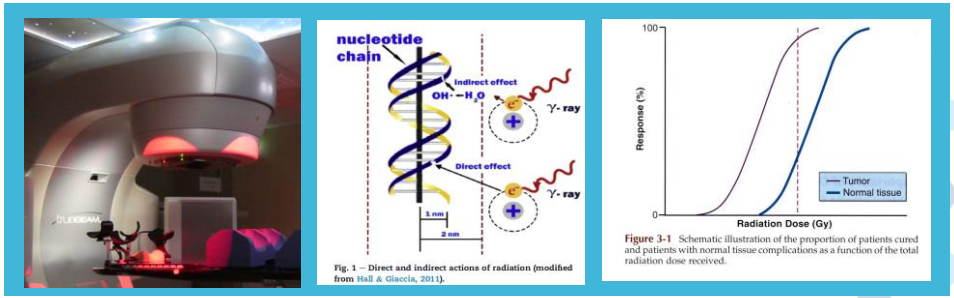
Radiotherapy for liver lesions

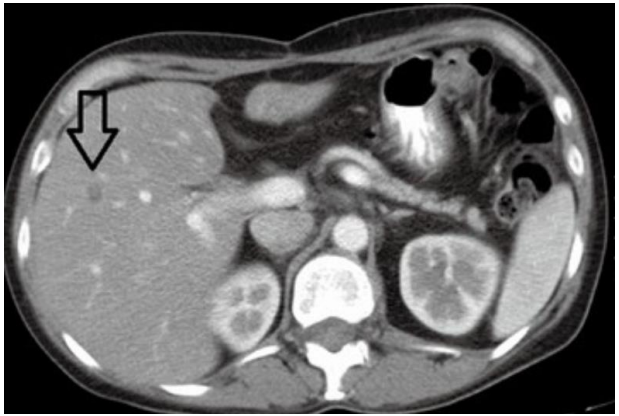
Ines Joye, MD PhD



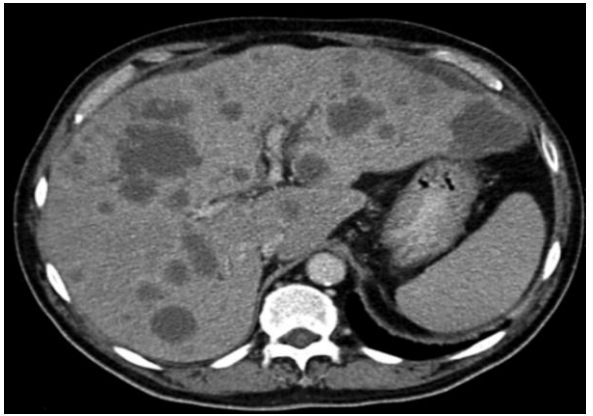
AZ Klina - AZ Monica - AZ Rivierenland
AZ Voorkempen - GZA Ziekenhuizen - UZA – Vitaz - ZNA

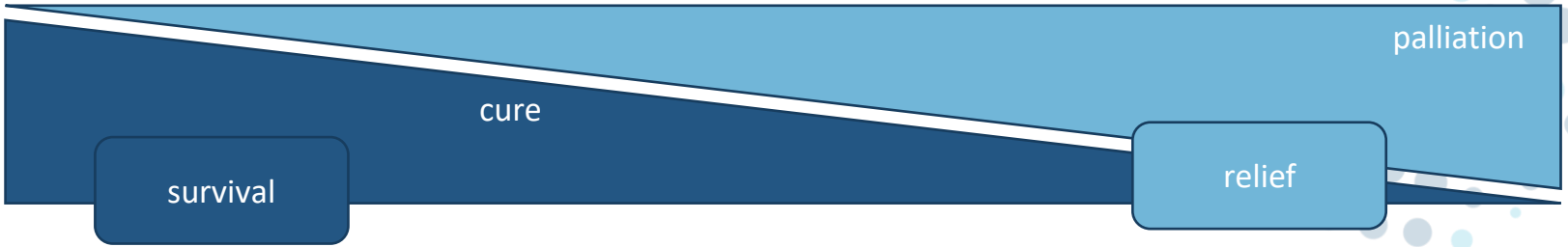
Spectrum of liver lesions

solitary/oligo

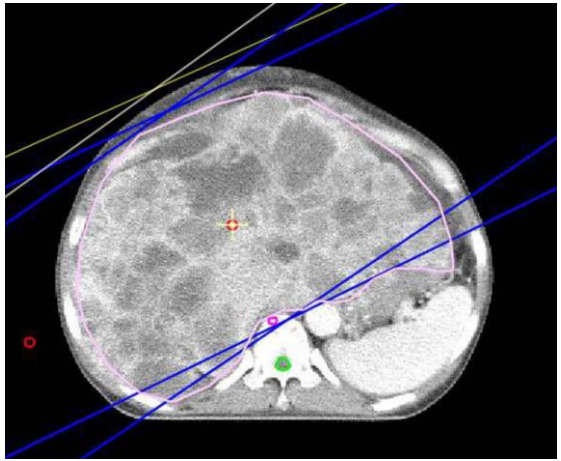


diffuse





Whole Liver RT



Yeo et al. Radiat Oncol 2010

- Simple opposing-field technique, excluding one kidney from RT fields
- Different RT schedules: 30-35Gy in 1,5-3Gy/fr, but 1x8 Gy is option

Pain relief 55-80%
Improvement in liver function
Well tolerated, prescribe antiemetics/CS
No data on better survival
No evidence to combine with systemic R/

Hoyer et al. IJROBP 2012

Whole Liver RT

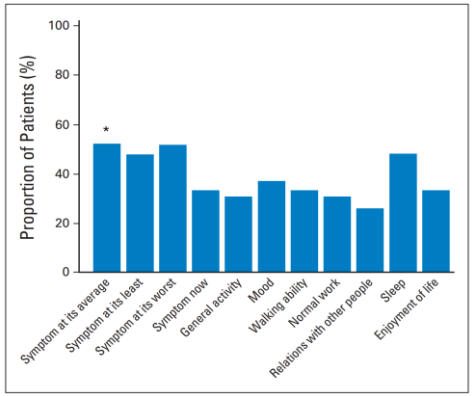
Phase II Trial of Palliative Radiotherapy for Hepatocellular Carcinoma and Liver Metastases

Hany Soliman, Jolie Ringash, Haiyan Jiang, Kawalpreet Singh, John Kim, Robert Dinniwell, Anthony Brade, Rebecca Wong, James Brierley, Bernard Cummings, Camilla Zimmermann, and Laura A. Dawson

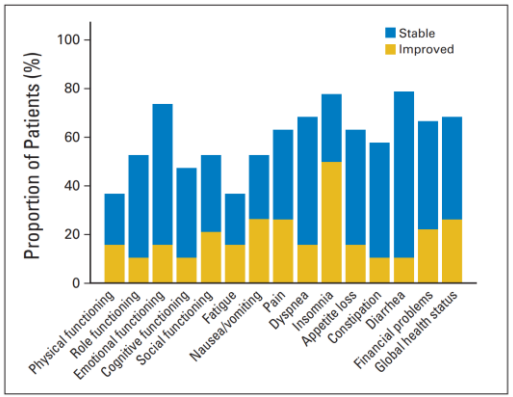
41 pts with **HCC (n=21) or LM (n=20) unsuitable or refractory to standard therapies** indicating pain, discomfort, nausea or fatigue

1x8 Gy to liver volume causing symptoms + 1cm (95% PTV >7 Gy; Dmax stomach, bowel, spinal cord <10 Gy); parallel opposing or oblique fields; anti-emetics

BPI



EORTC QoL-C30

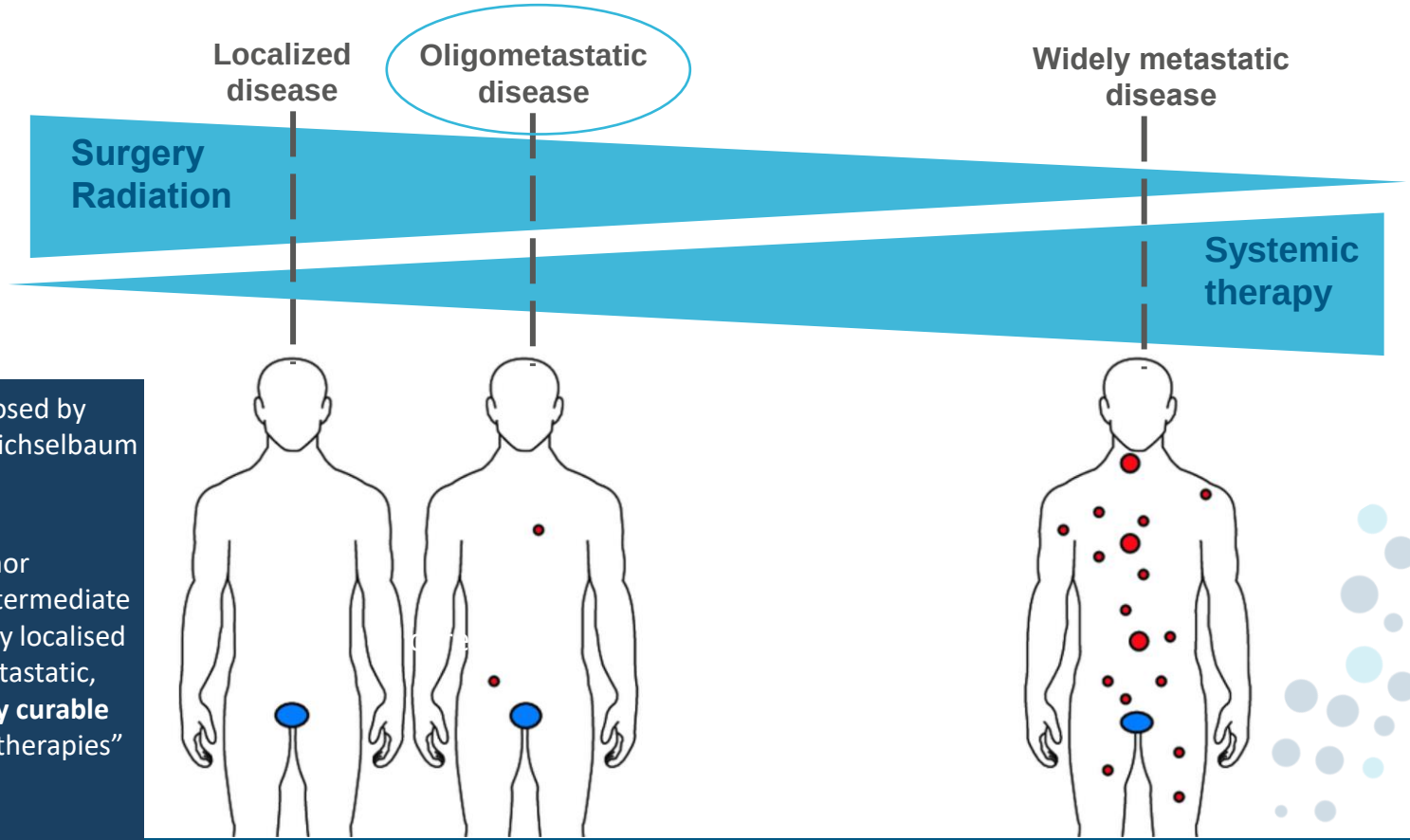


No difference HCC vs. LM

G3 toxicity 1 patient

Soliman et al. JCO 2013

Oligometastatic disease



- Formally proposed by Hellman & Weichselbaum in 1995
- “a state of tumor progression intermediate between purely localised and widely metastatic, and **potentially curable** with localised therapies”

Stereotactic Body RadioTherapy (SBRT)

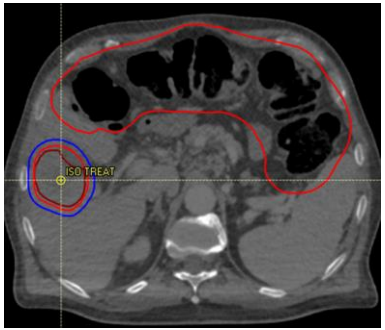
A method of external beam radiotherapy that accurately delivers a high dose of irradiation in one or few treatment fractions to an extracranial target

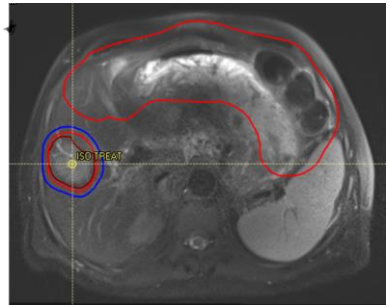
- high dose/fraction**: effective tumor cell kill** due to high radiobiological effectiveness (direct effect, vasculature, antitumor immunity)
- sharp dose gradients: **maximally sparing OARs**
- **non-invasive**

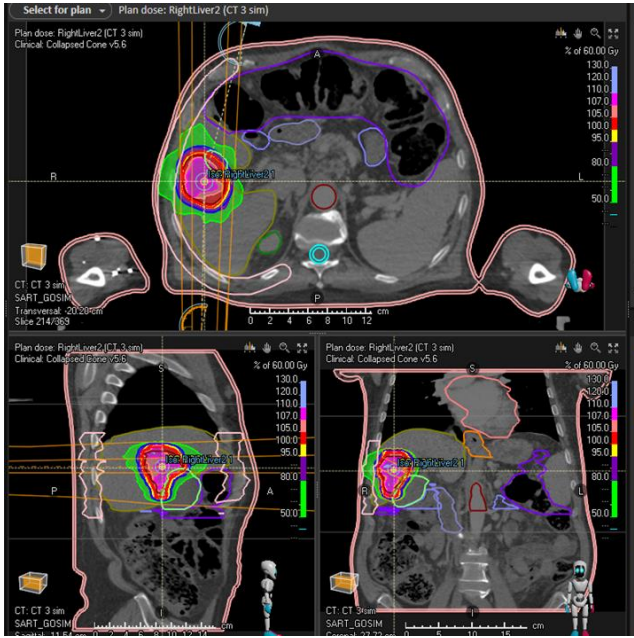
- Originally from brain SRS
- Standard treatment for small lung/brain mets or early stage NSCLC

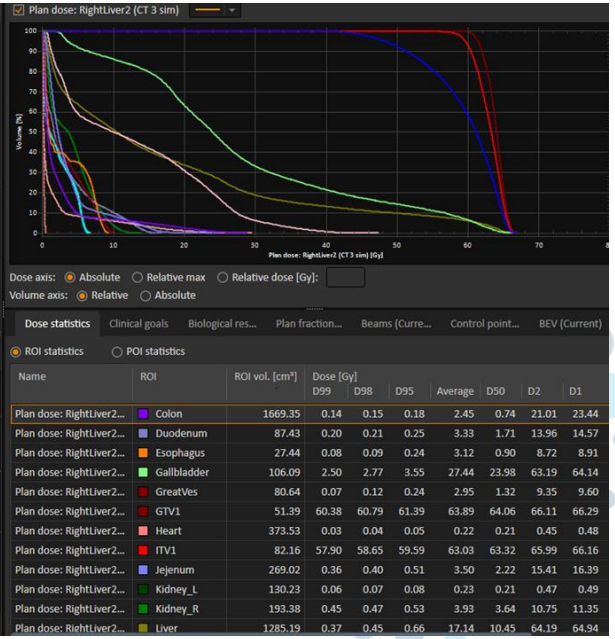
- Nowadays increasingly used for LN, liver, bony lesions; prostate and pancreatic tumors

SBRT liver









Name	ROI	ROI vol. [cm³]	Dose [Gy]						
			D99	D98	D95	Average	D50	D2	D1
Plan dose: RightLiver2...	Colon	1669.35	0.14	0.15	0.18	2.45	0.74	21.01	23.44
Plan dose: RightLiver2...	Duodenum	87.43	0.20	0.21	0.25	3.33	1.71	13.96	14.57
Plan dose: RightLiver2...	Esophagus	27.44	0.08	0.09	0.24	3.12	0.90	8.72	8.91
Plan dose: RightLiver2...	Gallbladder	106.09	2.50	2.77	3.55	27.44	23.98	63.19	64.14
Plan dose: RightLiver2...	GreatVes	80.64	0.07	0.12	0.24	2.95	1.32	9.35	9.60
Plan dose: RightLiver2...	GTV1	51.39	60.38	60.79	61.39	63.89	64.06	66.11	66.29
Plan dose: RightLiver2...	Heart	373.53	0.03	0.04	0.05	0.22	0.21	0.45	0.48
Plan dose: RightLiver2...	ITV1	82.16	57.90	58.65	59.59	63.03	63.32	65.99	66.16
Plan dose: RightLiver2...	Jejenum	269.02	0.36	0.40	0.51	3.50	2.22	15.41	16.39
Plan dose: RightLiver2...	Kidney_L	130.23	0.06	0.07	0.08	0.23	0.21	0.47	0.49
Plan dose: RightLiver2...	Kidney_R	193.38	0.45	0.47	0.53	3.93	3.64	10.75	11.35
Plan dose: RightLiver2...	Liver	1285.19	0.37	0.45	0.66	17.14	10.45	64.19	64.94

SBRT liver

- Inoperable patients
- *Maximal lesion diameter 6-7 cm*
- *Maximal number of M+1-3*
- Adequate liver function
- Life expectancy > 6m
- KI > 70

Exclusion:

- Prior abdominal radiotherapy, limiting safe liver RT within constraints
- Uncontrollable extrahepatic disease
- Active hepatitis, gross ascites
- Pregnant women

SBRT liver: advantages

- Lesions >3 cm
- Tumor location close to vessels, gallbladder or beneath diaphragm
- Short treatment time
- Non invasive, no recovery
- Favorable toxicity

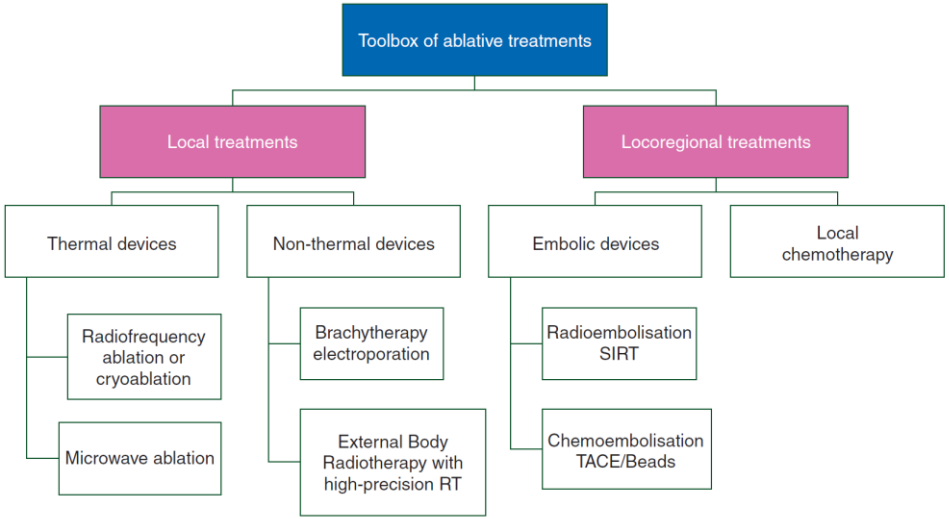
Acute:
- fatigue
- transient liver function disturbances
- vague abdominal discomfort, loss of appetite, nausea ==> anti-emetics, PPIs

Late: SELDOM!
rib fracture, skin redness, edema, fibrosis
GI toxicity (ulcera, perforations, stenosis), biliary complications, RILD

Liver metastases

Surgery is treatment of choice for resectable liver metastases; however only 10-15% are resectable

- R0 resection
- Sufficient liver remnant/liver function
- Location
- Comorbidities
- “Oncological resectability”



Van Cutsem, Ann Oncol 2016

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

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- 47 patients with ≤3 hepatic lesions, <6cm
- Phase 1: Dose escalation 36 Gy ➔ 60 Gy
- Phase 2: 60 Gy
- Primary endpoint: local control
- Median follow-up: 16m

- In-field LC at 1 and 2 years: 95% and 92%
- <3cm: 2y LC 100%
- Median OS 20,5m; 2y OS 30%
- ≥G3 toxicity 2%
- No RILD

Rusthoven, JCO 2009

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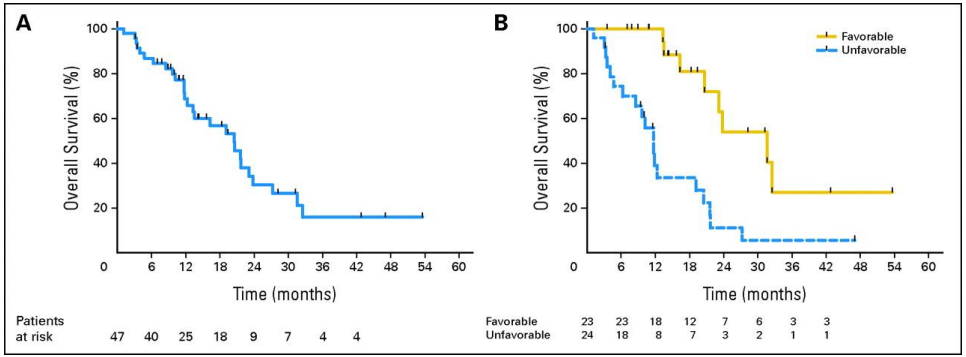
OS dependent on primary

- Favorable: breast, colorectal, renal, carcinoid, GIST, sarcoma
- Unfavorable: lung, ovary, noncolorectal GI malignancies (i.e. unfavorable primary sites)



Rusthoven, JCO 2009

SBRT for CRLM

Systematic review with pooled analysis

18 studies, 656 patients CRLM

OS: 67%@1y and 57% @2y
LC: 67%@1y and 59%@2y

Author/year	Median OS (months)	1y OS (%)	2y OS (%)	1y LC (%)	2y LC (%)	Median PFS (months)	Liver or GI toxicity (%)
Scorsetti/2015	29	–	65	95	91	12	G2 liver toxicity (25)
Stintzing/2013	34.4	–	–	85	80	–	Bleeding and rising bilirubin (3)
van de Voorde/2015	25	–	–	–	–	–	–
van der Pool/2010	34	100	83		74	11	Liver toxicity: G3 (10), G2 (90),
Vautravers-Dewas/2011	–	–	58	–	86	–	–
Ahmed/2016	–	100	73	79	59	–	–
Ambrosino/2009	–					–	G1-2 liver toxicity (36.4)
Berber/2013	–	56	–	60	–	–	G1 fatigue and nausea (21); death $n = 1$
Chang/2011	–	72	38	62	45	–	GI-G2 & G3 acute GI toxicity 17 & 3
Mendez Romero/2016	43 & 35*	94 & 95*	81 & 69*	90 & 96*	90 & 74*	–	G1-2 liver toxicity (97.5), G3 liver toxicity (7.5)
Doi/2017	45	82.3	67.1	67.2	35.9	16 (LC time)	G1-2 liver toxicity (16), duodenal ulcer (4)
Goodman/2016	38	95	78	93	88	10	Death $n = 1$
Hoyer/2006	19.2	–	38	–	78	6.5 (TTP)	G3 intestinal toxicity (5), liver failure (2), nausea & diarrhea G1-2 (34 & 23), G3 (3); death $n = 1$
Joo/2017	–	–	75	–	–	–	G1-2 nausea (34), G1-2 liver toxicity (15)
Kim/2009	25	53	40	80	60	–	G1 nausea and musculoskeletal discomfort (40)
Lee/2009	15	63	–	–	–	3.9	–
Liu/2013	25.2	–	–	86	67	–	–
McPartlin/2017	16	63	26	50	32	–	G3 nausea (2)

Petrelli, RO 2018

International Journal of Radiation Oncology biology • physics
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Clinical Investigation

The Dutch—Belgian Registry of Stereotactic Body Radiation Therapy for Liver Metastases: Clinical Outcomes of 515 Patients and 668 Metastases

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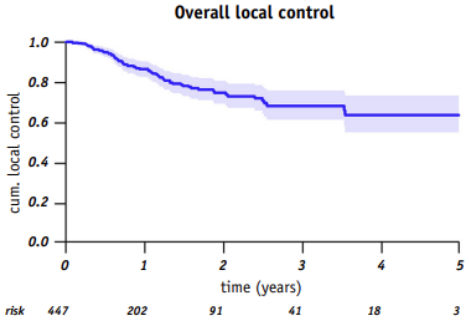
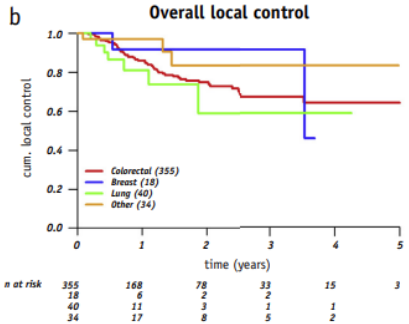
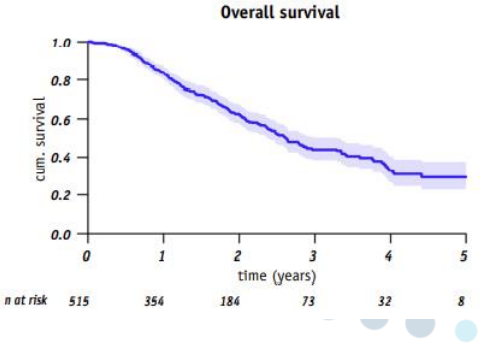
- web-based registry, common protocol across 13 centers
- N= 515 pts, 668 liver mets
- 1y LC 87%
- 1y OS 84%
- G3 toxicity 3.9%



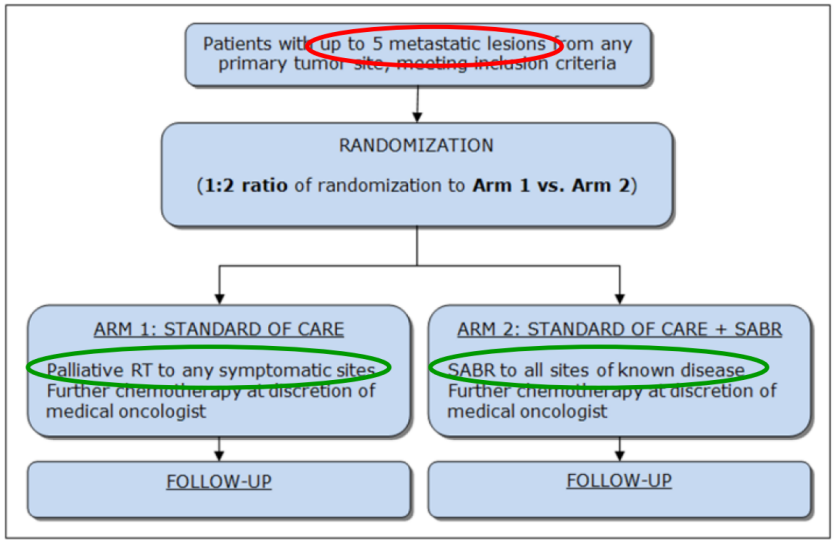




Mendez Romero, IJROBP 2021

SABR-COMET

- Multi-institutional randomized open label phase II trial
- SABR vs SOC palliative therapy
- 2012-2016: 99 pts with OMD of multiple types
- Inclusion: controlled primary tumor, max 5 mets amenable to SABR, max 3 mets in one organ



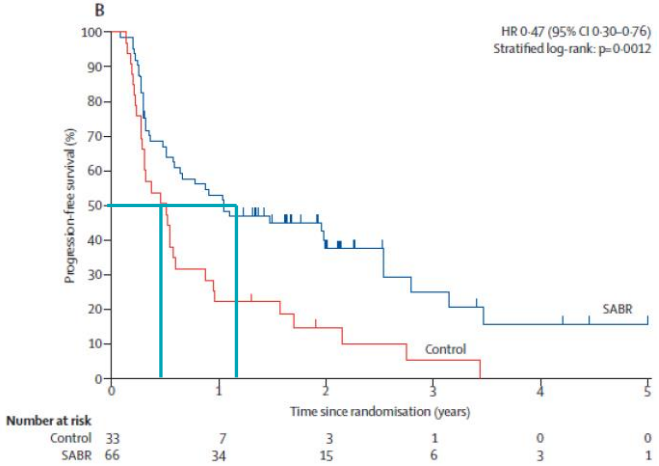
	Control group (n=33)	SABR group (n=66)
Age	69 (64-75)	67 (59-74)
Sex		
Men	19 (58%)	40 (61%)
Women	14 (42%)	26 (39%)
Site of original primary tumour		
Breast	5 (15%)	13 (20%)
Colorectal	9 (27%)	9 (14%)
Lung	6 (18%)	12 (18%)
Prostate	2 (6 %)	14 (21%)
Other	11 (33%)	18 (27%)
Time from diagnosis of primary tumour to randomisation (years)	2·3 (1·3–4·5)	2·4 (1·6–5·3)
Number of metastases		
1	12 (36 %)	30 (46%)
2	13 (40%)	19 (29%)
3	6 (18%)	12 (18%)
4	2 (6%)	2 (3%)
5	0 (0%)	3 (5%)
Location of metastases		
Adrenal	2/64 (3%)	7/127 (6%)
Bone	20/64 (31%)	45/127 (35%)
Liver	3/64 (5%)	16/127 (13%)
Lung	34/64 (53%)	55/127 (43%)
Other*	5/64 (8%)	4/127 (3%)

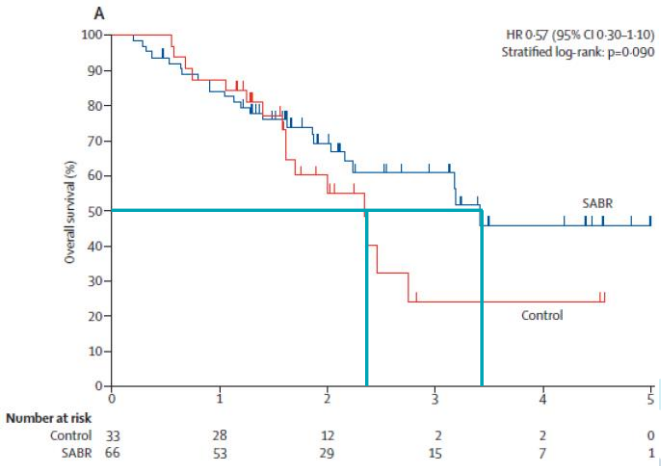
Data are n (%), n/N (%), or median (IQR). SABR=stereotactic ablative radiotherapy. *Other comprises brain (n=3 lesions in control group; n=1 lesion in SABR group), lymph nodes (n=1 lesion in control group; n=3 lesions in SABR group), and para-renal (n=1 lesion in control group).

***Table 1:* Baseline characteristics**

Palma, Lancet 2019

SABR-COMET





mPFS: 6m ➔ 12m

mOS: 28m ➔ 41m

Palma, Lancet 2019

SBRT vs. RFA

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Clinical Investigation

Comparison of Stereotactic Body Radiation Therapy and Radiofrequency Ablation in the Treatment of Intrahepatic Metastases

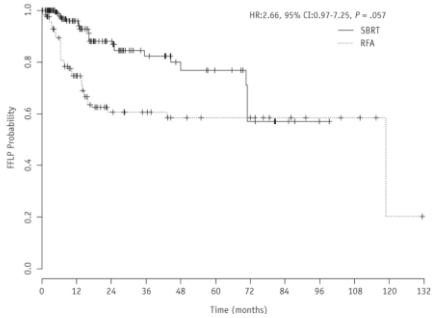
William C. Jackson, MD,* Yebin Tao, PhD,*
Mishal Mendiratta-Lala, MD,† Latifa Bazzi, BA,*
Dan R. Wahl, MD, PhD,* Matthew J. Schipper, PhD,*
Mary Feng, MD,† Kyle C. Cuneo, MD,* Theodore S. Lawrence, MD, PhD,*
and Dawn Owen, MD, PhD*

*Departments of *Radiation Oncology, and †Radiology, University of Michigan, Ann Arbor, Michigan; and ‡Department of Radiation Oncology, University of California, San Francisco, San Francisco, California*

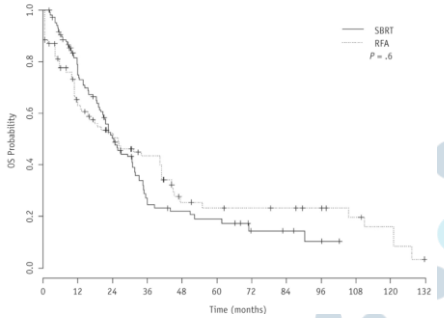
Non-randomized
161 pts with 282 **unresectable LM**
112 RFA; 170 SBRT

mFUP: 24,6m
2y FFLP 88% vs. 74% (p=0.06)
Tumors >2cm: improved FFLP (p<0.01)
2y OS 51% (ns=0.8)
G3 toxicity equal

FFLP



OS



Jackson, IJROBP 2018

HCC

- Most patients are no surgical candidates
  - ➔ regional arterial therapies
  - ➔ local ablation:
    - RFA
    - MWA
    - cryoablation
    - percutaneous ethanol injection
    - **(SB)RT**

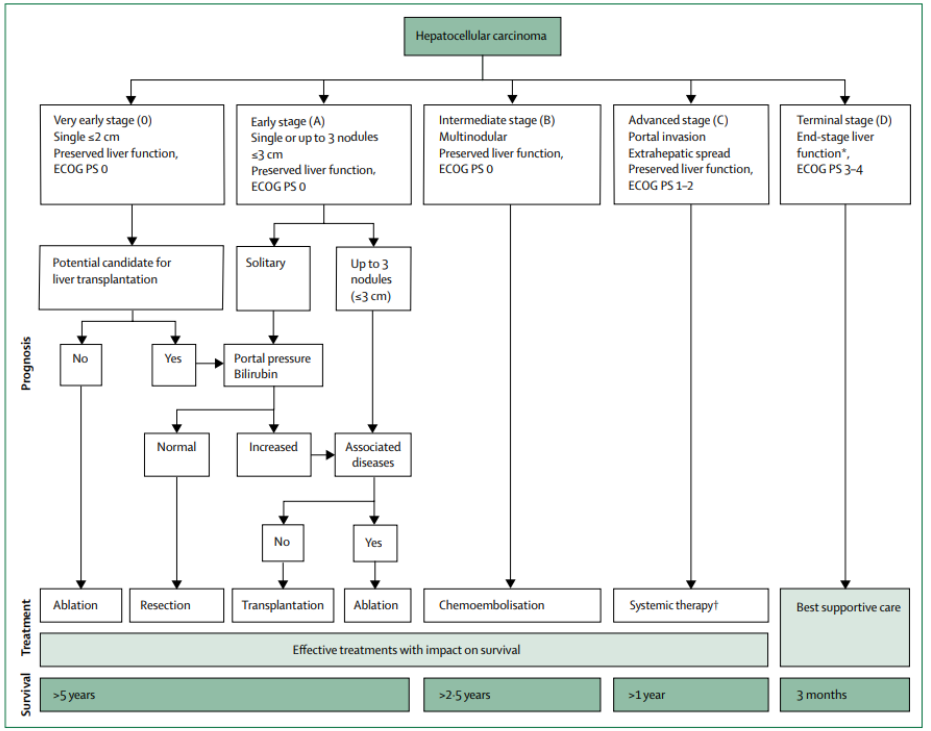


Figure 2: **Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy**

Forner, Lancet 2018

SBRT for HCC

No level I evidence!

Heterogeneity!

Selection bias

1y LC 65-100%; 1y OS 36-95%

Table 1 Prospective trials and large (> 100 patients) retrospective series evaluating stereotactic body radiation therapy in hepatocellular carcinoma

Author	Yr	Type	*n*	Size	VI	PVT	mf	PT	CP class	f/u	Dose	1y-LC	1y-OS
Méndez Romero *et al*[25]	2006	phase I/II	8 (11)	3.5 (0.5-7) cm	38%	25%	25%	NR	A: 63%, B: 25%, UK: 12%	13	25-37.5/3-5Fx	75%	75%
Tse *et al*[26]	2008	phase I	31 (NB)	173 (9-1913) mL	52%	NR	NR	61%	A: 100%	18[1]	24-54/6Fx	65%[1]	48%
Cárdenes *et al*[27]	2010	phase I	17 (25)	34 (8-95) mL	NR	18%	30%	24%	A: 35%, B: 65%	24	36-48/3-5Fx	100%	75%
Kang *et al*[28]	2012	phase II	47 (56)	15 (2-214) mL	NR	29%	17%	100%[2]	A: 87%, B: 13%	17	42-60/3Fx	95%[4]	69%[4]
Price *et al*[29]	2012	phase I/II	26 (29)	NR (21-253) mL	NR	12%	12%	27%	A: 54%, B: 46%	13	36-48/3-5Fx	96%	77%
Huang *et al*[30]	2012	phase II	36 (NB)	4.8 (1.1-12.3) cm	NR	NR	NR	NR	A: 78%, B: 19%, C: 3%	14	25-48/4-5Fx	88%	64%[4]
Bujold *et al*[31]	2013	phase I/II	102 (NB)	117 (1-1913) mL	55%	NR	61%	52%	A: 100%	31	24-54/6Fx	87%	55%
Culleton *et al*[32]	2014	phase II	29 (NB)	9 (4-27) cm	NR	76%	NR	14%	B: 97%, C: 3%	NR	21-49/5-15Fx	NR	32%
Sanuki *et al*[33]	2014	retro	185 (185)	8 (1.6-65) mL	NR	NR	0%	68%[2]	A: 85%, B: 15%	23	35-40/5Fx	99%	95%
Lasley *et al*[14]	2015	phase I/II	59 (65)	34 (2-107) mL	NR	NR	NR	NR	A: 64%, B: 36%	33/46[3]	36-48/3-5Fx	NR	91%/82%[3]
Scorsetti *et al*[34]	2015	phase II	43 (63)	5 (1-13) cm	NR	20%	43%	65%	A: 53%, B: 47%	8	36-75/3-6Fx	86%	78%
Su *et al*[35]	2016	retro	132 (175)	3 (1.1-5) cm	NR	NR	28%	30%	A: 86%, B: 14%	21	42-46/3-Fx	91%	94%
Takeda *et al*[36]	2016	phase II	90 (90)	NR (1-4) cm	NR	NR	0%	64%	A: 91%, B: 9%	42	35-40/5Fx	96%[5]	67%[5]
Moon *et al*[37]	2018	phase II	11 (NB)	23 (3-145) mL[1]	NR	NR	13%[1]	48%[1]	NR	13[1]	27.5-45/3-5Fx	82%	36%
Nabavizadeh *et al*[38]	2018	retro	146 (146)	NR	NR	10%	0%	92%	A: 46%,B: 41%,C: 13%	23	50/5Fx[6]	97%	NR
Jeong *et al*[39]	2018	retro	119 (139)	1.7 (NR) cm	0%	0%	NR	97%	A: 91%, B: 9%	26	30-60/3Fx	99%	99%

Gerum, WJGO 2019

SBRT vs. other therapies

Retrospective data

Table 2 Studies comparing stereotactic body radiation therapy to other local treatments

Author	Yr	Type	Treat.	*n*	Size	mf	PT	CP class	f/u	Dose	1y-LC	1y-OS	tox.	Comment
Su *et al*[40]	2017	pm	SBRT	33 (45)	3.3 (NR) cm	36%	0%	A: 100%	42	42-48/3Fx	84%[1]	100%	nausea[4]	LC/OS NS
			OP	33 (45)	3.3 (NR) cm	30%	0%	A: 100%	44		72%[1]	97%	bleed./pain[5]	
Wahl *et al*[19]	2016	retro	SBRT	63 (83)	2.2 (0.1-10) cm	29%	2 (0-7)[2]	A: 69%, B: 29%, C: 2%	13	30-50/3-5Fx	97%	74%	grade3+: 3%	LC/OS NS
			RFA	161 (249)	1.8 (0.6-7) cm	32%	0 (0-7)[2]	A: 50%, B: 42%, C: 8%	20		84%	70%	grade3+: 11%	> 2 cm LC sig↑ with SBRT
Sapir *et al*[20]	2018	retro	SBRT	125 (173)	2.3 (0.1-20.8) cm	NR	2 (NR)[2]	6 (5-9)[3]	12	30-50/3-5Fx	97%	75%	grade3+: 8%	LC sig↑ with SBRT
			TACE	84 (84)	2.9 (0.7-15) cm	NR	0 (NR)[2]	6 (5-9)[3]	23		47%	74%	grade3+: 13%	Tox sig↑ with TACE

Gerum, WJGO 2019

SBRT with RFA, MWA, TACE?

Feasible and potentially synergistic

- Lesion selection (RFA, MWA prior to SBRT)
- Combination with TACE seems promising
  - Smaller lesions
  - Radiosensitizing CT (! Hypoxia)

SBRT as bridge to transplantation

- Retrospective small series
- Heterogeneous patient selection, RT doses
- pCR described
- Low toxicity

Table 4 Summary of single institution retrospective series evaluating SBRT as a bridge to transplant for HCC

Study	No. patients, No. lesions	RT dose	Median tumor size	pCR rate	cCR rate	Dropout rate	Toxicity
Facciuto et al[8]	17, 22	24-36 Gy in 2-4 fx	2.01 cm	14%	30%	NR	2 patients with post-SBRT nausea, 1 patient with acute liver decompensation
O'Connor et al[9]	10, 11	33-54 Gy in 3 fx	3.4 cm	27%	NR	0%	40% with acute grade 1-2 toxicity, no ≥grade 3 toxicity
Gresswell et al[10]	12, 17	30-50 Gy in 4-6 fx	2.3 cm	46%	80%	8%	No ≥grade 3 acute toxicity
Moore et al[11]	23, NR	30-54 Gx in 3-5 fx	2.5 cm	27.3 %	NR	30%	1 patient (CP B8) developed RILD
Uemura et al[12]	22, 25	40-50 Gy in 4-6 fx	3.2 cm	28%	NR	9%	No ≥grade 3 toxicity
Jacob et al[13]	12, 18	27-45 Gy in 2-6 fx	4.2 cm	100%	NR	42%	No ≥grade 3 toxicity
Garg et al (current study)	20, 26	30-63 Gy in 3-6 fx	3.05 cm	62%	76%	22%	No ≥grade 3 toxicity

Abbreviations: cCR = clinical complete response; CP = Child-Pugh; HCC = hepatocellular carcinoma; NR = not reported; pCR = pathologic complete response; RILD = radiation-induced liver disease; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

Garg, Adv Radiat Oncol 2021

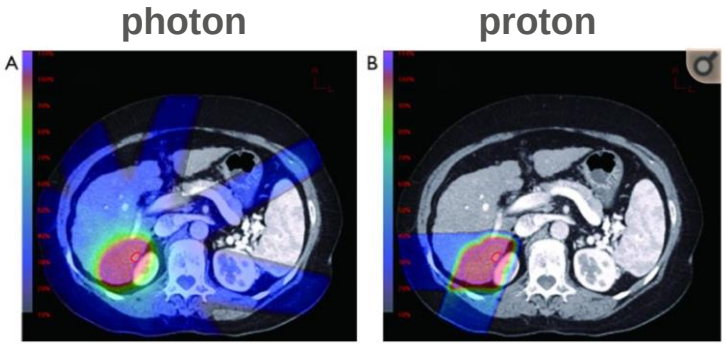
SBRT for liver lesions

- Pts who are not eligible for resection or other local therapies
  - Invasiveness
  - Lesions close to liver surface, major vessels, bile ducts, luminal organs
  - Portal thrombosis
  - Larger lesions (>2-3cm)
- In case of HCC as a bridge to transplantation
- Combination with other LDTs is feasible!

Individual estimation of liver function
- Liver volume
- Lesion size and number
- Prior treatments
- Current liver function

Proton SBRT

- Maybe beneficial because lack of exit dose, sparing more liver tissue
- Interesting for HCC, but also for large LM or after surgery



- Uncertainties regarding dose delivery (different interfaces), target motion
- Early reports show high local control and low toxicity
- Phase I-III studies ongoing (NCT03186898)

Kang et al. J Gastrointest Oncol 2019
Hong et al. JCO 2016

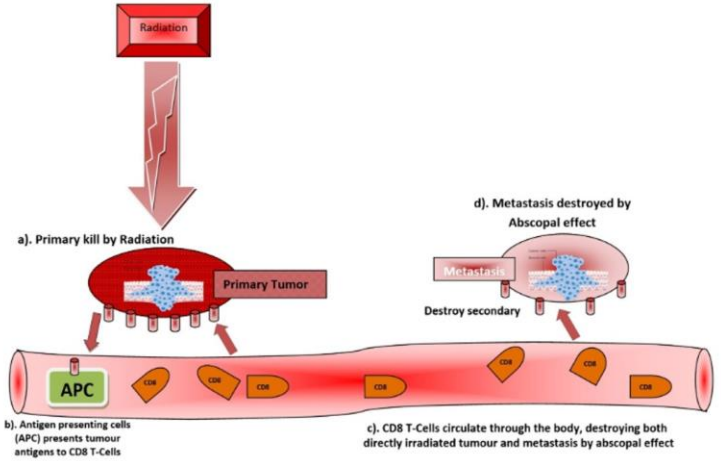
SBRT and immunotherapy

- Evolving field in case of **HCC** (inflammation-induced tumor)

  Either monotherapy or in combination with SBRT (combination of atezo/beva + SBRT seems safe)

- **Liver metastases**:
  - Lung cancer
  - Colon cancer

Triggering systemic cancer immune responses
Abscopal effect: T-lymphocyte mediated
Under investigation in clinical trials



Wani, Cureus 2019

Conclusion

- Resection of LM in selected patients can lead to 5y OS of 50%, but only 10-15% of patients are resectable
- RFA, MWA and SBRT are valuable options in unresectable LM or HCC

- SBRT might be a better option than RFA for lesions >2cm or nearby large vessels
- SBRT patients are usually heavily pretreated, biasing reported results.
- In view of OMD, localized therapies, including SBRT, will gain importance as they could improve OS, LC and QoL
  - SABR-COMET: mOS 41 vs. 28m (SBRT vs. SOC)
  - Randomized phase II/III trials ongoing
    - NCT03862911 (SABR-COMET-3); N=297; cf 2027
    - NCT03721341 (SABR-COMET-10); N=159; cf 2029
    - NCT02364557 (M+ breast cancer); N=402; cf 2027
    - NCT03137771 (M+ NSCLC); N=300; cf 2022
- Biomarkers are needed for patient selection
- Newer insights into tumor biology will potentially change the landscape of SBRT liver with dose adaptation and addition of immunotherapy