Stereotactic Radiation Therapy
Oligo Metastatic Disease

Ana Botero, MD
Radiation Oncology Department
Memorial Cancer Institute
Oligo Metastatic Disease (OMD)

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
Impressive Advancements in Radiation Therapy in the Last 70 years

1950’s
Cobalt machine

1960’s 1970’s 1980’s
Teletherapy Linear Accelerators
2D-CT scan
3D-CRT
IMRT
RapidArc
IGRT

1990’s
SBRT

Increase local control and decrease side effects
Oligodefinitions

• Synchronous
  Lesions at initial presentation, or within 6 months

• Metachronous
  Lesions appear later
  Presumably related to unresponsive clones, or those who have developed resistance

• Oligoprogression
  Most lesions are under control, but a few progress

• Oligopersistence
  Most lesions are responding, but a few remain
Premise

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 clinical significant oligometastatic disease state is that some patients so affected should be amenable to a curative therapeutic strategy”.

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
Survival from the Time of Distant Metastases

A

Surviving (%)

Patients at Risk: 383 185 111 89 18

Follow-up (years)

2 4 6 8 10

24%

B

Surviving (%)

NED

non-NED

78%

13%

2 4 6 8 10

Bishop AJ. Cancer. 2015, 121(24)
Patients Who Respond Do Better

<table>
<thead>
<tr>
<th>Time From NED</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)³</td>
<td>607</td>
<td>33</td>
<td>No 10-year follow up</td>
</tr>
<tr>
<td>Nordlinger et al. (1996)⁴</td>
<td>1,568</td>
<td>28</td>
<td>No 10-year follow up</td>
</tr>
<tr>
<td>Fong et al. (1999)⁵</td>
<td>1,001</td>
<td>37</td>
<td>22</td>
</tr>
<tr>
<td>Pawlik et al. (2005)⁶</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)
Is there level 1 evidence to support treatment?
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.”

Fig 2. Survival after metastasectomy or diagnosis in 70 operated and 12 control patients.
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>Overall Survival</td>
<td>5.7 mo</td>
<td>6.5 mo (p=ns)</td>
</tr>
<tr>
<td><strong>Overall Survival</strong> (Single lesion)</td>
<td>4.9 mo</td>
<td>6.5 mo (p=0.04)</td>
</tr>
<tr>
<td>Local Control (at one year)</td>
<td>71%</td>
<td>82% (p=0.01)</td>
</tr>
<tr>
<td>Stable or improved KPS at 6 months</td>
<td>27%</td>
<td>43% (p0.03)</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.
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%

J Natl Cancer Inst. 2017;109(9)
EORTC 40004
Systemic Therapy with or without RFA

Overall log-rank test P=0.01

First randomized study to demonstrate aggressive local treatment improves OS in unresectable colorectal liver metastases.
J Natl Cancer Inst. 2017;109(9)
Synchronous oligometastatic disease

De-novo presentation of oligo-metasases
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+/−BV
- 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/EML4ALK status

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

DSMC halted at n=49 → futility on primary endpoint
**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; \( p = 0.049 \)

*Lancet Oncology 17 (12) 2016*
Prognostic Factors for PFS

- Two other factors associated with PFS:
  - Number of Mets after FLST
  - EGFR/ALK Status

Updated analysis pending. Will a PFS benefit \( \rightarrow \) OS benefit?

\( n = 17 \) patients in standard arm crossed over (14 after progressing, 3 by choice)
NORTHSTAR (synchronous EGFR+ lung)

Randomized phase II trial of osimertinib with or without local consolidation therapy for patients with EGFR-mutant metastatic NSCLC

Same design as original Gomez study but allows for tx of up to 5 mets in polymetastatic disease
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>
<th>Arm 2: SBRT to all sites of metastases (≤ 3 discrete sites) plus irradiation of the primary site (SBRT or hypofractionated RT) followed by maintenance systemic therapy</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>
<td></td>
</tr>
</tbody>
</table>

**In contrast to MD Anderson study:**

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

Clinical Trials.gov. NCT03137771
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)
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. Clinical Trials. Gov 01446744
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

Royal Marsden
Clinicaltrials.gov 02759783
**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. Clinical Trials. 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 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
- ≤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: (pl1-54) / total 152
- NOVEL Primary endpoint: pain response
- Central review of all radiation plans
- Investigator-level credentialing!

PI: A. Sahgai. Canadian Clinical Trials Group
**Oligoprogressive disease**

**Definition:** Majority of metastatic disease controlled by systemic treatment, a few ‘resistant’ clones progress
STOP - Oligoprogression Trial

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

CI: 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 Treatment Era

Khalifa, JTO 2016


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

(1) SRS $\rightarrow$ EGFR-TKI
(2) WBRT $\rightarrow$ EGFR-TKI
(3) EGFR-TKI $\rightarrow$ 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

ALK+ and brain mets

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

- Same 6 institutions, n=90

Johung, JCO 2017
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

Esophageal Dose Tolerance to Hypofractionated Stereotactic Body Radiation Therapy: Risk Factors for Late Toxicity

Kevin L. Stephans, MD,* Toufik Djemil, PhD,* Claudiu Diaconu, MD,† Chandana A. Reddy, MS,* Ping Xia, PhD,* Neil M. Woody, MD,* John Greskovich, MD,* Vinit Makkar, MD,‡ and Gregory M.M. Videtic, MD, CM, FRCPC*

Caution with VEGF-modulating agents
• esophageal fistulae

Stephans, Red Journal 2018
New Agents and SABR/SRS
Who is Most Likely to Benefit From Aggressive Treatment of Oligometas?

- 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: NO
(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
Nomograms for Lung Mets

Training cohort: n=671
Validation cohort n=145 & 92

Lang, Ricardi, Hoyer, Guckenberger ELCC 2016

> NSCLC metastases associated with worse-than-average OS
> However: long-term OS even in the highest risk group
Limited Number of Brain Metastases
Multiple Brain Metastases
Multiple Brain Metastases
GammaKnife
Multiple Brain Metastases

47 yo male, lung mets
GammaKnife, 18 Gy min dose
Tumor Progression vs. Radiation Necrosis
What about SABR and IO?

- Safety?
- Timing?
- Side effects
- Results?

SABR and IO new standard of care?
A new paradigm has recently emerged where patient treatment must be tailored to the particular case.

“One size fits all” approach is no longer appropriate in patients with stage IV cancer patients!
Thank you!
Learning Objectives

• To explore how personalized medicine may provide unique opportunities for radiation oncologists
• To understand emerging techniques for detection of minimal residual disease or early recurrence of cancers treated with radiation
• To understand promising biomarkers that may predict for benefit from radiotherapy
Major Themes

• Personalization of therapy based on biomarkers of treatment resistance or response

• Predictive Biomarkers: Tissue and tumor derived biomarkers to predict benefit of treatment

• Prognostic Biomarkers: Tissue and tumor derived biomarkers that estimate outcome, regardless of treatment undertaken

• Personalized radiotherapy
Circulating Tumor DNA Analysis during Radiation Therapy for Localized Lung Cancer Predicts Treatment Outcome

AA Chaudhuri¹, AF Lovejoy¹, JJ Chabon¹, A Newman¹, H Stehr¹, DJ Merriott², JN Carter¹, TD Azad¹, S Padda¹, MF Gensheimer¹, HA Wakelee¹, JW Neal¹, BW LooJr.¹, AA Alizadeh¹, M Diehn¹

¹Stanford Cancer Institute, Stanford, CA
²Stanford University School of Medicine, Stanford, CA
**Background**

- **ctDNA** = circulating tumor DNA
  - Typically <1% of total cell-free DNA in cancer patients

- **MRD** = Minimal Residual Disease or Molecular Residual Disease
  - Prognostic biomarker important in the management of leukemia
  - Currently no role in lung cancer management

**Hypothesis:** ctDNA analysis can detect MRD after definitive intent lung cancer treatment. ctDNA MRD detection is prognostic.

Chaudhuri et al, Sem Rad Onc, 2015
Progression likely
High risk of toxicity
Low risk of recurrence

Personalized Medicine

Standard radiotherapy indicated
Alternative or intensified treatment
Likely to experience toxicity: modify or avoid treatment
No treatment indicated low risk of recurrence
Study Design

Localized Primary Lung Cancer

Treatment with Definitive Intent

Radiotherapy or Surgery +/- Chemotherapy

MRD assessment within 4 months
(~1st clinical follow-up)

ctDNA pre-tx

ctDNA mid-tx

ctDNA post-tx

Exploratory subgroup analysis
CAPP-Seq Design and Implementation

Population-level Bioinformatics

Recruent Mutations

TGATCTAGTGACGT
TGATATTGGACGG
TGATCTTGACGG

Custom Oligos

CAPP-Seq Selector Library

Patient-level Analysis

10cc Blood

Cell-Free DNA (cfDNA)

Hybrid Capture

Next Generation Sequencing

Mutation detection

ctDNA detection limit: ~0.0015%

Newman & Bratman et al, Nature Medicine, 2014
Newman, Lovejoy & Klass et al, Nature Biotech, 2K
<table>
<thead>
<tr>
<th>Parameter</th>
<th>$n = 41$</th>
</tr>
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<tbody>
<tr>
<td>Follow-up time (mo)</td>
<td>35.1 (6.9-56)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>66.8 (47-91)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (68%)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (32%)</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36 (88%)</td>
</tr>
<tr>
<td>No</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>Pack-years</td>
<td>30 (0-150)</td>
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<tr>
<td>Stage</td>
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<td>IA</td>
<td>1 (2%)</td>
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<td>IB</td>
<td>7 (17%)</td>
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<td>IIA</td>
<td>3 (7%)</td>
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<td>IIIA</td>
<td>15 (37%)</td>
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<td>11 (27%)</td>
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<tr>
<td>Histology</td>
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<tr>
<td>Adenocarcinoma</td>
<td>20 (49%)</td>
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<tr>
<td>Squamous carcinoma</td>
<td>15 (37%)</td>
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<tr>
<td>Small Cell</td>
<td>3 (7%)</td>
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<td>NOS</td>
<td>3 (7%)</td>
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<tr>
<td>Local therapy</td>
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<tr>
<td>Radiotherapy</td>
<td>36 (88%)</td>
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<td>Radiotherapy + Surgery</td>
<td>3 (7%)</td>
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<td>Surgery</td>
<td>2 (5%)</td>
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<td>Chemotherapy</td>
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<td>28 (68%)</td>
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<tr>
<td>No</td>
<td>13 (32%)</td>
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<tr>
<td>Circulating DNA</td>
<td></td>
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<tr>
<td>ctDNA detected pre-tx</td>
<td>39 (95%)</td>
</tr>
</tbody>
</table>
Patients with detectable ctDNA MRD have significantly worse outcomes

- Progression (%)
  - $P < 0.00001$
  - HR = 41.0

- Disease-Specific Survival (%)
  - $P < 0.00001$
  - HR = 25.3

- Overall Survival (%)
  - $P = 0.00002$
  - HR = 12.9
Early post-treatment CT imaging is not prognostic

30 patients had CT imaging analyzed by RECIST at the MRD landmark.
Patient with ctDNA MRD not detected who later recurred.

Radiology interpretation:
- Stage III Adeno
- No disease
- No disease
- Local Recurrence

Scan 1: chemoRT
Scan 2: chemo
Scan 3: ND
Scan 4: ND

ctDNA concentration (hGE/mL)

Chaudhuri et al, Cancer Discovery, in press
13 patients with ctDNA measured within 4 weeks of chemoRT start

- <0.1% ctDNA (n = 5)
- >0.1% ctDNA (n = 8)

Cox Regression
- \( P = 0.037 \)
- HR = 4.4
- \( P = 0.006 \)
- HR = 2.7

These findings are exploratory but suggest that ctDNA quantitation early during treatment could potentially identify patients at high risk for disease recurrence.
Strategies to combined ICI and RT