bjclub breast Journal club

L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

20 - 21 APRILE
2023 ROMA

THE HIVE HOTEL

Via Torino, 6

# THE OXFORD DEBATE EDITION

# Le terapie locoregionali dovrebbero essere sempre associate alla terapia sistemica nella malattia oligometastatica

## PRO

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# Oligometastases – Recent studies on breast cancer

- 50% of breast cancer patients with metastatic disease present with a limited number of metastases

**Salama JK, et al** Semin Oncol 2014

- Breast cancer is potentially well-suited for metastasis-directed therapy in selected patients

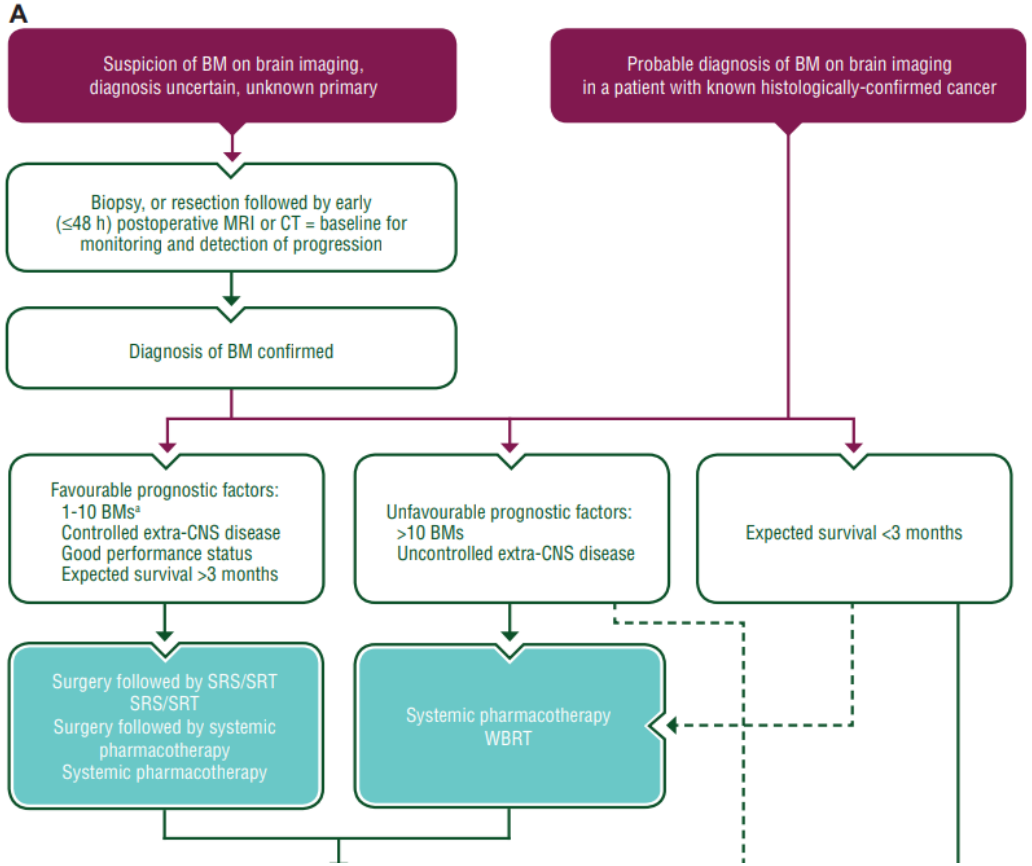
**Pockaj BA, et al**. Ann Surg Oncol 2010
**Di Lascio S, et al**. Breast Care 2014
**Drazer MV, et al**. Expert Rev Anticancer Ther 2016
**Ricardi U, et al**. J Radiat Res 2016

- In retrospective studies on oligometastatic breast cancer patients metastasis-directed surgery or radiation therapy was associated with significantly long-term survival outcomes

**Kobayashi T, et al**. Breast Cancer 2012
**Milano, et al.** Radiother Oncol 2019

# Intracranial Metastasis

- **Surgery:**
  - Single BMs should be considered for surgical resection [EANO: I, A; ESMO: II, A].
  - Multiple resectable BMs may be considered for surgical resection [EANO: IV, C; ESMO: V, C].
- **Radiotherapy:**
  - SRS is recommended for patients with a limited number
  - (1-4) of BMs [EANO: I, A; ESMO: I, A].
  - SRS may be considered for patients with a higher number
  - of BMs (5-10) with a cumulative tumour volume <15 ml
  - [EANO: II, B; ESMO: II, B].
  - SRS to the resection cavity is recommended after complete or incomplete resection of BMs [EANO: I, A;ESMO: I, A].



# Extracranial metastases

**Published SBRT studies focused on:**

- 1. Variety of primary tumors and metastasis's location
- 2. Single metastatic site
- 3. Single primary tumor

**Heterogeneity**

- SBRT technique, dose, fractionation
- Size of metastases
- Few data on oligometastatic breast cancer

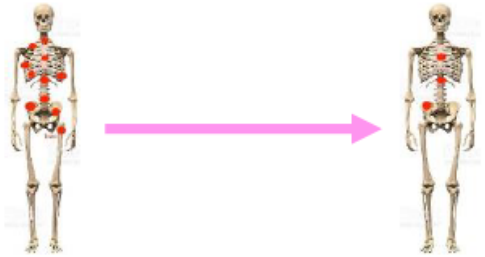
**Selection bias**

- Unfavorable prognosis, heavily pre-treated

**Salama JK, et al.** Nat Rev Clin Oncol 2012

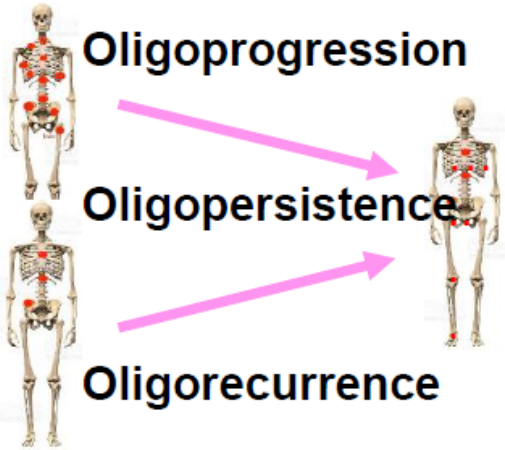
# Oligometastases – various entities

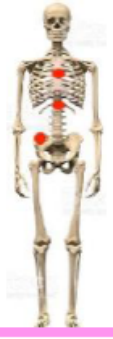
Genuine, de-novo, **synchronous** oligometastatic disease



**induced** oligometastatic disease

De-novo, **metachronous**, oligometastatic disease



**ESO-ESMO**: ≤5 M+, potentielly amenable for local treatment, aiming at complete remission

**ATRO-ESTRO**: ≤5 M+, all tumour locations safely treatable with curative intent

Cardoso, The Breast 2017
Lievens, Radiother Oncol 2020
Guckenberger, Lancet Oncol 2020

# Oligometastases – Recent prospective studies

**Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial**

*David A Palma, Robert Olson, Stephen Harrow, Stewart Gaede, Alexander V Louie, Cornelis Haasbeek, Liam Mulroy, Michael Lock, George B Rodrigues, Brian P Yaremko, Devin Schellenberg, Belal Ahmad, Gwendolyn Griffioen, Sashendra Senthi, Anand Swaminath, Neil Kopek, Mitchell Liu, Karen Moore, Suzanne Currie, Glenn S Bauman, Andrew Warner, Suresh Senan*

- 99 patients → randomization (1:2) to receive either palliative standard of care treatments alone (control group), or standard of care plus SBRT to all metastatic lesions (SBRT group)
- Controlled primary tumor and up to 5 metastatic lesions
- Stratification by number of metastases (1-3 vs 4-5)
- Primary endpoint → OS
- 18 breast cancer patients enrolled (13 in SBRT group)

| | Control group (n=33) | SABR group (n=66) |
|---|---|---|
| Age | 69 (64–75) | 67 (59–74) |
| Sex | | |
| Men | 19 (58%) | 40 (61%) |
| Women | 14 (42%) | 26 (39%) |
| Site of original primary tumour | | |
| Breast | 5 (15%) | 13 (20%) |
| Colorectal | 9 (27%) | 9 (14%) |
| Lung | 6 (18%) | 12 (18%) |
| Prostate | 2 (6 %) | 14 (21%) |
| Other | 11 (33%) | 18 (27%) |
| Time from diagnosis of primary tumour to randomisation (years) | 2·3 (1·3–4·5) | 2·4 (1·6–5·3) |
| Number of metastases | | |
| 1 | 12 (36 %) | 30 (46%) |
| 2 | 13 (40%) | 19 (29%) |
| 3 | 6 (18%) | 12 (18%) |
| 4 | 2 (6%) | 2 (3%) |
| 5 | 0 (0%) | 3 (5%) |
| Location of metastases | | |
| Adrenal | 2/64 (3%) | 7/127 (6%) |
| Bone | 20/64 (31%) | 45/127 (35%) |
| Liver | 3/64 (5%) | 16/127 (13%) |
| Lung | 34/64 (53%) | 55/127 (43%) |
| Other* | 5/64 (8%) | 4/127 (3%) |

Data are n (%), n/N (%), or median (IQR). SABR=stereotactic ablative radiotherapy. *Other comprises brain (n=3 lesions in control group; n=1 lesion in SABR group), lymph nodes (n=1 lesion in control group; n=3 lesions in SABR group), and para-renal (n=1 lesion in control group).

***Table 1:*** **Baseline characteristics**

Palma DA, et al. *Lancet 2019*

# Oligometastases – Recent prospective studies

Median follow-up 25.5 months

Median **OS** was **28 months** *(95% CI 19–33)* in the **control** group **vs 41 months** *(26–not reached)* in the **SABR** group

***(HR 0.57, 95% CI 0.30–1.10; p=0.090 with p<0.20 as positive trial)***

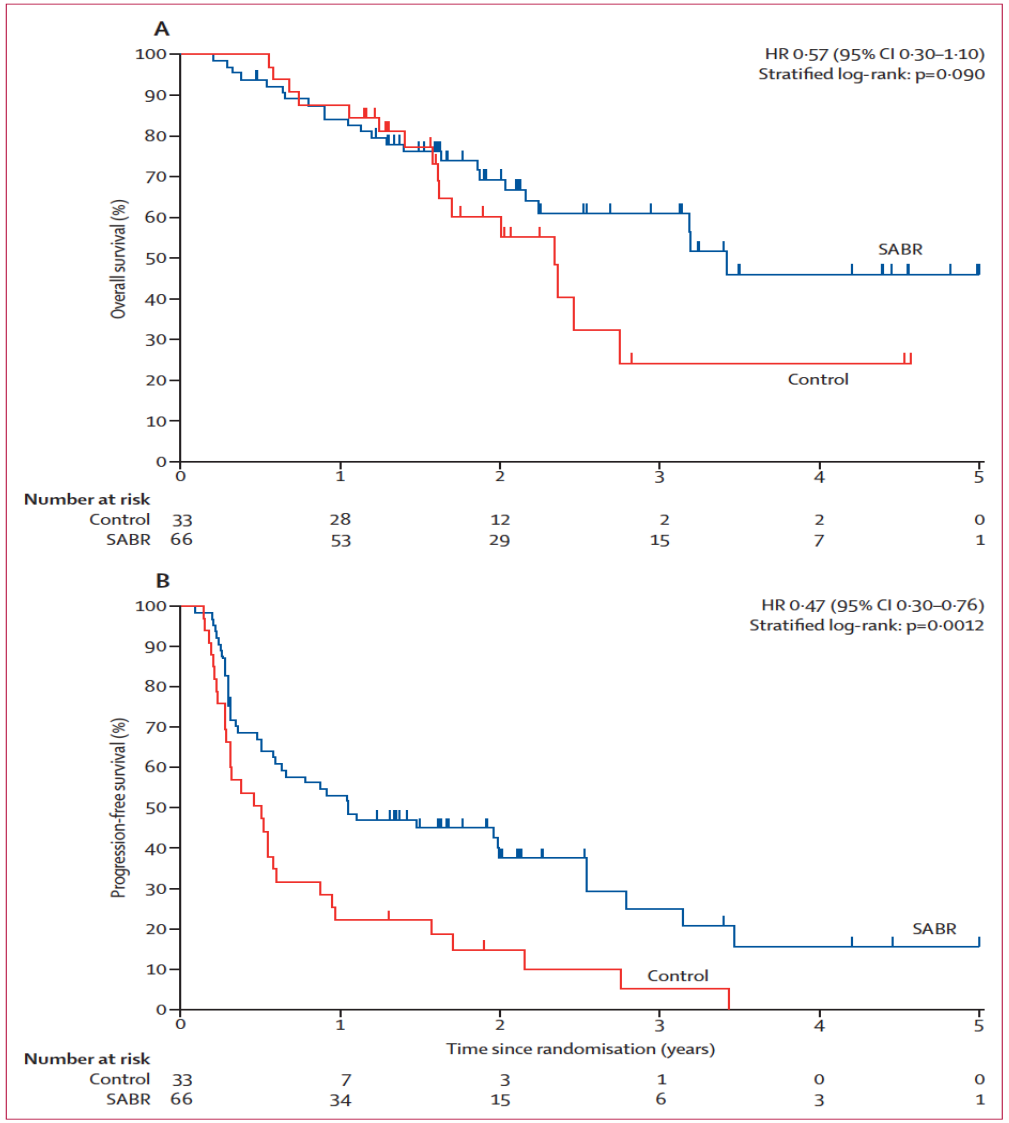



*Figure 2:* **Overall survival (A) and progression-free survival (B)**
SABR=stereotactic ablative radiotherapy. HR=hazard ratio.

Palma DA, et al. *Lancet 2019*

# Oligometastases – Recent prospective studies

- **Adverse events of grade 2 or worse** occurred in three (9%) of 33 controls and 19 (29%) of 66 patients in the SABR group (p=0.026), **an absolute increase of 20%**

- **4.5% of patients in the SABR group died as a result of toxicity**, despite stringent dose constraints and a requirement for peer review of all radiation plans

- SBRT should continue to focus on **minimization of toxicity** and that the use of SABR in patients with more than five lesions should be done **in the context of a clinical trial**

- **Phase 3 trials are needed to confirm an OS benefit** and to determine **the maximum number of metastatic lesions wherein SABR provides a benefit**

| | All patients (n=99) | Control group (n=33) | Stereotactic ablative radiotherapy group (n=66) | p value |
|---|---|---|---|---|
| Adverse event grade ≥2 | 55 (56%) | 15 (46%) | 40 (61%) | 0·15 |
| Related adverse event grade ≥2 | 22 (22%) | 3 (9%) | 19 (29%) | 0·026 |
| Adverse event associated with death (grade 5) | 3 (3%) | 0 | 3 (5%) | 0·55 |
| Fatigue* | .. | .. | .. | 0·45 |
| Grade 2 | 6 (6%) | 2 (6%) | 4 (6%) | .. |
| Grade 3 | 1 (1%) | 1 (3%) | 0 | .. |
| Dyspnoea* | .. | .. | .. | 1·00 |
| Grade 2 | 1 (1%) | 0 | 1 (2%) | .. |
| Grade 3 | 1 (1%) | 0 | 1 (2%) | .. |
| Pain (any type)* | .. | .. | .. | 0·14 |
| Grade 2 | 5 (5%) | 0 | 5 (8%) | .. |
| Grade 3 | 3 (3%) | 0 | 3 (5%) | .. |

Data are n (%). *Treatment related.

*Table 2:* **Summary of adverse events**

Palma DA, et al. *Lancet 2019*

# Predictable toxicity

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RADIATION ONCOLOGY • BIOLOGY • PHYSICS
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CLINICAL INVESTIGATION

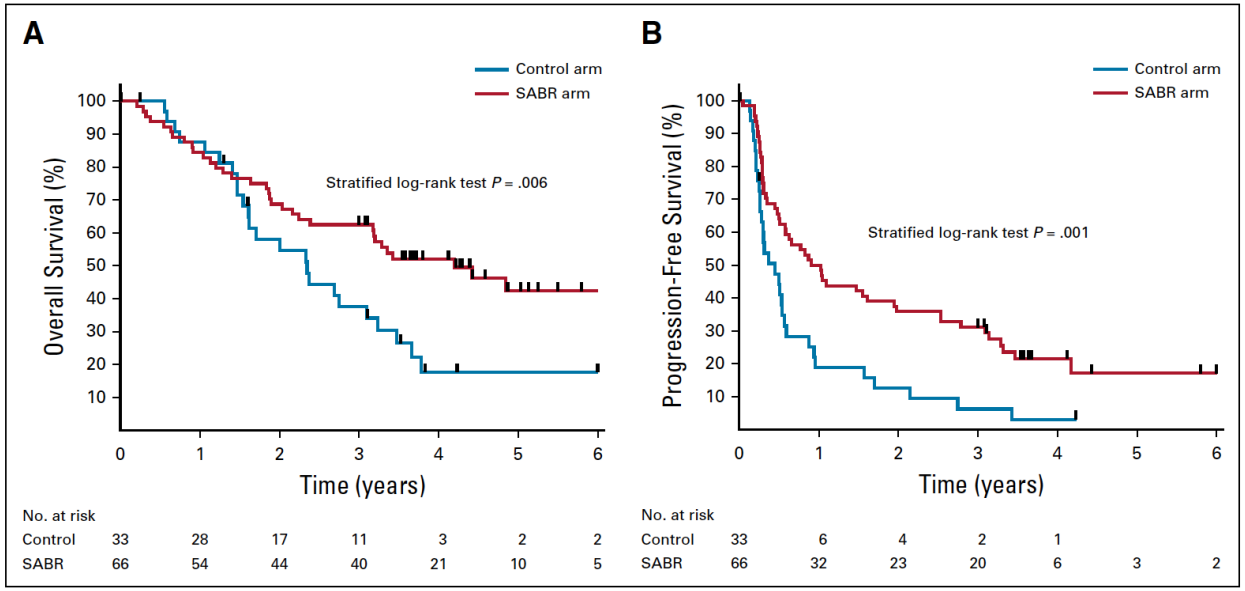
**Determining Planning Priorities for SABR for Oligometastatic Disease: A Secondary Analysis of the SABR-COMET Phase II Randomized Trial**

Matthew Van Oirschot,* Alanah Bergman, PhD,† Wilko F.A.R. Verbakel, PhD,‡ Lucy Ward, BSc,§ Isabelle Gagne, PhD,‖ Vicky Huang, MSc,# Nick Chng, PhD,** Peter Houston, MSc,†† Kerry Symes, BSc,† Christopher G. Thomas, PhD,§ Parminder Basran, PhD,‡‡ David Bowes, MD,§ Stephen Harrow, MBChB, PhD,†† Robert Olson, MD, MSc,** Suresh Senan, MBBS, PhD,‡ Andrew Warner, MSc,* David A. Palma, MD, PhD,* and Stewart Gaede, PhD*

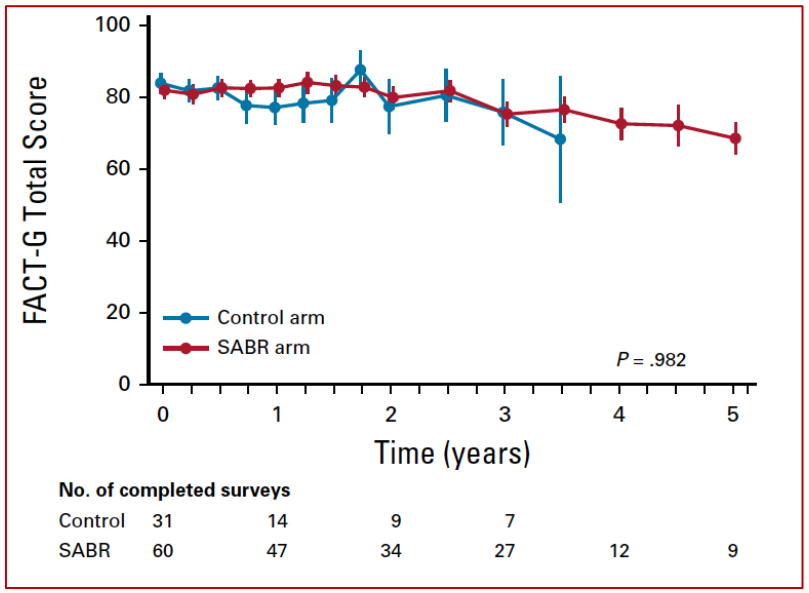
- Because **oligometastases occur at multiple different sites**, relevant OARs will vary, and trade-offs will depend on the exact location of the tumor and other physiological considerations.
- For example, **a lesion adjacent to the trachea may warrant a more conservative approach than a lesion against a less-critical structure**, such as the chest wall.
- It is also unclear whether it is preferable to prescribe higher dose that requires PTV coverage compromise versus lowering the prescription dose and covering them PTV fully.
- PTV compromise was required for approximately one-third of lesions, but was not associated with OS, PFS, or lesional control.

# Oligometastases – Recent prospective studies

Median follow-up 51 months




*Kaplan-Meier plots for (A) overall survival and (B) progression-free survival*




*Functional Assessment of Cancer Therapy: General*

The 5-year OS rate was 17.7% in arm 1 versus 42.3% in arm 2
The 5-year PFS rate was not reached in arm 1 (3.2%) and 17.3% in arm 2
There were no new grade 2-5 adverse events and no differences in QOL between arms

***Palma DA, et al.*** *2020, JCO; 38:2830-2838*

For Breast cancer patients (only 18 pts): **OS HR (95% CI) 0.77 (0.21, 2.88) and PFS HR (95% CI) 0.53 (0.18, 1.59)**
**Lower rate of chemotherapy use in the SABR** arm (33%) vs. the control arm (55%, p=0.043)

*Courtesy from D. Palma ESTRO 2022*

# Oligometastases – Recent prospective studies

**Methods:** OMBC pts with ≤ 4 extracranial mets on standard imaging with controlled primary disease were eligible if on first line SOC ST for ≤ 12 months without progression

Median age 54 years
79% ER+ or PR+/HER2-, 13% HER2+, 8% triple negative
60% with 1 metastasis and 20% presented synchronously with primary disease
The median follow-up 30 months

New mets*inside*index area (SOC) /RT field (SOC+A): Fewer for SOC+A: 7% vs. 29%

**Conclusions:** The addition of MDT to SOC ST did not show signal for improved PFS, nor OS difference in patients with OMBC, so the trial will not proceed to the Phase III component

Meeting Abstract | 2022 ASCO Annual Meeting I

BREAST CANCER—METASTATIC

NRG-BR002: A phase IIR/III trial of standard of care systemic therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical resection (SR) for newly oligometastatic breast cancer (NCT02364557).



Steven J. Chmura, Kathryn A. Winter, Wendy A. Woodward, Virginia F. Borges, Joseph Kamel Salama, Hania A Al-Hallaq, ...

| | ST (n=65) | ST+MDT (n=60) |
|---|---|---|
| mPFS | 23 months | 19.5 months |
| 24-mo PFS | 45.7% | 46.8% |
| 36-mo PFS | 32.8% | 38.1% |
| 36-mo OS | 71.8% | 68.9% |

# Oligometastases- Real Life

*JNCI Cancer Spectrum* (2021) 5(3): pkab010

doi: 10.1093/jncics/pkab010
First published online 4 February 2021
Article

## Characterization of Oligometastatic Disease in a Real-World Nationwide Cohort of 3447 Patients With de Novo Metastatic Breast Cancer

Tessa G. Steenbruggen, MD,[1] Michael Schaapveld, PhD,[2] Hugo M. Horlings, MD, PhD,[3] Joyce Sanders, MD, PhD,[3] Sander J. Hogewoning, MSc,[4] Esther H. Lips, PhD,[5] Marie-Jeanne T. Vrancken Peeters, MD, PhD,[6] Niels F. Kok, MD, PhD,[6] Terry Wiersma, MD,[7] Laura Esserman, MD, PhD[8] Laura J. van 't Veer, PhD,[9] Sabine C. Linn, MD, PhD,[1,10] Sabine Siesling, PhD,[4,11]

**Table 3.** Multivariable model of associations with overall survival in a weighed cohort of patients with oligometastatic breast cancer (≤3 metastases)

| Characteristic | Adjusted hazard ratio (95% CI)[a] | P |
|---|---|---|
| Local therapy primary tumor[c] | | |
| Yes | 0.58 (0.37 to 0.89) | .01 |
| No | Referent | |
| Local therapy metastases[d] | | |
| Yes | 0.57 (0.36 to 0.90) | .02 |
| No | Referent | |

In multivariable analyses, premenopausal and perimenopausal status, absence of lung metastases, and **local therapy of metastases (surgery and/or radiotherapy) added to systemic therapy were statistically significantly associated with better OS** and progression-free survival in OMBC, independent of local therapy of the primary tumor

# Primary Tumour treatment

## NCCN Guidelines Breast Cancer Version 2.2023

*“consideration of surgery after initial systemic treatment for those requiring palliation of symptoms or with impending complications, such as skin ulceration, bleeding, fungation, and pain”*

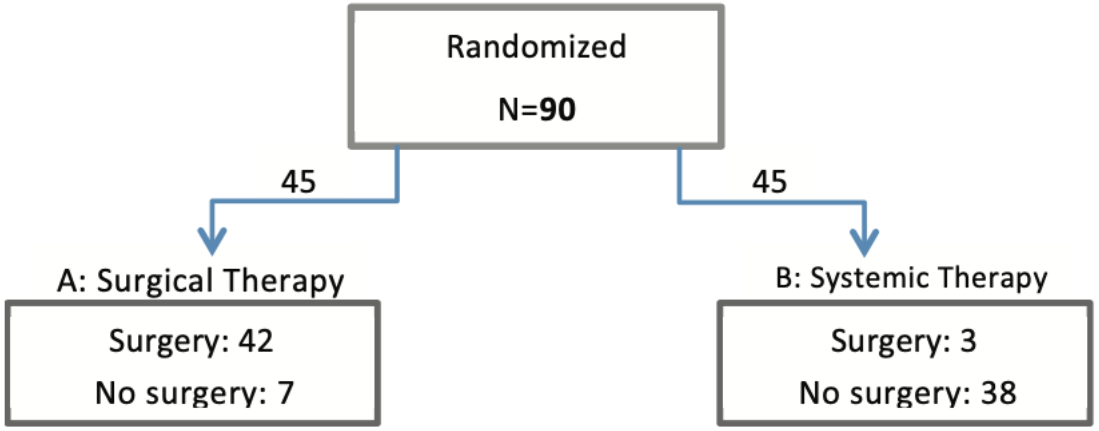
## ESMO Clinical Practice Guideline

*Surgery of the primary tumour may be considered for patients with bone-only metastasis, HR-positive tumours, HER2-negative tumours, patients <55 years, patients with Oligometastatic Diseas and those with a good response to initial systemic therapy [II, B]*

*Annals of Oncology, 2021*

# Primary Tumour treatment

**ABCSG-28 POSYTIVE Trial**




Inclusion criteria:

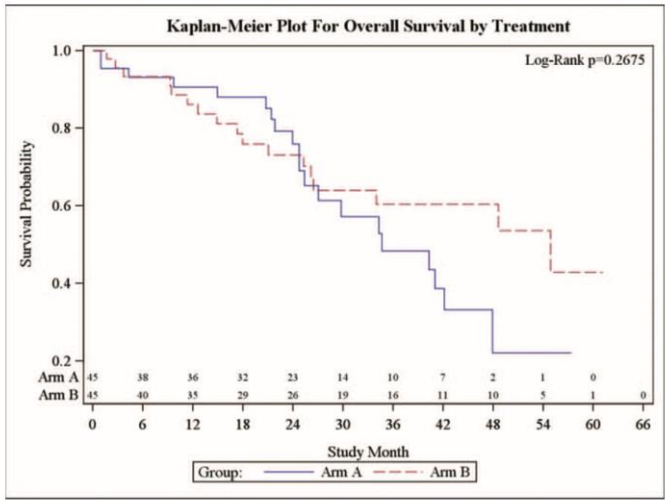
- age > 18 years
- Eastern Cooperative Oncology Group (ECOG) Performance Status Grade 0 to 2
- operable breast cancer of any size
- de novo metastatic breast cancer

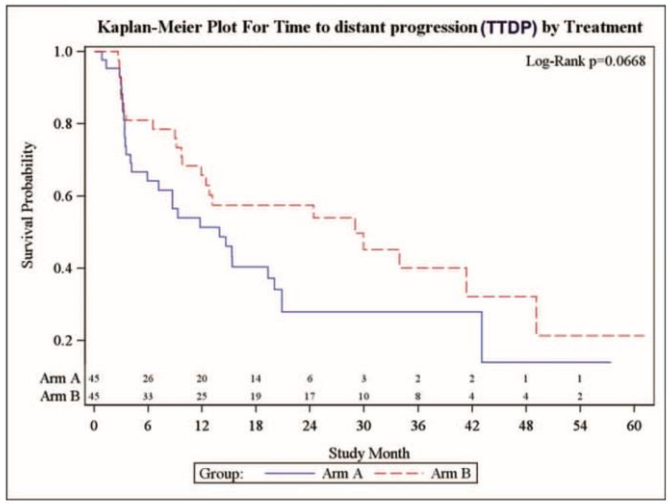
Exclusion criteria:

- inflammatory cancer
- brain metastases
- patient not eligible for general anesthesia and surgery

*F. Fitzal, Annals of Surgery Volume XX, Number XX, Month 2018*

# Primary Tumour treatment




Results:

- Median follow-up of 37.5 months
- Median OS: 42 months34.6 months in the surgery group and 54.8 in the nonsurgery group (HR for nonsurgery 0.691; 95% CI 0.358–1.333;P= 0.267)
- Time to distant progression (TTDP): 13.9 months in the surgery arm and 29.0 in the nonsurgery arm (HR 0.598; 95% CI 0.343–1.043; P= 0.0668; Fig. 3)
- Time to loco-regional progression (TTLP) was similar between the 2 arms,with a trend toward a lower number of patients with local progression in surgery Arm A (8.9% vs 17.8%; P=0.2148)
- cT3 and cN2 tumors were more represented in the surgery arm (22.2% vs 6.7% and 15.6% vs 4.4% respectively)
- This study was underpowered as it was stopped early due to poor recruitment

*F. Fitzal, Annals of Surgery Volume XX, Number XX, Month 2018*

# Primary Tumour treatment

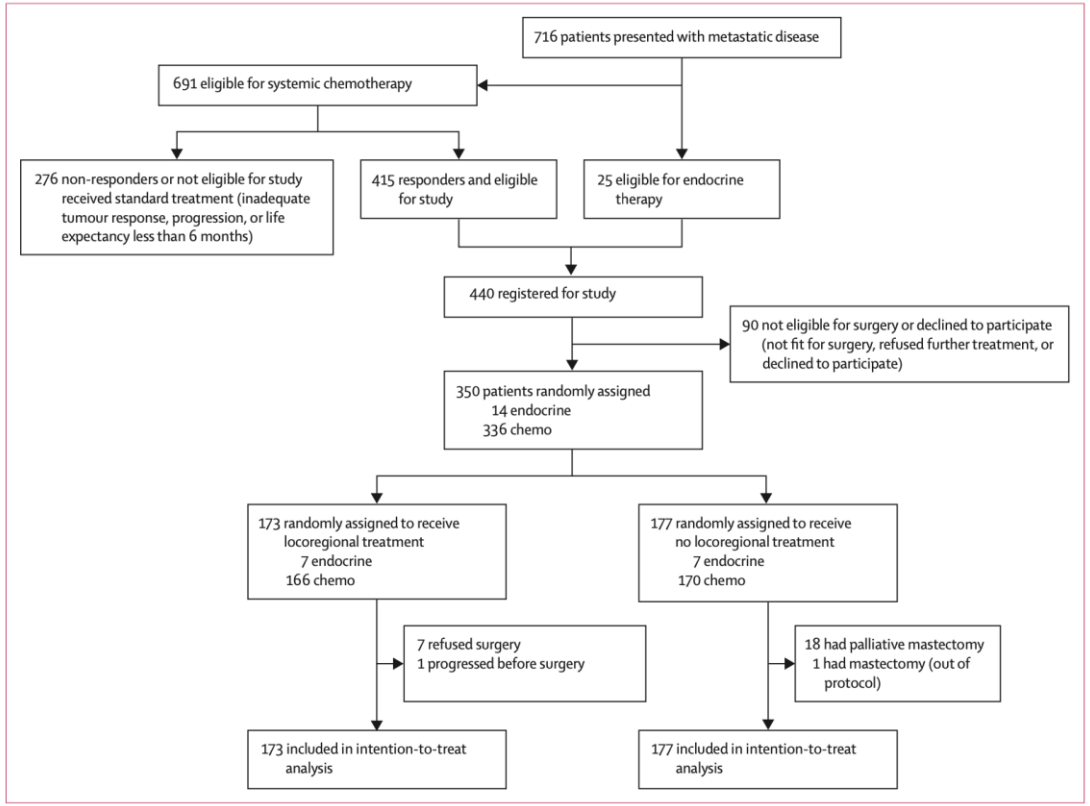
**Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial**

*Rajendra Badwe, Rohini Hawaldar, Nita Nair, Rucha Kaushik, Vani Parmar, Shabina Siddique, Ashwini Budrukkar, Indraneel Mittra, Sudeep Gupta*

- Feb 7, 2005 - Jan 18, 2013

- Inclusion criteria:

  - ≤65 years of age
  - an estimated remaining life expectancy of at least 1 year)
  - de-novo metastatic breast cancer (with measurable and non-measureable disease)
  - fit to receive anthracycline chemotherapy (adequate cardiac and liver functions)

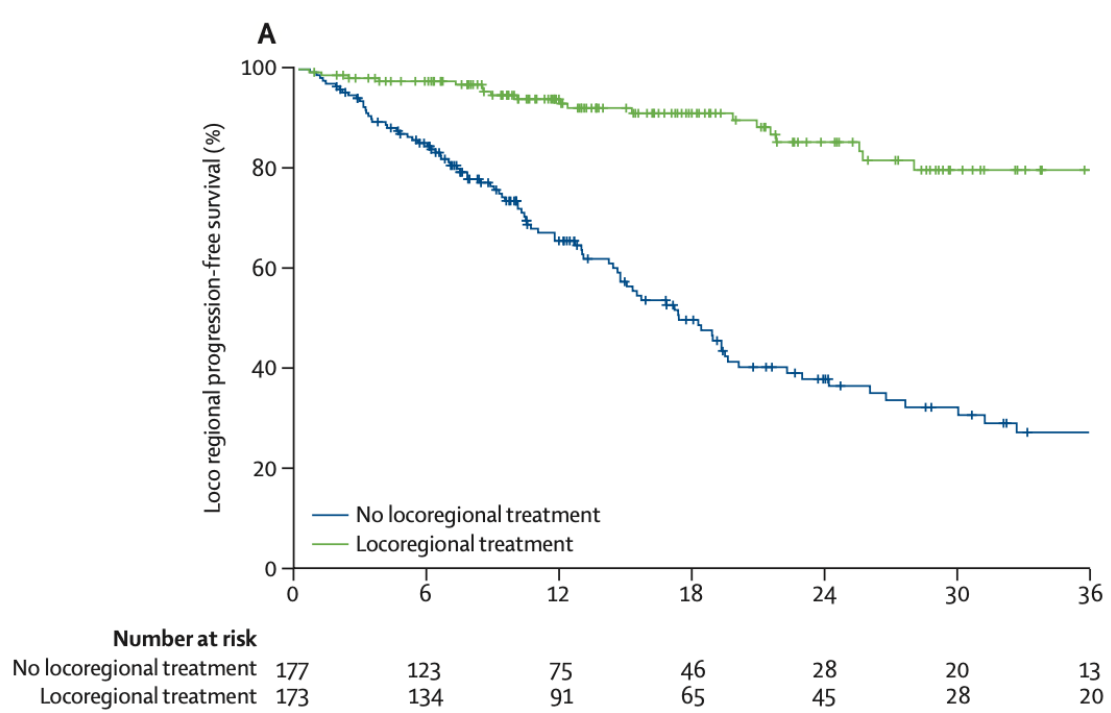


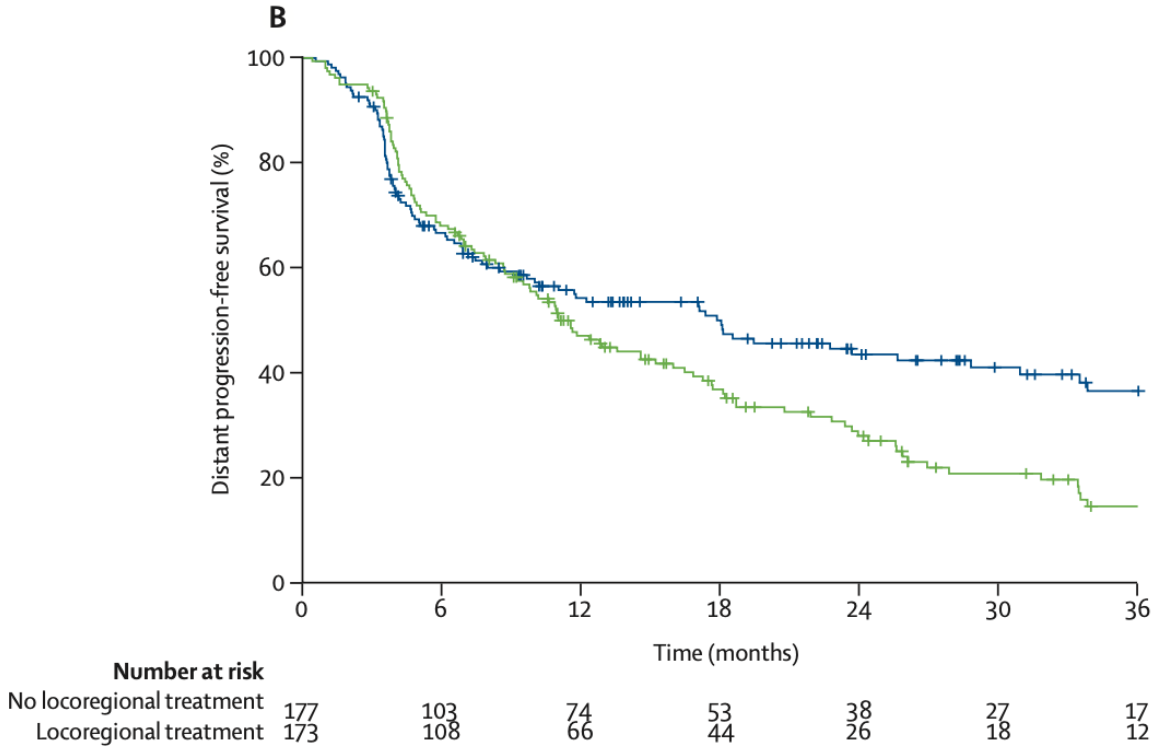

*Badwe, Lancet Oncol, 2015*

# Primary Tumour treatment

## Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial

Rajendra Badwe, Rohini Hawaldar, Nita Nair, Rucha Kaushik, Vani Parmar, Shabina Siddique, Ashwini Budrukkar, Indraneel Mittra, Sudeep Gupta

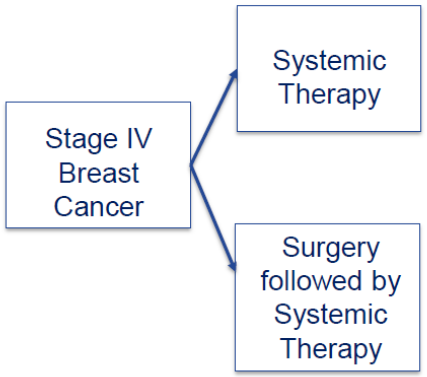


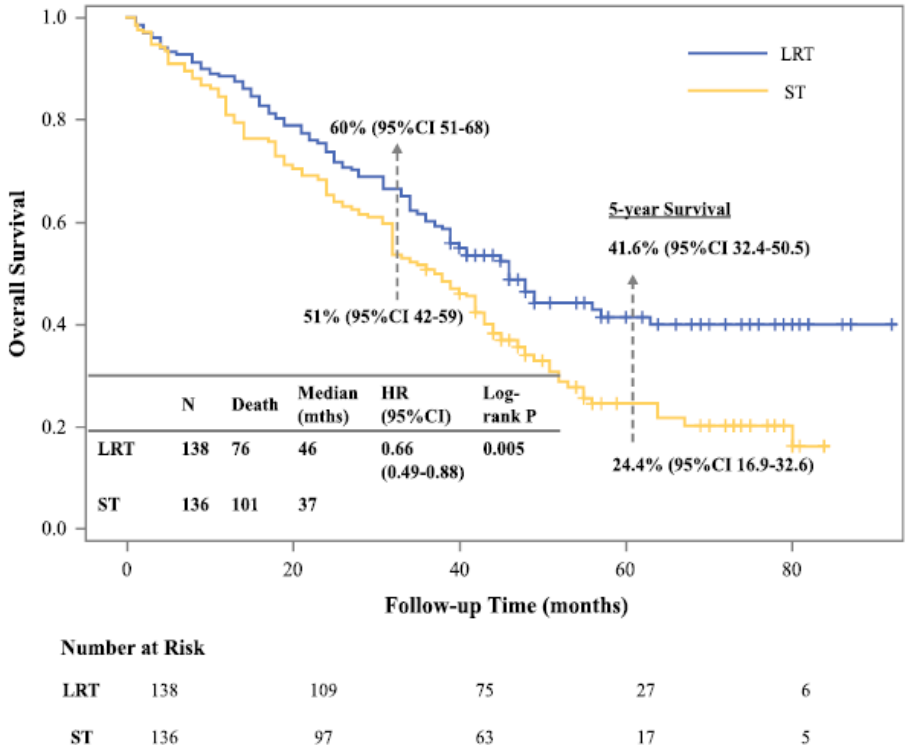




*Badwe, Lancet Oncol, 2015*

# Primary Tumour treatment – Turkish Trial, MF07-01

- N=274
- Primary endpoint = OS
- Assumed local therapy would ↑ 3-yr OS 18% (17%→35%)
- All patients received chemotherapy
- HR+ and HER2+ patients received targeted therapy




Median f/u 18 mo: No difference in OS

- HR=0.76 (0.49-1.16) p=0.20

Median f/u 40 mos: Difference in OS

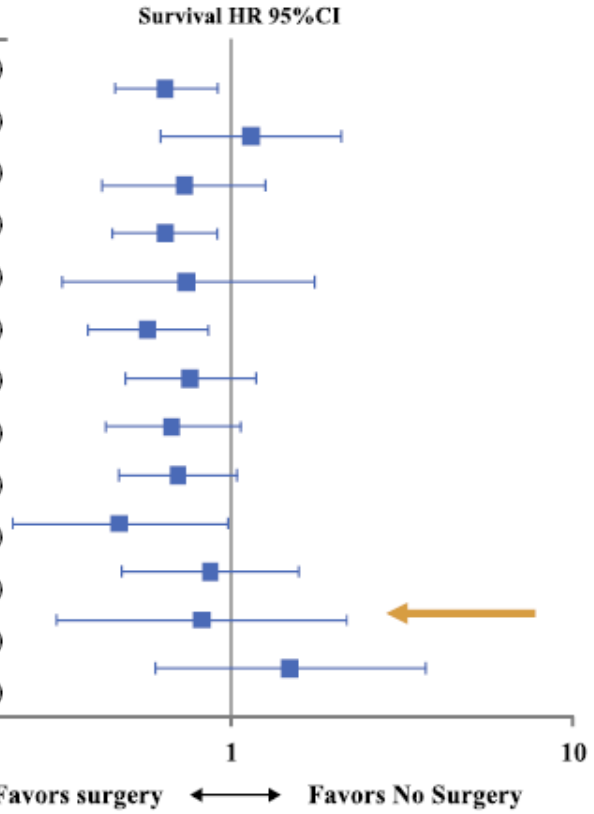
- HR=0.66 (0.49-0.88) p=.005

*Soran A et al. Ann Surg Oncol 2018*

# Primary Tumour treatment – **Turkish Trial, MF07-01**

## Unplanned, exploratory subgroup analyses

| Subgroup | Surgery Event | Surgery Total | No Surgery Event | No Surgery Total | Hazard Ratio (95% CI) |
|---|---|---|---|---|---|
| ER/PR Positive | 59 | 118 | 69 | 97 | 0.63 (0.44, 0.89) |
| ER/PR Negative | 31 | 38 | 30 | 36 | 1.22 (0.67, 2.23) |
| HER2 Positive | 23 | 42 | 29 | 42 | 0.73 (0.42, 1.26) |
| HER2 Negative | 53 | 96 | 71 | 93 | 0.64 (0.45, 0.91) |
| Triple Negative | 7 | 10 | 21 | 23 | 0.74 (0.32, 1.75) |
| Age<55 | 39 | 79 | 59 | 80 | 0.57 (0.38, 0.86) |
| Age≥55 | 37 | 59 | 42 | 56 | 0.76 (0.49, 1.18) |
| Bone only Met | 36 | 71 | 37 | 55 | 0.67 (0.43, 1.07) |
| Other Mets noBone | 40 | 67 | 64 | 81 | 0.7 (0.47, 1.04) |
| Solitary Bone Met | 14 | 33 | 15 | 20 | 0.47 (0.23, 0.98) |
| Multiple Bone Met | 22 | 38 | 22 | 35 | 0.87 (0.48, 1.58) |
| Solitary Pulmonary/Liver Met | 7 | 13 | 10 | 15 | 0.82(0.31, 2.18) |
| Multiple Pulmonary/Liver Met | 9 | 13 | 10 | 15 | 1.49 (0.60, 3.72) |




<u>Surgery associated w/improved survival</u>:

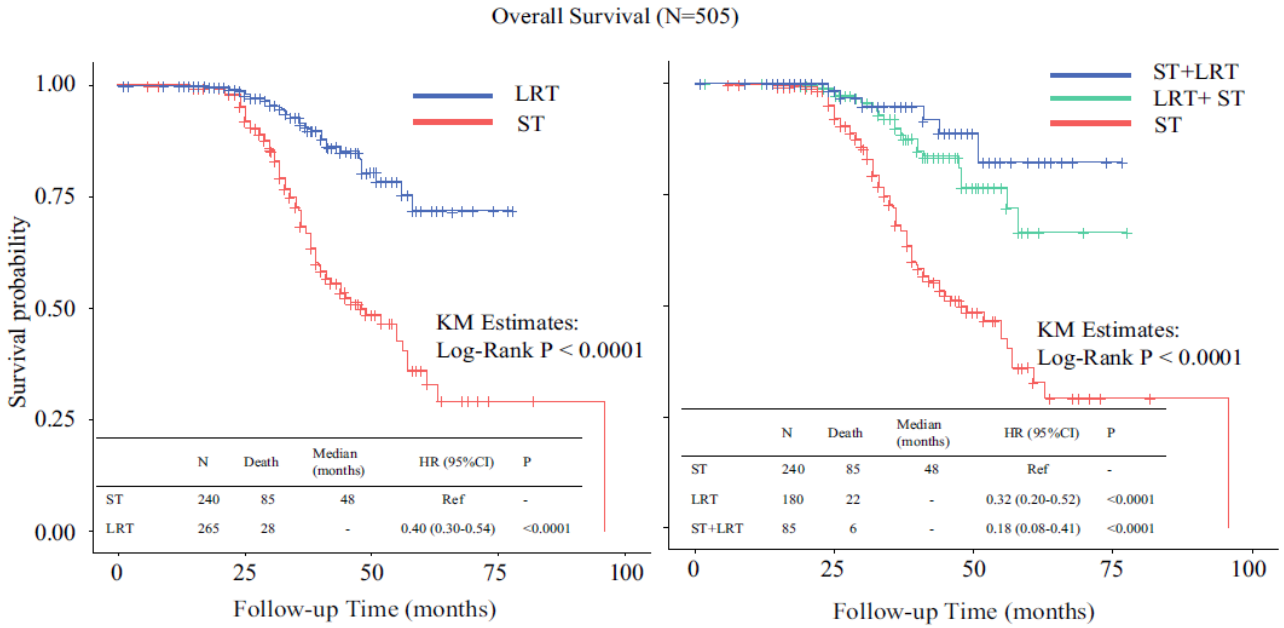
- ER/PR+
- HER2 –
- Age <55
- Solitary bone mets

*Soran A et al. Ann Surg Oncol 2018*

# Primary Tumour treatment – BOMET MF 14-01

- Prospective Multicenter Registry
- N=505

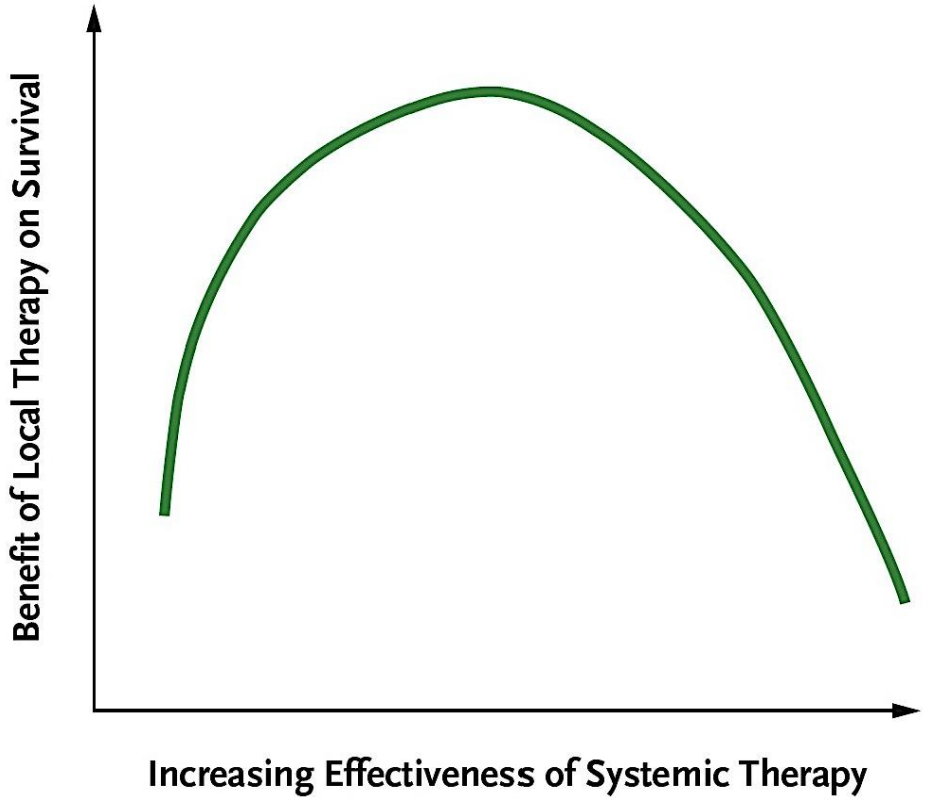
| | | ST n:240 (%) | LRT n:265 (%) | *P* |
|---|---|---|---|---|
| Age (mean, years ± SD) | | 54.0±13.8 | 51.1±12.9 | 0.02 |
| BMI (kg/m$^2$, mean ± SD) | | 28.3±4.5 | 27.8±4.5 | 0.21 |
| Median follow-up (months) | | 33 (25–41) | 34.9(24–45) | 0.66 |
| Tumor size | T1 | 28 (12) | 48 (18) | 0.0006 |
| | T2 | 192 (80) | 172 (65) | |
| | T3 | 20 (8) | 45 (17) | |
| Grade | I | 38 (16) | 27 (10) | 0.02 |
| | II | 95 (40) | 135 (51) | |
| | III | 107 (45) | 103 (39) | |
| Histology | IDC | 195 (81) | 218 (82) | 0.94 |
| | ILC | 20 (8) | 20 (8) | |
| | Other | 25 (10) | 27 (10) | |
| ER/PR (+) | | 206 (86) | 224 (85) | 0.67 |
| HER2/neu (+) | | 68 (28) | 76 (29) | 0.93 |
| Triple negative | | 20 (8) | 16 (6) | 0.32 |
| Bone metastasis number | Solitary | 76 (32) | 138 (52) | <0.0001 |
| | Oligometastases (< 4 metastases) | 128 (53) | 201 (76) | <0.0001 |
| | Multiple (≥ 4 metastases) | 111 (46) | 64 (24) | 0.003 |
| | > 5 metastases | 64 (27) | 41 (15) | 0.002 |




Prolonged survival in the median 3-year follow-up in favor of LRT of the primary (HR 0.40, p<0.0001)

*Soran A et al. Ann Surg Oncol 2021*

# Oligometastatic Disease - Conclusions




Contribution of improved locoregional control to survival depends on the effectiveness of systemic treatment

In this model the component of metastatic risk of the primary tumor is missing

Punglia RS, et al. N Engl J Med 2007


Punglia RS, et al. N Engl J Med 2007

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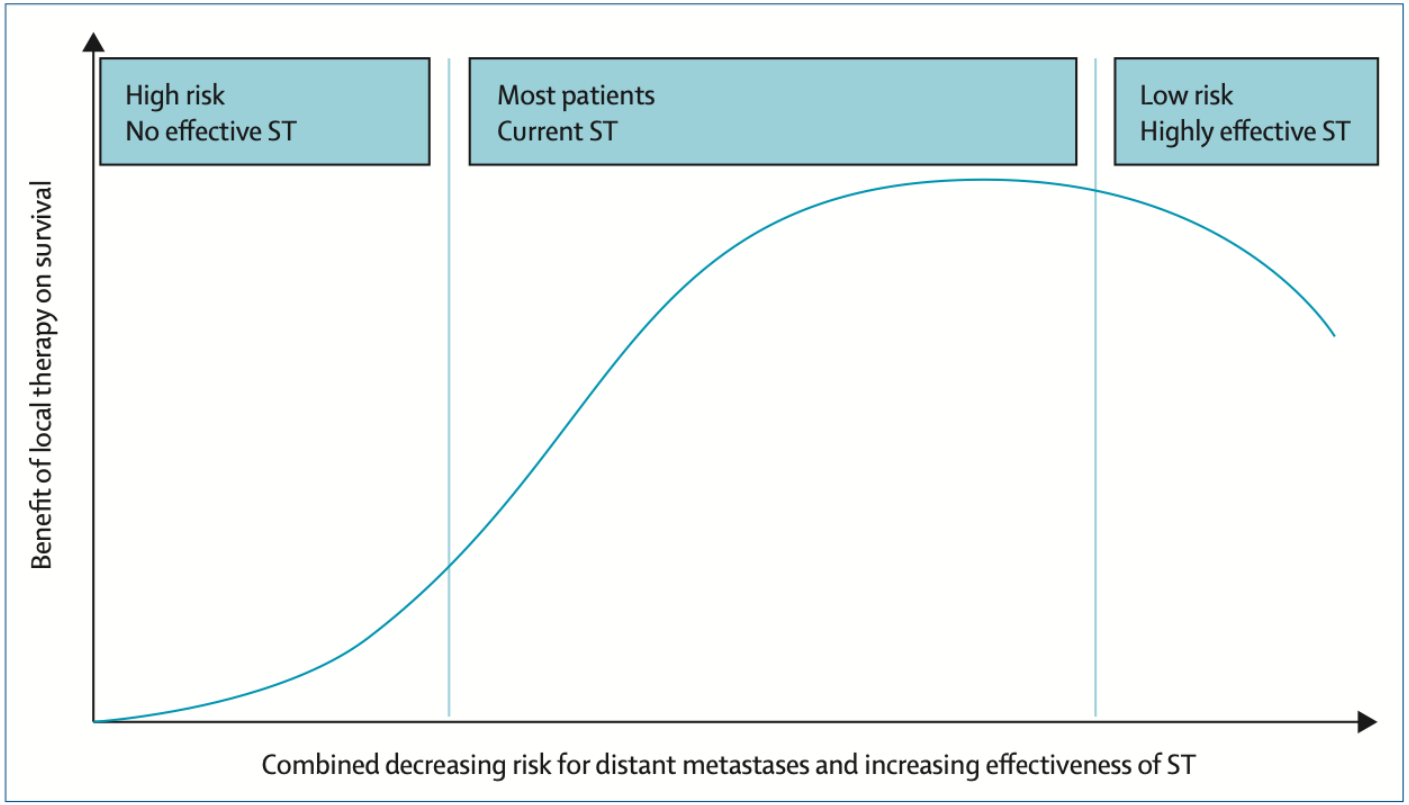



The influence of **both the effectiveness of systemic therapy and metastatic risk of the primary tumor** can be used to estimate the contribution of improved locoregional treatment to the final outcome

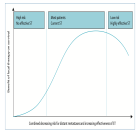
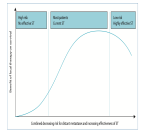
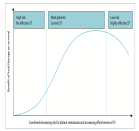
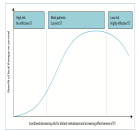
**Poortmans P, et al.** lancet 2014



Punglia RS, et al. N Engl J Med 2007

# Oligometastatic Disease - Conclusions

## Aims to locoregional treatment

- To prolong local control 
- To postpone further systemic therapy 
- To improve DFS/PFS/OS 
- To treat symptomatic critical sites 



Punglia RS, et al. N Engl J Med 2007

# Oligometastatic Disease – *Who? When? What?*

## Identification of metastatic patients suitable for *curative* treatment

- *prognostic/predictive models for patients selection*

## Improvement of *diagnostic* accuracy

- *metabolic imaging? CTC's? detection of minimal drug-resistant residual disease?*

## Combining SRT with *drugs* to investigate interactions

- high-dose radiotherapy, systemic immune cascade, regression of distant non-irradiated lesions

**Tharmalingham H, et al.** Tech Inn Pat Sup Radi Onc 2017

# Le terapie locoregionali dovrebbero essere sempre associate alla terapia sistemica nella malattia oligometastatica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