

24-25 Marzo 2023

Ospedaletto di Pescantina (VR)
Centro Congressi Park Hotel Villa Quaranta

Coordinatori scientifici:
Stefania Gori
Giovanni L. Pappagallo



Radioterapia ablativa nel carcinoma mammario metastatico: quali evidenze?

Prof Marta Scorsetti
Humanitas University
Humanitas Research Hospital

Agenda

- Definition of oligometastases
- Local therapies for oligometastases
- Oligometastases in breast cancer
- Clinical evidences
- Future directions

Oligometasts definition

EDITORIAL

Oligometastases

CANCER TREATMENT is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted^{1,2} clearly elucidated a mechanism of breast cancer spread and used it to design and support the radical mastectomy, surgical and radiotherapeutic approaches to most cancers have been based on this theory. The Halsted theory proposed that cancer spread is orderly, extending in a contiguous fashion from the primary tumor through the lymphatics to the lymph nodes and then to distant sites. Radical en bloc resection, as radical neck dissection in continuity with the primary tumor, radical hysterectomy with regional irradiation for a variety of gynecologic cancers, and the use of regional irradiation based on this notion of cancer spread have been based on this hypothesis. Another hypothesis has gained prominence in the past decade, suggested with regard to breast cancer.³⁻⁵ This hypothesis proposes that clinically apparent systemic disease. Small tumors are not a manifestation of such systemic disease. A tumor that is able to metastasize, has already metastasized. Systemic involvement is not orderly contiguous extension, but rather a marker of distant disease. Systemic metastases are multiple and widespread, and when subclinical are referred to as micrometastases. Under these circumstances, treatment of local or regional disease should not affect survival.

more about the multistep nature of the development of malignancy.¹¹⁻¹³ Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread.¹⁴ Therefore the likelihood, number, and even sites of metastases may reflect the state of tumor development. This suggests that there are tumor states intermediate between purely localized lesions and those widely metastatic. Such clinical circumstances are not accounted for by either the contiguous

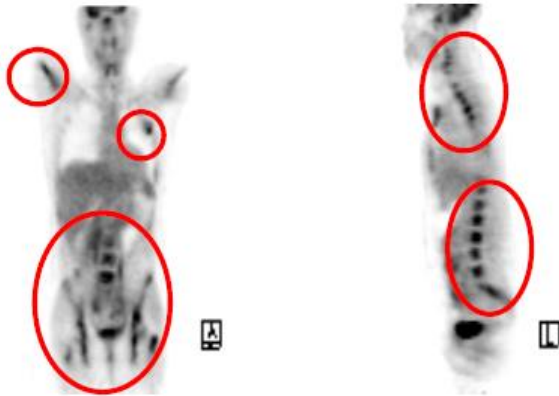
An oligometastatic state is an “intermediate state between purely localized lesions and those widely metastatic”. The state was expounded to be “amenable to a curative therapeutic strategy” and “amenable to localized therapy”.

or concentrate these metastases to a single or a limited number of organs. The likelihood of the oligometastatic state should correlate with the biology of tumor progression, rough clinical surrogates of which, for many tumors, might be primary tumor size and grade. Metastasizing cells may seed specific organs as a function of the seeding

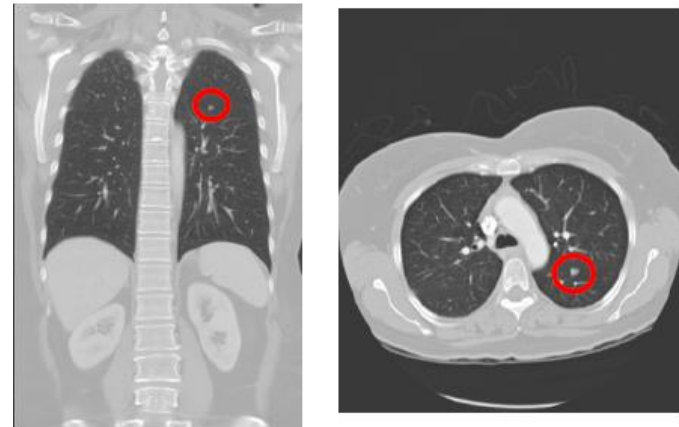
Hellman S, Weichselbaum RR. JCO 1995

Oligometets definition

Widely Metastatic Disease



Limited Metastatic Disease



- Distinct clinical state
- Metastases limited in number/destination organ (3 to 5 in 1-3 sites)
- More indolent biology earlier in the metastatic cascade
- Amenable to local ablative approaches

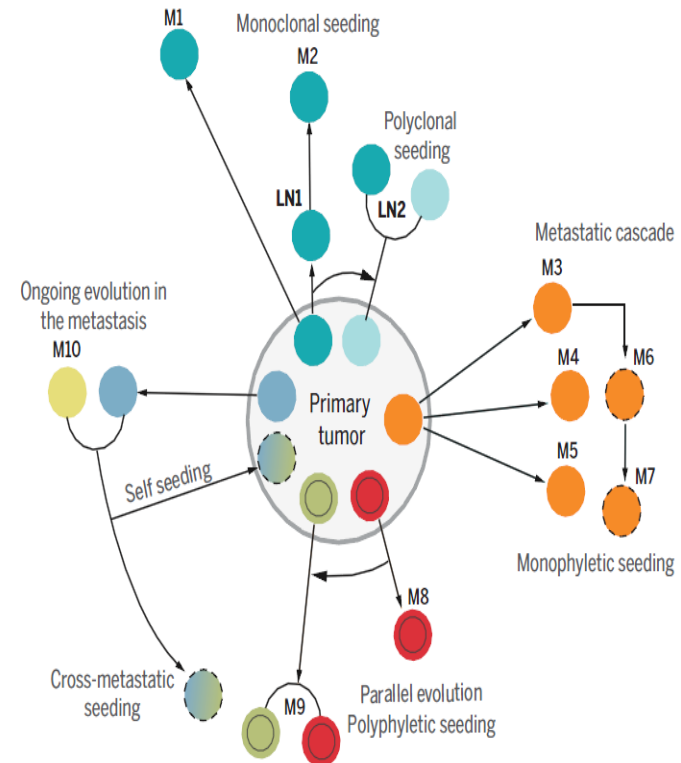
Oligometets definition

REVIEW

Metastasis as an evolutionary process

Samra Turajlic^{1,2} and Charles Swanton^{1,3*}

**Very complex
reality**



Palma D, WCLC 2018

Oligometas definition

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, Angélique 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

Consensus

Defining oligometastatic disease from a radiation oncology perspective:
An ESTRO-ASTRO consensus document



Yolande Lievens^{a,*}, Matthias Guckenberger^b, Daniel Gomez^c, Morten Hoyer^d, Puneeth Iyengar^e,
Isabelle Kindts^f, Alejandra Méndez Romero^g, Daan Nevens^h, David Palmaⁱ, Catherine Park^j,
Umberto Ricardi^k, Marta Scorsetti^l, James Yu^m, Wendy A. Woodward^c

*Guckenberger M et al. Lancet Oncol 2020
Lievens Y et al. RO 2020*

Oligomets definition

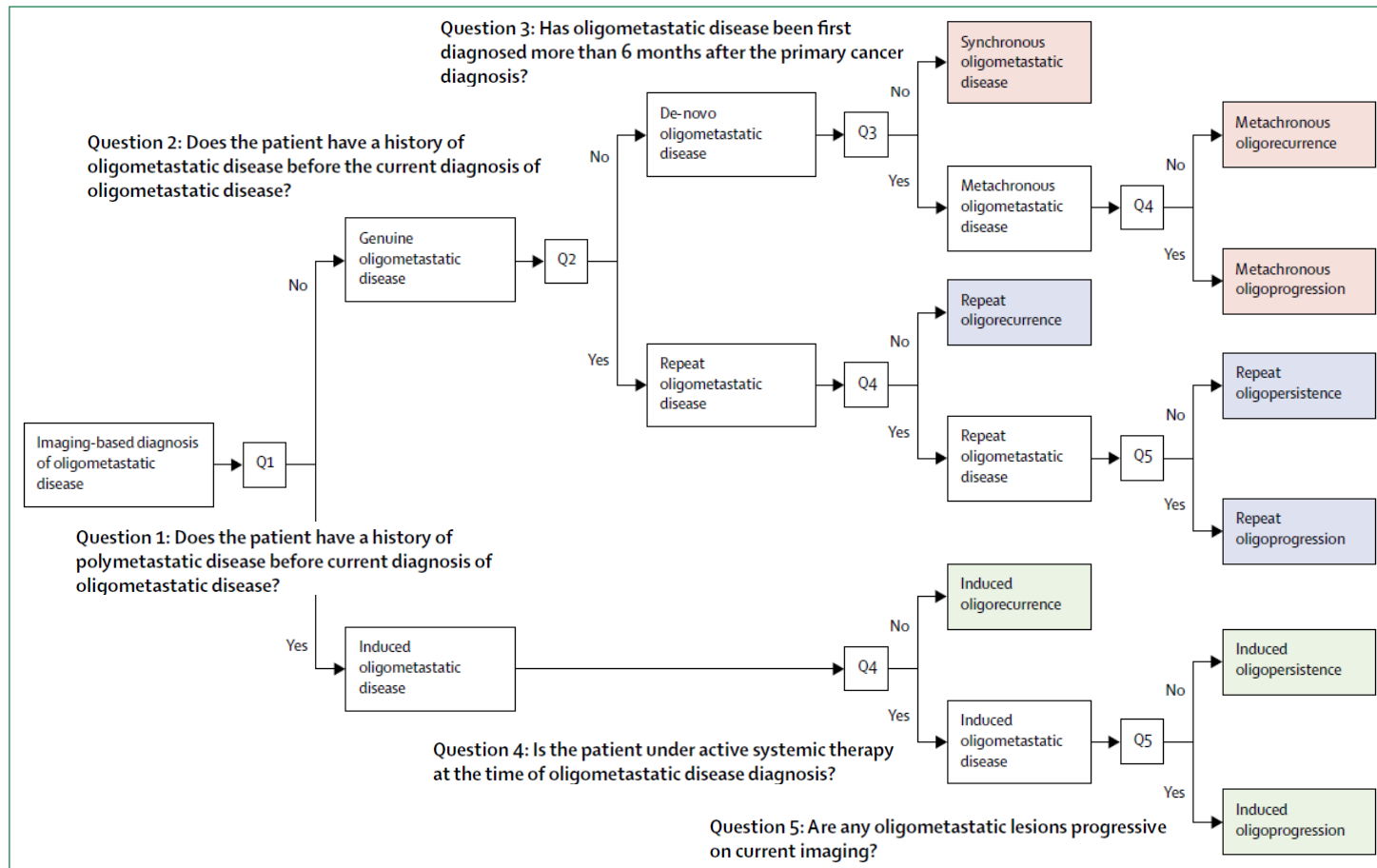
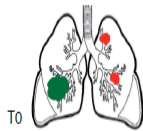


Figure 3: Decision tree for classification of oligometastatic disease

Oligometets definition

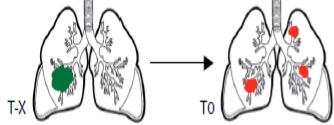
A De-novo oligometastatic disease

Synchronous oligometastatic disease



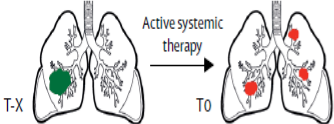
- T0: first time diagnosis of primary cancer (green) and oligometastases (red) within 6 months

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 oligopersistence



- 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

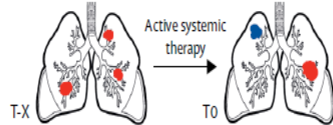
B Repeat oligometastatic disease

Repeat oligorecurrence



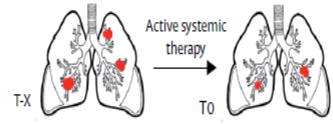
- T-X: diagnosis of oligometastases followed by local treatment or systemic treatment or both
- Systemic therapy-free interval
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases

Repeat oligopersistence



- 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

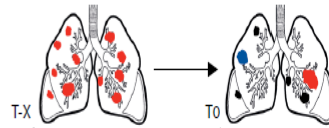
Repeat oligopersistence



- 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

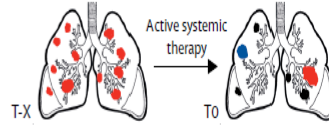
C Induced oligometastatic disease

Induced oligorecurrence



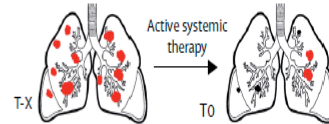
- T-X: diagnosis of polymetastatic metastatic disease followed by systemic treatment with or without local treatment
- Systemic therapy-free interval
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases, possible residual non-progressive metastases (black)

Induced 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 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)

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

Oligometastases are a heterogeneous scenario

Guckenberger M et al. Lancet Oncol 2020

Agenda

- Definition of oligometastases
- **Local therapies for oligometastases**
- Oligometastases in breast cancer
- Clinical evidences
- Future directions

Oligometets: rationale for local treatment

- **Increase local control** to prevent symptoms and maintain quality of life
- Ablate all visible metastases **to prolong PFS**
- Reduce tumor burden **to prolong OS**
- Ablate resistant clones **to prolong systemic therapy efficacy**
- **Delay further disease progression** to delay the need to start systemic therapy
- **Synergize with systemic therapies** to improve outcomes

Local ablative therapies: surgery

The Rise in Metastasectomy Across Cancer Types Over the Past Decade

Historically, the **role of surgery in patients with metastatic cancer** was predominately limited to **palliative or emergent operations**.

By the 1980s, a few centers were consistently performing **surgical resections for select patients** with metastatic cancer and reporting **promising results**. In addition, theories of cancer biology began to suggest that **in a subset of patients, oligometastatic disease might indeed represent the entire clinically relevant disease burden**.

In these cases, **complete resection was associated with prolonged disease-free survival and, in some patients, clinical cure**. As a result, in selected patients surgical resection is now considered for the treatment of oligometastatic disease to most anatomic sites from many different primary cancer types

Local ablative therapies: surgery

Of the 5 most common cancer types, **colorectal cancer** has been the subject of the largest number of studies of metastasectomy with demonstrated **5-year survival rates of >50%, and 10-year survival ranging from 17% to 36%.**

The role of metastasectomy in **other cancer types remains more controversial.** Multiple metastasectomy series have now been published for **breast cancer, lung cancer, and melanoma**, all of which with relatively favorable survival in carefully selected patients, but the series are smaller and less frequently report long-term follow-up.

TABLE 1. National Estimates of Admissions for Metastasectomy by Cancer Type, 2000 Through 2011

	Colorectal Cancer		Lung Cancer		Breast Cancer		Melanoma	
	No.	95% CI	No.	95% CI	No.	95% CI	No.	95% CI
All admissions	87,407	(86,307-88,507)	58,245	(57,453-59,036)	26,271	(25,672-26,870)	20,298	(19,897-20,699)
Mean age (SE), y	62.2	0.10	61.4	0.10	56.8	0.17	58.1	0.22
Female sex	46.0%	(45.3%-46.8%)	45.8%	(44.9%-46.7%)	99.4%	(99.2%-99.6%)	33.6%	(32.2%-35.1%)
Liver metastasectomy	41,312	(40,500-42,125)	503	(405-601)	1663	(1486-1839)	550	(448-652)
Lung metastasectomy	19,590	(18,994-20,185)	NA ^a	NA ^a	6609	(6266-6951)	5839	(5534-6144)
Brain metastasectomy	5588	(5263-5912)	52,944	(52,167-53,720)	16,091	(15,591-16,590)	11,094	(10,718-11,471)
Small bowel metastasectomy	20,916	(20,303-21,529)	2762	(2535-2988)	1724	(1544-1905)	2440	(2233-2646)
Adrenal metastasectomy	599	(493-705)	2067	(1870-2264)	230	(165-295)	471	(377-566)
Mean no. of Elixhauser comorbidities	1.98	(1.96-2.00)	2.72	(2.69-2.75)	1.87	(1.83-1.91)	1.84	(1.80-1.88)
Inpatient mortality rate	2.13%	(1.91%-2.34%)	3.18%	(2.86%-3.51%)	1.91%	(1.54%-2.28%)	1.65%	(1.26%-2.04%)

Local therapies for oligometastases

Metastasectomy increases local control with significant improvement of survival in selected patients



Most patients are inoperable for comorbidities or sites of metastases



Stereotactic body radiation therapy



AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY (ASTRO) AND AMERICAN COLLEGE OF RADIOLOGY (ACR) PRACTICE GUIDELINE FOR THE PERFORMANCE OF STEREOTACTIC BODY RADIATION THERAPY

LOUIS POTTERS, M.D.,* BRIAN KAVANAGH, M.D.,[†] JAMES M. GALVIN, D.Sc.,[‡] JAMES M. HEVEZI, Ph.D.,[§]
NORA A. JANJAN, M.D.,[¶] DAVID A. LARSON, M.D., Ph.D.,** MINESH P. MEHTA, M.D.,^{††}
SAMUEL RYU, M.D.,^{‡‡} MICHAEL STEINBERG, M.D.,^{§§} ROBERT TIMMERMAN, M.D.,^{¶¶}
JAMES S. WELSH, M.D.,*** AND SETH A. ROSENTHAL, M.D.^{†††}

Stereotactic body radiation therapy (SBRT) is an external beam radiation therapy method used to very precisely deliver a **high dose of radiation** to an extracranial target within the body, using either a **single dose or a small number of fractions**.

The ability to deliver a **single or a few fractions of high-dose ionizing radiation** with **high targeting accuracy** and rapid dose falloff gradients encompassing tumors within a patient provides the basis for the development of SBRT.

Stereotactic body radiation therapy

Goals are:

- margin reduction:
 - Reduce volume of normal tissue irradiated
 - **Reduce normal tissue toxicity**

- increase dose per fraction:
 - Deliver ablative doses
 - **Increase efficacy**



Stereotactic body radiation therapy

● SBRT PRO

- Non invasive
- Low toxicity
- Possible for almost every patient and every body site
- Possibility to treat multiple lesions simultaneously
- Possibility to be delivered with the majority of systemic therapies

● SBRT CONS

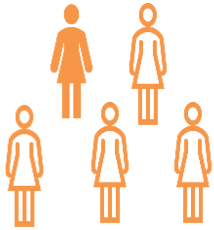
- No histopathological confirmation
- No tissue for further analysis



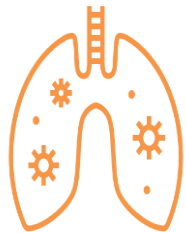
Agenda

- Definition of oligometastases
- Local therapies for oligometastases
- **Oligometastases in breast cancer**
- Clinical evidences
- Future directions

Oligometastases in breast cancer



- **5-10%** of patients present with metastatic disease
- **20% of patients** with localized disease **will develop metastases** within 5 years of their initial diagnosis
- Disease tends to reoccur at previously known sites of metastasis
- **Oligometastatic** breast cancer accounts for **20% of metastatic breast cancer** patients



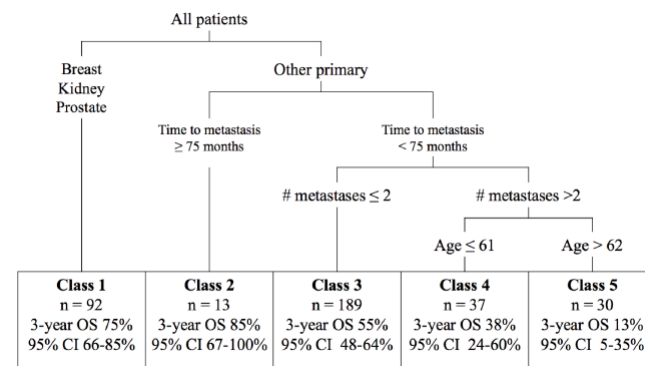
Oligometastases in breast cancer

Stereotactic body radiotherapy for oligometastases

- Patients most likely to benefit from stereotactic body radiotherapy have:
 - Long disease-free interval
 - Breast histology
 - One to three metastases
 - Small metastases
 - Higher radiation dose delivered (biologic effective dose >100 Gy)

Tree AC et al. Lancet Oncology 2013

Classification for long-term survival in oligometastatic patients treated with ablative radiotherapy: A multi-institutional pooled analysis



Hong JC et al. PlosONE 2018

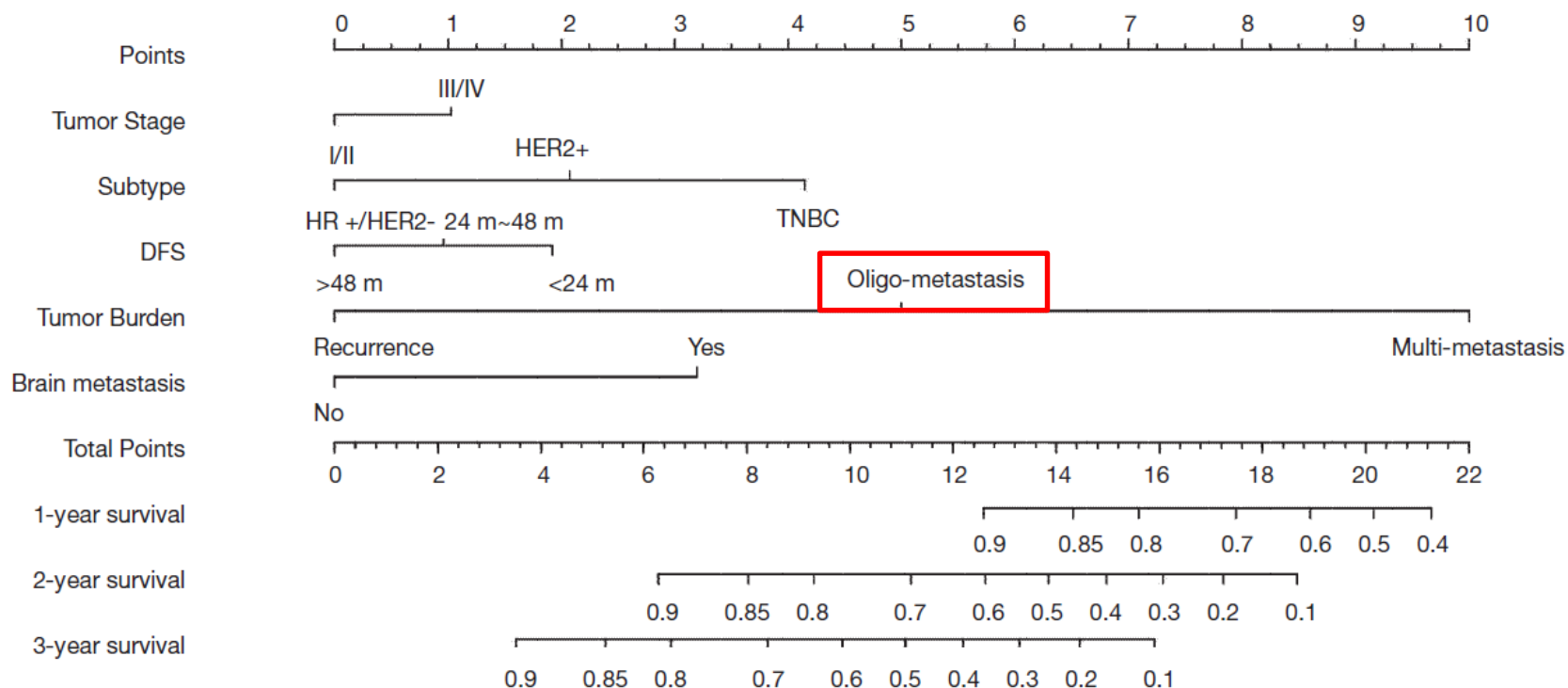
Clinical and Molecular Markers of Long-Term Survival After Oligometastasis-Directed Stereotactic Body Radiotherapy (SBRT)

Multivariate analysis			
Breast cancer histology	0.12	0.07-0.37	< .05
Distant metastasis-free interval	0.98	0.98-0.99	< .05
Time from metastatic diagnosis to end of protocol treatment	0.98	0.98-0.99	< .05
Rate of progression	1.44	1.24-1.82	< .05

Wong AC et al. Cancer 2016

Oligometastases in breast cancer

Development and validation of a nomogram in survival prediction among advanced breast cancer patients



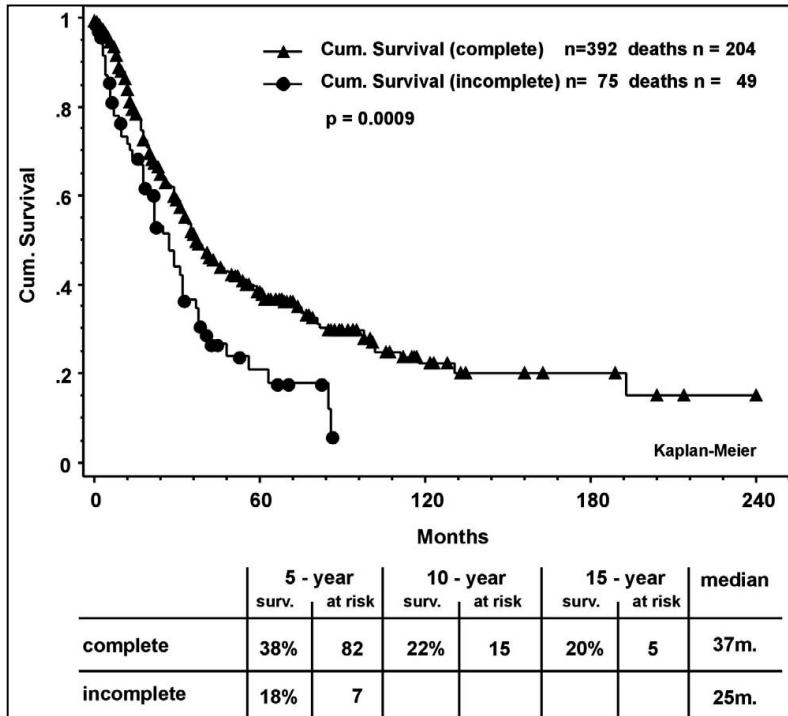
Agenda

- Definition of oligometastases
- Local therapies for oligometastases
- Oligometastases in breast cancer
- **Clinical results**
- Future directions

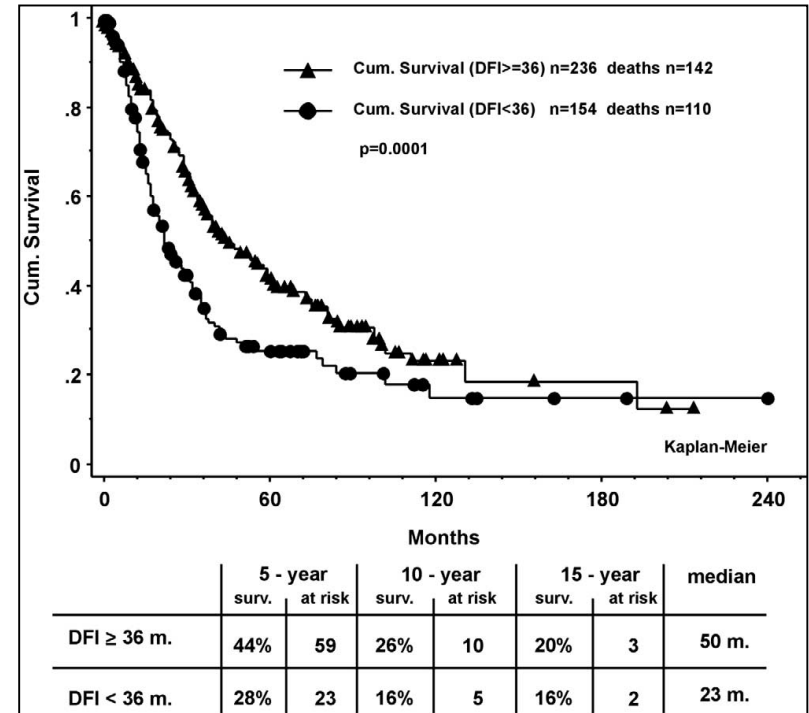
Clinical results: surgery



Results of lung metastasectomy from breast cancer: prognostic criteria on the basis of 467 cases of the international registry of lung metastases[☆]

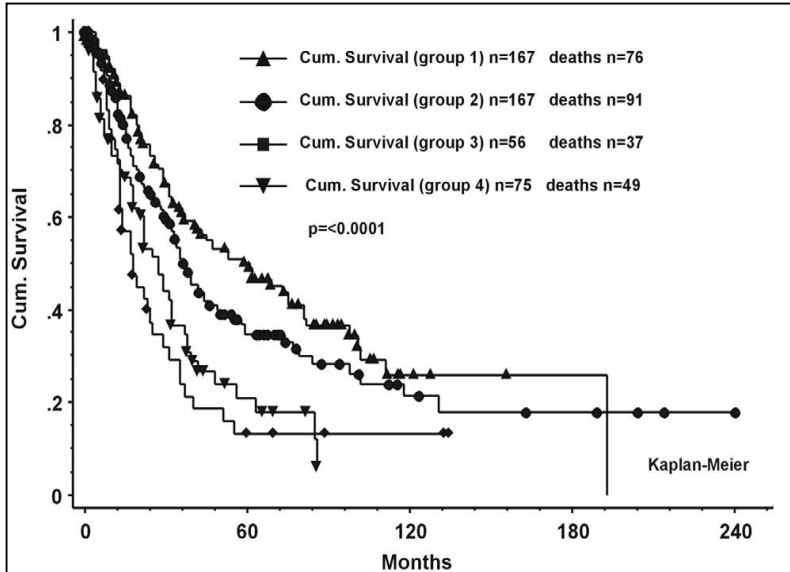


Complete resection better than incomplete



Better outcomes with longer disease free interval

Clinical results: surgery



	5 - year		10 - year		15 - year		median
	surv.	at risk	surv.	at risk	surv.	at risk	
Group 1 (no risk factor)	50%	47	26%	5	26%	1	59 m.
Group 2 (1 risk factor)	35%	31	21%	8	18%	4	36 m.
Group 3 (2 risk factors)	13%	4	13%	2			18 m.
Group 4 (incomplete res.)	18%	7					25 m.

Groups of factors that portend better outcomes

Group I: Complete resection, DFI \geq 36 months, solitary metastasis 5-year survival 50%, 10 and 15-year survival 26% with a median survival of 59 months.

Group II: Complete resection, DFI < 36 months or multiple metastases 5-year survival 35%, 10-year survival of 21% and 15-year survival of 18% with a median survival of 36 months.

Group III: complete resection, DFI < 36 months and multiple metastases survival after 5 and 10 years 13% with a median survival of 25 months.

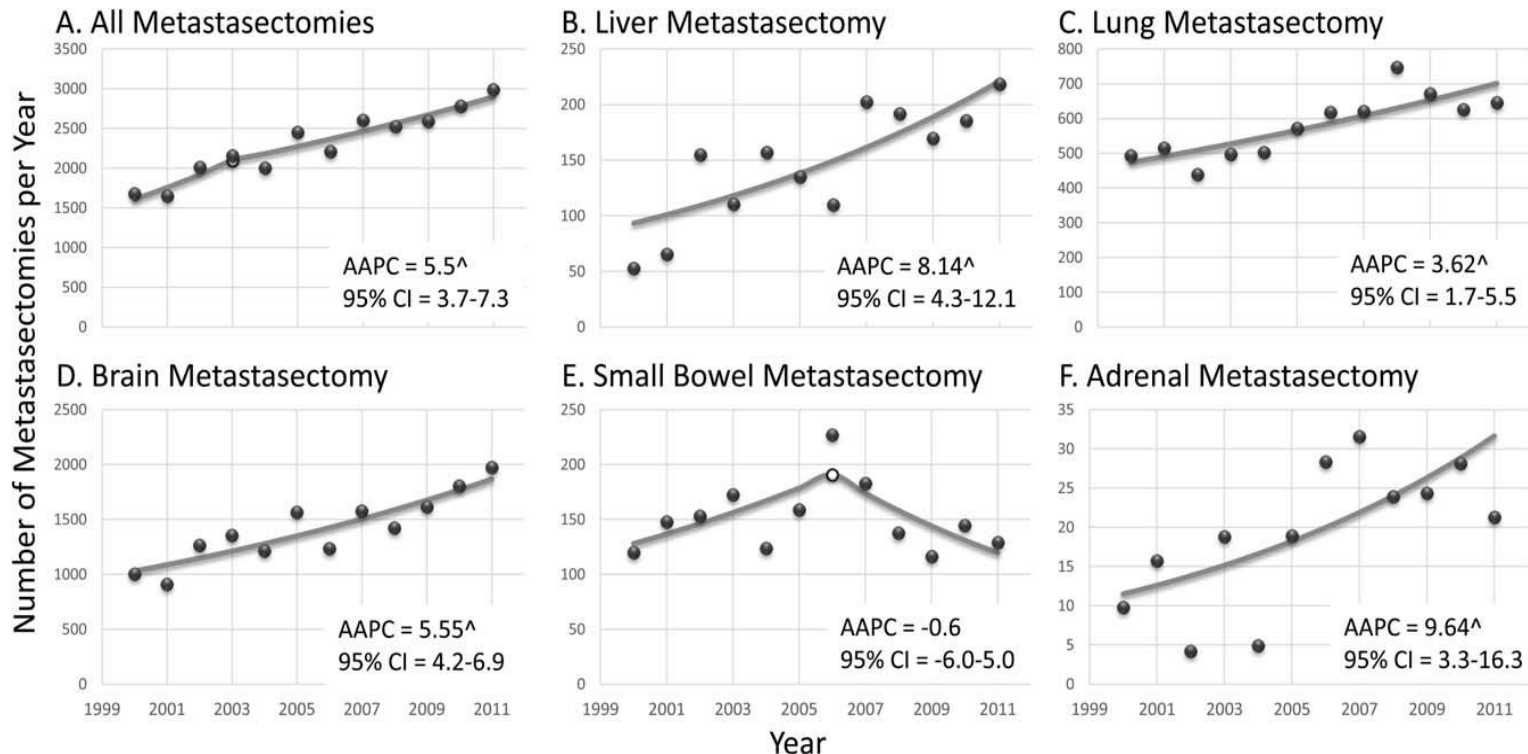
Group IV: Incomplete resection. Five-year survival of 18% with a median survival of 25 months.

In conclusion, this study with the largest documented number of resected lung metastases from breast cancer shows that **metastasectomy at present provides better long-term results** than chemotherapy and hormone therapy.

Clinical results: surgery

The Rise in Metastasectomy Across Cancer Types Over the Past Decade

Incidence-adjusted metastasectomies for breast cancer increased from 1680 metastasectomies to 2991 metastasectomies from 2000 to 2011



Clinical results: SBRT

Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial

Site of original primary tumor		
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)

Palma DA et al. JCO 2020

Progression-Free Survival and Local Control After SABR for up to 5 Oligometastases: An Analysis From the Population-Based Phase 2 SABR-5 Trial

Characteristic	Percentage (n)
Patient factors	
Sex: female	32% (122)
ECOG PS: 0; 1; 2	60% (227); 37% (139); 4% (15)
Decline in ECOG PS in preceding 6 mo	6% (23)
Current smoker	9% (33)
Tumor factors	
Primary histology: prostate; colorectal; breast; lung; renal cell carcinoma; head and neck*; melanoma; other†	32% (122); 17% (60); 11% (43); 9% (33); 9% (34); 5% (17); 5% (17); 14% (52)

Baker SA et al. IJROPB 2022

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

Primary tumour diagnosis	
Prostate cancer	406 (28.6%)
Colorectal cancer	397 (27.9%)
Renal cancer	143 (10.1%)
Breast cancer	78 (5.5%)
Lung cancer	64 (4.5%)
Melanoma	58 (4.1%)
Othert	276 (19.4%)

Chalkidou A et al. Lancet Oncol 2021

Clinical results: SBRT

Stereotactic Body Radiation Therapy for Lung and Liver Oligometastases from Breast Cancer: Toxicity Data of a Prospective Non-Randomized Phase II Trial

To evaluate stereotactic body radiation therapy schedules for liver and lung lesions in oligometastatic breast cancer in terms of safety and efficacy

PRIMARY ENDPOINTS

- Local control
- Acute and late toxicities

SECONDARY ENDPOINTS

- Distant progression free survival
- Overall survival

Clinical results: SBRT

Inclusion criteria

- >18 years
- Diagnosis of breast cancer
- ECOG performance status 0-2
- No life-threatening conditions
- Written informed consent
- **<= 5 Liver and lung lesions** with a maximum diameter of 5 cm
- Metastatic disease had to be confined to lungs and/or liver
- OR other metastatic sites stable or responding to chemotherapy

Exclusion criteria

- ECOG > 2
- Pregnancy
- Patients with inability to consent

Clinical results: SBRT

Acute toxicity	15 (23%)
G1	
Fatigue	7
Nausea and vomiting	4 (6%)
Abdominal pain	3 (5%)
Fever	1 (2%)
Malaise	1 (2%)
Chest pain	1 (2%)
G2	
Nausea and vomiting	2 (3%)

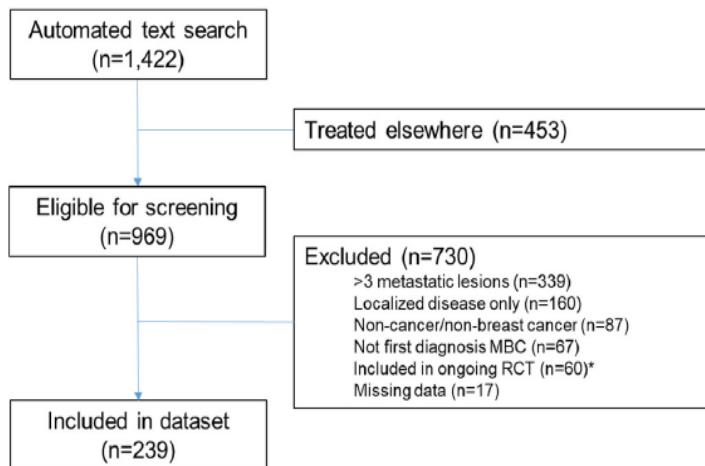
Late toxicity	9 (14%)
G1	
Chest pain	2 (3%)
Cough	1 (2%)
Pneumonia	1 (2%)
Gastritis	1 (2%)
Gastrointestina	1 (2%)
I pain	1 (2%)
Rib fracture	1 (2%)
G2	
Erythema	1 (2%)
Duodenal ulcer	1 (2%)

No patient experienced any \geq G3 toxicity

COPRIMARY ENDPOINT OF TOXICITY WAS MET
SURVIVAL OUTCOMES ARE STILL MATURING

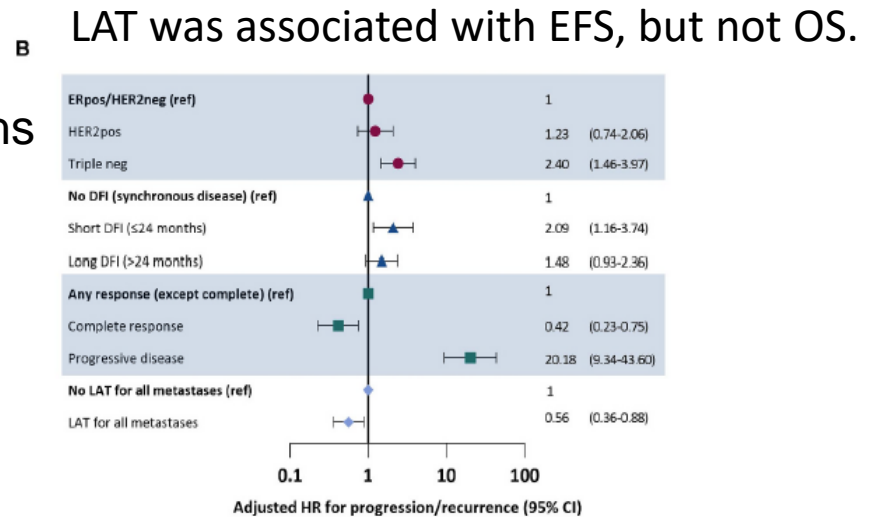
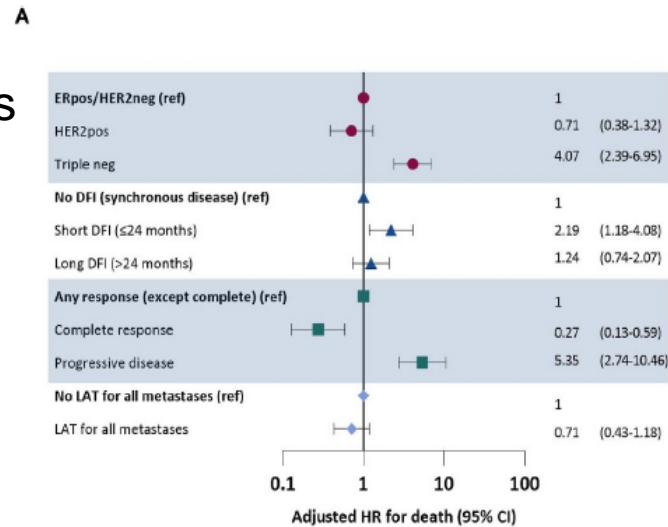
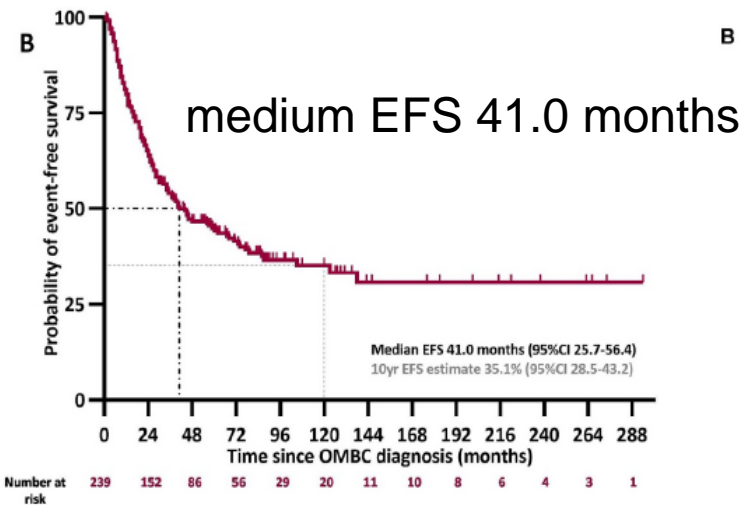
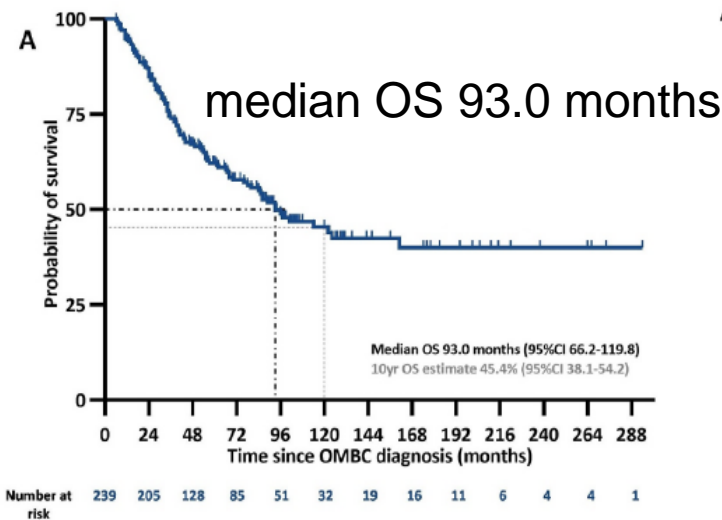
Clinical results: SBRT

Survival and prognostic factors in oligometastatic breast cancer



At OMBC diagnosis				
Surgical treatment breast	<i>Breast-conserving</i>	60	25.1	
	<i>Ablative</i>	34	14.2	
	<i>Re-surgery</i>	17	7.1	
Surgical treatment locoregional disease	<i>SN</i>	21	8.8	
	<i>MARI</i>	28	11.7	
	<i>ALND</i>	57	23.8	
	<i>Surgical debulking otherwise</i>	2	0.8	
	<i>Chest only or nodes only</i>	21	8.8	
Locoregional radiotherapy	<i>Chest + axilla and/or other nodes</i>	82	34.3	
	<i>Re-irradiation (± hyperthermia)</i>	26	10.9	
	<i>Unknown</i>	2	0.8	
	Local treatment of all metastatic lesions ^b	200	83.7	
Local treatment modality metastases	<i>Radiotherapy only</i>	155	64.9	
	<i>Surgery only</i>	29	12.1	
	<i>RFA/MWA</i>	6	2.5	
Ablative local treatment metastases ^d	<i>Two or more modalities^e</i>	13	5.4	
		111	46.4	
Systemic treatment (first-line) ^g	<i>Any</i>	236	98.7	
	<i>Chemotherapy</i>	195	81.6	
	<i>Endocrine therapy^f</i>	166	69.5	
	<i>HER2-targeted therapy</i>	52	21.8	
	<i>Anthracyclins + cyclophosphamide</i>	13	5.4	
Chemotherapy regimen	<i>Anthracyclins + cyclophosphamide + taxanes±platinum</i>	70	29.3	
	<i>Taxanes±platinum</i>	37	15.5	
	<i>Capecitabin + vinorelbin</i>	17	7.1	
	<i>Other, with anthracyclins and/or taxanes^g</i>	37	15.5	
	<i>Other, no anthracyclins or taxanes</i>	21	8.8	
	Radiologic response to first-line systemic therapy	<i>Complete response</i>	40	16.7
		<i>Any response, not complete</i>	124	51.9
<i>Progression</i>		21	8.8	
<i>Not evaluable</i>		54	22.6	

Clinical results: SBRT



Clinical results: SBRT

Stereotactic body radiotherapy to treat breast cancer oligometastases: A systematic review with meta-analysis

Selection criteria:

- **Prospective and retrospective studies**, > 10 patients and > 18 months FUP.
- **BC oligometastases** were defined as **5 lesions treated by SABR** with any fractionation or technique.
- Single or fractionated **treatment delivered to any site** (bone, liver, lung, or mixed sites) were included.
- SABR was defined as radiotherapy treatment with **doses per fraction ≥ 5 Gy** with ≤ 10 fractions.

Author	Milano	Scorsetti	Trovo	Onal	David	Milano 1	Milano 2	Weykamp	Li	Tan	Weitjunga
Design	R	R	P	R	P	P	P	R	R	R	R
Patients	40	33	54	22	15	36	12	46	10	120	79
Lesions	85	43	92	29	19	83	21	58	10	193	103
Age (median)	55	57	57	55	61	60	44	55	54	55	56
Number of mets (median)	≤ 5	≤ 5	≤ 5	≤ 3	≤ 3	≤ 5	≤ 5	≤ 3	≤ 5	≤ 5	≤ 5
Site of mets	Mixed	Mixed	Mixed	Mixed	Bone only	Mixed	Bone only	Mixed	Bone only	Mixed	Mixed
KPS (median)	>70	>70	>70	>70	>70	>70	>70	>70	>70	>70	>70
Number of sites (median)	2	2	2	1	1	1	1	1	2	1	1
ER/PR%	63	70	80	77	73	56	92	76	80	83	84
Her-2 (+) %	NR	48	20	32	20	NR	NR	20	20	17	10
RT technique	VMAT	VMAT	IMRT	IMRT	IMRT	NR	NR	IMRT	3DRT	3DRT/IMRT	IMRT
SBRT total dose Gy/fractions (median)	NR	75/3fx	36/3fx	54/3 fx	20/1fx	50/10fx	50/10fx	28/3fx	20/1fx	NR	BED >60 Gy4
Follow-up (median) months	56	24	30	18	24	52	52	21	32	50	50

10 studies / 467 patients / 653 treated metastases

Clinical results: SBRT

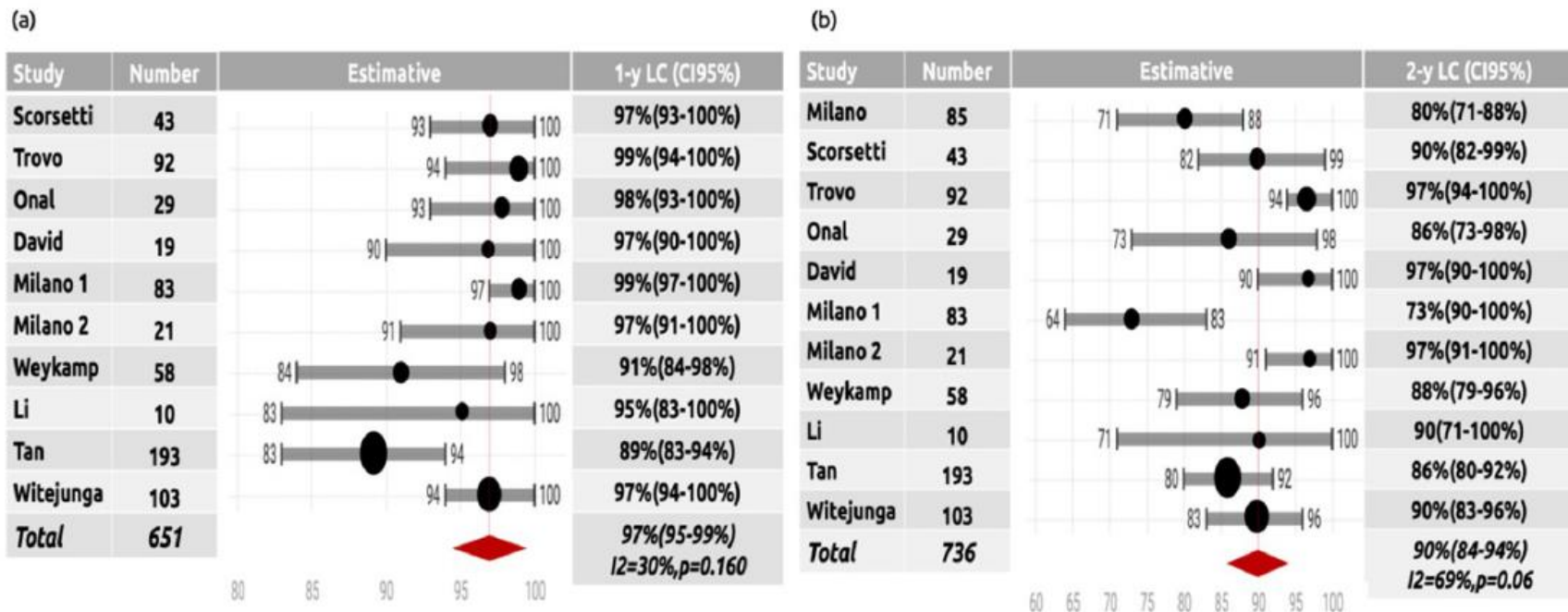


Fig. 1. Forrest plot of studies (a) 1-y Local control (b) 2-y local control.

Local Control at 2 years		
Bone only	0.05	0.297
Prospective design	0.009	0.210
%ER/PR	0.05	0.001
%HER-2 (+)	0.001	0.978
≤ 3 sites	-0.009	0.858
BEDGy10	-0.001	0.802

Clinical results: SBRT

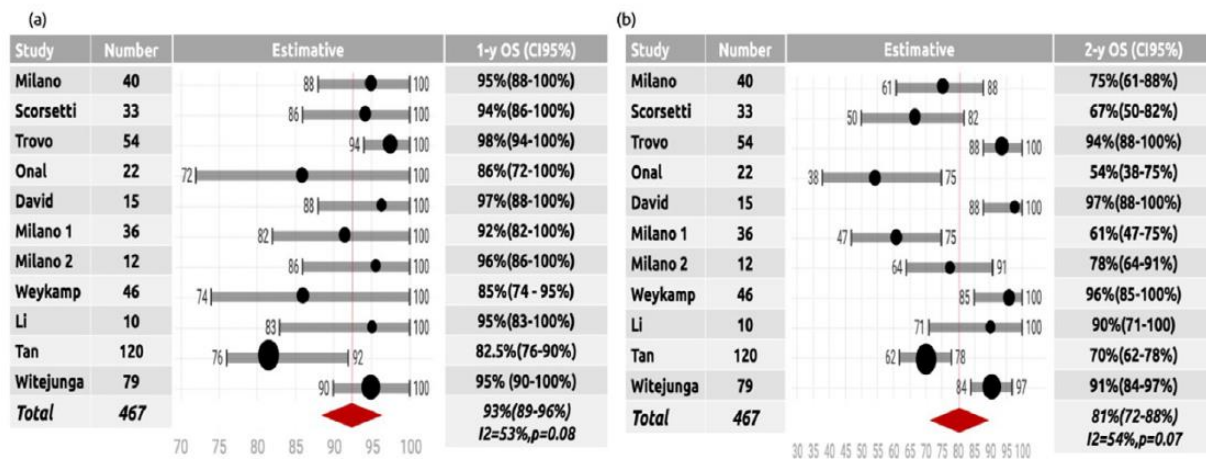
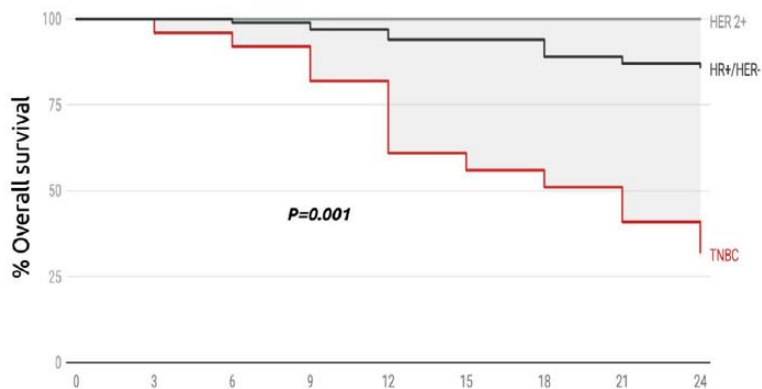


Fig. 2. Forrest plot of studies (a) 1-y Overall survival (b) 2-y overall survival.



Overall Survival at 2 years		
Bone only	0.20	0.01
Prospective design	0.18	0.001
%ER/PR	0.005	0.230
%HER-2 (+)	-0.007	0.105
≤ 3 sites	0.08	0.491
BEDGy10	-0.002	0.212

Clinical results: SBRT



Consolidative Use of Radiotherapy to Block (CURB) Oligoprogession: Interim Analysis of the First Randomized Study of Stereotactic Body Radiotherapy in Patients with Oligoprogessive Metastatic Cancers of the Lung and Breast

C. Jillian Tsai, MD, PhD

Memorial Sloan Kettering Cancer Center

Inclusion Criteria:

Oligoprogessive NSCLC or Breast cancer
≥ 1 line of systemic therapy
≤ 5 Extra-cranial oligoprogessive lesions

Randomization 1:1

Arm 1
Palliative Standard of care (SOC) + SBRT

Arm 2
Palliative SOC
(consider SBRT/Rt at further PD)

Accrual Goal:

160 patients (current accrual 106/160)

End points:

- PFS
- OS, Toxicity, QoL

Clinical results: SBRT

2019-2021

106 patients:

59 NSCL

47 Breast Cancer

Stratification:

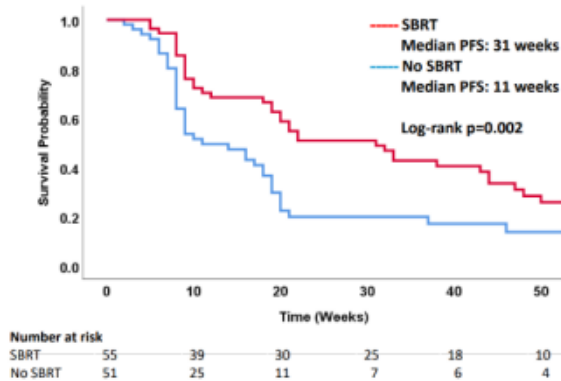
Primary tumor histology

Number of progressive metastases (1 vs. > 1)

Presence of driven mutation
(receptor/mutation status)

Prior immunotherapy

Results – Progression-Free Survival (Entire Cohort)



Median follow up:
45 weeks; 58 weeks
for living patients.

78 of 106 patients
further progressed.

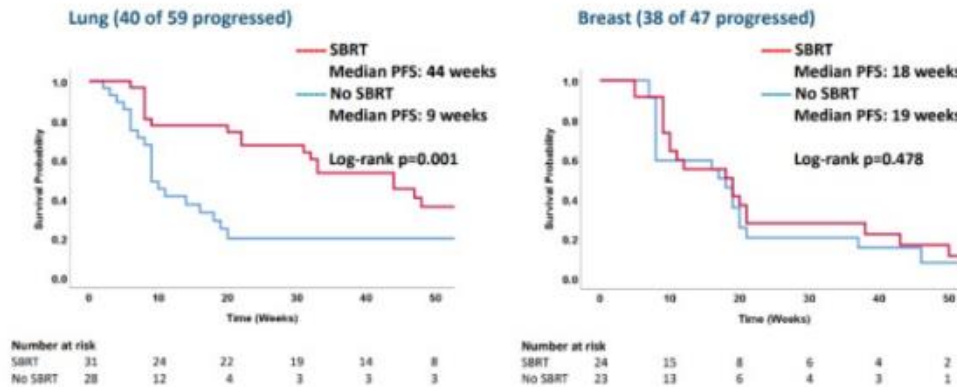
39 of 106 (37%) died.

Median PFS: 3.2 m in SOC vs. 7.2 m in SBRT

Grade ≥ 2 occurred in 8 patients after SBRT
(15%)

Clinical results: SBRT

Results – PFS by Primary Disease Sites



Second-line systemic therapy

Non-small-cell lung cancer (NSCLC)

- PDL-1 positive; Pembrolizumab; PFS= 4 months (Lancet 2016)
- After platinum; Ramucirumab + Docetaxel; PFS = 4.5 months (Lancet 2014)
- After first-line EGFR-TKI; Osimertinib; PFS = 10.1 months (NEJM 2017)
- After Osimertinib: No standard

Breast

- ER+ after first-line ET: Fulvestrant + CDK4/6 inhibitor; PFS = 9.5 -20.5 months
- TNBC after first-line: No standard; PFS = 2.3 -5.6 months

Is **oligoprogression** the right scenario for testing PFS in OMBC?

Is PFS the only and right **endpoint** in OMBC?

Clinical results: SBRT

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).

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.

ARM 1 – SOC ST
65 pts

ARM 2 – SOC ST with MDT of all mets
60 pts

Clinical results: SBRT

- **Median PFS:** 23 vs 19.5 months
- **24 and 36-mo PFS:** 45.7% and 32.8% vs 46.8 and 38.1; HR (70% CI): 0.92 (0.71, 1.17); 1-sided log-rank $p = 0.36$.
- **Median OS** was not reached
- **36-mo OS:** 71.8% vs 68.9% (2-sided log-rank $p = 0.54$).
- There were **no grade 5 treatment-related adverse events (AEs)**, 1 grade 4 AE in ARM 1, and 9.7% and 5.3% grade 3 AEs in ARMS 1 and 2, respectively.

Clinical results: SBRT

- OM-BC is overall associated with relatively favorable long-term outcome with approximately 70 % of OS probability at 3 years
- Median PFS with systemic therapy-only over-performed than expected
- The exploratory subgroup analysis for PFS of the NRG-BR002 trial captured a trend for improved PFS in favor of the addition of ablative strategies in patients with more than one metastasis, while an effect in the opposite direction was instead captured for TN subgroup

We need a better understanding of OMBC **biology**
to fine our results

Agenda

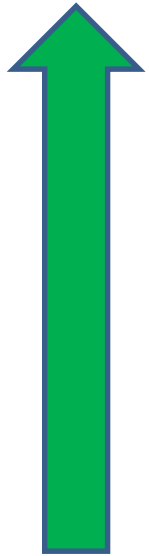
- Definition of oligometastases
- Local therapies for oligometastases
- Oligometastases in breast cancer
- Clinical results
- Future directions

Who is the real OMBC patient?



Who is the real OMBC patient?

Easily accessible



Difficult
availability

- Clinical
- Imaging
- Genetic/epigenetic

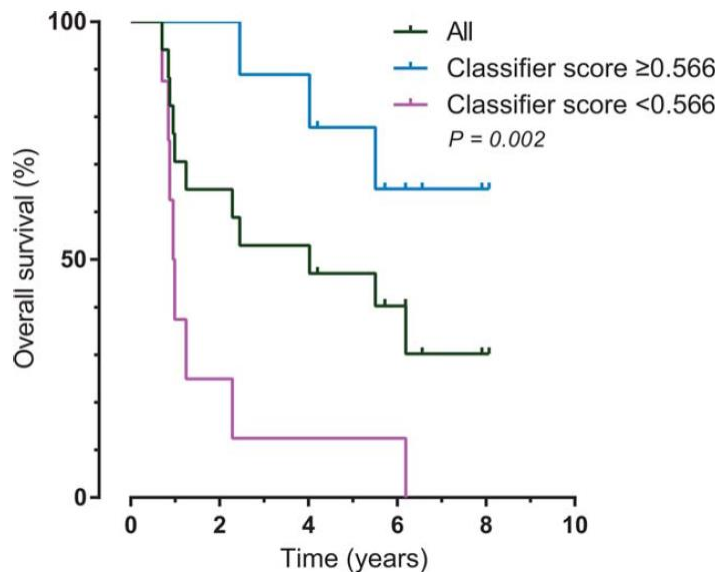
Less informative



Highly
informative

OMBC: selection

Clinical and Molecular Markers of Long-Term Survival After Oligometastasis-Directed Stereotactic Body Radiotherapy (SBRT)

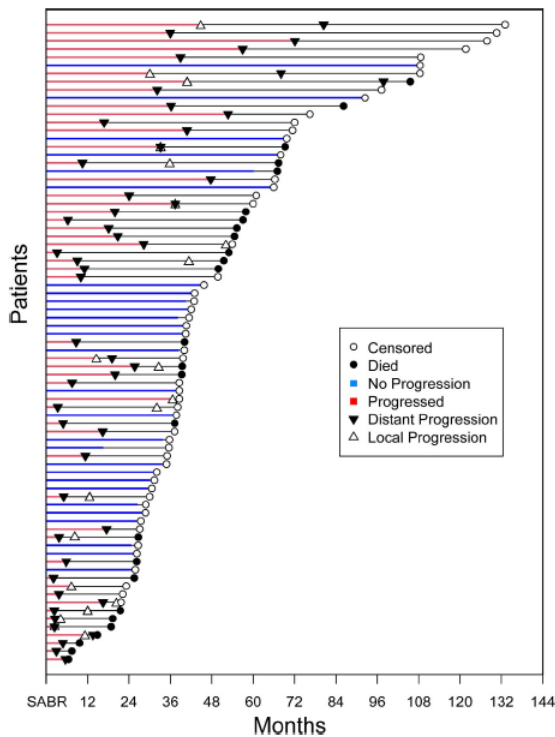


A candidate classifier using expression levels of 3 microRNAs (miR-23b, miR-449a, and miR-449b) predicted survival among 17 patients who had primary tumor microRNA expression data available

OMBC: selection

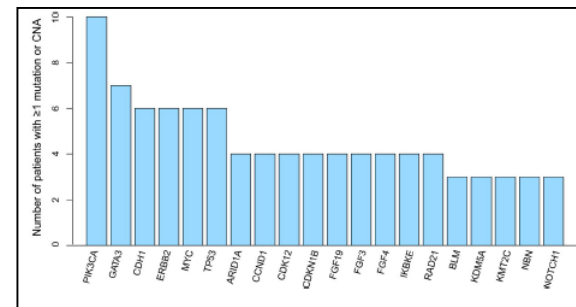
Long-term disease control and survival observed after stereotactic ablative body radiotherapy for oligometastatic breast cancer

79 patients



Median OS 86 months

Median PFS 33 months



Less than 5 years from diagnosis to SABR and triple-negative breast cancer (TNBC) were associated with worse OS. Advanced T stage, any prior chemotherapy, and TNBC were associated with worse PFS. Alterations in CEBPB, RB1, TBX3, PTEN, and CDK4 were associated with worse survival outcomes.

Personalized medicine

Clinical and/or molecular integrated stage

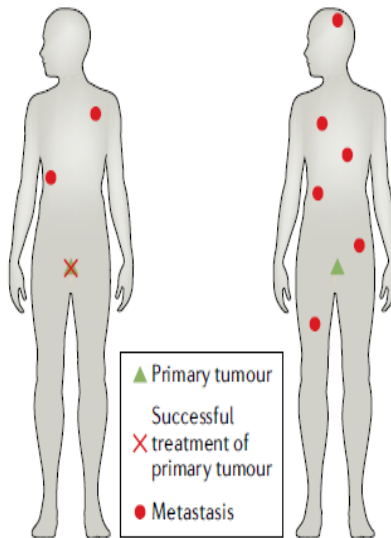
Low risk

High risk

Proposed magnitude of clinical benefit

Systemic therapy

Local ablative therapy



Box 1 | Characteristics of indolent clinical metastases

Clinical

- Low number (typically 1–5 lesions)
- Metachronous presentation
- No involvement of lymph nodes
- Slow rate of progression (typically <0.6 new lesions per year)
- Limited organ sites (typically 1–2 sites)
- Favourable histology (including, but not limited to, breast, prostate and kidney)

Biological

- Activation of innate and adaptive immunity
- Absence of mesenchymal features
- Low degree of tumour aneuploidy
- Low degree of intratumoural heterogeneity
- Intact 14q chromosomal arm
- Expression of microRNAs that suppress genes associated with metastasis

Treatment

Local ablative interventions (with stereotactic body radiotherapy, radiofrequency ablation or surgery) tend to be more beneficial for these patients than systemic therapy

Ongoing trials

Table 2
Ongoing randomized phase II/III trials of local ablative therapy + systemic therapy in BC.

Identifier	Phase	Patients	End of Study	Primary Endpoint(s)	Local treatment	Number and site of metastases allowed	Tumour biology
NCT04413409 (OMIT)	Phase III randomized	172	2025	OS	Surgery	≤3 metastatic lesions, involving 1–2 organs, single lesion ≤ 5 cm	Any
NCT04495309 (OLIGOMA)	Phase III randomized	564	2025	PFS HRQoL	SBRT	Up to 5 clinically manifest metastases (maximum 3 CNS lesions)	Any
NCT04698252 (LARA)	Phase II randomized	74	2031	PFS	SBRT, surgery, RFA	1–4 bone lesions; 1–4 lung and/ or liver lesions	HR+/HER2-
NCT04424732	Phase II single arm	50	2026	PFS	SBRT	1–3 bone metastases	Any
NCT03750396 (CLEAR)	Phase II single arm	110	2025	PFS	Palliative RT, SBRT, surgery, RFA	≤2 lesions in single organ or site (lung, bone, liver, adrenal glands, nodal)	HR+/HER2-
NCT02089100 (STEREO-SEIN)	Phase III randomized	280	2023	PFS	SBRT	≤5 metastatic lesions	HR+ (HER2 +/-)
NCT05301881 (COSMO)	Phase II single arm	118	2040	PFS	SBRT, surgery, RFA	Oligoprogression defined as 1–2 metastatic lesions, limited to one organ, or the primary tumour or regional nodes	Any
NCT05377047 (TAORMINA)	Phase III randomized	345	2027	OS	SBRT	1–5 lesions in 1–2 organs	Any

Pragmatic approach

ESTRO & EORTC initiative:

OligoCare

**A Pragmatic Observational Basket
Study to Evaluate Radical Radiotherapy
for Oligo-Metastatic Cancer Patients**



Take Home Message

There are different possible endpoints in the oligometastatic world:

- *Oligometastatic breast cancer* exists, although it is less studied and represented in clinical trials
- *Radiotherapy* represents the ideal treatment for oligometastases thanks to high efficacy and low toxicity
- *Clinical trials* focused on oligometastatic breast cancer are awaited and necessary to create strong evidences
- *Identification and selection of patients* are crucial in breast cancer due to its heterogeneity, translational research is needed
- *Different kinds* of oligometastases could require the same treatment with *different endpoints*, consider novel endpoints

Consider SBRT as another “line of therapy” in the treatment arsenal for metastatic cancer.

Thank you

