Dipartimento Oncologico
Presidenti del Congresso
Paolo Antognoni – Graziella Pinotti

Congresso del Gruppo Regionale
AIRO - Lombardia

Trattamento del paziente oligometastico

Barbara Alicja Jereczek-Fossa, MD PhD

European Institute of Oncology
& University of Milan, Milan, Italy

AIRC

UNIVERSITÀ DEGLI STUDI DI MILANO

Fondazione IEO·CCM
RICERCA ONCOLOGICA E CARDIOVASCOLARE

CORE FACULTY

Fondazione Umberto Veronesi
– per il progresso delle scienze

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AGENDA

- Numbers
- Distinct entity
- Standard of care
- Potential of combinations
- News!

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NUMBERS

La radiologia medica

RADIOTHERAPY FOR OLIGOMETASTATIC CANCER: A SURVEY AMONG RADIATION ONCOLOGISTS OF LOMBARDY (AIRO-Lombardy), ITALY

--Manuscript Draft--

Manuscript Number:	RAME-D-17-00281R1
Full Title:	RADIOTHERAPY FOR OLIGOMETASTATIC CANCER: A SURVEY AMONG RADIATION ONCOLOGISTS OF LOMBARDY (AIRO-Lombardy), ITALY
Article Type:	Original article
Keywords:	oligometastatic cancer; Lombardy; radiotherapy; survey; stereotactic body radiotherapy.
Corresponding Author:	Marianna Alessandra Gerardi Istituto Europeo di Oncologia Milano, ITALY

- **A total of 15.681 pts were treated in 2016 with EBRT in 12 responding centers**
- **1.087 pts were treated for oligometastatic cancer (7%)**
- **Range: 0.7-14.2 %**

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La radiologia medica

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Tumori. 2018 Oct;104(5):352-360. doi: 10.1177/0300891618784800. Epub 2018 Jul 9.

Equipment, staffing, and provision of radiotherapy in Lombardy, Italy: Results of three surveys performed between 2012 and 2016.

Palazzi MF[1], Soatti C[2], Jereczek-Fossa BA[3], Cazzaniga LF[4], Antognoni P[5], Gardani G[6], Amadori M[7], Baio A[8], Beltramo G[9], Bignardi M[10], Bracelli S[11], Buffoli A[12], Castiglioni S[13], Catalano G[14], Di Muzio N[15], Fallai C[16], Fariselli L[17], Frata P[18], Gramaglia A[19], Italia C[20], Ivaldi G[21], Lombardi F[22], Magrini SM[23], Nava S[24], Sarti E[25], Scandolaro L[26], Scorsetti M[27], Stiglich F[28], Tortini R[29], Valdagni R[30], Valvo F[31], Vavassori V[32], Sbicego EL[33], Tonoli S[34], Orecchia R[35].

Author information

Abstract

INTRODUCTION:: Several efforts are being implemented at the European level to measure provision of up-to-date radiation treatments across the continent.

METHODS:: A snapshot survey involving all radiation oncology centers within Lombardy, Italy, was performed in 2012 and repeated in 2014 and 2016, in cooperation with regional governmental officers. Centers were asked to provide detailed

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DISTINCT ENTITY

- Prognosis
- Patterns of failure
- Biology

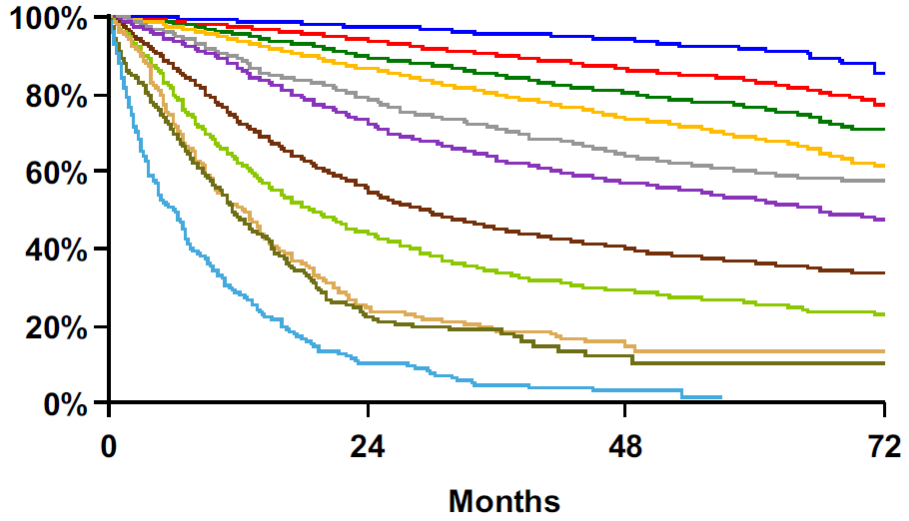
TNM 8th edition

M – Distant Metastasis
M0 No distant metastasis
M1

M1a Separate tumour nodule(s) in a contralateral lobe; tumour with pleural or pericardial nodules or malignant pleural or pericardial effusion

M1b Single extrathoracic metastasis in a single organ

M1c Multiple extrathoracic metastasis in a single or multiple organs

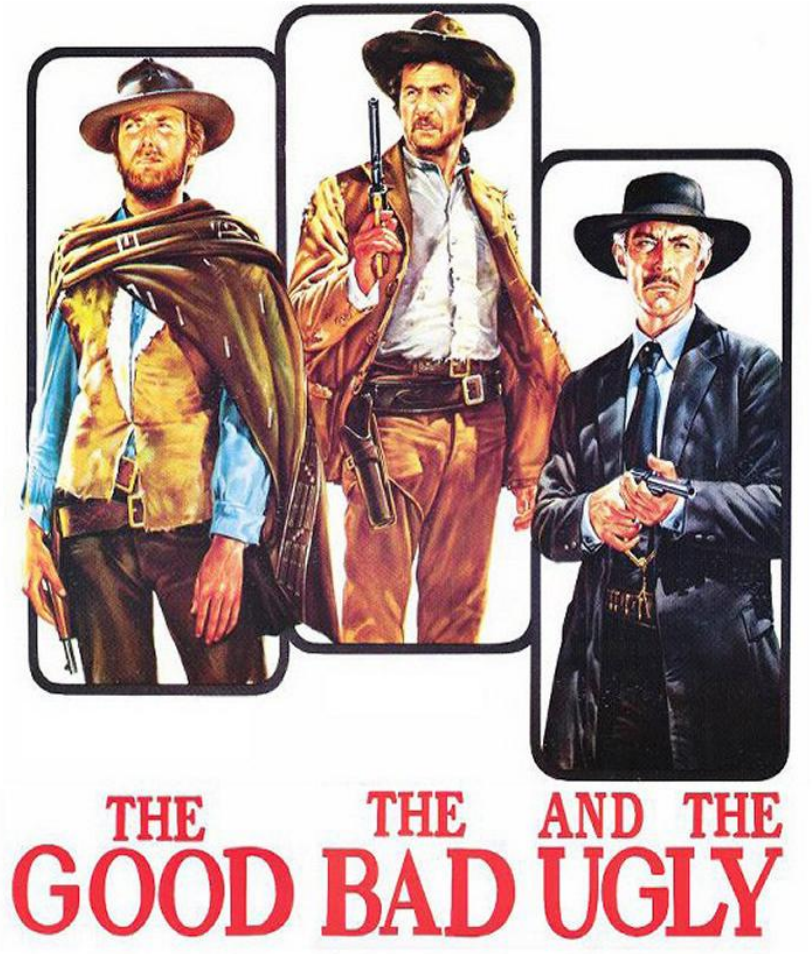


Journal of Thoracic Oncology Vol. 11 No. 1: 39-51

The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer

Peter Goldstraw, FRCS,[a,*] Kari Chansky, MS,[b] John Crowley, PhD,[b] Ramon Rami-Porta, MD,[c] Hisao Asamura, MD,[d] Wilfried E. E. Eberhardt, MD,[e] Andrew G. Nicholson, FRCP,[f] Patti Groome, PhD,[g] Alan Mitchell, MS,[b] Vanessa Bolejack, MPH,[b] on behalf of the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions

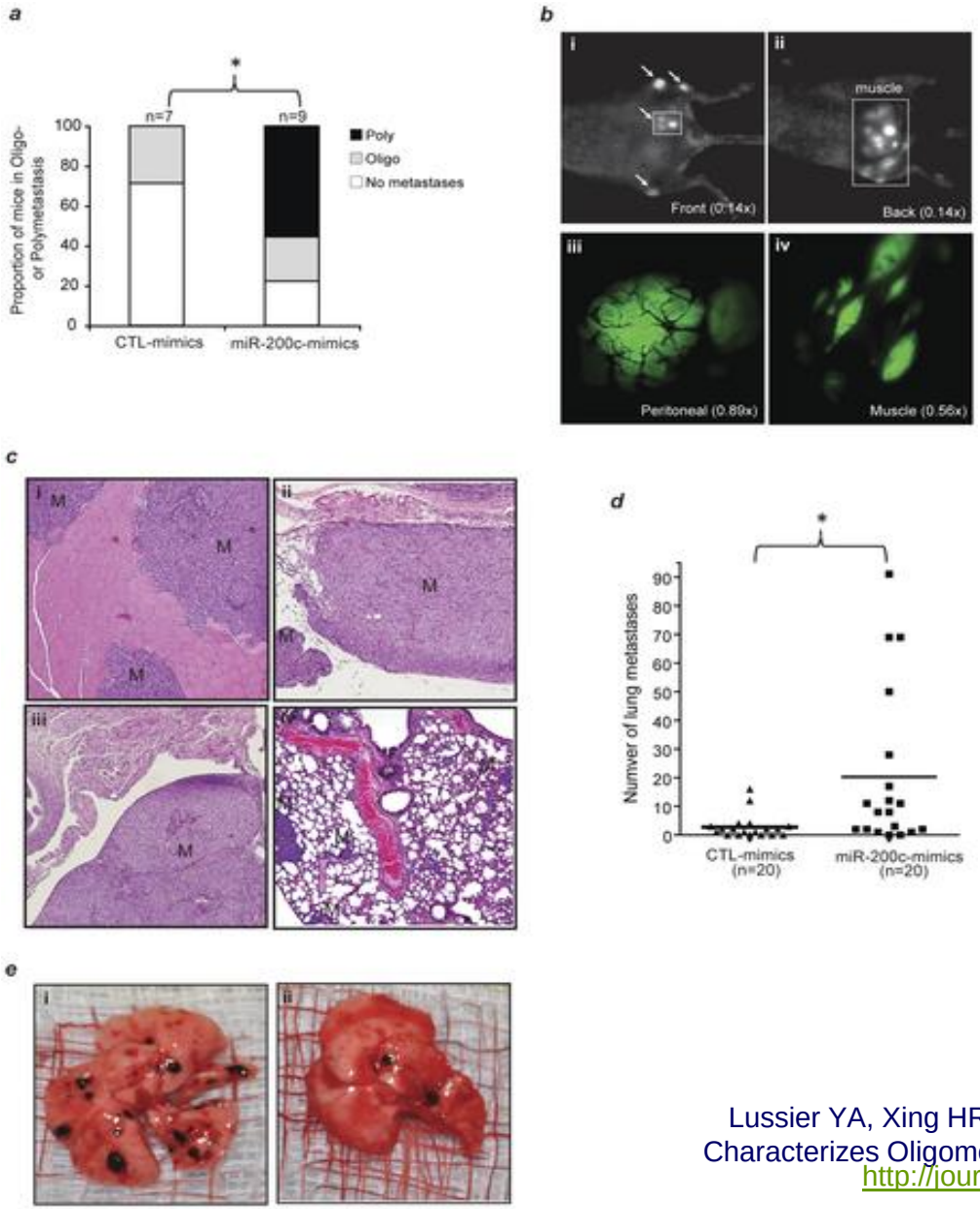
OLIGOMETS from BIOLOGY POINT OF VIEW



- Oligo and polymetastastic cancers are **more than two distinct entities**

- subclasses (molecular sybtypes not just number of mets)

microRNA-200c regulate oligo- to poly-metastasis(es) progression in the L1-R2-435-GFP xenograft model



Tumour microRNA expression patterns

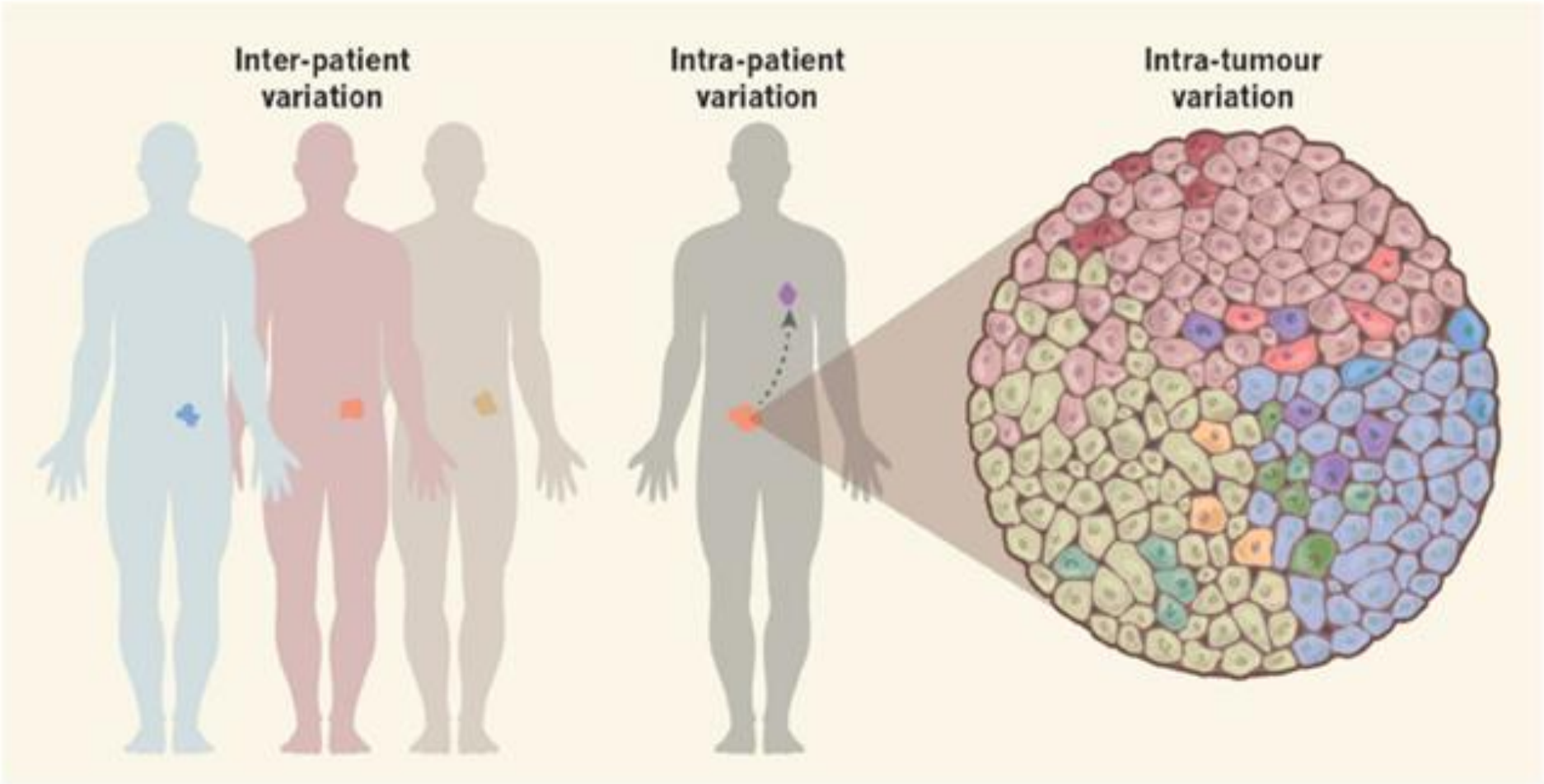
can distinguish:

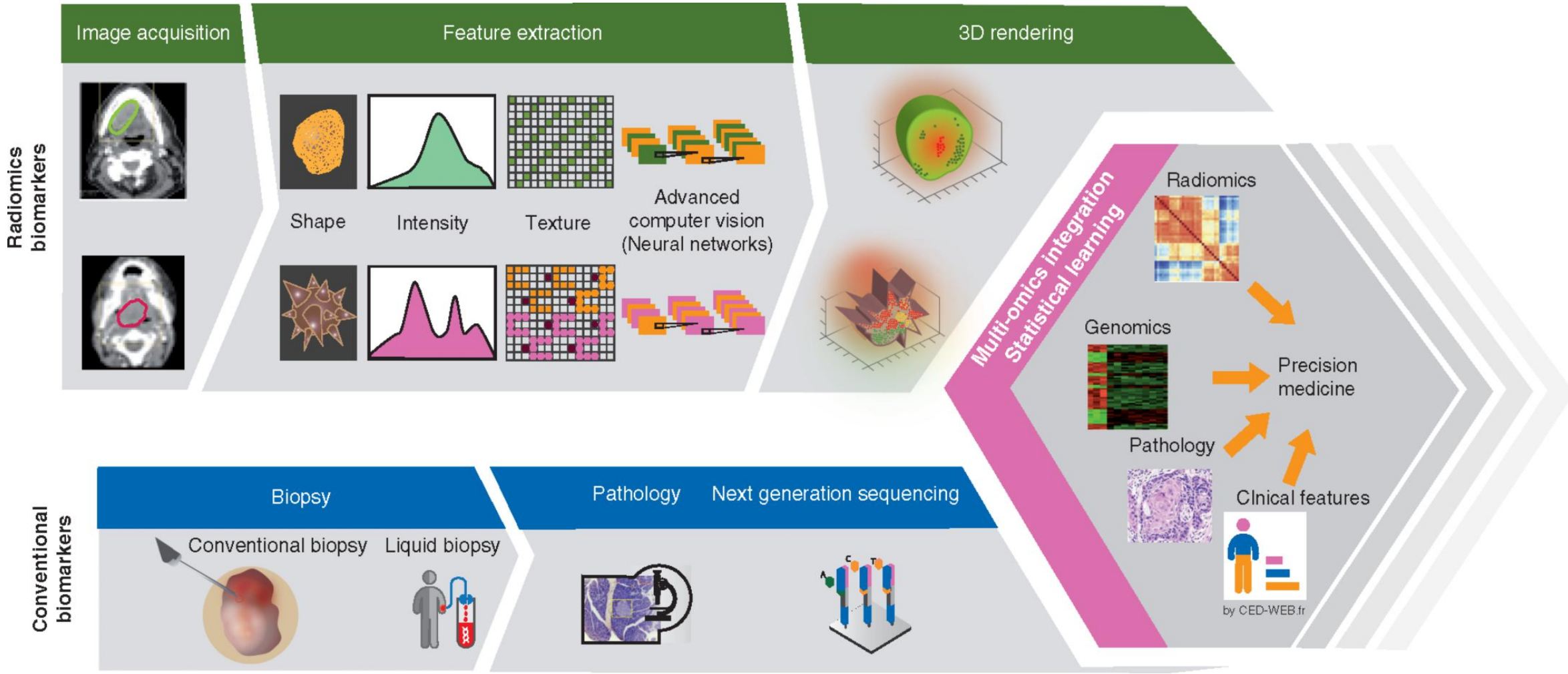
- cancers likely to remain in a stable oligometastatic state

- from those that will imminently progress to polymetastatic disease

Lussier YA, Xing HR, Salama JK, Khodarev NN, Huang Y, et al. (2011) MicroRNA Expression Characterizes Oligometastasis(es). PLOS ONE 6(12): e28650. doi:10.1371/journal.pone.0028650
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0028650

HETEROGENEITY of TUMORS





From: Promises and challenges for the implementation of computational medical imaging (radiomics) in oncology

Ann Oncol. 2017;28(6):1191-1206. doi:10.1093/annonc/mdx034

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- Numbers
- Distinct entity
- **Standard of care**
- Potential of combinations
- News!

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STANDARD OF CARE?

a) systemic therapy

b) metastasis-directed therapy (MDT)

c) a + b

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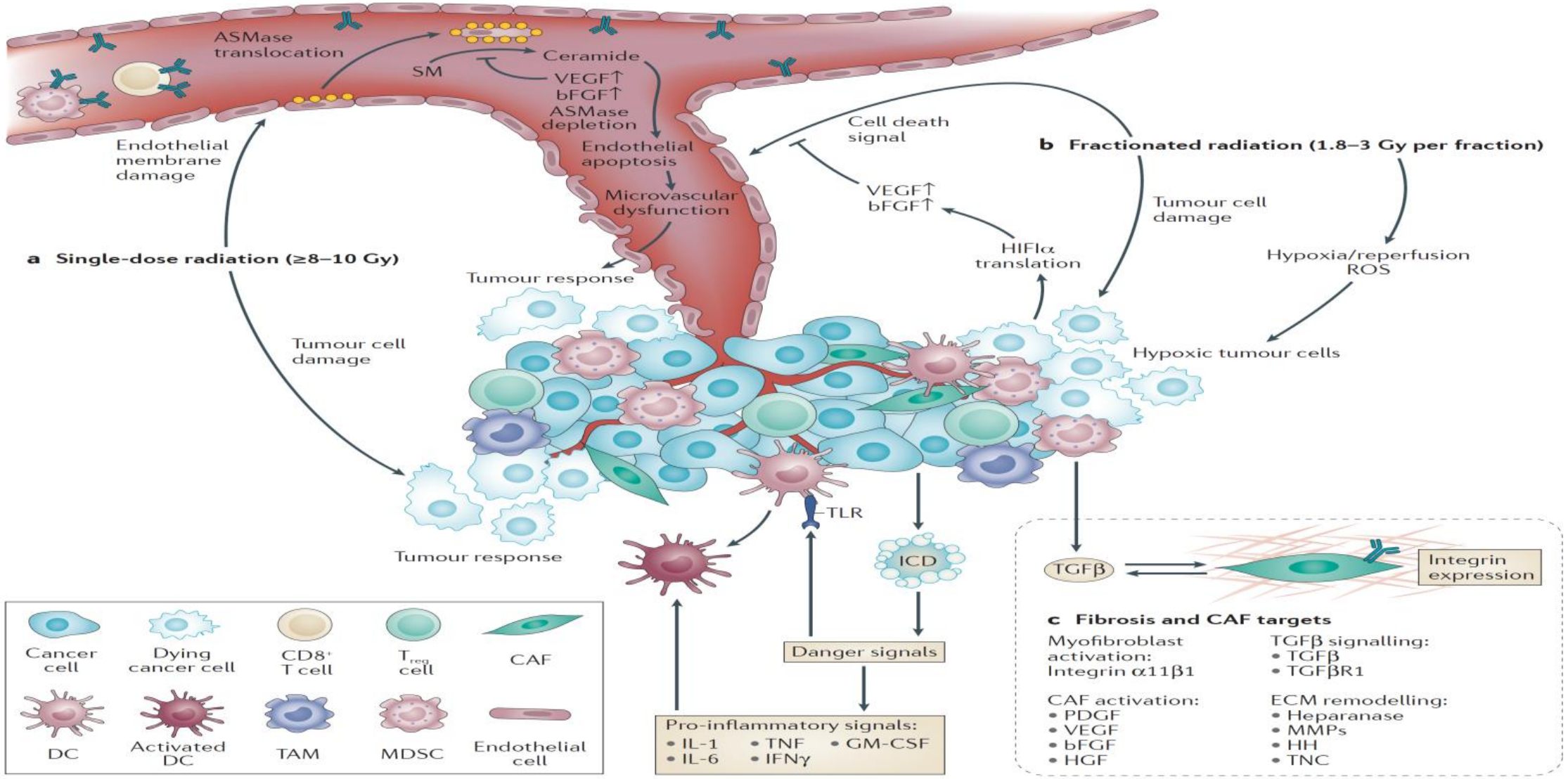
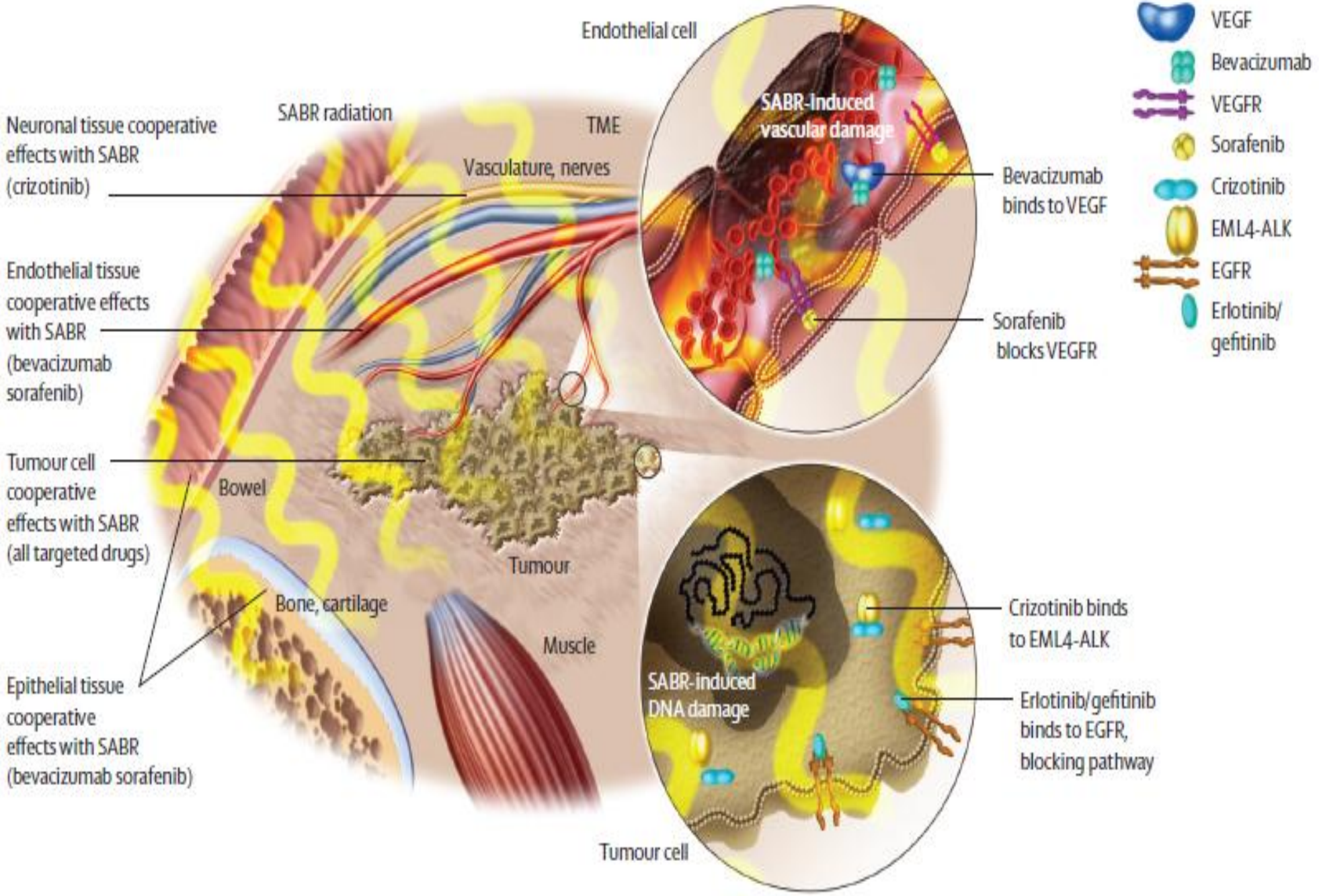
Endothelial damage
Activation of immune response against cancer

Siva S et al. Nat Rev Urol 2017





Zeng et al. Lancet Oncol 2014; 15: e426–34

SBRT and drugs

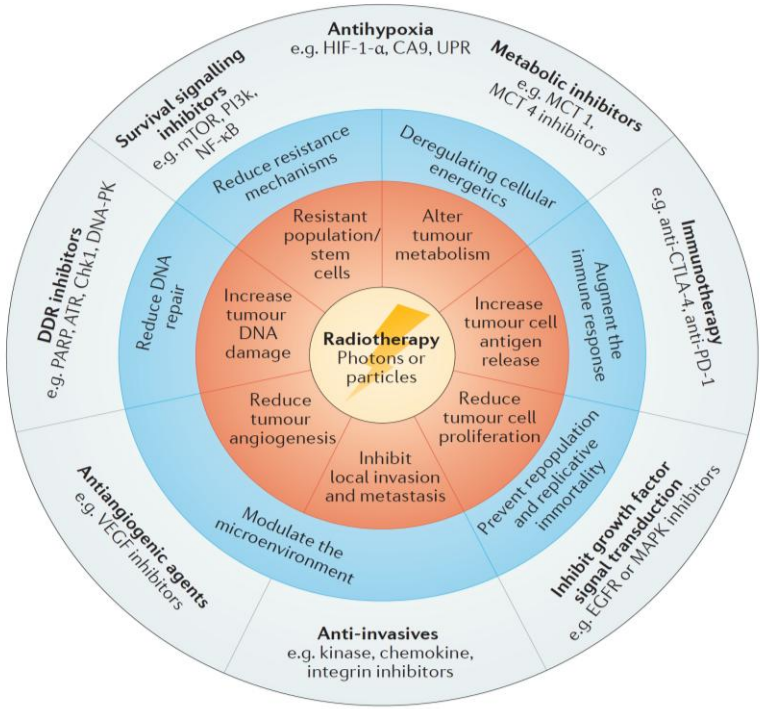
Mechanisms

1. **Reversal of hypoxia (normalisation of tumor flow)**
2. **Reduction of tumor size (direct and indirect)**
3. **Facilitation of apoptosis**
4. **Prevention of SBRT re-vascularisation**
5. **Improvement of immune response (microenvironment)**

Tree et al. Lancet Oncol 2013, De Meerleer et al. Lancet Oncol 2014
Grimaldi et al. Oncoimmunol 2014, Scheithauer et al. Radiat Oncol 2014

Sharma RA et al. Nature Reviews Clin Oncol 2016;13:627-

CONSENSUS STATEMENT



OPEN

Clinical development of new drug–radiotherapy combinations

Ricky A. Sharma[1], Ruth Plummer[2], Julie K. Stock[3], Tessa A. Greenhalgh[4], Ozlem Ataman[5], Stephen Kelly[6], Robert Clay[7], Richard A. Adams[8], Richard D. Baird[9], Lucinda Billingham[10], Sarah R. Brown[11], Sean Buckland[6], Helen Bulbeck[12], Anthony J. Chalmers[13], Glen Clack[14], Aaron N. Cranston[15], Lars Damstrup[16], Roberta Ferraldeschi[17], Martin D. Forster[1], Julian Golec[18], Russell M. Hagan[19], Emma Hall[20], Axel-R. Hanauske[21], Kevin J. Harrington[20], Tom Haswell[12], Maria A. Hawkins[4], Tim Illidge[22], Hazel Jones[3], Andrew S. Kennedy[23], Fiona McDonald[20], Thorsten Melcher[24], James P. B. O'Connor[22], John R. Pollard[18], Mark P. Saunders[22], David Sebag-Montefiore[11], Melanie Smitt[25], John Staffurth[8], Ian J. Stratford[22] and Stephen R. Wedge[2] on behalf of the NCRI CTRad Academia-Pharma Joint Working Group

J Natl Cancer Inst 2013;105:11–24

NCI–RTOG Translational Program Strategic Guidelines for the Early-Stage Development of Radiosensitizers

Yaacov Richard Lawrence, Bhadrasain Vikram, James J. Dignam, Arnab Chakravarti, Mitchell Machtay, Boris Freidlin, Naoko Takebe, Walter J. Curran Jr, Soren M. Bentzen, Paul Okunieff, C. Norman Coleman, Adam P. Dicker

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Combining precision radiotherapy with molecular targeting and immunomodulatory agents: a guideline by the American Society for Radiation Oncology

Robert G Bristow, Brian Alexander, Michael Baumann, Scott V Bratman, J Martin Brown, Kevin Camphausen, Peter Choyke, Deborah Citrin, Joseph N Contessa, Adam Dicker, David G Kirsch, Mechthild Krause, Quynh-Thu Le, Michael Milosevic, Zachary S Morris, Jann N Sarkaria, Paul M Sondel, Phuoc T Tran, George D Wilson, Henning Willers, Rebecca K S Wong, Paul M Harari

Lancet Oncol 2018; 19: e240–51

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PRACTICE CHANGING STUDIES

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NEWS

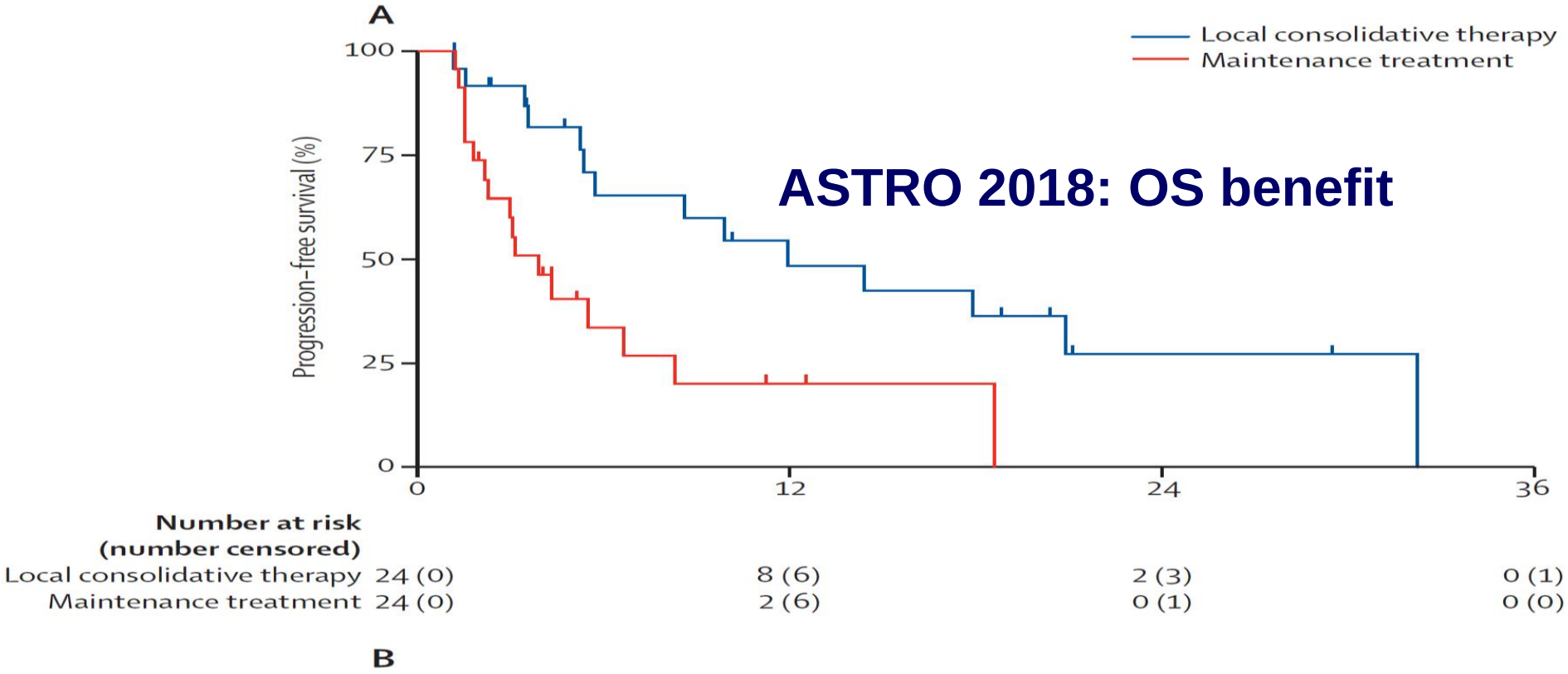
- Lung
- Prostate
- Breast
- Colon

Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study

Daniel R Gomez, George R Blumenschein Jr, J Jack Lee, Mike Hernandez, Rong Ye, D Ross Camidge, Robert C Doebele, Ferdinandos Skoulidis, Laurie E Gaspar, Don L Gibbons, Jose A Karam, Brian D Kavanagh, Chad Tang, Ritsuko Komaki, Alexander V Louie, David A Palma, Anne S Tsao, Boris Sepesi, William N William, Jianjun Zhang, Qiuling Shi, Xin Shelley Wang, Stephen G Swisher, John V Heymach**

Lancet Oncol 2016; 17: 1672–82

PFS: 3.9 months vs 11.9 months



ASTRO 2018: OS benefit

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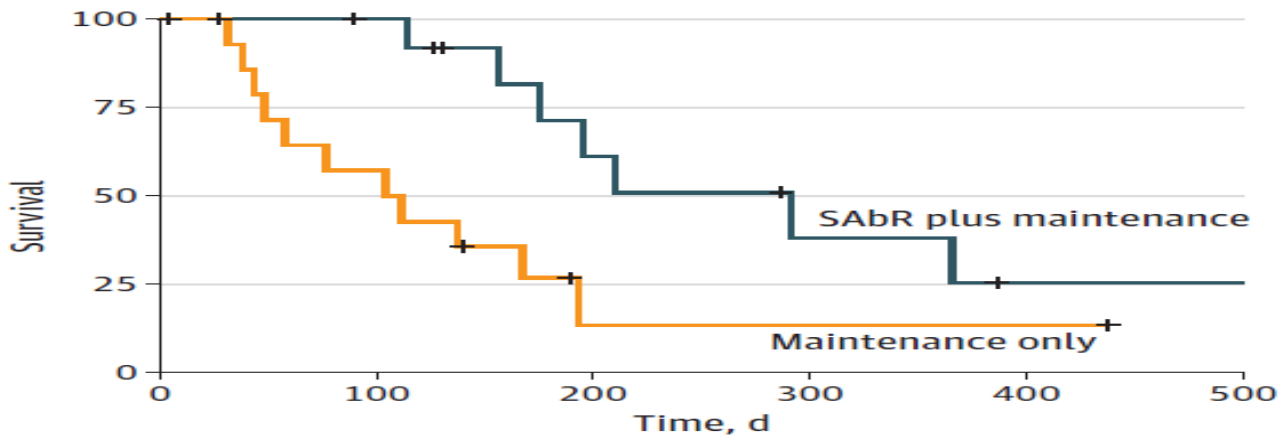
JAMA Oncology | Original Investigation

Consolidative Radiotherapy for Limited Metastatic Non–Small-Cell Lung Cancer

A Phase 2 Randomized Clinical Trial

Puneeth Iyengar, MD, PhD; Zabi Wardak, MD; David E. Gerber, MD; Vasu Tumati, MD; Chul Ahn, PhD; Randall S. Hughes, MD; Jonathan E. Dowell, MD; Naga Cheedella, MD; Lucien Nedzi, MD; Kenneth D. Westover, MD, PhD; Suprabha Pulipparacharuvil, PhD; Hak Choy, MD; Robert D. Timmerman, MD

Figure 2. Analysis of Progression-Free Survival



No. at risk

SAbR plus maintenance	14	12	6	3	1
Maintenance only	15	8	1	1	1

Log-rank testing reveals a statistically significant benefit in progression-free survival for SAbR-plus-maintenance chemotherapy (hazard ratio, 0.304; 95% CI, 0.113-0.815; P = .01). SAbR indicates stereotactic ablative radiotherapy.

Local aggressive therapy

"could change the natural history of cancer by

- limiting the potential for later spread
- altering systemic anticancer immune responses (control of subclinical disease)"

Lancet Oncol 2016; 17: 1672–82

PROSTATE CANCER

Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial

Piet Ost, Dries Reynders, Karel Decaestecker, Valérie Fonteyne, Nicolaas Lumen, Aurélie De Bruycker, Bieke Lambert, Louke Delrue, Renée Bultijnck, Tom Claeys, Els Goetghebeur, Geert Villeirs, Kathia De Man, Filip Ameye, Ignace Billiet, Steven Joniau, Friedl Vanhaverbeke, and Gert De Meerleer

Platinum Priority – Prostate Cancer

Editorial by Piet Ost on pp. 463–464 of this issue

Stereotactic Abative Body Radiotherapy (SABR) for Oligometastatic Prostate Cancer: A Prospective Clinical Trial

NEW!!

Shankar Siva [a,b,], Mathias Bressel [c], Declan G. Murphy [b,d], Mark Shaw [a], Sarat Chander [a], John Violet [a], Keen Hun Tai [a], Cristian Udovicich [a], Andrew Lim [a], Lisa Selbie [a], Michael S. Hofman [a,b], Tomas Kron [a,b], Daniel Moon [a], Jeremy Goad [a], Nathan Lawrentschuk [a,b], Farshad Foroudi [e]*

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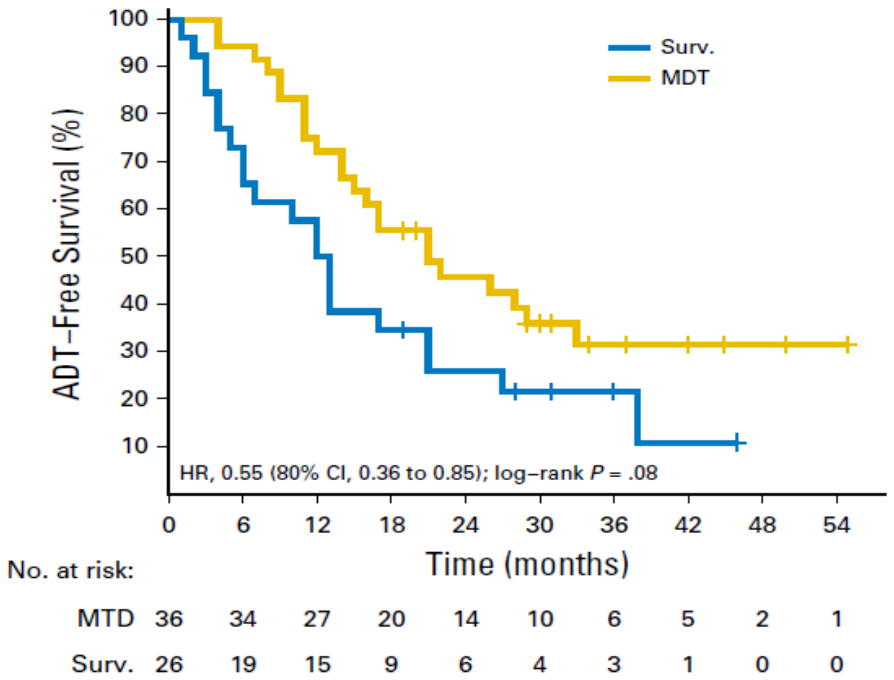
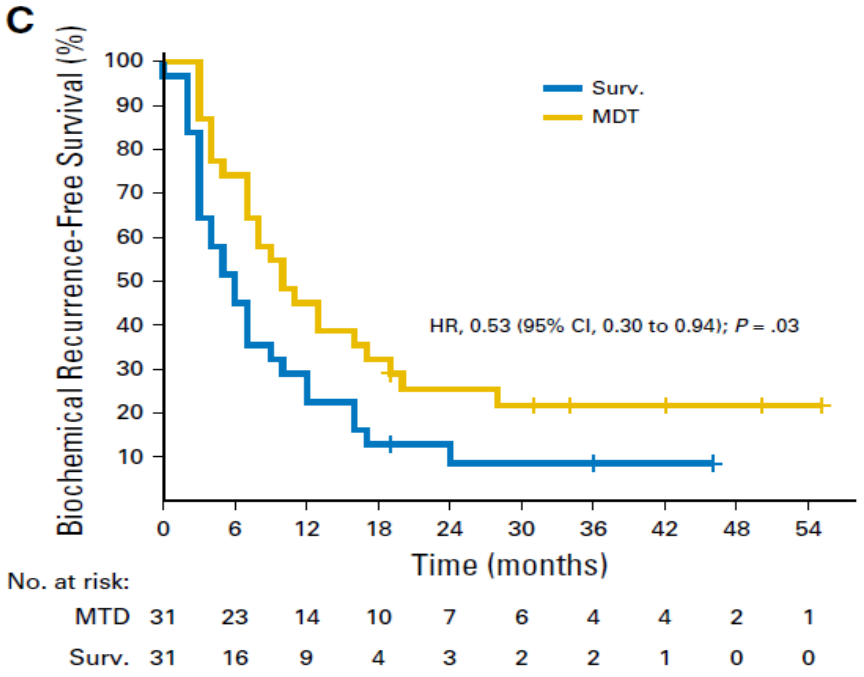
LOCAL APPROACH TO oligomets

STOMPT: observation vs MDT

Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial

Piet Ost, Dries Reynders, Karel Decaestecker, Valérie Fonteyne, Nicolaas Lumen, Aurélie De Bruycker, Bieke Lambert, Louke Delrue, Renée Bultijnck, Tom Claeys, Els Goetghebeur, Geert Villeirs, Kathia De Man, Filip Ameye, Ignace Billiet, Steven Joniau, Friedl Vanhaverbeke, and Gert De Meerleer





J Clin Oncol DOI: https://doi.org/10.1200/JCO.2017. 75.4853

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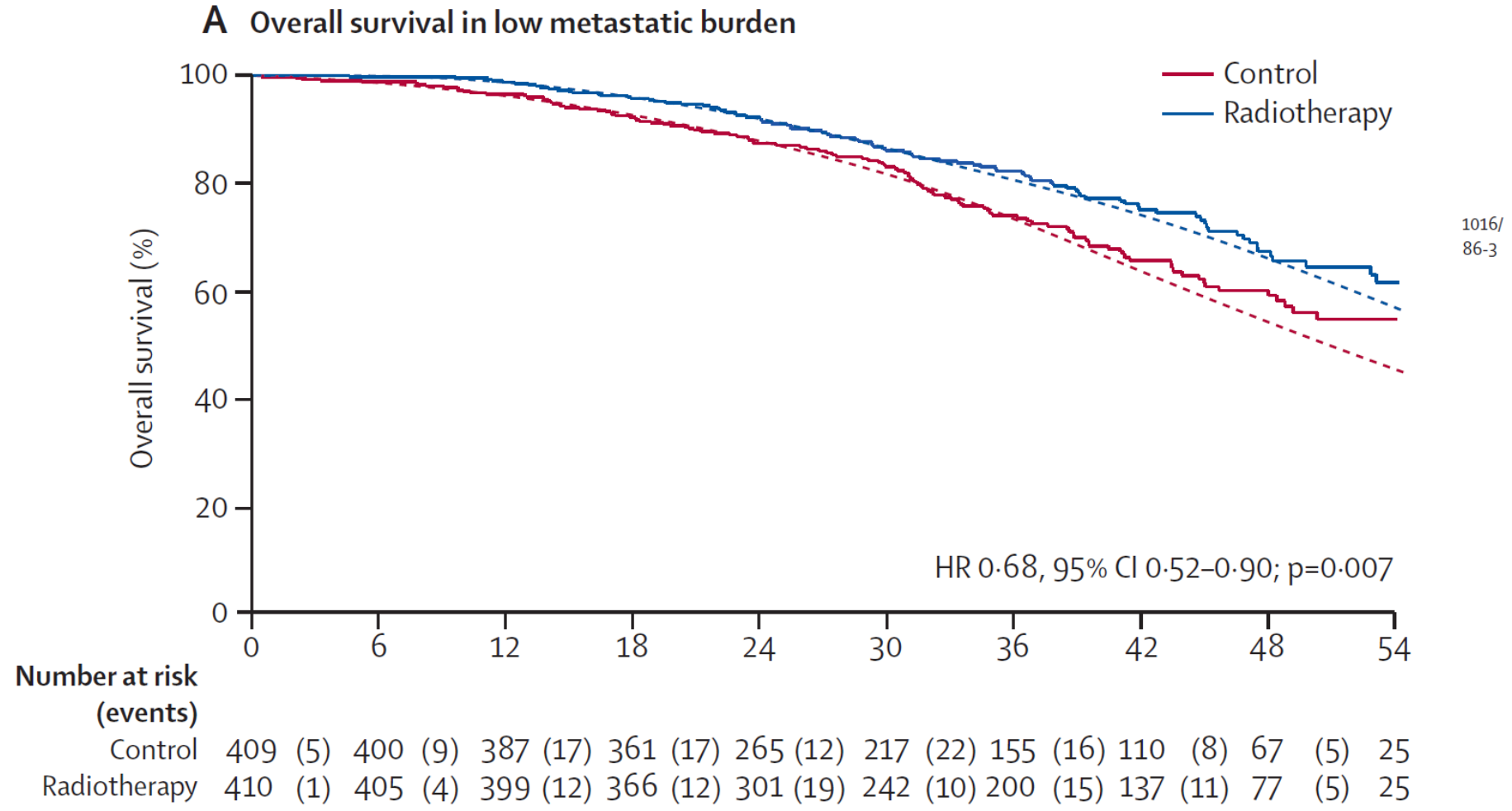
Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

Christopher C Parker, Nicholas D James, Christopher D Brawley, Noel W Clarke, Alex P Hoyle, Adnan Ali, Alastair W S Ritchie, Gerhardt Attard, Simon Chowdhury, William Cross, David P Dearnaley, Silke Gillessen, Clare Gilson, Robert J Jones, Ruth E Langley, Zafar I Malik, Malcolm D Mason, David Matheson, Robin Millman, J Martin Russell, George N Thalmann, Claire L Amos, Roberto Alonzi, Amit Bahl, Alison Birtle, Omar Din, Hassan Douis, Chinnamani Eswar, Joanna Gale, Melissa R Gannon, Sai Jonnada, Sara Khaksar, Jason F Lester, Joe M O'Sullivan, Omi A Parikh, Ian D Pedley, Delia M Pudney, Denise J Sheehan, Narayanan Nair Srihari, Anna T H Tran, Mahesh K B Parmar, Matthew R Sydes*, on behalf of the Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators†*

HIGH metastatic burden as in CHAARTED trial:

- **4 or more bone metastases with one or more outside the vertebral bodies or pelvis,**
- **or visceral metastases,**
- **or both**

RT improved OS from 73% to 81% at 3y <u>low burden Pca</u>



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Published Online
October 21, 2018
http://dx.doi.org/10.1016/
S0140-6736(18)32486-3

"Prostate RT should be

a standard treatment option

for men with newly diagnosed disease

with a low metastatic burden"

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Breast, colon, prostate and lung

Meeting Coverage > ASTRO

SBRT Doubles 5-Year Survival in Oligometastatic Cancers

— Most patients in phase II trial had up to three metastatic lesions

NEW!!

Randomized, phase II, open-label, multicentre

Stereotactic ABlative Radiotherapy for the Comprehensive treatment of OligoMEtastatic Tumors **(SABR-COMET) presented** at the 60th ASTRO from October 21 – 24 in San Antonio, Texas.

Median survival:

28 Vs 41 months

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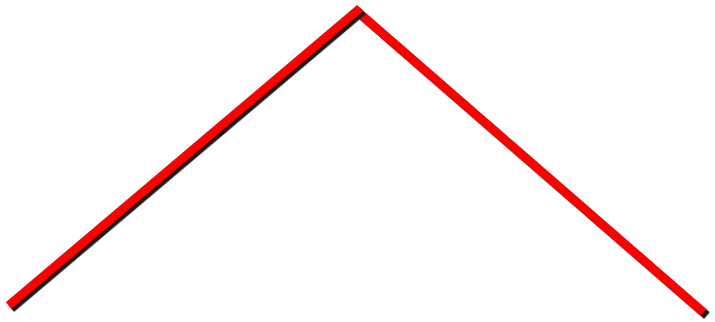
SABR-COMET

NEW!!

Oligometastatic breast, colon, prostate, lung cancer



Standard of care

Standard of care + SBRT

Median survival:

28 months

41 months

A CHANGE OF PARAGIGM?

Al-Batran *et al. BMC Cancer* (2017) 17:893
DOI 10.1186/s12885-017-3918-9

BMC Cancer

STUDY PROTOCOL Open Access

The RENAISSANCE (AIO-FLOT5) trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction – a phase III trial of the German AIO/CAO-V/CAOGI

Salah-Eddin Al-Batran[1*†], Thorsten O. Goetze[1†], Daniel W. Mueller[1], Arndt Vogel[2], Michael Winkler[3], Sylvie Lorenzen[4], Alexander Novotny[5], Claudia Pauligk[1], Nils Homann[6], Thomas Jungbluth[7], Christoph Reissfelder[8], Karel Caca[9], Steffen Retter[10], Eva Horndasch[11], Julia Gumpp[12], Claus Bolling[13], Karl-Hermann Fuchs[14], Wolfgang Blau[15], Winfried Padberg[16], Michael Pohl[17], Andreas Wunsch[18], Patrick Michl[19], Frank Mannes[20], Matthias Schwarzbach[21], Harald Schmalenberg[22], Michael Hohaus[23], Christian Scholz[24], Christoph Benckert[25], Jorge Riera Knorrenschild[26], Veit Kanngießer[27], Thomas Zander[28], Hakan Alakus[29], Ralf-Dieter Hofheinz[30], Claus Roedel[31], Manish A. Shah[32], Mitsuru Sasako[33], Dietmar Lorenz[34], Jakob Izbicki[35], Wolf O. Bechstein[36], Hauke Lang[37] and Stefan P. Moenig[38]

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TAKE HOME MESSAGES

RT is a standard for oligomet cancer

Mix of biologies

Combinations under investigation

FIRST high level evidence for oligomet RT

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