10th edition
GLOBAL CONGRESS ON PROSTATE CANCER
JUBILEE EDITION

# Oligorecurrent prostate cancer: what is it?

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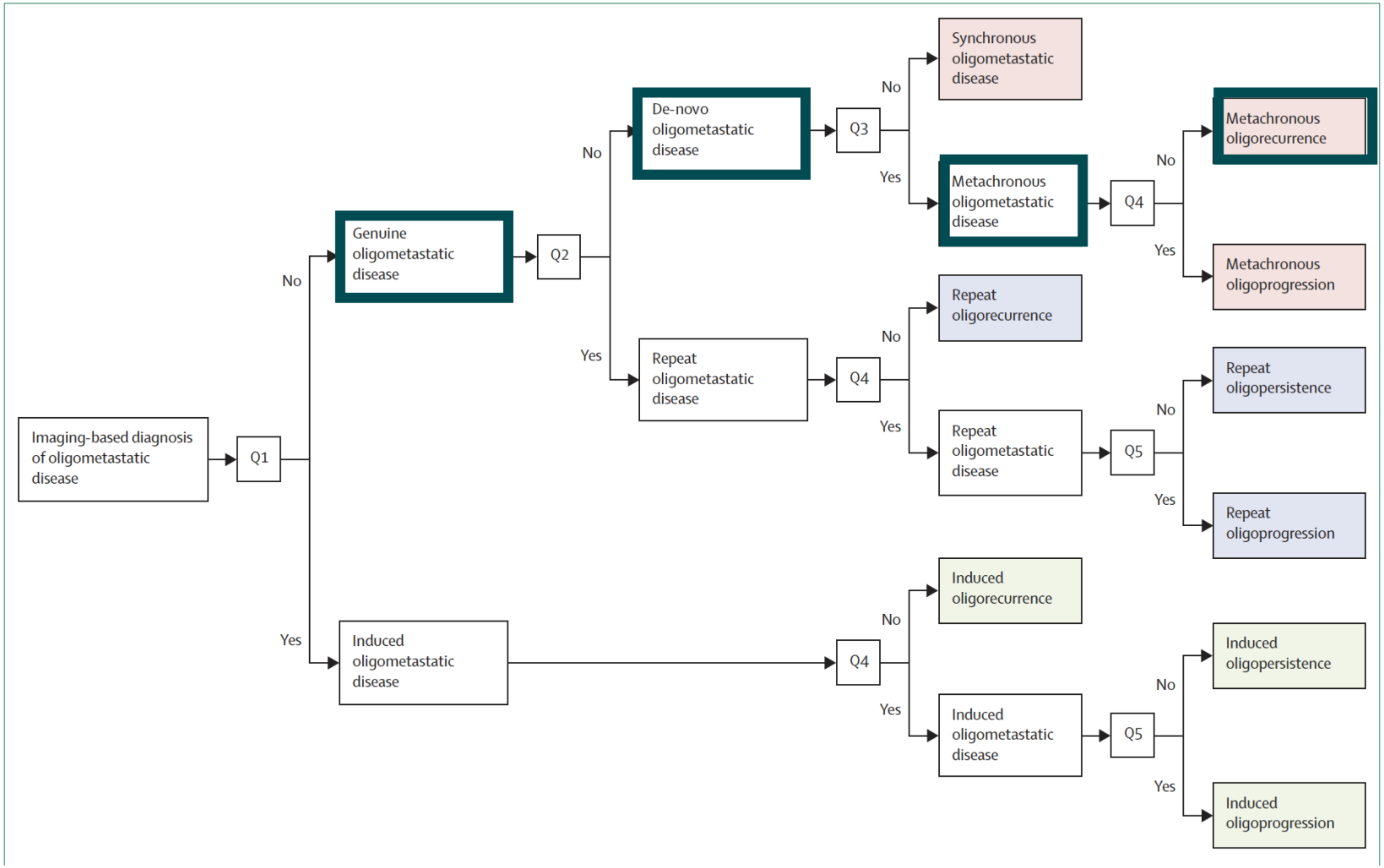
# Conflicts of interest

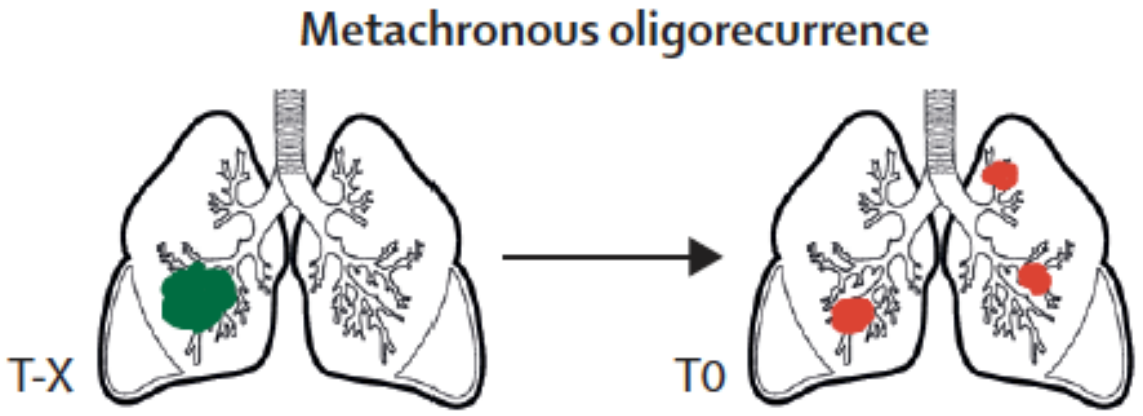
| Type of affiliation / financial interest | Name of commercial company |
|---|---|
| Receipt of grants/research supports | |
| Receipt of honoraria or consultation fees | Bayer, Ferring, Janssen |
| Stock shareholder | |
| Other support (please specify): | |

# Decision tree for classification of oligometastatic disease




*Lancet Oncol* 2020; 21: e18–28

# Metachronous oligorecurrence

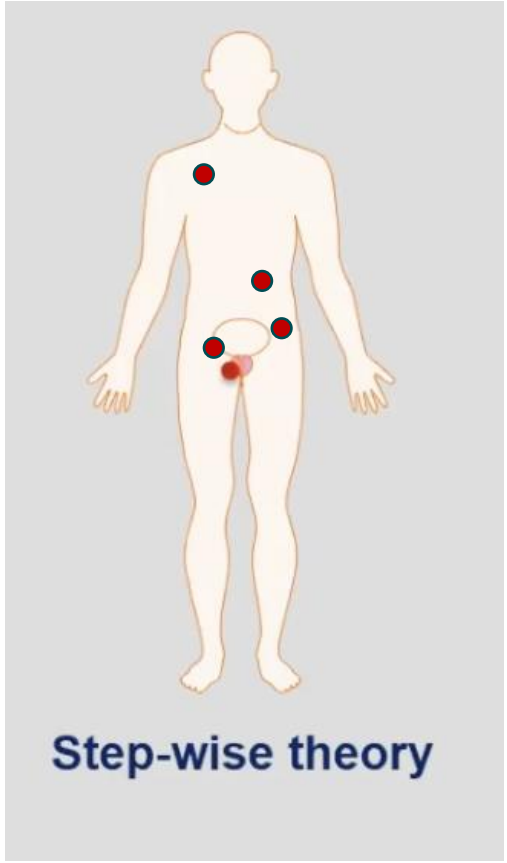



- T-X: diagnosis and treatment of primary cancer (green) in a non-metastatic state
- Systemic therapy-free interval
- T0: First time diagnosis of new oligometastases (red) >6 months after diagnosis of cancer

*Lancet Oncol* 2020; 21: e18–28

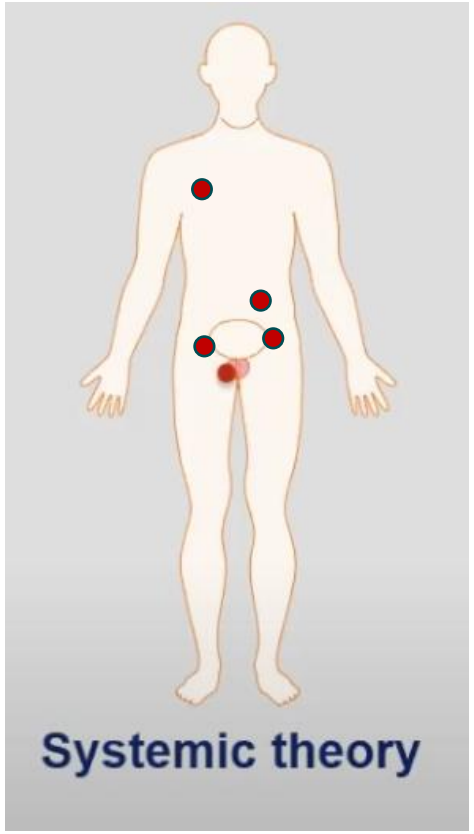
# Biology of prostate cancer metastasis

- Halsted theory (1894)
  - Cancer spreads in an orderly fashion from the primary site to regional lymphatics to distant locations



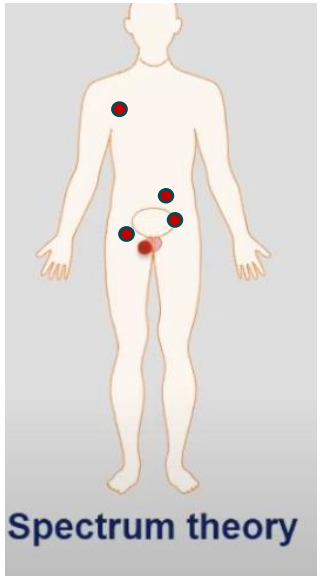
# Biology of prostate cancer metastasis

- Fisher theory (1980)
  - Cancer is inherently a systemic disease, even if it is evident only locally



# Biology of prostate cancer metastasis

- Hellman (1994)
  - Cancer exists in various degrees of clonal evolution, with varying metastatic potential, which evolves over time.
  - Concept of OMD represents just one timepoint along the evolution of disease - a point which could represent an intermediate state between localized and widely metastatic disease in which cancer cells have limited metastatic potential and thus may be amenable to cure with total elimination of disease burden



# Imaging in patients with biochemical recurrence

### 6.3.4.4. Summary of evidence and guidelines for imaging in patients with biochemical recurrence

| Recommendations | Strength rating |
|---|---|
| Prostate-specific antigen (PSA) recurrence after radical prostatectomy | |
| Perform prostate-specific membrane antigen (PSMA) positron emission tomography (PET) computed tomography (CT) if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions. | Weak |
| In case PSMA PET/CT is not available, and the PSA level is ≥ 1 ng/mL, perform fluciclovine PET/CT or choline PET/CT imaging if the results will influence subsequent treatment decisions. | Weak |
| PSA recurrence after radiotherapy | |
| Perform prostate magnetic resonance imaging to localise abnormal areas and guide biopsies in patients fit for local salvage therapy. | Weak |
| Perform PSMA PET/CT (if available) or fluciclovine PET/CT or choline PET/CT in patients fit for curative salvage treatment. | Strong |

# Imaging for oligometastatic disease

| Type | Imaging Method | Strengths | Limitations |
|---|---|---|---|
| **Conventional** | **Contrast-enhanced thoraco-abdomino-pelvic CT** | > Allows for whole-body imaging[21]<br>> Widely available and affordable[21] | > Poor sensitivity and specificity for detection of LN mets (sensitivity < 40%)[16,18]<br>> Suboptimal for detection of bone mets[16,21] |
| | **$^{99m}$Tc-MDP bone scintigraphy** | > Consistency for classification of M1 vs M0 disease[21]<br>> Most widely used method to detect BMs[21]<br>> Widely available and affordable[17,21] | > Misses metastatic lesions in bone marrow[21] |
| **Next generation** | **Fluciclovine ($^{18}$F)-PET** | > As good as choline-PET[12]<br>> Identify both bony and soft tissue lesions[12] | > Accuracy depends on PSA levels[12] |
| | **$^{18}$F/$^{11}$C-choline PET/CT** | > Good specificity (92–95%) in LN mets[77,78] | > LNs: Modest sensitivity in detecting LN mets (49.2–62%)[12]<br>> High false positive rates with reactive LNs[12]<br>> Reduced sensitivity with low PSA values[12] |
| | **$^{68}$Ga-PSMA PET/CT** | > Superior detection rates compared to other PET tracers[12]<br>> Able to identify small lesions at low PSA values[12] | > High false negative rates at low PSA values[12]<br>> Additional studies are needed to confirm results |
| | **WB-MRI** | > High sensitivity and specificity (>98%)[12]<br>> High inter-observer agreement[21,22]<br>> No exposure to ionizing radiations[11] | > Long scanning time, inter-scanner variability, susceptibility to motion and other artefacts, high costs[17]<br>> Not widely used at present[12] |

Marvaso G et al. Cancer Management and Research 2022:14 89–101

# Oligorecurrent nodal disease

- PET has enabled recurrences to be detected earlier and more accurately
  - Nodal recurrences the most dominant pattern of relapse
- Retrospective studies have explored:
  - Salvage lymph node dissection
  - Stereotactic body radiotherapy
  - Elective nodal radiotherapy

# Oligorecurrent nodal disease

- OLIGOPELVIS GETUG P07 trial *(reported)*
  - First prospective, non randomized phase 2 trial
  - Median PFS: 3.8 years (Supiot S et al. Eur Urol 2021)
- OLIGOPELVIS2 trial *(recruiting)*
  - Phase 3 trial comparing intermittent ADT versus intermittent ADT + salvage pelvic RT
- PEACE V – STORM trial *(follow up)*
  - MDT + 6/12 ADT versus salvage pelvic RT + 6/12

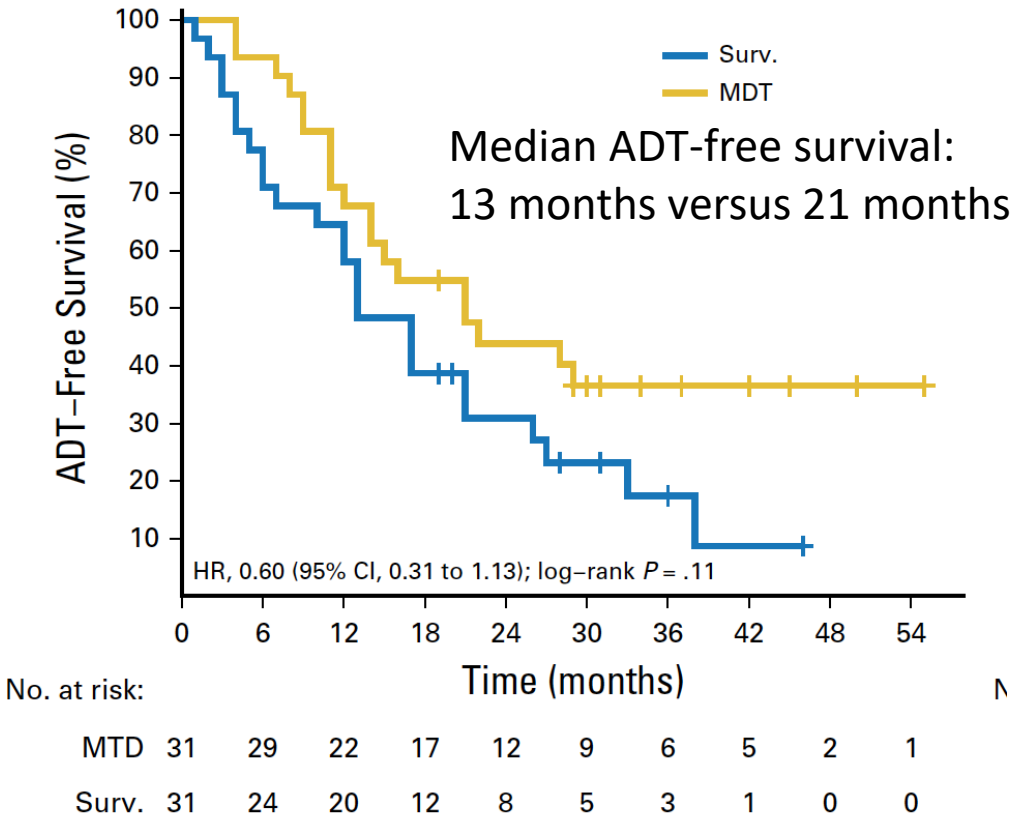
# Reported prospective clinical trials

| Study | Disease Type | Metastatic Burden | Study Type | N | Randomization (if applicable) | Primary Outcome | Result | Toxicity |
|---|---|---|---|---|---|---|---|---|
| SABR-COMET | ORD | 1-5 metastases | Phase II RCT | 99** | RT MDT vs. Standard of care for their respective malignancies | OS | OS improved in MDT arm (5-year OS 42.3% vs. 17.7%, p=0.006) | G5 in 4.5% of patients |
| STOMP | ORD | ≤ 3 metastases | Phase II RCT | 62 | MDT vs. Observation | ADT-free survival | Median ADT-free survival improved in MDT arm (5-year ADT-free survival 34% vs. 8%, p=0.06) | No G2 or higher |
| ORIOLE | ORD | ≤ 3 metastases | Phase II RCT | 54 | MDT vs. Observation | Rate of disease progression at 6 months | Disease progression was improved in MDT cohort (Progression at 6 months 19% vs. 61%, p=0.005) | No G3 or higher toxicities |
| Glicksman et al. | ORD | No limit | Single-arm Phase II Trial | 37 | PSMA-PET-guided MDT with SBRT or surgery, without ADT | Biochemical response | 60% overall response rate with 22% having complete response | No G3 or higher toxicities |
| Kneebone et al. | ORD | 1-3 nodal or bone metastases | Single-arm Phase II Clinical Trial | 57 | SBRT to metastatic sites without ADT | Biochemical failure*** | At median follow up of 16 months, median bDFS was 11 months, with 31.9% bDFS at 15 months | No G3 or higher |
| Siva et al. | ORD | 1-3 nodal or bone metastases | Feasibility Study | 33 | One fraction of SBRT to each lesion | Feasibility and tolerability | All but one patient completed the prescribed dose to metastatic sites | One patient with G3 |

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

Ost P et al. JCO 2017

- BCR after primary PCa treatment with curative intent
- 3 or fewer extracranial metastases on choline PET/CT and non-castrate testosterone
- Random assignment 1:1 to either surveillance or MDT of all detected lesions (surgery or stereotactic body radiotherapy)
- Primary endpoint: ADT-free survival
  - ADT started at symptomatic progression, progression to >3 metastases, or local progression of known metastases



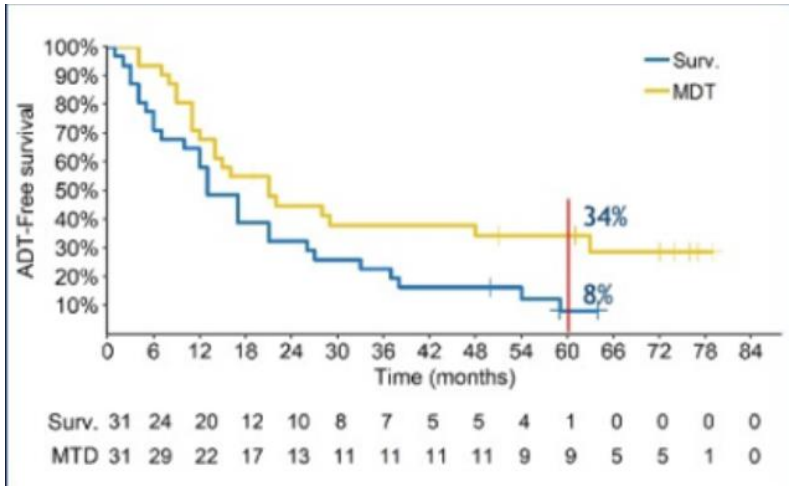

Median F/U = 3 years

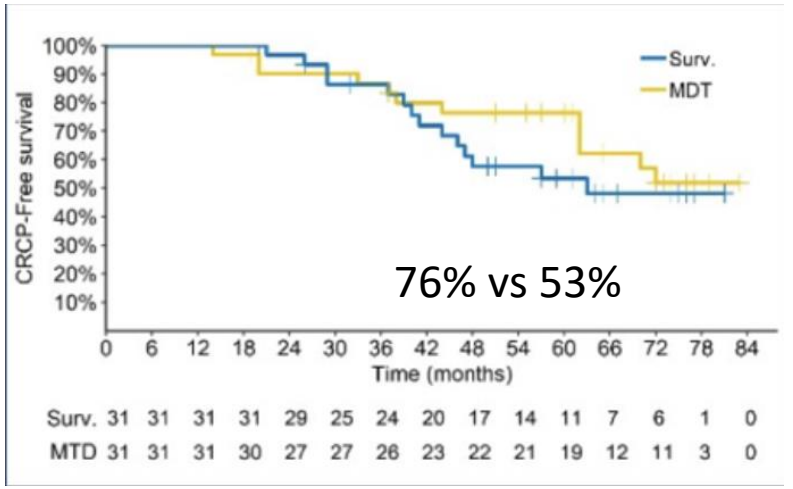
# Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial

Median F/U = 5 years

Ost P et al. JCO 2020

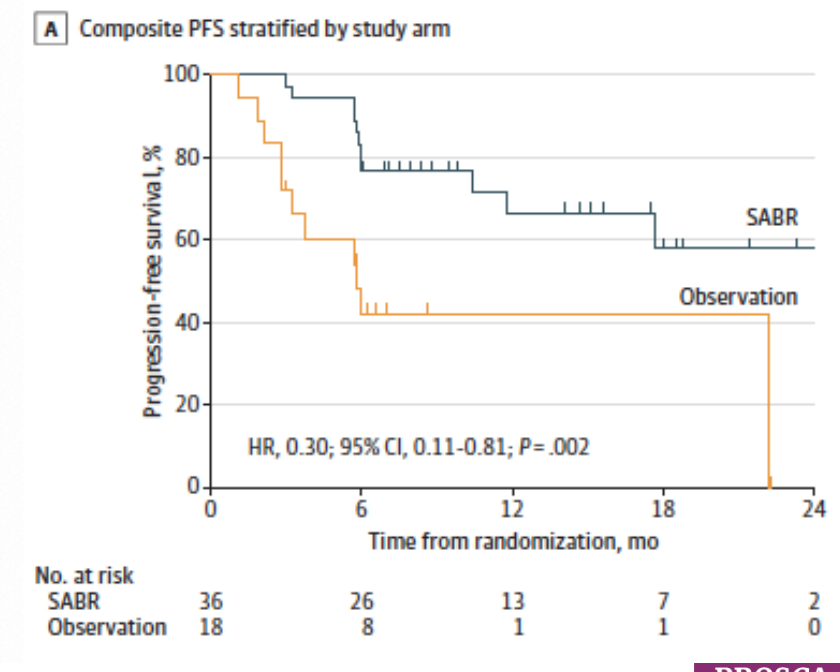
- BCR after primary PCa treatment with curative intent
- 3 or fewer extracranial metastases on choline PET/CT and non-castrate testosterone
- Random assignment 1:1 to either surveillance or MDT of all detected lesions (surgery or stereotactic body radiotherapy)
- Primary endpoint: ADT-free survival
  - ADT started at symptomatic progression, progression to >3 metastases, or local progression of known metastases



# ORIOLE Phase 2 RCT
# Observation vs SABR for oligometastatic prostate cancer

- 54 patients randomised 2:1
- 1-3 asymptomatic mets on conventional imaging, no larger than 5cm
- Primary outcome: proportion of men with disease at 6 months
- Initial management: 83% surgery and 17% RT
- Time to first recurrence: median – 22 months




JAMA Oncology 2020

# Long-Term Outcomes and Genetic Predictors of Response to Metastasis-Directed Therapy Versus Observation in Oligometastatic Prostate Cancer: Analysis of STOMP and ORIOLE Trials

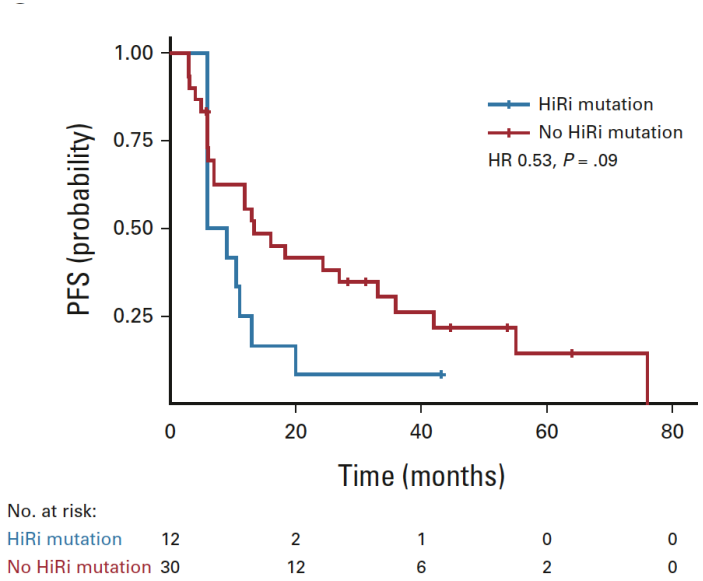
Deek et al. JCO 2022

- Long term outcomes of MDT – PFS
- Assess ability of a high-risk mutational signature to risk stratify outcomes after MDT
- High risk mutations defined as pathogenic somatic mutations within ATM, BRCA1/2, Rb1 or TP53
- Median F/U = 52.5 months

- Gemonic alterations appear to have prognostic value

# Findings

- MDT + no high-risk mutation experienced the best outcomes
  - (median PFS 13.4 months versus 7.5 months)




- Observation + high-risk mutation experienced the poorest outcomes = median PFS 2.8 months

Deek et al. JCO 2022

# Ongoing clinical trials

| Study | Disease Type | Metastatic Burden | Study Type | Randomization (if applicable) | Primary Outcome |
|---|---|---|---|---|---|
| PLATON | *De novo* OMD and ORD | ≤5 lesions | Phase III RCT | SOC* vs. SOC* + MDT | FFS at 6 years |
| NRG-GU011 | ORD | ≤5 lesions | Phase II RCT | MDT + placebo vs. MDT + relugolix | rPFS by conventional imaging |
| DART | ORD | ≤5 lesions | Phase II RCT | MDT vs. MDT + darolutamide | MFS at 2 years by PET |
| RADIOSA | ORD | ≤3 lesions | Phase II RCT | MDT vs. MDT + LHRH agonist/antagonist | PFS |

# OligoCare

EORTC European Organisation for Research and Treatment of Cancer
The future of cancer therapy

## Real-world disease and treatment characteristics of oligometastatic cancer – initial results of the ESTRO & EORTC E²-RADIatE OligoCare cohort

Matthias Guckenberger[1], Umberto Ricardi[2],MartaScorsetti[3], Panagiotis Balermpas[1], Yolande Lievens[4], Filippo Alongi[5], Lorenzo Livi[6], Pètra Braam[7], Barbara Alicja Jereczek-Fossa[8], Karin Stellamans[9], Luc Verbeke[10], Heike Peulen[11], Kaouthar Khanfir[12], Sara Ramella[13], Thomas Zilli[14], Xavier Geets[15], Hossein Hemmatazad[16], Giovanni Battista Ivaldi[17], Ivica Ratosa[18], Paul Jeene[19], Beatrice Fournier[20], Nicolas Sauvé[20], Catherine Fortpied[20], Piet Ost[4]

Poster #PD-PD-0740

ESTRO

### BACKGROUND

- Oligometastatic disease (OMD) has been recognized as a heterogeneous cancer state, and optimal multimodality treatment strategies remain unknown.
- OligoCare is a pragmatic prospective observational cohort of the E²-RADIatE platform, born of a collaboration between ESTRO and EORTC. Its aims are to identify patient, tumor, staging and treatment characteristics influencing overall survival after radical radiotherapy for oligometastatic breast, colorectal, prostate and non-small-cell lung cancers (NSCLC).

### METHODS

- Here we report the first results from the OligoCare cohort, based on a snapshot of the database taken on the 4th of February 2021.
- Patients were eligible to the OligoCare cohort if all cancer lesions were treated with radical intent. Radical radiotherapy must be a component of treatment, without a limit regarding the maximum number of oligometastases.
- The population for this analysis was a subset of eligible patients with information on primary disease, history of metastatic disease and current OMD lesions.

**FIGURE 1:** Flowchart of the analysis population

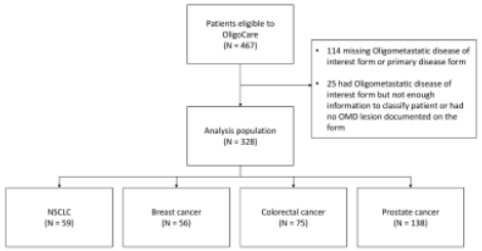


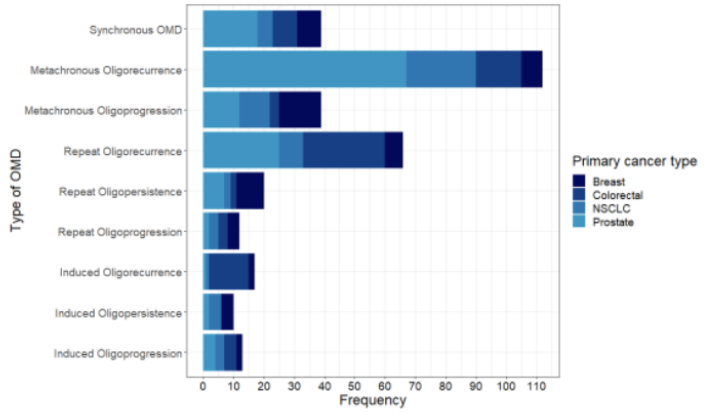

**TABLE 1**: Number of fractions (N = 395 irradiated lesions)

| Number of fractions | |
|---|---|
| 1 | 45 (12.0) |
| 3 | 128 (34.2) |
| 4 | 21 (5.6) |
| 5 | 122 (32.6) |
| 6 | 21 (5.6) |
| 7 | 1 (0.3) |
| 8 | 15 (4.0) |
| 10 | 19 (5.1) |
| 12 | 2 (0.5) |
| Missing | 21 |

**TABLE 2**: Dose per fraction, BED (N = 395 irradiated lesions)

| | |
|---|---|
| **Planned mean dose per fraction to the CTV/ITV (Gy)** | |
| Median | 9.8 |
| Max | 39.0 |
| Q1-Q3 | 7.7 - 13.0 |
| N obs | 320 |
| **Biologically Effective Dose (BED, in Gy)** | |
| Median | 74.0 |
| Max | 219.9 |
| Q1-Q3 | 59.7 - 107.7 |
| N obs | 320 |

**FIGURE 2:** Frequency of OMD type per primary cancer type




### RESULTS

- 328 / 467 eligible patients were selected for this analysis (Figure 1).
- Prostate cancer was the most frequent primary tumor (42%).
- Diagnosis of OMD included PET-imaging in 77% and MRI imaging in 16% of the patients.
- Patients were treated for de-novo, repeat or induced OMD in 58%, 30% or 12% of the cases, respectively (Figure 2).
- The vast majority of patients in the analysis population (89.9%) had oligometastatic lesions in only one organ site.
- 395 irradiated lesions were reported for the 328 patients:
  - The most commonly used radiotherapy delivery device, image guidance technology and treatment delivery techniques were C-arm linacs (84% of OMD lesions), Cone-beam CT image guidance (82% of OMD lesions) and VMAT treatment delivery (77% of OMD lesions), respectively.
  - Median number of fractions was 4 ( range 1-12), median planned mean CTV/ITV dose per fraction was 9.8 Gy (maximum: 39.0 Gy) and median BED was 74.0 Gy (α/β=10, maximum: 219.9 Gy) (Tables 1 and 2).

### CONCLUSION

- Feasibility of the OligoCare prospective registry trial has been demonstrated to assess real-world patterns of practice of radical radiotherapy for oligometastatic disease.
- Patients with all OMD states were included, most frequently de-novo OMD.
- High-quality follow-up data capture will be required to assess factors influencing outcome of oligometastatic patients treated with radical radiotherapy.

For more information on the E2-RADIatE platform: E2-RADIatE – The new platform for radiotherapy

www.eortc.org

# In summary…

- Management of biochemical recurrence evolving with next generation imaging such as PSMA PET-CT
    - ? allow modification of thresholds for investigation
- Oligometastatic recurrence – role of SBRT to delay time for lifelong ADT
- Development of clinical, molecular and genetic biomarkers to aid classification and personalisation for management of oligometastatic disease