Only the Tip of the Iceberg –
Can we predict true oligometastastic disease?

Evolution of breast cancer

- Halstedt 1907 Cancer spreads contiguously
Evolution of breast cancer

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- Keynes 1954  Macroscopic Primary means Systemic disease

- Hellman 1994  There is an Intermediate Stage (Spectrum theory)
Evolution of breast cancer

- Halstedt 1907  Cancer spreads contiguously
  Radical Local treatment

- Keynes 1954  Macroscopic Primary means Systemic disease
  Function preservation and systemic treatment

- Hellman 1994  There is an Intermediate Stage (Spectrum Theory)
  Oligometastasis : Local ablation

What is Oligometastasis ?
Definitions vary :
- most frequent 1-5 mets
  1-2 organs
  maximum of 3 mets in 1 organ
  <= 3 organs
  1-2 organs with < 5 mets < 5 cm

Clinical data may hit different icebergs
Clinically:

Primary Tumor with a few synchronous metastases

Primary Tumor controlled -> some (oligo) metastases during follow up

Most Metastases respond to systemic treatment with (oligo) progression of very few lesions

Enthusiasm for local ablative procedures in advanced malignant disease grows in different settings

If you have a hammer nails should beware

Linear theory of cancer progression

Parallel theory of cancer progression

Malignant progression

heterogeneity low
growth rate similar

time

heterogeneity high
growth rate varies
dormancy?
Clinical evidence

„Old“ Surgical series : Proof of Principle

Long follow up
Limited efficacy of systemic treatment
No modern „biomarkers“
No modern imaging techniques
(like PET CT)

Selection Bias
Probable Understaging according to present standards
Surgery of metastasis

Liver metastasis only in colorectal cancer (in 25% pts.)
  25 - 29% 10 y survival
  (Hughes et al. 1986, Nordlinger et al. 1996, Fong et al. 1999)

Liver or lung metastases only in breast cancer (1-3% pts.)
  34 – 62% 5 y survival, 26% 10 y survival

Lung metastases only in sarcoma (< 10% pts.)
  38% 5 y survival
  (van Geel et al. 1996)

Solitary / few lung metastases only in renal cell carcinoma (< 5% pts.)
  46–49% 5 y survival
  (Friedel et al. 1996, Loh et al. 2014)

Lung metastases only in melanoma (rare)
  22% 5 y survival
  (Leo et al. 2000)

Can You stop the spreading of metastasis from the primary region

Update: Meta-Analysis on LN-irradiation in early breast cancer

Distant metastasis free survival

Comparison: (MS-IM)+(WBI/CWI) vs. (WBI/CWI)

MA.20 [16]: n=1832; HR 0.76 (95% CL 0.60 - 0.97)

EORTC [17]: n=4004; HR 0.86 (95% CL 0.76 - 0.98)

Total: n=5836; HR 0.84 (95% CL 0.75 – 0.94)  p=0.002

fixed effect model  LN RT better  no LN RT better

W. Budach et al. Radiat Oncol 2015
Can You stop further spreading of metastasis from the primary region

**Prostate Cancer with „limited“ metastasis**

better 5 and 10 y. survival

*in retrospective multiinstitutional series or data registries*

after treatment of primary (Engel et al. 2010, Heidenreich et al. 2015, Culp et al. 2014)

*in phase III trials*

by adding radiotherapy to endocrine Tx in N+ disease (Widmark et al. 2009, Abdollah et al. 2014)

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**SBRT Experience**

Can this experience be reproduced in SBRT cohorts?

**Prostate**: Bony Metastasis Radar trial
176 / 1071 patients developed < 3 bone mets as first site of progression
152 / 176 progressed under AHT
24 / 176 (14%) did not

Fit for ablation?

Prostate: Lymph node Metastasis

40 pts. with 47 treated nodes (SBRT high dose)
Loc. control 98 % 2 Y. b-PFS 40% without AHT

72 pts. with 89 treated nodes (SBRT high dose)
Median PFS 21 months 31 / 72 pts. without relapse (43%)
Relapses mostly nodal and pelvic

Bone metastasis

n = 36 mostly renal and breast cancer fractionated SBRT
    solitary 47 % Mizzumoto score A 44 %
5 Y. Local control 81 % 5 Y. Survival 23 %

n = 61 mostly renal and thyroid single dose SBRT
    solitary 92 %
4 Y. Local control 78 % 4 Y. Survival 29 %
Lung metastasis

Multicenter retrospective cohort

n = 700 primary mostly NSCLC and colorectal cancer
42 % solitary

5 y. survival 24 % 5 y. LC 64 % 2 year DMFS 21.1 %

Prognostic:

Interval to metastasis
BED dose,
Number of Mets Histology

Rieber et al. Lung Cancer 2016

Local treatment of pulmonary oligometastasis
head to head comparison

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<thead>
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<th>Surgery</th>
<th>SABRT</th>
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<tr>
<td>n</td>
<td>68</td>
<td>42</td>
</tr>
<tr>
<td>5 year Survival</td>
<td>41 %</td>
<td>49 %</td>
</tr>
<tr>
<td>2 year LC</td>
<td>90 %</td>
<td>94 %</td>
</tr>
<tr>
<td>3 year PFS</td>
<td>17 %</td>
<td>18 %</td>
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Single institution, mostly solitary metastasis, no chemotherapy
Pts. were offered surgery first choice

How to find the right patient?

Prognostic and Predictive factors?

- Imaging -> shifting the subclinical threshold
- Biomarkers -> biological behaviour
- Clinical -> biological behaviour

Better Imaging

Cannot prove Oligometastasis excludes more patients with Polymetastasis

Brain CT < MRI -> detects more lesions in 30 %

Extracranial: FDG-PET
Biomarkers

Presently there are no validated biomarkers to suggest oligometastatic disease

Gene signatures are being tested
Tumor/normal tissue miRNAs are being studied
( regulating important steps in seed and soil, interaction tumor cell microenvironment)

Problem of lesion heterogeneity $\rightarrow$ liquid biopsy ?
Problem of predictive power in a multidimensional space
Micro RNAs

34 pts. with 1-5 metastatic sites all treated with SBRT
tissue samples retrieved

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<th>Polymetastatic progression</th>
<th>&gt; 5 sites within 4 months after SBRT (n=24)</th>
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<tr>
<td>Oligometastatic</td>
<td>no progression or &lt; 5 sites (n=10)</td>
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Significant differential expression of microRNA-200 family

Lussier et al. PloS One 2011

However,

n= 61 (113 sites) prospective dose escalation trial: oligometastasis directed SBRT
3 x 8 Gy -> 3 x 16 Gy)
1-5 metastatic (multiorgan) sites PET Staging

26 % Pts. with > 3 sites
5 Y. survival 32 % 5 Y. PFS 20 % for doses > 30 Gy
76 % progressed at new sites (and 24 % not)

significance microRNA – 200 family not reproduced
new 3 microRNA –classifier proposed

Wong et al. Cancer 2016
Oncotype DX in node negative ER+ early breast cancer

best validated gene signature for prediction of systemic failure

- low risk: 6% systemic recurrence
- intermediate: 14% systemic recurrence
- high risk: 33% systemic recurrence

However, not even predictive in node positive cancer!

Cockburn et al, BMC Cancer 2016

How accurate will differentiation between "oligo and widespread" be?

Clinical

Lessons learned „Prognosis“:

- Long interval between Primary and Metastasis
- One Site only
- < 3 Lesions
- Size < 5 cm
- Complete Ablation/Removal
- Breast > Colorectal > Renal > Lung

Does local intervention really change the course of disease?
We dont know yet!

But this can be studied in a randomized fashion

clear entry criteria : -> best systemic treatment +/- local intervention
(some trials ongoing)

Reviewed data suggest that „Spectrum Theory“ may be correct:

up to 20-30 % of carefully selected patients in many advanced tumor entities could be truly oligometastatic and could benefit from intensified local treatment

Conversion of polymetastatic disease