Oligometastatic (PCa) State: hype, hope and holes in knowledge

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## Disclosures

*No relevant for this talk*

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Disclosures
First let's contextualize the non-‘extreme’
Oh boy....
Presentation Schema

• Oligometastatic (OM) State in Oncology
  • Overarching hypothesis
  • Evidence of existence and treatment benefit
  • Some definitions

• OM/OR State in PCa
  • Evidence supporting existence
  • Treatment results

• Final thoughts
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Oligometastatic State

• M1 = incurable…. but….
  • “Cancer comprises a biological spectrum, extending from when a disease is localized to one that is systemic when first detectable but with many intermediate states.”
  • “An attractive consequence [of the] oligometastatic state is that some patients should be amenable to a curative therapeutic strategy”

• Hot topic

Hellman & Weichselbaum. JCO 1995
Substantiation of the Paradigm

• Translational research
• Improved imaging methods
• Improved systemic therapies to treat additional microscopic sites (contradictory?)
• Advancements in surgery (e.g. laparoscopic, robotic)
• Advancements in radiotherapy (e.g. SBRT)

But question remains: Fact or Fantasy?
Example in PCa: Biologic Correlate

- Complex (and various) seeding patterns
- Mets can evolve capacity to seed subsequent Mets: rapid succession, little intervening evolution

Potential(s): Prevent/Delay CRPC emergence? Cure?

OM State: Clinical arguments (aka evidence)

- Subset of patients with M1 disease do well
- Non-randomized experience(s)
- Randomized evidence
- Refining definitions:
  - synchronous vs metachronous
  - de novo vs OM recurrence vs OM progression
- Recent trials

Models simpler that reality: Complexity imported into the clinics
Observational & Obstinate-ional Evidence

Weichselbaum and Hellman, Nat Rev Clin Onc 2011;
Gomez’s (MDACC) Trial

Ph 2 RCT: UT Southwestern

Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer
A Phase 2 Randomized Clinical Trial

Punaach Iyengar, MD, PhD; Zabi Wardak, MD; Davide E. Garber, MD; Vasu Tamati, MD; Chul Ahn, PhD; Randall S. Hughes, MD; Jonathan E. Dowell, MD; Naga Cheedella, MD; Lucien Nedzi, MD; Kenneth L. Wistow, MD; Pradeepa Paliparachchana, PhD; Hao Cang, MD; Robert U. Temimman, MD

No. at risk
SAbR plus maintenance
Maintenance only
14 12 6 3 1
15 8 1 1 1

SAbR indicates stereotactic ablative radiotherapy.

Iyengar et al. JAMA Oncol 2018
Phase 2 RCT: SABR-COMET

Patients with up to 5 metastatic lesions from any primary tumor site, meeting inclusion criteria

RANDOMIZATION
(1:2 ratio of randomization to Arm 1 vs. Arm 2)

ARM 1: STANDARD OF CARE
Palliative RT to any symptomatic sites
Further chemotherapy at discretion of medical oncologist

FOLLOW-UP

ARM 2: STANDARD OF CARE + SABR
SABR to all sites of known disease
Further chemotherapy at discretion of medical oncologist

FOLLOW-UP

Increased AEs G2-5; No differences in OS, QoL or use of systemic agents

Courtesy of D Palma - ASTRO 2018
Context: Natural History of PCa

Rao et al. – ASCO Book 2019
Definitions

Others:
• Oligo-recurrence: systemic, regional
• Oligo-metastasis: synchronous, metachronous

Different disease states with distinct biology/prognosis
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2 (less uncommon) scenarios
OM in PCa: Does exist?

Ost et al. Eur Urol 2018
First study in PCa: STOMP Trial

Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP): study protocol for a randomized phase II trial

Karel Decaestecker¹, Gert De Meerleer², Filip Ameye³, Valerie Fonteyne⁴, Bieke Lambert⁵, Steven Joniau⁶, Louke Delruë⁷, Ignace Billiet⁷, Wim Duthoy⁸, Sarah Junius⁹, Wouter Huysse⁷, Nicolaas Lumen¹ and Plet Ost²*
STOMP Trial

Ost et al. JCO 2018
Randomized Phase 2: SBRT vs Observation

Ost et al. JCO 2018
Clinical Problem
Recurrent PCa post Surgery + Radiotherapy
No evidence of disease
In conventional studies (BS and CT)

Work Package 1: Diagnostics

[18F]DCFPyL PET/MRI

Unveil and characterize new early molecularly-defined oligometastatic state

Work Package 2: Therapeutics

MRgRT SABR

Discover new curative-intent treatment
Unprecedented precision and accuracy

Work Package 3: Translational

PSA² liquid biopsy
Tissue/Fluids samples

Response monitoring and outcome prediction.
Seed translational studies.
Primary endpoint:
**NED** (biochemical CR [PSA <0.05])
- \( H_0: RR < 5\% \)
- \( H_a: RR > 20\% \)
2-stage design, \( n=37 \)

Secondary endpoints:
- SABR toxicities
- Qualitative and quantitative imaging metrics of PET/MR
- Correlates of SABR treatment outcomes and PSA2 kinetics.
- ^{18}F-DCFPyL PET/MRI molecular response post SABR
- Comparative performance between ^{18}F-DCFPyL PET/MR and PET/CT

Post maximal local therapy (RadP + RT)
- Rising PSA (>0.4ng/ml and <3ng/ml)
  - Negative conventional staging
  - No previous use of salvage ADT

\[^{18}F\]DCFPyL PET-MR/CT
Study Intervention- Diagnostic

SABR or Surgery
Study Intervention- Therapeutic
PSMA MRgRT: Consort

1. PET MR/CT
   - n=72

2. Positive PET MR/CT
   - n=56
   - Negative PET
     - n=16
   - Poly-metastatic n=10; Prostate bed recurrence n=4; other n=5
   - Treatment response-evaluable
     - n=37
       - SABR
         - n=27
       - Surgery
         - n=10
       - Lost to follow-up
         - n=0
PSMA MRgRT: Response @ 3 (n=6) or 6mo (n=29)
2 (less uncommon) scenarios
STAMPEDE (H)

Let’s see STAMPEDE M...

Parker et al. NEJM 2018
Fundamental elements of a crime

- Action or omission
- Defined by the law (“criminality”)
- Unlawful
- *Dolus* (intent or overt negligence)
- Culpability
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**Discussion**

This randomised comparison of more than 2000 patients with metastatic prostate cancer showed that local radiotherapy to the prostate did not improve overall survival for unselected patients. However, a prespecified analysis showed that prostate radiotherapy did improve overall survival (from 73% to 81% at 3 years) in those with a low metastatic burden, which represented 40% of the comparison population.
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Discussion
This randomised comparison of more than 2000 patients with metastatic prostate cancer showed that local radiotherapy doses did not improve overall survival, and the speciﬁed outcomes were no differences in progression-free survival (45% vs. 41% at 24 months) in those randomised to 160 Gy and 108 Gy, respectively. Therefore, 40% of

Only in **very few** instances can we be confident that subgroup analyses provide a better estimate of effect than the overall results of trials

#staysafe #stayconsistent
Evidence to treat? to cut?

**SWOG S1802 (n=1273)**

**PEACE-1 (n=1168)**

OS yet to come...
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• Personal opinion(s)
Questions remain: Why MDT in PCa?

• Cure (?): alone?, combined with systemic therapy?
• Delay ADT and other systemic agents
• Improve local control (symptomatic progression)
• Decrease metastases seeding sources (PFS?)
• Improved response to AR-targeting agents (?)
• Delay emergence of mCRPC (?)
• Improve OS?

IMO: Oligorecurrent > Oligometastatic
What’s Old Is New Again

Earlier treatment (when lower disease burden) = Higher response to ADT and PCSS/OS

MRC Trial. BJU 1997
Will Rogers: here we go again! #weloveyou

New kid in block: PSMA
(Prostate-Specific Membrane Antigen)

- High ratio (1:100-1000) tumour to non-target expression
- 11p (commonly intact in PCA)
- Internalization upon binding (improved imaging and therapeutic efficacy)

All what we’ve discussed pertains to the pre-PSMA era
So Far...

- The lower the burden of (untreated) disease, the better the response to systemic Tx.

- But:
  - Cure has not been shown
  - OM state remains a working hypothesis

Further modulated (at least) by:
- Burden of disease
- Biology

Punglia et al. NEJM 2007
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