Oligometastatic NSCLC:

The changing role of radiotherapy

Professor Suresh Senan
VU University Medical Center






Disclosures

- The Department of Radiation Oncology at VUMC has a research agreement with Varian Medical Systems.

- S Senan has received speakers honoraria from Varian Medical Systems.

The changing role of radiotherapy

- Use of ablative radiotherapy (SRS, SABR/SBRT)
- Which patients are most likely to benefit?
- SABR/SRS versus other ablative treatments

Issues to address:

Clinical trials

Tumor biology

Immunology

Toxicity issues

SRS- stereotactic radiosurgery; SABR/SBRT – stereotactic body radiotherapy

Oligomets: Who are the eligible patients?

VUmc

An Individual Patient Data Meta-Analysis of Outcomes and Prognostic Factors after Treatment of Oligometastatic Non-Small Cell Lung Cancer

Allison B. Ashworth[1], Suresh Senan[2,] David A. Palma[1], Marc Riquet[3], Yong Chan Ahn[4], Umberto Ricardi[5], Maria T. Congedo[6], Daniel R. Gomez[7], Gavin M. Wright[8,] Giulio Melloni[9], Michael T. Milano[10], Claudio V. Sole[11], Tommaso M. De Pas[12], Dennis L. Carter[13], Andrew J. Warner[1] and George B. Rodrigues[1].

Systematic review of the literature to identify reports.

- 757 NSCLC patients with 1-5 synchronous or metachronous metastases
- Median patient age at diagnosis was 61 years
- 98% of patients had a good performance status
- 2/3 had otherwise early-stage intra-thoracic disease staged IA-IIB (after excluding metastatic disease)

Manuscript under review

Individual Patient Data Meta-Analysis after Treatment of Oligometastatic NSCLC [Ashworth A, submitted]

Median OS of 26 months, 1-year OS 70.2%, and 5-year OS 29.4%.

Surgery was the most commonly used treatment modality for the primary (n=635, 83.9%) and for metastases (n=339 62.3%).

Predictors of OS: synchronous vs. metachronous metastases ($p<0.001$), N-stage ($p=0.002$) and adenocarcinoma histology ($p=0.036$)

Recursive Partitioning Analysis for risk groups;

Low-risk: metachronous metastases (5-year OS 47.8%);

Intermediate risk: synchronous metastases and N0 disease (5-year OS 36.2%);

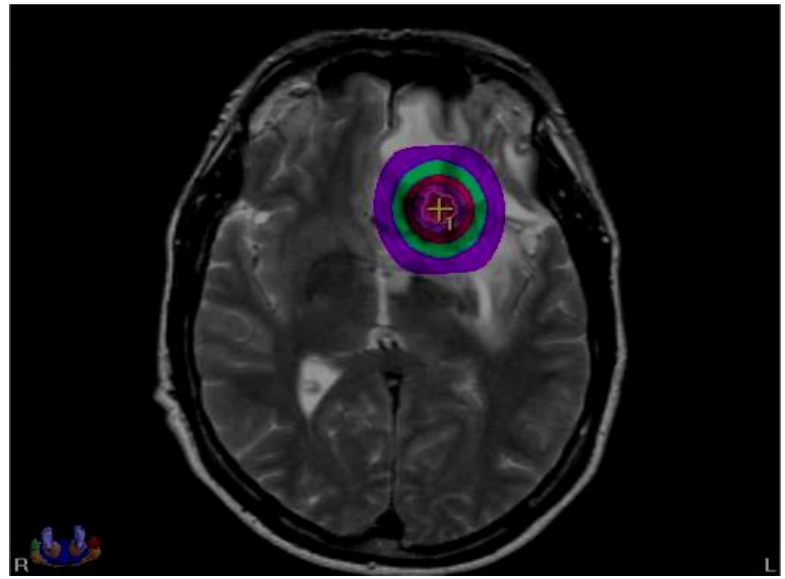
High risk: synchronous metastases and N1/N2 disease (5-year OS 13.8%).

Stereotactic radiosurgery (SRS) for brain mets

Table 2. Advantages of Surgery and Stereotactic Radiosurgery for Brain Metastases.

Suh J, NEJM 2010

Surgery
Treatment of larger lesions (>4 cm in diameter)
Rapid resolution of mass effect and edema
Removal of cancer
Histologic confirmation of cancer
Rapid tapering of the dose of corticosteroids used to treat symptomatic lesions
Less intensive follow-up
Lower risk of radiation necrosis when combined with whole-brain radiation therapy
Stereotactic Radiosurgery
Treatment of small, deep lesions or eloquent areas
Minimally invasive or noninvasive approach
General anesthesia not required
Outpatient procedure
Treatment of multiple lesions during same session
Short recovery time (<1 wk)
Potential avoidance of whole-brain radiation therapy
Rapid initiation of systemic therapies



Stereotactic ablative radiotherapy (SABR / SBRT)

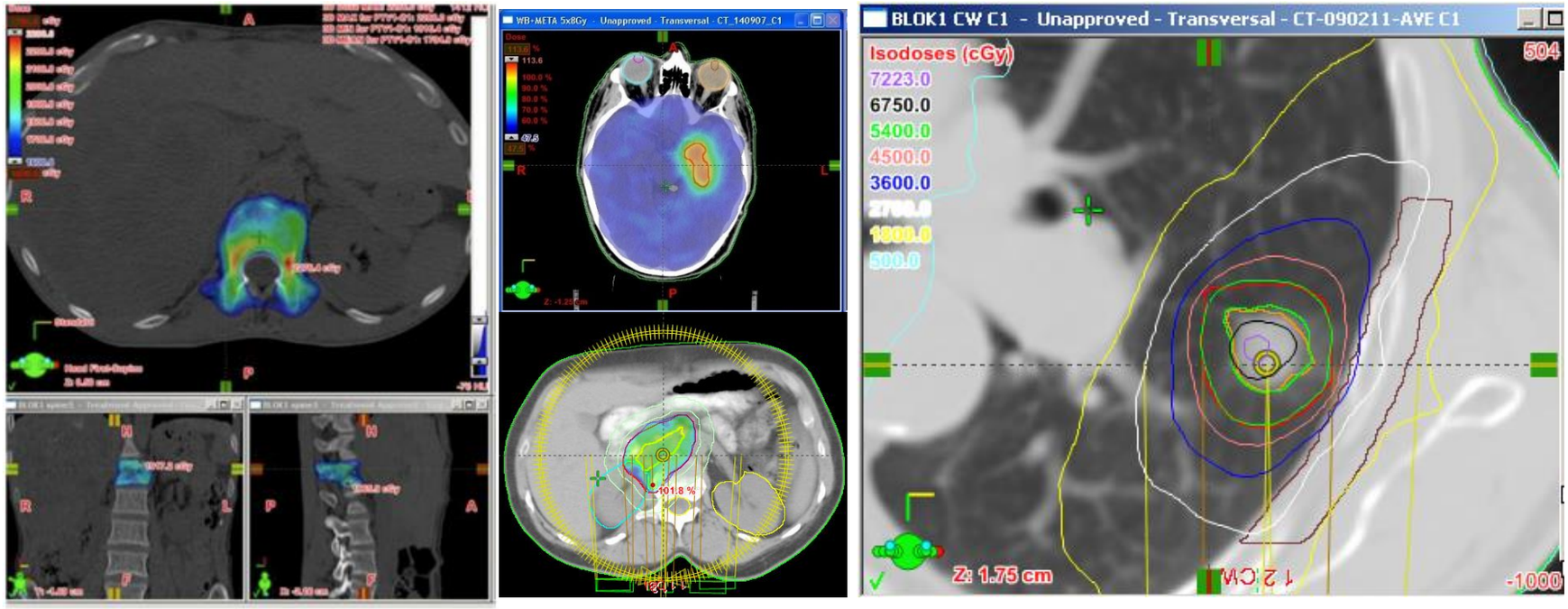
A technique for delivering external beam radiotherapy to an extra-cranial target

(i) with a high degree of accuracy,

(ii) using high doses of irradiation,

(iii) delivered in 1-8 treatment fractions.

Senan, Guckenberger, Ricardi, IASLC textbook 2014



Extracranial Oligometastases: A Subset of Metastases Curable With Stereotactic Radiotherapy

Radiation Series	Year	No. Patients	No. Lesions	Local Control (%)	Survival (%)	Site
Blomgren et al	1995	31	42	80	Not reported	Liver, lung, and retroperitoneum
Wulf et al	2004	41	51	80	33[a]	Lung
Hoyer et al (colorectal cancer)	2006	64	141	86[a]	38[a], 13[h]	Lung, liver, and adrenal
Hof et al	2007	61	71	63[i]	47.8[i]	Lung
Rusthoven et al	2009	47	63	92[a]	30[a]	Liver
Rusthoven et al	2009	38	63	96[a]	39[a]	Lung
Kang et al (colorectal cancer)	2010	59	78	66[j]	49[j]	Multiple
Okunieff et al	2006	49	125	83[j]	25[j]	Lung
Katz et al	2007	69	174	57[k]	24[l,m]	Liver
Lee et al	2009	70	143	71[m]	47[m]	Liver
Milano et al	2011	121				Multiple[p]
Breast cancer		39		87[o]	74[a], 47[o]	
All others		82		65[o]	39[a], 9[o]	
Salama et al	2011	61	111	66.7[a,q]	56.7[a]	Multiple
Bae et al (colorectal cancer)	2012	41	50	64[i], 57[h]	64[i], 38[h]	Lung, liver, and lymph node
Norihisa et al	2008	34		90[a]	84.3[a]	Lung

Corbin KS, JCO 2013

The changing role of radiotherapy

- Use of ablative radiotherapy (SRS, SABR/SBRT)
- Which patients are most likely to benefit?
- **SABR/SRS versus other ablative treatments**

Issues to address:

Immunology

Clinical trials

Tumor biology

Toxicity issues

SRS- stereotactic radiosurgery; SABR/SBRT – stereotactic body radiotherapy

Pulmonary oligometastases: metastasectomy or SABR?

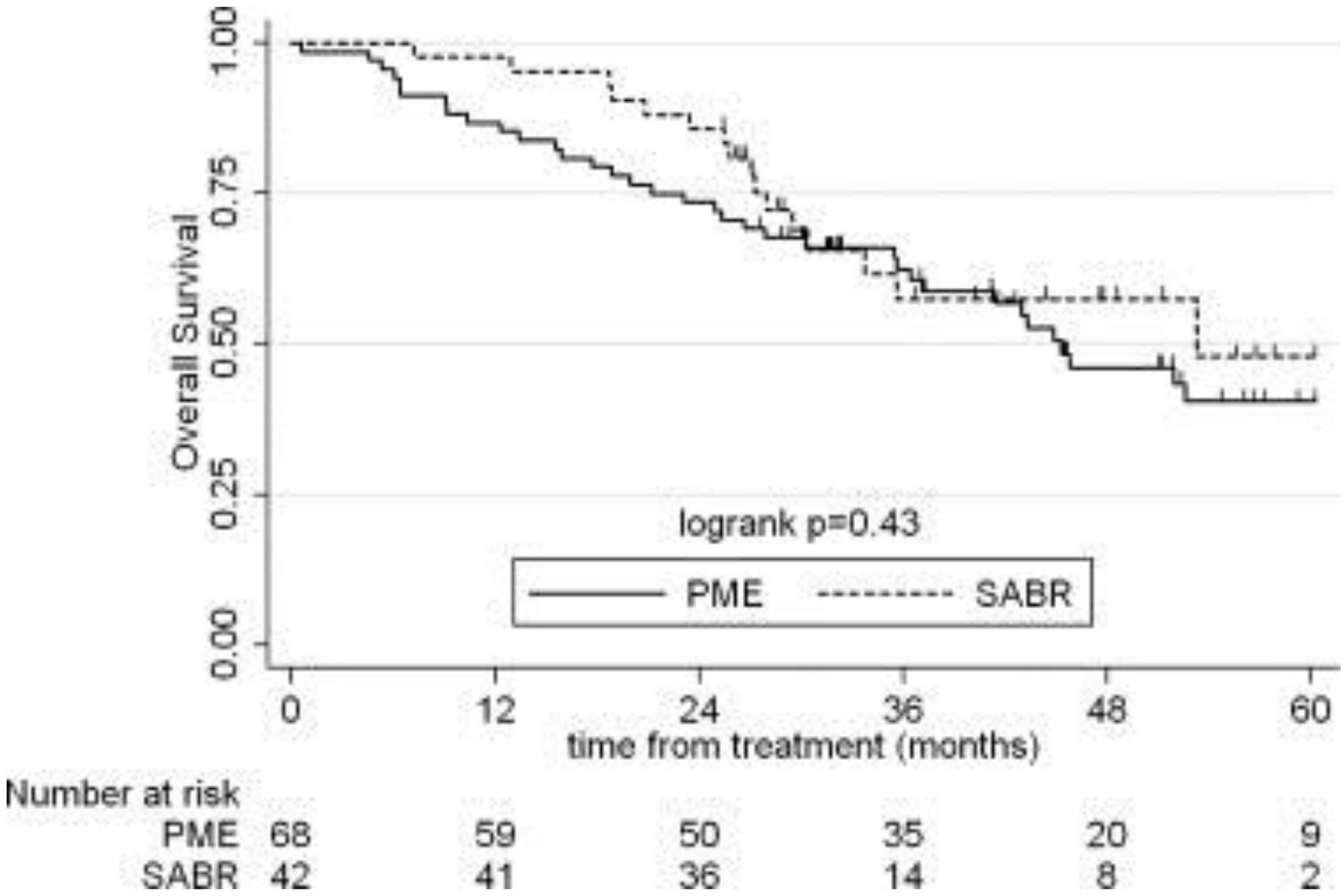
- Consecutive patients referred to a multidisciplinary team in a university-hospital from 2007-2010.
- Surgery was considered the first choice, and SABR otherwise
- 110 patients (surgery, n=68; SABR, n=42)

- Estimated OS rates at 1, 3 and 5 years:
- 87%, 62%, and 41% for surgery, and
- 98%, 60%, and 49% for SABR, respectively (logrank-test, p=0.43).

- Local control at two years was 94% (SABR) and 90% (surgery)
- Progression-free survival was 17% at three years

Widder J, Radioth Oncol 2013

Pulmonary oligometastases: metastasectomy or SABR?



Overall survival, PME (pulmonary metastasectomy) versus SABR (stereotactic ablative radiotherapy).

Widder J, Radioth Oncol 2013

SABR and immunity

Kwilas AR, 2012

Low dose

SABR doses

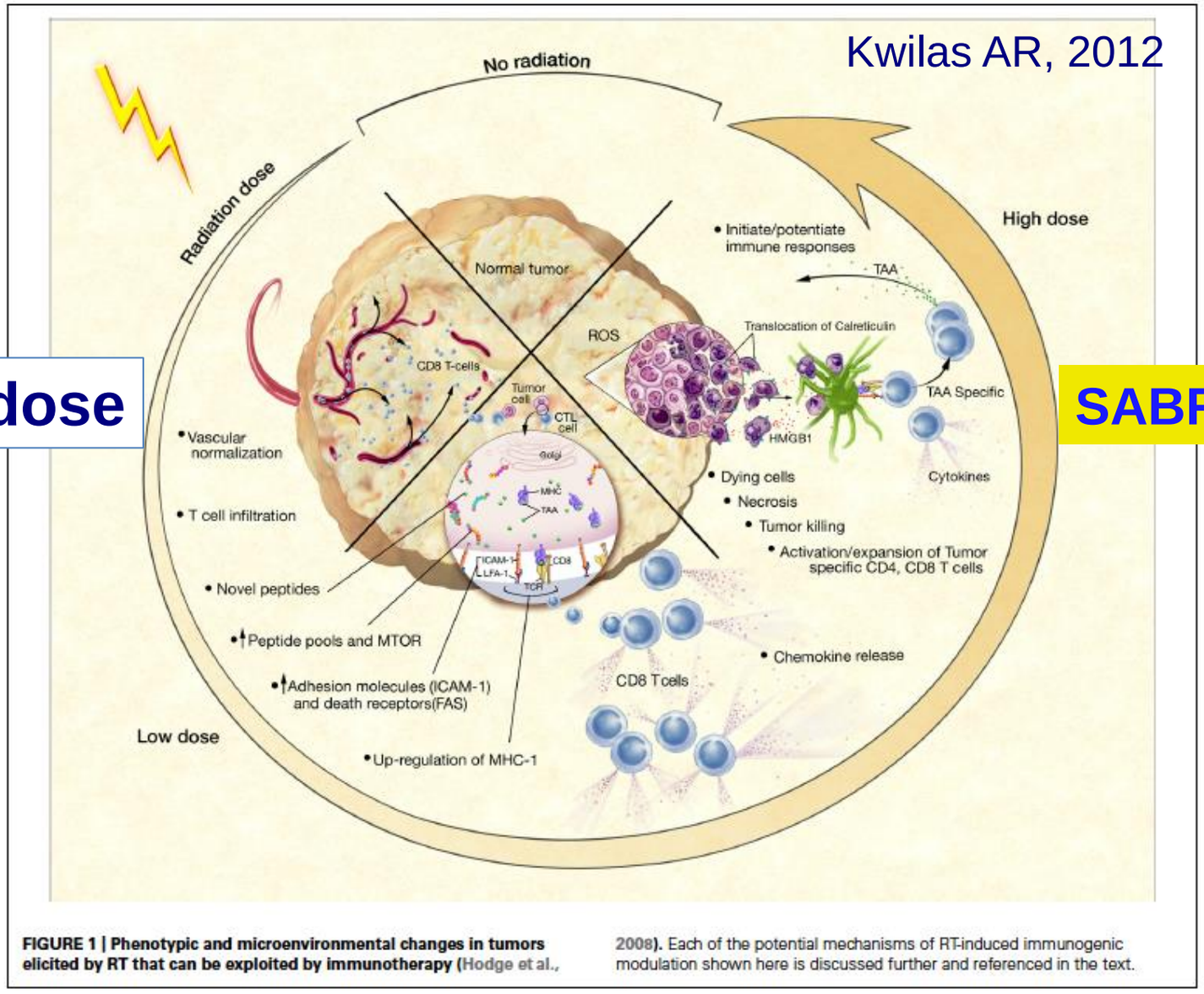


FIGURE 1 | Phenotypic and microenvironmental changes in tumors elicited by RT that can be exploited by immunotherapy (Hodge et al., 2008). Each of the potential mechanisms of RT-induced immunogenic modulation shown here is discussed further and referenced in the text.

Radiation Therapy to Convert the Tumor into an In Situ Vaccine [Formenti SC, IJROBP 2012]

ClinicalTrials.gov

Rank	Status	Study
1	Completed	Concurrent and Non-concurrent Chemo-radiotherapy or Radiotherapy Alone for Patients With Oligo-metastatic Stage IV Non-small Cell Lung Cancer (NSCLC) **Conditions:** Stage IV (Oligo-metastases); Non-small Cell Lung Cancer **Intervention:** Radiation: Radiotherapy
2	Unknown †	Chemotherapy With or Without Radiosurgery for Asymptomatic Oligo Brain Metastasis **Condition:** Nonsmall Cell Lung Cancer **Interventions:** Radiation: Radiosurgery; Radiation: Observation
3	Not yet recruiting	Assessment of Toxicity of the Immunocytokine L19-IL2 Administered Directly After the Course of Stereotactic Ablative Body Radiotherapy in Patients Suffering From Oligometastatic Non-small Cell Lung Cancer. **Condition:** Non-small Cell Lung Cancer **Intervention:** Drug: L19-IL2
4	Recruiting	ATOM_local Ablative Therapy **Conditions:** NSCLC; Activating EGFR Mutation **Intervention:** Radiation: preemptive local ablative therapy

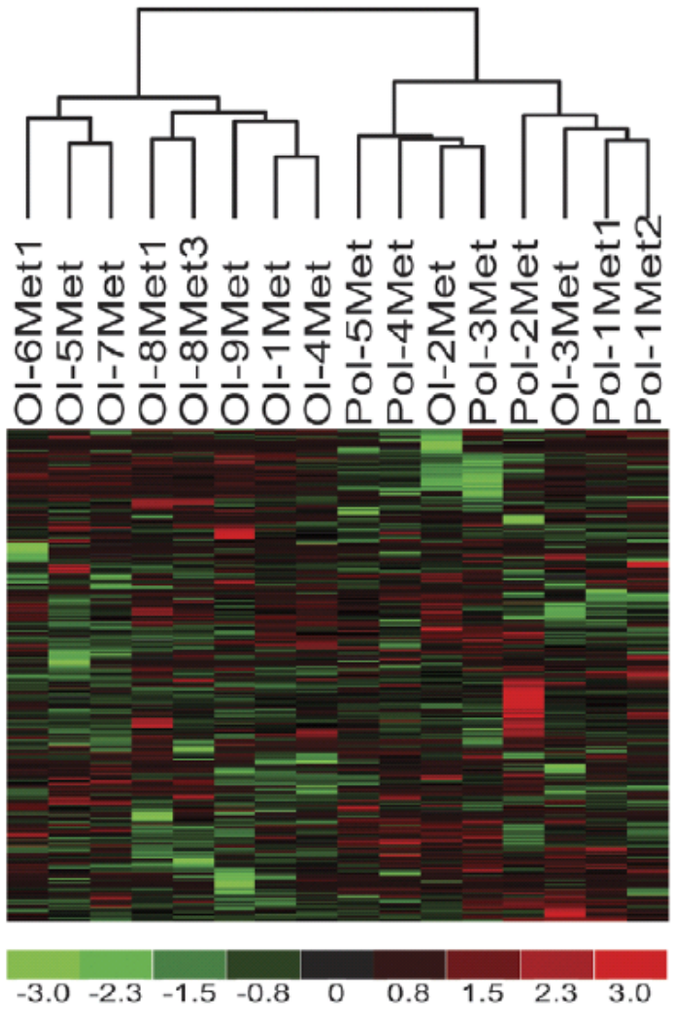
Accessed on 23 March 2013

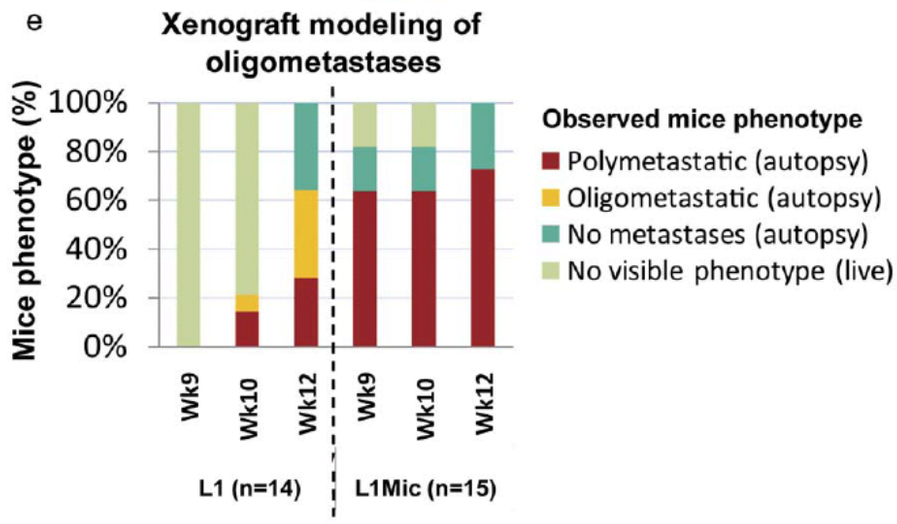
OPEN ACCESS Freely available online

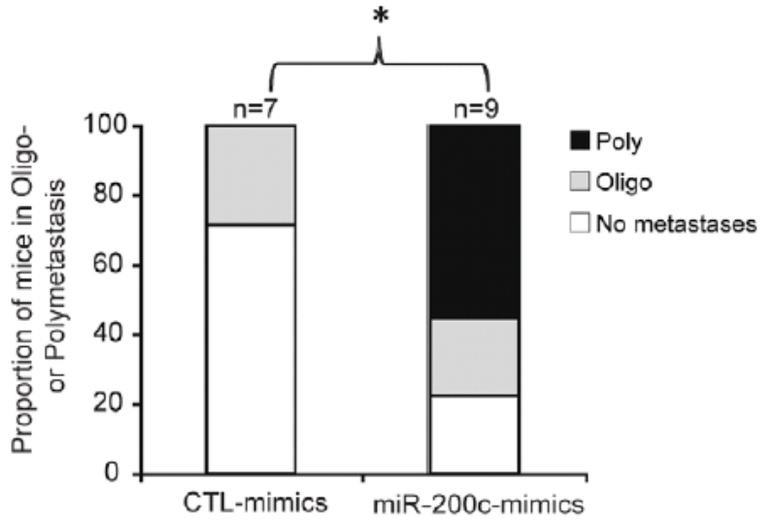
PLoS one

MicroRNA Expression Characterizes Oligometastasis(es)

Yves A. Lussier[1,2,3,4]*, H. Rosie Xing[1,2,5,6☯], Joseph K. Salama[8☯], Nikolai N. Khodarev[1,5☯], Yong Huang[1,3☯], Qingbei Zhang[3,6☯], Sajid A. Khan[7☯], Xinan Yang[3☯], Michael D. Hasselle[5☯], Thomas E. Darga[5], Renuka Malik[5], Hanli Fan[6], Samantha Perakis[5], Matthew Filippo[5], Kimberly Corbin[5], Younghee Lee[3], Mitchell C. Posner[7], Steven J. Chmura[5], Samuel Hellman[2,5], Ralph R. Weichselbaum[1,2,5]*

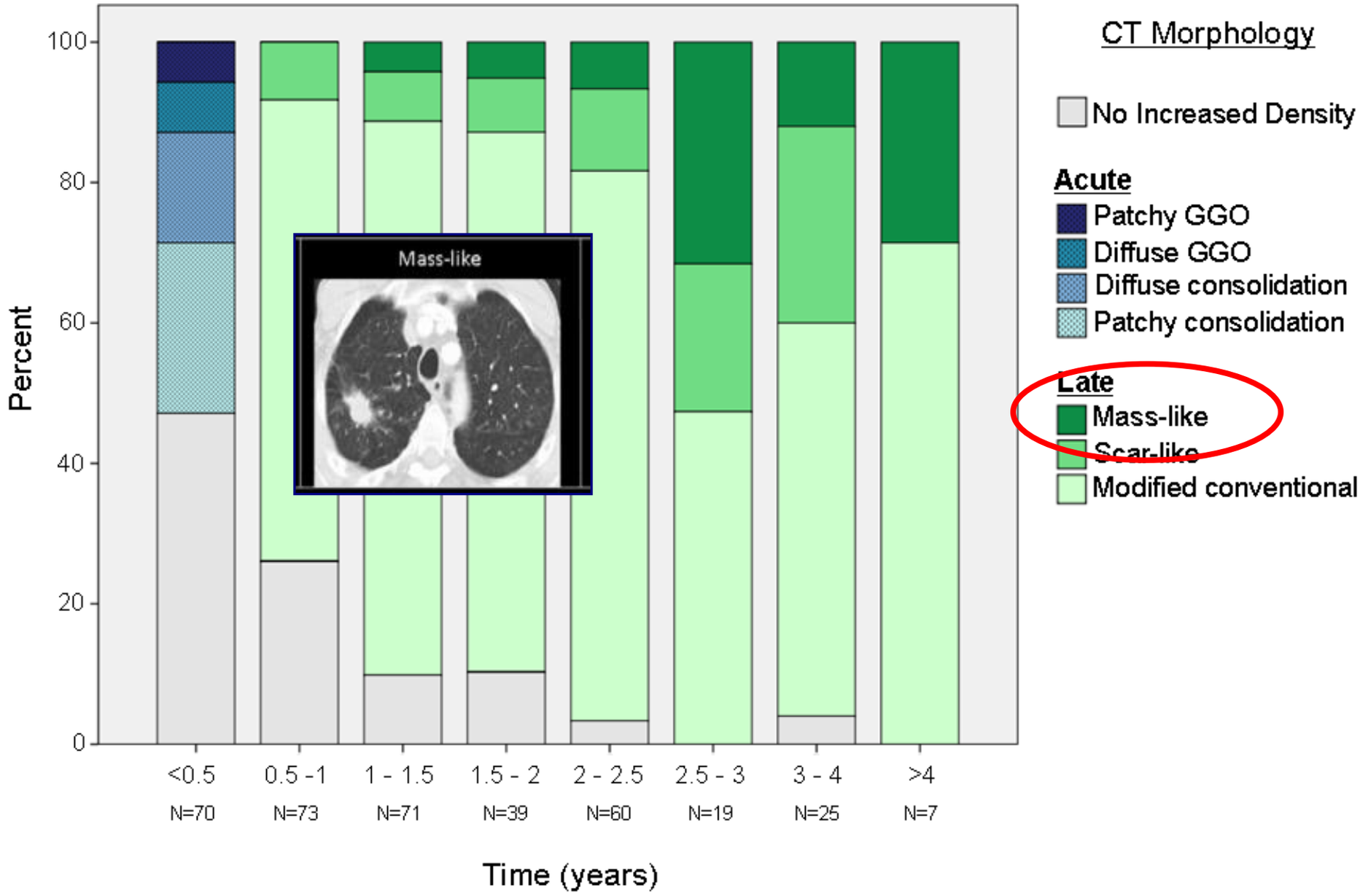






Lussier YA et al. PlosOne 2011

Post-SABR radiological changes



Dahele M, JTO 2011

Lung fibrosis vs. recurrence after SABR

VUmc

Systematic review of literature on recurrences

High-risk features (HRF):

- enlargement of mass
- sequential enlargement on CT
- growing mass after 12 months

- bulging margin
- linear margin disappears

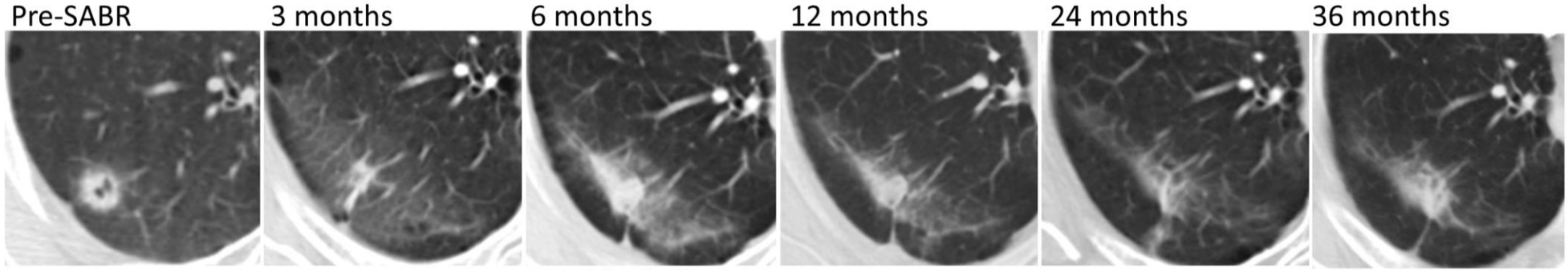
- air bronchograms disappear

Huang K, Radioth Oncol 2012

Fibrosis or recurrence after SABR?

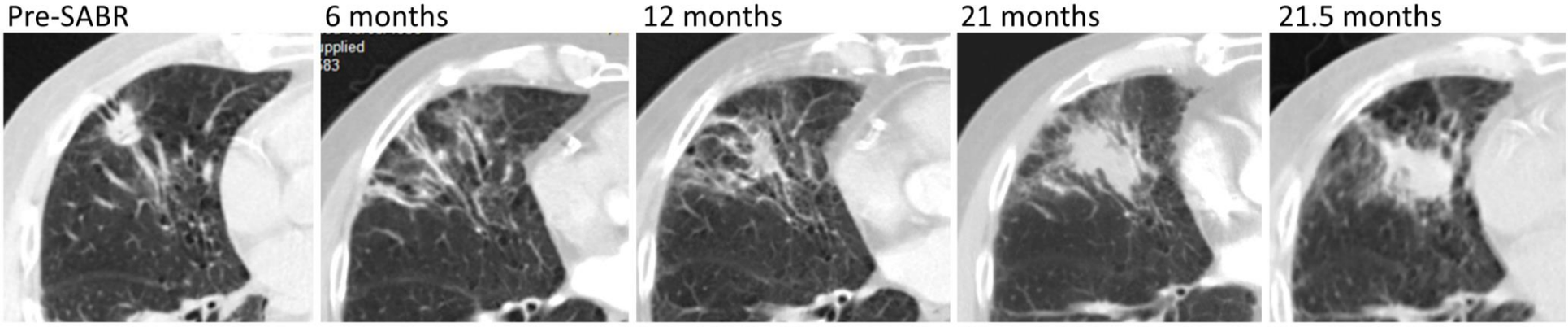
Blinded scoring of 12 path. proven recurrences matched with 24 non-reccurences

A. No Recurrence



HRF: Enlarging Opacity

B. Recurrence



HRFs: Enlarging Opacity
Craniocaudal Growth

Sequential Enlargement
Enlargement after 12 months
Linear Margin Disappearance
Bulging Margin

Loss of Air Bronchogram

Huang K, Radioth Oncol 2013

The changing role of radiotherapy

- Use of ablative radiotherapy (SRS, SABR/SBRT)
- Which patients are most likely to benefit?
- SABR/SRS versus other ablative treatments

Issues to address:

Immunology

Clinical trials

Tumor biology

Toxicity issues

SRS- stereotactic radiosurgery; SABR/SBRT – stereotactic body radiotherapy

Toxicity concerns: SABR and systemic Rx

Issues: treatment beyond progression, tumor flares, oligoprogression.

Weickhardt et al. *Journal of Thoracic Oncology* • Volume 7, Number 12, December 2012

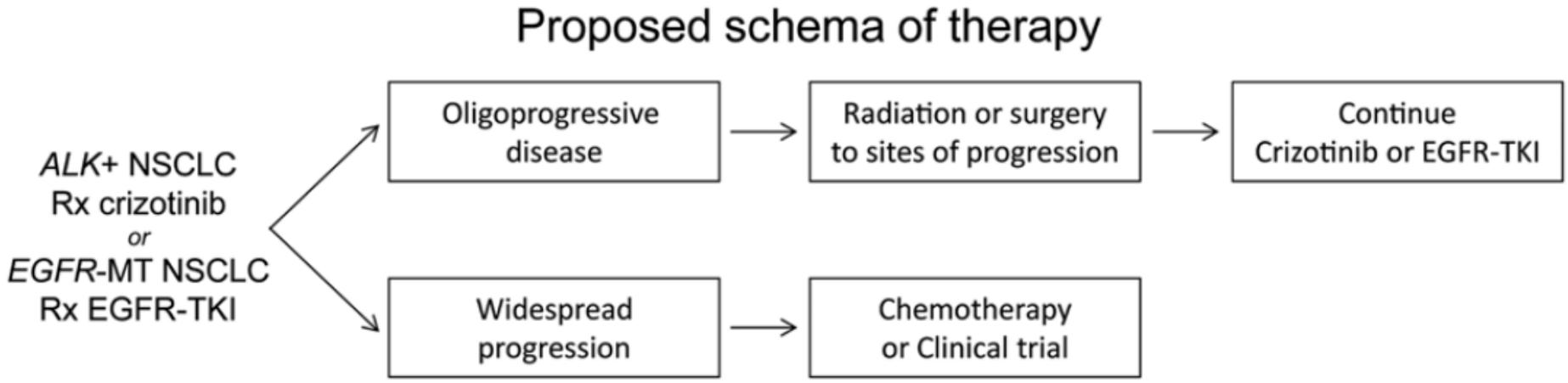


FIGURE 2. Proposed schema for incorporating local ablative therapy into therapy at time of first progression with *ALK*+ or *EGFR*-MT NSCLC patients treated with TKI therapy. *ALK*+, anaplastic lymphoma kinase gene rearrangement; *EGFR*-MT NSCLC, epidermal growth factor receptor-mutant non–small-cell lung cancer; TKI, tyrosine kinase inhibitors.

Changing approach to metastases

How should oligometastatic progression during TKI be managed?

Local therapies including radiation, radiofrequency ablation, and metastasectomy are established treatment strategies in certain cancers including renal cell carcinoma, sarcoma, and colorectal cancer. Several experiences also support the use of local therapies (surgery, stereotactic radiation) with continued EGFR or ALK inhibition in cases of oligometastatic progression, resulting in minimal toxicity and in months to years of disease control [65].
Prior to proceeding with local therapy, patients should have a full evaluation of the extent of disease, including CNS imaging.

Recommendation 27: In case of oligometastatic progression during TKI treatment, use a local treatment (such as surgery or radiotherapy) and continue/resume TKI
Strength of recommendation: C
Level of evidence: V

Besse B, 2nd ESMO Consensus Conference, Ann Oncol 2014

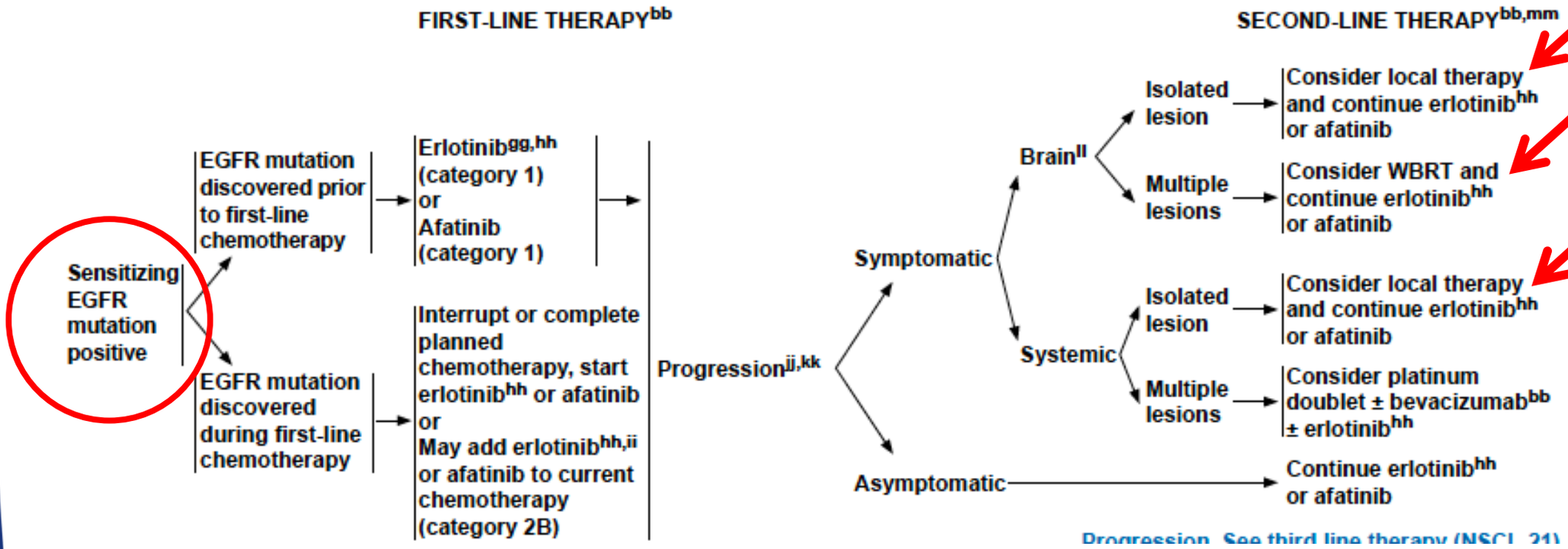
Changing approach to metastases

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2014
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

ADENOCARCINOMA, LARGE CELL, NSCLC NOS: SENSITIZING EGFR MUTATION POSITIVE[a]



Toxicity: systemic therapy after SABR

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation: Gastrointestinal Cancer

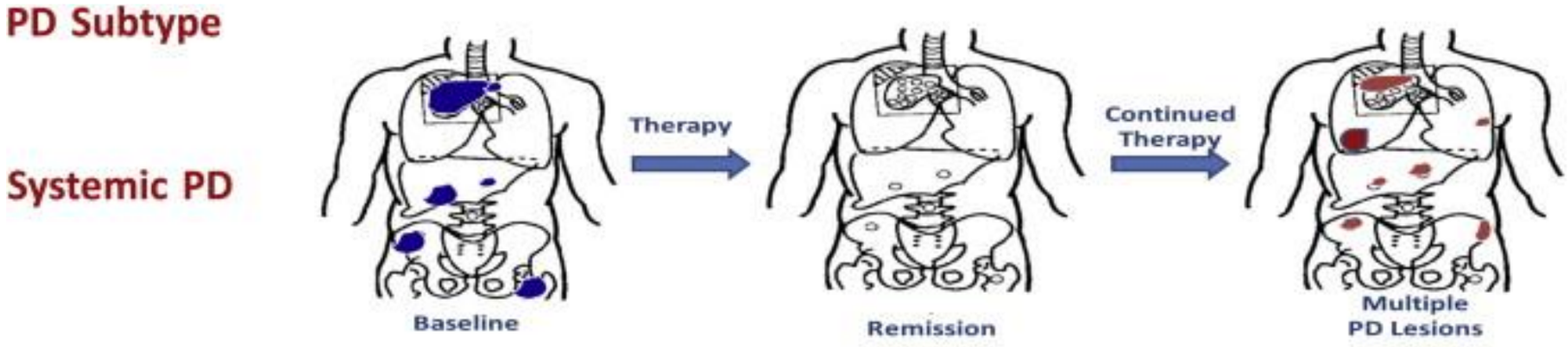
Increased Bowel Toxicity in Patients Treated With a Vascular Endothelial Growth Factor Inhibitor (VEGFI) After Stereotactic Body Radiation Therapy (SBRT)

Brandon M. Barney, MD,* Svetomir N. Markovic, MD, PhD,† Nadia N. Laack, MD,* Robert C. Miller, MD,* Jann N. Sarkaria, MD,* O. Kenneth Macdonald, MD,‡ Heather J. Bauer, RN,* and Kenneth R. Olivier, MD*

**Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota; †Division of Medical Oncology, Mayo Clinic, Rochester, Minnesota; and ‡Therapeutic Radiologists Incorporated, Kansas City, Kansas*

Received Mar 29, 2013, and in revised form May 3, 2013. Accepted for publication May 5, 2013

Acquired Resistance to Targeted Therapies



Gandara D, Clin Lung Cancer 2014

The changing role of radiotherapy

- Timing of SABR (consider planned post-ablative systemic therapy; phased SABR)

- Registries; expert radiological assessment post-SABR

- Trial enrollment according to RPA groups (*Ashworth A*)
- Low-risk: metachronous metastases (5-year OS 47.8%);
- Intermediate risk: synchronous metastases and N0 disease (5-year OS 36.2%);
- High risk: synchronous metastases and N1/N2 disease (5-year OS 13.8%).



Thank you for listening

