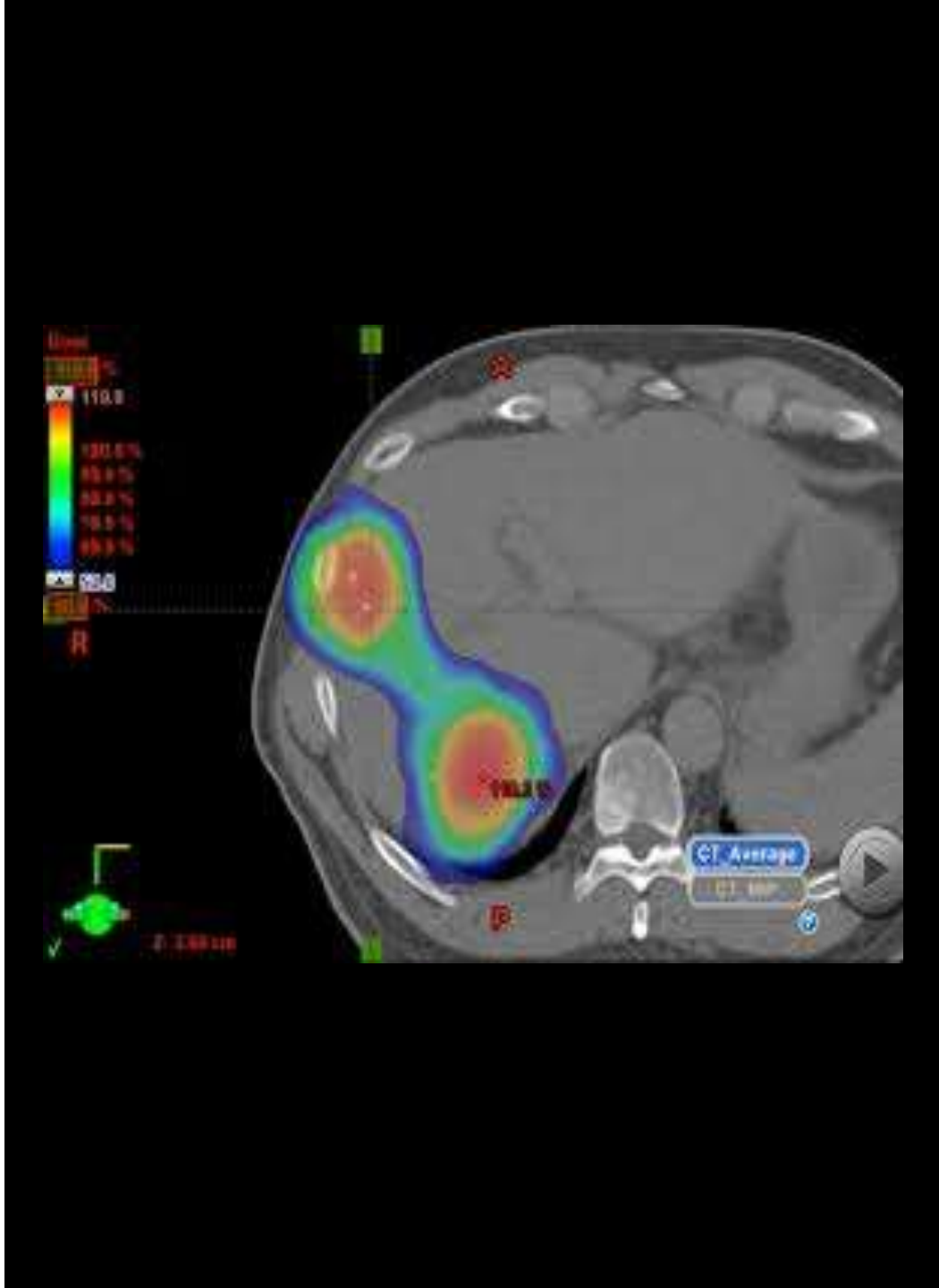
SBRT Liver Mets

Indications & Evidence



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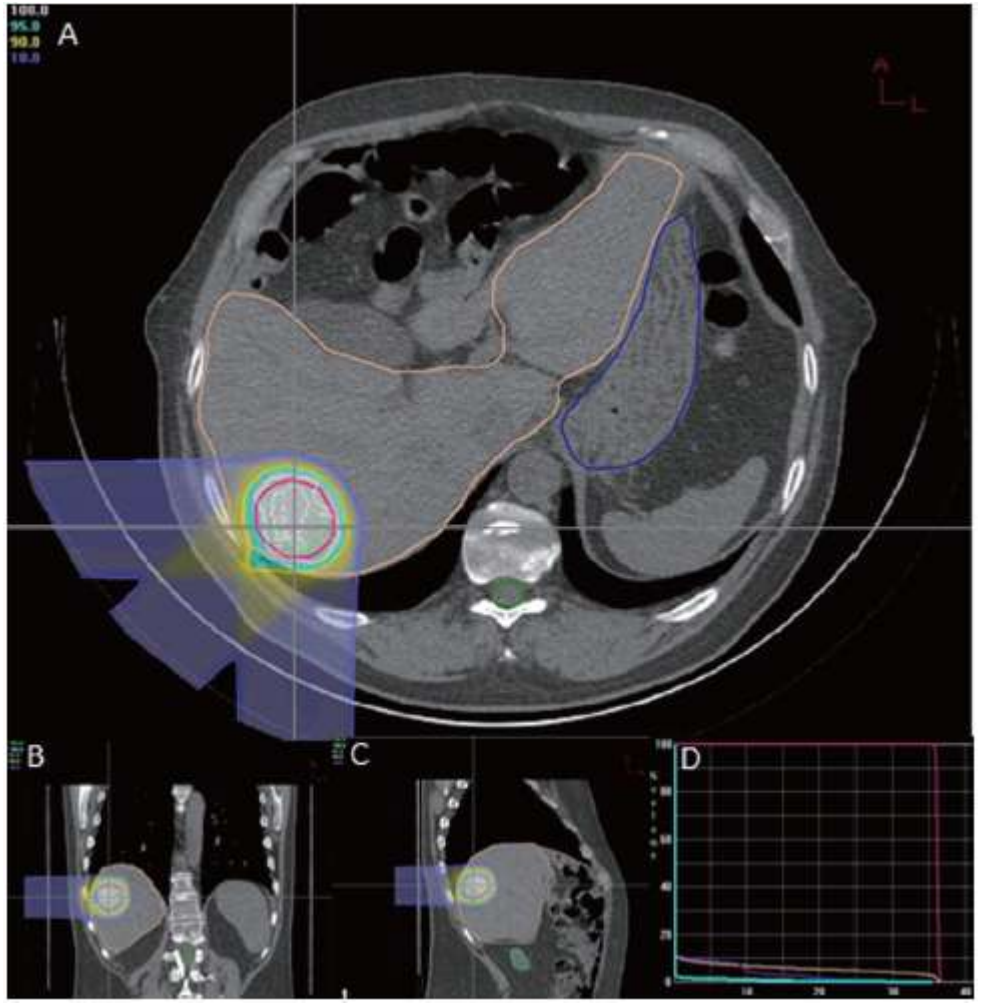
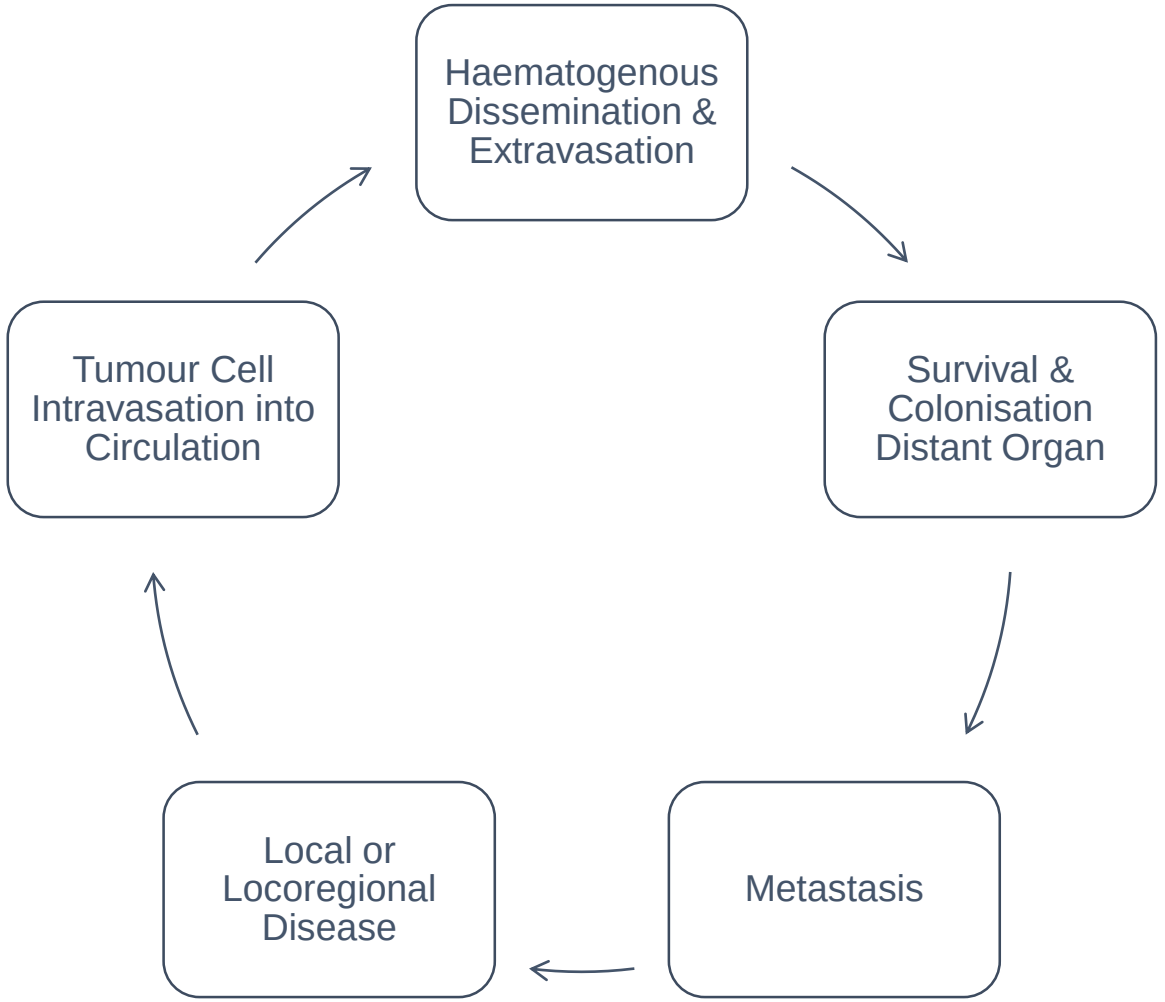
Learning objectives

- Oligometastases
- Concept of SBRT
- Radiobiology
- Indications of SBRT
- Available evidence



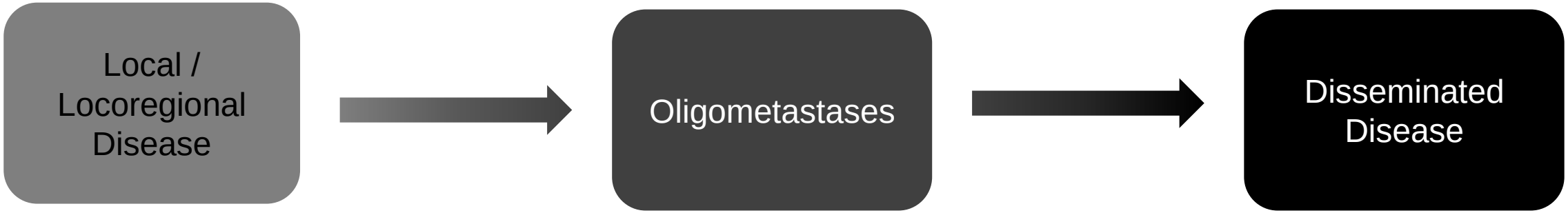
Spectrum of disease

Invasion-Metastasis Cascade



Valastyan et al, Cell 2011

Hellman & Weischelbaum 1995



> *“such patients may be amenable to a curative therapeutic strategy”*

Mode & Intent of Treatment

Curative Local/locoregional Treatment	Local / Locoregional Disease
Metastasis Directed Therapy :*curative*	Oligometastases
Palliative therapy -Systemic Agents	Disseminated Disease

Gomez et trial (ph II RCT for OM in NSCLC) - ≤ 3 lesions

Lancet Oncol. 2016 Dec;17(12):1672-1682

STOMP trial (ph II RCT for OM in Prostate Ca) - ≤ 3 lesions

J Clin Oncol. 2018 Feb 10;36(5):446-453

Iyengar et al trial (ph II RCT for OM in NSCLC) - ≤ 5 lesions

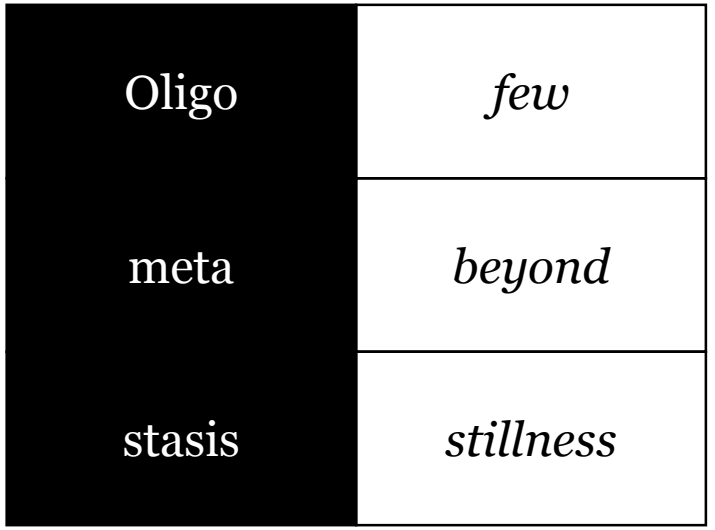
JAMA Oncol. 2018 Jan 11;4(1):e173501

SABR-COMET trial (ph II RCT for OM in NSCLC) - ≤ 5 lesions

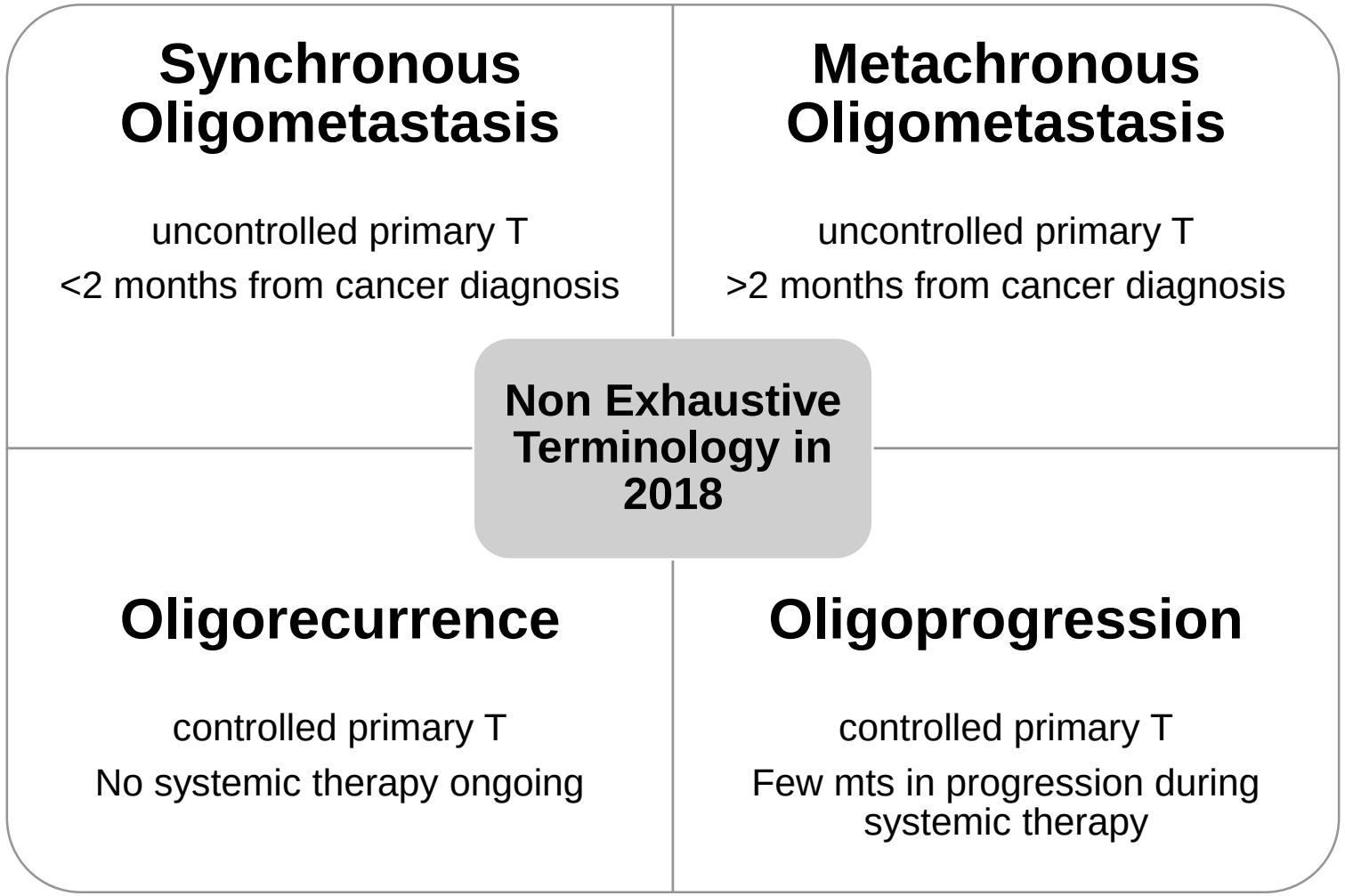
Lancet. 2019 May 18;393(10185):2051-2058

No consistent / official / scientific / tumour biological definition

Accepted definition is 1 – 5 metastasis, not organ specific



Non Exhaustive Terminology



ASTRo Annual refresher course 2018

Epidemiology of liver mets

Liver is a common site of metastases

- Primary from breast, GI, lung

In CRC, upto 50% patients have liver metastases as the only site of disease
25-30% patients progress to develop DM

Local radical treatment challenging due to

- Poor liver function
- Tumour location and progression
- Anatomical barriers
- Necessary to reserve Normal liver as recurrence common

Systemic therapy preferred

Goal

- Improve PFS and OS

Epidemiology of liver mets

Increasing incidence of OMD due to

More investigations in asymptomatic individuals during follow up

Routine use of PET CT for staging

In lung cancers, up-staging seen in upto 20% patients

Prognostic factors for OMD (Liver)

Patient related	Tumour related	Treatment related
Age	No. of lesions	Pre SBRT systemic therapy
	Size of lesions	
	Extrahepatic disease	
Performance score	Tumour marker levels	Surgical margins
	Stage of primary	
	Synchronous vs metachronous	
	Histology	

Metastasis Directed Therapy

Surgery

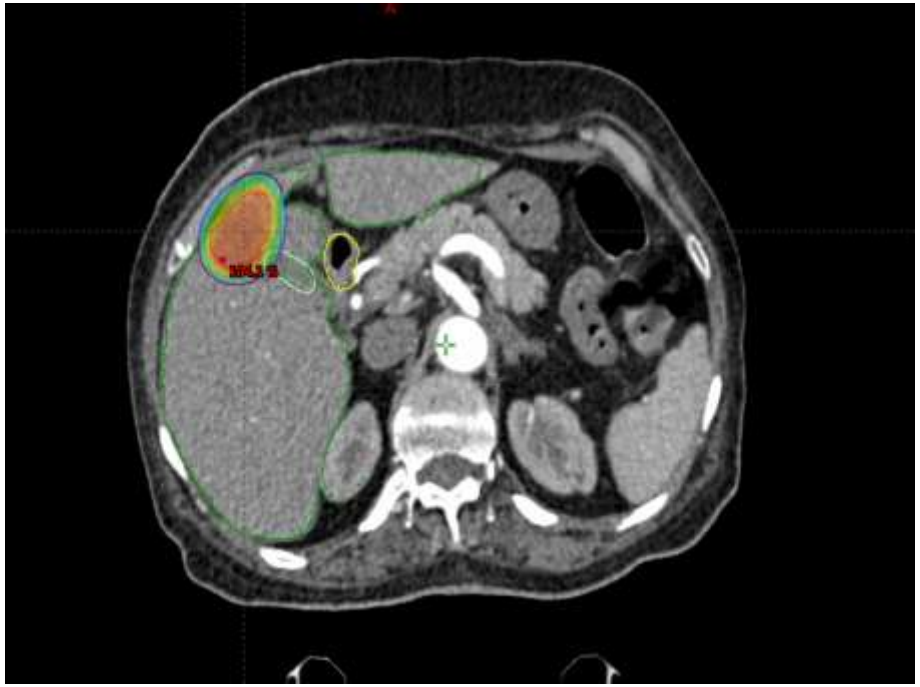
- Standard of care with improvement in OS correlates with Local control
- Fong et al reported outcomes in 1001 cases of liver mets
- OS at 10 & 20 years in the range of 20-26%
- However, surgery feasible in only 10-20% cases of liver mets
  - Poor PS
  - Comorbidities
  - Residual functional liver volume
  - Approximity to major vessels
- Leaving systemic therapy as the only option associated with significant toxicities.
- Even after downstaging of lesions, remain ineligible for surgery

Non surgical options

- Invasive
  - Radiofrequency ablation (RFA)
  - Micro-wave ablation (MWA)
  - Cryotherapy
  - Trans Arterial Chemoembolization (TACE)
  - Selective Internal Radiotherapy (SIRT)
  - High intensity focal ultrasound (HIFU)

- Non-Invasive
  - Stereotactic body radiotherapy (SBRT)

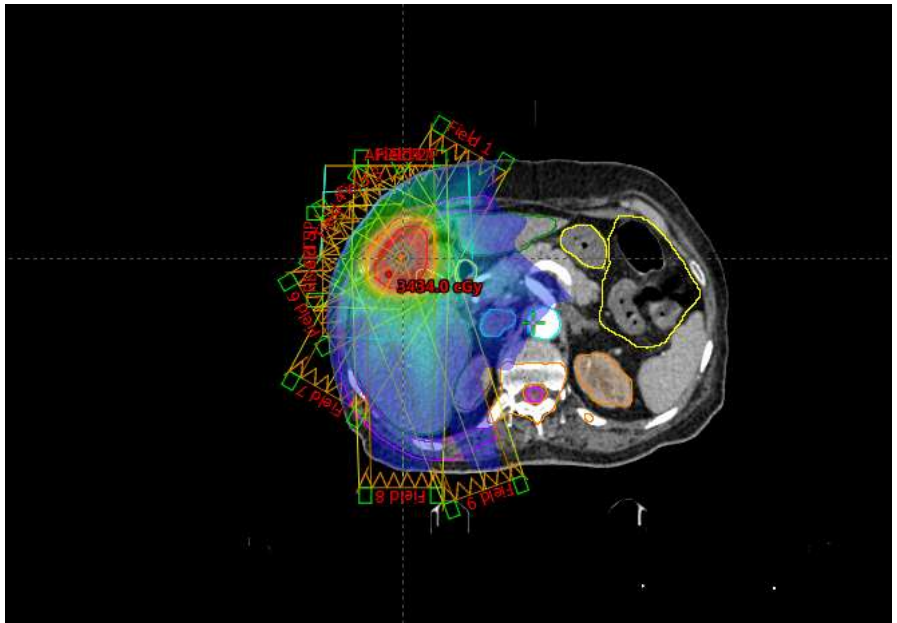
SBRT /SABR



> *Technique that delivers high dose of radiation in few fractions(1-6) to extracranial sites with high precision and steep dose gradients towards adjacent normal tissues*

Thus achieving maximal treatment efficacy

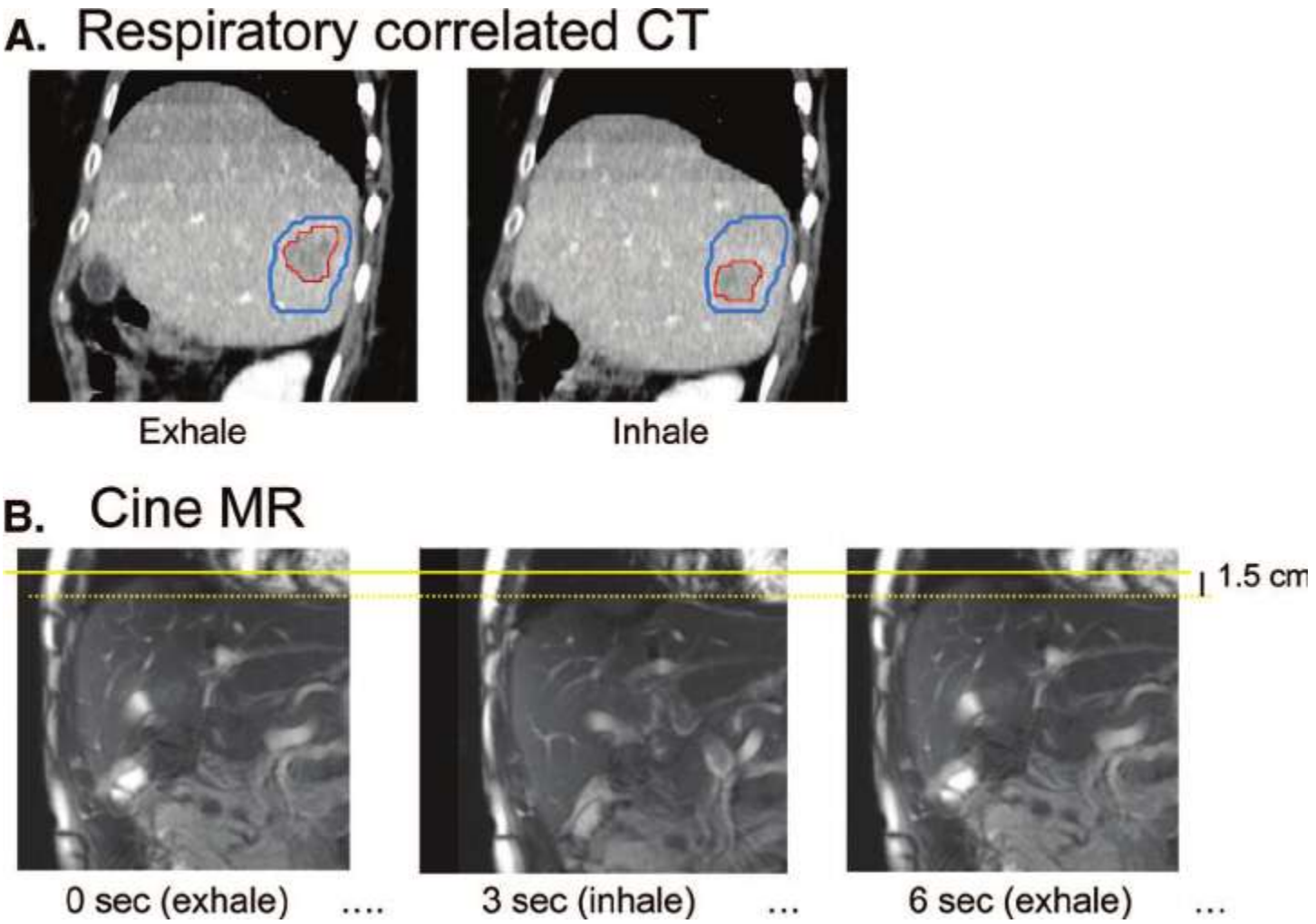
- Minimal treatment toxicity
- Better therapeutic ratio



More challenging than SRS

In delivering high dose with extra precision

- Uncertainties like respiratory motion
- Immobilise and localise target accurately and consistently
- Use a delivery system capable of creating highly conformal radiation



Why SBRT for liver mets ?

- Liver parallel structure with Central series anatomy
  - Inbuilt redundancy
  - certain fraction of the organ parenchyma can be sacrificed and the organ will maintain function
- Tolerance of whole liver with conventional techniques
  - Mean dose upto 30Gy
  - Non curative
- Delivery of ablative doses to large volumes of liver challenging
  - Risk of RILD
- RILD classical
  - Anicteric hepatomegaly
  - Ascites
  - Raised alk Po4 out of proportion as compared to transaminases
- Non classical RILD
  - Jaundice
  - Raised transaminase
- Advance in technology
  - Best of both worlds achievable

Radiobiology of SBRT

Treatment time in SBRT longer

- may lead to sub lethal damage repair in vitro cell lines
- Correction factor of 1.01-1.3 may be applied if the treatment lasts for approx. 25-30 min

LQ model not useful to calculate BED at larger dose per fraction, especially >=7Gy per fraction dose

- Underestimates the effect of fractionated radiation at high doses

Reoxygenation

- cause of discrepancy in cell kill response
- compensates for the SLDR, thus improving the cell kill
- More effectively seen in fractionated regimens as compared to single fraction
- Few cell lines may need >24 hrs for reoxygenation

Alternate day schedule or inter-fraction interval of 72 hrs recommended in 4-5 sessions SBRT

However, the reoxygenation in human tumours is still an investigational topic

Modes of Cell Kill with SBRT

Vascular damage at doses above 10Gy , leading to indirect cell kill

- Park et al, radiat res 2012

Anti-tumour immunity

- Radiation increases antigenicity of tumours
- Mostly seen at high dose per fraction
- Commonly seen in fractionated regimens as compared to single fraction

> *Shibamoto et al, J radiat Research 2016*

Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2014 February 1; 88(2): 254–262. doi:10.1016/j.ijrobp.2013.07.022.

The Tumor Radiobiology of SRS and SBRT: Are More than the 5 R's Involved?

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Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), are rapidly becoming accepted practice for the radiotherapy of certain tumors. Typically SRS and SBRT involve the delivery of one or a few large dose fractions of 8 to 30 Gy per fraction: a major paradigm shift from radiotherapy practice over the past 90 years when, with relatively large amounts of normal tissues receiving high doses, the goal was to maximize tumor response for an acceptable level of normal tissue injury. The development of SRS and SBRT have come about because of technological advances in image guidance and treatment delivery techniques that enable the delivery of large doses to tumors with reduced margins and high gradients outside of the target, thereby minimizing doses to surrounding normal tissues. Because the results obtained with SRS and SBRT have been impressive they have raised the question of whether classic radiobiological modeling, and the linear-quadratic (LQ) model, are appropriate for large doses per fraction. In addition to objections to the LQ model, the possibility of additional biological effects resulting from endothelial cell damage and/or enhanced tumor immunity, have been raised to account for the success of SRS and SBRT. In this review, we conclude that the available preclinical and clinical data do not support a need to change the LQ model nor invoke phenomena over and above the classic 5 R's of radiobiology/radiotherapy with the likely exception that for some tumors high doses of irradiation may produce enhanced antitumor immunity. Thus, we suggest that for most tumors the standard radiobiology concepts of the 5 R's are sufficient to explain the clinical data, and the excellent results obtained from clinical studies are the result of the much larger biologically effective doses (BEDs) that are delivered with SRS and SBRT.

Indications for SBRT Liver metastases

Primaries of solid tumours

With limited metastases (upto 5 lesions)

Liver only site of metastases (upto 3 lesions, <6cm)

Good PS(ECOG 0-1)

Adequate hepatic function(Child Pugh A&B)

Uninvolved liver >700ml

Contraindications of RFA

Unresectable liver metastases

Table 2. Contraindications to hepatic resection in patients with CRC liver metastases (adapted from Adam et al. [148] with permission from AlphaMed Press)

Category	Contraindication
Technical (A)	
1. Absolute	Impossibility of R0 resection with ≥30% liver remnant
	Presence of unresectable extrahepatic disease
2. Relative	R0 resection possible only with complex procedure (portal vein embolisation, two-stage hepatectomy, hepatectomy combined with ablation[a])
	R1 resection
Oncological (B)	
1.	Concomitant extrahepatic disease (unresectable)
2.	Number of lesions ≥5
3.	Tumour progression

Patients should be categorised as A1 or A2/B1, B2 or B3.

[a]All methods, including radiofrequency ablation.

“There is an art to case selection for SBRT, but for easier job, the guidelines are

Good Candidates for SBRT	Poor Candidates for SBRT
1–3 liver lesions	5 or more liver lesions
Liver lesions <5 cm	Liver lesions >8 cm
Good liver function	Child’s C cirrhosis
Controlled extra-hepatic disease	Life-limiting extra-hepatic disease
Total liver size >1,000 cc	Liver size <800 cc
Relative or absolute contraindication to surgery or RFA	Broad interface between metastasis and bowel
	Good candidate for potentially curative surgery

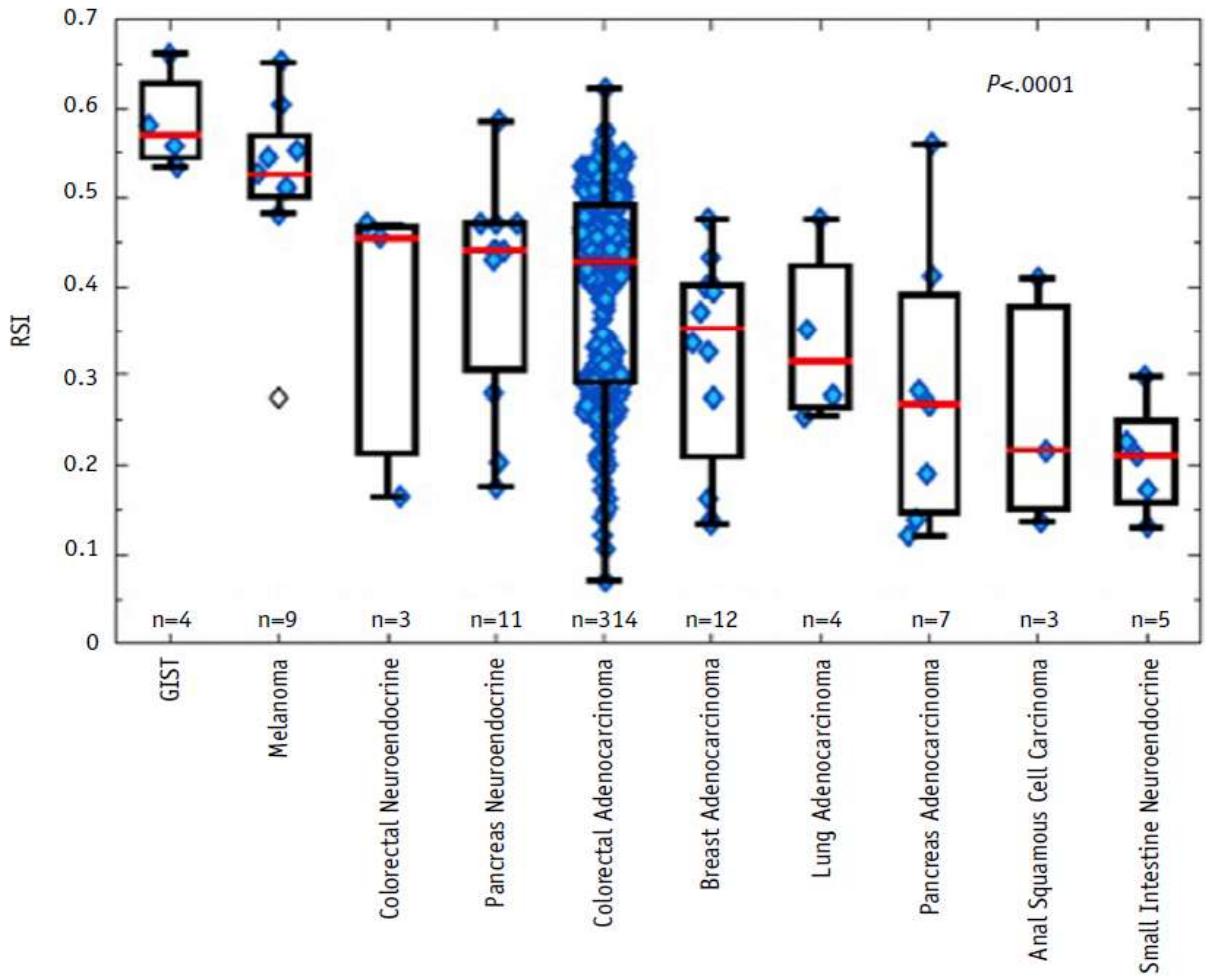
Pocinho et al, 2012, gastrointestinal cancer

Factors affecting outcomes post SBRT

- Dose of RT , BED
- Size of lesions
- Histology of primary
  - CRC mets fare poorer as compared to breast, lung, anal canal
  - Liver mets more radioresistant than lung mets
- Presence of extrahepatic disease
- Previous systemic therapy
- PET CT (SUV values)

Ahmed et al, IJROBP 2016
Mazzola et al, Br J radiol, 2018

Histology based radio sensitivity



Ahmed et al, IJROBP 2016

Evidence /literature review

Single fraction SBRT

Extrapolated from results of SRS for brain

First prospective results from single fraction SBRT :university of heidelburg

37 pts with 52 lesions

Dose escalated 14-26Gy

LC at 18 months:67%

- 14-20Gy v/s 22-26Gy (LR 81% v/s 0%)

LC was better for those treated late in the study

- Learning curve
- More appropriate expansions applied

Trend towards fractionated approach due to potential toxicity of GI structures

Another phase I dose escalation single fraction SABR 35Gy and 40Gy

- Lesions outside the central zone
- 2cm expansion around course of portal vein contoured to its bifurcation in liver

Local control was 100% with a median follow up of 2.5 years

No grade 3 or higher toxicity

4 patients developed biliary stenosis, managed conservatively

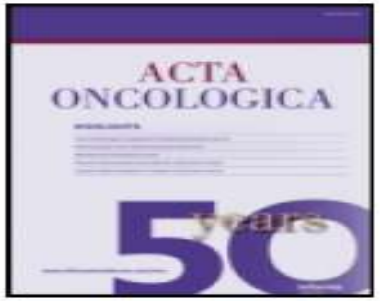
2 year OS 78%, no treatment related death reported

Structure	Constraint
Uninvolved liver	700 mL receives <9.1 Gy
Spinal cord	<0.35 mL exceeds 10 Gy
	<1.2 mL exceeds 7 Gy
	Maximum allowed point dose[a]: 14 Gy
Stomach	<10 mL exceeds 11.2 Gy
	Maximum allowed point dose: 12.4 Gy
Duodenum	<5 mL exceeds 11.2 Gy
	<10 mL exceeds 9 Gy
	Maximum allowed point dose: 12.4 Gy
Jejunum/ileum	<5 mL exceed 11.9 Gy
	Maximum allowed point dose: 15.4 Gy
Colon	<20 mL exceed 14.3 Gy
	Maximum allowed point dose: 18.4 Gy
Skin	<10 mL exceed 23 Gy
	Maximum allowed point dose: 26 Gy

[a] Point dose = 0.035 mL

Jefferey et al, Ann Surg Oncol 2016

Fractionated SBRT



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Stereotactic High Dose Fraction Radiation Therapy of Extracranial Tumors Using An Accelerator: Clinical experience of the first thirty-one patients

Henric Blomgren, Ingmar Lax, Ingemar Näslund & Rut Svanström

- 31 patients, 14 with liver mets, SBRT body frame used (1991-95)
- 7.7-45Gy in 1-4 fractions
- LC in 80%, tumour regression in 50% within 3-16 mths
- Bias in response evaluation due to confusing radiological changes
- SRT is safe, convenient and effective

Mahadevan *et al. Radiation Oncology* (2018) 13:26
https://doi.org/10.1186/s13014-018-0969-2

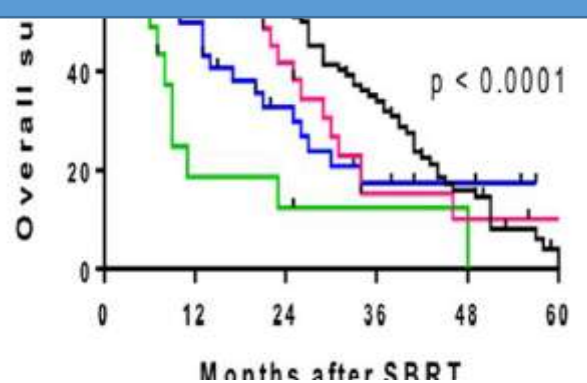
Radiation Oncology

RESEARCH Open Access

Stereotactic Body Radiotherapy (SBRT) for liver metastasis – clinical outcomes from the international multi-institutional RSSearch® Patient Registry

Anand Mahadevan[1*], Oliver Blanck[2,3], Rachelle Lanciano[4], Anuj Peddada[5], Srinath Sundararaman[6], David D'Ambrosio[7], Sanjeev Sharma[8], David Perry[9], James Kolker[10] and Joanne Davis[11]

Median OS as per tumour vol
- 25mths(<40cm3) vs 15 mths(>40cm3)
- p=0.0014
- 27 mths vs 15 mths as per BED>100Gy
- p<0.0001



No effect of systemic therapy on survival
No effect of histology on LC
No grade 3 or higher toxicity reported

Median LC and OS:52 months and 22 months resp

Local Control After Stereotactic Body Radiation Therapy for Liver Tumors

Nitin Ohri, MD[*], Wolfgang A. Tomé, PhD[*], Alejandra Méndez Romero, MD[†], Moyed Miften, PhD[‡], Randall K. Ten Haken, PhD[§], Laura A. Dawson, MD[‖], Jimm Grimm, PhD[¶], Ellen Yorke, PhD[#], and Andrew Jackson, PhD[#]

Results: Thirteen articles met all inclusion criteria and formed the dataset for this analysis. The 1-, 2-, and 3-year actuarial local control rates after SBRT for primary liver tumors (n = 431) were 93%, 89%, and 86%, respectively. Lower 1- (90%), 2- (79%), and 3-year (76%) actuarial local control rates were observed for liver metastases (n = 290, logerank $P = .011$). Among patients treated with SBRT for primary liver tumors, there was no evidence that local control is influenced by BED within the range of schedules used. For liver metastases, on the other hand, outcomes were significantly better for lesions treated with BEDs exceeding 100 Gy_{10} (3-year local control 93%) than for those treated with BEDs of 100 Gy_{10} (3-year local control 65%, $P < .001$).

Total 649 patients(721 lesions)
394 lesions (290pts mets) 6 studies

First author (country) (reference)	Disease	Sample size	SBRT schedule	Prescription point/volume	Median (range) follow-up
Dewas (France) (17)	HCC	42 patients,* 48 lesions*	Median 45 Gy, 3 fx	PTV (80% IDL)	15 mo
Honda (Japan) (26)	HCC	30 patients*	Median 48 Gy, 4 fx	Isocenter	12 (6–38) mo
Jang (Korea) (24)	HCC	82 patients, 95 lesions	<45 Gy, 3fx(n = 11) 45–54 Gy, 3 fx (n = 47) >54 Gy, 3 fx (n = 57)	PTV (70–80% IDL)	30 (4–81) mo
Kwon (Korea) (18)	HCC	42 patients	Median 33 Gy, 3 fx	PTV (70–85% IDL)	29 (8–49) mo
Sanuki (Japan) (25)	HCC	185 patients	35 Gy, 5 fx (n = 48) 40 Gy, 5 fx (n = 137)	PTV (70–80% IDL)	25† (3–80) mo
Barney (United States) (19)	CCA	9 patients,* 10 lesions*	45–60 Gy, 3–5 fx	NR	14 (2–26) mo
Kopek (Denmark) (23)	CCA	27 patients	45 Gy, 3 fx	Isocenter	5.4 (2.3–8.6) y
Mendez Romero (The Netherlands) (20)	Mets (82% CRC)	17 patients,* 34 lesions*	Median 37.5 Gy, 3 fx	PTV (65% IDL)	13 (1–31) mo
Rusthoven (United States) (27)	Mets (32% CRC, 21% lung)	36 patients,* 49 lesions*	60 Gy, 3 fx	PTV (80–90% IDL)	16 (6–54) mo
Scorsetti (Italy) (28)	Mets (48% CRC)	61 patients, 76 lesions	75 Gy, 3 fx	PTV	12 (2–26) mo
Stintzing (Germany) (21)	Mets (100% CRC)	30 patients, 35 lesions	24–26 Gy, 1 fx	70% IDL	35 (6–96) mo
Vautravers-Dewas (France) (22)	Mets (67% CRC)	42 patients, 62 lesions	40 Gy, 4 fx (n = 29) 45 Gy, 3 fx (n = 16)	80% IDL	14 (2–23) mo
Wulf (Germany) (29)	Mets (45% CRC)	39 patients, 51 lesions	Median 30 Gy, 3 fx (n = 25) Median 37.5 Gy, 3 fx (n = 26)	PTV (65% IDL)	15 (2–85) mo

Ohri et al, IJROBP 2019

Overall 56% CRC mets

Dose range 24-60 Gy (1-5 fractions)

Median BED 88Gy(72-125Gy)

Median FU 14 mths 9(IQR 8-23 mths)

Actuarial LC at 1, 2 and 3 yrs: 90, 79 and 76%

BED depedent LC

- BED >100Gy vs BED <100Gy (p=0.011)
- 1 yr : 96% vs 84%
- 2 yr: 93% vs 70%
- 3 yr:93% vs 65%

2 yr LC inc from 76%(BED 100Gy) to 90%(BED 180Gy)

Ohri et al, IJROBP 2019

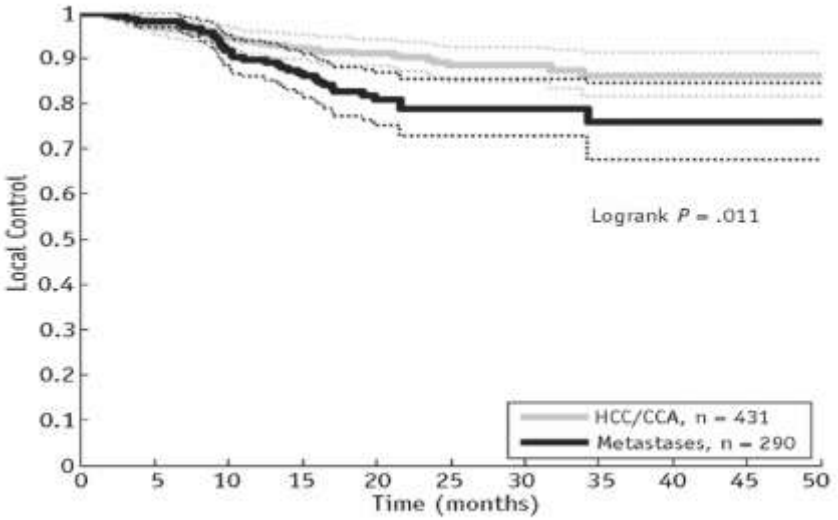
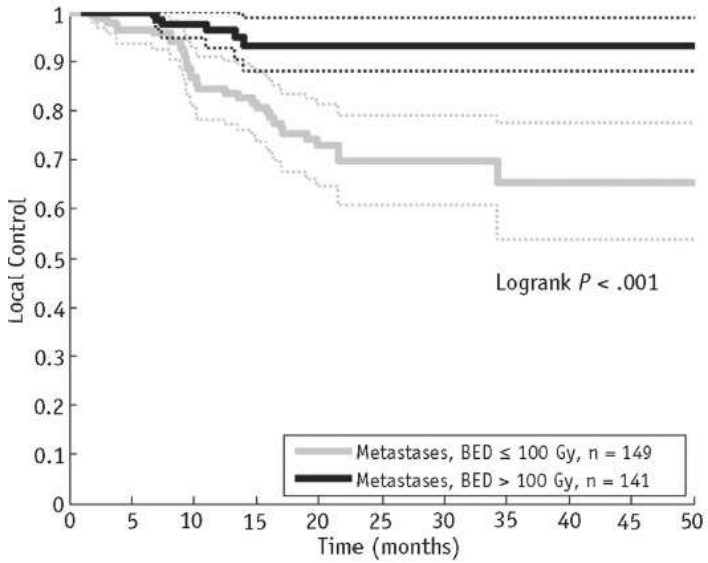
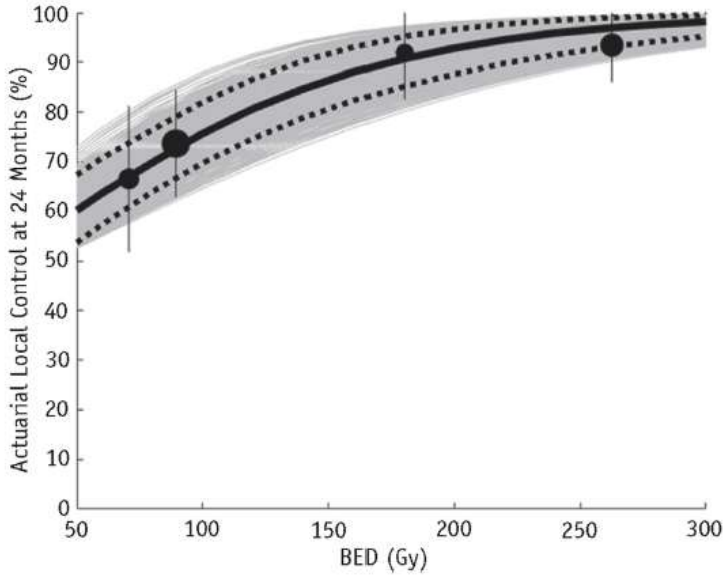


Fig. 1.
Kaplan-Meier curves for local control of primary and metastatic liver tumors after





Ohri et al, IJROBP 2019

Dose Escalation

VOLUME 27 · NUMBER 10 · APRIL 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

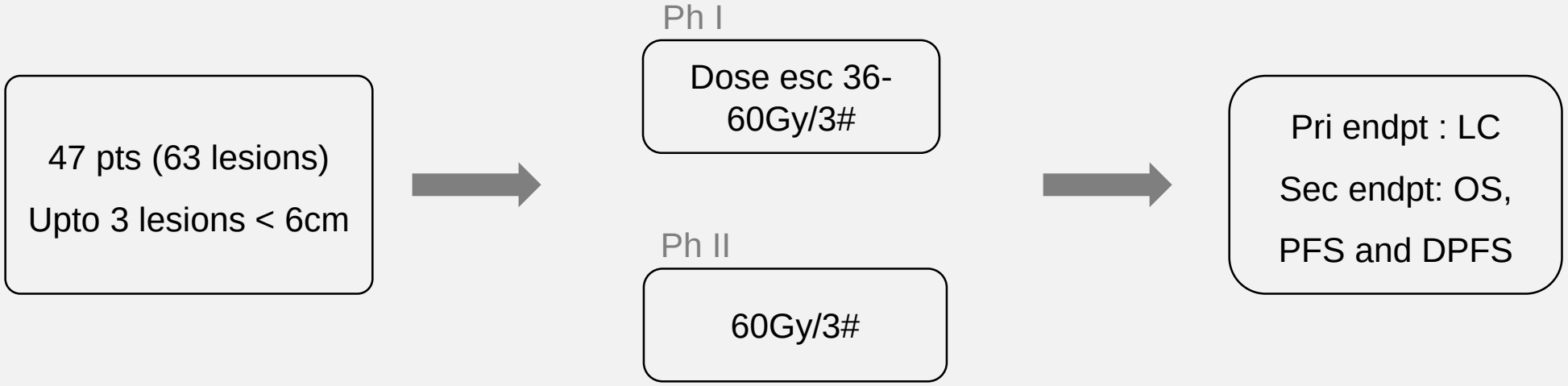
Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases

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

From the University of Colorado—Denver, Departments of Radiation Oncology, Pathology, and Medical

ABSTRACT

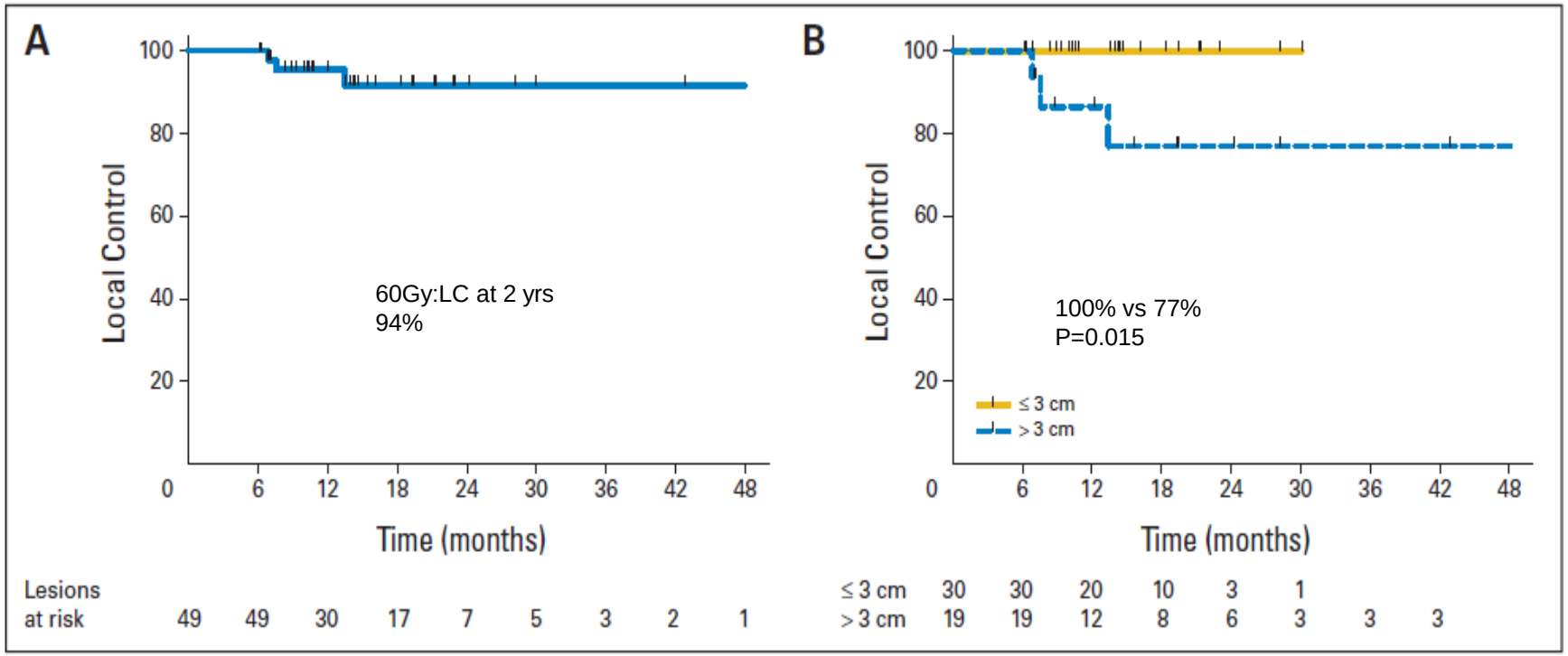
Ph I/II pros RCT(dose escalation)

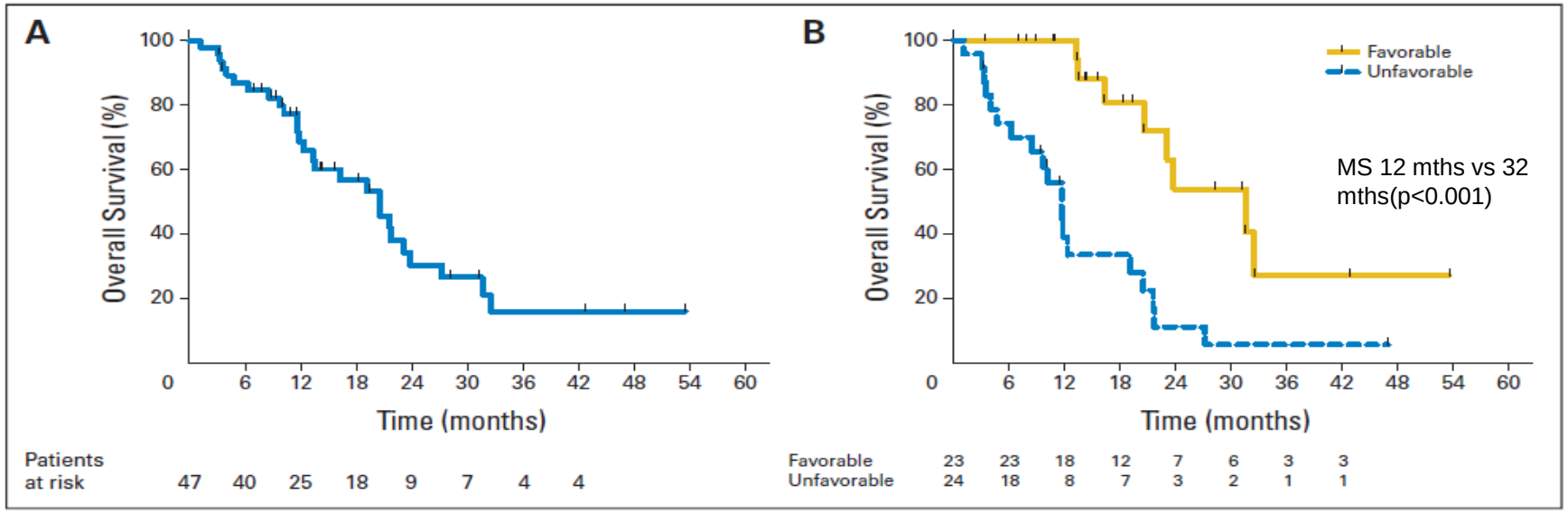


Med FU:27 mths

In field LC at 1yr & 2 yr: 95% &92% resp,

LR 3 pts at mFU 7.5mths





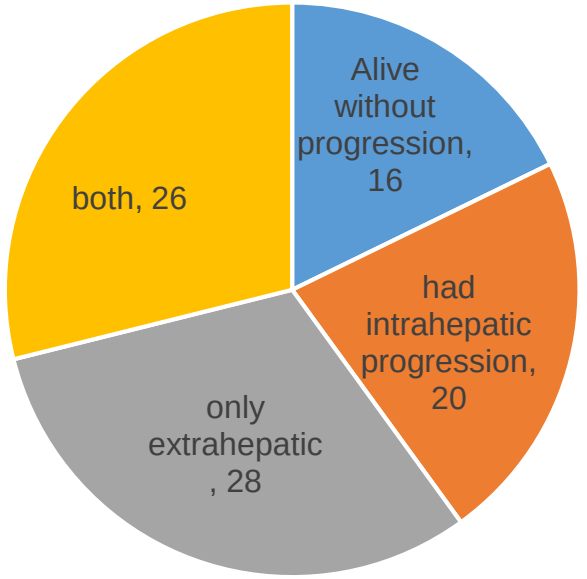
Median OS and OS at 2 years :20.5mths and 30% resp

RESEARCH Open Access

Phase II trial on SBRT for unresectable liver metastases: long-term outcome and prognostic factors of survival after 5 years of follow-up

Marta Scorsetti[1,2], Tiziana Comito[1], Elena Clerici[1], Ciro Franzese[1], Angelo Tozzi[1], Cristina Iftode[1], Lucia Di Brina[1], Pierina Navarria[1], Pietro Mancosu[1], Giacomo Reggiori[1], Antonella Fogliata[1], Stefano Tomatis[1], Guido Torzilli[2,3] and Luca Cozzi[1,2,4*]

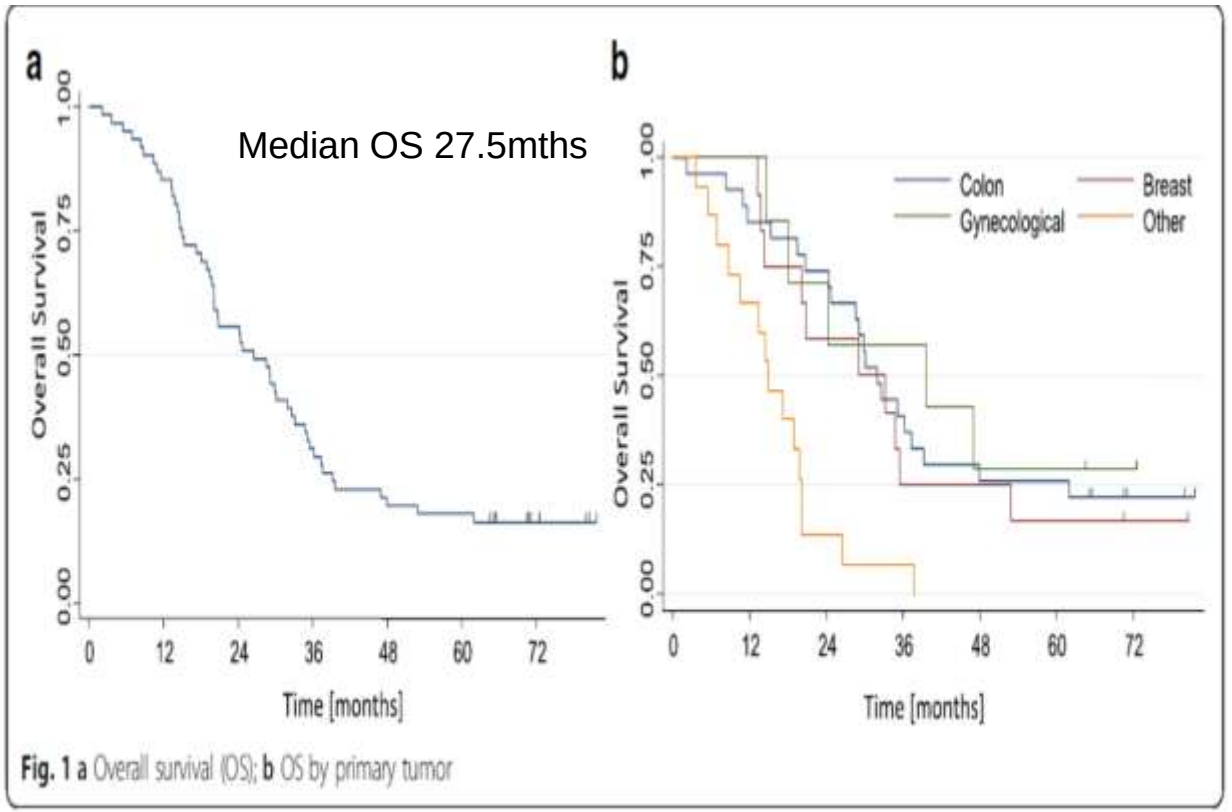
Gender							
Male	35	20.6 ± 6.9	11.8 ± 5.5	0.01	78.1 ± 4.3	78.1 ± 5.4	0.97
Female	26	44.4 ± 9.6	25.9 ± 8.4		81.8 ± 4.1	81.8 ± 5.4	
Cancer type							
Colorectal	29	41.1 ± 7.5	27.3 ± 8.1	< 0.001	75.3 ± 4.7	75.3 ± 5.7	0.47
Breast cancer	11	33.0 ± 7.3	20.1 ± 6.9		86.8 ± 4.8	86.8 ± 5.7	
Gynecological cancer	7	56.8 ± 6.9	27.8 ± 7.3		86.1 ± 4.7	86.1 ± 5.6	
Other	14	10.2 ± 7.2	–		80.0 ± 4.4	–	
Number of metastases							
1	48	42.8 ± 13.2	28.6 ± 12.1	0.22	82.0 ± 4.5	82.0 ± 5.4	0.28
2–3	13	27.7 ± 6.5	14.9 ± 5.2		67.3 ± 4.7	67.3 ± 5.6	
Size of metastases							
< 3 cm	32	28.1 ± 7.9	15.6 ± 6.4	0.46	77.2 ± 4.3	77.2 ± 5.5	0.60
> 3 cm	29	34.4 ± 8.8	20.7 ± 7.5		81.9 ± 4.3	81.9 ± 5.9	
Timing of metastasis							
Synchronous	24	29.3 ± 6.5	17.0 ± 5.5	0.93	–		–
Metachronous	37	32.2 ± 8.1	19.3 ± 6.9				
Time since diagnosis, mo							
≤ 12	35	31.4 ± 7.8	17.1 ± 6.4	0.91	–		–
> 12	26	30.8 ± 9.0	19.2 ± 7.7				
Prior local therapy							
Yes	27	33.3 ± 9.1	11.1 ± 6.1	0.54	65.8 ± 4.6	66.7 ± 5.7	0.06
No	34	29.4 ± 7.8	23.5 ± 7.3		87.1 ± 4.8	87.1 ± 5.8	
Pre-SBRT chemotherapy							
0–1 schedule	23	43.5 ± 10.3	30.4 ± 9.6	0.10	–		–
2–3-4 schedules	38	23.7 ± 6.9	10.5 ± 5.0				
Extrahepatic disease							
Yes	21	33.3 ± 10.3	14.3 ± 7.6	0.88	–		–
No	40	30.0 ± 7.1	20.0 ± 6.3				



61 pts with 76 lesions, feb 2010 to sep 2011

Prescription dose

- 75 Gy/ 3 fractions (Full dose) 82%
- 67.5 Gy/ 3 fractions (Reduction of 10%) 08%
- 60 Gy/ 3 fractions (Reduction of 20%) 05%
- 52.5 Gy/ 3 fractions (Reduction of 30%) 05



OS was independent of lesion size 1 vs 2-3 lesions NS diff , prior chemo aso no impact on OS

LC median not reached, mean LC 74.8mths, breast and gyb 85% at 5 yr, CRC 75%

Clinical and Translational Radiation Oncology 20 (2020) 45–50

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Original Research Article

High versus low dose Stereotactic Body Radiation Therapy for hepatic metastases

Esther N.D. Kok [a,*], Edwin P.M. Jansen [b], Birthe C. Heeres [c], Niels F.M. Kok [a], Tomas Janssen [b], Erik van Werkhoven [d], Fay R.K. Sanders [e], Theodore J.M. Ruers [a,f], Marlies E. Nowee [b,1], Koert F.D. Kuhlmann [a,1]

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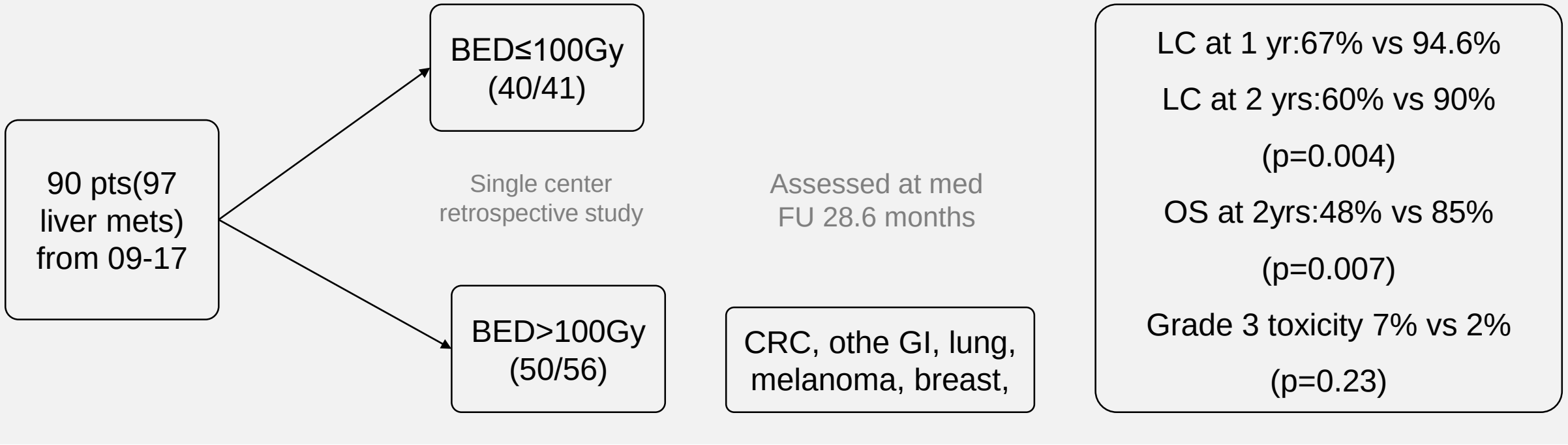
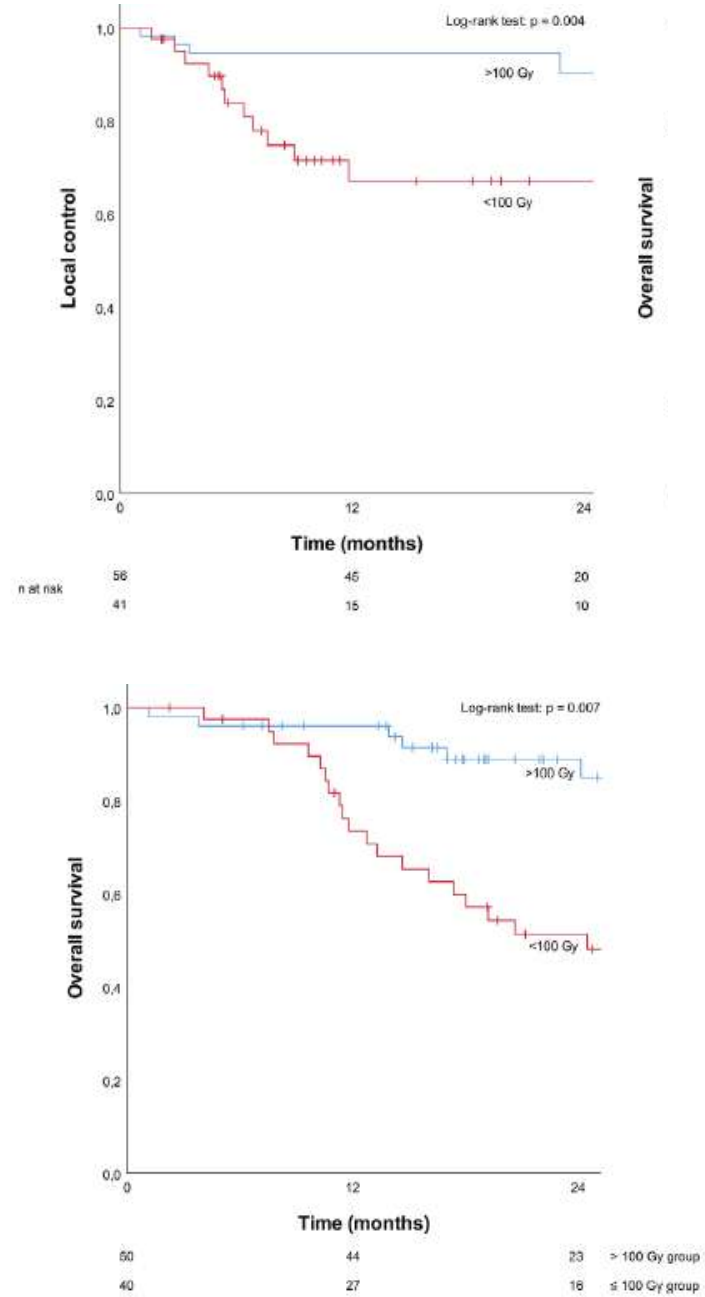
High dose vs low dose



> *On multivariate analysis, dose in BED and tumour volume(GTV) significantly correlated with LC(HR 3.61 and 1.01 resp) and OS(HR 2.38 and 1.01 resp)*

Univariable and multivariable analyses for local control and overall survival.

	Local control			Overall survival		
	HR	95% CI	P-value	HR	95% CI	P-value
Univariate analysis						
Group dose (≤100 Gy vs. >100 Gy)	4.20	1.47 – 11.98	0.007	2.67	1.34 – 5.33	0.005
Age at treatment (continues)	1.00	0.95 – 1.05	0.99	1.00	0.97 – 1.04	0.80
Primary tumor (CRC vs. other)	2.09	0.48 – 9.17	0.33	0.76	0.37 – 1.55	0.45
Extrahepatic disease (present vs. absent)	0.91	0.32 – 2.57	0.85	1.16	0.58 – 2.30	0.67
Prior chemotherapy (Yes vs. no)	1.49	0.55 – 4.02	0.43	1.04	0.54 – 1.99	0.91
GTV (cm^3)	1.02	1.01 – 1.03	0.001	1.02	1.01 – 1.02	<0.001
$BED_{98\%}$ (Gy) per 10 Gy	0.90	0.78 – 0.95	0.013	0.90	0.84 – 0.99	<0.001
$BED_{2\%}$ (Gy) per 10 Gy	0.94	0.85 – 0.97	0.029	0.95	0.91 – 0.99	0.012
Relative near-min. PTV dose	0.99	0.97 – 1.01	0.20	0.99	0.90 – 1.01	0.27
Infield recurrence[a]				3.55	1.77 – 7.13	<0.001
Multivariate analysis						
Group dose (≤100 Gy vs. >100 Gy)	3.61	1.25 – 10.40	0.017	2.38	1.16 – 4.90	0.005
Age at treatment (continues)						
Primary tumor (CRC vs. other)						
Extra hepatic disease (present vs. absent)						
Prior chemotherapy (Yes vs. no)						
GTV (cm^3)	1.01	1.00 – 1.02	0.005	1.01	1.01 – 1.02	<0.0001
$BED_{98\%}$ (Gy) per 10 Gy						
$BED_{2\%}$ (Gy) per 10 Gy						
Relative near-min. PTV dose						



LC affects OS

EORTC 40004 (CLOCC trial)

Klement et al studied outcome with SBRT for liver and lung mets in 500 CRC patients

- After 10 months of LC, the importance of local failure leading to death was more common
- Hence suggesting the transition of improved Local control into survival benefit

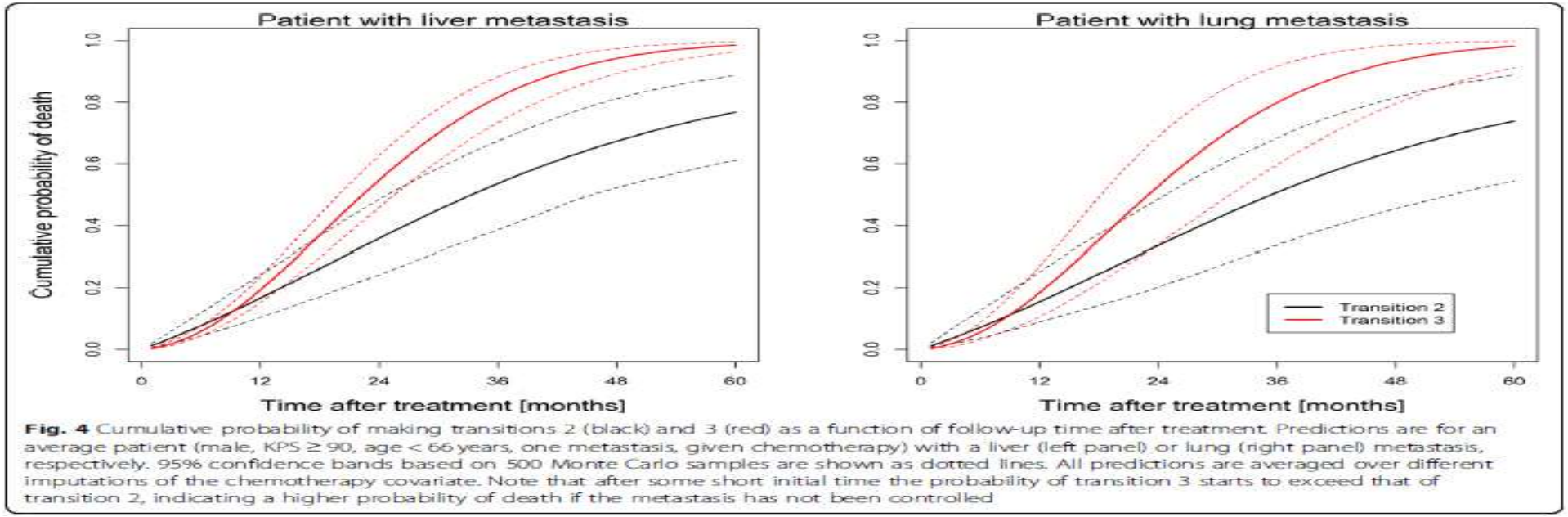


Fig. 4 Cumulative probability of making transitions 2 (black) and 3 (red) as a function of follow-up time after treatment. Predictions are for an average patient (male, KPS ≥ 90, age < 66 years, one metastasis, given chemotherapy) with a liver (left panel) or lung (right panel) metastasis, respectively. 95% confidence bands based on 500 Monte Carlo samples are shown as dotted lines. All predictions are averaged over different imputations of the chemotherapy covariate. Note that after some short initial time the probability of transition 3 starts to exceed that of transition 2, indicating a higher probability of death if the metastasis has not been controlled

rapid communications

Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial

David A. Palma, MD, PhD[1]; Robert Olson, MD, MSc[2]; Stephen Harrow, MBChB, PhD[3]; Stewart Gaede, PhD[1]; Alexander V. Louie, MD, PhD[4]; Cornelis Haasbeek, MD, PhD[5]; Liam Mulroy, MD[6]; Michael Lock, MD[1]; George B. Rodrigues, MD, PhD[1]; Brian P. Yaremko, MD, PEng[1]; Devin Schellenberg, MD[7]; Belal Ahmad, MD[1]; Sashendra Senthi, MD, PhD[8]; Anand Swaminath, MD[9]; Neil Kopek, MD[10]; Mitchell Liu, MD[11]; Karen Moore, MSc[3]; Suzanne Currie, MSc[3]; Roel Schlijper, MD[2]; Glenn S. Bauman, MD[1]; Joanna Laba, MD[1]; X. Melody Qu, MD, MPH[1]; Andrew Warner, MSc[1]; and Suresh Senan, MBBS, PhD[5]

Open label Ph II randomised study(1:2), 1-5 mets

99 pts from 2010 to 2016(10 institutes)

Breast, lung, CRC:18 each and prostate 16

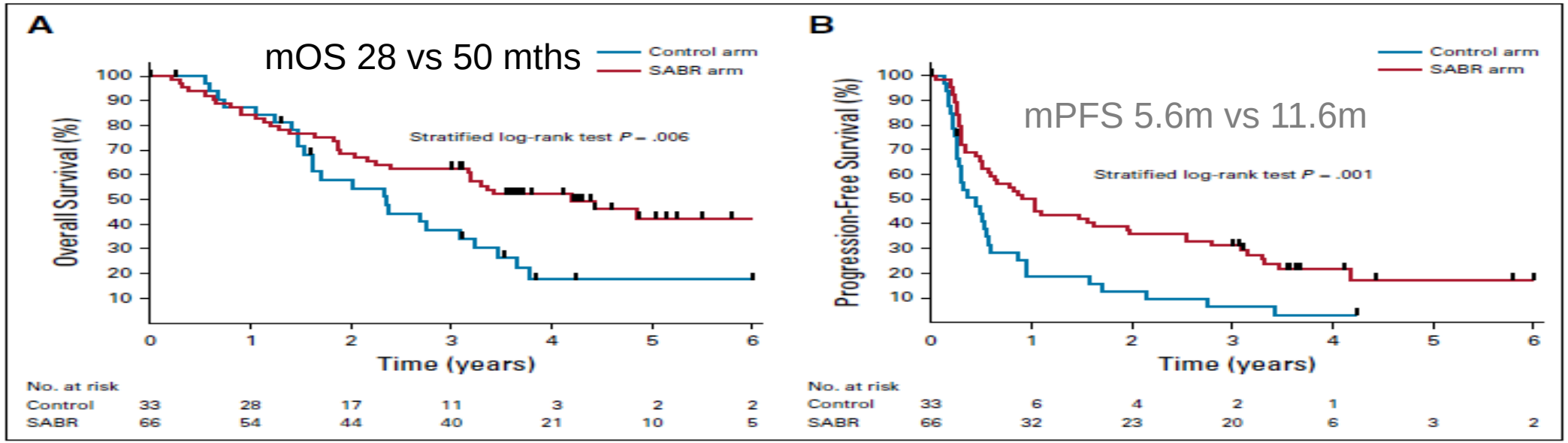
SOC (arm 1, 33) vs SOC & SABR(arm 2, 66)

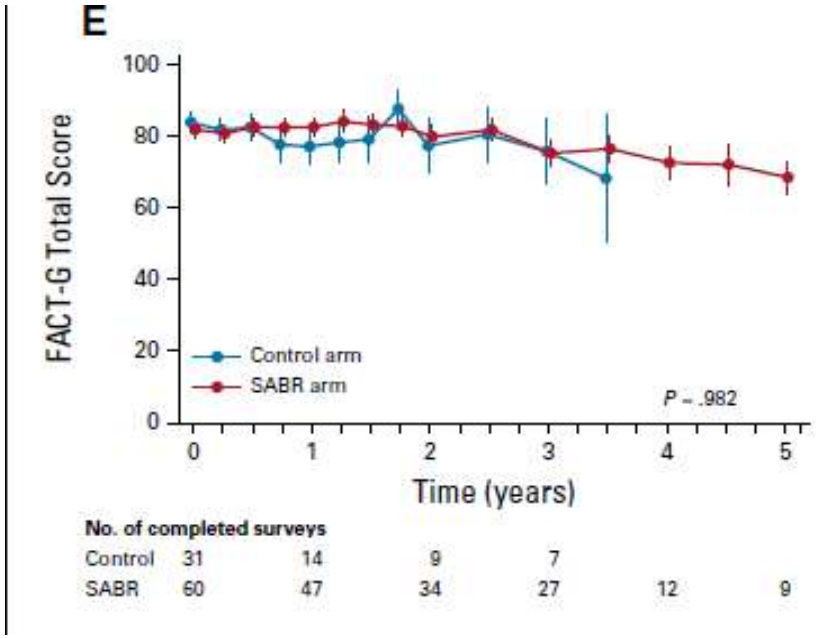
Med FU 51 mths

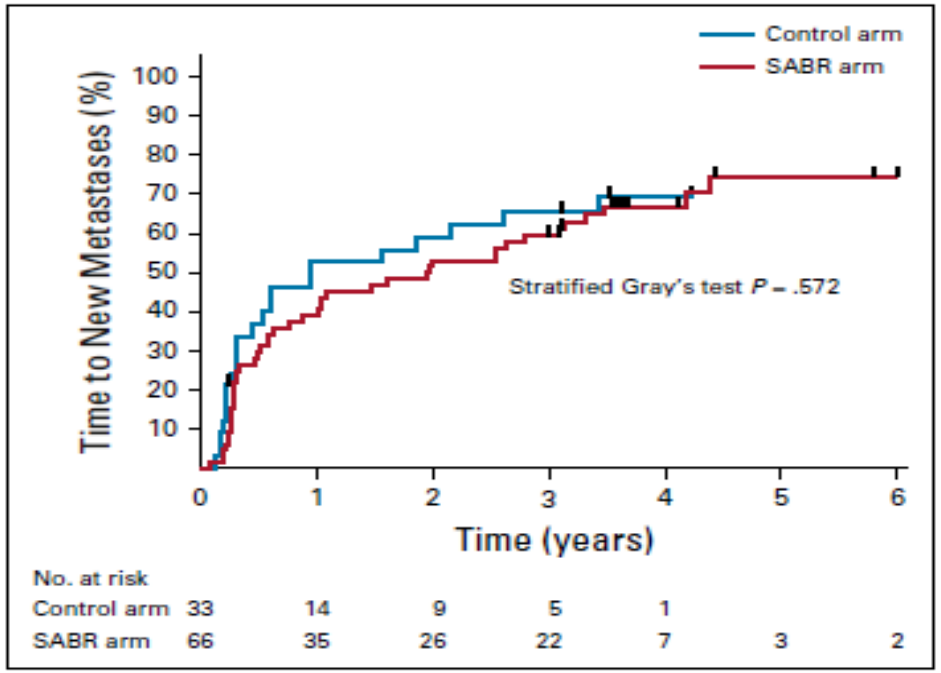
Primary endpt: 5 yr OS:17.7 vs 42.3% (p=0.085)

Sec endpts,

- PFS, Toxicity, QOL,
- 30% of those alive at 5 years required another SABR for new mets


A
mOS 28 vs 50 mths
Control arm
SABR arm
Overall Survival (%)
Stratified log-rank test P = .006
Time (years)
No. at risk
Control 33 28 17 11 3 2 2
SABR 66 54 44 40 21 10 5
B
Control arm
SABR arm
mPFS 5.6m vs 11.6m
Progression-Free Survival (%)
Stratified log-rank test P = .001
Time (years)
No. at risk
Control 33 6 4 2 1
SABR 66 32 23 20 6 3 2


E
FACT-G Total Score
Control arm
SABR arm
P = .982
Time (years)
No. of completed surveys
Control 31 14 9 7
SABR 60 47 34 27 12 9


Control arm
SABR arm
Time to New Metastases (%)
Stratified Gray's test P = .572
Time (years)
No. at risk
Control arm 33 14 9 5 1
SABR arm 66 35 26 22 7 3 2

SBRT v/s Other Local Therapies

MWA vs SBRT

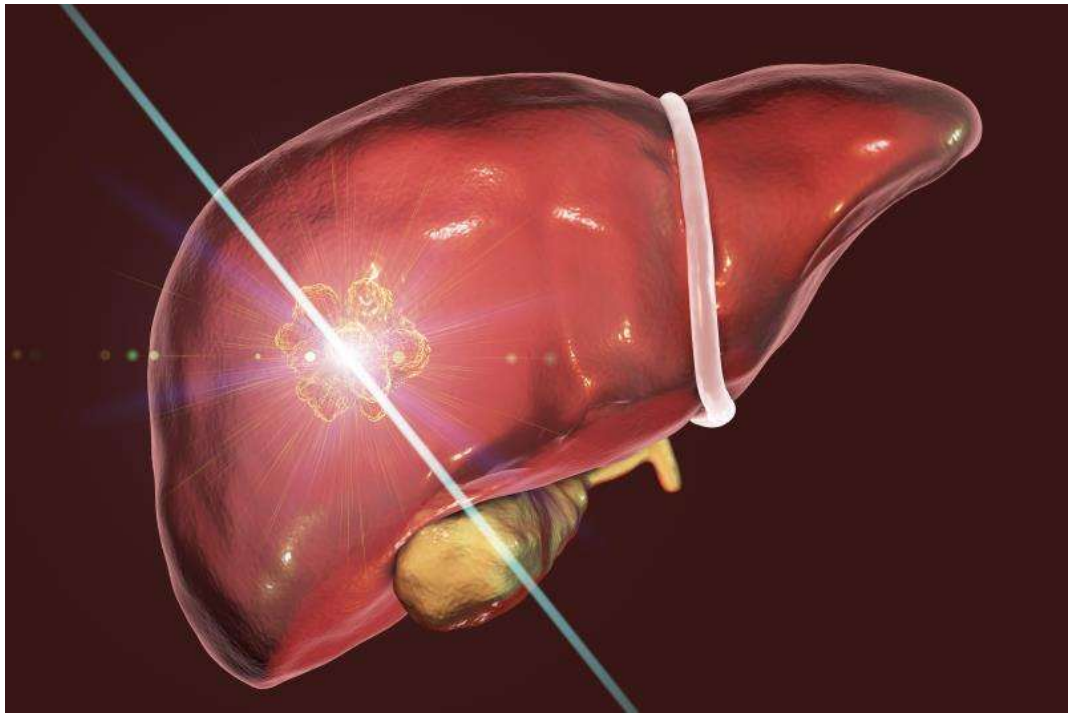
Retrospective comparison of SBRT vs MWA for 135 patients

FFLP at 1 year , better with SBRT

Duration of FFLP longer with SBRT

SBRT beneficial over MWA , especially for lesions >3cm

> *Franzese et al, Clin Oncol 2018*



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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**[*]

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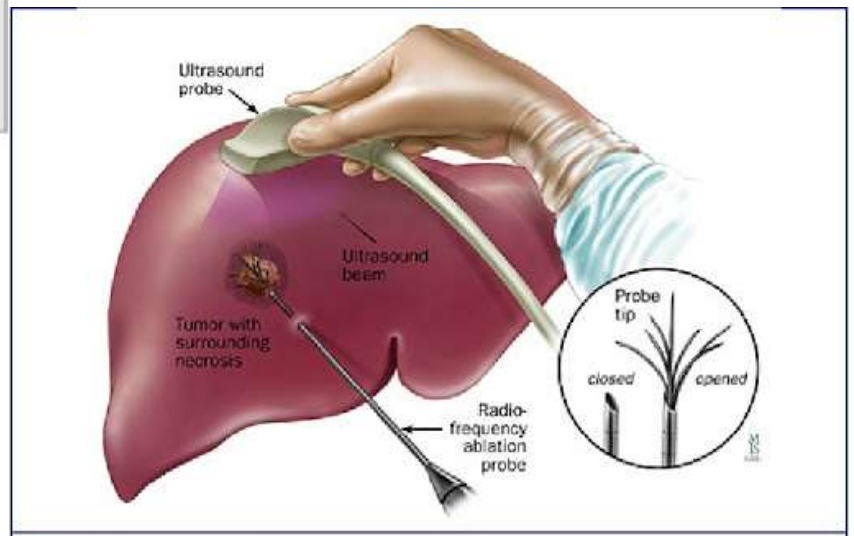


Figure 15. Radiofrequency ablation (RFA) in hepatocellular carcinoma.

For pts with limited no. of mets, SBRT and RFA have shown good results with local recc<20%
Proven excellent LC with RFA and SBRT for HCC <2cm, SBRT better for larger HCC lesions

M.C histology CRC, Pancreatobiliary

	RFA	SBRT
Sample	(69 pts, 112 lesions)	(92 pts, 170 lesions)
Size of lesion	IQR 1.2-2.5cm	IQR 1.8-4.0cm Median dose 50Gy/5# (BED > 80Gy)
FFLP at 1 and 2 years (P=0.057)	74.7% and 60.6%	96% and 88.2%
Extrahepatic and intrahepatic progression (P>0.1)	64%	58%
Median OS	25.9 months	24.5 months

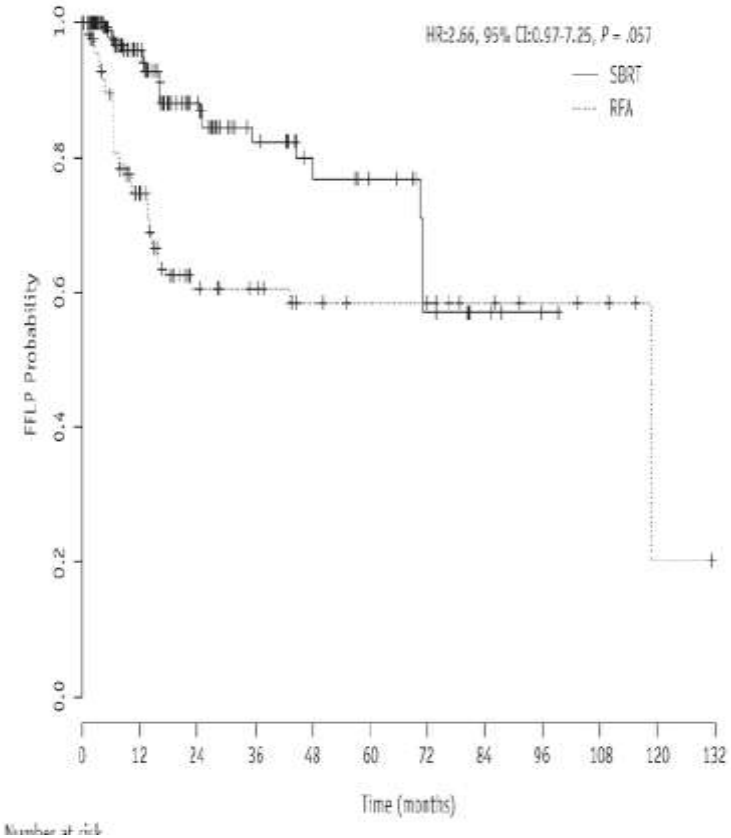
lesions close to vessels/biliary structure/hollow viscera

50Gy/5#, 60Gy/3#,30-45Gy/5#, 24-54Gy/3#

Most of the patients had received >1 liver directed therapy

Univariate analysis of variables predictive of local progression

Variable	All lesions HR	All lesions 95% CI	All lesions *P* value	RFA HR	RFA 95% CI	RFA *P* value	SBRT HR	SBRT 95% CI	SBRT *P* value
Treatment: RFA vs SBRT	2.66	0.97–7.25	.057		-			-	
Age	1.06	1.01–1.10	.018	1.09	1.06–1.14	<.001	1.03	0.93–1.15	.562
Tumor size	1.57	1.15–2.14	004	1.95	1.05–3.62	.035	1.38	0.76–2.51	.294
	2.42	0.21–27.8	.480	4.94	0.57–43.1	.147	0.92	0.03–27.7	.960
	0.56	0.18–1.82	.340	0.17	0.03–1.11	.064	2.50	0.25–24.7	.430
	0.96	0.77–1.18	.670	0.63	0.31–1.28	.201	1.45	0.85–2.47	.171
	1.08	0.60–1.92	.801	0.92	0.74–1.14	.428	1.36	0.66–2.77	.406
		-			-		0.98	0.86–1.12	.749



Multivariate Cox proportional hazards analysis of factors associated with local progression

	HR	95% CI	*P* value
Treatment: RFA vs SBRT	4.75	1.60–14.1	.005
Age (per year)	1.05	1.00–1.11	.053
Tumor size (per centimeter)	1.53	1.10–2.14	.011
ECOG score (≥2 vs < 2)	1.69	0.24–10.6	.638
Histology (colon and/or rectal adenocarcinoma vs other)	0.65	0.20–2.11	.470

RRS vs RFA

- Retrospective study , Matched Pair Design
- Colorectal Mets
- RFA v/s Robotic Radiosurgery for CRLM from 2005-2011
- No extrahepatic disease at the time of treatment
- Heavily pre-treated with chemotherapy(72%) and liver sx(57%)

Taylor & Francis

Acta Oncologica

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Percutaneous radiofrequency ablation (RFA) or robotic radiosurgery (RRS) for salvage treatment of colorectal liver metastases

Sebastian Stintzing, Alexander Grothe, Saskia Hendrich, Ralf-Thorsten Hoffmann, Volker Heinemann, Markus Rentsch, Christoph Fuerweger, Alexander Muacevic & Christoph G. Trumm

	RFA	RRS
Sample	(30 pts, 35lesions)	(30 pts, 35 lesions) 24-26Gy
Med Size of lesion	33mm	34mm
LC at 1 and 2 years (P=0.057)	65% and 61% (P NS)	85% and 80%
Local DFS	6.1 months (P<0.001) mFFDR 7 months (P=0.25)	34.4 months mFFDR 11.4 months
Median OS	34.4 months (P=0.06)	52.3 months

lesions close to vessels/liver capsule, patient's wish

Med FU 23.3mths

RRS favoured for lesion>3cm in last 2 yrs of study

Dose regimens

- MECC registry suggests dose prescription as per tuour location
  - Lesion >2cm from porta hepatis:20Gy*3#
  - Lesion <2cm from porta hepatis: 10Gy*5#

- Dose escalation studies have shown dose fractionation of 75Gy/3# is safe and provides better LC
- Radio-resistant histologies should be treated with higher BED dose regimens

Dose Constraints

Organ	Dose constraints
Liver-GTV (normal liver)	700mL ≤ 15Gy Dmean <15Gy
Stomach /Duodenum	Dmax <30Gy(D5mL <22.5Gy)
Bowel	Dmax<30Gy
Esophagus	Dmax ≤27Gy D1mL <21Gy
Kidneys (both)	D35% <15Gy
Spinal Cord	Dmax<18-20Gy
Heart	D1mL <30Gy
Chest wall/soft tissue	V30Gy <30cc
Lungs	<1000cc rec ≥11.4Gy
Skin	Max point dose 24Gy

QUANTEC data

Toxicity post SBRT

Risk of RILD is very low

Grade 1-2 is common, grade 3 or more very uncommon

M.c fatigue, cytopenia, dermatitis, rib fractures, nausea, diarrhoea

Depend on dose and volume of treatment, site of lesion,

Hepatic:

- Transient rise in liver enzymes within 3 months post RT

Uncommon events

- Duodenal/colonic ulcer/perforation:<10% in various studies(those received >30Gy in 3#)
- Use of VEGF inhibitor with SBRT inc GI toxicity
- Asymptomatic bile duct stenosis(hepatic hilar lesions)
- Soft tissue toxicity/dermatitis:self limiting
- Non traumatic rib fractures

> *Sawrie et al, cancer control 2010*

Response Assessment

Assessment of tumour response post SBRT may be challenging due to post radiation changes

On follow up CT scan, local control is seen as

- Distinct contrast enhancement
- Shrinkage of hypodensity
- Displacement of vessels

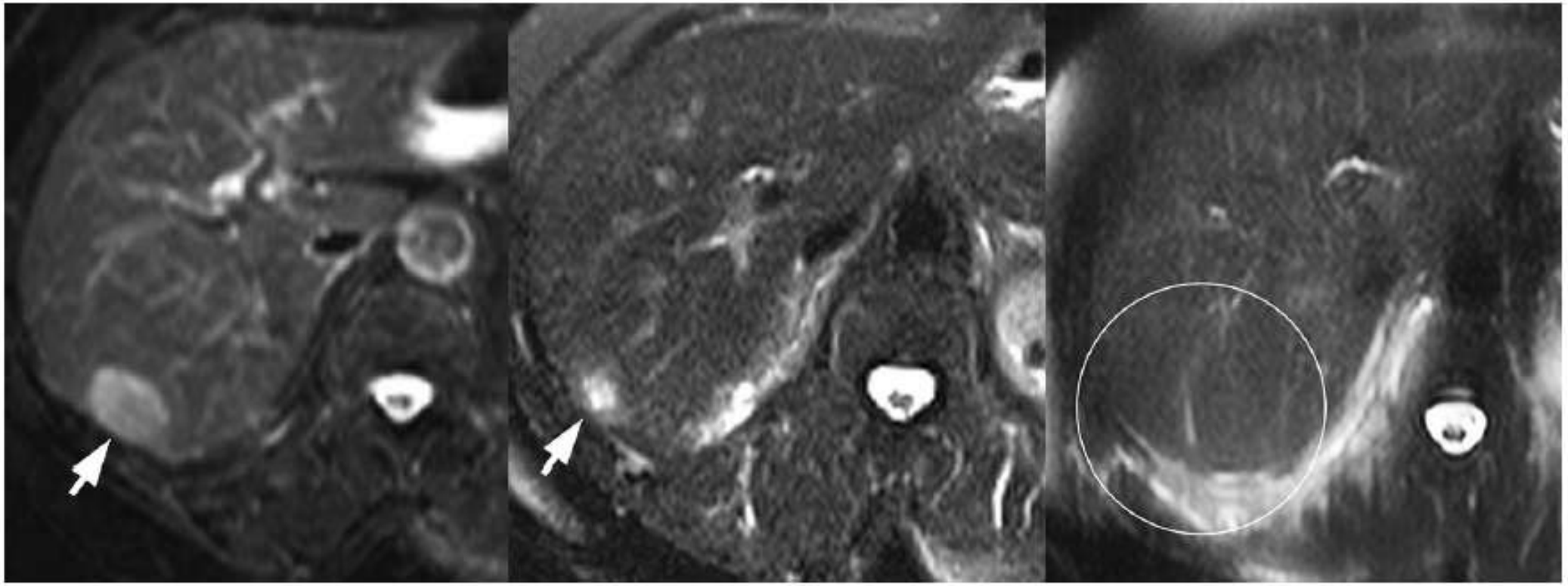
MRI can be a better option, especially T2 sequence to reportchanges post SBRT

PET CT can help with SUV values

- Nadir upto SUV max 3.1 (corresponds to normal liver) seen in CR
- SUV max >6 may sugest local recurrence/progression

> *Mazzola et al, Br J Radiol, 2018*

Evolution of Lesion on MRI after SBRT



Pre SBRT

1 month post SBRT

6 months post SBRT

SBRT with Immunotherapy

Abscopal effect

Ab scopus Latin away from the target

Described by Mole in 1953

Additional regression of tumour burden in non irradiated sites after local irradiation

Analog to *distant bystander effect*

Potentially important therapeutic opportunity in the era of advances in immunotherapy

SBRT with Immunotherapy

Abscopal effect(Mole et al, 1950)

- Regression or disappearance of lesion, outside the irradiated field

Radio-resistance usually occurs through programmed death ligand-1 (PD-L1) upregulation after radiation

Indirect effect on T4 lymphocytes

Local RT wth systemic PD-L1 blockade augment T cell responses not only in local region but also at distant sites

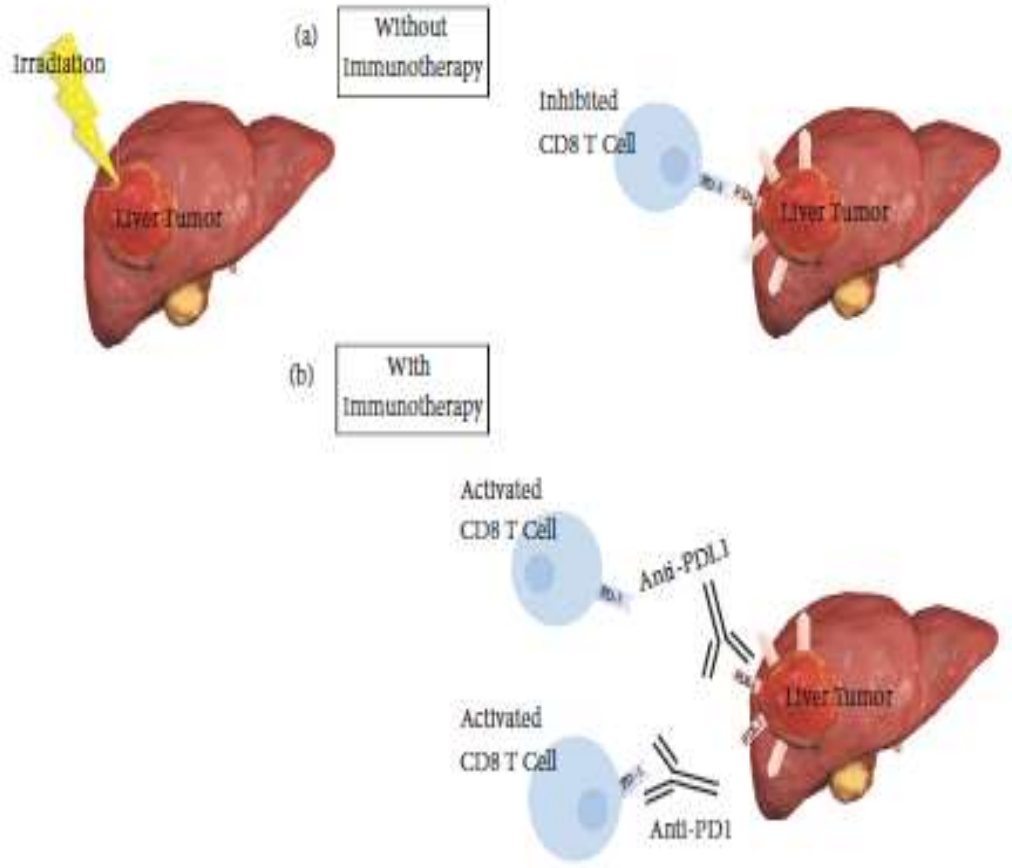
- Rarely seen with RT alone
- seen in mice with primaries like melanoma, CRC,RCC and breast

Anti cytotoxic T-cell mediated protein 4 (CTLA-4) ipilimumab for melanoma and lung cancer

Timing of delivering immuno-modulators with respect to RT is also a topic of investigation

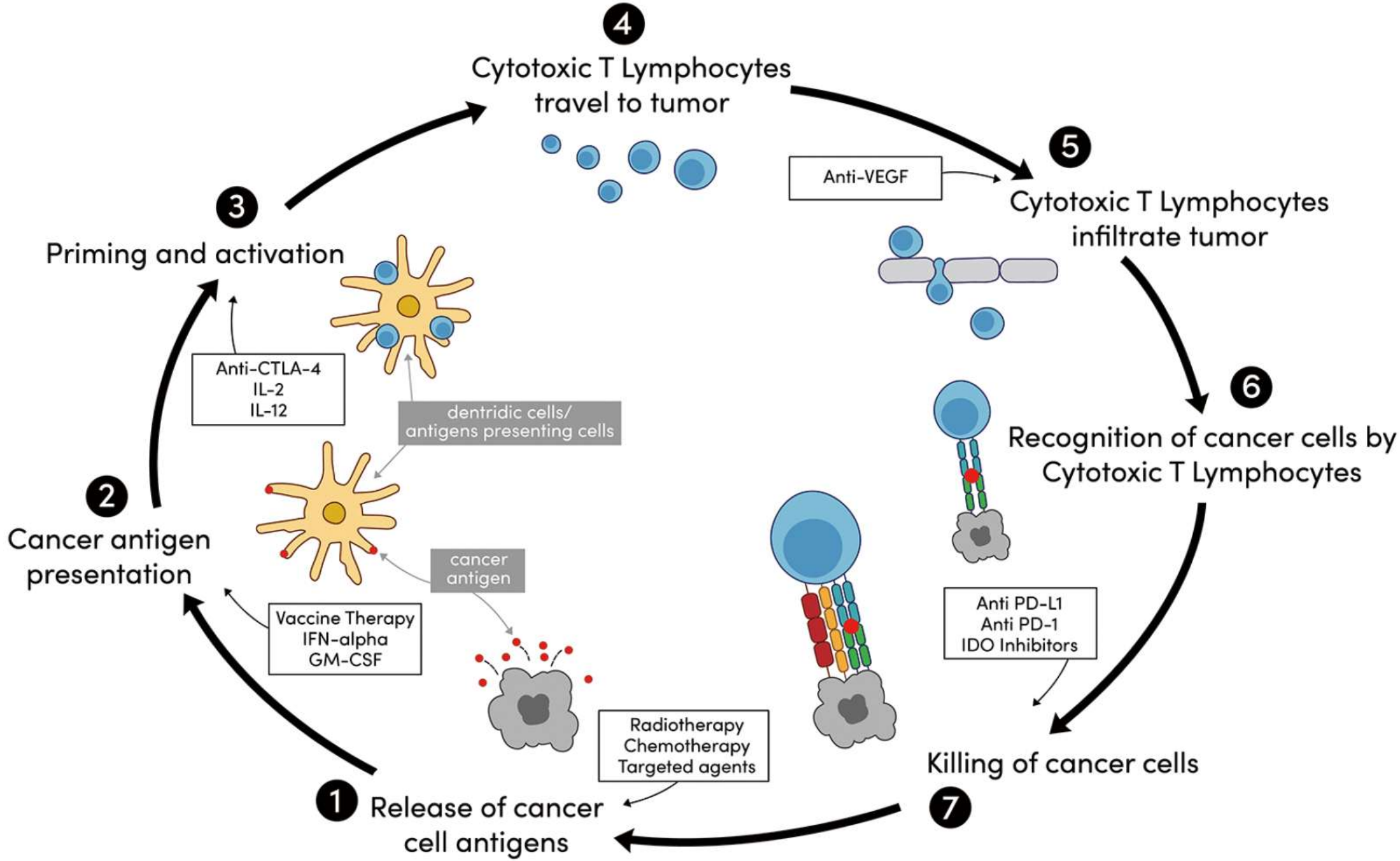
Abscopal effect is dose dependent

- Better with fractionated regimes as compared to single fraction



- In situ vaccination
  - *Eat me* signals upregulated by RT
  - DC activated
  - SBRT with immune activation pathways lead to antigen specific adaptive immunity
  - Modifying tumour microenvironment in residual tumours is of utmost importance to improve response and achieve cure

The Cancer-Immunity Cycle



- Combined 2 phase II trials, using ipilimumab and nivoumab(PD-L1 & CTLA4I) with SBRT and SBRT alone by H.J Roberts et al
  - Pancreatic and CRC with liver & lung mets
  - Mean BED 49.6 vs 79.4Gy
  - No diff in ORR, disease control rate
- Suggesting synergistic effect of IO with SBRT
- Tang et al at MDACC, phase I study results of ipilimubab with SBRT for NSCLC and CRC with liver & lung mets
  - 4 arms: concurrent and sequential IO with 50Gy & 60Gy SBRT
  - De-escalation design followed
  - 12/25 pts completed 4 cycles of IO
  - Response in distant lesions from those treated with SBRT was reported

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ipi-RT

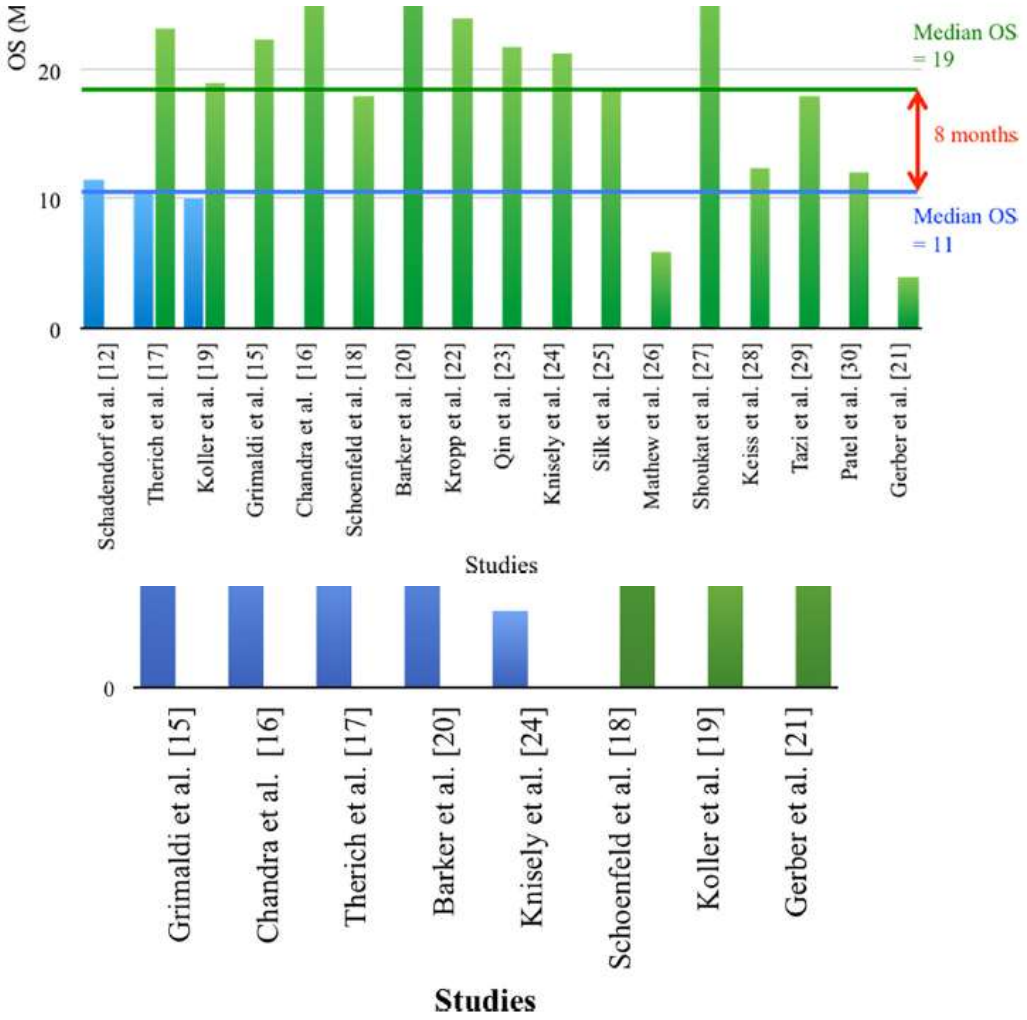
Review Article

Combining radiotherapy and ipilimumab induces clinically relevant radiation–induced abscopal effects in metastatic melanoma patients: A systematic review

Rodolfo Chicas-Sett [a,*], Ignacio Morales-Orue [a], Delvys Rodriguez-Abreu [b], Pedro Lara-Jimenez [a]

[a] Department of Radiation Oncology, "Dr. Negrín" University Hospital of Gran Canaria, Barranco de la Ballena s/n, 35010 Las Palmas de Gran Canaria, Spain
[b] Department of Medical Oncology, Insular University Hospital of Gran Canaria, Plaza Doctor Pasteur s/n, 35016 Las Palmas de Gran Canaria, Spain

- Systematic review of 16 trials showing Ipilimumab with malignant melanoma
  - 451 pts
  - Abscopal effect in 25-30% patients
  - Inc in median OS from 11.5 mths to 19.8mths
  - Toxicity comparable, incidence of 10-20%



Ongoing studies

Pembrolizumab and Stereotactic Body Radiation Therapy in Treating Patients with Liver Metastatic Colorectal Cancer

SABR COMET 3 and SABR COMET 10 with the use of clinical biomarkers and use of immunotherapy

Outcomes Post SBRT …are promising

Local control 70-100% at 1 year

60-90% at 2 years

Depends on tumour volume, RT dose, prior treatment

Median OS 10-33 mths, 2 yr OS 30-83%, occassional long term survivors

Extrahepatic progression: common occurrence

Need to combine systemic therapy with SBRT

Repeat SBRT for new lesions is an option

Better local control with smaller lesions, metachronous, non CRC, no prior chemotherapy

> *Hoyer et al, IJROBP 2012, Vol 82*

To summarise…..

- SBRT is a promising ablative treatment for OMD
  - Improving LC and OS,
  - may lead to cure in selected patients
  - Preferred over RFA in selected situations
- Proper selection of patients: prime importance
- Dose regimens with BED>100Gy achieve better local control
  - Histology of primary to be taken into consideration

- SBRT with immunotherapy is way forward
  - Achieve better DMFS
  - May be new normal as concurrent chemo-radiation

Unanswered questions…..

- Randomised Ph III trials between surgery and SABR for OMD
  - To further establish its role in management of OMD
- Optimizing radiation doses to maximize immune stimulation,
- Determining the most favorable radiation sequence,
- Defining the optimal combination of immune therapeutics to use alongside radiation,
  - Further neutralizing the immunosuppressive elements involved

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EDITORIAL

Curing Metastatic Disease With Ablative Radiation Therapy: Separating Truth From Wish

Sophia C. Kamran, MD, and Anthony L. Zietman, MD

Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

SBRT assures that the patients *live longer*,
it is necessary to ensure that they *live better*

Thank you for patient hearing