SBRT Liver Mets
Indications & Evidence

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Consultant Radiation Oncologist
Alexis Multi-speciality Hospital
Nagpur
Learning objectives

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

Local / Locoregional Disease → Disseminated Disease
Invasion-Metastasis Cascade

Valastyan et al, Cell 2011
“such patients may be amenable to a curative therapeutic strategy”
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

Synchronous Oligometastasis
uncontrolled primary T
<2 months from cancer diagnosis

Metachronous Oligometastasis
uncontrolled primary T
>2 months from cancer diagnosis

Oligorecurrence
controlled primary T
No systemic therapy ongoing

Oligoprogression
controlled primary T
Few mts in progression during systemic therapy

ASTRo Annual refresher course 2018
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
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)

<table>
<thead>
<tr>
<th>Patient related</th>
<th>Tumour related</th>
<th>Treatment related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>No. of lesions</td>
<td>Pre SBRT systemic therapy</td>
</tr>
<tr>
<td></td>
<td>Size of lesions</td>
<td></td>
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<td></td>
<td>Extrahepatic disease</td>
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<tr>
<td>Performance score</td>
<td>Tumour marker levels</td>
<td>Surgical margins</td>
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<td></td>
<td>Stage of primary</td>
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<td></td>
<td>Synchronous vs metachronous</td>
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<td></td>
<td>Histology</td>
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</tbody>
</table>
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
  - Approximinity 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
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 up to 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
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
The Tumor Radiobiology of SRS and SBRT: Are More than the 5 R’s Involved?

J. Martin Brown, PhD¹, David J. Carlson, PhD², and David J. Brenner, PhD³

¹Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA 94305
²Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, CT 06520
³Center for Radiological Research, Columbia University Medical Center, 630 W 168th St, New York, NY 10032

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.
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

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**Table 2. Contraindications to hepatic resection in patients with CRC liver metastases** (adapted from Adam et al. [14] with permission from AlphaMed Press)

<table>
<thead>
<tr>
<th>Category</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical (A)</td>
<td></td>
</tr>
<tr>
<td>1. Absolute</td>
<td>Impossibility of R0 resection with ( \geq 30% ) liver remnant</td>
</tr>
<tr>
<td></td>
<td>Presence of unresectable extrahepatic disease</td>
</tr>
<tr>
<td>2. Relative</td>
<td>R0 resection possible only with complex procedure (portal vein embolisation, two-stage hepatectomy, hepatectomy combined with ablation)</td>
</tr>
<tr>
<td></td>
<td>R1 resection</td>
</tr>
<tr>
<td>Oncological (E)</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Concomitant extrahepatic disease (unresectable)</td>
</tr>
<tr>
<td>2.</td>
<td>Number of lesions ( \geq 5 )</td>
</tr>
<tr>
<td>3.</td>
<td>Tumour progression</td>
</tr>
</tbody>
</table>

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

*All methods, including radiofrequency ablation.
“There is an art to case selection for SBRT, but for easier job, the guidelines are

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

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
Extrapolated from results of SRS for brain

First prospective results from single fraction SBRT: University of Heidelberg

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


<table>
<thead>
<tr>
<th>Structure</th>
<th>Constraint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninvolved liver</td>
<td>700 mL receives &lt;9.1 Gy</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>&lt;0.35 mL exceeds 10 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;1.2 mL exceeds 7 Gy</td>
</tr>
<tr>
<td></td>
<td>Maximum allowed point dose(^a): 14 Gy</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;10 mL exceeds 11.2 Gy</td>
</tr>
<tr>
<td></td>
<td>Maximum allowed point dose: 12.4 Gy</td>
</tr>
<tr>
<td>Duodenum</td>
<td>&lt;5 mL exceeds 11.2 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;10 mL exceeds 9 Gy</td>
</tr>
<tr>
<td></td>
<td>Maximum allowed point dose: 12.4 Gy</td>
</tr>
<tr>
<td>Jejunum/ileum</td>
<td>&lt;5 mL exceed 11.9 Gy</td>
</tr>
<tr>
<td></td>
<td>Maximum allowed point dose: 15.4 Gy</td>
</tr>
<tr>
<td>Colon</td>
<td>&lt;20 mL exceed 14.3 Gy</td>
</tr>
<tr>
<td></td>
<td>Maximum allowed point dose: 18.4 Gy</td>
</tr>
<tr>
<td>Skin</td>
<td>&lt;10 mL exceed 23 Gy</td>
</tr>
<tr>
<td></td>
<td>Maximum allowed point dose: 26 Gy</td>
</tr>
</tbody>
</table>

\(^a\) Point dose = 0.035 mL
Fractionated SBRT
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
Stereotactic Body Radiotherapy (SBRT) for liver metastasis – clinical outcomes from the international multi-institutional RSSearch® Patient Registry

Anand Mahadevan, Oliver Blanck, Rachelle Lanciano, Anuj Peddada, Srinath Sundararaman, David D’Ambrosio, Sanjeev Sharma, David Perry, James Kolker and Joanne Davis

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

Median OS as per tumour vol
25 mths (<40cm³) vs 15 mths (>40cm³)
p = 0.0014
27 mths vs 15 mths as per BED > 100Gy
p < 0.0001
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, logrank 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
<table>
<thead>
<tr>
<th>First author (country) (references)</th>
<th>Disease</th>
<th>Sample size</th>
<th>SBRT schedule</th>
<th>Prescription point/volume</th>
<th>Median (range) follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dewar (France) (17)</td>
<td>HCC</td>
<td>42 patients</td>
<td>Median 45 Gy, 3 fr</td>
<td>PTV (80% IDL)</td>
<td>15 mo</td>
</tr>
<tr>
<td>Honda (Japan) (26)</td>
<td>HCC</td>
<td>30 patients</td>
<td>Median 48 Gy, 4 fr</td>
<td>Isocenter</td>
<td>12 (8–38) mo</td>
</tr>
<tr>
<td>Jung (Korea) (24)</td>
<td>HCC</td>
<td>82 patients</td>
<td>Median 54 Gy, 5 fr (n = 57); 54 Gy, 3 fr (n = 47); 45 Gy, 3 fr (n = 113); 45 Gy, 3 fr (n = 31)</td>
<td>PTV (70–80% IDL)</td>
<td>30 (21–81) mo</td>
</tr>
<tr>
<td>Kwon (Korea) (18)</td>
<td>HCC</td>
<td>42 patients</td>
<td>Median 55 Gy, 3 fr</td>
<td>PTV (70–85% IDL)</td>
<td>29 (8–49) mo</td>
</tr>
<tr>
<td>Sanuki (Japan) (25)</td>
<td>HCC</td>
<td>185 patients</td>
<td>Median 55 Gy, 5 fr (n = 127); 40 Gy, 5 fr (n = 48); 40 Gy, 3 fr (n = 137)</td>
<td>PTV (70–80% IDL)</td>
<td>25 (3–82) mo</td>
</tr>
<tr>
<td>Ramsay (United States) (19)</td>
<td>CCA</td>
<td>9 patients</td>
<td>Median 45 Gy, 3 fr</td>
<td>Isocenter</td>
<td>14 (2–26) mo</td>
</tr>
<tr>
<td>Kope (Denmark) (23)</td>
<td>CCA</td>
<td>27 patients</td>
<td>Median 45 Gy, 3 fr</td>
<td>Isocenter</td>
<td>5.4 (2.3–8.6) y</td>
</tr>
<tr>
<td>Mendez Romero (The Netherlands) (20)</td>
<td>Mets (82% CRC)</td>
<td>17 patients</td>
<td>Median 37.5 Gy, 3 fr</td>
<td>PTV (65% IDL)</td>
<td>13 (1–31) mo</td>
</tr>
<tr>
<td>Rutschow (United States) (27)</td>
<td>Mets (82% CRC, 21% lung)</td>
<td>36 patients</td>
<td>Median 60 Gy, 3 fr</td>
<td>PTV (80–90% IDL)</td>
<td>16 (6–54) mo</td>
</tr>
<tr>
<td>Scorsetti (Italy) (28)</td>
<td>Mets (48% CRC)</td>
<td>61 patients</td>
<td>Median 75 Gy, 3 fr</td>
<td>PTV</td>
<td>12 (2–26) mo</td>
</tr>
<tr>
<td>Stamm (Germany) (21)</td>
<td>Mets (100% CRC)</td>
<td>30 patients</td>
<td>Median 24–26 Gy, 1 fr</td>
<td>70% IDL</td>
<td>35 (6–96) mo</td>
</tr>
<tr>
<td>Vautravers-Dewar (France) (22)</td>
<td>Mets (67% CRC)</td>
<td>42 patients</td>
<td>Median 40 Gy, 4 fr (n = 29); 40 Gy, 3 fr (n = 16)</td>
<td>PTV (80% IDL)</td>
<td>14 (2–23) mo</td>
</tr>
<tr>
<td>Wolf (Germany) (25)</td>
<td>Mets (45% CRC)</td>
<td>39 patients</td>
<td>Median 65 Gy, 3 fr (n = 25); Median 37.5 Gy, 3 fr (n = 26)</td>
<td>PTV (65% IDL)</td>
<td>15 (1–85) mo</td>
</tr>
</tbody>
</table>
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
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. Scheffer

From the University of Colorado—Denver, Departments of Radiation Oncology, Pathology, and Medical
47 pts (63 lesions)  
Upto 3 lesions < 6cm

**Ph I**
- Dose esc 36-60Gy/3#

**Ph II**
- 60Gy/3#

Pri endpt: LC  
Sec endpt: OS, PFS and DPFS

Med FU: 27 mths  
In field LC at 1yr & 2 yr: 95% & 92% resp,  
LR 3 pts at mFU 7.5 mths
60Gy: LC at 2 yrs 94% 100% vs 77% P=0.015

MS 12 mths vs 32 mths (p<0.001)

Median OS and OS at 2 years: 20.5 mths and 30% resp
Phase II trial on SBRT for unresectable liver metastases: long-term outcome and prognostic factors of survival after 5 years of follow-up

Martina Scorsetti, Tiziana Comito, Elena Clerici, Ciro Franzese, Angelo Tozzi, Cristina Iftode, Lucia Di Brina, Pierina Navarra, Pietro Mancosu, Giacomo Reggiori, Antonella Fogliata, Stefano Tomatis, Guido Torzilli, and Luca Cozzi

<table>
<thead>
<tr>
<th>Feature</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>35</td>
<td>26%</td>
</tr>
<tr>
<td>Female</td>
<td>36</td>
<td>25%</td>
</tr>
<tr>
<td>Cancer type</td>
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</tr>
<tr>
<td>Colorectal</td>
<td>29</td>
<td>21%</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>11</td>
<td>8%</td>
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<tr>
<td>Gynecological cancer</td>
<td>7</td>
<td>5%</td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
<td>10%</td>
</tr>
<tr>
<td>Number of metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>44</td>
<td>33%</td>
</tr>
<tr>
<td>2-3</td>
<td>13</td>
<td>10%</td>
</tr>
<tr>
<td>Size of metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 cm</td>
<td>32</td>
<td>33%</td>
</tr>
<tr>
<td>&gt;3 cm</td>
<td>29</td>
<td>23%</td>
</tr>
<tr>
<td>Timing of metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synchronous</td>
<td>24</td>
<td>26%</td>
</tr>
<tr>
<td>Metachronous</td>
<td>37</td>
<td>33%</td>
</tr>
<tr>
<td>Time since diagnosis, mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤12</td>
<td>38</td>
<td>27%</td>
</tr>
<tr>
<td>&gt;12</td>
<td>28</td>
<td>21%</td>
</tr>
<tr>
<td>Physical therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37</td>
<td>27%</td>
</tr>
<tr>
<td>No</td>
<td>34</td>
<td>25%</td>
</tr>
<tr>
<td>Pre-SBRT chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 cycles</td>
<td>39</td>
<td>30%</td>
</tr>
<tr>
<td>3 cycles</td>
<td>39</td>
<td>30%</td>
</tr>
<tr>
<td>Extracranial metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>16%</td>
</tr>
<tr>
<td>No</td>
<td>48</td>
<td>36%</td>
</tr>
</tbody>
</table>

61 pts with 76 lesions, Feb 2010 to Sep 2011

- 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%
Original Research Article

High versus low dose Stereotactic Body Radiation Therapy for hepatic metastases

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High dose vs low dose

90 pts (97 liver mets) from 09-17

BED≤100Gy (40/41)

BED>100Gy (50/56)

Single center retrospective study

Assessed at med FU 28.6 months

CRC, othe GI, lung, melanoma, breast,

LC at 1 yr: 67% vs 94.6%
LC at 2 yrs: 60% vs 90%
(p=0.004)
OS at 2yrs: 48% vs 85%
(p=0.007)
Grade 3 toxicity 7% vs 2%
(p=0.23)

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.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Local control</th>
<th>Overall survival</th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Univariable analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group dose (≤100 Gy vs. &gt;100 Gy)</td>
<td>4.20</td>
<td>1.47 - 11.98</td>
</tr>
<tr>
<td>Age at treatment (continues)</td>
<td>1.00</td>
<td>0.95 - 1.05</td>
</tr>
<tr>
<td>Primary tumor (CRC vs. other)</td>
<td>2.09</td>
<td>0.48 - 9.17</td>
</tr>
<tr>
<td>Extrahepatic disease (present vs. absent)</td>
<td>0.91</td>
<td>0.32 - 2.57</td>
</tr>
<tr>
<td>Prior chemotherapy (Yes vs. no)</td>
<td>1.49</td>
<td>0.55 - 4.02</td>
</tr>
<tr>
<td>GTV (cm³)</td>
<td>1.02</td>
<td>1.01 - 1.03</td>
</tr>
<tr>
<td>BED_{H3} (Gy) per 10 Gy</td>
<td>0.90</td>
<td>0.78 - 0.95</td>
</tr>
<tr>
<td>BED_{H2} (Gy) per 10 Gy</td>
<td>0.94</td>
<td>0.85 - 0.97</td>
</tr>
<tr>
<td>Relative near-min. PTV dose</td>
<td>0.99</td>
<td>0.97 - 1.01</td>
</tr>
<tr>
<td>Infield recurrence</td>
<td>3.55</td>
<td>1.77 - 7.13</td>
</tr>
<tr>
<td>Multivariable analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group dose (≤100 Gy vs. &gt;100 Gy)</td>
<td>3.61</td>
<td>1.25 - 10.40</td>
</tr>
<tr>
<td>Age at treatment (continues)</td>
<td></td>
<td></td>
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<tr>
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<tr>
<td>Prior chemotherapy (Yes vs. no)</td>
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<td>1.01</td>
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<td>BED_{H3} (Gy) per 10 Gy</td>
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<tr>
<td>Relative near-min. PTV dose</td>
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</table>
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

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**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.
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
**mOS 28 vs 50 mths**

- **Overall Survival (%)**
  - **Stratified log-rank test P = .006**

**mPFS 5.6m vs 11.6m**

- **Progression-Free Survival (%)**
  - **Stratified log-rank test P = .001**

**FACT-G Total Score**

- **Control arm** vs **SABR arm**: $P = .062$

**Time to New Metastases (%)**

- **Stratified Gray’s test P = .572**
SBRT v/s Other Local Therapies
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
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
Most of the patients had received >1 liver directed therapy

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

lesions close to vessels/biliary structure/hollow viscera

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

M.C histology CRC, Pancreatobiliary
Univariate analysis of variables predictive of local progression

<table>
<thead>
<tr>
<th>Variable</th>
<th>All lesions</th>
<th>RFA</th>
<th>SBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment: RFA vs SBRT</td>
<td>2.66</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td>1.06</td>
<td>1.09</td>
<td>1.03</td>
</tr>
<tr>
<td>Tumor size</td>
<td>1.57</td>
<td>1.95</td>
<td>1.38</td>
</tr>
<tr>
<td></td>
<td>2.42</td>
<td>4.94</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>0.56</td>
<td>0.17</td>
<td>2.50</td>
</tr>
<tr>
<td></td>
<td>0.96</td>
<td>0.63</td>
<td>1.45</td>
</tr>
<tr>
<td></td>
<td>1.08</td>
<td>0.92</td>
<td>1.36</td>
</tr>
<tr>
<td>Treatment: RFA vs SBRT</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Multivariate Cox proportional hazards analysis of factors associated with local progression

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment: RFA vs SBRT</td>
<td>4.75</td>
<td>1.60–14.1</td>
<td>.005</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.05</td>
<td>1.00–1.11</td>
<td>.053</td>
</tr>
<tr>
<td>Tumor size (per centimeter)</td>
<td>1.53</td>
<td>1.10–2.14</td>
<td>.011</td>
</tr>
<tr>
<td>ECOG score (≥ 2 vs &lt; 2)</td>
<td>1.69</td>
<td>0.24–10.6</td>
<td>.638</td>
</tr>
<tr>
<td>Histology (colon and/or rectal adenocarcinoma vs other)</td>
<td>0.65</td>
<td>0.20–2.11</td>
<td>.470</td>
</tr>
</tbody>
</table>
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%)
<table>
<thead>
<tr>
<th></th>
<th>RFA</th>
<th>RRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>(30 pts, 35 lesions)</td>
<td>(30 pts, 35 lesions) 24-26Gy</td>
</tr>
<tr>
<td>Med Size of lesion</td>
<td>33mm</td>
<td>34mm</td>
</tr>
<tr>
<td>LC at 1 and 2 years (P=0.057)</td>
<td>65% and 61% (P NS)</td>
<td>85% and 80%</td>
</tr>
<tr>
<td>Local DFS</td>
<td>6.1 months (P&lt;0.001)</td>
<td>34.4 months</td>
</tr>
<tr>
<td></td>
<td>mFFDR 7 months (P=0.25)</td>
<td>mFFDR 11.4 months</td>
</tr>
<tr>
<td>Median OS</td>
<td>34.4 months (P=0.06)</td>
<td>52.3 months</td>
</tr>
</tbody>
</table>

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

• MECC registry suggests dose prescription as per tumor 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

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

*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
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 report changes 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 suggest local recurrence/progression

Mazzola et al, Br J Radiol, 2018
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
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 with 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

1. Release of cancer cell antigens
2. Cancer antigen presentation
3. Priming and activation
   - Anti-CTLA-4
   - IL-2
   - IL-12
   - Vaccine Therapy
   - IFN-alpha
   - GM-CSF
4. Cytotoxic T Lymphocytes travel to tumor
5. Cytotoxic T Lymphocytes infiltrate tumor
   - Anti-VEGF
6. Recognition of cancer cells by Cytotoxic T Lymphocytes
   - Anti PD-L1
   - Anti PD-1
   - IDO inhibitors
7. Killing of cancer cells
   - Radiotherapy
   - Chemotherapy
   - Targeted agents
• 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
• 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%
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
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%, occasional 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
SBRT assures that the patients *live longer*, it is necessary to ensure that they *live better*.
Thank you for patient hearing