TREATMENT DELIVERY AND CLINICAL EVIDENCE FOR THE TREATMENT OF OLIGOMETASTASIS

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1) I or one of my co-authors hold a position as an employee, consultant, assessor or advisor for a pharmaceutical, device or biotechnology company.

Boehringer Ingelheim, Amgen, Merck and AstraZeneca

2) I or one of my co-authors receive support from a pharmaceutical, device or biotechnology company.

Research Agreement with AstraZeneca and Dermal Laboratories
Outline

- Background to oligometastases
- Treatment options / techniques in Oligometastatic Cancer
- Radiotherapy Dose for SABR in Oligometastases
- Timing of SABR in Oligometastastic disease
- Recent and ongoing clinical trails in oligometastases
Oligometastases

- Term initially proposed by Hellman and Weischelbaum
- Presence of a limited number of metastatic sites of disease (<4 or <6)
- Clinical entity implies that cure may be possible because:
  - there are no viable micrometastases
  - and that all the metastases that are present have declared themselves
- Potentially an extension of locally advanced disease
- An intermediate state between locoregional and widespread metastatic disease.

Oligometastatic Presentation

**Synchronous**
- Red Circle: Primary Lesion
- Red Dot: Distant Metastases

**Metachronous**
- Orange Circle: Primary Lesion Controlled
- Red Dot: Distant Metastases
ADENOCARCINOMA OF THE KIDNEY WITH METASTASIS TO THE LUNG

CURED BY NEPHRECTOMY AND LOBECTOMY

J. DELLINGER BARNEY AND EDWARD J. CHURCHILL

From the Surgical Services of the Massachusetts General Hospital

May 2, 1938.
55 yr old woman with renal adenocarcinoma primary and solitary lung metastasis

Treated with nephrectomy and radiotherapy to metastasis (8Gy in 11 fractions)

Partial lobectomy after progression

Patient died 23 years later from other causes
Level 1 Evidence
Level 1 Evidence

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

Level 1 Evidence

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.

Hepatic Resection for Metastatic Colorectal Ca

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>
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<tr>
<td>Hughes, KS; 1986</td>
<td>607</td>
<td>33</td>
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<td>Scheele, J; 1995</td>
<td>434</td>
<td>33</td>
<td>40</td>
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<td>Nordlinger, B; 1996</td>
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<td>280</td>
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<td>Fong, Y; 1999</td>
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<td>37</td>
<td>42</td>
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<td>Iwatsuki, S; 1999</td>
<td>305</td>
<td>32</td>
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<td>Choti, M; 2002</td>
<td>133</td>
<td>58</td>
<td>NR</td>
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<td>Abdalla, E; 2004</td>
<td>190</td>
<td>58</td>
<td>NR</td>
</tr>
<tr>
<td>Fernandez, FG; 2004</td>
<td>100</td>
<td>58</td>
<td>NR</td>
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<td>Wei, AC; 2006</td>
<td>423</td>
<td>47</td>
<td>NR</td>
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<tr>
<td>Rees, 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>
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<td>Morris, EJ; 2010</td>
<td>3116</td>
<td>44</td>
<td>NR</td>
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</table>

NR: not reported; OS: overall survival.

Phase II Data in NSCLC

Radical Treatment of Non-Small-Cell Lung Cancer Patients with Synchronous Oligometastases: Long-Term Results of a Prospective Phase II Trial (Nct01282450)

<table>
<thead>
<tr>
<th>Localization</th>
<th>Number</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Adrenal gland</td>
<td>4</td>
<td>10.3%</td>
</tr>
<tr>
<td>Bone</td>
<td>7</td>
<td>17.9%</td>
</tr>
<tr>
<td>Brain</td>
<td>17</td>
<td>43.9%</td>
</tr>
<tr>
<td>Gastro-hepatic ligament</td>
<td>1</td>
<td>2.6%</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
<td>2.6%</td>
</tr>
<tr>
<td>Lung</td>
<td>1</td>
<td>2.6%</td>
</tr>
<tr>
<td>Lymph node</td>
<td>2</td>
<td>5.1%</td>
</tr>
<tr>
<td>Muscle</td>
<td>2</td>
<td>5.1%</td>
</tr>
<tr>
<td>Ovary</td>
<td>1</td>
<td>2.6%</td>
</tr>
<tr>
<td>Pleura</td>
<td>3</td>
<td>7.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Metastases</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>87.2%</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>10.3%</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

**FIGURE 1.** Overall survival (n = 39).
Prognostic Factors for NSCLC Oligometas

# Prognostic Factors for NSCLC Oligometastases

## Table III. Prognostic Factors for Survival Assessed by Multivariate Analyses (MVA) in at Least Two Studies

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
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<th>Comments</th>
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<tbody>
<tr>
<td>controlled primary tumour</td>
<td>13</td>
<td>7/13</td>
<td>better OS with radical/definitive treatment/controlled primary/complete resection vs. supportive/palliative treatment/uncontrolled primary/incomplete resection</td>
</tr>
<tr>
<td>primary tumour N-stage</td>
<td>12</td>
<td>6/12</td>
<td>NO better OS than N+ (5 studies) NO/1 better OS than N2/3 (1 study)</td>
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<tr>
<td>disease free interval</td>
<td>4</td>
<td>3/4</td>
<td>better OS with DFI &gt; 360 days vs. &lt;360 days (brain metastases) with DFI &gt; 1 yr. vs. &lt; 1 yr. (multiple metastatic sites), better OS if DFI &gt; 6 months vs. less (adrenal metastases)</td>
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<td>2/2</td>
<td>decreased OS with presence of extra-cranial metastases</td>
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<td>use of PET-CT</td>
<td>2</td>
<td>2/2</td>
<td>PET CT associated with better OS than CT alone</td>
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<tr>
<td>RPA Classification</td>
<td>2</td>
<td>1/2</td>
<td>RPA 1 better OS than RPA 2</td>
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<tr>
<td>primary tumour size</td>
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<td>type of thoracic resection</td>
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Prognostic Factors for NSCLC Oligometas

Prognostic Factors for NSCLC Oligometastases

Techniques for Treating Oligometastases in NSCLC

Surgery
+/- Radiotherapy

Radiotherapy
- Conventional Fractionation
- SABR
  ➢ Linac Based
  ➢ Cyberknife

Other Ablative Techniques:
- Radiofrequency Ablation
- Thermal Ablation / Cryo-ablation

Systemic Therapy
Techniques for Treating Oligometastases in NSCLC

Surgery +/− Radiotherapy

Advantages:
• Pathological confirmation /
• Margin status

Disadvantages:
• Acute morbidity and mortality
• Centre / Operator Dependent
Surgery vs SABR in stage I NSCLC

3-year overall survival (95% CI):
SABR 95% (85–100); surgery 79% (64–97)
HR (95% CI): 0.14 (0.017–1.190)
log-rank p=0.037
SABR for lung oligometastatic disease

- High local control rates following SABR for oligometastatic disease to the lung
- Potential to combine with systemic therapy

Oligomets – Wishful thinking…? 

- Until recently, no randomized data...

- No contemporary controls… (effect of Targeted therapy and I.O.)

- Selection bias… (good PS, good biology tumours)

- Lack of data on treatment related toxicity and mortality
Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study


Key Eligibility Criteria:

- Stage IV NSCLC \(\leq\) 3 metastatic lesions after 1\(^{st}\)-line systemic therapy. Regional nodes counted as 1 lesion, regardless of number of nodes.

- 1\(^{st}\)-line therapy \(\geq\) 4 cycles of platinum doublet or \(\geq\) 3 months of TKI for EGFR mutations or ALK re-arrangements.
Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study

Daniel R Gomez, George R Blumenschein Jr, Jack Lee, Mike Hernandez, Rong Ye, D Ross Camidge, Robert C Doebele, Ferdinandos Skoulidis, Laurie E Gaspar, Don L Gibbons, Jose A Karam, Brian D Kavanagh, Chad Tang, Ritsuko Komaki, Alexander V Louie, David A Palma, Anne S Tsao, Boris Sepesi, William N Williams, Jianjun Zhang, Qiuling Shi, Xin Shelley Wang, Stephen G Swisher*, John V Heymach*

Primary Endpoint = PFS

Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study

Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study


Treating the Primary – Surgery vs Radiotherapy

Recursive Partitioning

Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): Patient outcomes and prognostic factors

A

ALL PATIENTS (n=52+)
1yr OS: 54.3%
2yr OS: 37.7%

Lung Surgery (n=9)

LOW RISK
1yr OS: 100.0%
2yr OS: 100.0%

No Lung Surgery (n=43)

Lung PTV < 639 cc (n=25)
INTERMEDIATE RISK
1yr OS: 61.2%
2yr OS: 38.4%

Lung PTV ≥ 639 cc (n=18)
HIGH RISK
1yr OS: 36.7%
2yr OS: 12.2%

References:
Gwendolyn H.M.J. Griffioen, Daniel Toguri, Max Dahaie, Andrew Warmer, Patricia F. de Haan, George B. Rodrigues, Ben J. Slotman, Brian P. Yaremko, Suresh Senan, David A. Palma

*: Department of Radiation Oncology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands
*: Department of Radiation Oncology, London Regional Cancer Program, 796 Commissioners Rd E, London, Ontario, Canada
SABR Dose in Stage I NSCLC

All Patients

SABR Dose in Stage I NSCLC

All Patients

Medically Operable

SABR Dose in Stage I NSCLC

All Patients

Medically Operable

Medically Operable and BED >100 Gy

Dose matters... to a point.

Not all metastases are equal…

Not all metastases are equal... Will different pathological and molecular sub-types in NSCLC respond differently?
**Not all metastases are equal...but dose matters**

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<tr>
<th>Predictor</th>
<th>Univariate analyses</th>
<th>Multivariable analyses</th>
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<tbody>
<tr>
<td></td>
<td>Unadjusted SHR</td>
<td>Adjusted SHR</td>
</tr>
<tr>
<td></td>
<td>(95% CI)†</td>
<td>(95% CI)</td>
</tr>
<tr>
<td></td>
<td>Test statistic</td>
<td>Test statistic</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Wald $\left[\chi^2(df, P)\right]$</td>
<td>0.222 (0.066-0.750)</td>
<td>0.271 (0.078-0.940)</td>
</tr>
<tr>
<td>Dose 60 Gy (ref &lt;60 Gy/4 fractions)*</td>
<td>5.874</td>
<td>4.230</td>
</tr>
<tr>
<td>Age (per y)</td>
<td>0.997 (0.959-1.037)</td>
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</tr>
<tr>
<td>Male (ref female)</td>
<td>1.289 (0.578-2.876)</td>
<td></td>
</tr>
<tr>
<td>Size (per cm)</td>
<td>1.853 (1.193-2.876)</td>
<td></td>
</tr>
<tr>
<td>Central location of lesion (ref peripheral)*</td>
<td>6.441 (2.478-16.744)</td>
<td>5.522 (2.253-13.535)</td>
</tr>
<tr>
<td>$\text{BED}_{10}$ dose (per Gy)*</td>
<td>0.941 (0.905-0.978)</td>
<td></td>
</tr>
<tr>
<td>Indication for SABR (ref single metastasis)</td>
<td>3.005</td>
<td></td>
</tr>
<tr>
<td>Oligometastasis</td>
<td>1.542 (0.367-6.474)</td>
<td></td>
</tr>
<tr>
<td>Oligoprogression</td>
<td>3.563 (0.480-26.427)</td>
<td></td>
</tr>
<tr>
<td>Dominant tumor</td>
<td>2.946 (0.540-16.086)</td>
<td></td>
</tr>
<tr>
<td>Number of pulmonary lesions treated (ref 1)</td>
<td>2.023 (0.897-4.050)</td>
<td></td>
</tr>
</tbody>
</table>

* Variables kept in the multivariable analysis on the basis of a 10% change of the parameter estimate of the key predictor “primary site of disease.”
† Subdistribution hazard ratio (SHR) and the corresponding 95% confidence interval (CI).
‡ Removed from the multivariable model because of collinearity with dose.

Abbreviations as in Table 1.
Bold values indicate statistically significant result ($P<0.05$).

Not all metastases are equal...but dose matters

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<tr>
<td>Way [r² (df), P]</td>
<td>Test statistic</td>
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<td>Dose 60 Gy (ref &lt;60 Gy/4 fractions)*</td>
<td>0.222 (0.066-0.750)</td>
<td>0.271 (0.078-0.940)</td>
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<tr>
<td>Age (per y)</td>
<td>6.997 (6.539-18.37)</td>
<td>17.461 (2)</td>
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<tr>
<td>Male (ref female)</td>
<td>1.289 (0.578-2.876)</td>
<td>0.878</td>
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<td>Size (per cm)</td>
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<td>0.806</td>
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<td>BED10 dose (per Gy)†</td>
<td>0.941 (0.905-0.978)</td>
<td>0.941</td>
</tr>
<tr>
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<td>3.005 .391</td>
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<tr>
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<td>1.542 (0.367-6.474)</td>
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<td>1.556 .212</td>
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<td>2.387 .122</td>
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<tr>
<td>Well [42,46, 94]</td>
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<td>.015</td>
<td>0.271 (0.078-0.940)</td>
<td>4.230</td>
<td>.040</td>
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<tr>
<td>Dose 60 Gy (ref &lt;60 Gy/4 fractions)*</td>
<td>0.597 (0.539-1.837)</td>
<td>0.624</td>
<td>.578</td>
<td>1.289 (0.578-2.876)</td>
<td>0.3853</td>
<td>.535</td>
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<tr>
<td>Male (ref female)</td>
<td>1.852 (1.192-2.876)</td>
<td>7.551</td>
<td>.006</td>
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<td>13.954</td>
<td>&lt;.001</td>
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Abbreviations as in Table 1
Bold values indicate statistical significance
* Variables kept in the multivariable analysis on the basis of a 10% change of the parameter estimate of the key predictor “primary site of disease.”
† Subdistribution hazard ratio (SHR) and the corresponding 95% confidence interval (CI).
‡ Removed from the multivariable model because of colinearity with dose.

When treating oligometastatic NSCLC with RT – give the highest safe dose

## Normal Tissue Dose Constraints – UK Consensus

<table>
<thead>
<tr>
<th>Description</th>
<th>3 Fractions Optimal</th>
<th>3 Fractions Mandatory</th>
<th>5 Fractions Optimal</th>
<th>5 Fractions Mandatory</th>
<th>8 Fractions Optimal</th>
<th>8 Fractions Mandatory</th>
<th>Source</th>
<th>Endpoint (and magnitude of risk where quantified)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial Plexus</td>
<td>DMax (0.5 cc)</td>
<td>&lt; 24Gy</td>
<td>&lt; 26Gy</td>
<td>&lt; 27Gy</td>
<td>&lt; 29Gy</td>
<td>&lt; 27Gy</td>
<td>&lt; 38Gy</td>
<td>3 and 5 fractions plus Optimal constraints for 8 fractions: UK SABR Consortium[18] 8 fractions Mandatory constraints from LungTECH trial[24] (excluding heart and great vessels) Grade 3+ neuropathy</td>
</tr>
<tr>
<td>Heart</td>
<td>DMax (0.5 cc)</td>
<td>&lt; 24Gy</td>
<td>&lt; 26Gy</td>
<td>&lt; 27Gy</td>
<td>&lt; 29Gy</td>
<td>&lt; 50Gy</td>
<td>&lt; 60Gy</td>
<td>As above (8 fraction heart constraints from UK SABR Consortium[18]) Grade 3+ pericarditis</td>
</tr>
<tr>
<td>Trachea and bronchus</td>
<td>DMax (0.5 cc)</td>
<td>&lt; 30Gy</td>
<td>&lt; 32Gy</td>
<td>&lt; 32Gy</td>
<td>&lt; 35Gy</td>
<td>&lt; 32Gy</td>
<td>&lt; 44Gy</td>
<td>As above Grade 3+ stenosis/ fistula</td>
</tr>
<tr>
<td>Normal Lungs* (Lungs-GTV)</td>
<td>V20 Gy</td>
<td>-</td>
<td>&lt; 10%</td>
<td>-</td>
<td>&lt; 10%</td>
<td>-</td>
<td>&lt; 10%</td>
<td>As above Grade 3+ pneumonitis</td>
</tr>
<tr>
<td>Chest Wall</td>
<td>DMax (0.5 cc)</td>
<td>&lt; 37Gy</td>
<td>-</td>
<td>&lt; 39Gy</td>
<td>-</td>
<td>&lt; 39Gy</td>
<td>-</td>
<td>As above Grade 3+ fracture or pain</td>
</tr>
<tr>
<td></td>
<td>D30 cc</td>
<td>&lt; 30Gy</td>
<td>-</td>
<td>&lt; 32Gy</td>
<td>-</td>
<td>&lt; 35Gy</td>
<td>-</td>
<td>As above</td>
</tr>
<tr>
<td>Great Vessels</td>
<td>DMax (0.5 cc)</td>
<td>-</td>
<td>&lt; 45Gy</td>
<td>-</td>
<td>&lt; 53Gy</td>
<td>-</td>
<td>-</td>
<td>As above (8 fractions great vessels constraints from UK SABR Consortium[18]) Grade 3+ aneurysm</td>
</tr>
</tbody>
</table>

RCTs on the Horizon: SABR-COMET

Principal Investigators
D. Palma, S. Senan

Participants
Canada
Netherlands
Scotland
Australia

http://clinicaltrials.gov/ct2/show/NCT01446744

Palma et al, BMC Cancer 2012, 12:305
2 cycles platinum-based chemotherapy

CT Scan

WITHDRAWN:
Patients with:
- Disease progression
- Deteriorating PS (3+)

Maximum of 2 further cycles of chemotherapy

+ Conventional RT or SABR to primary (± nodes) & SABR/SRS to metastases

Maximum of 2 further cycles of chemotherapy

+ Maintenance therapy according to local practice

REGISTRATION
340 patients

RANDOMISATION
306 patients, 1:1 ratio

Primary tumour (± nodes) suitable for radical RT or SABR, with 1-3 metastases* treatable by SABR/SRS
PS 0-1, PET staged and brain CT/MRI

PI: David Landau, UCL
Thoracic SABR Safety Sub-Study

Assess toxicity of thoracic SABR following conventional lung RT and QA

First 20* patients treated with thoracic metastases - only in selected centres

Feasibility Sub-Study

Assess recruitment, logistics and withdrawal

First 50 randomised patients

* More patients may be recruited if required to confirm safety

PI: David Landau, UCL
## RCTs on the Horizon: NRG-LU002

<table>
<thead>
<tr>
<th>Patients with metastatic NSCLC having completed 4 cycles of first-line/induction systemic therapy</th>
<th><strong>Histology:</strong> Squamous vs. Non-squamous</th>
<th><strong>RANDOMIZE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Restaging studies reveal no evidence of progression and limited (≤ 3 discrete sites) metastatic disease, all of which must be amenable to SBRT</td>
<td><strong>Arm 1:</strong> Maintenance systemic therapy alone*</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Arm 2:</strong> SBRT to all sites of metastases (≤ 3 discrete sites) plus irradiation of the primary site (SBRT or hypofractionated RT) followed by maintenance systemic therapy*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>* As noted in Section 5</td>
<td></td>
</tr>
</tbody>
</table>

PI: Patrick Cheung
More than OS and PFS...

- Treatment of Oligomets may have other benefits besides OS or PFS:
  - Improving QOL or preventing decline
  - Delaying chemotherapy (saving money?)
  - Providing an extra line of treatment
Step-By-Step Practical Approach

1. Address any life-threatening lesions (i.e. brain mets)

2. Synchronous: start with systemic therapy (chemotherapy or targeted agent)

3. If stable disease or response to systemic therapy, consider ablative therapies
   
   • More enthusiasm if:
     • Low competing risk of death from other causes (young, good KPS)
     • Metachronous presentation
     • Low N-stage
     • Fewer lesions

Courtesy of David Palma
How we choose the treatment

• Generally, surgical resection is favored when risk of surgical morbidity is low
  – Particularly wedge resections, or lobectomies in patients with good pulmonary status
  – Ultra-high-volume center (>200 resections/yr, 4 surgeons)

• For radiation, follow principles of the COMET, CORE or SARON trials if using SABR (OARs take precedence over targets; see protocol for doses)

• For stage II/III disease in the chest, consider concurrent chemoradiation, and radiation alone (e.g. 60/30, 45/15, 40/15)

Courtesy of David Palma
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