Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

La gestione dei pazienti candidati a radioterapia ablativa nella malattia oligoprogressiva

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Società Italiana di Radiobiologia

DICHIARAZIONE

Relatore: CHIARA REVERBERI

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

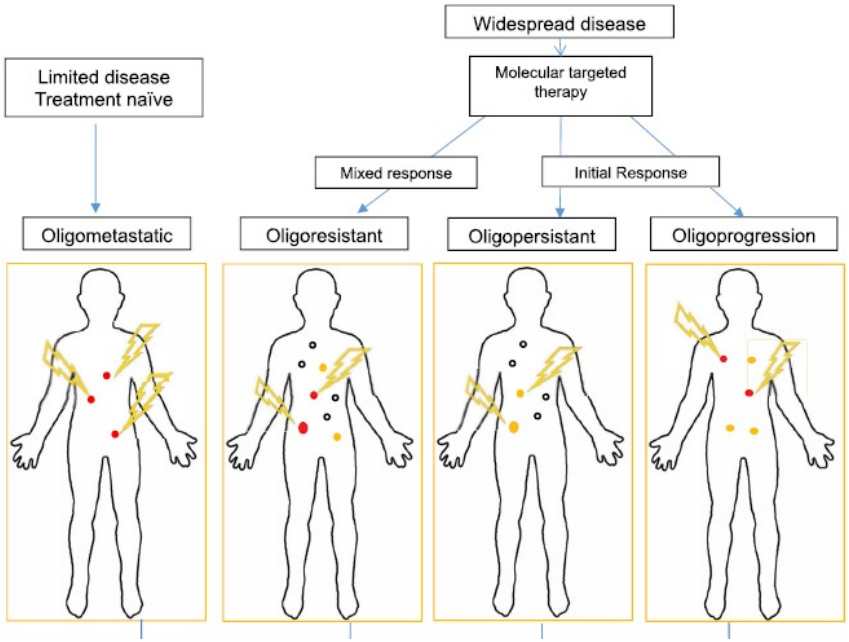
OligoProgressive Disease
OPD

1 Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol 1995;13:8–10.

2 Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: A European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol 2020;21:e18–e28.

“Oligoprogressive disease refers to a limited number of progressive sites on active or ongoing systemic therapy”

—SOMEONE FAMOUS



3 Kim H, Venkatesulu BP, McMillan MT et Al. Local Therapy for Oligoprogressive Disease: A Systematic Review of Prospective Trials. Int J Radiation Oncol Biol Phys, Vol. 114, No. 4, pp. 676–683, 2022

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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 Palma [i], Catherine Park [j], Umberto Ricardi [k], Marta Scorsetti [l], James Yu [m], Wendy A. Woodward [c]

Oligo-Progression

Few lesions progress on a background of widespread but stable metastatic disease

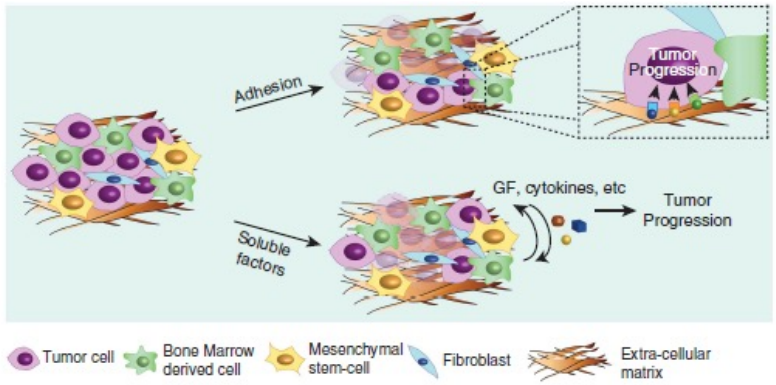
+ *Link with other therapies*
  Progression occurs in a limited number of tumors/metastases while the majority of other metastases are responding or stable while on a systemic treatment strategy
  Progression occurs after a cytoreductive treatment
  Progression while other sites including the primary disease remain stable on systemic treatment or observation
  Resistant clones can result in isolated progression

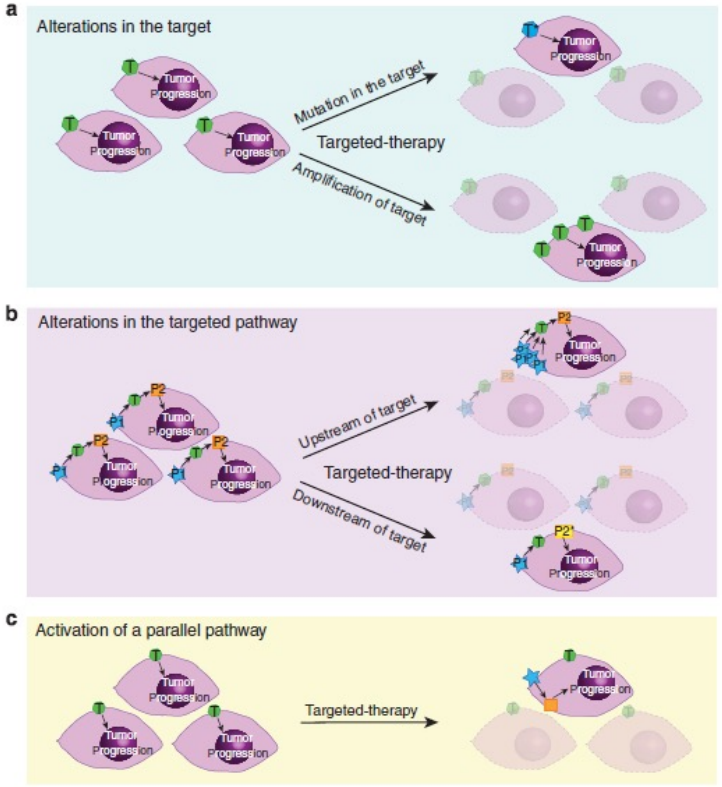
+ *Disease load*
  <5 enlarging metastases in an otherwise well-controlled disease state
  <5 sites of metastatic disease progression while other sites including primary remain stable on systemic treatment
  3–5 slowly progressive metastases

4 Lievens Y, Guckenberger M, Gomez D, et Al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. Radiotherapy and Oncology 148 (2020) 157–166.

SCIENTIFIC RATIONALE

Recent genomic studies have revealed that there is distinct clonal evolution at each site of metastatic disease such that individual sites may obtain treatment resistance or increased metastatic potential **independent of the primary site** of disease **or even other metastatic sites.**





5 Patel PH, Palmaz D, McDonald F, et Al. The Dandelion Dilemma Revisited for Oligoprogression: Treat the Whole Lawn or Weed Selectively? Clin Oncol (R Coll Radiol). 2019 Dec;31(12):824-833.
6 Ramos P and Bentires-Alj M. Mechanism-based cancer therapy: resistance to therapy, therapy for resistance. Oncogene. 2015 Jul;34(28):3617-26.

Literature data LIMITATIONS

1. **Heterogeneous** population:
    a. Variety of radiation dosing/fractionation regimens
    b. Variety of definitions of OPD
    c. Some trials continued the existing systemic therapy, and some switched the agent at the time of SABR
2. Small **sample sizes**
3. Short **follow-up periods** (toxicity)
4. Many did not use the most contemporary **systemic therapies**
5. Different type of **tumor histology** (interaction between tumor biology and its particular systemic therapy)
6. Primary **End-Point** (PFS vs OS)
7. **Single arm trials** without comparator arms
8. Methodology issue: the **unpublished** abstracts

EMBRACING CHANGE
ADVANCING PERSON-CENTERED CARE
ASTRO
ANNUAL MEETING 2021

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

C. Jillian Tsai, MD, PhD

Memorial Sloan Kettering Cancer Center

Randomization 1:1

Arm 1
Palliative Standard of care (SOC) + SBRT

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

Inclusion Criteria:
Oligoprogressive NSCLC or Breast cancer
≥ 1 line of systemic therapy
≤ 5 Extra-cranial oligoprogressive lesions

Accrual Goal:
160 patients (current accrual 106/160)

End points:
- ➔ PFS
- ➔ OS, Toxicity, QoL

2019-2021

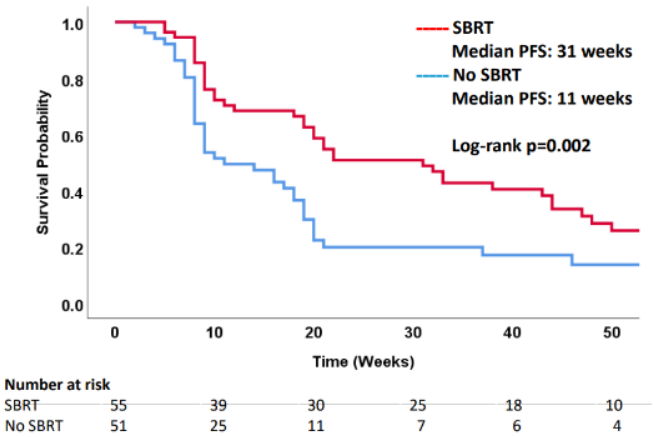
106 patients:

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.

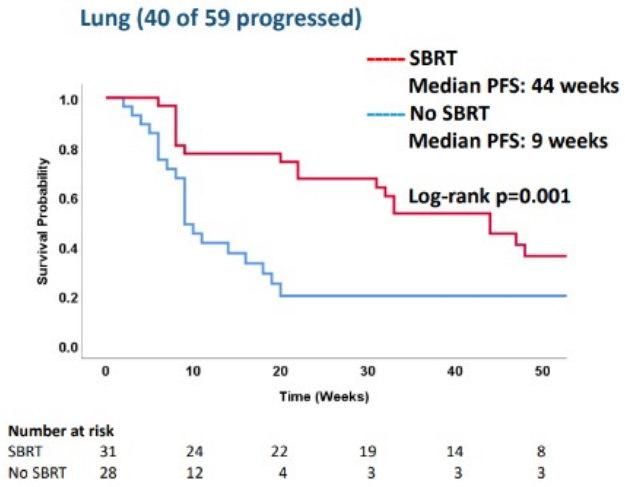
78 of 106 patients further progressed.

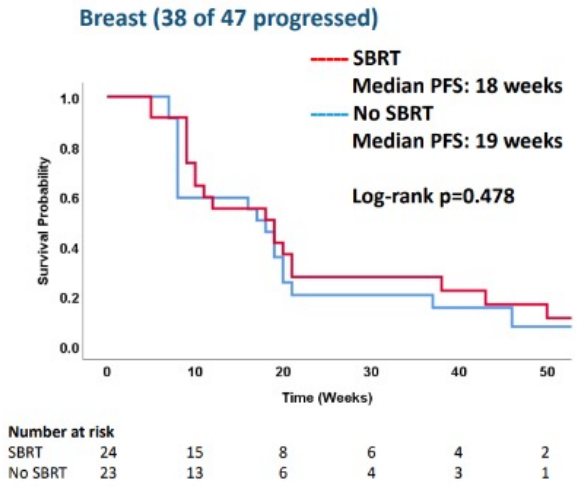
39 of 106 (37%) died.

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

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

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

NSCLC

NSCLC

	Design	Nr of patients	Histology	Systemic therapy	Progressive Sites	End point	Toxicity
Tsai CJ[7] (2021)	Randomized phase II (SBRT vs Systemic Therapy)	59	NSCLC	SOC	1-5 EC	Median PFS 11 m (SBRT) vs 2.3 m (ST)	15% of SBRT patients had Grade ≥ 2
Iyengar P[8] (2014)	Single arm Phase II	24	EGFR +	Erlotinib	< 5 EC 67% had > 1 s	Median PFS 14m Median OS 20.4 m	8.3% had Grade ≥ 3
Weiss J[9] (2019)	Single arm Phase II	25	EGFR m	Erlotinib	Any CNS (no LMD) and/or ≤ 3 EC	Median PFS 6 m Median OS 29 m (Close early → 2° linee therapy with Osimertinib)	No Grade ≥ 2
Kim C[10] (2018)	Single arm Phase II	24	EGFR m	Osimertinib	≤ 5 sites	Median PFS 11.2 m (no prior EGRF-TKI therapy) vs 15.8 m (T790M_positive who start Osimertinib after the 1st EGFR-TKI therapy)	Not reported

NSCLC							
	Design	**Nr of patients**	**Histology**	**Systemic therapy**	**Progressive Sites**	**End point**	**Toxicity**
Weickhardt AJ[11] (2012)	Retrospective	38 (ALK) 27 (EGFR)	ALK + EGFR m	Crizotinib Erlotinib	≤ 4 EC ± any CNS	Median PFS 9 m (ALK +) vs 13.8 m (EGFR)	8% Grade 3 (fatigue)
Yu HA[12] (2013)	Retrospective	18	EGFR m	TKI not specified	< 5 EC	Median PFS 10 m (median time until change systemic therapy: 22m) Median OS 41 m	Grade ≥ 3 Pneumonia (11%)
Hu C[13] (2022)	Retrospective	33	EGFR m	TKI (Gefitinib or Erlotinib or Icotinib)	EC ± CNS	Median PFS 6.5m Median OS 21.8 m	No Grade ≥ 3
Chan OSH[14] (2017)	Retrospective (SBRT vs CHT)	25 (SBRT)	EGFR +	TKI not specified	< 3 EC sites ± any CNS	Median PFS 7 m (SBRT) vs 4 (CHT) Median OS 28.2 m (SBRT) vs 14.7 m	Grade 3 Oesophagitis (4%)

NSCLC							
	Design	**Nr of patients**	**Histology**	**Systemic therapy**	**Progressive Sites**	**End point**	**Toxicity**
Qiu B[15] (2017)	Retrospective	46	EGFR +	TKI not specified	Any EC ± any CNS	Median PFS 7m OS 13 m	Grade 3 pneumonitis (4.3%) Grade 3 neutropenia (21.7%) Grade 3 skin rush (4.3%)
Gan GN[16] (2014)	Retrospective	14	ALK +	Crizotinib	≤ 4 EC sites	Median PFS 14m (median time until change systemic therapy: 28m)	No Grade ≥ 3
Shukuya T[17] (2011)	Retrospective	17	EGFR +	Gefitinib or Erlotinib	CNS	Median PFS 2.7m Median OS 13.4 m	No Grade ≥ 2
Xu Q[18] (2019)	Retrospective	206	EGFR +	first-line EGFR-TKI	≤ 5 lesions EC ± CNS	Median time until change systemic therapy: 18.3 m Median OS 37.4m	Grade 3 Skin rash (5.3%) G3 diarrhea (3.9%), G3 pneumonitis (1.5%). No Grade 4-5 toxicity

7. Iyengar P, Kavanagh BD, Wardak Z, et al. Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. J Clin Oncol 2014;32:3824–3830.
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13. Hu C, Wu S, Deng R, et Al. Radiotherapy with continued EGFR-TKIs for oligoprogressive disease in EGFR-mutated non-small cell lung cancer: A real-world study. Cancer Med. 2022 Jun 5
14. Chan OSH, Lee VHF, Mok TSK, et Al. The role of radiotherapy in epidermal growth factor receptor mutation-positive patients with oligoprogression: a matchedcohort analysis. Clin Oncol 2017;29:568e575.
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18. Xu Q, Liu H, Meng S, et Al. First-line continual EGFR-TKI plus local ablative therapy demonstrated survival benefit in EGFR-mutant NSCLC patients with oligoprogressive disease. J Cancer. 2019;10(2):522–9.

Breast Cancer

BREAST CANCER

	Design	Nr of patients	Histology	Systemic therapy	Progressive Sites	End point	Toxicity
Tsai CJ[7] (2021) CURB	Randomized phase II (SBRT vs Systemic Therapy)	47	All Histological subtypes	Any	1-5 EC	PFS 4.5 m (SBRT) vs 4.7 m (ST)	Grade ≥ 2 61% (SBRT) vs 40% (ST)
Tan H[19] (2021)	Retrospective, single arm	36 (36/120_30%)	All Histological subtypes (63% Luminal A; 12% TNBC)	Any	≤ 5 growing EC lesions	*1- and 2-ys OS: 78% - 58%.* *Overall: Median OS 53m, median PFS 11m*	4.2% had Grade ≥ 3 (1 pneumonitis and 2 vertebral body fractures)
Wijetunga NA[20] (2021)	Retrospective, single arm	37 (37/79_47%)	All Histological subtypes (67% Luminal A; 6% TNBC)	Any	≤ 5 EC lesions (80% had single lesion)	*Overall:* Median OS 86m Median PFS 33m	No grading given
Weykamp F[21] (2020)	Retrospective, single arm	14 (14/46_30%)	All Histological subtypes (76% ER +; 7.7% TNBC)	Any	1 progressive EC lesion	*Overall: 1- and 2-ys OS: 85% - 62%* *1- and 2-ys PFS: 54% - 17%*	No grade 3

BREAST CANCER							
	Design	**Nr of patients**	**Histology**	**Systemic therapy**	**Progressive Sites**	**End point**	**Toxicity**
Onal C[22] (2018)	Retrospective, single arm	19 (19/22_86%)	All Histological subtypes (77% ER +; 9% TNBC)	Any	≤ 3 **Liver** metastases < 6cm diameters	Overall: 1- and 2-ys OS: 85% - 57% Median PFS 7.4m	No grade > 3
Alomran R[23] (2021) AVATAR ***ONGOING***	Multicentric phase II	32	ER +, HER2 -	Endocrine therapy + CDK4/6 inhibitor	1-5 sites	? time to change Systemic Therapy OS PFS	/

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OTHERS

	Design	Nr of patients	Histology	Systemic therapy	Progressive Sites	End point	Toxicity
MAHMOOD U[24] (2022)	Retrospective	120	Mostly: Lung (49%), Melanoma (30%)	ICI	≤ 5 EC ± CNS	Median PFS 6.4 m Median OS 30 m	Not assessed
CHICAS-SETT R[25] (2022)	Prospective observational study	61	NSCLC or melanoma	anti-PD-1 (pembrolizumab or nivolumab)	1-5 measurable EC lesions	Median PFS 14.2m Median OS 37.4 m	Not assessed
CHEUNG P[26] (2021)	Single arm, phase 2	37	RCC	TKI	≤ 5 (all enrolled had 1-3 lesions)	Median PFS 9.3 m	No Grade 3 toxicity
HANNAN R[27] (2021)	Single arm, phase 2	20	RCC	Systemic therapy	≤ 3	Median PFS 8.7 m Median time to next systemic therapy: 11 m	1 Grade 3 GI toxicity

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26.. Cheung P, Patel S, North SA, et al. Stereotactic radiotherapy for oligoprogression in metastatic renal cell cancer patients receiving tyosine kinase inhibitor therapy: A phase 2 prospective multicenter study. Eur Urol 2021;80:693–700.
27. Hannan R, Christensen M, Garant A, et al. Phase II trial of stereotactic ablative radiation (SAbR) for oligoprogressive kidney cancer. J Clin Oncol 2021;39:abstr4564.

TAKE HOME MESSAGES:

- ✓ Toxicity and QoL
- ✓ OPD and Target Therapy
- ✓ Critical interpretation of data