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LUNG CANCER SYMPOSIUM

10/28/2023

PIM Postgraduate Institute for Medicine

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17th Annual

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LUNG CANCER SYMPOSIUM

Consolidation Radiation Therapy in Oligometastatic NSCLC

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Disclosures

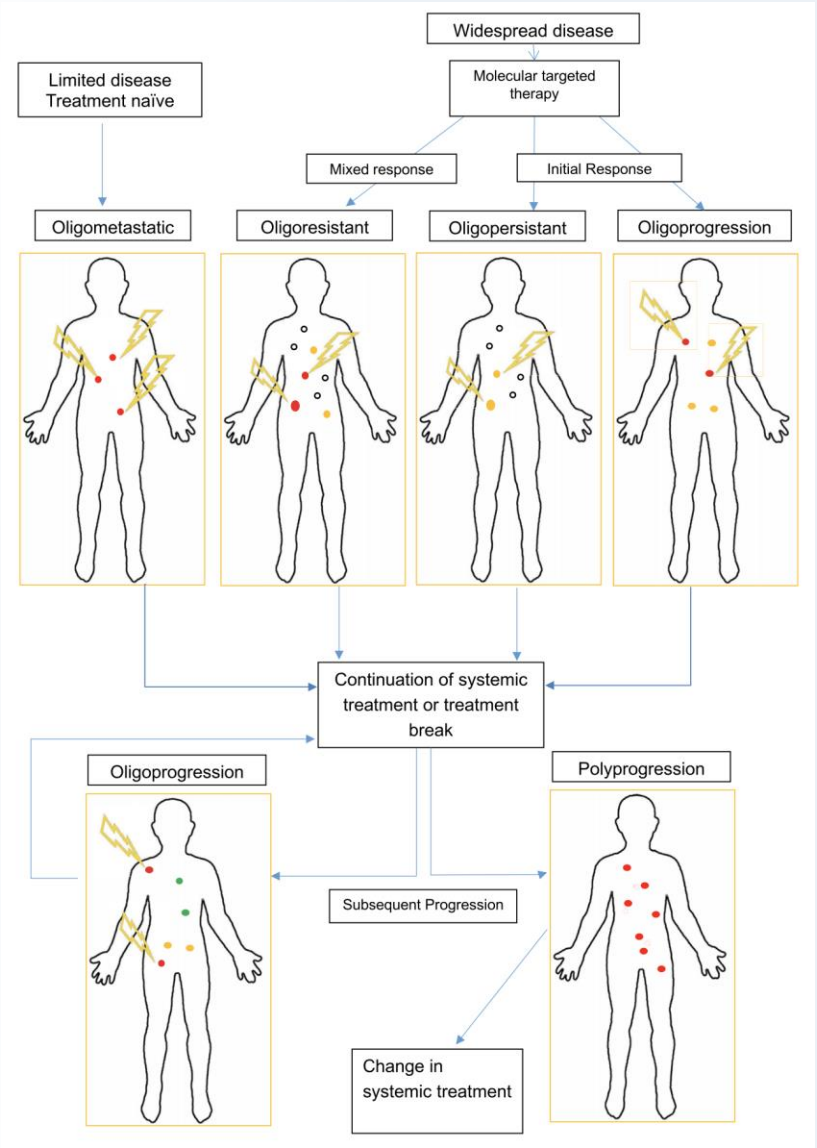
Consultant: Genentech, Merck (RTOG Foundation)

Research funding: Varian Medical Systems

Employment: Emory University

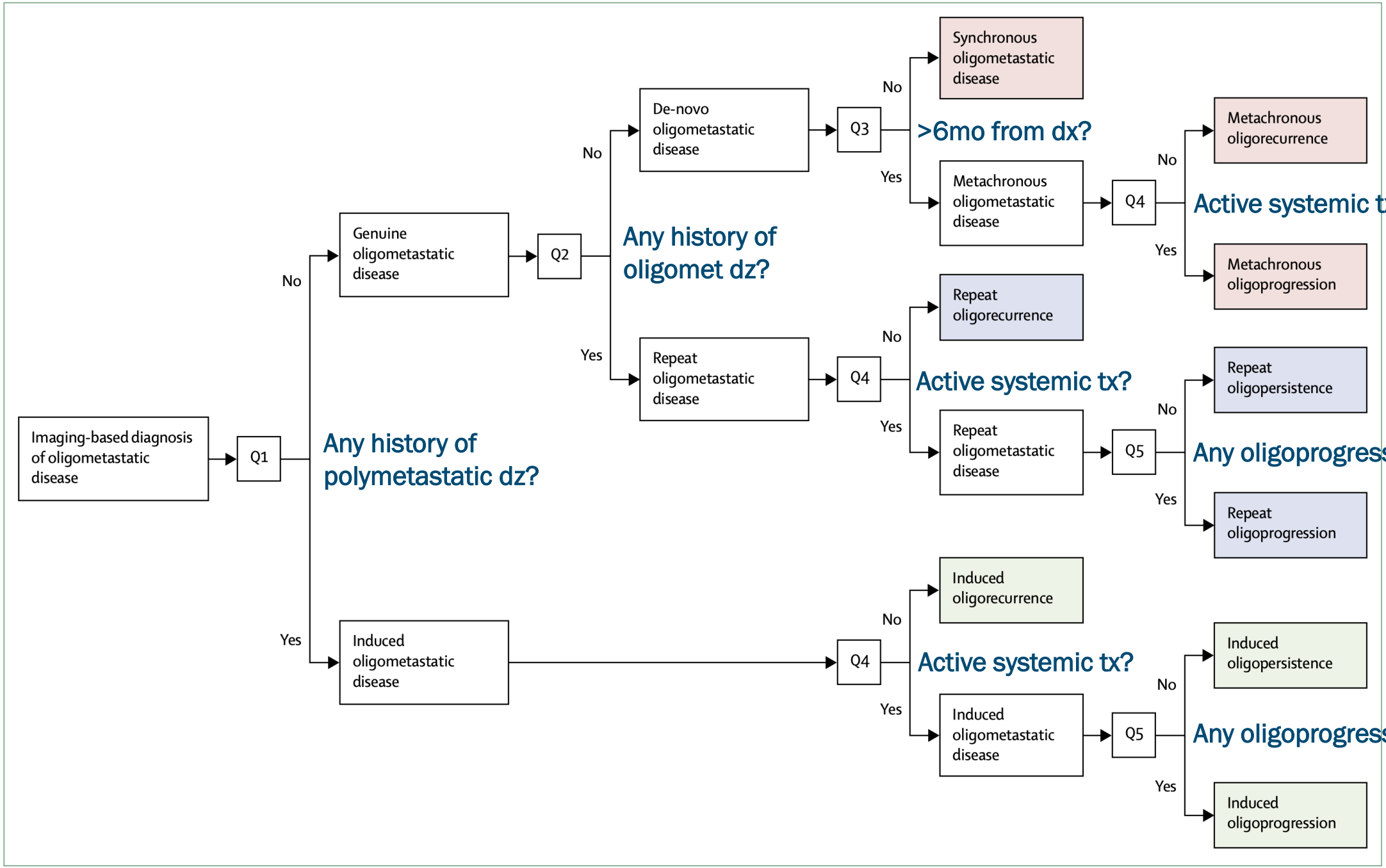
State of oligometastatic disease in 2023

- "An attractive consequence of the presence of a clinically significant oligometastatic state is that some patients so affected should be amenable to a curative therapeutic strategy"
- Prevalence ~35-40% of stage IV NSCLC[1]
- No phase III randomized studies
- No biomarkers
- No consensus definition
  - Maximum of 3-5 metastases in 3 organs proposed[2]
  - Challenges of defining by numerical threshold
    - Patients who may be potentially cured by local therapies
    - Patients who may potentially benefit from ablative treatments



1 - No et al. *Int J Radiat Oncol Biol Phys* 2022 PMID 35654305

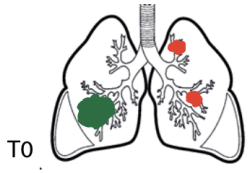
2 - Dingemans et al. *J Thorac Oncol* 2019 PMID 31398540



Guckenberger et al. *Lancet Oncol* 2020 PMID 31908301

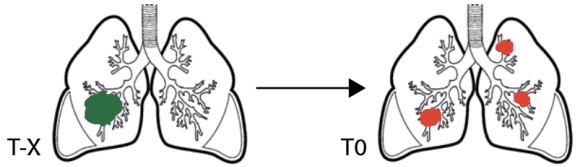
A De-novo oligometastatic disease

Synchronous oligometastatic disease



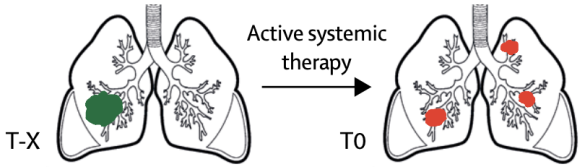
- T0: first time diagnosis of primary cancer (green) and oligometastases (red) within 6 months

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

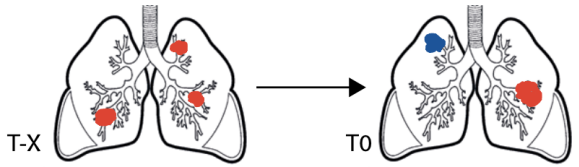
Metachronous oligoprogression



- T-X: diagnosis and treatment of primary cancer (green) in a non-metastatic state
- Under treatment with active systemic therapy
- T0: first time diagnosis of new oligometastases (red) >6 months after diagnosis of cancer

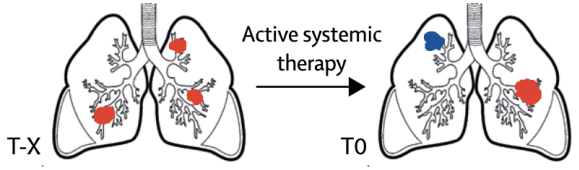
B Repeat oligometastatic disease

Repeat oligorecurrence



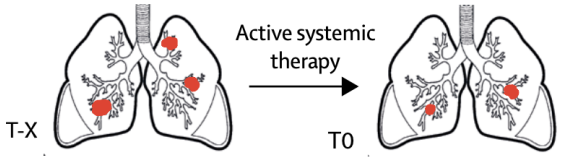
- T-X: diagnosis of oligometastases followed by local treatment or systemic treatment or both
- Systemic therapy-free interval
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases

Repeat oligoprogression



- T-X: diagnosis of oligometastases followed by local treatment or systemic treatment or both
- Under treatment with active systemic therapy
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases

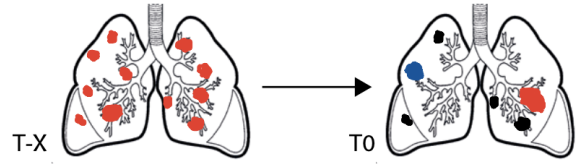
Repeat oligopersistence



- T-X: diagnosis of oligometastases followed by local treatment or systemic treatment or both
- Under treatment with active systemic therapy
- T0: diagnosis of persistent non-progressive (red) oligometastases

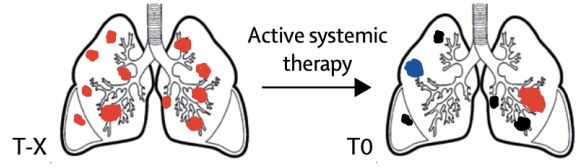
C Induced oligometastatic disease

Induced oligorecurrence



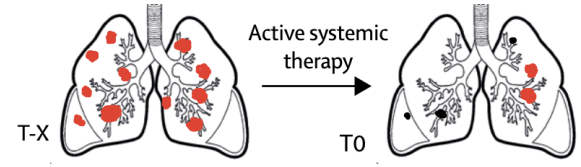
- T-X: diagnosis of polymetastatic metastatic disease followed by systemic treatment with or without local treatment
- Systemic therapy-free interval
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases, possible residual non-progressive metastases (black)

Induced oligoprogression



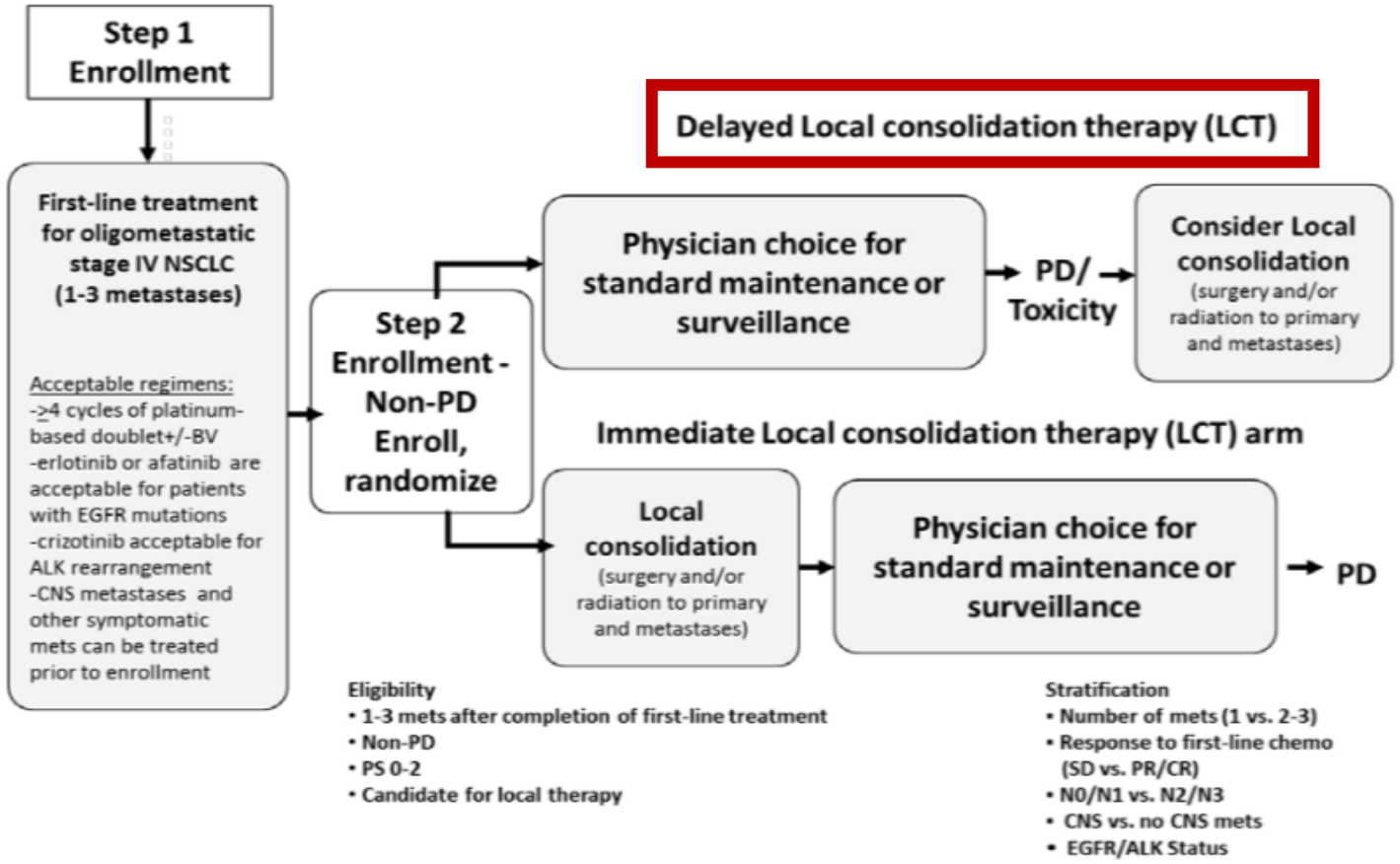
- T-X: diagnosis of polymetastatic metastatic disease followed by systemic treatment with or without local treatment
- Under treatment with active systemic therapy
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases, possible residual non-progressive metastases (black)

Induced oligopersistence



- T-X: diagnosis of polymetastatic metastatic disease followed by systemic treatment with or without local treatment
- Under treatment with active systemic therapy
- T0: diagnosis of persistent non-progressive oligometastases (red), where response is worse compared with other residual metastases (black)

'OliGomez'

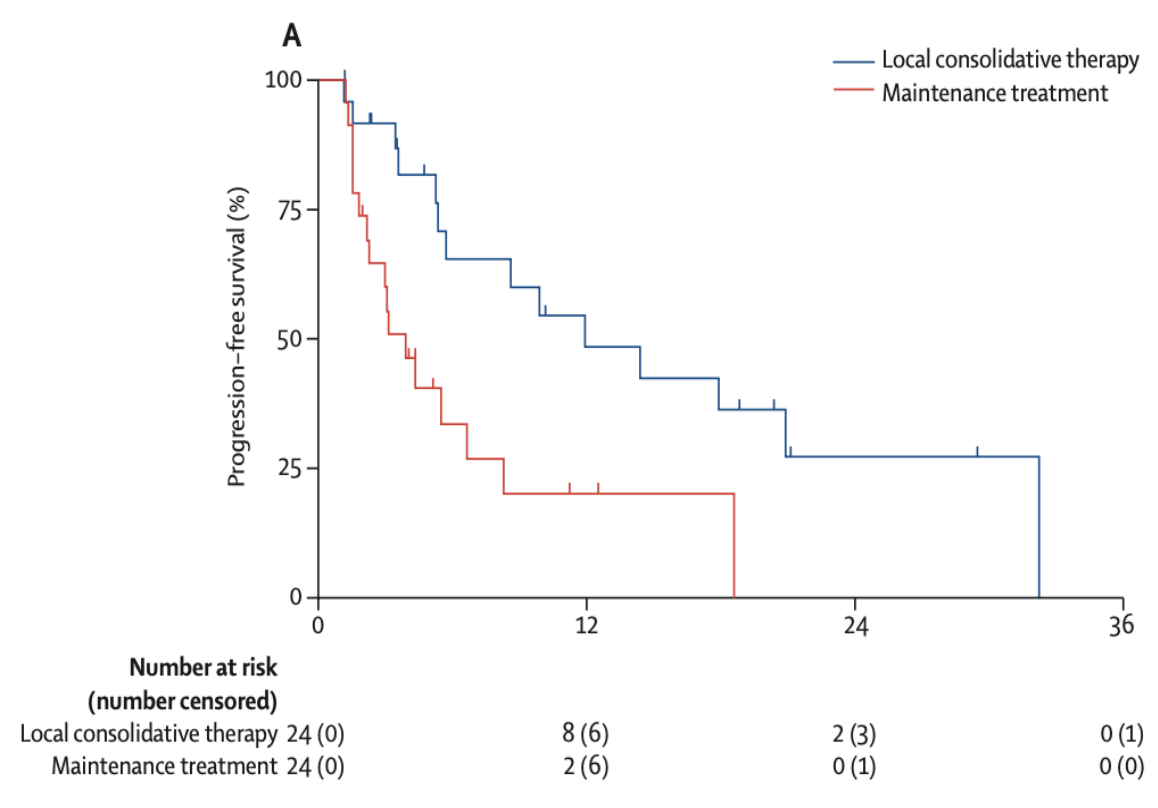


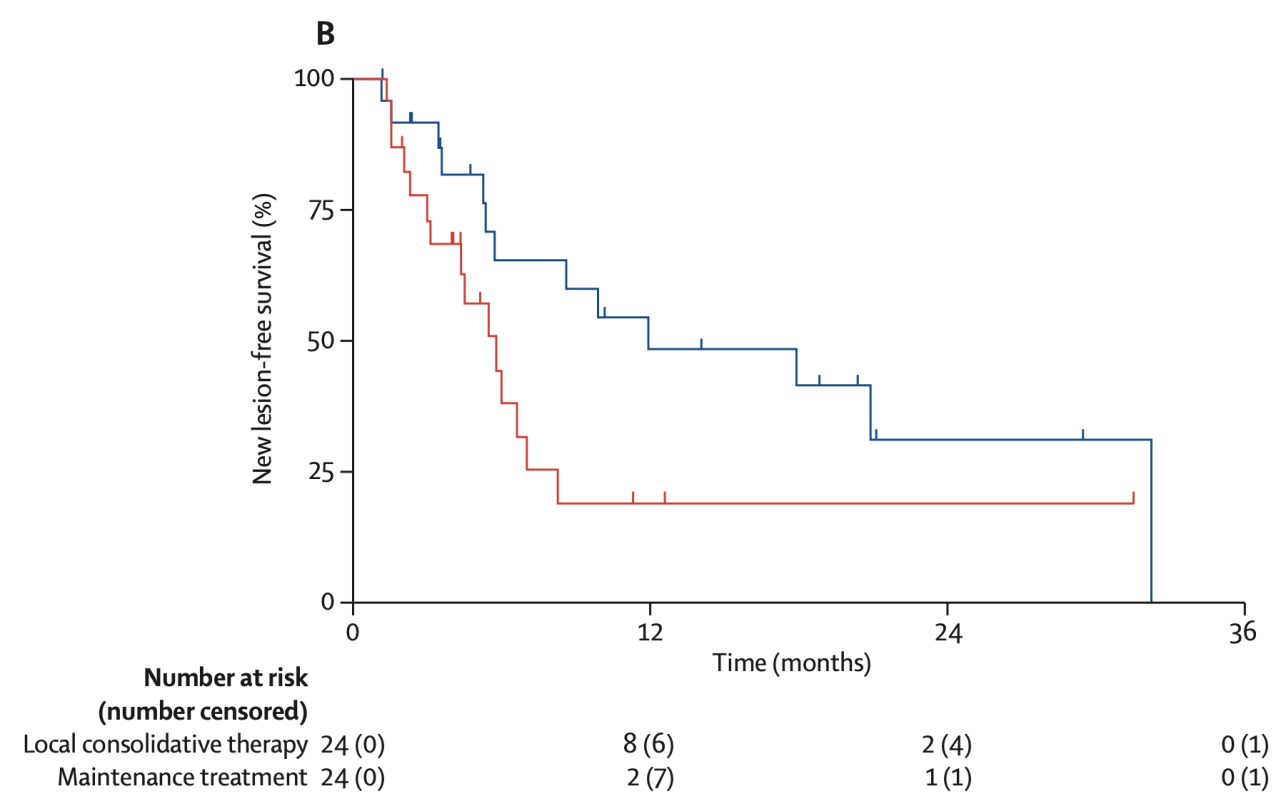
Study schema. Oligometastatic (1-3 metastases) NSCLC patients with non-progressive disease (PD) after first line therapy will be randomized to immediate local consolidation therapy (LCT) arm vs. delayed/no LCT arm of primary and metastases. **Crossover of treatment arms is allowed for disease progression or toxicity, at the treating physician's discretion (see Off-Study Criteria below).**

- N = 49 (randomized)
- Primary: PFS
- Crossover allowed at time of progression
- 76% had nodal dz counted as one of oligometastatic sites
- 16% EGFR/ALK
- Synchronous oligometastatic disease
- Induced oligopersistence

Gomez et al. *Lancet Oncol* 2016 PMID 27789196; Gomez et al. *JCO* 2019 PMID 31067138

Initial results (12.4 months follow-up)



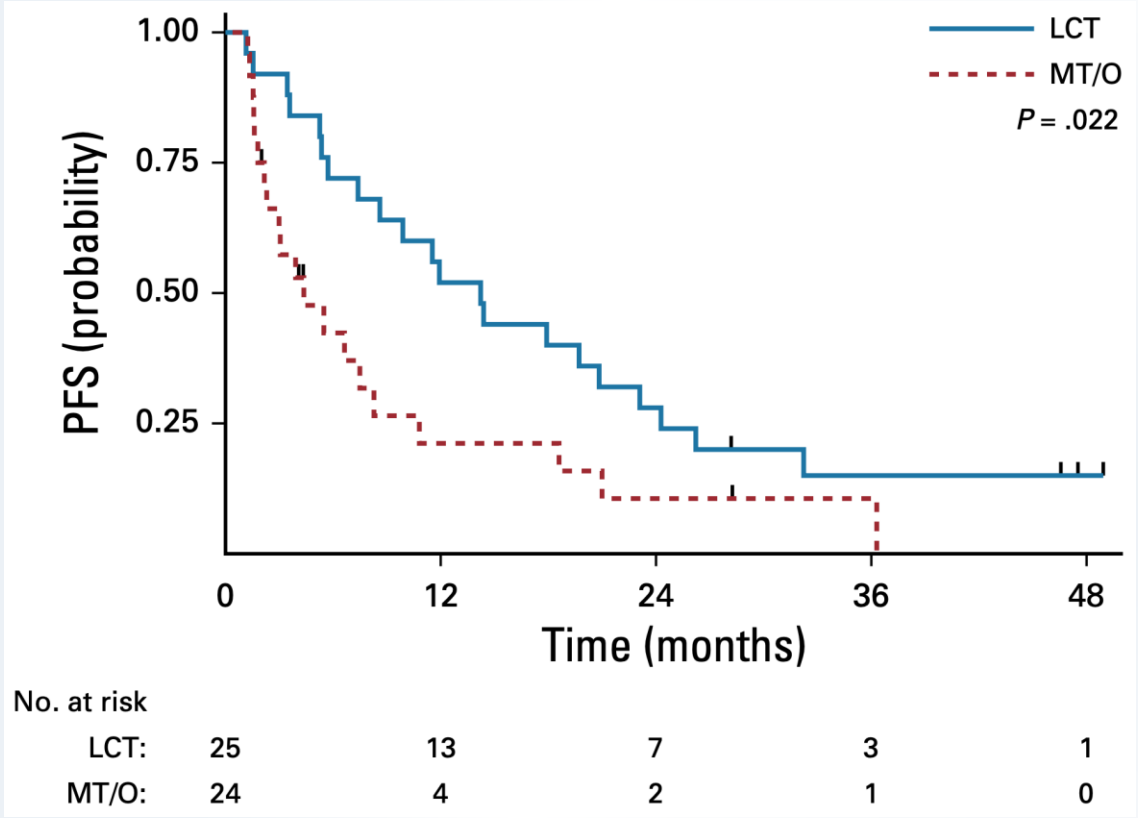


Med PFS 11.9 vs 3.9 mo (HR 0.35, P = 0.0054)

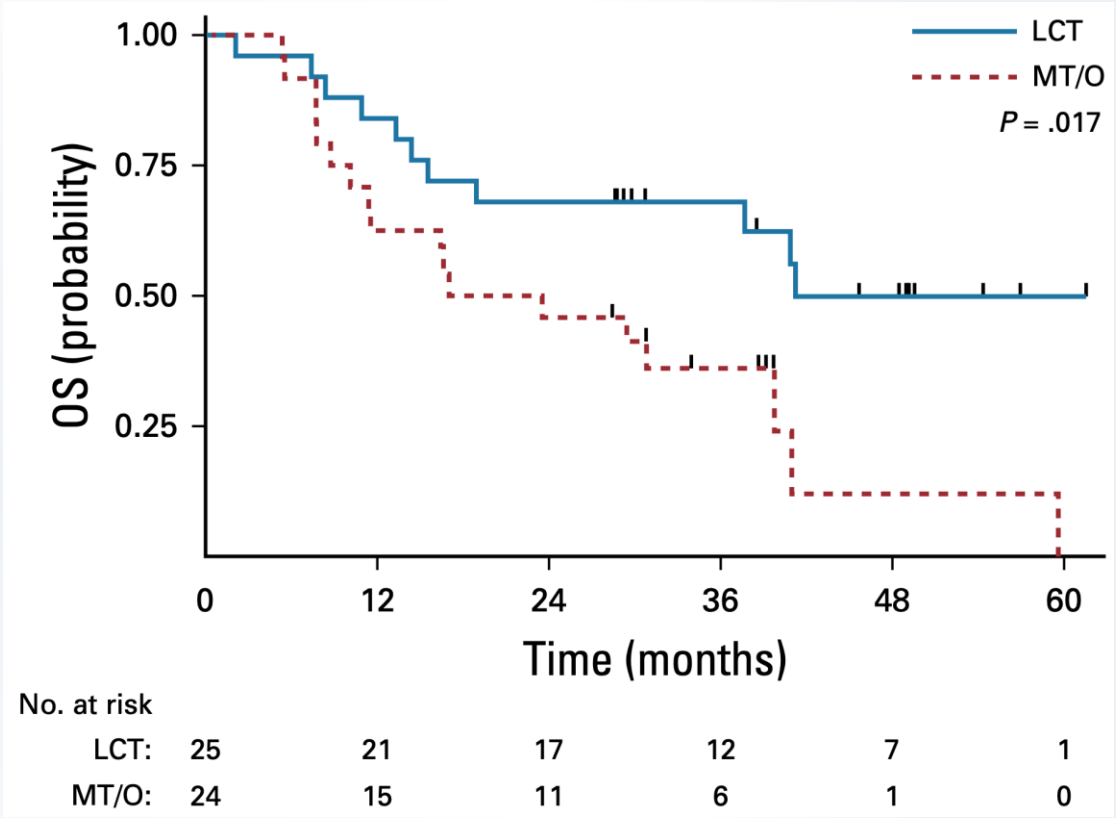
Med. time to new lesion 11.9 vs 5.7 months (*P* = 0.05)

Gomez et al. *Lancet Oncol* 2016 PMID 27789196

Updated results (38.8 months follow-up)



Med. PFS 14.2 vs 4.4 months (*P* = 0.022)



Med. OS 41.2 vs 17 months (*P* = 0.017)

Gomez et al. *JCO* 2019 PMID 31067138

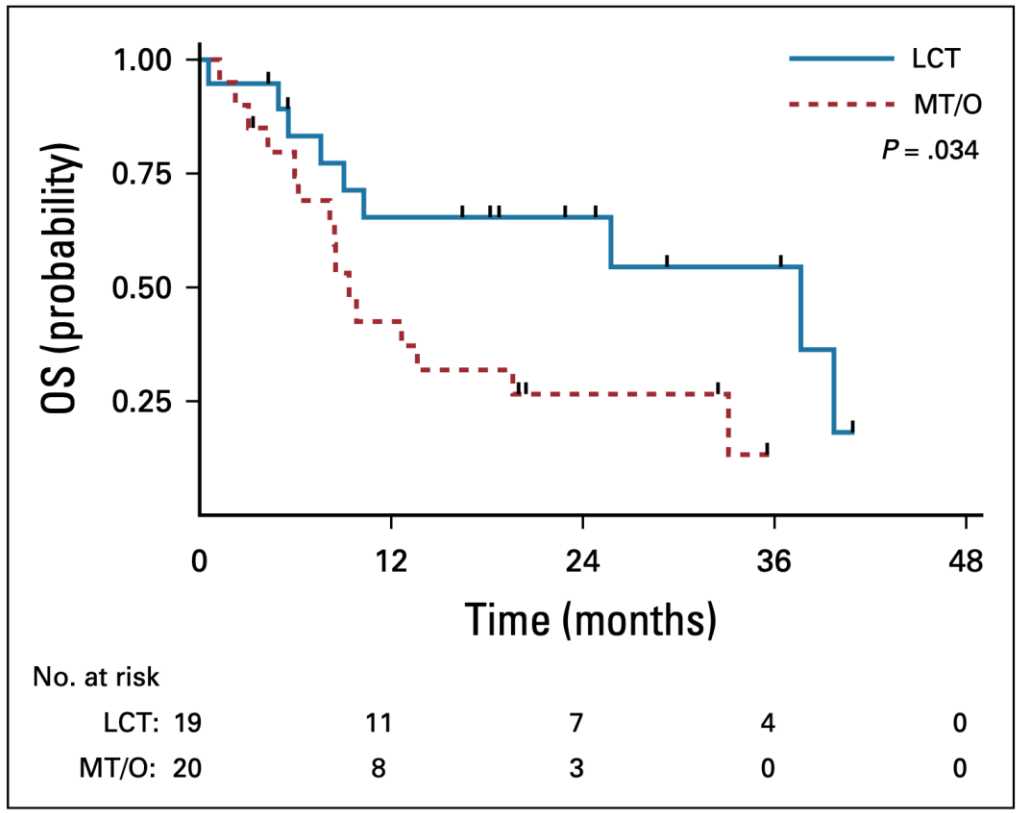


FIG 2. Overall survival (OS) after disease progression among patients originally assigned to local consolidative therapy (LCT) or maintenance therapy or observation (MT/O).

Med. OS after PD 37.6 vs 9.4 months ($P = 0.034$)
37.6mo (by original arm, LCT vs M/O)

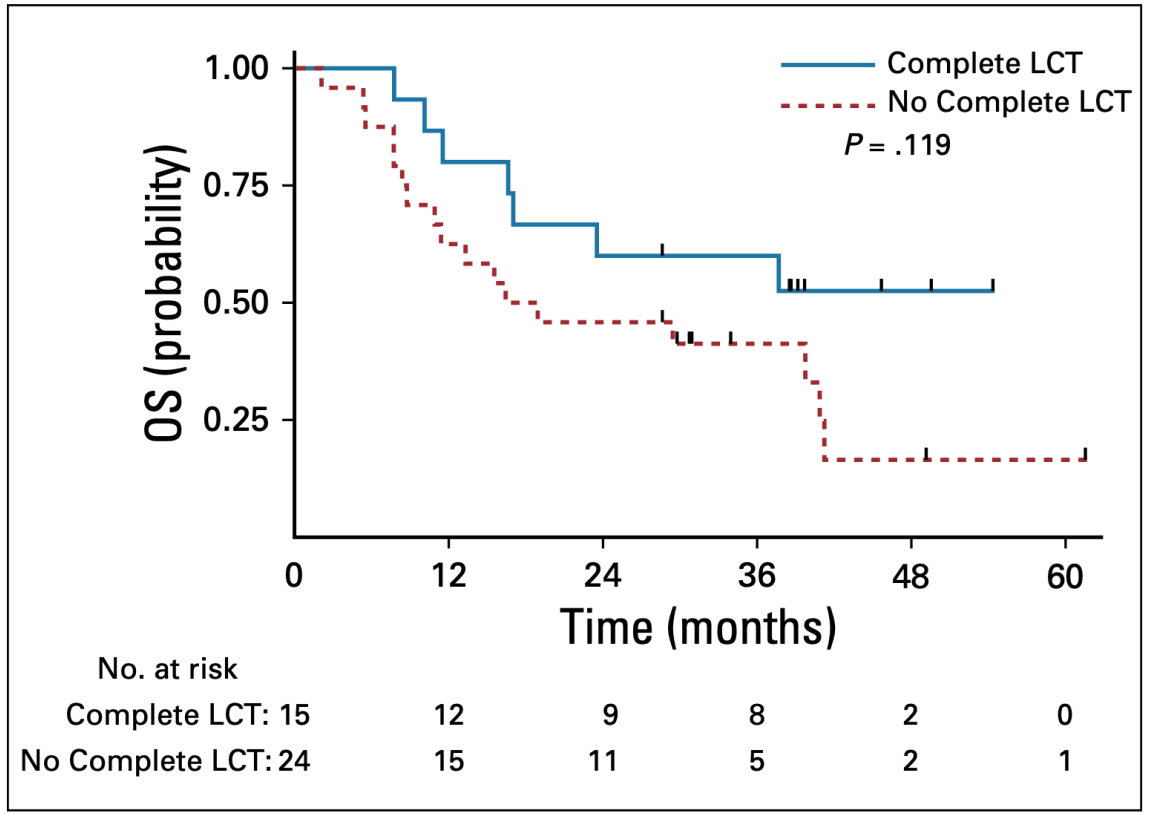


FIG 3. Overall survival (OS) from time of progression, for patients who did or did not receive late local consolidation therapy (LCT) for that progression. "Complete" LCT designates radiation therapy or surgery to all active sites of disease at the time of progression.

Med. OS from PD NR vs 16.4 (late LCT vs no, $P = 0.119$)
65% received LCT at PD (crossover allowed)

Takeaways from 'OliGomez'

- Local consolidative therapy may change the disease course for synchronous oligometastatic NSCLC
  - Either by limiting the potential for later spread or possibly by altering systemic anti-cancer immune responses to facilitate longer control of subclinical disease
- Early LCT is better than no LCT
  - However, late LCT at progression, if feasible, can partly compensate by improving OS to a lesser extent
- Primary risk of reserving LCT until progression (late LCT) is that definitive treatment to all sites of disease can be achieved in only a subset of patients

SBRT is very safe

- N=1,422 from 17 NHS centers in UK
- Prospective registry study
- SABR for 1-3 extracranial oligomets
- Most common G3 AE – fatigue (2%)
- No treatment-related deaths

- N=943 from 21 prospective studies
- SBRT (≤8fx) treating up to 5 mets
- Acute G3-5 AE rate 1.2%
- Late G3-5 AE rate 1.7%
- Weighted random-effects model

Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: a prospective, registry-based, single-arm, observational, evaluation study

Anastasia Chalkidou, Thomas Macmillan, Mariusz T Grzeda, Janet Peacock, Jennifer Summers, Saskia Eddy, Bola Coker, Hannah Patrick, Helen Powell, Lee Berry, Gareth Webster, Peter Ostler, Peter D Dickinson, Matthew Q Hatton, Ann Henry, Stephen Keevil, Maria A Hawkins, Nick Slevin, Nicholas van As

JAMA Oncology | Original Investigation

Safety and Survival Rates Associated With Ablative Stereotactic Radiotherapy for Patients With Oligometastatic Cancer
A Systematic Review and Meta-analysis

Eric J. Lehrer, MD, MS; Raj Singh, MD; Ming Wang, MS, PhD; Vernon M. Chinchilli, PhD; Daniel M. Trifiletti, MD; Piet Ost, MD, PhD; Shankar Siva, PhD, MBBS; Mao-bin Meng, MD, PhD; Leila Tchelebi, MD; Nicholas G. Zaorsky, MD, MS

Chalkidou et al. *Lancet Oncol* 2021 PMID 33387498

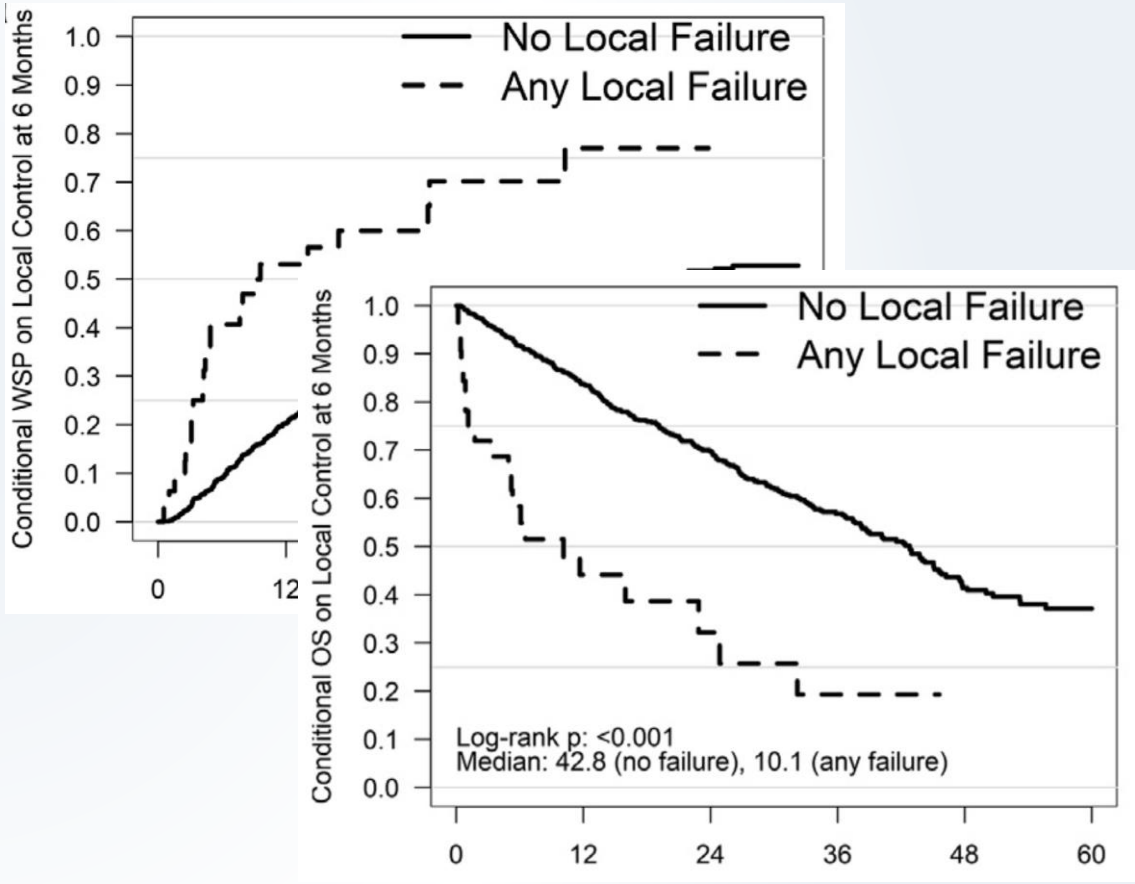
Lehrer et al. *JAMA Oncol* 2021 PMID 33237270

Local control – does it matter?

- N= 1,700 oligomets (1,006 patients)
- By primary site: 25.2% NSCLC
- By location: 46.1% lung
- 5 new/untreated lesions = widespread progression
- Any local failure predicts for widespread progression (HR 2.6) and death (HR 3.7)
- Similar results at 12, 18, 24, 36 mo
- 1-yr threshold for >95% LC
  - 41.2 Gy in 5fx (BED ~75.3)
  - Or 55.2 Gy in 5fx if >27.7cc or radioresistant

The impact of local control on widespread progression and survival in oligometastasis-directed SBRT: Results from a large international database

Yilin Cao [a], Hanbo Chen [b], Arjun Sahgal [b], Darby Erler [b], Serena Badellino [c], Tithi Biswas [d], Roi Dagan [e], Matthew C. Foote [f], Alexander V. Louie [b], Ian Poon [b], Umberto Ricardi [c], Kristin J. Redmond [a,*]



Cao et al. *Radiother Oncol* 2023 PMID 37385379

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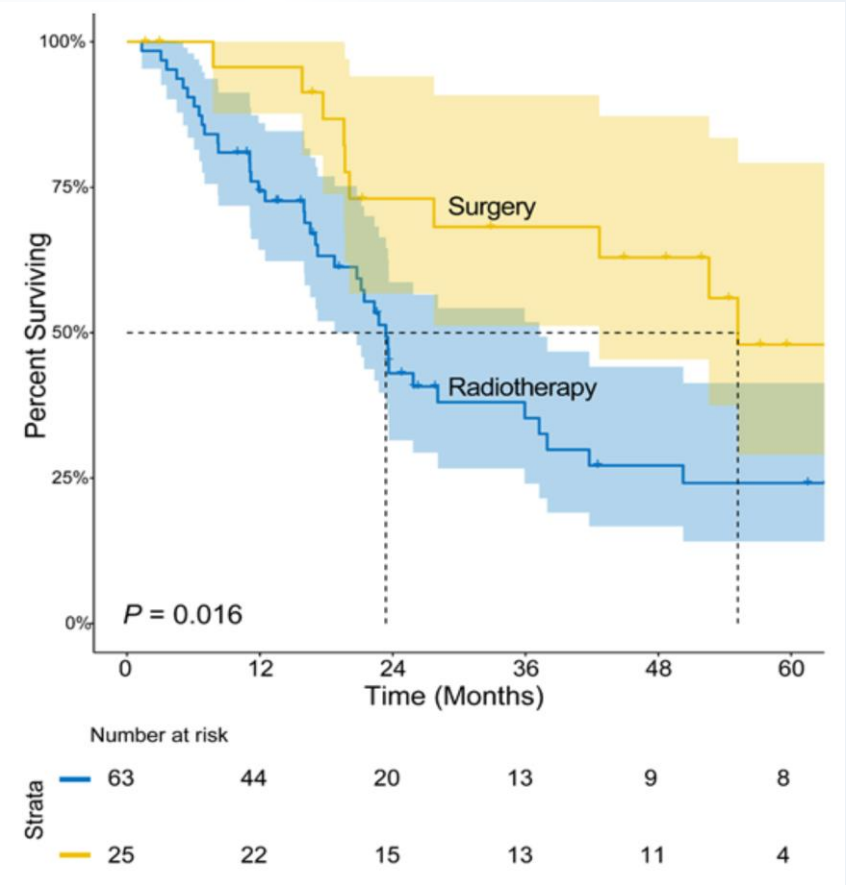
Role for surgery as LCT in OMD

- Synchronous stage IV NSCLC
- N=25 (surgery), N=63 (RT)
- 56% with single met. in surgery group
- Surgery performed
  - 80% lobectomy
  - 12% pneumonectomy
  - 8% sublobar resection
- 90-day post-treatment mortality
  - Surgery 0% (0 of 25)
  - RT 1.6% (1 of 63)
- Med. OS 55.2 months (surgery)
- Med. OS 23.4 months (RT)

Pulmonary resection is associated with long-term survival and should remain a therapeutic option in oligometastatic lung cancer

Check for updates

Kyle G. Mitchell, MD,[a] Ahsan Farooqi, MD, PhD,[b] Ethan B. Ludmir, MD,[b] Erin M. Corsini, MD,[a] Boris Sepesi, MD,[a] Daniel R. Gomez, MD,[b] and Mara B. Antonoff, MD,[a] the MD Anderson Cancer Center Oligometastatic Lung Cancer Working Group*



Mitchell et al. *JTCVS* 2021 PMID 32331820

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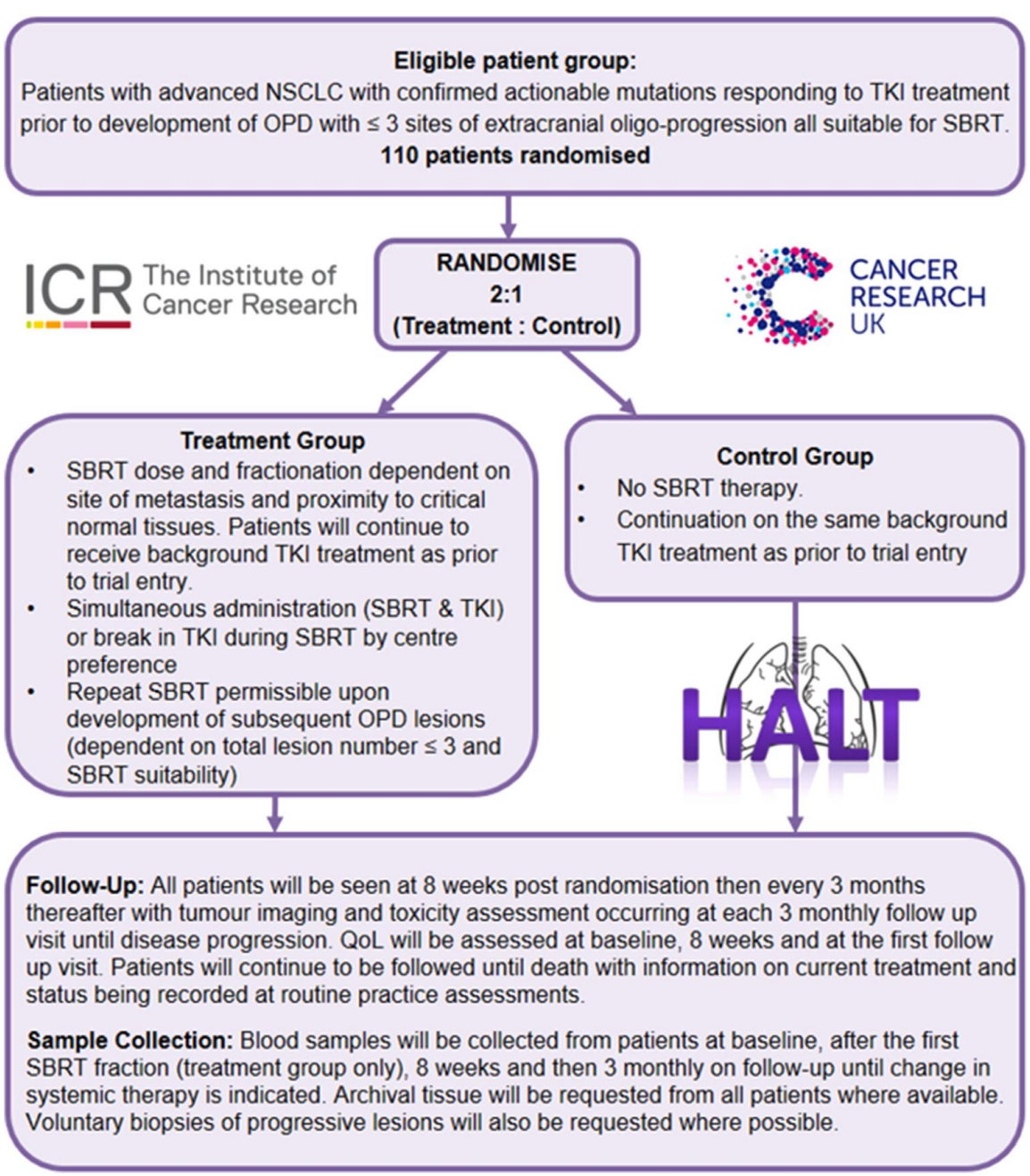
Patients with metastatic NSCLC having completed 4 cycles or courses of first-line/induction systemic therapy Restaging studies reveal no evidence of progression and limited (≤ 3 discrete sites) metastatic disease, all of which must be amenable to SBRT +/- Surgery A minimum of one disease site (metastasis or primary) needs to be present after first-line/induction systemic therapy and treatable with local consolidative therapy	STRATIFY	Histology: Squamous vs. Non-squamous Systemic Therapy: Immunotherapy vs Cytotoxic Chemotherapy	RANDOMIZE	Arm 1: Maintenance systemic therapy alone Arm 2: SBRT or SBRT and Surgery to all sites of metastases (≤ 3 discrete sites) plus irradiation (SBRT or hypofractionated RT) of the primary site followed by maintenance systemic therapy. All Arm 2 patients, even if treated with Surgery, must have one site of disease (metastasis or primary) treated with radiation.

- N=400 (378 randomized)
- 218 accrued (phase II)
- 11/12/21 - Temporarily closed to accrual

- Synchronous oligometastatic disease
- Induced oligopersistence
- Metachronous oligorecurrence

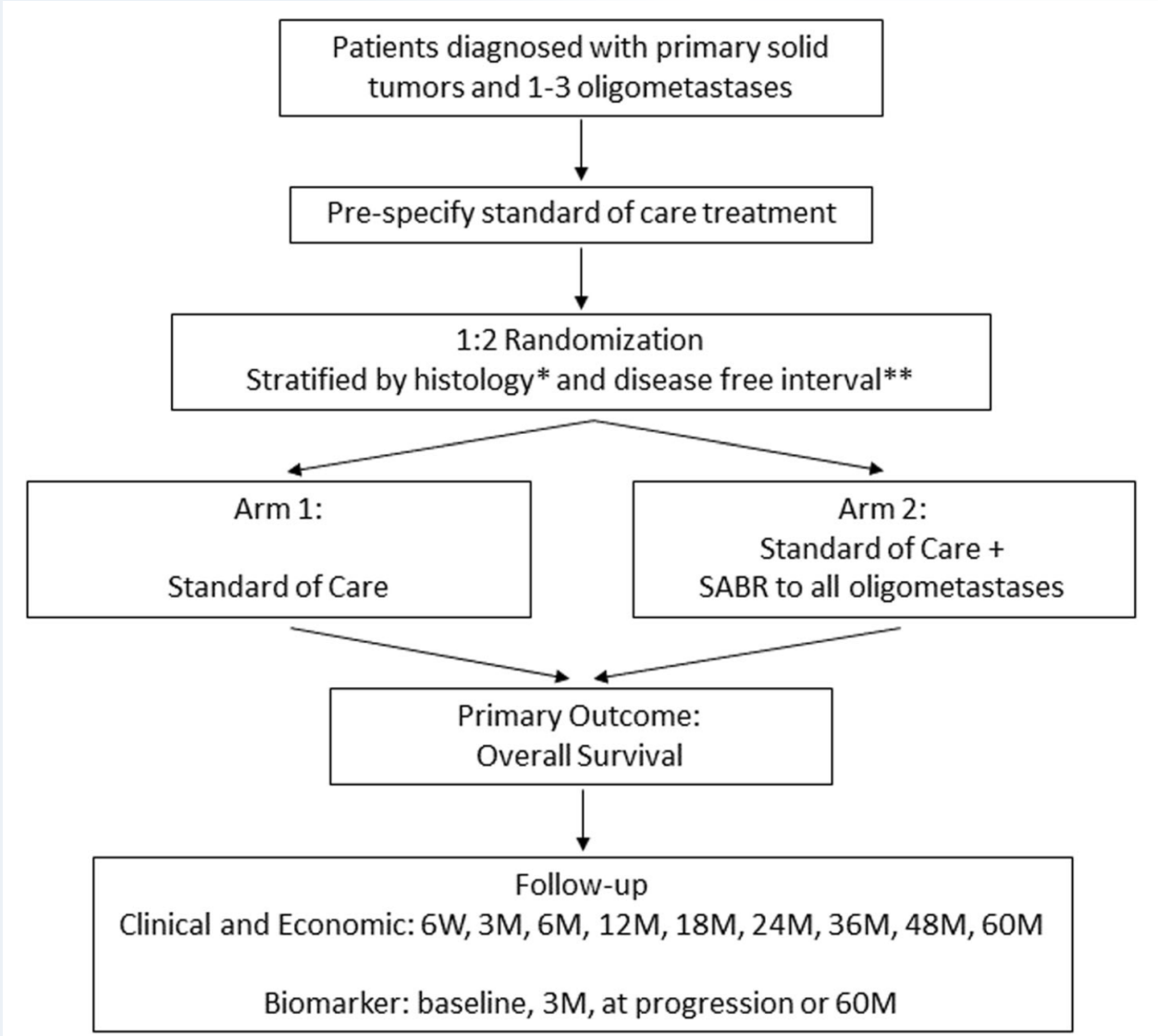
HALT (UK)



- Stage IV EGFR/ALK NSCLC
- N=110
- Primary: PFS
- Amended inclusion: ≤ 5 OPD lesions
- November 2017- Opened
- July 2023 – Completed accrual
- Induced oligoprogression
- Repeat oligoprogression

McDonald et al. EP08.03-005 *JTO* 2022 (WCLC)

SABR-COMET 3



- N=330 (phase III)
- Controlled primary, at least 1 extracranial lesion to be randomized for SOC vs SABR
- Primary: OS
- Translational: CTC, cfDNA
- Arm 2 eligible for additional SABR to subsequent metastases
- Metachronous oligorecurrence
- Metachronous oligoprogression
- Repeat oligorecurrence
- *Histology: breast, prostate, RCC vs other)
- *Disease free interval ≤ vs > 2 years

Olson et al. *BMC Cancer* 2020 PMID 32370765

SABR-COMET 10

A Randomized Phase III Trial of Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of 4-10 Oligometastatic Tumors
(NCT03721341)

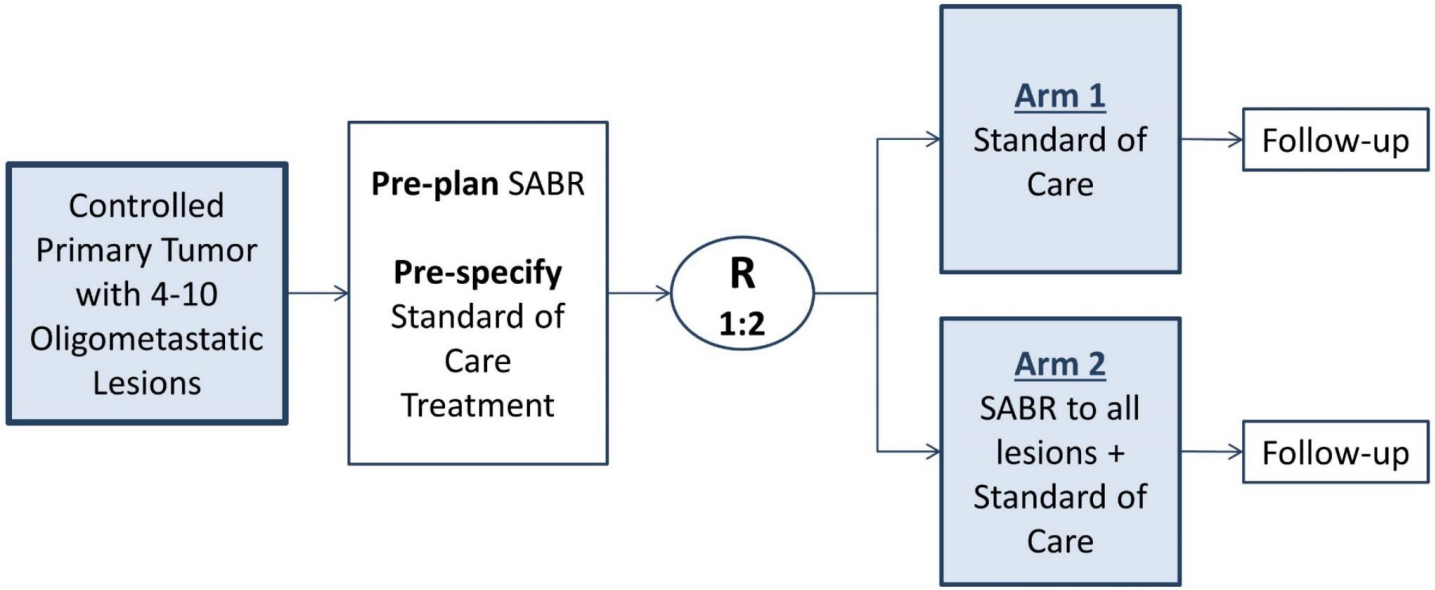


Table 1 Allowable doses and fractionations

Number of fractions	Preferred dose	Acceptable doses	Major deviation
1	20 Gy	16-24 Gy	<16 Gy or >24 Gy
3	30 Gy	24-33 Gy	<24 Gy or >33 Gy
5	35 Gy	25-40 Gy	<25 Gy or >40 Gy

- N=159
- Controlled primary, at least 1 extracranial lesion to be randomized for SOC vs SABR
- Primary: OS
- Eligibility: all sites can be safely treated based on pre-planning
- 57% had 4 target lesions in first 60 pts

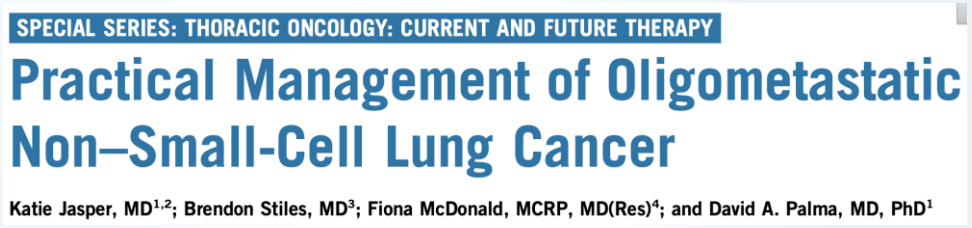
Palma et al. *BMC Cancer* 2019 PMID 31426760

Final Thoughts

- Role of RT and (LCT) evolving
- Multi-disciplinary evaluation necessary
- Principles of RT in OMD management
  - Careful patient selection
  - Balance probability of control against risk of toxicity
  - Minimize treatment time
  - Favor (early) consolidation over at time of progression
  - Favor comprehensive over partial consolidation
- Need to support to ongoing randomized trials!
  - 2023 updates - CORE (ESTRO 2023), STOP (ASTRO 2023), SARON


Clinical Practice Guideline

Treatment of Oligometastatic Non-Small Cell Lung Cancer: An ASTRO/ESTRO Clinical Practice Guideline


SPECIAL SERIES: THORACIC ONCOLOGY: CURRENT AND FUTURE THERAPY

Practical Management of Oligometastatic Non–Small-Cell Lung Cancer

Katie Jasper, MD[1,2]; Brendon Stiles, MD[3]; Fiona McDonald, MCRP, MD(Res)[4]; and David A. Palma, MD, PhD[1]


Clinical Investigation

American Radium Society Appropriate Use Criteria for Radiation Therapy in Oligometastatic or Oligoprogressive Non-Small Cell Lung Cancer