New Treatment Paradigms in MBC: Local Therapy for Metastases?

First known X-ray radiographs produced by Roentgen

2.5D planning

Stereotactic Body Radiotherapy to lung metastasis

A Century of Sharpening the Knife
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Department of Radiation and Cellular Oncology
University of Chicago

Disclaimer

• Funding from Merk

• My Wife is a Medical Oncologist
Outline in 20 Minutes

• Radiation Technology has driven research for 100 years
• Evidence for Oligometastases
• Time for a trial: Does eliminated metastasis lead to cure?

First known X-ray radiographs produced by Roentgen
Emil Grubbe (1875-1960)
Over his lifetime, he required > 100 operations and amputations due to his excessive exposure to x-rays

First brachytherapy treatment of cervical cancer performed
By Margaret Cleaves M.D. (1848-1917)
Below is her original report of the first patient treated
Soon RT was being used instead of surgery in many countries
• Despeignes (France 1896) treats a patient with gastric cancer noting significant symptom relief

• Stenbeck (Sweden 1899) → Treats a 49 year old patient with a basal cell tumor on the nose (100 times over 9 months). The patient was alive and well 30 years later

• Sjogren (Sweden 1900) → successfully treats a patient with a squamous cell cancer (50 times over 50 months)

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**Early Treatment Machines**

1 MeV Vicker’s Unit, St Bart’s → Hospital London 1937
Equipped with a movable couch and variable field sizes

←1st Van de Graaf Generator, Royal Marsden Hospital, London, 1933
Medical linear accelerator

Breast

Opposed tangents

Better sparing of heart and lung
Stereotactic Body Radiotherapy
SBRT/SABR/HIGRT

An Idea:
Limited or Oligometastases
Figure 2. Patterns of Metastatic Spread of Solid Tumors.
Early reports of chest wall and lung surgery

<table>
<thead>
<tr>
<th>Year</th>
<th>Name</th>
<th>Country</th>
<th>Cases or Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1855</td>
<td>C. Sédillot</td>
<td>France</td>
<td>1 case</td>
</tr>
<tr>
<td>1882</td>
<td>K. Weishechler</td>
<td>Austria</td>
<td>1 case</td>
</tr>
<tr>
<td>1883</td>
<td>U. Krönlein</td>
<td>Switzerland</td>
<td>1 case</td>
</tr>
<tr>
<td>1898</td>
<td>F.W. Parham</td>
<td>USA</td>
<td>2 cases, review of 95 cases</td>
</tr>
<tr>
<td>1898</td>
<td>Quémé and Longuet</td>
<td>France</td>
<td>34 cases</td>
</tr>
</tbody>
</table>

Early reports of pulmonary metastasis resection

<table>
<thead>
<tr>
<th>Year</th>
<th>Name</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>1921/1937</td>
<td>W. Röpke</td>
<td>Germany</td>
</tr>
<tr>
<td>1926</td>
<td>G. Divia</td>
<td>Czechoslovakia</td>
</tr>
<tr>
<td>1927</td>
<td>A.T. Edwards</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>1930</td>
<td>F. Torek</td>
<td>USA</td>
</tr>
<tr>
<td>1933</td>
<td>E.D. Churchill</td>
<td>USA</td>
</tr>
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</table>

10/29/2015
EDITORIAL

Oligometastases

Spectrum of Metastatic Disease

Limited Spread (Oligometastasis)  Widely Disseminated (Polymetastases)

Does the oligometastatic state exist?
T-N-M

ANNALS OF SURGERY

Vol. XLVI JULY, 1907 No. 1

ORIGINAL MEMOIRS.

THE RESULTS OF RADICAL OPERATIONS FOR THE CURE OF CARCINOMA OF THE BREAST.*

BY WILLIAM STEWART HALSTED, M.D.,
OF BALTIMORE, MD.
Surgeon to Johns Hopkins Hospital.

It is especially true of breast cancer that the surgeon interested in furnishing the best statistics may in perfectly honorable ways provide them. The most conscientious man may refuse to operate upon any but favorable cases, and, by performing an incomplete operation, exclude from his list of complete operations such bad ones as he finds himself operating upon. Or the pathologist on whom he relies may classify as carcinomas, tumors which on microscopic examination show dangerous spots—i.e., a few epithelial cells here and there escaping into the stroma.

But you will concede that little notion of the value of an operative procedure can be gained unless some attempt be made to exclude or consider apart cancers so far advanced that, however radical the operation, only a portion of the disease can be removed.

The Results.—As affecting the ultimate result, the variety of the cancer, the time elapsed since its appearance, the degree of overlying involvement, the activity of the gland (lactation, age of patient), the thoroughness of the operation, are important factors.

* Read before the American Surgical Association, May 8, 1907.
The Halsted Model

“Based on clinical observations in the late 19th and early 20th century, Halsted described an orderly and direct spread of malignancy from the primary tumor to regional lymph nodes and then directly connected metastases”.

The Systemic Hypothesis (Keynes/Fisher)

Wide spread dissemination of disease could potentially occur before clinical detection of the primary tumor.
Hellman’s Spectrum Hypothesis

“Cancer comprises a biologic spectrum extending from a disease that remains localized to one that is systemic when first detectable but with many intermediate states.”

Patients with oligometastases have indolent disease: Metastatic Breast Cancer Patients

Multivariate Analysis of Prognostic Factors in Metastatic Breast Cancer


- 1.7% of 1,581 patients remained alive/complete remission >10 year
- 619 patients treated with anthracycline chemo

Table 7: Regression Model Relating Survival to Pretreatment Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Regression Coefficient</th>
<th>Significance Level of Entry</th>
<th>Favorable</th>
<th>Unfavorable</th>
<th>Relative Risk</th>
<th>Ratio U/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH</td>
<td>0.382</td>
<td>&lt;0.01</td>
<td>0.83</td>
<td>1.70</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Performance status</td>
<td>0.281</td>
<td>&lt;0.01</td>
<td>0.81</td>
<td>1.41</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>0.470</td>
<td>&lt;0.01</td>
<td>0.58</td>
<td>1.42</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Prior radiotherapy</td>
<td>0.302</td>
<td>&lt;0.01</td>
<td>0.76</td>
<td>1.40</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>0.188</td>
<td>&lt;0.01</td>
<td>0.63</td>
<td>1.45</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Extent of disease</td>
<td>0.154</td>
<td>&lt;0.01</td>
<td>0.99</td>
<td>1.26</td>
<td>1.6</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Favorable risk was IDH ≤ 233; performance status 0–1; lung not involved; no prior radiotherapy; alkaline phosphatase ≤ 85; and extent of disease ≤ 3. Unfavorable risk was IDH > 450; performance status 3–4; lung involved; prior radiotherapy > 3; alkaline phosphatase > 330; and extent of disease > 20.
Survival of patients undergoing pulmonary resection of metastatic tumors

Survival after 2nd metastasectomy
• 5 yr: 44%
• 10 yr: 29%
Survival with extrapulmonary resection:
• 5 yr: 29%
• 10 yr: 21%

N=4572

Treatment of oligometastatic state of GI-associated liver metastases

• 1001 consecutive patients
• 1985-1998
• Median # mets: 2 (1-20)
• Median size: 4.2 cm
• Extent of resection: 63% lobe or greater
• Mortality:
  – 2.8% within 30 days
  – 4.1% if lobectomy or greater
Molecular Determinants of oligometastasis

Molecular Basis of Metastasis

Clonal heterogeneity of primary tumors and selection of developing secondary tumors drive metastatic phenotype

Oligometastases

Progression?

Polymetastases

SBRT/SABR/HIGRT
Biology

Oligometastases
Control of Respiratory Motion

Tracking of Respiratory Motion

Pretreatment Imaging Confirmation
Onward toward Trials and Tomorrow

2 year OS: 56.7%

Table 2. Selected Studies of Oligometastatic Patients Treated With Irradiation of All Known Metastases

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>No. of Metastases per Patient</th>
<th>Median Dose (Gy)</th>
<th>Total No. of Fractions</th>
<th>Follow-Up (months)</th>
<th>Metastasis Control (%)</th>
<th>OS (%)</th>
<th>Toxicity Grade ≥ 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mt Sinai (New York, NY)</td>
<td>21</td>
<td>1.5</td>
<td>40-60</td>
<td>10</td>
<td>2-10</td>
<td>1 year: 65</td>
<td>1 year: 76</td>
<td>NA</td>
</tr>
<tr>
<td>University of Rochester (NY)</td>
<td>121</td>
<td>2</td>
<td>50</td>
<td>10</td>
<td>6-12</td>
<td>2 years: 67</td>
<td>4 years: 28</td>
<td>10†</td>
</tr>
<tr>
<td>University of Chicago (IL)</td>
<td>61</td>
<td>1.5</td>
<td>24-48</td>
<td>2</td>
<td>6-12</td>
<td>2 years: 50</td>
<td>2 years: 97</td>
<td>10†</td>
</tr>
<tr>
<td>Vrije University (Brussels, Belgium)</td>
<td>303</td>
<td>2</td>
<td>40-60</td>
<td>12</td>
<td>1-84</td>
<td>2 years: 33</td>
<td>3 years: 32</td>
<td>NG</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; NS, not stated; OS, overall survival.
*Surviving patients with breast cancer.
†Crude rate.
A Phase 1 Study of Stereotactic Body Radiotherapy (SBRT) for the Treatment of Multiple Metastases

- Hypothesis: 3-4 or 2 anatomically close metastases can be safely treated with established SBRT doses
- Primary Objective: To determine the recommended SBRT dose for each of the metastatic locations
- Inclusion: Metastatic NSCLC, Breast, and Prostate patients
- Sample size: 42-84 patients

<table>
<thead>
<tr>
<th>Table 6-1</th>
<th>Prescription Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic Locations</td>
<td>Initial Starting Dose</td>
</tr>
<tr>
<td>Lung—Peripheral</td>
<td>45 Gy (3 fractions)</td>
</tr>
<tr>
<td>Lung—Genital</td>
<td>50 Gy (5 fractions)</td>
</tr>
<tr>
<td>Metastatic/Cervical Lymph Node</td>
<td>50 Gy (2 fractions)</td>
</tr>
<tr>
<td>Liver</td>
<td>45 Gy (3 fractions)</td>
</tr>
<tr>
<td>Spinal/Paraspinal</td>
<td>50 Gy (3 fractions)</td>
</tr>
<tr>
<td>Osseous</td>
<td>20 Gy (2 fractions)</td>
</tr>
<tr>
<td>Abdominal/pelvic metastases (lymph nodal/soft tissue)</td>
<td>45 Gy (2 fractions)</td>
</tr>
</tbody>
</table>

Establish Level 1 Evidence to Guide Practice
Do we always need Level 1 Evidence to adopt new technologies

NRG BR002
OLIGOMETASTATIC BREAST CANCER
Controlled Locoregional Disease and ≤ 2 Metastases
≤ 6 months systemic therapy without progression

STRATIFICATION
Number of metastases
Hormone receptor status
HER2 status
First-line standard systemic chemotherapy

RANDOMIZATION

ARM 1
Standard of care systemic therapy

ARM 2
- Standard of care systemic therapy
- Ablation of all metastases (SBRT or surgery ablation)

RND
Overall Survival Primary Endpoint

NOW OPEN

Principal Investigator
S. Chmura

Target Sample Size
Phase II: 146
Phase III: 402
CTC Collection

RND → Time of Progression

CTC
Before treatment

CTC
4-6 weeks (if SBRT/Surgery)

CTC Draw

Epithelial cell adhesion molecule enrichment

HD-CTCs

- 4 slides from one “Streck” tube
- Prepared and stored
- NGS from single cells feasible
- cfDNA extracted and stored from same tube
- Shipping will use the standard proprietary shipper that maintains and records continuous temp during shipping
Anticipated Outcomes

• If *Ablative Therapy of all Metastases* improves OS when added to standard systemic therapy, then the **paradigm shifts** to multidisciplinary treatment

• If *Ablative Therapy of all Metastases* does not improve OS when added to standard systemic therapy, then **off-protocol use of SBRT stops**
  • Cost reduction and toxicity avoidance

These Trials will Only Accrue with your help!!!!
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James Galvin, NRG Physics Committee
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Susan McNulty, IROC-Philadelphia
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