Stereotactic Radiation Therapy Oligo Metastatic Disease

Ana Botero, MD

Radiation Oncology Department

Memorial Cancer Institute

Memorial Global Health

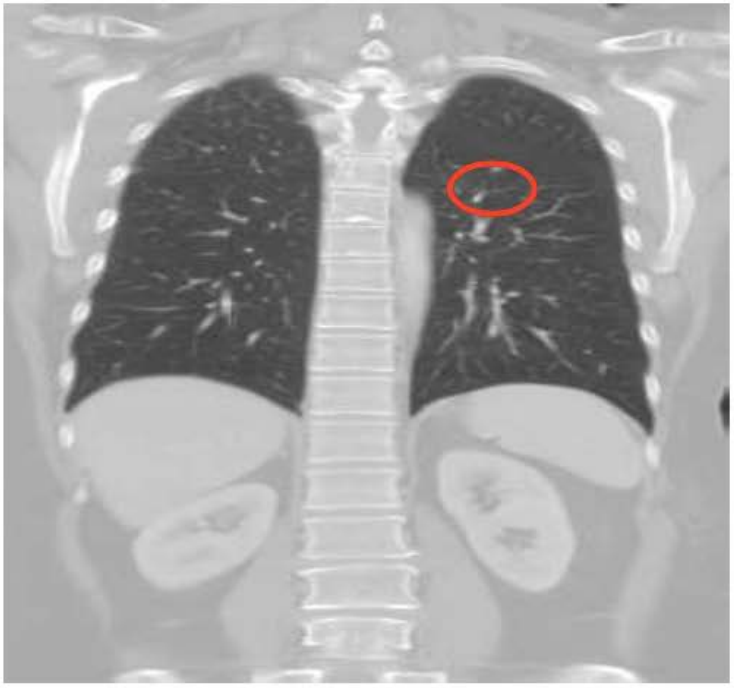
Oligo Metastatic Disease (OMD)

Learning Objectives

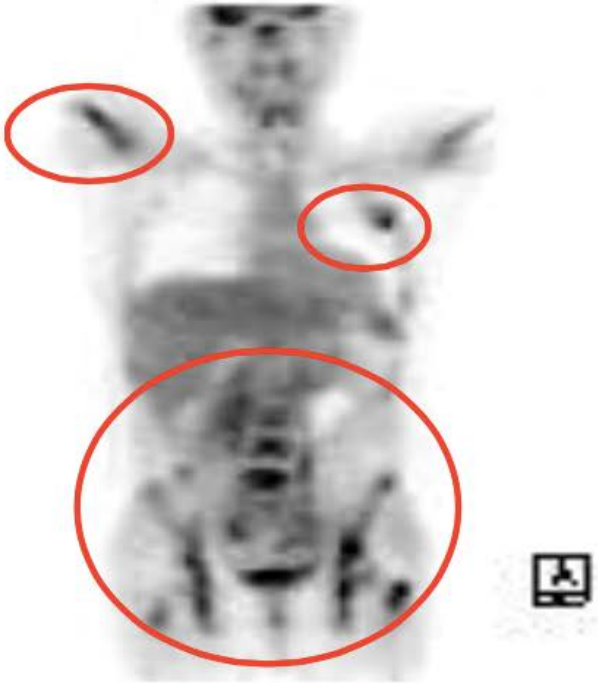
- Describe the various types of oligometastatic disease as well as pros versus cons of treatment
- Identify prognostic factors associated with improved outcome that may lend to appropriateness of aggressive treatment in oligometastatic disease
- Be aware of ongoing clinical trials evaluating the role 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)



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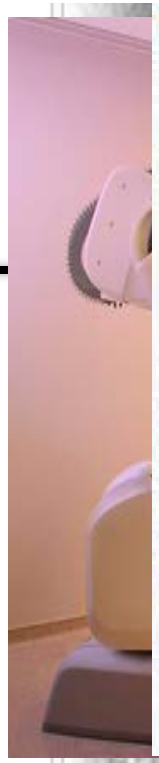
Increased Interest in Recent Years

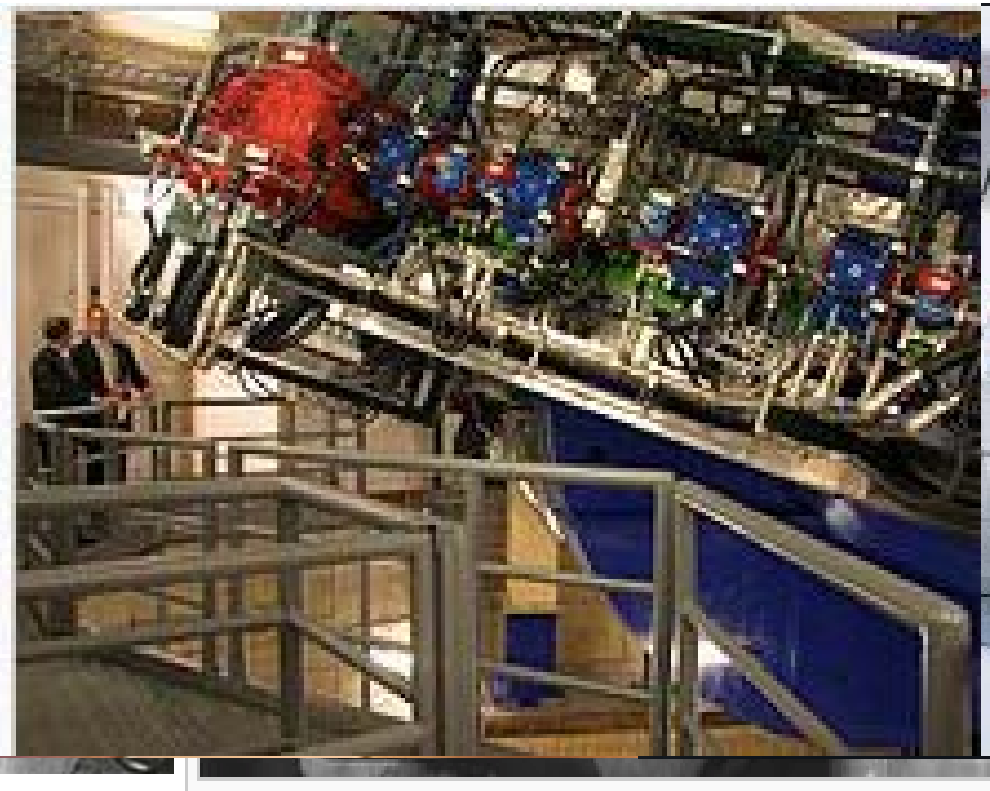
- Improved imaging to identify more extensive distant metastases
- Improved systemic therapy to treat additional sites of microscopic disease
- Less invasive surgery
  - e.g. VATS
- More conformal radiation (SBRT)
  - Ablative dose
  - Fewer side effects

Impressive Advancements in Radiation Therapy in the Last 70 years

1950's

Cobalt machine





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
- **Oligoprogession**
  - Most lesions are under control, but a few progress
- **Oligopersistence**
  - Most lesions are responding, but a few remain

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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".

Hellman and Weichselbaum, J Clin Oncol 13:8 (1995)

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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)

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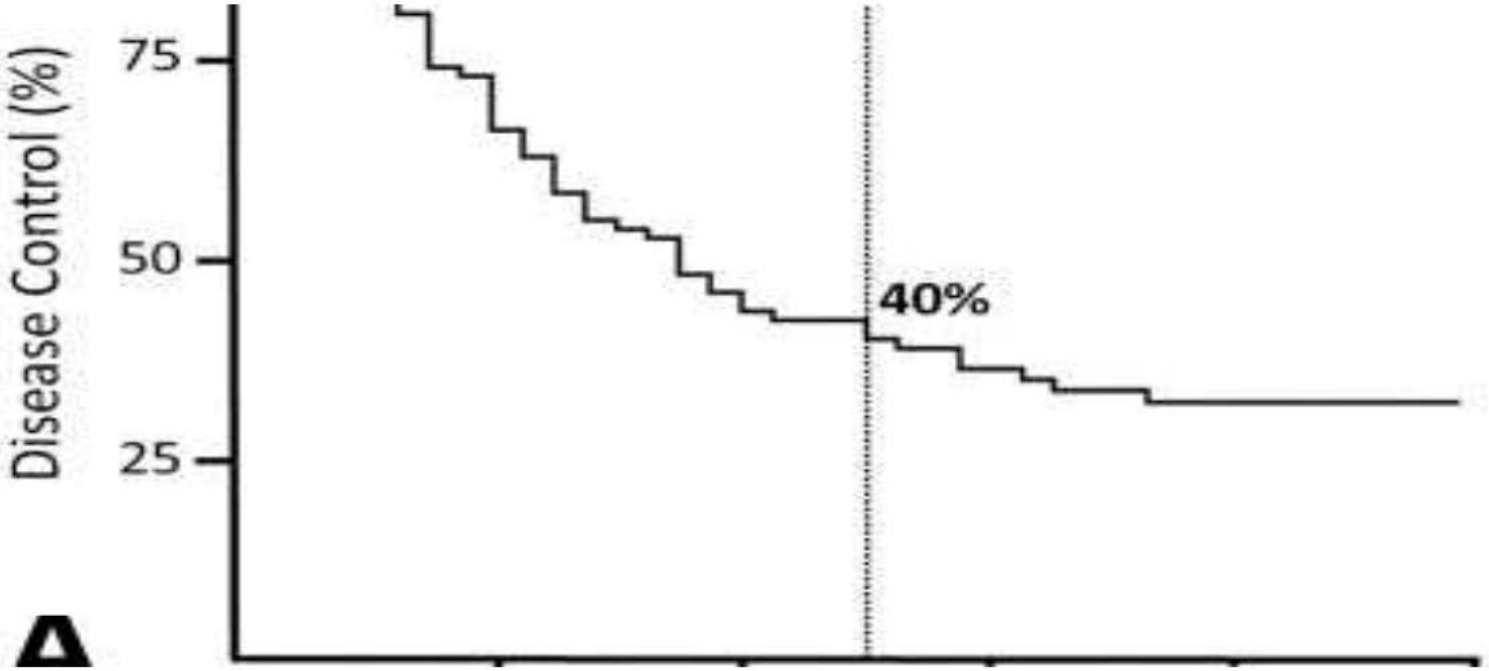
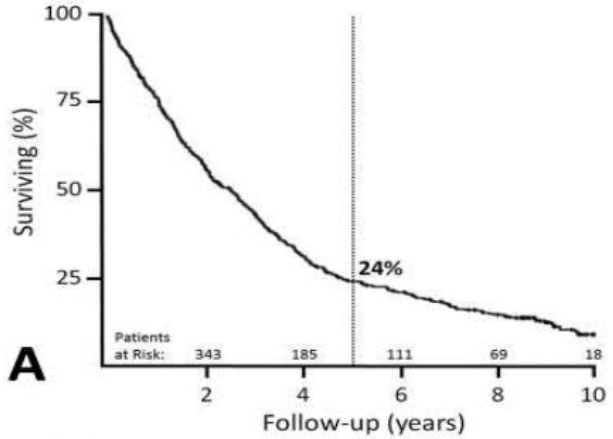
PFS From Time of NED



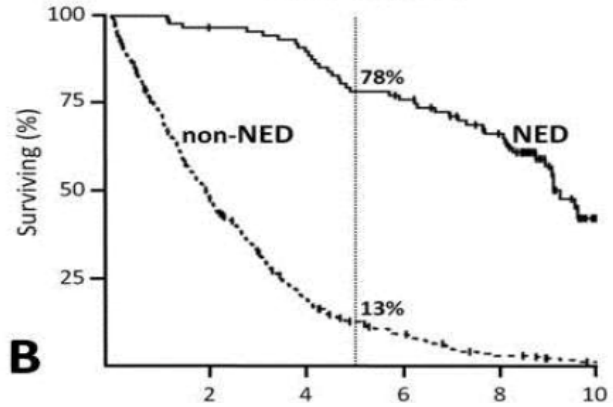
Bishop AJ, Cancer. 2015

Survival from the Time of Distant Metastases

All Patients



Those Attaining NED or Not Attaining NED



Bishop AJ. Cancer. 2015, 121(24)

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Patients Who Respond Do Better

Time From NED	Overall Survival (%)	Progression-Free Survival (%)
1-year	98	87
3-year	89	54
5-year	77	40

Bishop AJ. Cancer. 2015, 121(24)

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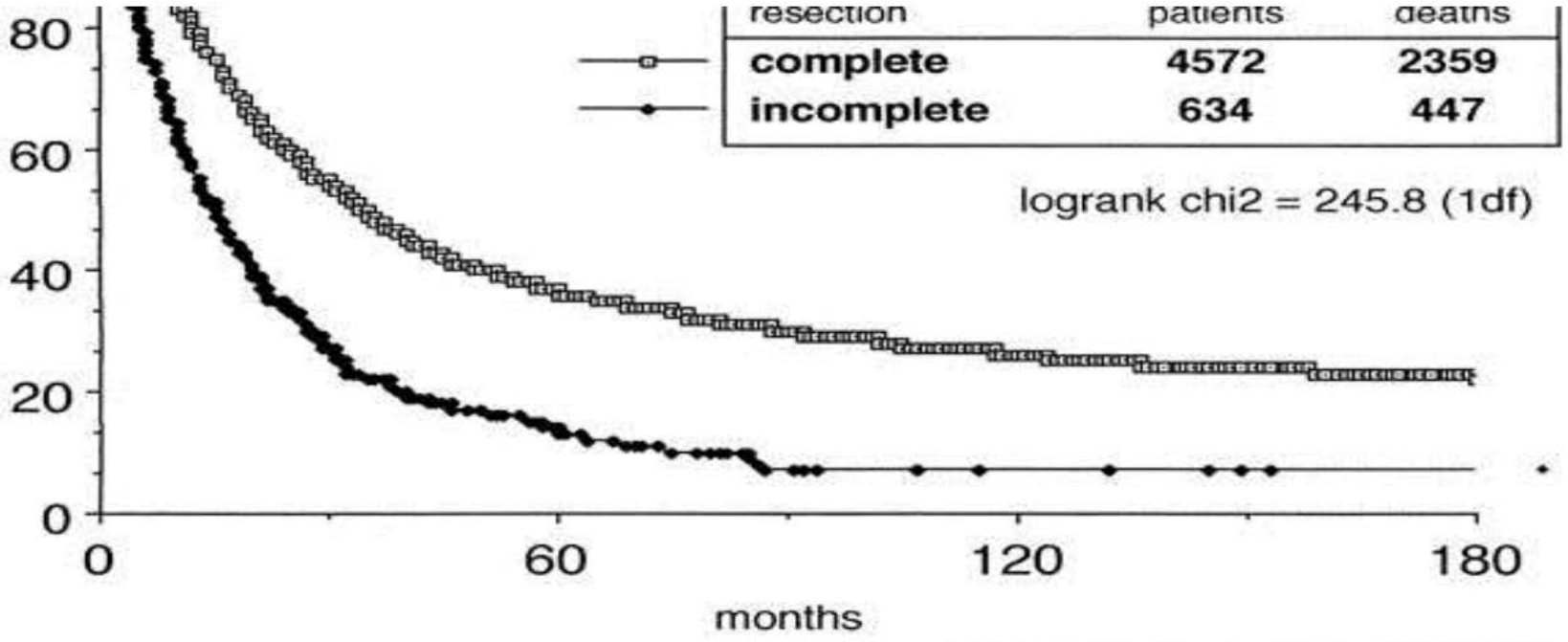
Non-randomized Studies
Resection of Colorectal Hepatic Metastasis

Study	*n*	5-year survival rate (%)	10-year survival rate (%)
Hughes *et al.* (1986)[3]	607	33	No 10-year follow up
Nordlinger *et al.* (1996)[4]	1,568	28	No 10-year follow up
Fong *et al.* (1999)[5]	1,001	37	22
Pawlik *et al.* (2005)[6]	557	58	No 10-year follow up

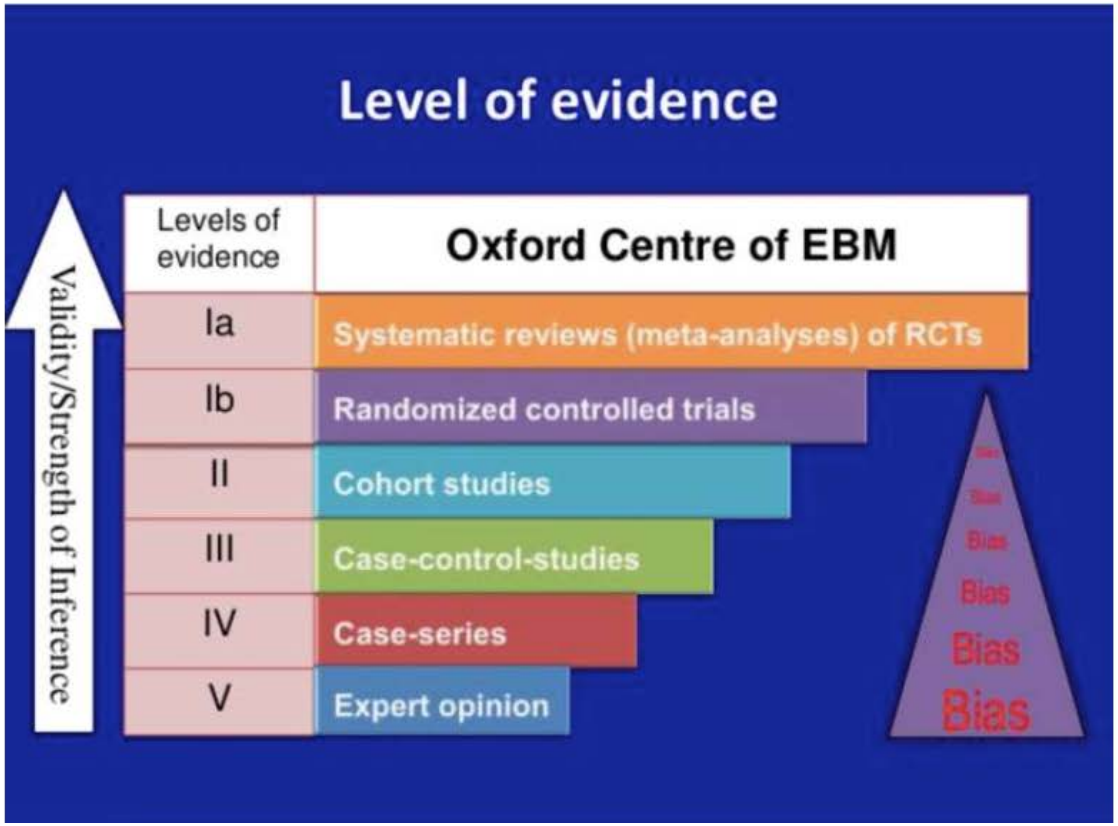
Weischelbaum, R and Hellman, S. Oligometastatic revised. Nat Rev.Clin.Oncol. 2011

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?

Torkel Åberg, M.D., Kjell-Åke Malmberg, M.D.,
Bert Nilsson, M.D., and Enn Nõu, M.D.

Ann Thorac Surg 1980;30:378-384

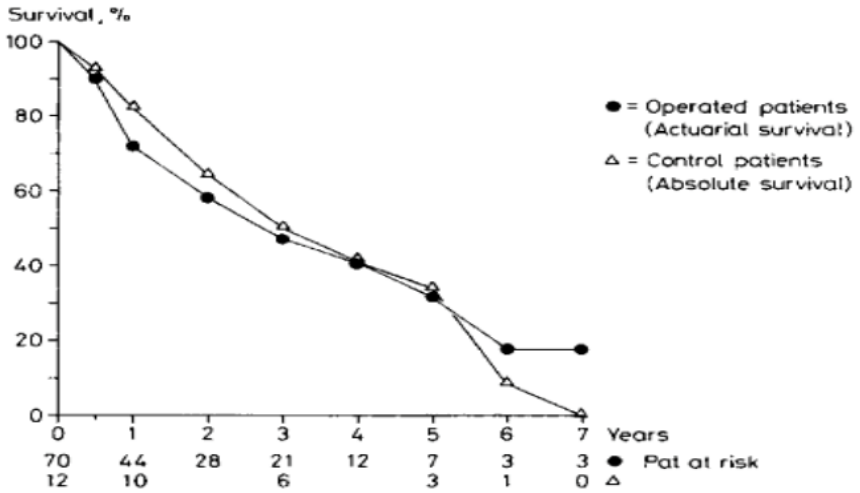


Fig 2. Survival after metastasectomy or diagnosis in 70 operated and 12 control patients.

"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."

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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

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RTOG 9508: Results

	Whole Brain	Whole Brain + SRS
Overall Survival	5.7 mo	6.5 mo (p=ns)
Overall Survival (Single lesion)	4.9 mo	6.5 mo (p=0.04)
Local Control (at one year)	71%	82% (p=0.01)
Stable or improved KPS at 6 months	27%	43% (p0.03)

Andrews DW, Lancet 363, 2004

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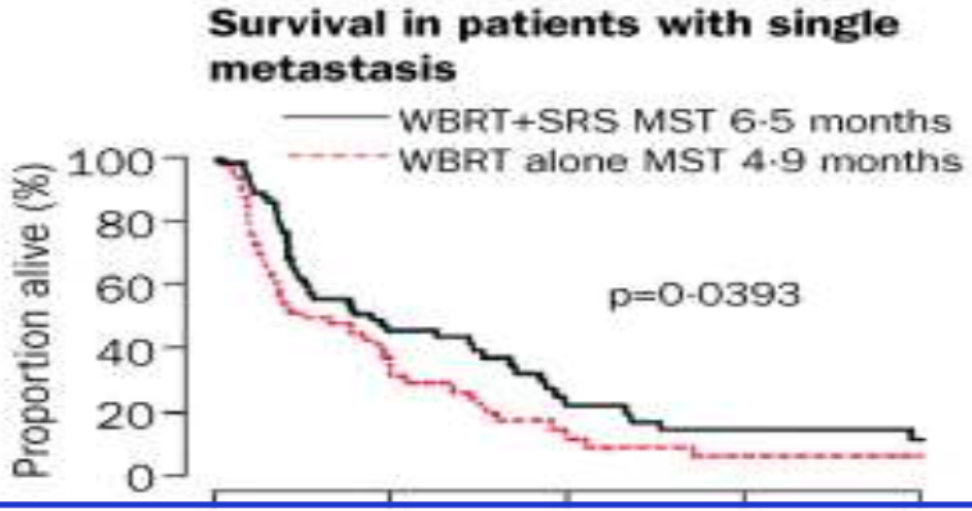
Survival in Patients with a Single Brain Metastasis



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

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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)

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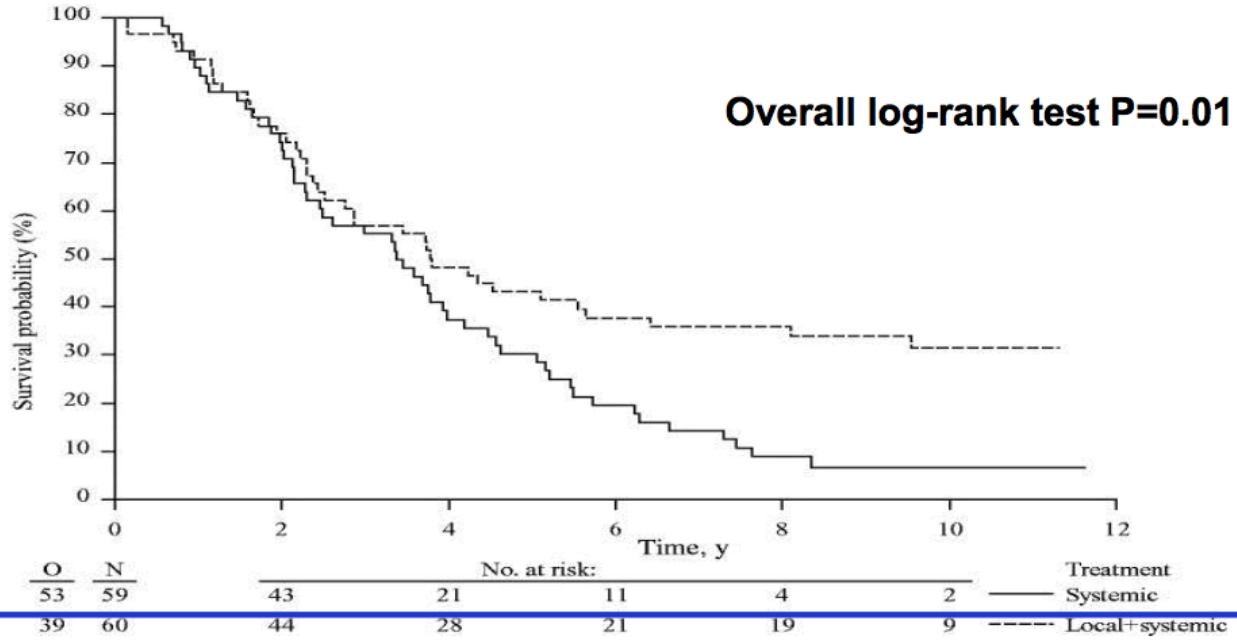
EORTC 40004
Systemic Therapy with or without RFA



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

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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

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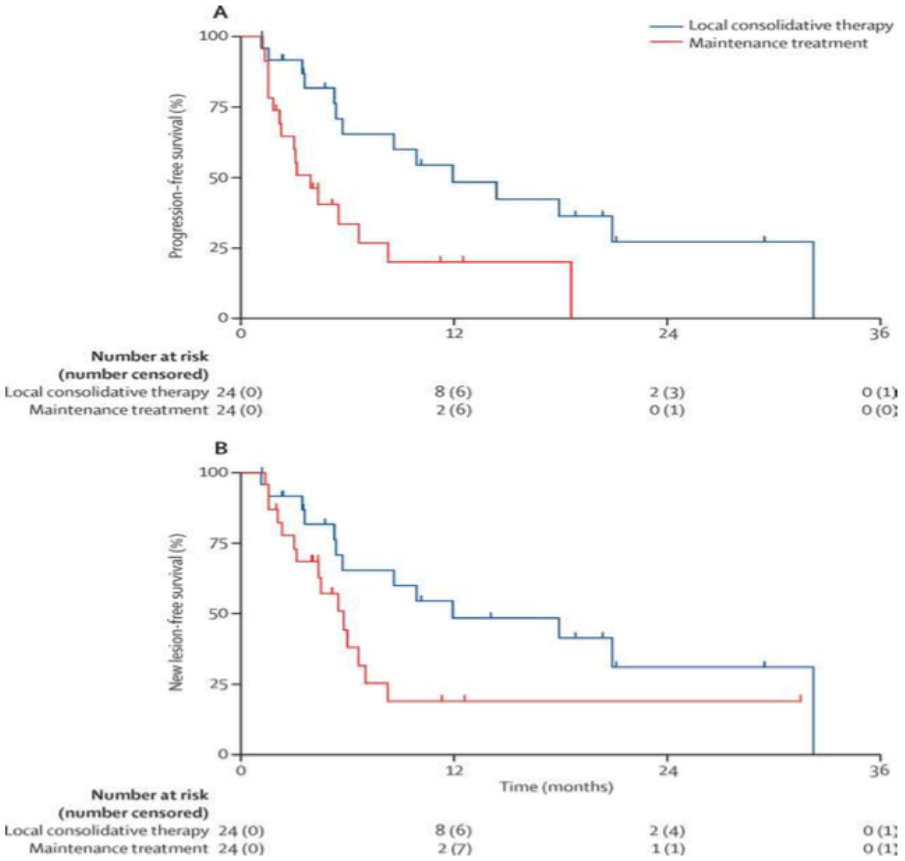

Progression free survival :
11.9 vs 3.9 months; p=0.007

Time to appearance of disease at a new site:
11.9 vs 5.7 months; p=0.049

Lancet Oncology 17 (12) 2016

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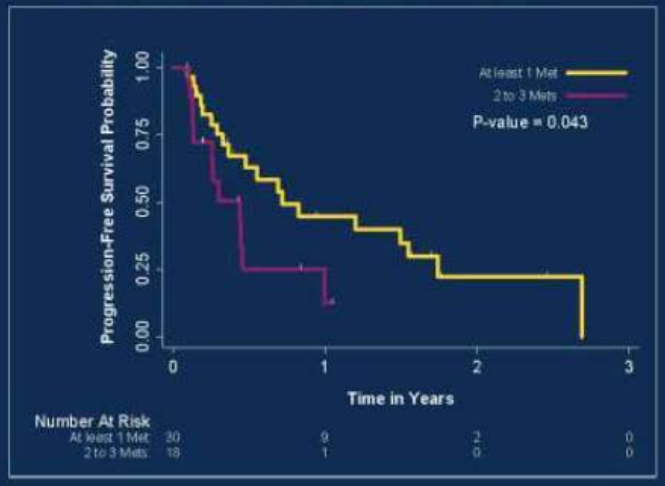
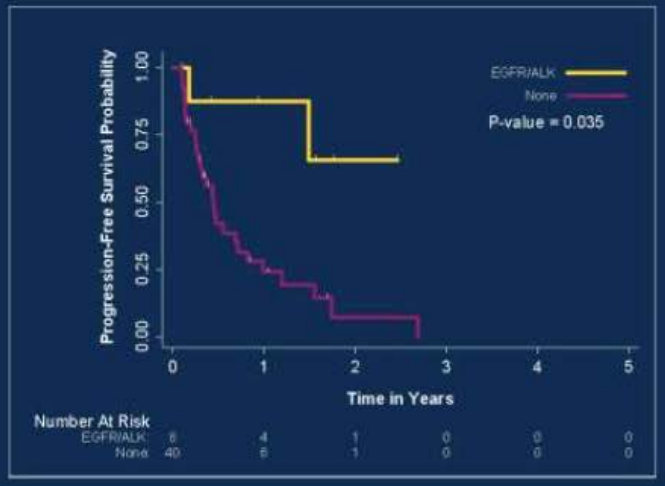
Prognostic Factors for PFS

- Two other factors associated with PFS:

Number of Mets after FLST



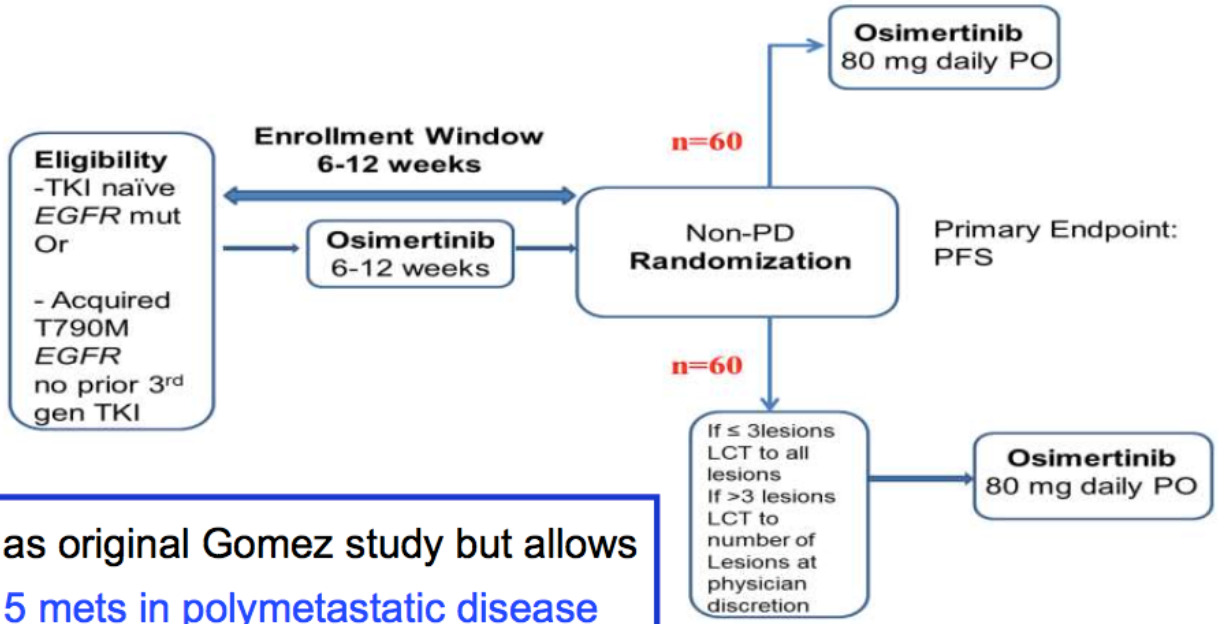
EGFR/ALK Status



Updated analysis pending. Will a **PFS benefit → 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

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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

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Schema of LU002 Phase II/III Study

Patients with metastatic NSCLC having completed 4 cycles of first-line/induction systemic therapy Restaging studies reveal no evidence of progression and limited (≤ 3 discrete sites) metastatic disease, all of which must be amenable to SBRT	STRATIFY	Histology: Squamous vs. Non-squamous	RANDOMIZE	Arm 1: Maintenance systemic therapy alone 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

In contrast to MD Anderson study:

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

Clinical Trials.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)

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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

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Metachronous oligometastatic disease

Definition: After period initial disease-free interval, new presentation of oligo-metastases

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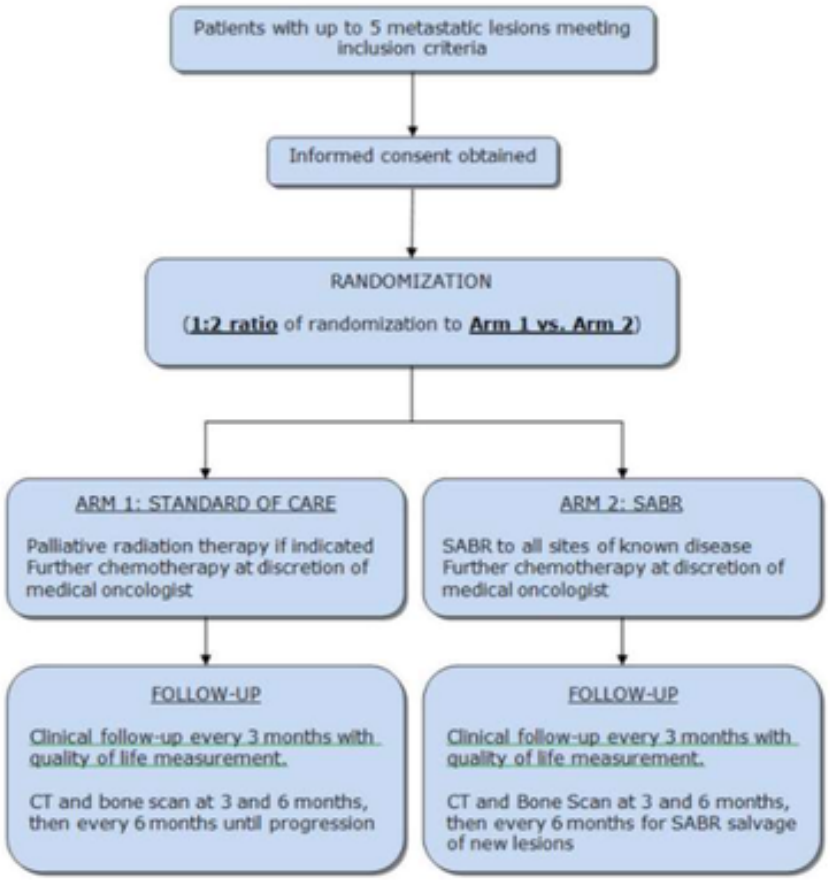

SABR for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET)

- 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

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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

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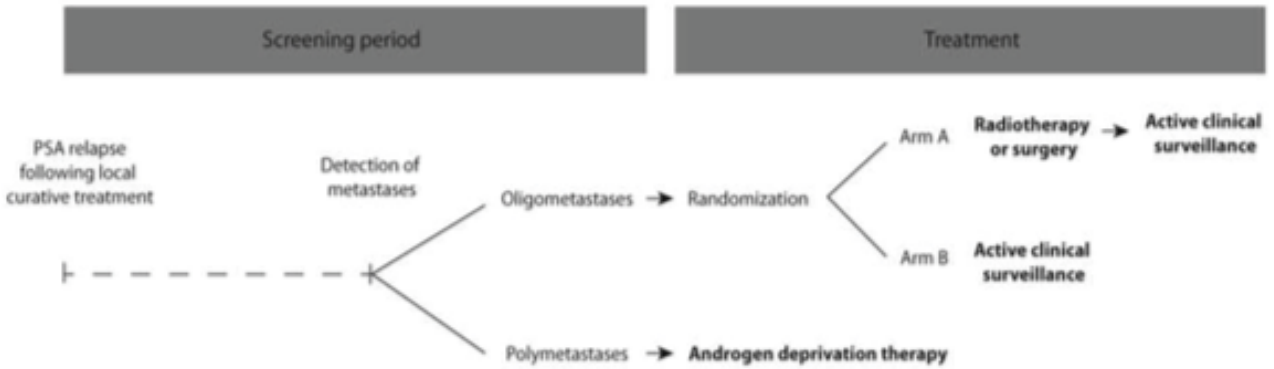
STOMP (metachronous prostate)

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

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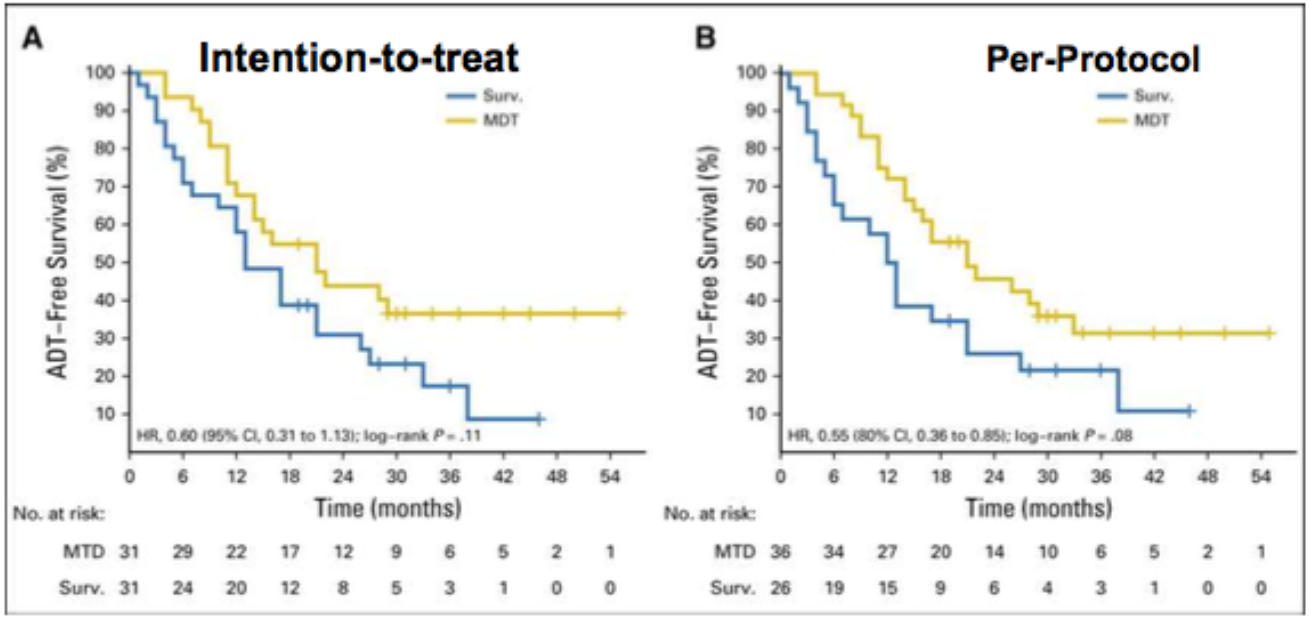
ADT-Free Survival

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

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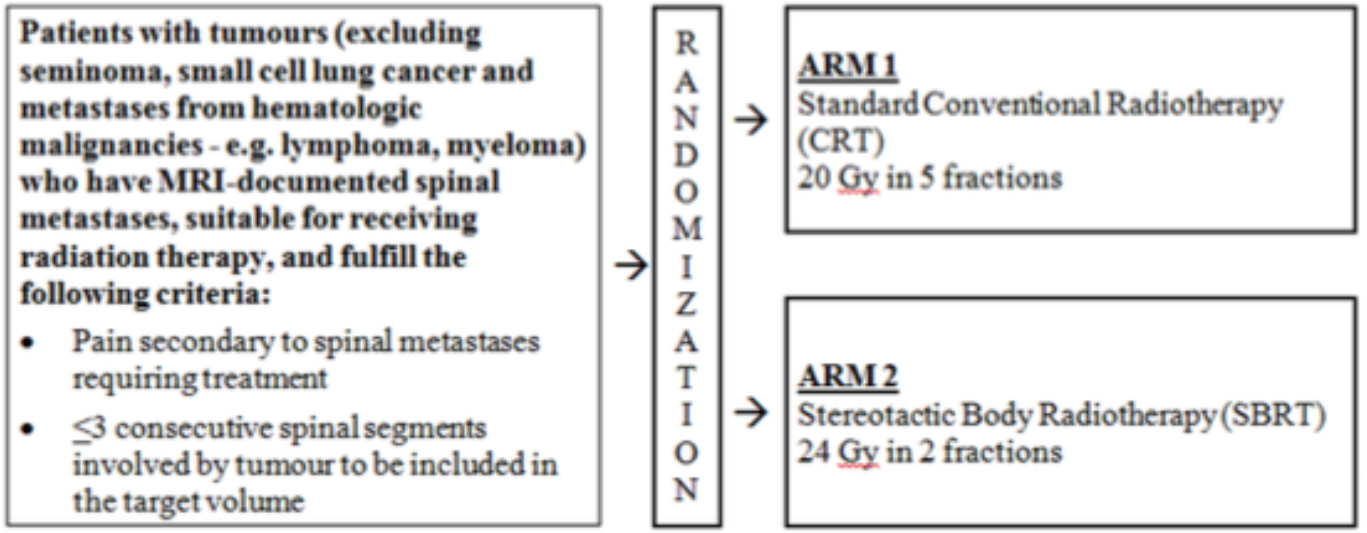
SC.24 (oligomet spine)



- **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. 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

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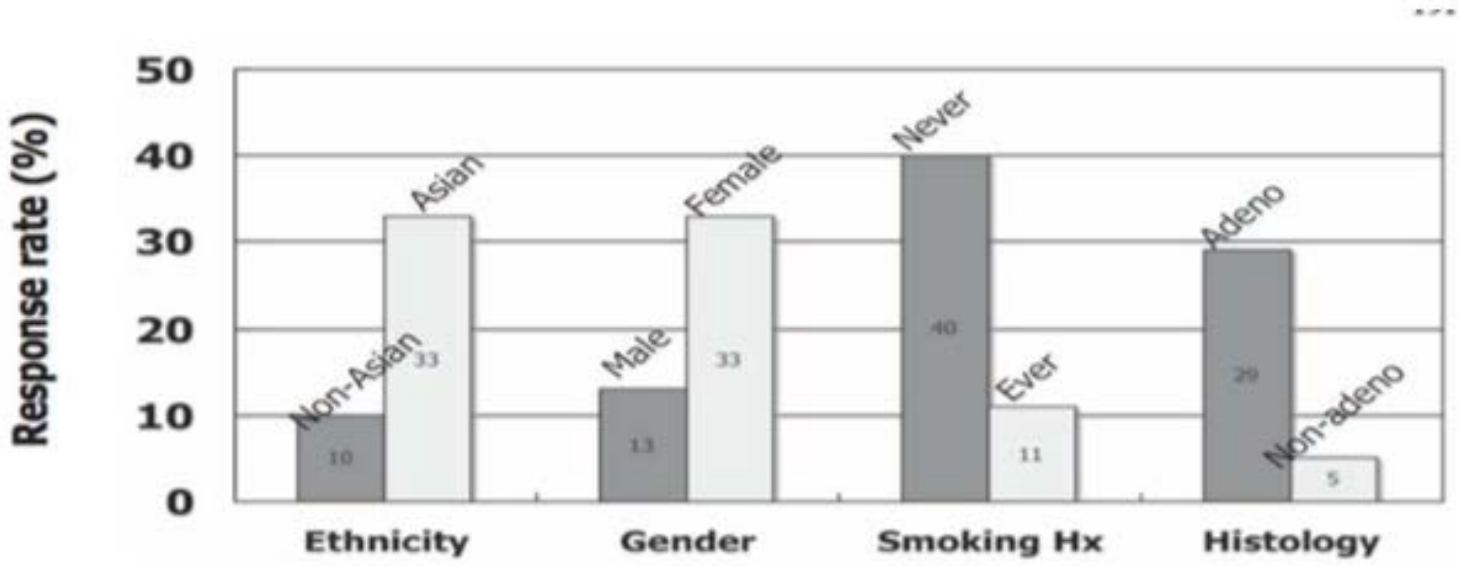
HALT

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

CI: Fiona McDonald

EGFR and ALK mutations



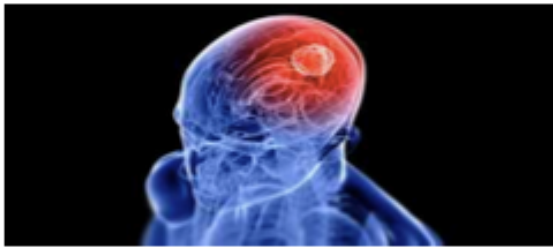
Mitsudomi IJCO 2006

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

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Brain Mets in Targeted Treatment Era

REVIEW ARTICLE

IASLC

Brain Metastases from NSCLC: Radiation Therapy in the Era of Targeted Therapies

CrossMark

Jonathan Khalifa, MD,[a,*] Arya Amini, MD,[b] Sanjay Popat, PhD,[c] Laurie E. Gaspar, MD, MBA,[d] Corinne Faivre-Finn, MD, PhD,[e,f] on behalf of the International Association for the Study of Lung Cancer Advanced Radiation Technology Committee

Khalifa, JTO 2016

EGFR(+) and Brain Mets

Management of Brain Metastases in Tyrosine Kinase Inhibitor–Naïve Epidermal Growth Factor Receptor–Mutant Non–Small-Cell Lung Cancer: A Retrospective Multi-Institutional Analysis

William J. Magnuson, Nataniel H. Lester-Coll, Abraham J. Wu, T. Jonathan Yang, Natalie A. Lockney, Naamit K. Gerber, Kathryn Beal, Arya Amini, Tejas Patil, Brian D. Kavanagh, D. Ross Camidge, Steven E. Braunstein, Lauren C. Boreta, Suresh K. Balasubramanian, Manmeet S. Ahluwalia, Niteshkumar G. Rana, Albert Attia, Scott N. Gettinger, Joseph N. Contessa, James B. Yu, and Veronica L. Chiang

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

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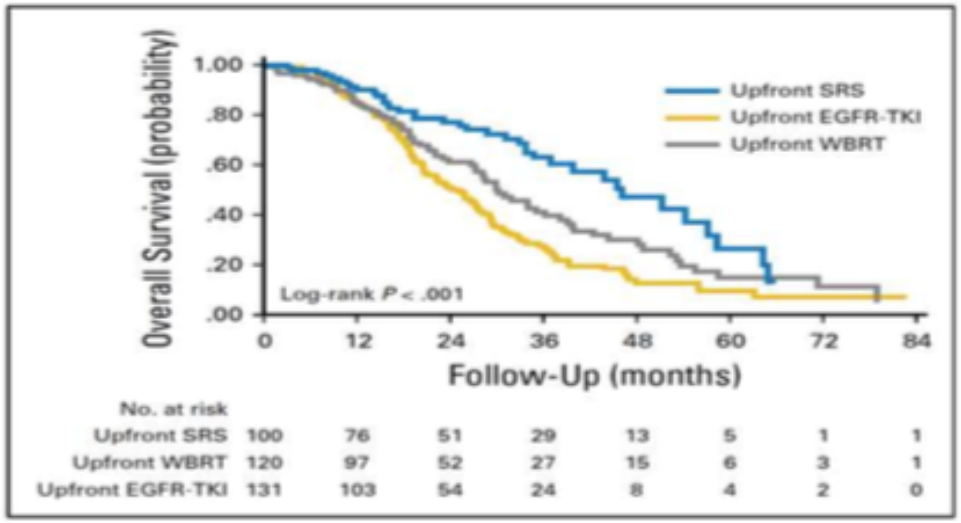
Take home points



- 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

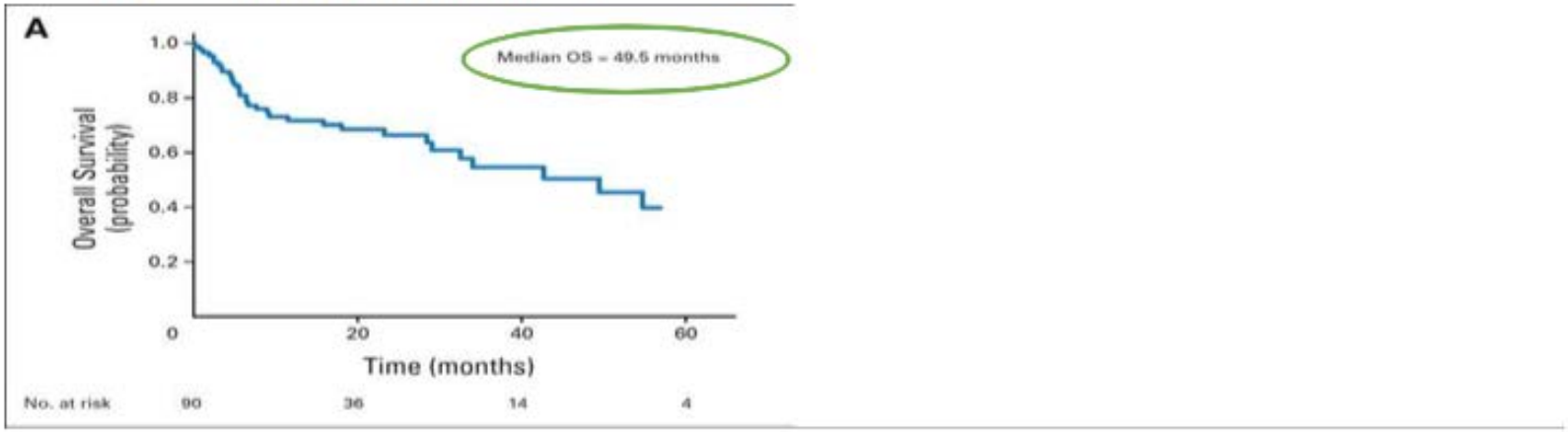
ALK+ and brain mets

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

Kimberly L. Johung, Norman Yeh, Neil B. Desai, Terence M. Williams, Tim Lautenschlaeger, Nils D. Arvold, Matthew S. Ning, Albert Attia, Christine M. Lovly, Sarah Goldberg, Kathryn Beal, James B. Yu, Brian D. Kavanagh, Veronica L. Chiang, D. Ross Camidge, and Joseph N. Contessa

See accompanying editorial on page 107

- Same 6 institutions, n=90



Johung, JCO 2017

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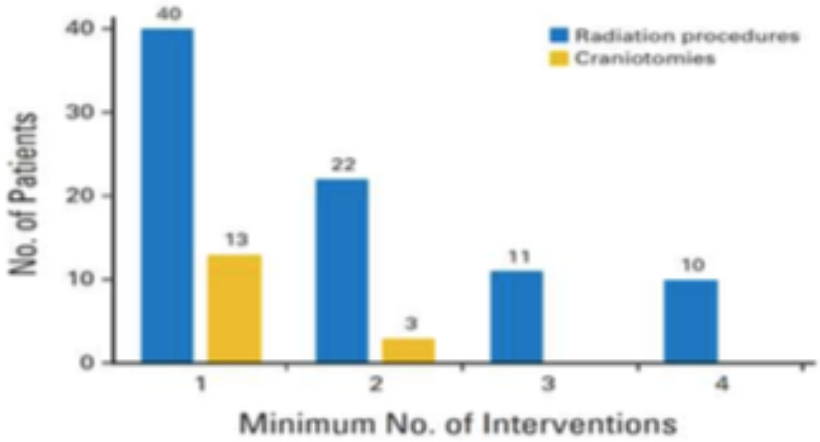
ALK(+) and Brain Mets

- 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

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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

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Systematic or Meta-analysis Studies

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

Stephanie G.C. Kroeze [a,*], Corinna Fritz [a], Morten Hoyer [b], Simon S. Lo [c], Umberto Ricardi [d], Arjun Sahgal [e], Rolf Stahel [f], Roger Stupp [f], Matthias Guckenberger [a]

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

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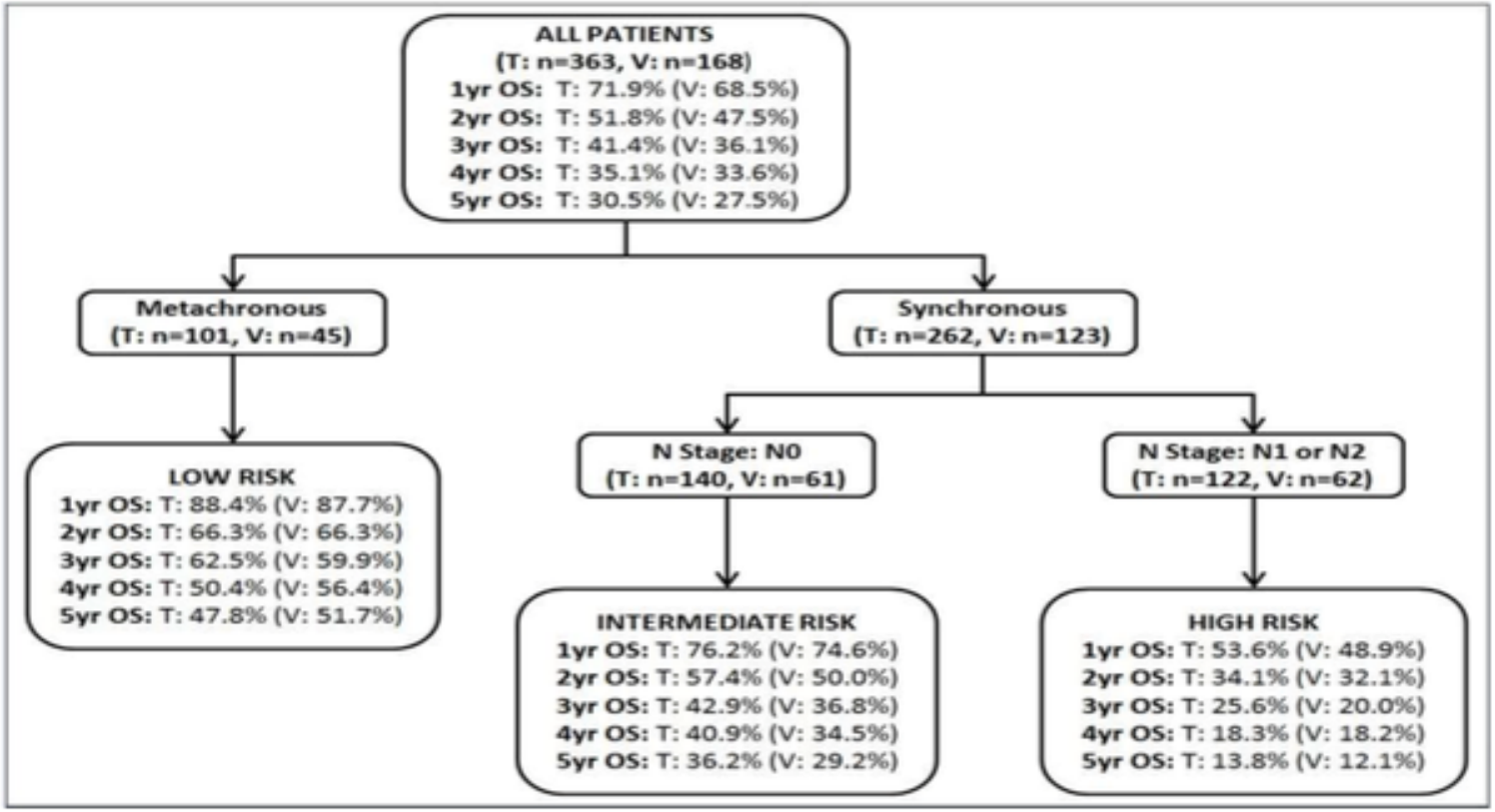
RPA – Oligometastatic NSCLC



Ashworth et al, Clin Lung Ca 2014

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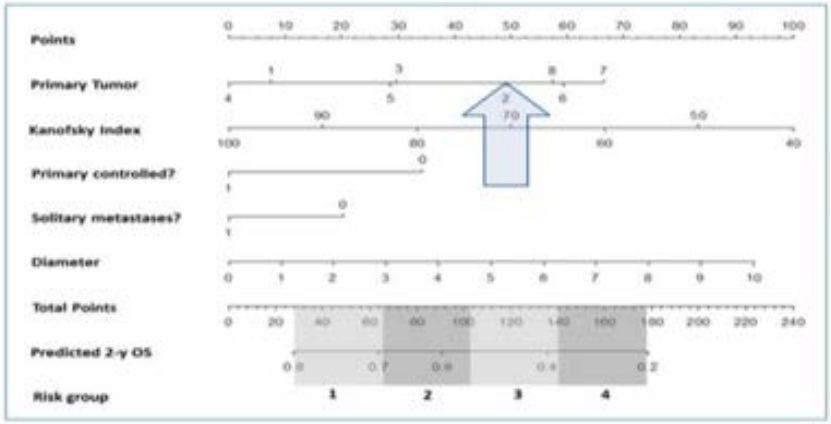
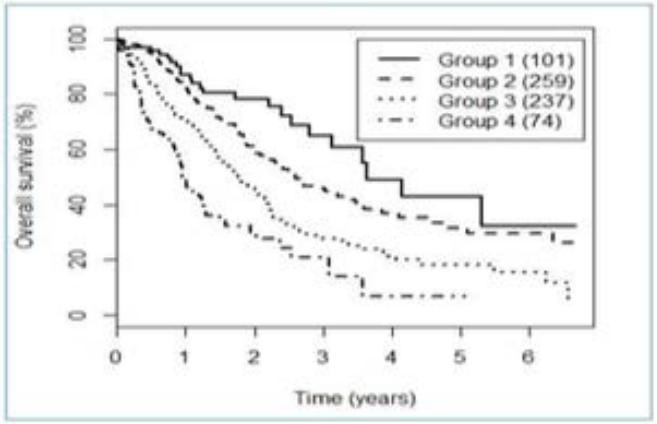
Nomograms for Lung Mets

Training cohort: n=671



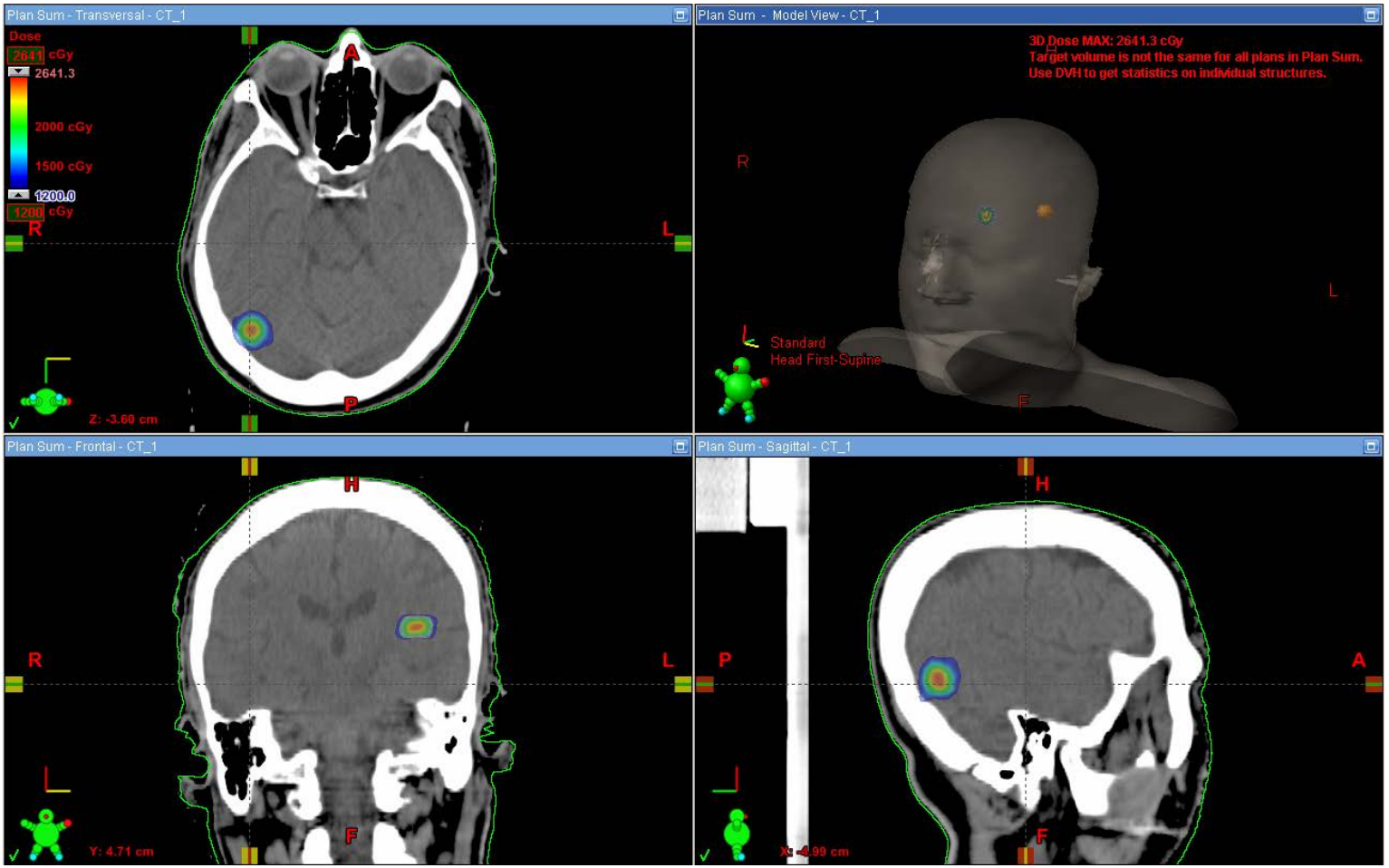
Validation cohort n=145 & 92



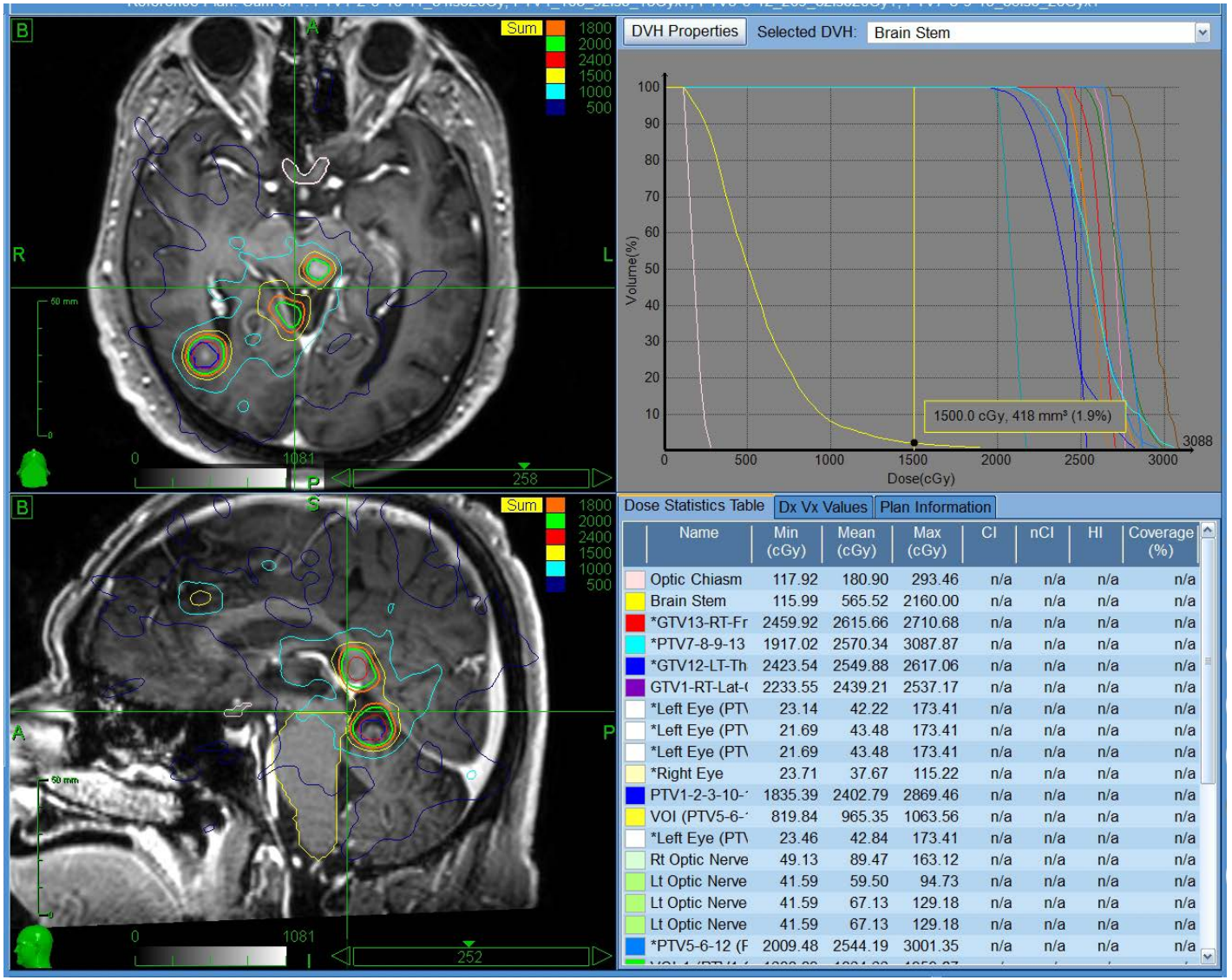
Lang, Ricardi, Hoyer, Guckenberger ELCC 2016

- NSCLC metastases associated with worse-than average OS
- However: long-term OS even in the highest risk group

Limited Number of Brain Metastases

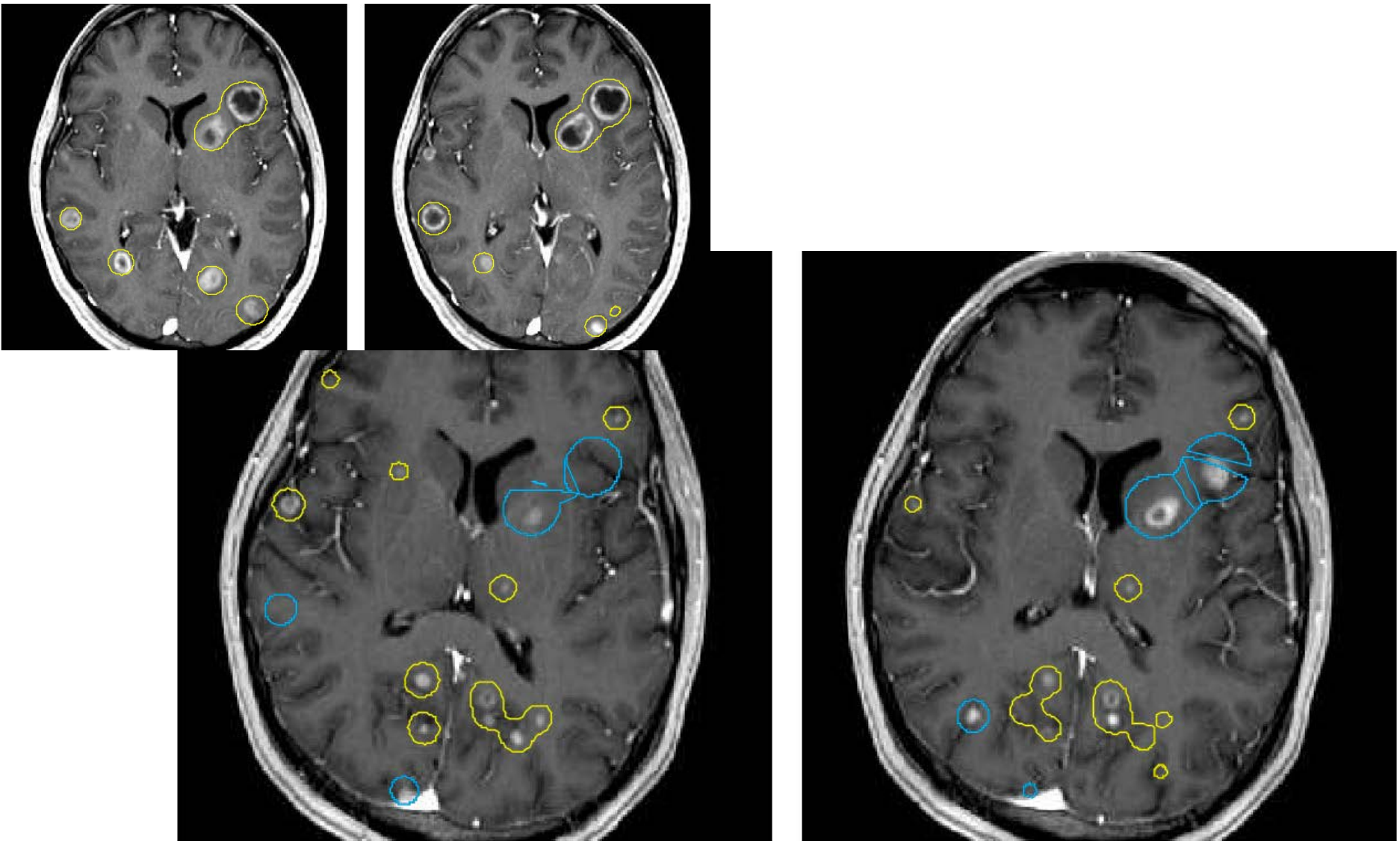


Multiple Brain Metastases



Multiple Brain Metastases

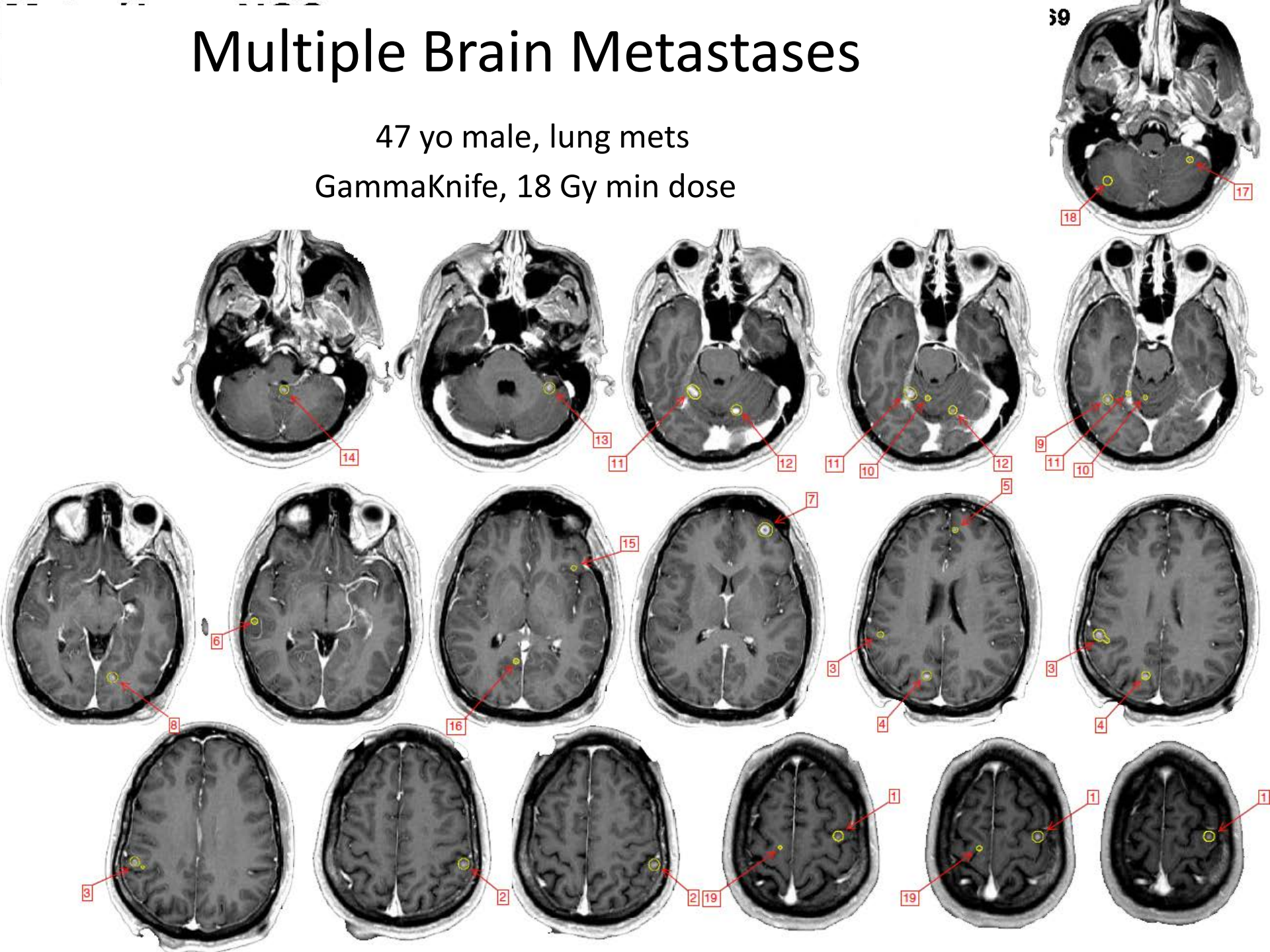
GammaKnife



Multiple Brain Metastases

47 yo male, lung mets

GammaKnife, 18 Gy min dose

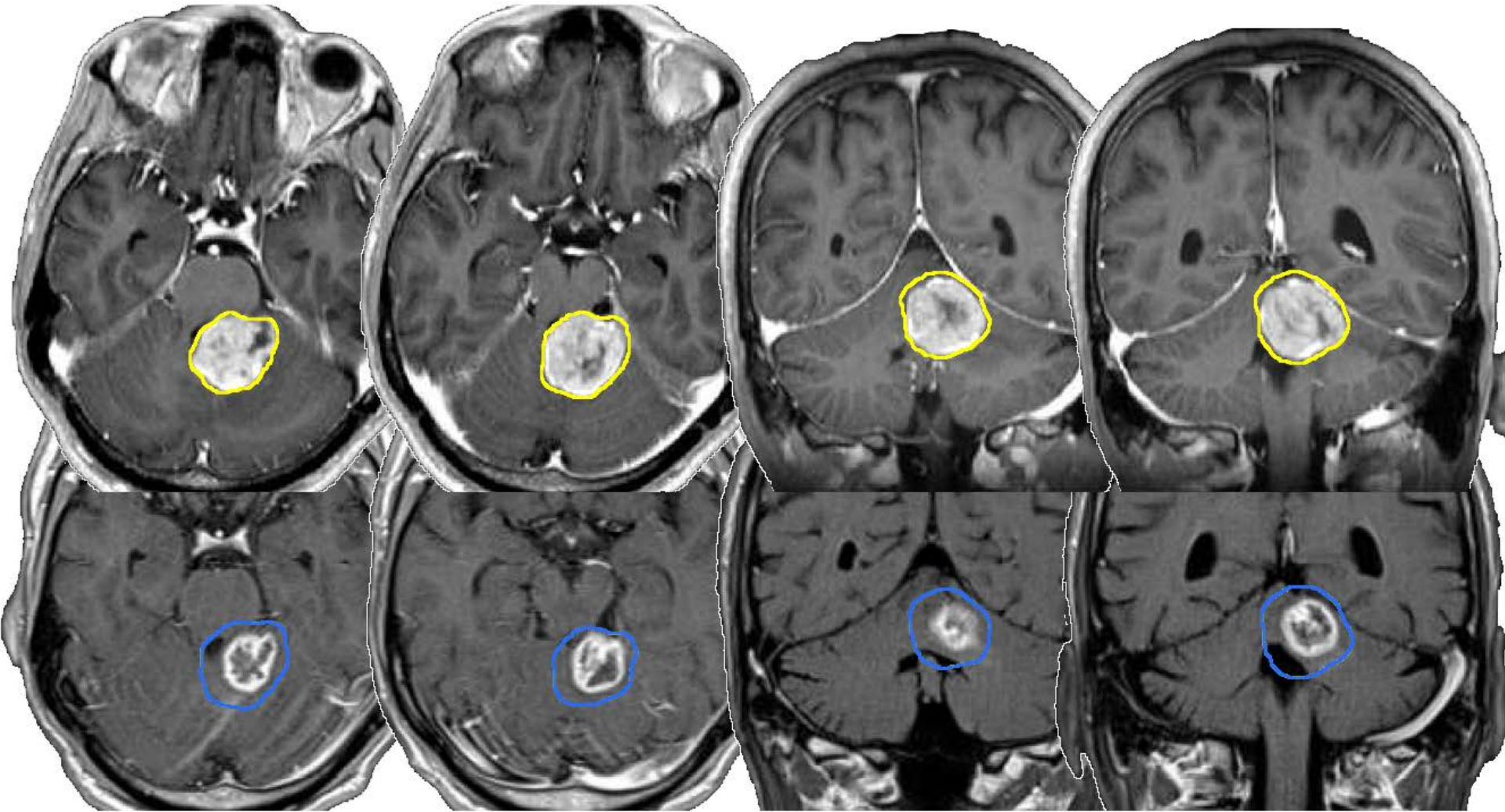


Mets/lung.NSC
Male age 51
noRT

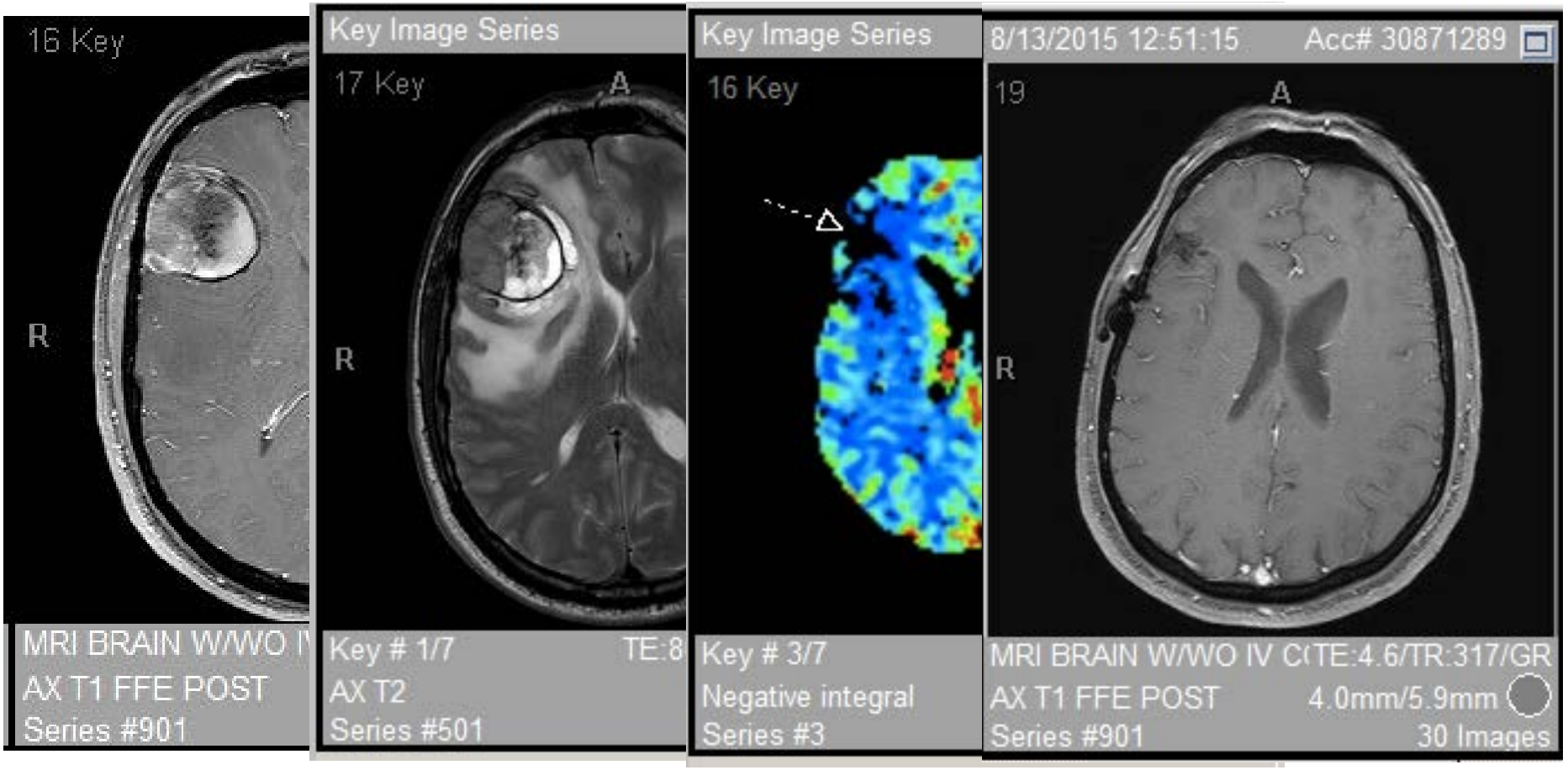
FW07091963

02/05/2015 16Gy-50% 13.5cc
03/05/2015 One Month Follow-up

16Gy



Tumor Progression vs. Radiation Necrosis



Memorial Cancer Institute
MEMORIAL REGIONAL HOSPITAL | MEMORIAL HOSPITAL WEST
MEMORIAL AVENTURA GROUP

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!

Biology and Radiation Therapy
Best of ASTRO 2017

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

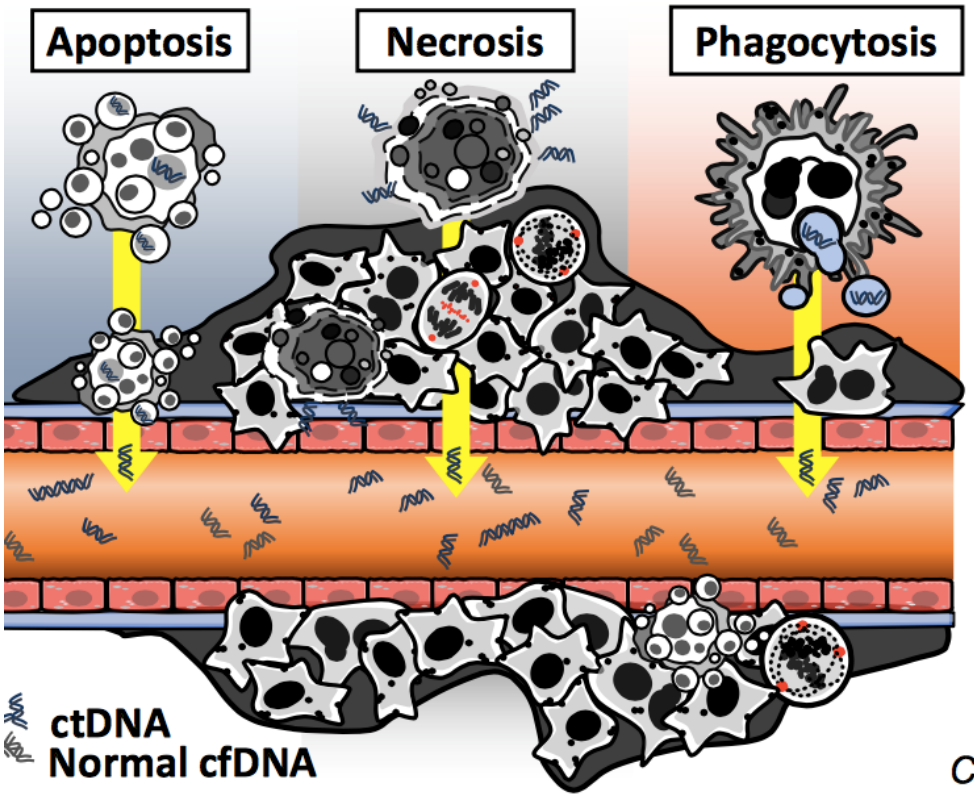
- Personalization of therapy based on biomarkers of treatment resistance or response
- *Predictive Biomarkers*: Tissue and tumor derived biomarkers to predict benefit of treatment
- *Prognostic Biomarkers*: Tissue and tumor derived biomarkers that estimate outcome, regardless of treatment undertaken
- *Personalized radiotherapy*

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

AA Chaudhuri[1], AF Lovejoy[1], JJ Chabon[1], A Newman[1], H Stehr[1], DJ Merriott[2], JN Carter[1], TD Azad[1], S Padda[1], MF Gensheimer[1], HA Wakelee[1], JW Neal[1], BW LooJr.[1], AA Alizadeh[1], M Diehn[1]

[1]Stanford Cancer Institute, Stanford, CA
[2]Stanford University School of Medicine, Stanford, CA

Background

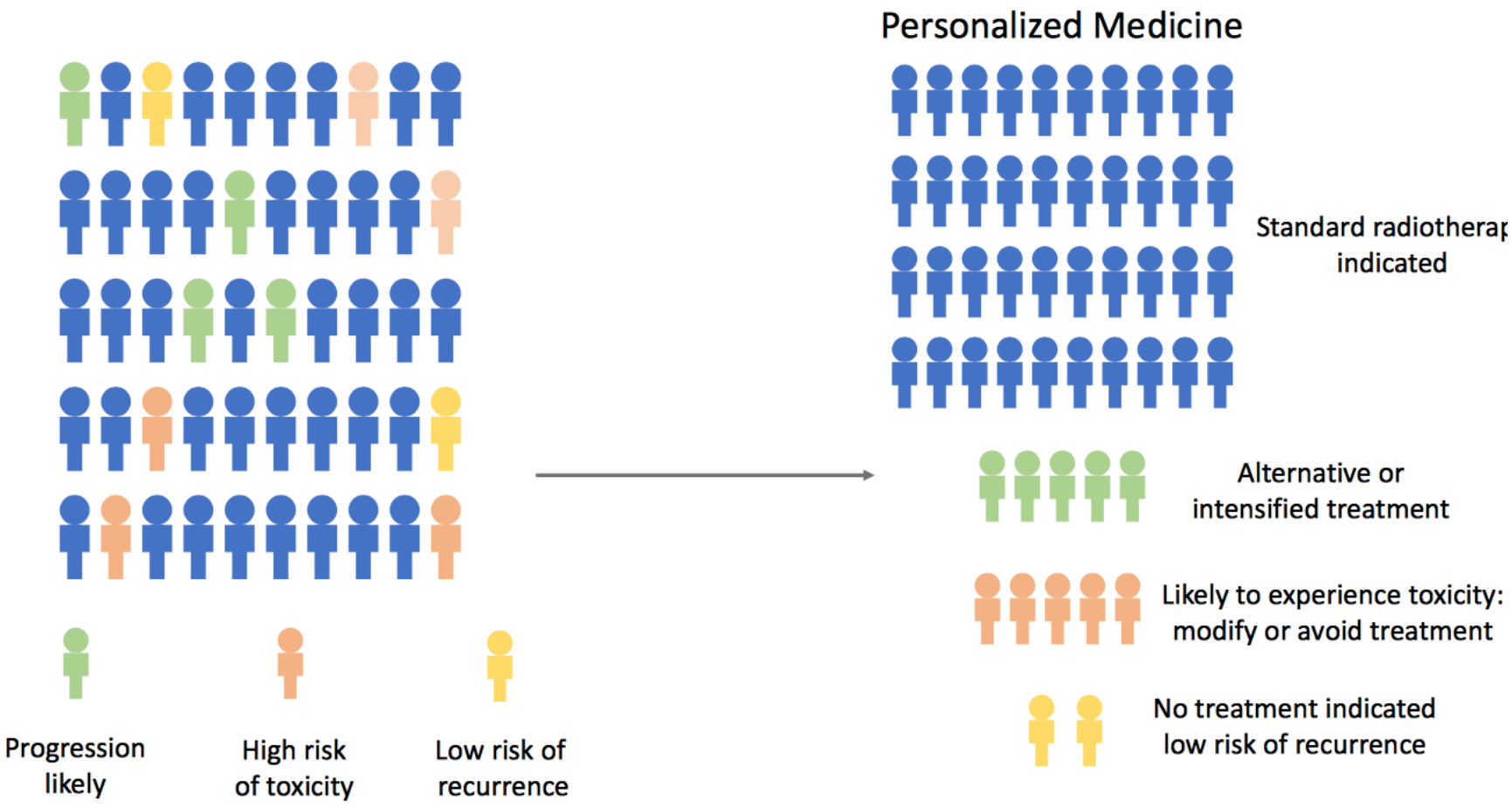


ctDNA = circulating tumor DNA
-Typically <1% of total cell-free DNA in cancer patients

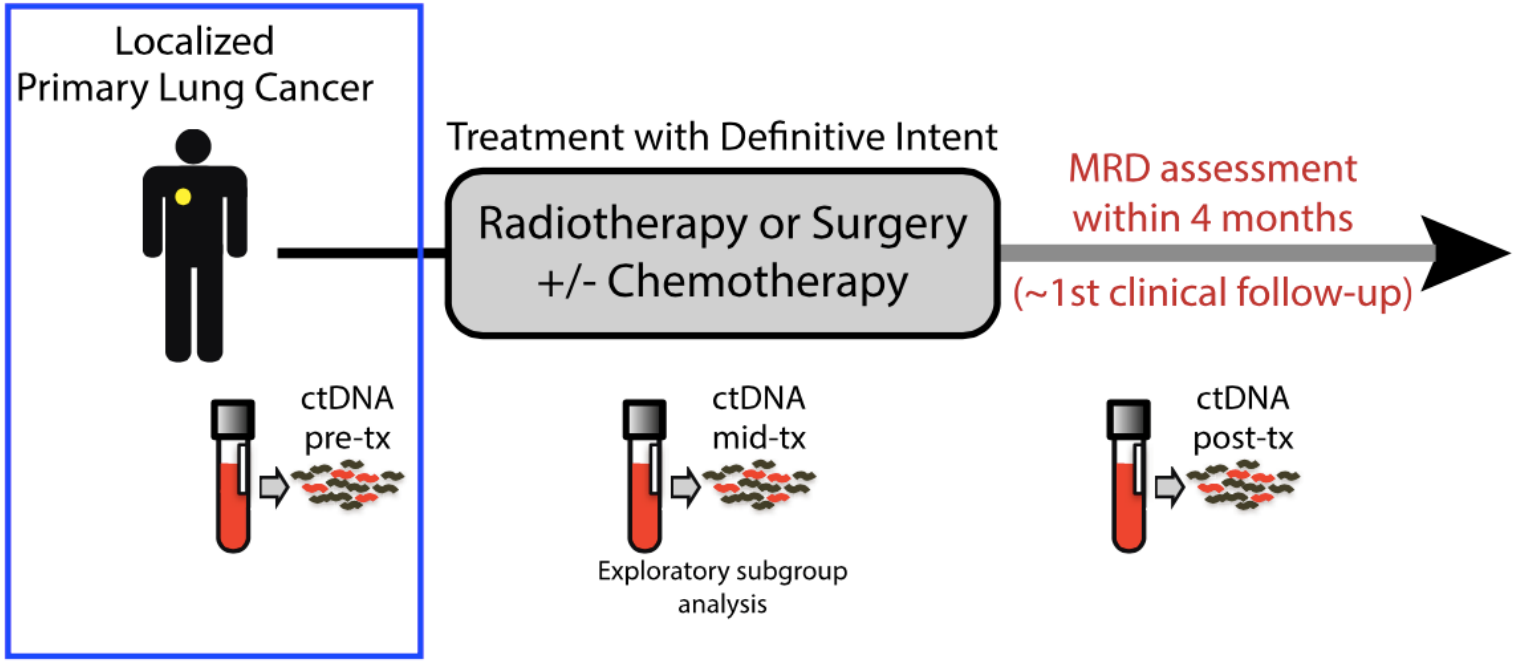
MRD = Minimal Residual Disease or **Molecular Residual Disease**
-Prognostic biomarker important in the management of leukemia
-Currently no role in lung cancer management

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

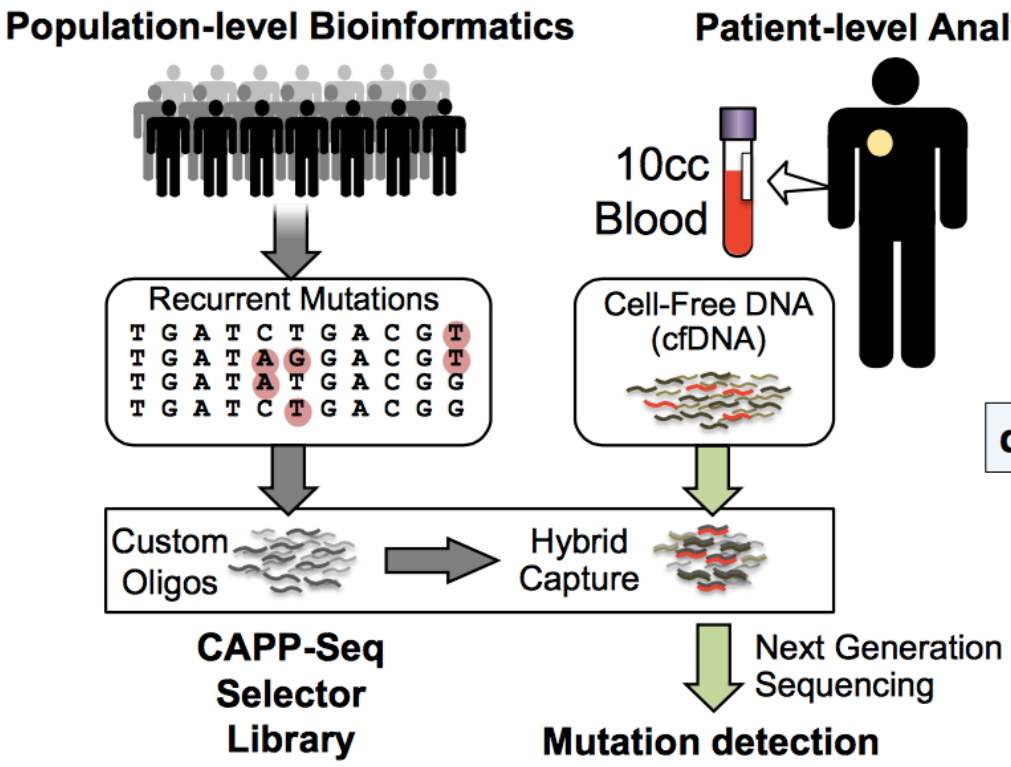
Chaudhuri et al, Sem Rad Onc, 2015


Personalized Medicine
Standard radiotherap
indicated
Alternative or
intensified treatment
Likely to experience toxicity:
modify or avoid treatment
No treatment indicated
low risk of recurrence
Progression
likely
High risk
of toxicity
Low risk of
recurrence

Study Design



CAPP-Seq Design and Implementation



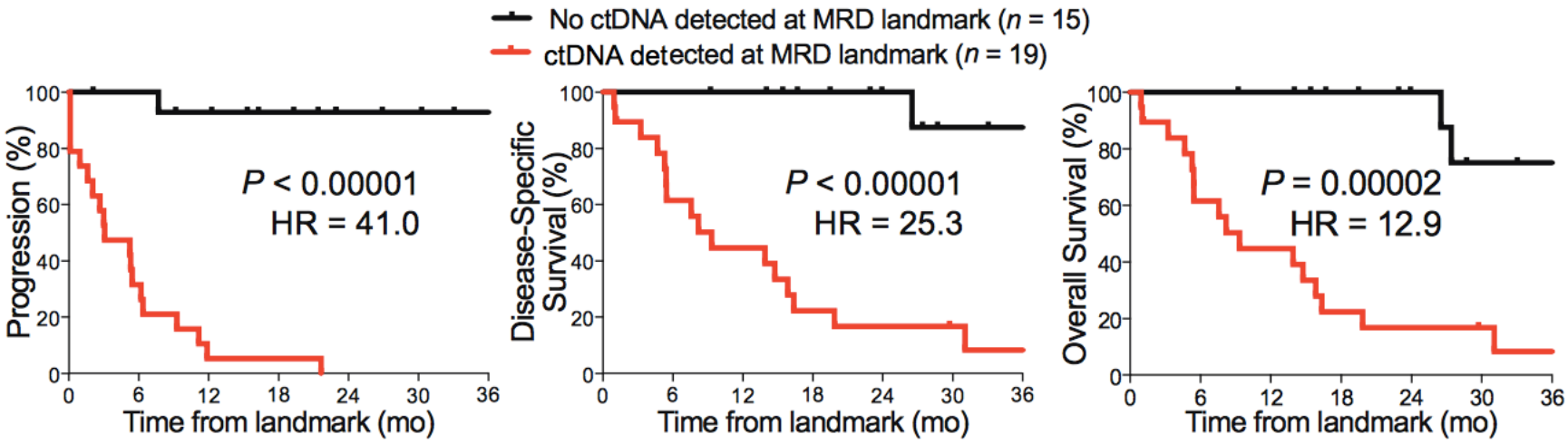
ctDNA detection limit: ~0.0015%

Newman & Bratman et al, Nature Medicine, 2014

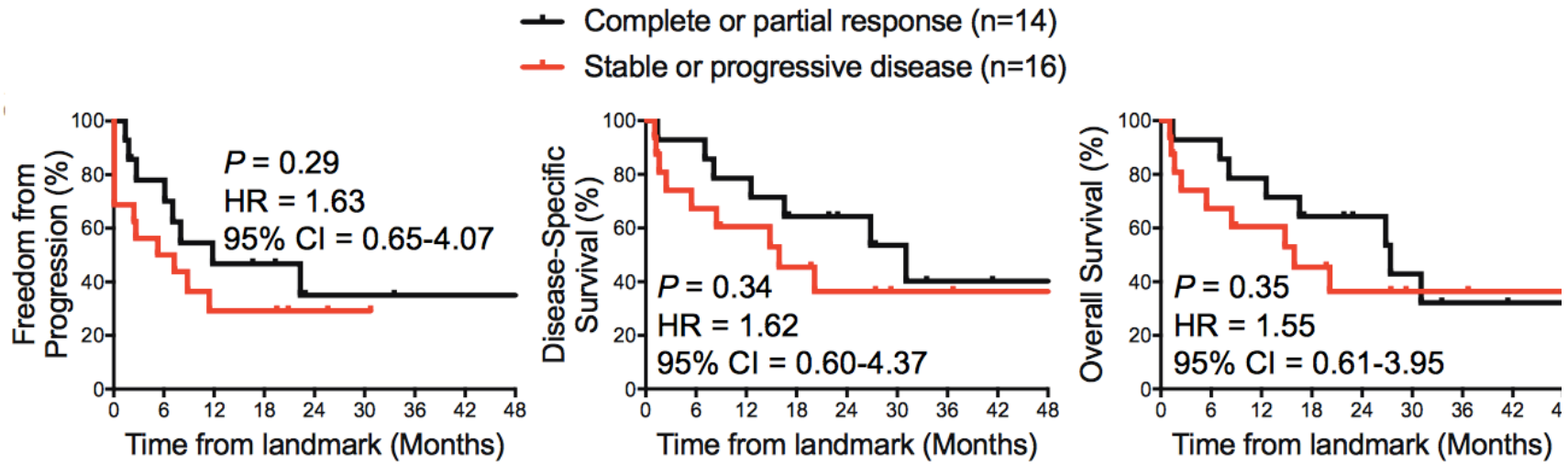
Newman, Lovejoy & Klass et al, Nature Biotech, 20

Parameter	*n* = 41
Follow-up time (mo)	35.1 (6.9-56)
Age (y)	66.8 (47-91)
Gender	
Male	28 (68%)
Female	13 (32%)
Smoking history	
Yes	36 (88%)
No	5 (12%)
Pack-years	30 (0-150)
Stage	
IA	1 (2%)
IB	7 (17%)
IIA	3 (7%)
IIB	4 (10%)
IIIA	15 (37%)
IIIB	11 (27%)
Histology	
Adenocarcinoma	20 (49%)
Squamous carcinoma	15 (37%)
Small Cell	3 (7%)
NOS	3 (7%)
Local therapy	
Radiotherapy	36 (88%)
Radiotherapy + Surgery	3 (7%)
Surgery	2 (5%)
Chemotherapy	
Yes	28 (68%)
No	13 (32%)
Circulating DNA	
ctDNA detected pre-tx	39 (95%)

Patients with detectable ctDNA MRD have significantly worse outcomes

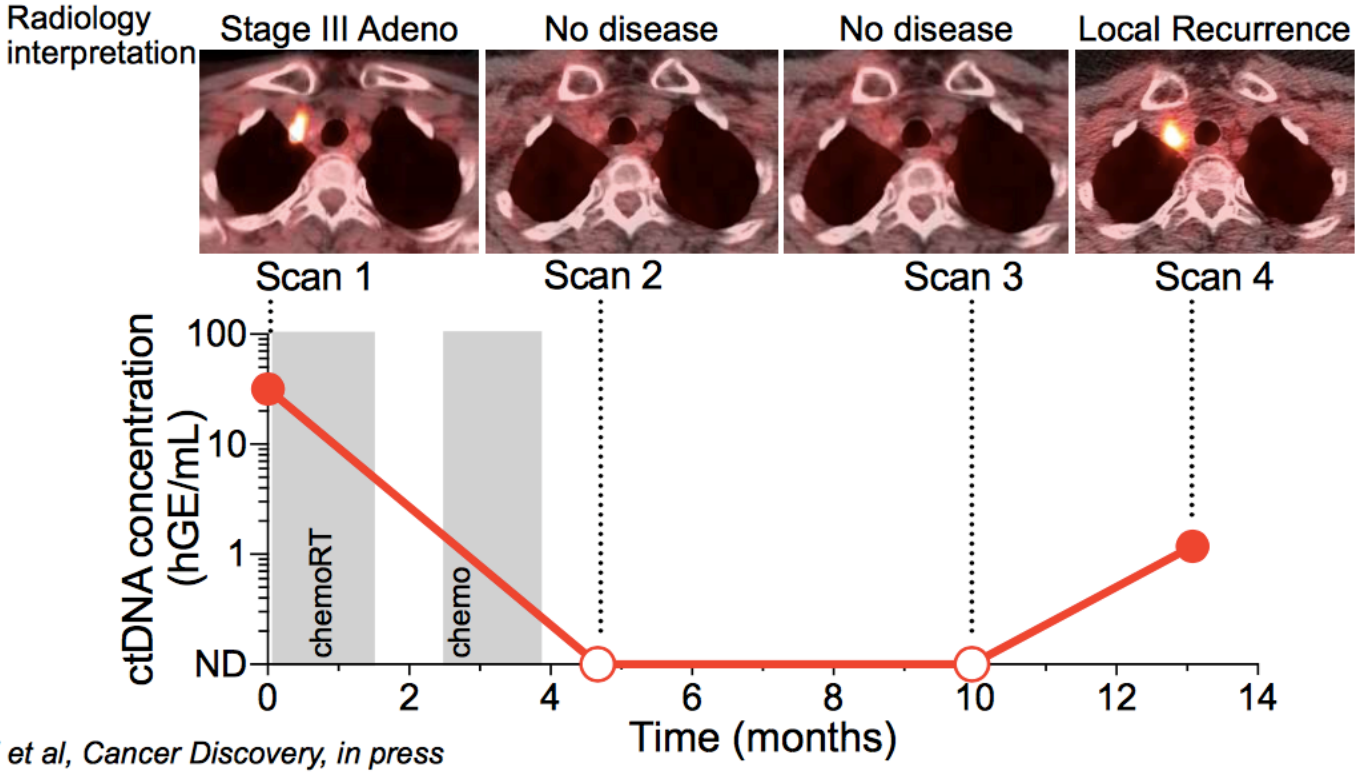


Early post-treatment CT imaging is not prognostic



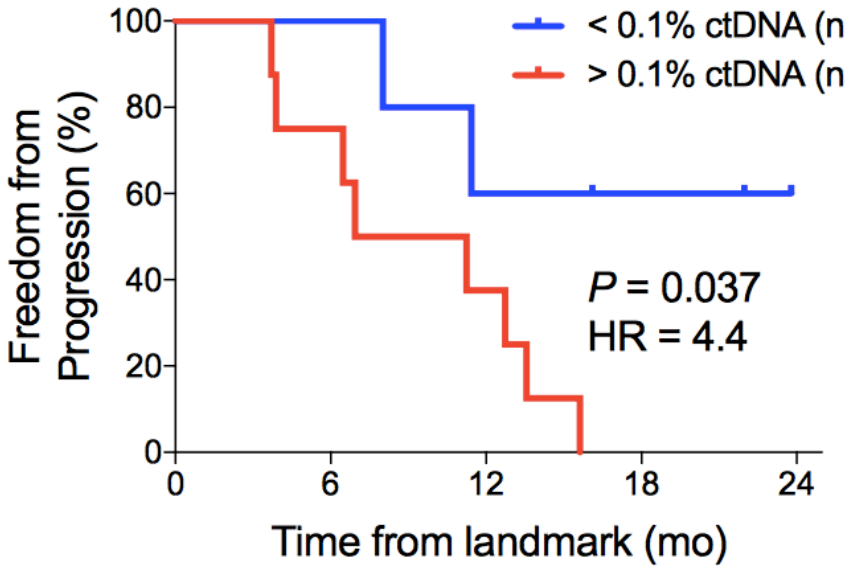
30 patients had CT imaging analyzed by RECIST at the MRD landmark.

Patient with ctDNA MRD not detected who later recurred



Chaudhuri et al, Cancer Discovery, in press

13 patients with ctDNA measured within 4 weeks of chemoRT start



Cox Regression
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

OMD ASTRO Refresher