Oligometastatic Disease
Fact or Fantasy?

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Learning Objectives

• Describe the various types of oligometastatic disease as well as pros versus cons of treatment
• Identify prognostic factors associated with improved outcome that may lend to appropriateness of aggressive treatment in oligometastatic disease
• Be aware of ongoing clinical trials evaluating the role of radiotherapy in the oligometastatic state
• Describe potential interactions between radiotherapy and other emerging treatment modalities when treating oligometastatic disease
Spectrum of Metastatic Disease

Limited Spread (Oligometastasis)

Widely Disseminated (Polymetastases)
Increased Interest in Recent Years

• Improved imaging to identify more extensive distant metastases

• Improved systemic therapy to treat additional sites of microscopic disease

• Less invasive surgery
  • e.g. VATS

• More conformal radiation (SBRT)
  • Ablative dose
  • Fewer side effects
There exists a subset of patients with limited volume metastatic disease who not only have an improved prognosis, but in whom treatment of the oligometastatic site(s) impacts survival. An attractive consequence of the presence of a clinically significant oligometastatic state is that some patients so affected should be amenable to a curative therapeutic strategy. The occasional success of surgical excision or 

A Subset of Patients with Metastatic Disease May do Well

MDACC Study Cohort

- 570 Patients
- 2003-2005
- De novo Stage IV or Stage III recurrent
- 90 (16%) achieved NED status

Bishop AJ. Cancer. 2015, 121(24)
PFS From Time of NED

Bishop AJ. Cancer. 2015, 121(24)
Survival from the Time of Distant Metastases

All Patients

Those Attaining NED or Not Attaining NED
Patients Who Respond Do Better

<table>
<thead>
<tr>
<th></th>
<th>Overall Survival (%)</th>
<th>Progression-Free Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year</td>
<td>98</td>
<td>87</td>
</tr>
<tr>
<td>3-year</td>
<td>89</td>
<td>54</td>
</tr>
<tr>
<td>5-year</td>
<td>77</td>
<td>40</td>
</tr>
</tbody>
</table>

Bishop AJ. Cancer. 2015, 121(24)
## Non-randomized Studies

### Resection of Colorectal Hepatic Metastasis

<table>
<thead>
<tr>
<th>Study</th>
<th>( n )</th>
<th>5-year survival rate (%)</th>
<th>10-year survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hughes et al. (1986)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>607</td>
<td>33</td>
<td>No 10-year follow up</td>
</tr>
<tr>
<td>Nordlinger et al. (1996)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1,568</td>
<td>28</td>
<td>No 10-year follow up</td>
</tr>
<tr>
<td>Fong et al. (1999)&lt;sup&gt;5&lt;/sup&gt;</td>
<td>1,001</td>
<td>37</td>
<td>22</td>
</tr>
<tr>
<td>Pawlik et al. (2005)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>557</td>
<td>58</td>
<td>No 10-year follow up</td>
</tr>
</tbody>
</table>
International Registry of Lung Metastasectomy

J Thorac Cardiovasc Surg. 1997;113(1)
The Importance of Adequate Controls

The Effect of Metastasectomy: Fact or Fiction?


“Patients who fulfill the criteria for lung metastasectomy probably comprise a selected group with a particularly benign tumor-host relationship.”

“Randomized studies are needed in all groups for which we do not have sufficiently strong evidence that metastasectomy contributes to the longevity of the patients.”

![Graph showing survival rates after metastasectomy or diagnosis in 70 operated and 12 control patients.](image-url)

**Fig 2.** Survival after metastasectomy or diagnosis in 70 operated and 12 control patients.
Oligometastases

...oligomeanings

**Terminology**

- Oligo-metastases
  - synchronous
  - metachronous

- Oligo-recurrence
  - regional
  - systemic

- Oligo-persistance
- Oligo-progression
Is there level 1 evidence to support treatment?
Whole Brain Radiation With or Without SRS: RTOG 9508

333 patients randomized to WB alone (37.5 Gy in 15 fx) vs WB + SRS

- KPS >70; 1-3 lesions
- 75% controlled or absent primary site
- 10% breast primary (2/3 lung)
- SRS dose 15-24 Gy (size dependent)

Andrews DW, Lancet 363, 2004
### RTOG 9508: Results

<table>
<thead>
<tr>
<th></th>
<th>Whole Brain</th>
<th>Whole Brain + SRS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Survival</strong></td>
<td>5.7 mo</td>
<td>6.5 mo (p=ns)</td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Single lesion)</td>
<td>4.9 mo</td>
<td>6.5 mo (p=0.04)</td>
</tr>
<tr>
<td><strong>Local Control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(at one year)</td>
<td>71%</td>
<td>82% (p=0.01)</td>
</tr>
<tr>
<td><strong>Stable or improved</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KPS at 6 months</td>
<td>27%</td>
<td>43% (p=0.03)</td>
</tr>
</tbody>
</table>

Andrews DW, Lancet 363, 2004
Survival in Patients with a Single Brain Metastasis

RTOG 95-08 is the **ONLY level 1 evidence** to demonstrate an **overall survival** benefit with **SBRT/SRS** in oligometastatic disease

Andrews DW, Lancet 363, 2004
EORTC 40004

- Randomized phase II colorectal liver metastases
- N=119
- Systemic therapy alone or with RFA +/- resection
- Median follow-up 9.7 years
- 5-year OS 43.1% vs 30.3%
Overall log-rank test P=0.01

First randomized study to demonstrate aggressive local treatment improves OS in unresectable colorectal liver metastases.

EORTC 40004
Systemic Therapy with or without RFA

J Natl Cancer Inst. 2017;109(9)
Synchronous oligometastatic disease

Definition: De-novo presentation of oligo-metastases
Synchronous Oligometastatic NSCLC

Multicenter phase II RCT (MD Anderson, Colorado, London)

First-line treatment for oligometastatic stage IV NSCLC (1-3 metastases)

Acceptable regimens:
- ≥4 cycles of platinum-based doublet +/- BeV
- Erlotinib and crizotinib are acceptable for patients with EGFR mutations and EML4-ALK fusions, respectively.
- CNS metastases can be treated prior to enrollment

Eligibility
- 1-3 mets after completion of first-line treatment
- Non-PD
- PS 0-2
- Candidate for local therapy

Covariates
- Number of mets (1 vs. 2-3)
- Response to first-line chemo (SD vs. PR/CR)
- N0/N1 vs. N2/N3
- CNS Mets (yes/no)
- EGFR/EML4-ALK status

**Recommended systemic therapy options include bevacizumab, pemetrexed, and erlotinib

DSMC halted at n=49 → futility on primary endpoint

Slide courtesy D Gomez MDACC
Progression free survival:
11.9 vs 3.9 months; p=0.007

Time to appearance of disease at a new site:
11.9 vs 5.7 months; p=0.049
Updated analysis pending. Will a PFS benefit → OS benefit?

n = 17 patients in standard arm crossed over (14 after progressing, 3 by choice)
Randomized phase II trial of *osimertinib* with or without local consolidation therapy for patients with EGFR-mutant metastatic NSCLC

- Eligibility
  - TKI naïve
  - *EGFR* mut
  - Acquired T790M
  - *EGFR* no prior 3rd gen TKI

- Enrollment Window: 6-12 weeks
- Randomization
  - Non-PD
  - 60 patients
  - Primary Endpoint: PFS

- Osimertinib
  - 80 mg daily PO

- If ≤3 lesions
  - LCT to all lesions
- If >3 lesions
  - LCT to number of Lesions at physician discretion
- Osimertinib
  - 80 mg daily PO
  - 60 patients

Same design as original Gomez study but allows for tx of up to 5 mets in polymetastatic disease

Slide courtesy D Gomez MDACC
NRG-LU002: Randomized Phase II/III Study
NRG ONCOLOGY

Maintenance Systemic Therapy
Versus
Consolidative SBRT
Plus Maintenance Systemic Therapy For Limited Metastatic Non-Small Cell Lung Cancer (NSCLC)

PI: P. Iyengar, ClinicalTrials.gov: NCT03137771
## Schema of LU002 Phase II/III Study

<table>
<thead>
<tr>
<th>Patients with metastatic NSCLC having completed 4 cycles of first-line/induction systemic therapy</th>
<th>Histology: Squamous vs. Non-squamous</th>
<th>Arm 1: Maintenance systemic therapy alone</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></td>
<td></td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
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**In contrast to MD Anderson study:**

1. Phase II/III powered for OS
2. Allows for immunotherapy first line

ClinicalTrials.gov: NCT03137771

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NRG BR002 – (Synchronous breast)

- Patients with controlled local-regional disease, ≤ 4 mets and ≤ 12 months systemic therapy

- Randomization

  Standard systemic therapy with treatment of symptomatic metastases

  **vs.**

  Total ablation of all metastases (symptomatic and asymptomatic)

PI: Steve Chmura ClinicalTrials.gov  NCT02364557
NRG BR002

- **Phase IIr:**
  - Hypothesis: ablative local therapy all visible lesions with systemic therapy gives a signal for meaningful improvement in the PFS to warrant continuation to Phase III trial
  - Power to improve PFS from 10.5 to 19.5 months
  - Current enrollment 67/125

- **Phase III:**
  - Hypothesis: Multi-modality tx of oligometastases improves 5-yr OS
  - Additional 246 patients
  - Power to improve overall survival 28% to 42.5%

PI: Steve Chmura
ClinicalTrials.gov NCT02364557
Metachronous oligometastatic disease

Definition: After period initial disease-free interval, new presentation of oligo-metastases
SABR for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET)

- Any primary site ≤ 5 *metachronous* metastases
- 1:2 randomization of standard tx vs SABR
- Accrual goal: n=99
- Primary outcome: Overall survival
- Accrual completed – Results ASTRO 2018!

PI David Palma
ClinicalTrials.Gov 01446744

Figure 1
*Study design.* Patients will be randomized in a 1:2 ratio between Arm 1 (Standard of care) vs. Arm 2 (SABR).
Conventional Care vs Radioablation for Extracranial Oligometastases (CORE)

• Phase II/III

• Primary breast, NSCLC, prostate, ≤3 *metachronous* metastases

• Randomized phase II to demonstrate feasibility of recruitment, deliverability in a multi-center setting, and activity of SBRT

• If all 3 are achieved, this will roll into parallel disease-specific phase III

• Estimated accrual, 206
STOMP (metachronous prostate)

Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence

- Randomized Phase II
- Accrual goal: 58
- Maximum 3 extracranial metachronous metastases
- NOVEL Primary endpoint: androgen deprivation therapy-free survival
- Recruitment at 6 hospital in Belgium

PI: Piet Ost  Clinicaltrials.gov NCT01558427
ADT-Free Survival
Metastasis-directed Therapy vs Surveillance

- Median follow-up 3 years
- ADT-free survival 21 vs. 13 months
- QoL similar at baseline and comparable at 1 year
- No Grade 2-5 toxicity

Ost et al, J Clin Oncol epub 2017
SC.24 (oligomet spine)

Patients with tumours (excluding seminoma, small cell lung cancer and metastases from hematologic malignancies - e.g. lymphoma, myeloma) who have MRI-documented spinal metastases, suitable for receiving radiation therapy, and fulfill the following criteria:

- Pain secondary to spinal metastases requiring treatment
- \( \leq 3 \) consecutive spinal segments involved by tumour to be included in the target volume

**Randomization**

**ARM 1**
Standard Conventional Radiotherapy (CRT)
20 Gy in 5 fractions

**ARM 2**
Stereotactic Body Radiotherapy (SBRT)
24 Gy in 2 fractions

- Phase II/III RCT
- Accrual goal: (pII-54) / total 152
- **NOVEL** Primary endpoint: pain response
- Central review of all radiation plans
- **Investigator-level** credentialing!

PI A. Sahgal, Canadian Clinical Trials Group

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Oligoprogresive disease

Definition: Majority of metastatic disease controlled by systemic treatment, a few ‘resistant’ clones progress

Key question: can SBRT be considered a treatment line?
Stereotactic Radiotherapy for Oligo-Progressive Non-Small Cell Lung Cancer (STOP-NSCLC): A randomized phase II trial

Canadian Pulmonary Radiotherapy Investigators Group

www.capriclinicaltrials.com
Coincidence...?

HALT
Ablative Local Therapy for Oligo-Progressive Disease in Oncogene-Addicted Lung Tumours

Advanced NSCLC EGFR / ALK + with response to TKI

TKI

Progression

Oligo-Progression

Widespread Progression

Randomise (2:1)

SABR & continue TKI

Continue TKI

Primary Endpoint: Progression Free Survival

Target: 120 patients

Cl: Fiona McDonald
EGFR and ALK mutations

Mitsudomi IJCO 2006
EGFR and ALK TKIs

EGFR and ALK mutations are both **PROGNOSTIC** and **PREDICTIVE**

Often present in advanced stage, control of brain mets → QoL

**Can brain RT be omitted in patients with intracranial mets?**

- Newer TKIs have increased BBB penetration
- Intracranial response rates up to 85%
- Mets may be small and asymptomatic
Brain mets in targeted tx era
EGFR+ and brain mets


Multi-institutional (n=6) study of 351 EGFR TKI naïve patients

(1) SRS → EGFR-TKI
(2) WBRT → EGFR-TKI
(3) EGFR-TKI → SRS or WBRT (at intracranial progression)

Magnuson, JCO 2017
Take home points

- Initial SRS vs. initial TKI groups similar patient characteristics

**Rationale for upfront SRS as SOC**
- High BED of SRS ablates brain mets
- TKIs controls extracranial disease (and micromets in brain)
- Avoids neurocognitive effects of WBRT

Magnuson, JCO 2017
ALK+ and brain mets

Extended Survival and Prognostic Factors for Patients With ALK-Rearranged Non–Small-Cell Lung Cancer and Brain Metastasis


See accompanying editorial on page 107

• Same 6 institutions, n=90
ALK+ and brain mets

- TKI used (crizotinib) – 1st generation with limited brain penetrance
- High risk for brain recurrence after SRS, RT and surgery
- 40% found to have progressive brain mets at death

Johung, JCO 2017
New agents and SABR/SRS

Safety of TKIs and Radiotherapy

- Phase 2, single arm study
- n=24
- SBRT used to treat oligoprogression
- TKIs continued during SBRT
- No associated toxicity with SBRT and TKI delivered concurrently

Iyengar JCO 2014

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Caution with VEGF-modulating agents

- esophageal fistulae
Systematic or Meta-analysis Studies

Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: A systematic review

Stephanie G.C. Kroeze, Corinna Fritz, Morten Hoyer, Simon S. Lo, Umberto Ricardi, Arjun Sahgal, Rolf Stahel, Roger Stupp, Matthias Guckenberger

Kroeze Cancer Treatment Reviews 2017
Who is Most Likely to Benefit From Aggressive Treatment of Oligomets?

• Controlled primary / limited disease burden

• Good performance status

• Long disease-free interval (metachronous >> synchronous)

• Absence of regional/nodal disease

• Chemosensitive primary
RPA – Oligometastatic NSCLC

ALL PATIENTS
(T: n=363, V: n=168)
1yr OS: T: 71.9% (V: 68.5%)
2yr OS: T: 51.8% (V: 47.5%)
3yr OS: T: 41.4% (V: 36.1%)
4yr OS: T: 35.1% (V: 33.6%)
5yr OS: T: 30.5% (V: 27.5%)

Metachronous
(T: n=101, V: n=45)

LOW RISK
1yr OS: T: 88.4% (V: 87.7%)
2yr OS: T: 66.3% (V: 66.3%)
3yr OS: T: 62.5% (V: 59.9%)
4yr OS: T: 50.4% (V: 56.4%)
5yr OS: T: 47.8% (V: 51.7%)

Synchronous
(T: n=262, V: n=123)

N Stage: N0
(T: n=140, V: n=61)

INTERMEDIATE RISK
1yr OS: T: 76.2% (V: 74.6%)
2yr OS: T: 57.4% (V: 50.0%)
3yr OS: T: 42.9% (V: 36.8%)
4yr OS: T: 40.9% (V: 34.5%)
5yr OS: T: 36.2% (V: 29.2%)

N Stage: N1 or N2
(T: n=122, V: n=62)

HIGH RISK
1yr OS: T: 53.6% (V: 48.9%)
2yr OS: T: 34.1% (V: 32.1%)
3yr OS: T: 25.6% (V: 20.0%)
4yr OS: T: 18.3% (V: 18.2%)
5yr OS: T: 13.8% (V: 12.1%)

Ashworth et al, Clin Lung Ca 2014
Nomogram for lung mets

Lang, Ricardi, Hoyer, Guckenberger ELCC 2016

- NSCLC metastases associated with worse-than average OS
- However: long-term OS even in the highest risk group
What about SABR and IO?

Objectives
- Common toxicities
- Response rate (SABR lesion, non-SABR lesion, overall)
- Standard time-to-event outcomes
What about RT and IO?

KEYNOTE-001 (pembroluzimab)
- n=495
- Established cutoff of >50% PD-L1

Secondary analysis of UCLA patients
- 42 of 97 (43%) with prior RT
- 39% extracranial, 25% thoracic RT
- Prior RT \(\rightarrow\) improved PFS and OS

Shaverdian Lancet Oncology 2017

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IO + RT = increased pneumonitis?

<table>
<thead>
<tr>
<th>All recorded pulmonary toxicities*</th>
<th>No previous thoracic radiotherapy</th>
<th>Previous thoracic radiotherapy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any pulmonary toxicity</td>
<td>29 (40%)</td>
<td>15 (63%)</td>
<td>0.052</td>
</tr>
<tr>
<td>Specific pulmonary toxicities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>15 (21%)</td>
<td>6 (25%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Cough</td>
<td>16 (22%)</td>
<td>7 (29%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Wheezing</td>
<td>3 (4%)</td>
<td>1 (4%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1 (1%)</td>
<td>2 (8%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Respiratory failure†</td>
<td>4 (6%)</td>
<td>3 (13%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Grade ≥3 pulmonary toxicity</td>
<td>9 (12%)</td>
<td>4 (17%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>6 (8%)</td>
<td>0</td>
<td>..</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1 (1%)</td>
<td>1 (4%)</td>
<td>..</td>
</tr>
<tr>
<td>Respiratory failure†</td>
<td>2 (3%)</td>
<td>3 (13%)</td>
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</tr>
<tr>
<td>Treatment-related pulmonary toxicities‡</td>
<td></td>
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</tr>
<tr>
<td>Any pulmonary toxicity</td>
<td>1 (1%)</td>
<td>3 (13%)</td>
<td>0.046</td>
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<tr>
<td>Specific pulmonary toxicities</td>
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<tr>
<td>Dyspnoea</td>
<td>0</td>
<td>2 (8%)</td>
<td>0.059</td>
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<tr>
<td>Pneumonitis</td>
<td>1 (1%)</td>
<td>2 (8%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Grade ≥3 pulmonary toxicity</td>
<td>1 (1%)</td>
<td>1 (4%)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Shaverdian Lancet Oncology 2017
RT + IO key(note) points

Was the benefit due to the use of high-dose SABR?

X 64% of patients were treated with palliative RT

Was benefit due to brain mets RT (where IO not effective)?

X Inferior HR for PFS (0.59) and OS (0.62)

Was there an increased risk of pneumonitis with RT?
Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen, F. Carbonnel, C. Robert, K. M. Kerr, S. Peters, J. Larkin, K. Jordan, on behalf of the ESMO Guidelines Committee

Annals of Oncology, Volume 28, Issue suppl_4, 1 July 2017, Pages iv119–iv142,

Any respiratory event
- 20-40%

Grade 3+
cough 2-9%, dyspnea 1-2%

Treatment-related pneumonitis
fatal 0.2%, discontinuation 4%
Assigning and quantifying risks

Scoring of RT pneumonitis may be challenging due to confounding medical conditions

RT Fibrosis  OR

? Infection

? COPD exacerbation

? Tumor progression

? Cardiac causes

Kocak et al IJROBP 2005
IO + RT = increased pneumonitis?

- John Hopkin’s institutional experience (n=188) with IO
- IR-pneumonitis incidence significantly higher than clinical trials
- Incidence the same (19%), regardless of prior chest RT
- Risk higher in prior definitive/adjuvant (28%) vs. palliative (8%) RT

Naidoo, World Lung Cancer Conference 2017
Guidelines

UK Consensus on Normal Tissue Dose Constraints for Stereotactic Radiotherapy

G.G. Hanna*, L. Murray §, R. Patel †, S. Jain *, K.L. Aitken ‰, K.N. Franks §, N. van As †, A. Tree †, P. Hatfield §, S. Harrow ¶, F. McDonald †, M. Ahmed †, F.H. Saran †, G.J. Webster a, V. Khoo †, D. Landau b, D.J. Eaton †, M.A. Hawkins c

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