Stereotactic Ablative Radiotherapy (SABR) for Oligometastatic Disease: Is a New Treatment Paradigm Coming?

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Department Head, Radiation Oncology, BC Cancer – Prince George
Research Lead, UBC/UNBC Northern Medical Program
MSFHR Health Professional - Investigator
Disclosures

• I have received funding from Varian Medical Systems (radiation machine manufacturer), which was not related to this research

• I am a skeptic, and was surprised by COMET trial results
  – I was concerned we were overtreating with radiotherapy

• Many of these slides are edited (with permission) from David Palma (London, ON), and Devin Schellenberg (Surrey)
Learning Objectives

• Define the oligometastatic State
• Understand the unique aspects of Stereotactic Ablative Radiotherapy (SABR)
• Review the recent clinical trials of SABR in the oligometastatic state
• Discuss the need for further research for SABR and surgery in the oligometastatic state
Background

• In BC, we have a unique ability to test radiotherapy techniques, such as SABR, because:
  – We are on salary (no financial incentive)
  – Leaders are constrained by finances (don’t have funding for more physicists)
  – We rely on evidence before adopting new techniques

• Other countries are using SABR for oligometastases without these constraints

• Our patients receive these treatments late, in comparison
The Oligometastatic Paradigm

- Term formally named in 1990s\(^1\) but anecdotally reported as early as the 1930s\(^2\)
- Hypothesized some patients could be cured with surgery & now SABR

The Oligometastatic Paradigm

• Variously defined as patients with
  – A limited (1-3 or 1-5) sites of metastatic disease
  – From primary solid tumours (e.g. breast, colon, prostate, lung)

• Historically treated with systemic therapies to delay
  progression, palliate, and extend life, but not to “cure”
  – Radiotherapy (RT) reserved for palliation at low doses
  – Surgery used in select patients (e.g. colon cancer with liver mets)
Stereotactic Ablative Radiotherapy (SABR)

- High doses of RT achieved by:
  - Limiting the volumes to highly conformal areas in and around the tumours, while avoiding normal tissues
  - Using imaging devices attached to linear accelerators to position accurately every day

Conventional palliative

SABR
Volumetric Modulated Arc Therapy
Total Yearly SABR treatments
BC Cancer - Provincially

352 in 2017
SABR Distribution (BC wide)

2014

2017

- Lung
- Liver
- Spine
- Bone
- Prostate
- Other
- Adrenal
How is SABR used now in BC?

• Most common indication for SABR is stage I lung cancer
  – Generally confined to patients not fit for surgery

• Also used in primary liver cancer patients who are not surgical candidates

• SABR for body metastases is confined to trials*
SABR-5 phase II trial

- Accruing patients with oligometastases or oligoprogression
- BC only trial, awaiting phase III trials
How does SABR compare to surgery?

• The level of evidence does not deserve slides

• In general, both SABR and surgery have great local control
  – Side effect profiles differ; surgery often associated with more morbidity

• We should focus our efforts on when to use our ablative techniques
Level 1 evidence exists for solitary brain mets only

A RANDOMIZED TRIAL OF SURGERY IN THE TREATMENT OF SINGLE METASTASES TO THE BRAIN
Roy A. Patchell, M.D., Phillip A. Tibbs, M.D., John W. Walsh, M.D., Robert J. Dempsey, M.D., Yosh Maruyama, M.D., Richard J. Kryscio, Ph.D., William R. Markesbery, M.D., John S. Macdonald, M.D., and Byron Young, M.D.

Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial

Patchell et al NEJM 1990

Andrews et al Lancet 2004
Level of evidence for ablation of mets is low

- Outside of the brain
- E.g. there is no level 1 evidence for liver resection
## Hepatic Metastectomy

Results of hepatic resection for metastatic colorectal cancer

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Number of patients</th>
<th>5 yr OS, percent</th>
<th>Median survival, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hughes, KS; 1986</td>
<td>507</td>
<td>33</td>
<td>NR</td>
</tr>
<tr>
<td>Scheele, I; 1995</td>
<td>434</td>
<td>33</td>
<td>40</td>
</tr>
<tr>
<td>Nordlinger, B; 1996</td>
<td>1558</td>
<td>28</td>
<td>NR</td>
</tr>
<tr>
<td>Jamison, RL; 1997</td>
<td>280</td>
<td>27</td>
<td>33</td>
</tr>
<tr>
<td>Fong, Y; 1999</td>
<td>1001</td>
<td>37</td>
<td>42</td>
</tr>
<tr>
<td>Iwatsuki, S; 1999</td>
<td>305</td>
<td>32</td>
<td>NR</td>
</tr>
<tr>
<td>Choti, M; 2002</td>
<td>133</td>
<td>58</td>
<td>NR</td>
</tr>
<tr>
<td>Abdalla, E; 2004</td>
<td>190</td>
<td>56</td>
<td>NR</td>
</tr>
<tr>
<td>Fernandez, FG; 2004</td>
<td>100</td>
<td>58</td>
<td>NR</td>
</tr>
<tr>
<td>Wei, AC; 2005</td>
<td>423</td>
<td>47</td>
<td>NR</td>
</tr>
<tr>
<td>Roes, M; 2008</td>
<td>929</td>
<td>36</td>
<td>42.5</td>
</tr>
<tr>
<td>de Jong, M; 2009</td>
<td>1669</td>
<td>47</td>
<td>36</td>
</tr>
<tr>
<td>Morris, BJ; 2010</td>
<td>3116</td>
<td>44</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR: not reported; OS: overall survival.

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Morris et al, Brit J Surg, 2010
Figure 1 | Survival of patients undergoing pulmonary resection of metastatic tumors. Each curve represents the survival of patients with an increasing number of risk factors for recurrence as determined by a retrospective review of the data. These categories are: group I, a single resectable metastasis with a disease-free interval from primary tumor to metastasis of ≥36 months; group II, multiple metastases or a disease-free interval <36 months; group III, multiple metastases and a disease-free interval <36 months. The size, number and tumor type are risk factors for recurrence. Permission obtained from Elsevier © Pastorino, U. et al. J. Thorac. Cardiovasc. Surg. 113, 37–49 (1997).

Weichselbaum and Hellman, Nat Rev Clin Onc 2011
Other Histologies

Pulmonary Resection of Metastatic Sarcoma: Prognostic Factors Associated With Improved Outcomes
Samuel Kim, MD, Harald C. Ott, MD, Cameron D. Wright, MD, John C. Wain, MD, Christopher Morse, MD, Henning A. Gaisser, MD, Dean M. Donahue, MD, Douglas J. Mathisen, MD, and Michael Lanuti, MD
Division of Thoracic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Liver metastases from breast cancer: Long-term survival after curative resection
Markus Selzner, MD, Michael A. Morse, MD, James J. Vredenburgh, MD, William C. Meyers, MD, and Pierre-Alain Clavien, MD, PhD, Durham, NC
SABR for Oligometastatic Disease

Stereotactic Body Radiotherapy for Multisite Extracranial Oligometastases

Final Report of a Dose Escalation Trial in Patients With 1 to 5 Sites of Metastatic Disease

Joseph K. Salama, MD2; Michael D. Hasselle, MD2; Steven J. Chmura, MD, PhD3,5; Renuka Malik, MD2; Neil Mehta, MD2; Kamil M. Yanico, MD2; Victoria M. Villafior, MD3,5; Walter M. Stadler, MD3,4; Philip C. Hoffman, MD3,4; Ezra E. Cohen, MD3,4; Philip P. Connell, MD3,5; Daniel J. Haraf, MD2,3; Everett E. Vokes, MD2,3,4; Samuel Hellman, MD2; and Ralph R. Weichselbaum, MD3,5.
The Evidence Looks Good,

...But:

- Nearly all studies are single-arm studies
- Appropriate controls lacking
- Selection of very fit patients
- Slow tumor doubling times
- Immortal Time Bias
Radiofrequency Ablation

Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004)

Ruers et al, Ann Oncol 2012
Is it all selection bias and slow doubling time?

- Most ablative series (surgery, RFA, SABR) report on a small subset of patients, and rarely report on the size of the population from which they are drawn.
- EXCEPTION: Wade et al (1996): 36% 5 yr survival after lung met resection from CRC.

- 22,715 who had CRC
- 2659 who had lung mets
- 514 with lung only mets
- 76 lung resections of met CRC

< 0.5%
Is it all selection bias and slow doubling time?

Population: 5% alive

Among long DFI and good KPS: 40% alive

Utley and Treasure, JTO 2010
What's the harm?

Surgical Resection of Pulmonary Metastases From Colorectal Cancer: A Systematic Review of Published Series

Joachim Pfannschmidt, MD, PhD, Hendrik Dienemann, MD, PhD, and Hans Hoffmann, MD, PhD
Department of Thoracic Surgery, University of Heidelberg, Heidelberg, Germany

Table 1. Studies Reporting on Patients With R0 Resections

<table>
<thead>
<tr>
<th>Author Institution</th>
<th>Recruitment Period</th>
<th>Selection of Patients</th>
<th>Characteristics of Patients</th>
<th>Median Follow-up (mos)</th>
<th>Postoperative Mortality</th>
<th>5-Year Survival R0 (%)</th>
<th>Median Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higashiyama Osaka, 2003 [13]</td>
<td>1991–2001</td>
<td>R0/94 patients, R1/6 patients</td>
<td>n = 108; age range, 39–79 yrs Mean, 60.3 yrs Men, 61; women, 39</td>
<td>30.3</td>
<td>NR</td>
<td>52.3</td>
<td></td>
</tr>
<tr>
<td>Lee Seoul 2006 [18]</td>
<td>1994–2004</td>
<td>R0 only</td>
<td>n = 59; age range, 33–76 yrs Mean age, 55 yrs Men, 39; women, 20</td>
<td>34.7</td>
<td>0%</td>
<td>50.3</td>
<td>NR</td>
</tr>
<tr>
<td>Mellon Milan, 2006 [19]</td>
<td>1991–2004</td>
<td>R0/74 patients, R1/7 patients</td>
<td>n = 31; age range, 38–83 yrs Median, 61 yrs Men, 49; women, 32</td>
<td>20</td>
<td>30 days 0%</td>
<td>44</td>
<td>37</td>
</tr>
<tr>
<td>Moore Sydney, 2001 [20]</td>
<td>1984–1997</td>
<td>R0/41 patients, R1/6 patients</td>
<td>n = 47; age mean, 65 yrs Men, 24; women, 23</td>
<td>21</td>
<td>1/47, 1.7%</td>
<td>24</td>
<td>R0.28</td>
</tr>
<tr>
<td>Pfannschmidt Heidelberg, 2003 [21]</td>
<td>1985–2000</td>
<td>R0 only</td>
<td>n = 167; age range, 25–81 yrs Median, 60.2 yrs Men, 103; women, 64</td>
<td>58.6</td>
<td>30 days 5/167, 1.8%</td>
<td>32.4</td>
<td>40.2</td>
</tr>
<tr>
<td>Rena Torino Nowara, 2002 [22]</td>
<td>1980–2000</td>
<td>R0/71 patient, R3/9 patients</td>
<td>n = 80; age range, 38–79 yrs Median, 63 yrs Men, 57; women, 43</td>
<td>26.8 mean</td>
<td>2/80, 2.02%</td>
<td>41</td>
<td>26.8 mean</td>
</tr>
<tr>
<td>Saito Osaka, 2002 [23]</td>
<td>1980–2000</td>
<td>R0 only</td>
<td>n = 165; age range, 33–84 yrs Median, 61.6 yrs Men, 97; women, 68</td>
<td>56.5</td>
<td>0%</td>
<td>39.6</td>
<td></td>
</tr>
<tr>
<td>Sakamoto Akashi, 2001 [24]</td>
<td>1986–2000</td>
<td>R0 only</td>
<td>n = 47; age range, 40–80 years Median, 51 yrs</td>
<td>NR</td>
<td>1/47, 1.7%</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>

ATS 2007
Stereotactic Body Radiation Therapy for Extracranial Oligometastases: Does the Sword Have a Double Edge?

Madeleine Carey Sampson, MD, Alan Katz, MD, MPH, and Louis S. Constine, MD

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>% NSCLC (w/mets) (%)</th>
<th>Median Lesion Size (mL)</th>
<th>Total dose (Gy)</th>
<th>Crude Local Control (LC) (%)</th>
<th>Median Follow-up Time in months (range)</th>
<th>Acute Toxicity (Grade 1-2) (%)</th>
<th>Acute Toxicity (Grade 3-5) (%)</th>
<th>Chronic Toxicity (Grade 3-5) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blomgren et al²¹</td>
<td>13</td>
<td>18</td>
<td>48 mL</td>
<td>15-45</td>
<td>94</td>
<td>8.2</td>
<td>NR</td>
<td>NR</td>
<td>6</td>
</tr>
<tr>
<td>Uematsu et al²²</td>
<td>45</td>
<td>35</td>
<td>7.2 mL (mean)</td>
<td>30-75</td>
<td>97</td>
<td>11</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wulf et al²³</td>
<td>26</td>
<td>44</td>
<td>57 mL</td>
<td>30</td>
<td>85</td>
<td>8</td>
<td>22</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Nakagava et al²⁴</td>
<td>15</td>
<td>5</td>
<td>Lung 4.5 mL (CW 40 mL)</td>
<td>15-25</td>
<td>95</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fukumoto et al²³</td>
<td>22</td>
<td>100</td>
<td>10 mL</td>
<td>48-60</td>
<td>94</td>
<td>24 (2-44)</td>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nagata et al²⁵</td>
<td>40</td>
<td>78</td>
<td>12.6 mL</td>
<td>40-48</td>
<td>94 (lung ca)</td>
<td>19-19</td>
<td>NR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hof et al²⁷</td>
<td>10</td>
<td>100</td>
<td>12 mL</td>
<td>19-26</td>
<td>89</td>
<td>14.9</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Timmerman et al²⁸</td>
<td>37</td>
<td>100</td>
<td>22.5 mL</td>
<td>24-60</td>
<td>84 (resp 87)</td>
<td>15.2</td>
<td>49</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Hara et al²⁹</td>
<td>23</td>
<td>22</td>
<td>5.8 mL (mean)</td>
<td>20-30</td>
<td>83</td>
<td>13</td>
<td>13</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Lee et al³⁰</td>
<td>28</td>
<td>32</td>
<td>41.4 mL (PTV)</td>
<td>30-40</td>
<td>89</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Onimaru et al³¹</td>
<td>45</td>
<td>57</td>
<td>9.2 mL³</td>
<td>48-60</td>
<td>88</td>
<td>17</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Uematsu et al³²,³³</td>
<td>50</td>
<td>100</td>
<td>17 mL</td>
<td>50-60</td>
<td>94</td>
<td>60</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Whyte et al³⁴</td>
<td>23</td>
<td>65</td>
<td>NR (range 0.5-65 mL³)</td>
<td>15</td>
<td>~91 (2/23)</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Onishi et al³⁵</td>
<td>245</td>
<td>100</td>
<td>11.5 mL³</td>
<td>18-75</td>
<td>85.5</td>
<td>24</td>
<td>11</td>
<td>4</td>
<td>1.2</td>
</tr>
<tr>
<td>Wulf et al³⁶</td>
<td>61</td>
<td>33</td>
<td>22 mL</td>
<td>10-26</td>
<td>95 (lung ca)</td>
<td>9-11</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Randomized Data is emerging for lung cancer

- Gomez (MD Anderson); phase II; closed early (n=49)
- Stage IV; synchronous oligometastases (≤ 3)
- After systemic therapy

Crossover allowed at the time of progression
Randomized Data is emerging for lung cancer

**Progression Free Survival**

**Survival After Progression**

**Median PFS**
- LCT = 14.2 months
- MT/O = 4.4 months

Statistically significant
- $P = 0.022$

**Median 37.6 months**
- LCT [95% CI 9.0-not reached] vs. 9.4 months
- MT/O [95% CI 5.9–19.6, $P=0.034$]
COMET trial results, which BC participated in..
SABR-COMET: Stereotactic Ablative Radiation (SABR) for the Comprehensive Treatment of Oligometastatic Cancers – Results of a Randomized Study

Endpoints

**Primary Endpoint**
- Overall Survival

**Secondary endpoints:**
- Progression-free survival
- Toxicity (CTC-AE 4.0)
- Quality of life (FACT-G)
- Lesional control rate
- Number of cycles of further systemic therapy
Main Inclusion Criteria

• Controlled primary tumor
  – defined as: at least 3 months since original tumor treated definitively, with no progression at primary site

• Up to to 5 metastases  Most were 1-2

• Maximum 3 metastases in any single organ system

• All sites of disease safely treatable
Phase II Randomized Screening Design

- Moderate sample size to provide an initial, non-definitive comparison between two arms
- Once trial is complete, a finding can be considered definitive if $p<0.005$

Phase III RCT $\alpha = 0.05$

Phase II Screening RCT $\alpha = 0.20$
SABR Details

• Number of fractions dependent on tumor size and location
  – Lung: 54/3, 55/5, 60/8
  – Bone: 35/5, 30/3, 16-20/1
  – Brain: SRS (18-24/1) or SABR (40/5), WBRT optional
  – Liver: 45-60 Gy in 3-8
  – Adrenal: 60/8

• Normal tissue tolerances not to be exceeded
  – PTV coverage compromised wherever needed

Big doses in comparison to adjuvant/curative

Unique
Not possible in surgical trials
Sample Size and Analyses

- Estimated median survival of 9 months in control arm. To detect a 6-month improvement in OS, with 80% power, a two-sided alpha of 0.2, and 5% rate of dropout, 99 patients needed.

- All analyses *intention-to-treat* and *pre-specified*

- Protocol assumed 4 years of accrual and 1 year of additional follow-up. Data locked as of Jan 2018 for this analysis.
Results
### Baseline Characteristics

Between February 2012 and August 2016, 99 patients were randomized at centres in Canada, Scotland, Netherlands and Australia.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=99)</th>
<th>Control Arm (n=33)</th>
<th>SABR Arm (n=66)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – median, (min, max)</td>
<td>68 (43, 89)</td>
<td>69 (44, 87)</td>
<td>67 (43, 89)</td>
<td>0.494</td>
</tr>
<tr>
<td>Sex – n(%)</td>
<td></td>
<td></td>
<td></td>
<td>0.772</td>
</tr>
<tr>
<td>Male</td>
<td>59 (59.6)</td>
<td>19 (57.6)</td>
<td>40 (60.6)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>40 (40.4)</td>
<td>14 (42.4)</td>
<td>26 (39.4)</td>
<td></td>
</tr>
<tr>
<td>Site of Original Primary Tumor – n(%)</td>
<td></td>
<td></td>
<td></td>
<td>0.204</td>
</tr>
<tr>
<td>Breast</td>
<td>18 (18.2)</td>
<td>5 (15.2)</td>
<td>13 (19.7)</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>18 (18.2)</td>
<td>9 (27.3)</td>
<td>9 (13.6)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>18 (18.2)</td>
<td>6 (18.2)</td>
<td>12 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>16 (16.2)</td>
<td>2 (6.1)</td>
<td>14 (21.2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>29 (29.3)</td>
<td>11 (33.3)</td>
<td>18 (27.3)</td>
<td></td>
</tr>
<tr>
<td>Characteristic</td>
<td>All Patients (n=99)</td>
<td>Control Arm (n=33)</td>
<td>SABR Arm (n=66)</td>
<td>p-value</td>
</tr>
<tr>
<td>------------------------------------</td>
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<td>---------</td>
</tr>
<tr>
<td><strong>Number of Metastases – n(%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>42 (42.4)</td>
<td>12 (36.4)</td>
<td>30 (45.5)</td>
<td>0.591</td>
</tr>
<tr>
<td>2</td>
<td>32 (32.3)</td>
<td>13 (39.4)</td>
<td>19 (28.8)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>18 (18.2)</td>
<td>6 (18.2)</td>
<td>12 (18.2)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4 (4.0)</td>
<td>2 (6.1)</td>
<td>2 (3.0)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3 (3.0)</td>
<td>0 (0.0)</td>
<td>3 (4.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Location of Metastases – n(%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.181</td>
</tr>
<tr>
<td>Adrenal</td>
<td>9 (4.7)</td>
<td>2 (3.1)</td>
<td>7 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>65 (34.0)</td>
<td>20 (31.3)</td>
<td>45 (35.4)</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>19 (10.0)</td>
<td>3 (4.7)</td>
<td>16 (12.6)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>89 (46.6)</td>
<td>34 (53.1)</td>
<td>55 (43.3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (4.7)</td>
<td>5 (7.8)</td>
<td>4 (3.2)</td>
<td></td>
</tr>
</tbody>
</table>
Overall Survival

Median OS

Control Arm: 28 months (95% CI: 19-33 months)

SABR Arm: 41 months (95% CI: 26 months to ‘not reached’)

Number at risk:

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>SABR</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk</td>
<td>33</td>
<td>66</td>
</tr>
<tr>
<td>After 1 year</td>
<td>28</td>
<td>53</td>
</tr>
<tr>
<td>After 2 years</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td>After 3 years</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td>After 4 years</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>After 5 years</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>
Progression-Free Survival

Median PFS

Control Arm: 6 months
(95% CI: 3.4-7.1 months)

SABR Arm: 12 months
(95% CI: 6.9-30 months)

stratified log-rank test: p = 0.001

Number at risk:
Control 33  7  3  1
SABR    66  34  15  6  3  1
## Adverse Events

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=99)</th>
<th>Control Arm (n=33)</th>
<th>SABR Arm (n=66)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related AE Grade ≥ 2 – n(%)</td>
<td>22 (22.2)</td>
<td>3 (9.1)</td>
<td>19 (28.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>AE Associated with Death (Grade 5) – n(%)</td>
<td>3 (3.0)</td>
<td>0 (0.0)</td>
<td>3 (4.5)</td>
<td>0.55</td>
</tr>
<tr>
<td>Fatigue – n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>6 (6.1)</td>
<td>2 (6.1)</td>
<td>4 (6.1)</td>
<td>0.45</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (1.0)</td>
<td>1 (3.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea – n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>1 (1.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>1 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Pain (any type) – n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>5 (5.1)</td>
<td>0 (0.0)</td>
<td>5 (7.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3 (3.0)</td>
<td>0 (0.0)</td>
<td>3 (4.6)</td>
<td></td>
</tr>
</tbody>
</table>

Related Events as determined by the treating investigator (Possibly, Probably, or Definitely Related)
### Additional Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>SABR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QOL - FACT-G @ 6 months</strong></td>
<td>82.5 ± 16.4</td>
<td>82.6 ± 16.6</td>
<td>0.99</td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1) Excluded all prostate patients to see if HR for OS and PFS remain <1
   - OS HR = 0.83
   - PFS HR = 0.61

2) Multivariable analyses for OS and PFS (to control for histology):

<table>
<thead>
<tr>
<th>Factor</th>
<th>OS</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P-value</td>
</tr>
<tr>
<td>Lung Primary (vs. other)</td>
<td>4.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SABR Arm (vs control)</td>
<td>0.60</td>
<td>0.12</td>
</tr>
</tbody>
</table>
Discussion
Limitations

• **Not Histology Specific**
  – Most SRS/SABR trials for metastases are not (brain, spine)
  – Histology specific trials have not accrued well, as numbers are lower

• **Pragmatic Selection of Systemic Agents**
  – It was impossible to mandate specific systemic therapy, given the multiple disease sites and expected changes in SOC over time

• **Phase II Design**
  – OS results not definitive
Is a Clear PFS Benefit Enough to Treat?

• There is ample precedent in oncology
  – Aromatase Inhibitors for Breast Cancer
  – Crizotinib in ALK-rearranged NSCLC

• Majority of FDA approvals for cancer drugs are not based on OS.\textsuperscript{1,2}

1. Brooks et al, Drugs Context, 2017
2. Kim et Prasad, JAMA Internal Medicine 2015
Next Steps

**SABR-COMET 3**

Phase III RCT for patients with a controlled primary tumor and 1-3 metastatic lesions

PI: Robert Olson

**SABR-COMET 10**

Phase III RCT for patients with a controlled primary tumor and 4-10 metastatic lesions

PI: David Palma
COMET-3 Funding

- Varian granted $500K last week
- BC Cancer Foundation has committed to helping with staff support
COMET-3: BCCF support

• I was prepared to give a short 2 minute blurb on why the Precision Radiotherapy fundraising goal was a priority

• I did not know what was being unveiled
COMET-3 Funding

Oh dear, that is terrible! I wish someone would have asked me if I wanted my love handles enlarged and hung on the wall at the place of my employment.

Ha ha . We are on the wall!
Further Information

**Protocol**

Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors (SABR-COMET): Study protocol for a randomized phase II trial

BMC Cancer 2012, 12:305
(open access)

**Manuscript**

THE LANCET

In Press
Conclusions

• Evidence for the use of SABR in the setting of oligometastatic disease is emerging
  – Could be Paradigm changing
  – But there is a real risk of side effects; even mortality
  – I believe we should continue to treat these patients on trial and in a well coordinated provincial program, with robust peer-review and QA
• But, patients (and medical oncologists) might start asking for this treatment off-trial
  – Should we?
  – Do we have the resources in BC to treat?