6	A/B	50 Gy/10 fr	14,5	94%	-	86%	-	-

References.

1. Andolino DL, Johnson CS, Maluccio M, Kwo P, Tector AJ, et al.: Stereotactic body radiotherapy for primary hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 81, e447-453, 2011.
2. Dawson LA. Sequential Phase I and II trials of stereotactic Body radiotherapy for locally advanced Hepatocellular carcinoma. JCO, 2013.
3. Iwata H, Shibamoto Y, Hashizume C, Mori Y, Kobayashi T, et al.: Hypofractionated stereotactic body radiotherapy for primary and metastatic liver tumors using the novalis image-guided system: preliminary results regarding efficacy and toxicity. Technol Cancer Res Treat 9, 619-627, 2010.
4. Cárdenes HR. Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. Clin Transl Oncol (2010) 12:218-225

HCC and RapidArc

Radiat Oncol. 2014 Jan 10;9(1):18. [Epub ahead of print]

Feasibility of stereotactic body radiation therapy with volumetric modulated arc therapy and high intensity photon beams for hepatocellular carcinoma patients.

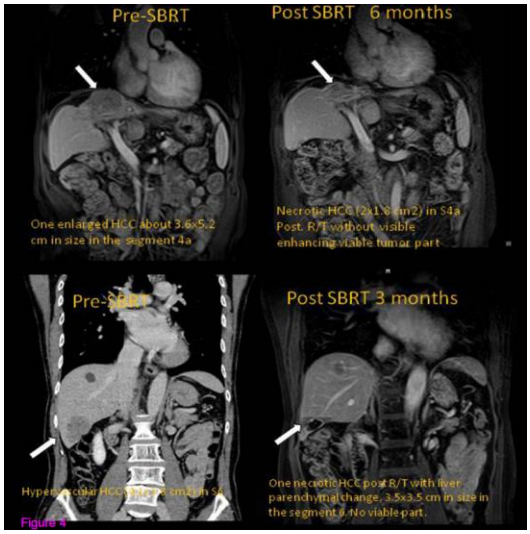
Wang PM, Hsu WC, Chung NN, Chang FL, Jang CJ, Fogliata A, Scorsetti M, Cozzi L.

Methods: Twenty patients (22 lesions) were prospectively enrolled in a feasibility study. Dose prescription was 50Gy in 10 fractions.

Results: **Median follow-up** time was **7.4 months** (range: 3–13). All patients completed treatment without interruption.
Mean actuarial overall survival was of 9.6 ± 0.9 months (95%C.L. 7.8-11.4), median survival was not reached; **complete response** was observed in 8/22 (**36.4%**) lesions; **partial response** in 7/22 (**31.8%**), **stable disease** in 6/22 (**27.3%**), 1/22 (**4.4%**) showed **progression**.
Toxicity was mild with only 1 case of grade 3 RILD and all other types were not greater than grade 2.

Conclusions: Clinical results could suggest to **introduce VMAT-RapidArc as an appropriate SBRT technique** for patients with HCC in view of a **prospective dose escalation trial**.

HCC and RapidArc



The radiological response for two patients at MR at 6 and 3 months after treatment.

In both cases, a residual necrotic mass was detected in the position of the primary HCC without visible enhancing of any viable tumor residual.

Wang PM, Radiat. Oncol., 2014

HCC: Humanitas Experience

SBRT for HCC

unsuitable for standard locoregional therapies

HCC: Humanitas Experience

INCLUSION CRITERIA:

- ✓ Unsuitable for resection, TACE, RFA or alcohol ablation.
- ✓ Maximum tumor diameter < 8cm
- ✓ ≤ 3 discrete lesions
- ✓ Performance status 0-2
- ✓ Child-Turgotte-Pugh A or B liver score
- ✓ Absence of clinical ascites, encephalopathy, active hepatitis or gastric, duodenal or variceal bleed within 2 months of SABR start.
- ✓ No concomitant chemotherapy.

Patient characteristics

February 2011 and April 2014

Patients characteristics	Value
No. of patients	**54**
Age (y)	72 (46–87)
Sex (male:female)	39:15
Baseline KPS	> 90

All patients had **Child-Turcotte-Pugh class A or B disease**

Treatment characteristics

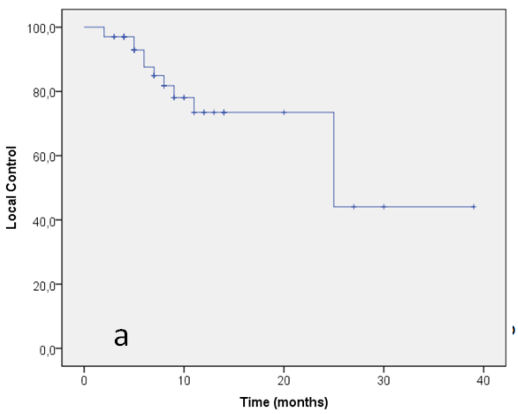
Treatment charateristics	Value
No. of lesions	**82**
No. of lesions per patient	1 for 31 pts (57%) 2 for 18 pts (34%) 3 for 5 pts (9%)

Dose prescription	Lesions
48-75 Gy/3fr	**30 (37 %)**
36-45 Gy/6fr	**33 (40 %)**
40-50 Gy/10fr	**19 (23 %)**

Dose prescription and fractionation were according to **lesions size** and **liver function**.

Local Control

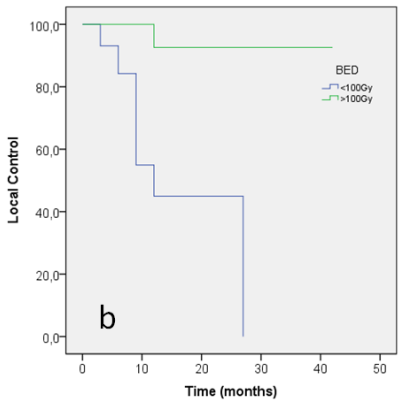
Median FU 7 months (range 3-39)



Actuarial **LC**:
✓ 7 months 85%
✓ 12 months 74%

Local Control

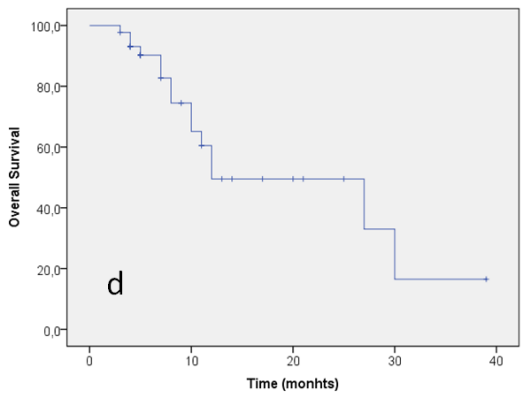
Regimens with **Equivalent Dose >100Gy** in 3 and 6 fractions was a significant prognostic factors for **LC (p<0.001)** in univariate analysis.



p<0.001

Overall Survival

Median OS: 12 months

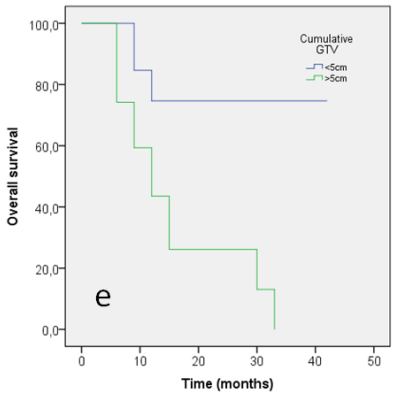


Actuarial OS

- **12 months= 50%**

Overall Survival

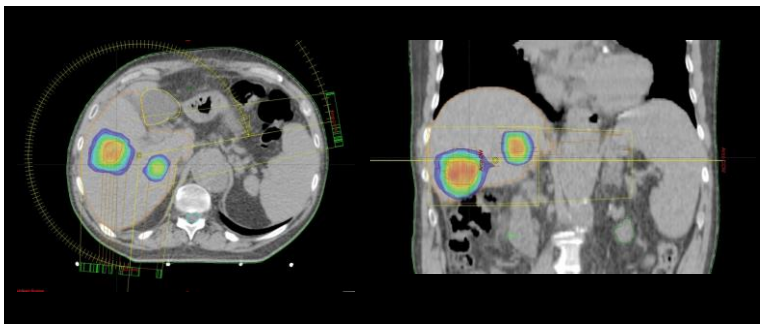
Univariate analysis showed that OS significantly decreased in the subgroup of patients with Cumulative GTV >5cm.



p<0.008

SABR for HCC

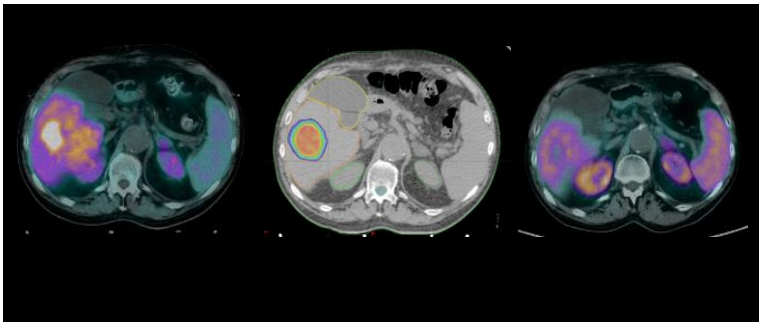
CR after SABR:
RapidArc Treatment plan



SABR HCC dose: 75 Gy /3 fr Beam 10 FFF Two arcs BOT = 03':10" 6178 MU

SABR for HCC

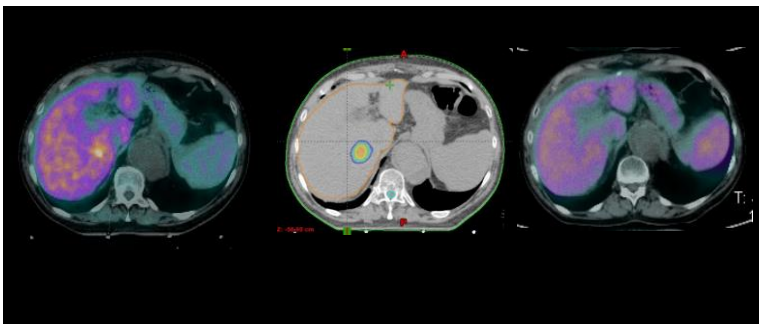
CR after SABR:
CT-PET evaluation



CT PET before SABR | RapidArc Treatment plan | CT PET after SABR

SABR for HCC

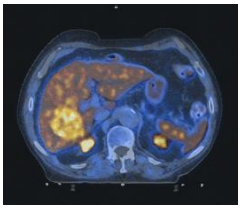
CR after SABR:
CT-PET evaluation



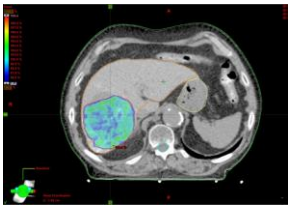
CT PET before SABR | RapidArc Treatment plan | CT PET after SABR

SABR for HCC

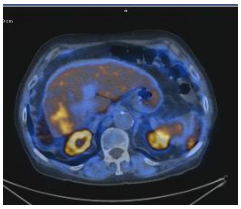
Partial remission after incomplete TACE plus SABR
CT-PET evaluation



before SABR



RA Treatment plan



after SABR

SABR HCC dose: 50 Gy /10 fr Beam 10 FFF Two arcs BOT = 01':40'' 1272 MU

Toxicity

ACUTE TOXICITY:

•G3 transient transaminase increase 16% (9pts)

• No G4 or G5 toxicity observed

LATE TOXICITY:

• Two patients had a decline in Child class

NO RILD

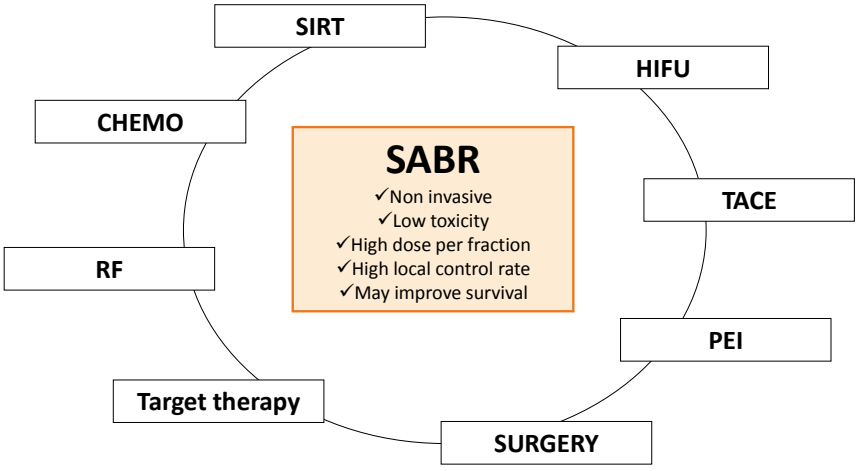
Challenges and Opportunities

Table 1 Challenges and opportunities in HCC RT

Challenge	Barrier	Opportunity
Late presentation	Lack of screening of high-risk patients	Patient/physician education Improved screening techniques
Limited standard therapies	Complex HCC pathophysiology and diseased liver	Targeted therapies - Preclinical research - Phase 1 studies of RT and new agents
Concurrent liver disease	Competing risks of from hepatitis/ cirrhosis vs HCC	Cross-disciplinary collaboration
Patient selection for RT	Lack of level 1 evidence	Randomized trials
	Limited dissemination of RT literature to non-RT experts	Multidisciplinary education
Tumor identification	Imaging requires technical expertise	Standardize imaging protocols Radiation oncology education/radiology collaboration Radiology/pathology correlative research Functional imaging
RT contour variability	Few published guidelines	Consensus guidelines
Appropriate RT dose	Uncertainty in dose-response	Clinical studies to improve dose-outcome models Deformable image registration and dose accumulation Research of high dose per fraction biologic effects
Conforming dose to tumor	Not enough liver	Advanced RT planning - Stereotactic body RT - Volume-modulated arc therapy - Charged particle therapy
	Identifying tumor at treatment	Image-guided radiation therapy - Technology advances (eg, magnetic resonance linac) - Respiratory correlated imaging (eg, 4D CBCT) - Contrast agents to identify tumor
Liver toxicity	Understanding mechanism Few effective interventions	Regenerative research - Stem cell/hepatocyte transplant - Novel agents to mitigate injury
Luminal gastrointestinal toxicity	Proximity of duodenum, bowel to liver	Spacers to move luminal tissue away from hepatocellular carcinoma Normal tissue protectors

Klein and Dawson, IJROBP 2012

CONCLUSIONS



THANKS