Society of Interventional Oncology

Oligometastatic Disease: Offering Local Therapies in Systemic Disease

Developed in partnership with the Society of Interventional Oncology (SIO)

Moderator & Presenter: Alda Tam, MD
Presenters: Thomas Atwell, MD; Jack Jennings, MD; Kevin Kim, MD; Constantinos Sofocleous, MD

Disclosures

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Brand names are included in this presentation for participant clarification purposes only.

No product promotion should be inferred.

Definitions

- ≤ 5 sites of disease
- Can occur early as a result of a tumor's limited biologic capacity to spread
  - May represent a distinct intermediate stage between localized tumor and widespread metastases
- Can occur following positive response to chemotherapy where most metastases are eradicated, but a limited number of metastatic sites remain
  - May represent sites of origin for metastatic disease progression

McMenomy BP, et al. *J Vasc Interv Radiol*. 2013;24(2):207-13.

Rationale for Treatment

- **International Registry of Lung Metastases**
  - 5,206 patients
  - 4,752 (88%) complete resection

Resection	5 Yrs.	10 Yrs.	Median
Complete	36%	26%	35 mos.
Incomplete	13%	7%	15 mos.

- **Complete ablation may have the same effect**
  - Number
  - Size
  - Location

Pastorino U, et al. *J Thorac Cardiovasc Surg.* 1997;113(1):37-49.

Oligometastatic Disease

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available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Opinion

"Gotta Catch 'em All", or Do We? *Pokemet* Approach to Metastatic Prostate Cancer

Declan G. Murphy[a,b,c,*], *Christopher J. Sweeney*[d], *Bertrand Tombal*[e]

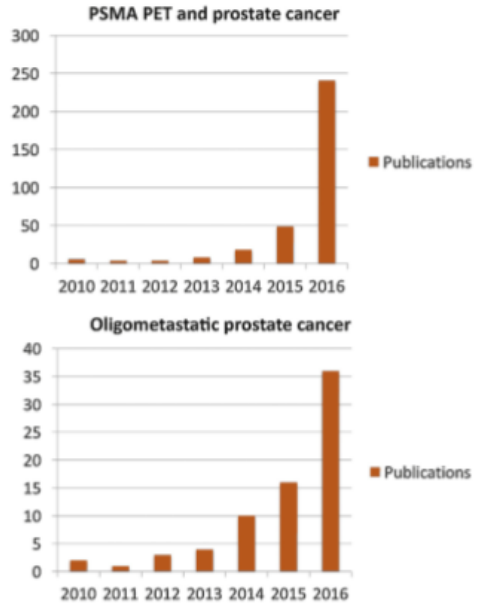
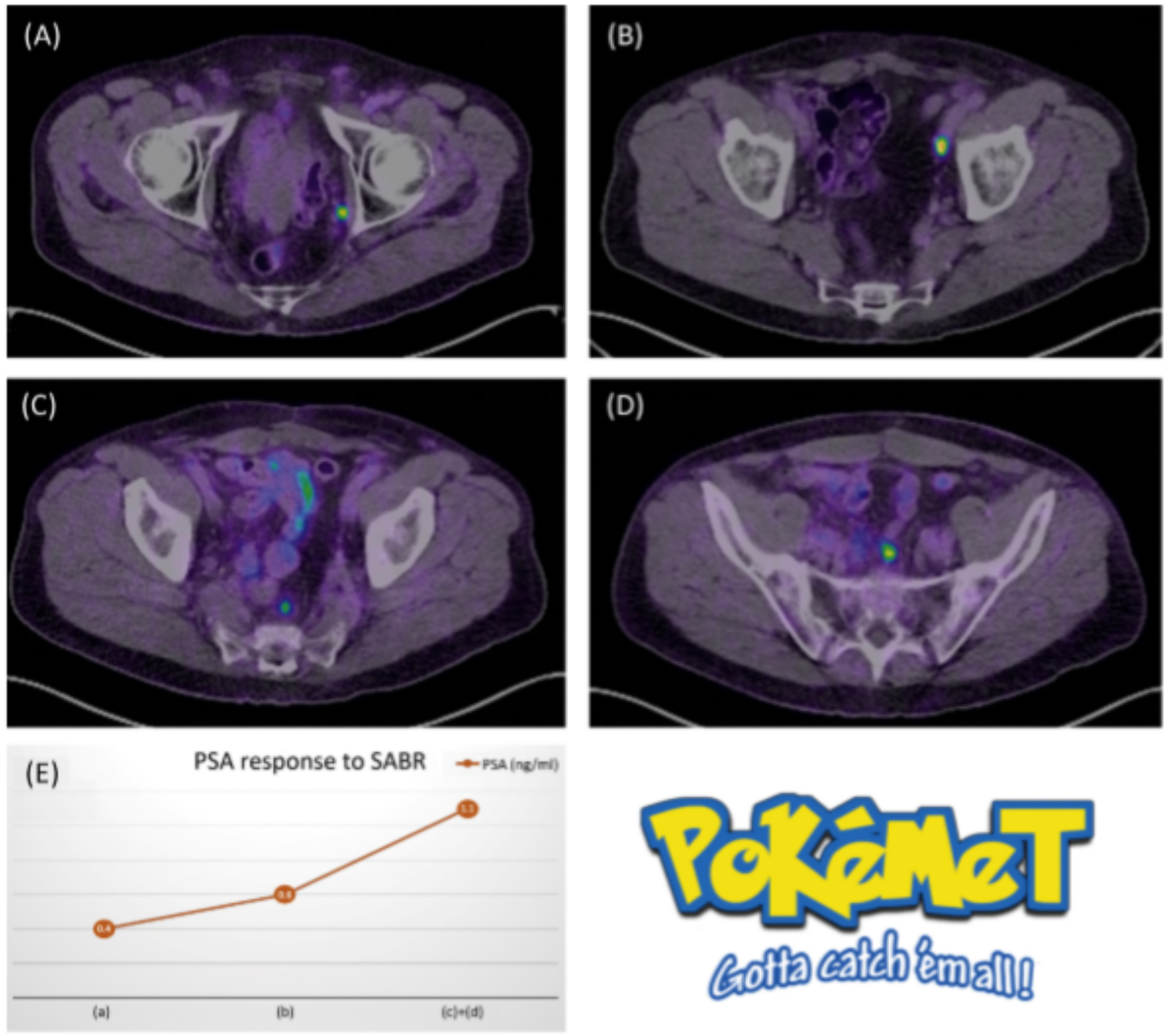


Fig. 1 – The growth in publications on oligometastatic prostate cancer is paralleled by the growth in publications on prostate-specific membrane antigen (PSMA) positron-emission tomography (PET) imaging of prostate cancer.



Cryoablation of Bone Metastases from Renal Cell Carcinoma for Local Tumor Control

Carly S. Gardner, MD, Joe E. Ensor, PhD, Kamran Ahrar, MD, Steven Y. Huang, MD, Sharjeel H. Sabir, MD, Nizar M. Tannir, MD, Valerae O. Lewis, MD, and Alda L. Tam, MD

Investigation performed at the University of Texas MD Anderson Cancer Center, Houston, Texas

JBJS 2017;99:1916-1926

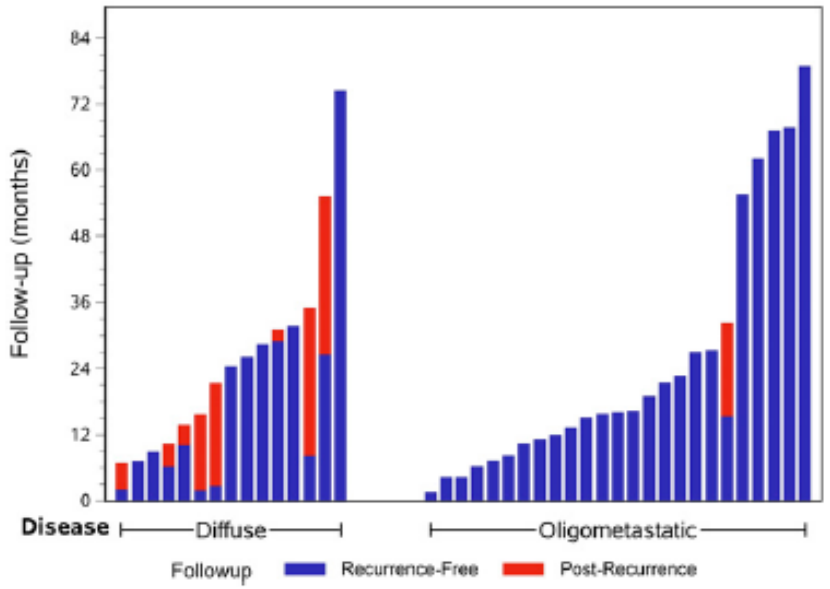


Fig. 2

Waterfall plot of survival of patients demonstrates local tumor control as stratified by disease burden. Only 1 of the patients with oligometastatic disease demonstrated tumor recurrence at the site of ablation. In contrast, 8 of the 15 patients with diffuse disease demonstrated tumor recurrence at the site of ablation, with most of the recurrences occurring within 12 months following the cryoablation procedure.

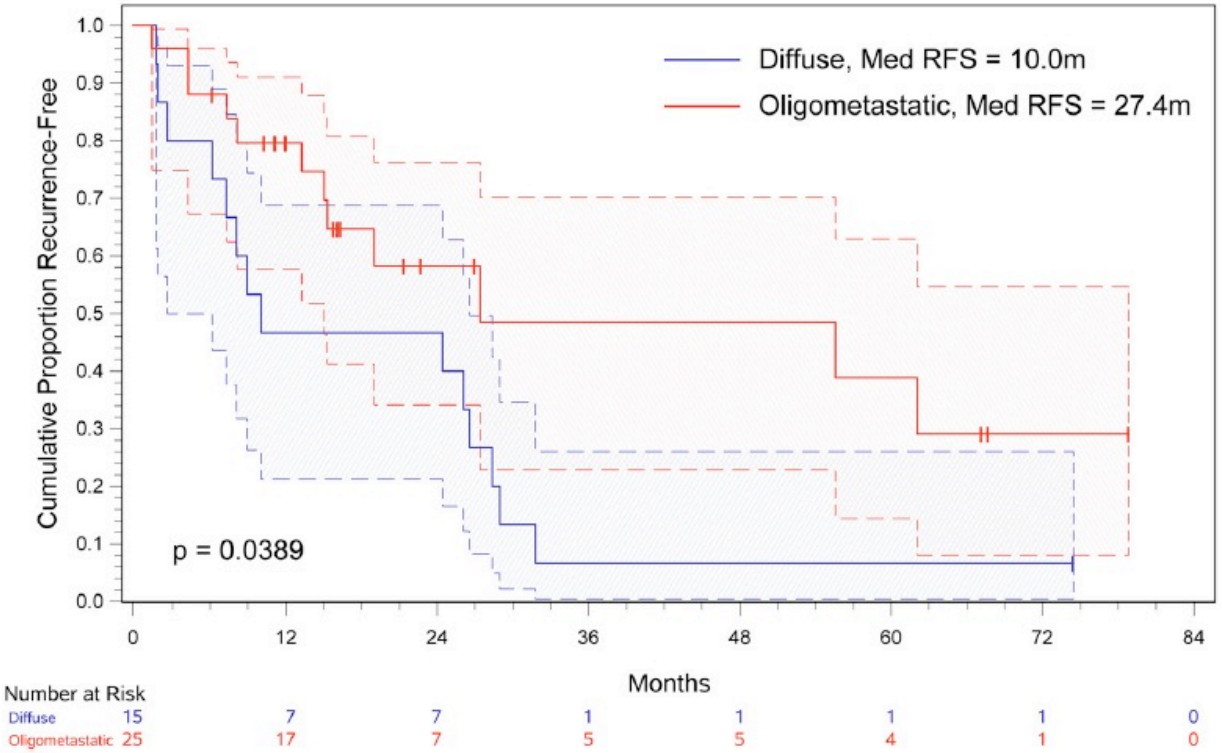


Fig. 3

Kaplan-Meier curve of recurrence-free survival (RFS) as stratified by disease burden. The median (med) duration of recurrence-free survival among the patients with oligometastatic disease (27.4 months [95% CI, 15.0 months to an upper limit not reached]) differed significantly from that of patients with diffuse disease (10.0 months [95% CI, 2.7 to 26.5 months]) (p – 0.04).

Oligometastatic Disease

Ability to distinguish true oligometastatic vs. transformation into polymetastatic

OPEN ACCESS Freely available online

PLOS ONE

Oligo- and Polymetastatic Progression in Lung Metastasis(es) Patients Is Associated with Specific MicroRNAs

Yves A. Lussier[1,2,3,4,5,6,7¶*], Nikolai N. Khodarev[3,8¶], Kelly Regan[4¶], Kimberly Corbin[8¶], Haiquan Li[4¶], Sabha Ganai[9], Sajid A. Khan[9], Jennifer Gnerlich[9], Thomas E. Darga[9], Hanli Fan[4], Oleksiy Karpenko[6], Philip B. Paty[10], Mitchell C. Posner[9], Steven J. Chmura[8], Samuel Hellman[3,8], Mark K. Ferguson[9], Ralph R. Weichselbaum[1,3,8*]

Abstract

Rationale: Strategies to stage and treat cancer rely on a presumption of either localized or widespread metastatic disease. An intermediate state of metastasis termed oligometastasis(es) characterized by limited progression has been proposed. Oligometastases are amenable to treatment by surgical resection or radiotherapy.

Methods: We analyzed microRNA expression patterns from lung metastasis samples of patients with ≤5 initial metastases resected with curative intent.

Results: Patients were stratified into subgroups based on their rate of metastatic progression. We prioritized microRNAs between patients with the highest and lowest rates of recurrence. We designated these as high rate of progression (HRP) and low rate of progression (LRP); the latter group included patients with no recurrences. The prioritized microRNAs distinguished HRP from LRP and were associated with rate of metastatic progression and survival in an independent validation dataset.

Conclusion: Oligo- and poly- metastasis are distinct entities at the clinical and molecular level.

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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*]

Abstract

Background: Cancer staging and treatment presumes a division into localized or metastatic disease. We proposed an intermediate state defined by ≤5 cumulative metastasis(es), termed oligometastases. In contrast to widespread polymetastases, oligometastatic patients may benefit from metastasis-directed local treatments. However, many patients who initially present with oligometastases progress to polymetastases. Predictors of progression could improve patient selection for metastasis-directed therapy.

Methods: Here, we identified patterns of microRNA expression of tumor samples from oligometastatic patients treated with high-dose radiotherapy.

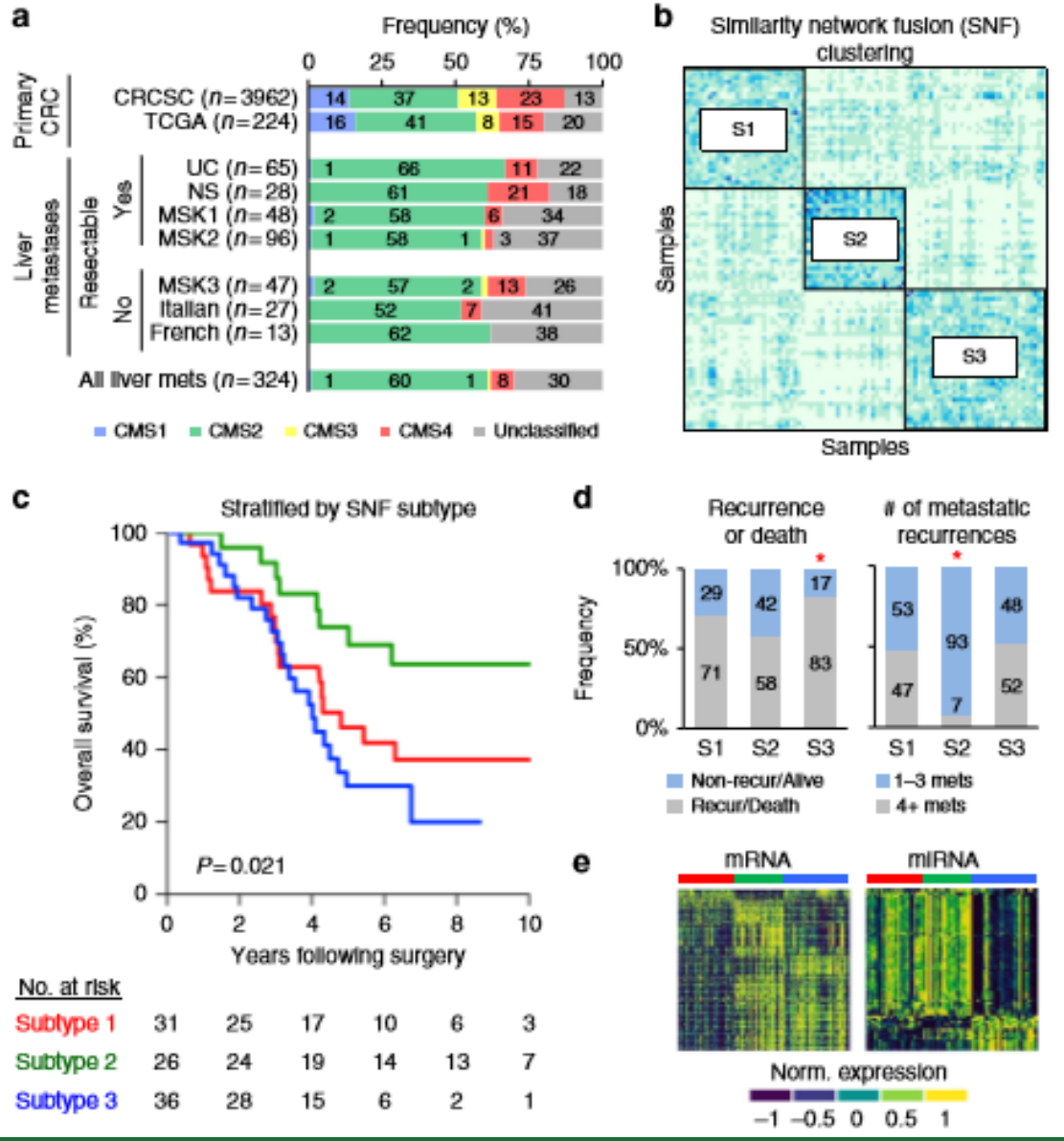
Results: Patients who failed to develop polymetastases are characterized by unique prioritized features of a microRNA classifier that includes the microRNA-200 family. We created an oligometastatic-polymetastatic xenograft model in which the patient-derived microRNAs discriminated between the two metastatic outcomes. MicroRNA-200c enhancement in an oligometastatic cell line resulted in polymetastatic progression.

Conclusions: These results demonstrate a biological basis for oligometastases and a potential for using microRNA expression to identify patients most likely to remain oligometastatic after metastasis-directed treatment.

MicroRNAs are small, non-encoding RNA molecules:
-regulate as many at 200 genes
-expression profiles appear to classify cancers
-may be better for classifying subtypes of cancers vs. protein coding genes

CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high Hypermutation	SCNA high	Mixed MSI status SCNA low, CIMP low	SCN high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration TGF beta activation Angiogenesis
Worse survival after relapse	Better survival after relaspe		Worse relapse-free and overall survival

Guinney et al Nat Med 2015



ARTICLE

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nature COMMUNICATIONS

2018

Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis

Sean P. Pitroda[1,2], Nikolai N. Khodarev[1,2], Lei Huang[3], Abhineet Uppal[4], Sean C. Wightman[4], Sabha Ganai[5], Nora Joseph[6], Jason Pitt[7], Miguel Brown[7], Martin Forde[7], Kathy Mangold[6], Lai Xue[4], Christopher Weber[8], Jeremy P. Segal[8], Sabah Kadri[8], Melinda E. Stack[4], Sajid Khan[9], Philip Paty[10], Karen Kaul[6], Jorge Andrade[3], Kevin P. White[7,11], Mark Talamonti[12], Mitchell C. Posner[4], Samuel Hellman[1,2] & Ralph R. Weichselbaum[1,2]

	Subtype 1 canonical	Subtype 2 Immune	Subtype 3 stromal
Frequency	33%	28%	39%
Molecular signatures	↓Immune and stroma E2F/MYC signaling DNA damage and cell cycle	↑Immune Interferon signaling p53 pathway	↑Stroma KRAS signaling EMT and angiogenesis
Specific mutations	*NOTCH1* and *PIK3C2B*	*NRAS, CDK12,* and *EBF1*	*SMAD3*
Metastatic recurrences	Many	Few	Many
Overall survival	Intermediate	Favorable	Unfavorable

Image-guided percutaneous cryotherapy for the management of gynecologic cancer metastases

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Gynecologic Oncology 111 (2008) 202–207

Percutaneous Cryoablation of Metastatic Lesions from Non–Small-Cell Lung Carcinoma: Initial Survival, Local Control, and Cost Observations

Hyun J. Bang, MD, Peter J. Littrup, MD, Brandt P. Currier, BS, Dylan J. Goodrich, BS, Hussein D. Aoun, MD, Lydia C. Klein, BS, Jarret C. Kuo, MD, Lance K. Heilbrun, PhD, Shirish Gadgeel, MD, and Allen C. Goodman, PhD

J Vasc Interv Radiol 2012; 23:761–769

Percutaneous Cryoablation of Metastatic Renal Cell Carcinoma for Local Tumor Control: Feasibility, Outcomes, and Estimated Cost-effectiveness for Palliation

Hyun J. Bang, MD, Peter J. Littrup, MD, Dylan J. Goodrich, BS, Brandt P. Currier, BS, Hussein D. Aoun, MD, Lance K. Heilbrun, PhD, Ulka Vaishampayan, MD, Barbara Adam, NP, and Allen C. Goodman, PhD

J Vasc Interv Radiol 2012; 23:770–777

Percutaneous Cryoablation of Musculoskeletal Oligometastatic Disease for Complete Remission

Brendan P. McMenomy, MD, A. Nicholas Kurup, MD, Geoffrey B. Johnson, MD, PhD, Rickey E. Carter, PhD, Robert R. McWilliams, MD, Svetomir N. Markovic, MD, PhD, Thomas D. Atwell, MD, Grant D. Schmit, MD, Jonathan M. Morris, MD, David A. Woodrum, MD, Adam J. Weisbrod, MD, Peter S. Rose, MD, and Matthew R. Callstrom, MD, PhD

J Vasc Interv Radiol 2013; 24:207–213

CLINICAL STUDY

Retrospective Review of Percutaneous Image-Guided Ablation of Oligometastatic Prostate Cancer: A Single-Institution Experience

Andrew J. Erie, MD, Jonathan M. Morris, MD, Brian T. Welch, MD, A. Nicholas Kurup, MD, Adam J. Weisbrod, MD, Thomas D. Atwell, MD, Grant D. Schmit, MD, Eugene D. Kwon, MD, and Matthew R. Callstrom, MD, PhD

JVIR 2017;28:987-992

Cardiovasc Intervent Radiol
https://doi.org/10.1007/s00270 017 1843 6

CLINICAL INVESTIGATION

Percutaneous Image-Guided Ablation in the Treatment of Osseous Metastases from Non-small Cell Lung Cancer

Yuntong Ma[1] · Adam N. Wallace[2] · Saiama N. Waqar[3] · Daniel Morgensztern[3] · Thomas P. Madaelil[2] · Anderanik Tomasian[4] · Jack W. Jennings[2]

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**

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See Comment page 1625

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Summary

Background Evidence from retrospective studies suggests that disease progression after first-line chemotherapy for metastatic non-small-cell lung cancer (NSCLC) occurs most often at sites of disease known to exist at baseline. However, the potential effect of aggressive local consolidative therapy for patients with oligometastatic NSCLC is unknown. We aimed to assess the effect of local consolidative therapy on progression-free survival.

Methods In this multicentre, randomised, controlled, phase 2 study, eligible patients from three hospitals had histological confirmation of stage IV NSCLC, three or fewer metastatic disease lesions after first-line systemic therapy, an Eastern Cooperative Oncology Group performance status score of 2 or less, had received standard first-line systemic therapy, and had no disease progression before randomisation. First-line therapy was four or more cycles of platinum doublet therapy or 3 or more months of EGFR or ALK inhibitors for patients with *EGFR* mutations or *ALK* rearrangements, respectively. Patients were randomly assigned (1:1) to either local consolidative therapy ([chemo] radiotherapy or resection of all lesions) with or without subsequent maintenance treatment or to maintenance treatment alone, which could be observation only. Maintenance treatment was recommended based on a list of approved regimens, and observation was defined as close surveillance without cytotoxic treatment. Randomisation was not masked and was balanced dynamically on five factors: number of metastases, response to initial therapy, CNS metastases, intrathoracic nodal status, and *EGFR* and *ALK* status. The primary endpoint was progression-free survival analysed in all patients who were treated and had at least one post-baseline imaging assessment. The study is ongoing but not recruiting participants. This study is registered with ClinicalTrials.gov, number NCT01725165.

Findings Between Nov 28, 2012, and Jan 19, 2016, 74 patients were enrolled either during or at the completion of first-line systemic therapy. The study was terminated early after randomisation of 49 patients (25 in the local consolidative therapy group and 24 in the maintenance treatment group) as part of the annual analyses done by the Data Safety Monitoring Committee of all randomised trials at MD Anderson Cancer Center, and before a planned interim analysis of 44 events. At a median follow-up time for all randomised patients of 12·39 months (IQR 5·52–20·30), the median progression-free survival in the local consolidative therapy group was 11·9 months (90% CI 5·7–20·9) versus 3·9 months (2·3–6·6) in the maintenance treatment group (hazard ratio 0·35 [90% CI 0·18–0·66], log-rank p=0·0054). Adverse events were similar between groups, with no grade 4 adverse events or deaths due to treatment. Grade 3 adverse events in the maintenance therapy group were fatigue (n=1) and anaemia (n=1) and in the local consolidative therapy group were oesophagitis (n=2), anaemia (n=1), pneumothorax (n=1), and abdominal pain (n=1, unlikely related).

Interpretation Local consolidative therapy with or without maintenance therapy for patients with three or fewer metastases from NSCLC that did not progress after initial systemic therapy improved progression-free survival compared with maintenance therapy alone. These findings suggest that aggressive local therapy should be further explored in phase 3 trials as a standard treatment option in this clinical scenario.

Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation

Matthias Guckenberger, Yolande Lievens, Angelique B Bouma, Laurence Collette, Andre Dekker, Nandita M deSouza, Anne-Marie C Dingemans, Beatrice Fournier, Coen Hurkmans, Frédéric E Lecouvet, Icro Meattini, Alejandra Méndez Romero, Umberto Ricardi, Nicola S Russell, Daniel H Schanne, Marta Scorsetti, Bertrand Tombal, Dirk Verellen, Christine Verfaillie, Piet Ost

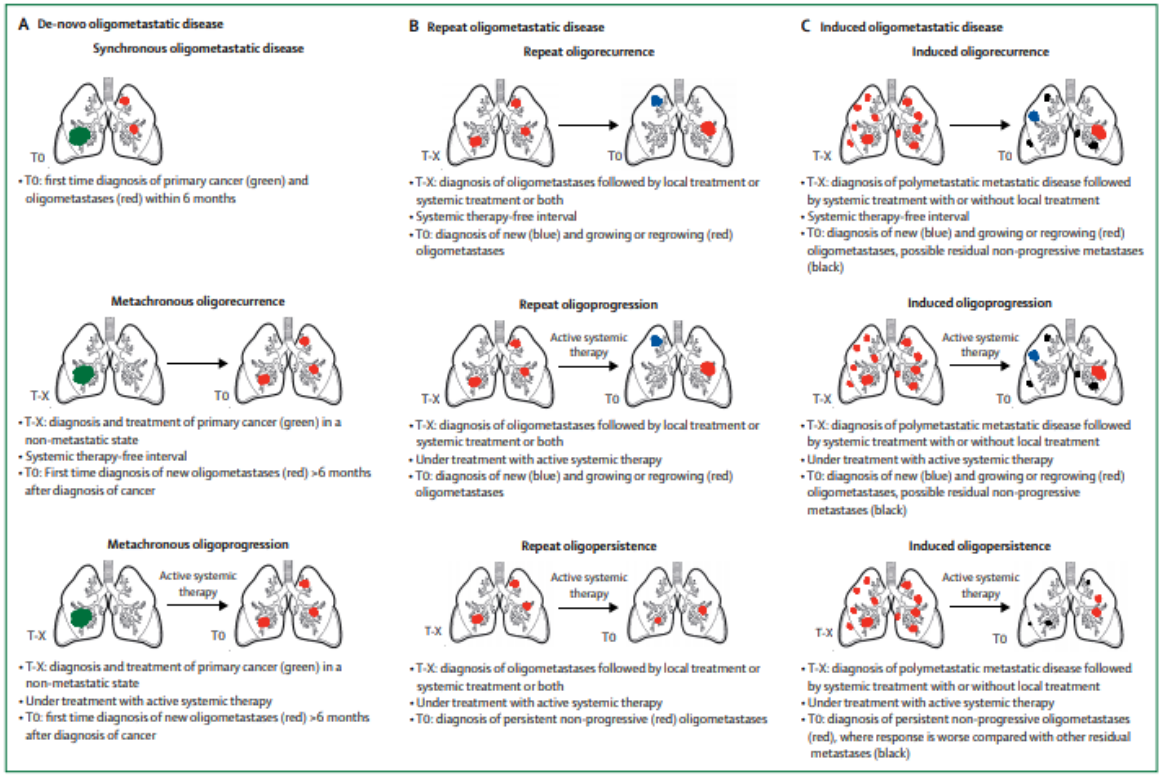

Figure 4: **Illustration of the oligometastatic disease classification system**
(A) De-novo oligometastatic disease. (B) Induced oligometastatic disease. (C) Repeat oligometastatic disease. In repeat and induced oligometastatic disease the primary tumour is assumed to be controlled by ongoing or previous treatment. Oligometastases are confirmed by imaging or biopsy to exclude simultaneous or secondary primary tumours. T0=at this current point of time. T-x=any previous point in time.

Lancet Oncol. 2020;21:e18-28

Conclusions

- Metastases may have a different molecular signature
- Rapidly progressing field in terms of clinical trials and molecular subtyping
- Next frontier for local therapy delivery: multimodal; multidisciplinary increases options for patients
- Extends IR therapies beyond the liver
- Radiation oncology leading the efforts