UNIVERSITA' DEGLI STUDI DI MESSINA

FACOLTA' DI MEDICINA E CHIRURGIA

DIPARTIMENTO DI SCIENZE BIOMEDICHE E DELLE IMMAGINI MORFOLOGICHE E FUNZIONALI

U.O.C. DI RADIOTERAPIA

Direttore: Prof. Stefano PERGOLIZZI

Nuovi farmaci e radioterapia con frazionamenti alternativi nei pazienti oligoricorrenti ed oligometastatici

Dott. Giuseppe IATI'

STORIA

- Hellman e Weichselbaum nel 1995 hanno proposto l'esistenza di uno stato di oligometastasi.
- Stato intermedio tra quello localizzato e quello diffusamente metastatico
- Suscettibile di una strategia terapeutica curativa
- Suscettibile di una terapia locale

DEFINIZIONI

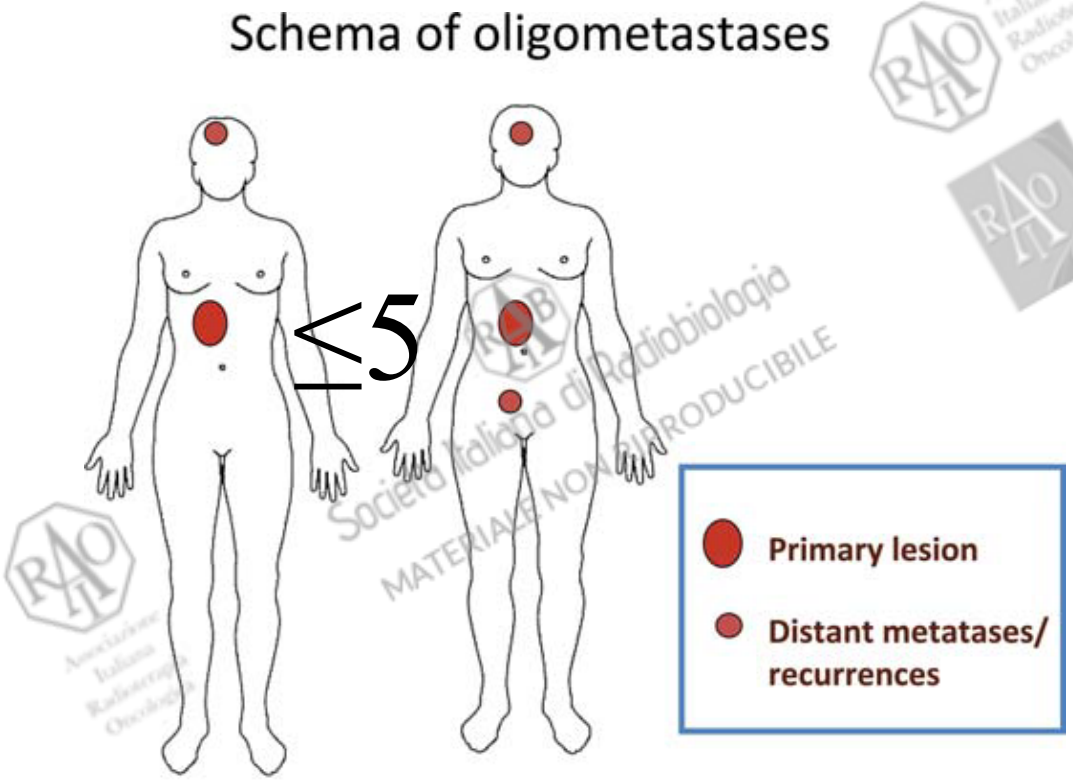
Terms	Definition
Oligometastasis	"…metastases (from tumors early in the chain of progression) limited in number and location because the facility for metastatic growth has not been fully developed and the site for growth is restricted…"
Oligometastatic disease	Solitary or few detectable metastatic lesions that are usually confined to a single organ
Oligometastases	Due to limited metastatic competence and does not occur following otherwise successful systemic treatment. New metastases in this situation, albeit even limited, is likely to have more extensive malignant capabilities that were somehow spared from eradication by therapeutic means, or from the development of resistant clones
Induced oligometastases	Occurs when widespread micrometastatic disease is mostly eradicated by systemic chemotherapy but drug resistant clones are left behind, or tumor foci is located in a site not accessed by chemotherapy
Oligorecurrence	Limited metastases in the presence of a controlled primary lesion
Sync-oligometastases	≤5 metastatic or recurrent lesions in the presence of active primary lesions
Synchronous oligometastasis	Oligometastatic disease is detected at the time of diagnosis of the primary tumor, therefore there is an active primary tumor
Metachronous oligometastasis	Development of oligometastatic disease after treatment of the primary tumor; interval for classification of metachronous versus synchronous is not standardized; between Controlled primary lesion except for concomitant primary and distant recurrence
Oligoprogression	Progression of a limited number of metastatic deposits, while remaining metastases are controlled with systemic therapy
Oligometastasis (specific to prostate cancer)	Rising PSA following primary therapy, with oligometastasis on imaging, in whom local treatment (surgical metastasectomy (usually LN dissection), or SBRT for bony mets or LN recurrence) is required to defer initiation of ADT
Oligometastasis (specific to prostate cancer)	Castrate resistant prostate cancer with a rising PSA and oligometastasis on imaging, in whom local treatment (surgical metastasectomy (usually LN dissection), or SBRT for bony mets or LN recurrence) may allow deferral of ADT

Oncotarget, Vol. 6, No. 11

The biology and treatment of oligometastatic cancer

Diane K. Reyes[1], Kenneth J. Pienta[1,2] April 13, 2015

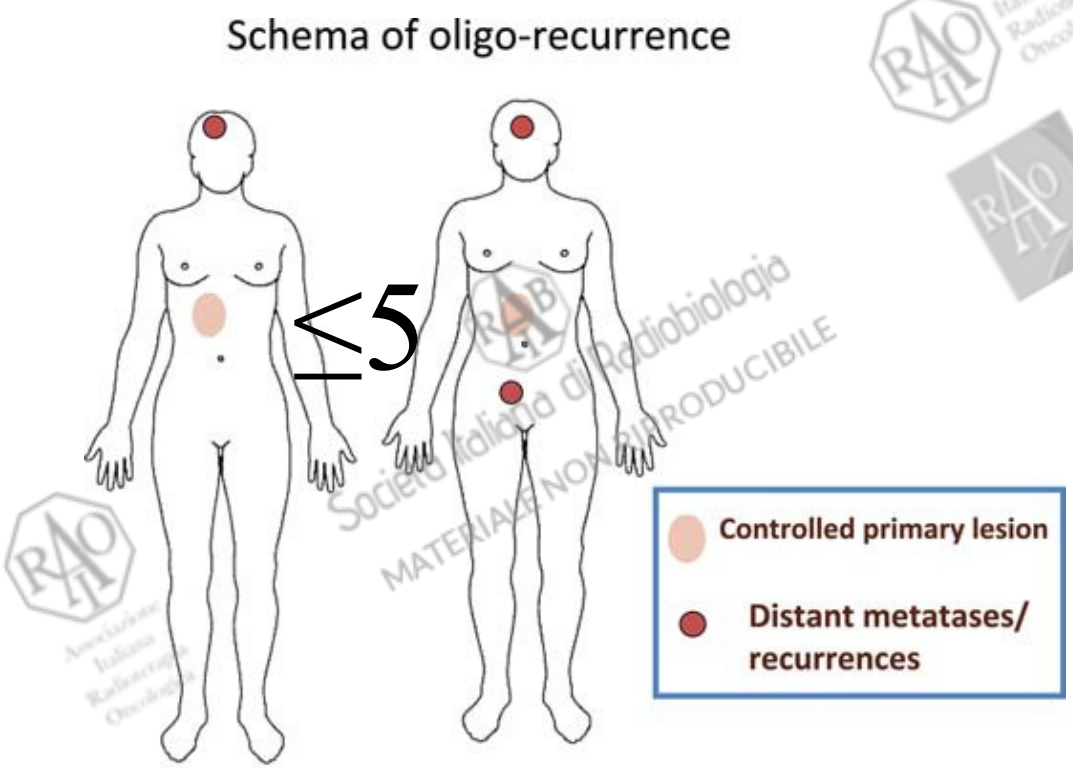
OLIGOMETASTASI



JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010;40(2)107–111

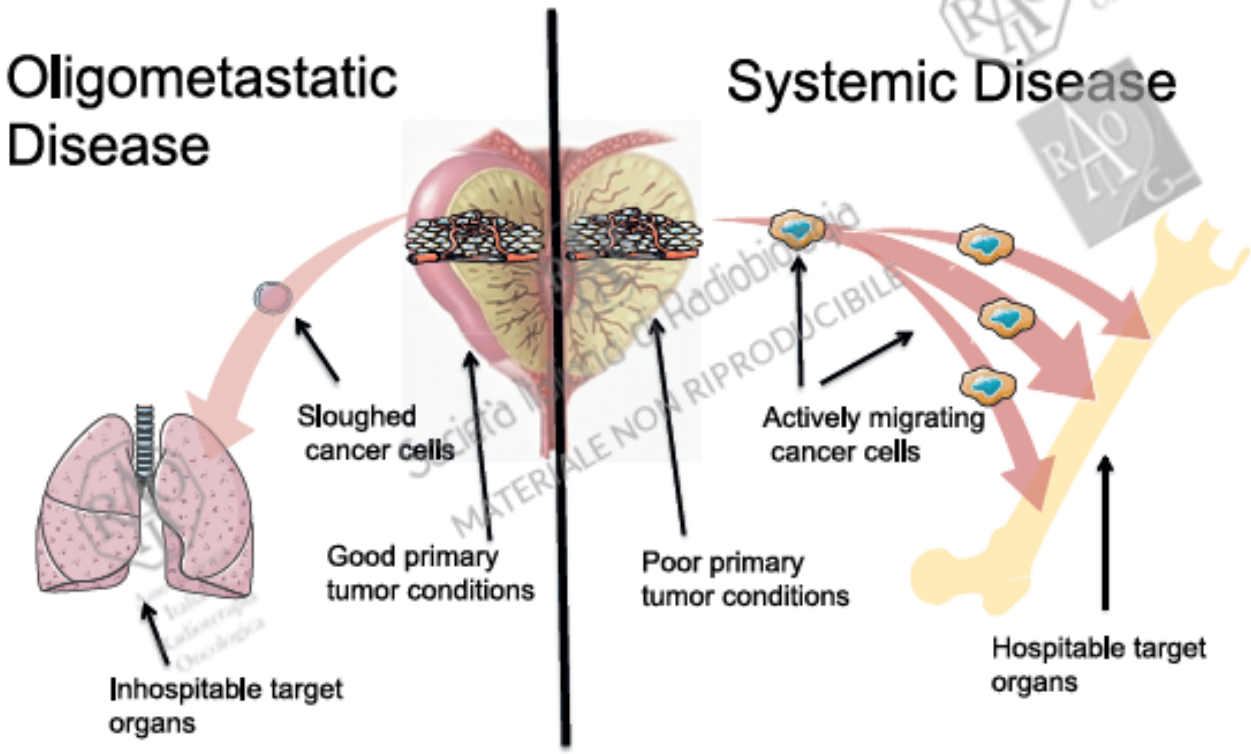
OLIGORECIDIVA



JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010;40(2)107–111

OLIGOMETASTASES vs SYSTEMIC DISEASE



Oncotarget, Vol. 6, No. 11 *April 13, 2015*

The biology and treatment of oligometastatic cancer

Diane K. Reyes[1], Kenneth J. Pienta[1,2]

MECCANISMO DELLE OLIGOMETASTASI

- Lo stato di oligometastasi è caratterizzato dalla presenza di lesioni secondarie ≤ 5 con il primitivo attivo.
- L'oligometastasi deriva dalle stem cells neoplastiche che hanno subito una o più mutazioni geniche all'interno della lesione primitiva
- Alcuni studi hanno evidenziato l'importanza della mutazione di un sottotipo di microRNA (microRNAc).
- Tale mutazione sembra trasformare la capacità metastatizzante delle cellule tumorali da *oligometastatica* a *polimetastastica*
- La organo specificità delle oligometastasi sembra legato a caratteristiche genetiche del tumore primitivo

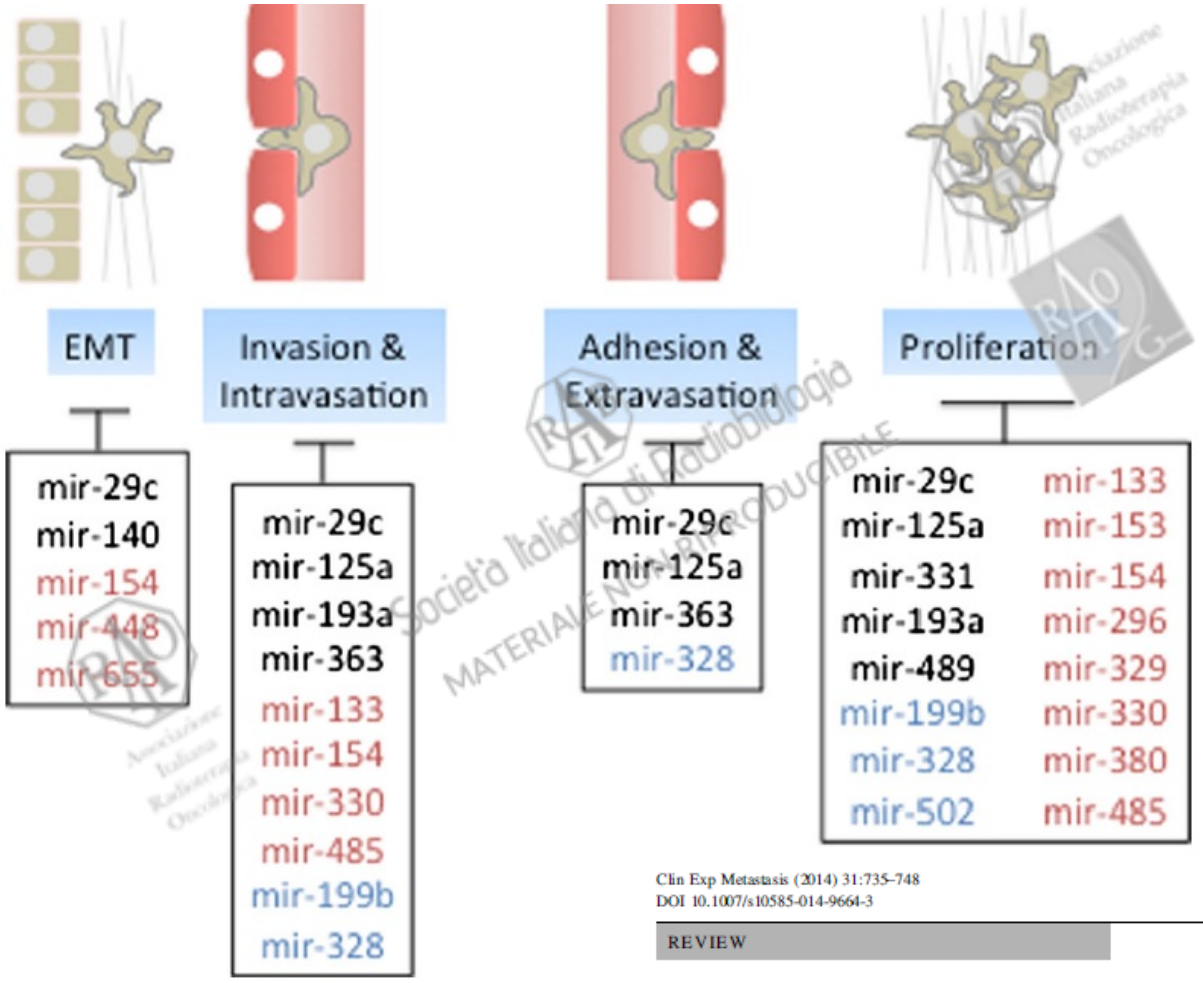
Niibe Y, Chang J Y. ***Novel Insights of Oligometastases and Oligo-Recurrence and Review of the Literature.*** Pulmonary Medicine, 2012.

MECCANISMO DELLE OLIGORECIDIVE

- L'oligorecidiva è lo stato in cui le lesioni secondarie ≤ 5 complessive si presentano una volta eradicato il primitivo.
- Le metastasi sono metacrone rispetto al primitivo.
- Le micrometastasi sono già presenti al tempo del trattamento del primitivo.
- La prognosi dello stato di oligorecidiva è migliore rispetto a quello di oligometastasi.
- Un ruolo importante nella progressione delle micrometastasi sembra essere giocato dalle interleukine.
- La organo specificità delle oligometastasi sembra legato a caratteristiche genetiche del tumore primitivo

Niibe Y, Chang J Y. ***Novel Insights of Oligometastases and Oligo-Recurrence and Review of the Literature.*** Pulmonary Medicine, 2012.

GENETICA DELLE OLIGOMETASTASI



Clin Exp Metastasis (2014) 31:735–748
DOI 10.1007/s10585-014-9664-3

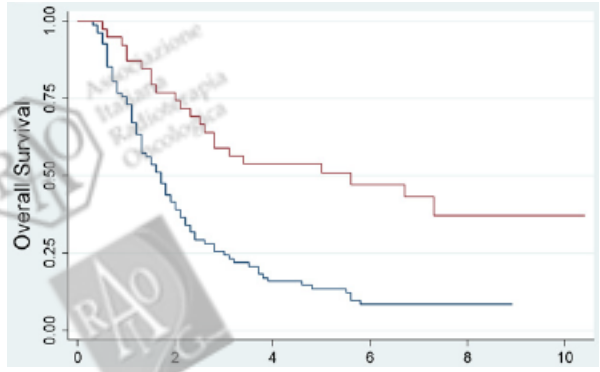
REVIEW

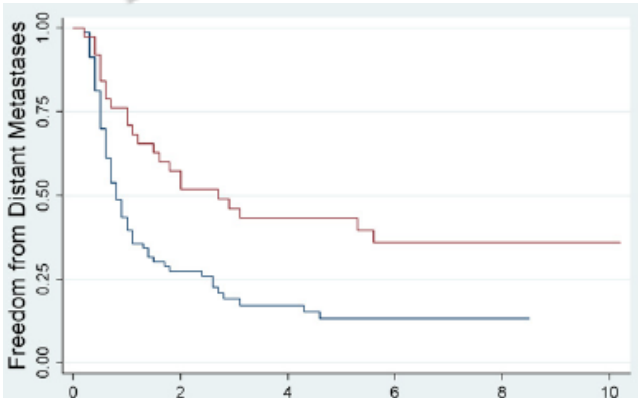
Towards a molecular basis of oligometastatic disease: potential role of micro-RNAs

Abhineet Uppal · Mark K. Ferguson · Mitchell C. Posner · Samuel Hellman · Nikolai N. Khodarev · Ralph R. Weichselbaum

RADIOTERAPIA E OLIGOMETASTASI

Characteristic	All patients	Breast cancer patients	Nonbreast cancer patients	*p*
Patients (*n*)	121	39	82	
Age (y)				0.001*,†
Range	34–88	34–83	41–88	
Mean ± SD	58 ± 12	53 ± 14	61 ± 11	
Median	60	52	60	
Primary cancer				
Breast	39 (32)	39 (100)	0	NA
Colorectal	31 (26)	0	31 (38)	
Lung, head/neck, esophagus	23 (19)‡	0	23 (28)	
Other	28 (23)§	0	28 (34)	
Primary histologic type				NA
Adenocarcinoma	89 (74)	39 (100)	50 (61)	
Squamous cell carcinoma	7 (6)	0	7 (9)	
Sarcoma	7 (6)¶	0	7 (9)	
Other	18 (15)¶	0	18 (22)	
Initial sites involved with oligometastatic disease				
Lung	50 (41)	11 (28)	39 (48)	0.044
Thoracic lymph nodes‖	24 (20)	9 (23)	15 (18)	0.54
Liver	54 (45)	13 (33)	41 (50)	0.085
Pelvis/abdomen	6 (5)	2 (5)	4 (5)	0.95
Brain	5 (4)	1 (3)	4 (5)	0.55
Bone	15 (12)	11 (28)	4 (5)	0.0003*,†
Initial oligometastatic lesions (*n*)				0.16*,†
1	37 (31)	15 (38)	22 (27)	0.20
2	32 (26)	12 (31)	20 (24)	
3	28 (23)	6 (15)	22 (27)	
4–5	24 (20)	6 (15)	18 (22)	
Initial involved organs (*n*)				0.33*
1	92 (76)	32 (82)	60 (73)	
2–3	29 (24)	7 (18)	22 (27)	
Sum of GTVs (cm^3)				0.58*
Range	0.3–422	1–402	0.3–422	
Mean ± SD	52 ± 75	47 ± 73	55 ± 76	
Median	28	23	30	
Reason for referral for SBRT				
Not candidates for/declined systemic therapy	26 (21)	2 (5)	21 (26)**	0.007†
Disease progression after systemic therapy	31 (26)	11 (28)	20 (24)	0.65
Consolidation after response or stable disease from systemic therapy	36 (30)	16 (41)	20 (24)	0.062
New limited metastases (systemic therapy just before or after SBRT)	23 (19)	9 (23)	14 (17)	0.43
Growing metastases >6 mo after systemic therapy	8 (7)	1 (3)	7 (9)	0.22





Milano et al.
Oligometastases Treated With Stereotactic Body Radiotherapy: Long-Term Follow-Up of Prospective Study.
Int J Radiation Oncol Biol Phys, Vol. 83, No. 3, pp. 878-886, 2012

RADIOTERAPIA E OLIGOMETASTASI

The Oncologist®
2012;17:1100–1107

Radiation Oncology

Review and Uses of Stereotactic Body Radiation Therapy for Oligometastases

FILIPPO ALONGI,[a] STEFANO ARCANGELI,[a] ANDREA RICCARDO FILIPPI,[b] UMBERTO RICARDI,[b] MARTA SCORSETTI[a]

ABSTRACT

In patients with proven distant metastases from solid tumors, it has been a notion that the condition is incurable, warranting palliative care only. The term "oligometastases" was coined to refer to isolated sites of metastasis, whereby the entire burden of disease can be recognized as a finite number of discrete lesions that can be potentially cured with local therapies. Stereotactic body radiation therapy (SBRT) is a novel treatment modality in radiation oncology that delivers a very high dose of radiation to the tumor target with high precision using single or a small number of fractions. SBRT is the result of technological advances in patient and tumor immobilization, image guidance, and treatment planning and delivery. A number of studies, both retrospective and prospective, showed promising results in terms of local tumor control and, in a limited subset of patients, of survival. This article reviews the radiobiologic, technical, and clinical aspects of SBRT for various anatomical sites. *The Oncologist* 2012;17:1100–1107

RADIOTERAPIA E OLIGOMETASTASI

Radiation Series	Year	Patients	Lesions	Local Control (%)	Survival (%)	Site
Blomgren et al	1995	31	42	80	Not reported	Liver, lung, and retroperitoneum
Wulf et al	2004	41	51	80	33[a]	Lung
Hoyer et al (colorectal cancer)	2006	64	141	86[a]	38[a], 13[h]	Lung, liver, and adrenal
Hof et al	2007	61	71	63[i]	47.8[i]	Lung
Rusthoven et al	2009	47	63	92[a]	30[a]	Liver
Rusthoven et al	2009	38	63	96[a]	39[a]	Lung
Kang et al (colorectal cancer)	2010	59	78	66[j]	49[j]	Multiple
Okunieff et al	2006	49	125	83[j]	25[j]	Lung
Katz et al	2007	69	174	57[k]	24[l,m]	Liver
Lee et al	2009	70	143	71[m]	47[n]	Liver
Milano et al	2011	121				Multiple[p]
Breast cancer		39		87[o]	74[a], 47[n]	
All others		82		65[o]	39[a], 9[o]	
Salama et al	2011	61	111	66.7[q,q]	56.7[a]	Multiple
Bae et al (colorectal cancer)	2012	41	50	64[i], 57[h]	64[i], 38[h]	Lung, liver, and lymph node
Norihisa et al	2008	34		90[a]	84.3[a]	Lung

Corbin et al. **Extracranial Oligometastases: A Subset of Metastases Curable With Stereotactic Radiotherapy.** Journal of Clinical Oncology, Vol 31, No 11 (April 10), 2013: pp 1384-1390

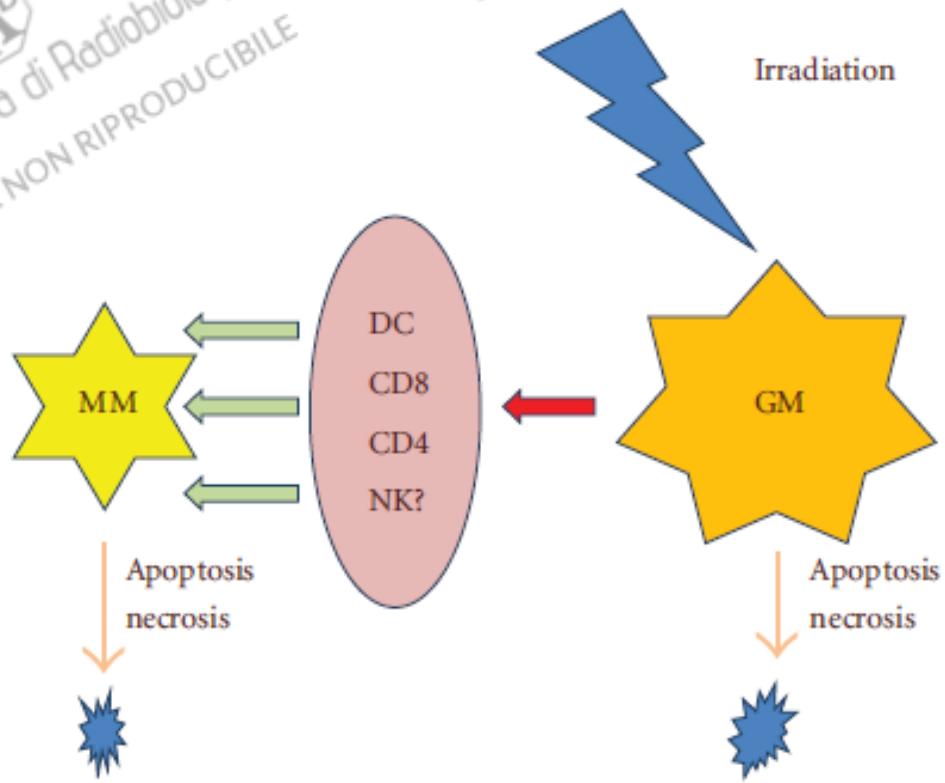
EFFETTO ABSCOPALE E OLIGOMETASTASI

Hindawi Publishing Corporation
Pulmonary Medicine
Volume 2012, Article ID 261096, 5 pages
doi:10.1155/2012/261096

Review Article

Novel Insights of Oligometastases and Oligo-Recurrence and Review of the Literature

Yuzuru Niibe[1] and Joe Y. Chang[2]



RISPOSTA IMMUNOLOGICA E RADIOTERAPIA

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 3, pp. 655–666, 2005

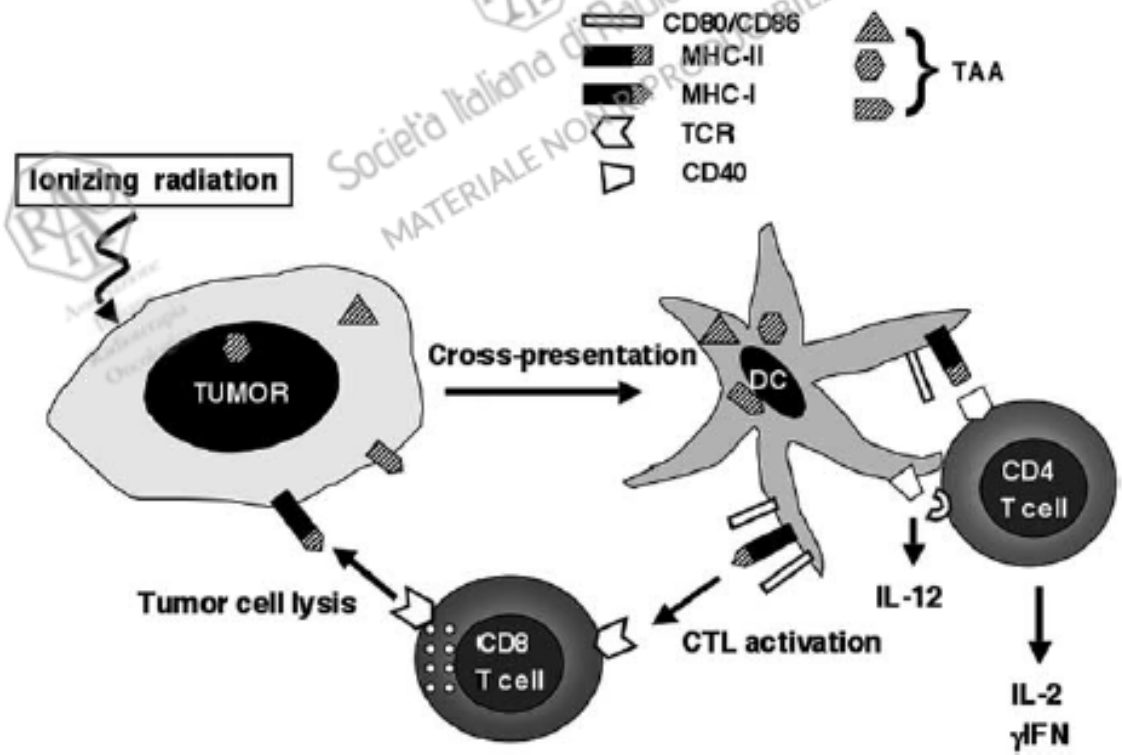
0360-3016/05/$–see front matter

doi:10.1016/j.ijrobp.2005.06.032

CRITICAL REVIEW

COMBINING RADIOTHERAPY AND IMMUNOTHERAPY: A REVIVED PARTNERSHIP

SANDRA DEMARIA, M.D.,* NINA BHARDWAJ, M.D, PH.D.,† WILLIAM H. MCBRIDE, PH.D.,§ AND SILVIA C. FORMENTI, M.D.‡



EFFETTO ABSCOPALE DELLA RADIOTERAPIA

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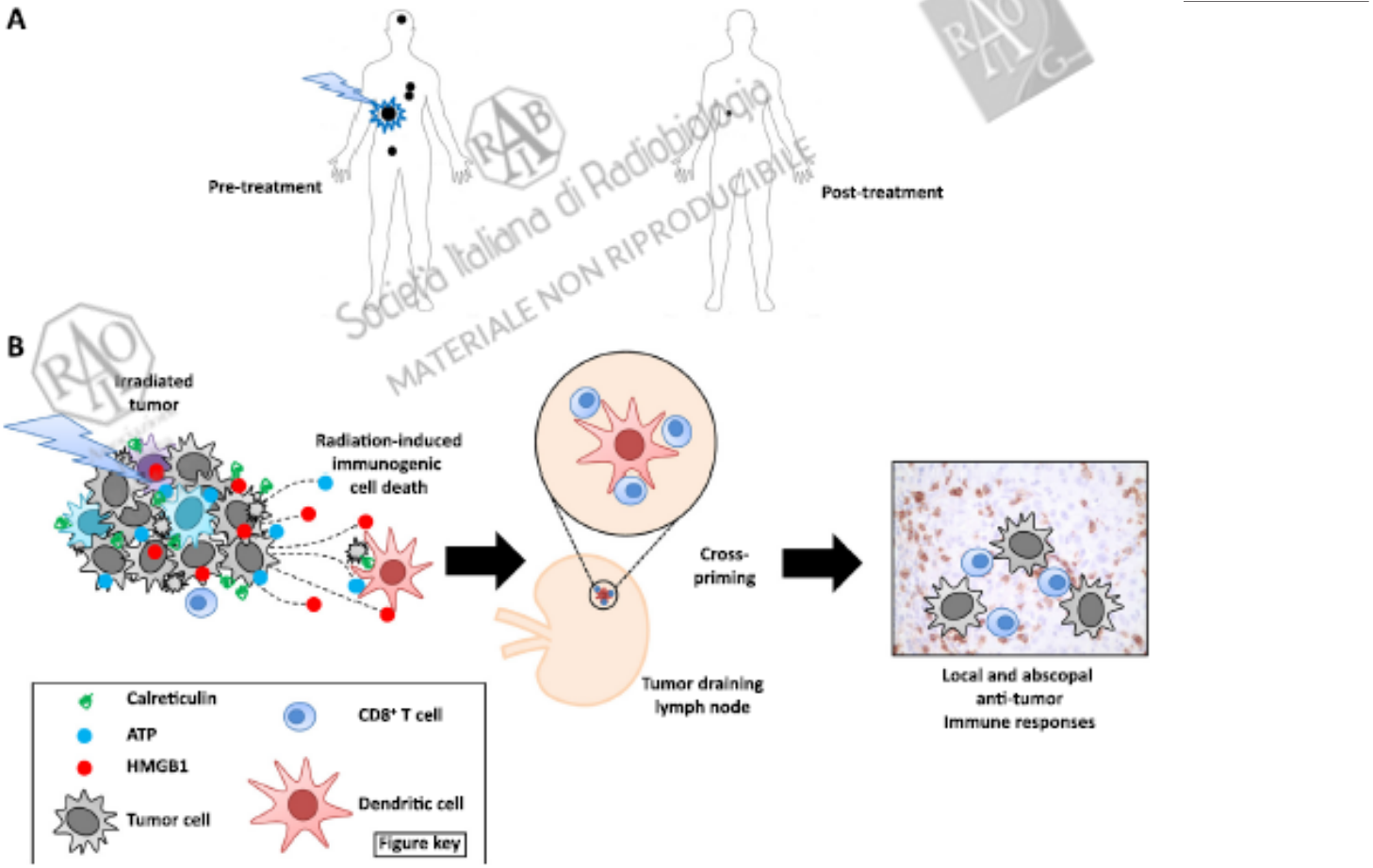
Semin Radiat Oncol 25:11-17 © 2015
Seminars in RADIATION ONCOLOGY

Radiotherapy and Immunogenic Cell Death

Encouse B. Golden, MD, PhD,* and Lionel Apetoh, PhD†,‡,§



EFFETTO ABSCOPALE DELLA RADIOTERAPIA

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Andrews JR. Radiobiology of Human Cancer Radiotherapy. 1978

Wersäll PJ, Blomgren H, Pisa P, Lax I, Kälkner KM, Svedman C. Regression of non-irradiated metastases after extracranial stereotactic radiotherapy in metastatic renal cell carcinoma. Acta Oncol 2006;45:493–7.

Siva S, Callahan J, MacManus MP, Martin O, Hicks RJ, Ball DL. Abscopal [corrected] effects after conventional and stereotactic lung irradiation of non small- cell lung cancer. J Thorac Oncol 2013:e71–2.

Stamell EF, Wolchok JD, Gnjatic S, Lee NY, Brownell I. The abscopal effect associated with a systemic anti-melanoma immune response. Int J Radiat Oncol Biol Phys 2013;85:293–5.

Ishiyama H, Teh BS, Ren H, et al. Spontaneous regression of thoracic metastases while progression of brain metastases after stereotactic radiosurgery and stereotactic body radiotherapy for metastatic renal cell carcinoma: abscopal effect prevented by the blood-brain barrier? Clin Genitourin Cancer 2012;10(3):196–8

Formenti SC, Demaria S. Systemic effects of local radiotherapy. Lancet Oncol 2009;10:718–26.

Lugade AA, Moran JP, Gerber SA, Rose RC, Frelinger JG, Lord EM. Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. J Immunol 2005;174:7516–23.

RADIOTERAPIA E MORTE CELLULARE IMMUNOMEDIATA

- Senescenza, apoptosi, danno al DNA e autofagia indotta dalle basse dosi di radioterapia (calreticulina, heat schock proteins)
- Necrosi, necroptosi, indotta dalle alte dosi.
- Tali eventi sono indotti dalla liberazione di antigeni cellulari quali stress/eat-me/ danger signals (antigeni FAS) che legandosi a recettori presenti sulle cellule tumorali o sulla mebrana delle APCs attivano il sistema immunitario citotossico (Linfociti T CD8+, NK)
- ↑ di molecole di adsività cellulare (ICAM-1, VCAM) che permettono una maggiore interazione con le cellule citotossiche

Radiotherapy and Oncology 120 (2016) 185–194

Contents lists available at ScienceDirect

Radiotherapy and Oncology

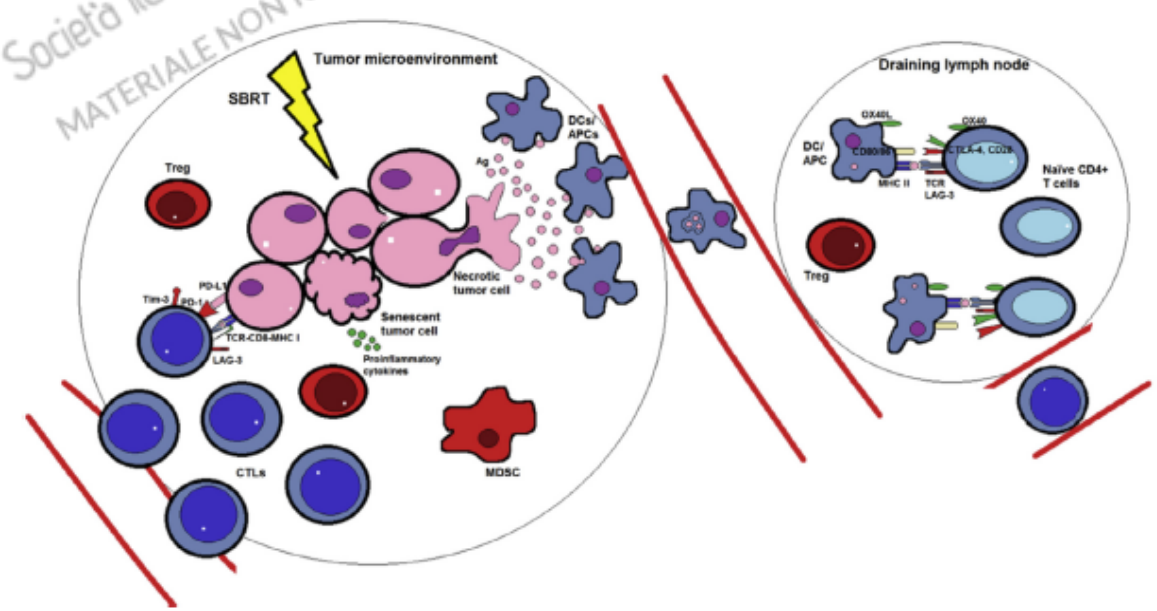
journal homepage: www.thegreenjournal.com

Review

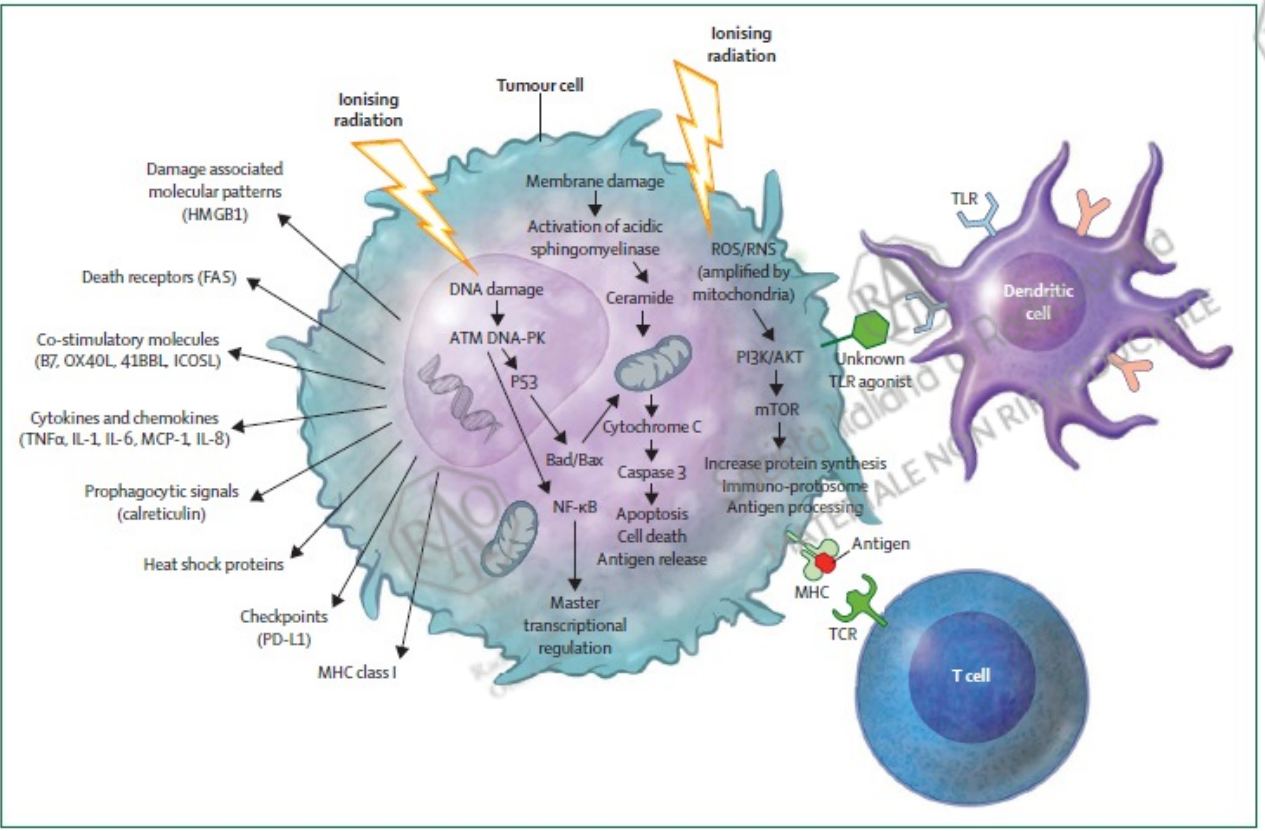
Immune modulation by hypofractionated stereotactic radiation therapy: Therapeutic implications

Ilinca Popp [a,b], Anca Ligia Grosu [a,b], Gabriele Niedermann [a,b], Dan G. Duda [c,*]

[a] Department of Radiation Oncology, University Medical Center Freiburg, Germany; [b] German Cancer Consortium (DKTK), Partner Site Freiburg, Germany; and [c] Steele Laboratories, Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, USA



ANTIGENI TUMORE SPECIFICI, CITOCHINE E RADIOTERAPIA



- ↑ **TNF-a, IL 1, IL 8, IL 6** da parte di linfociti T e delle cellule neoplastiche apoptotiche che determina la selettiva eliminazione delle MDSCs.
- ↑ **OX40L, 41, BBL, ICOSL** che hanno una funzione di co-stimolazione sui linfociti T CD8 e CD4 verso un attività antitumorale.
- ↑ Espressione di molecole di superficie con effetto tolerogenico come **B7L, PD-L1 e L2, Tim-3 e LAG 3.**
- ↑ **Heat schock proteins** che richimana APC e DC

Sharaby et al. **Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy** *Lancet Oncology* 2015; 16: e498–509

SISTEMA IMMUNITARIO E RADIOTERAPIA

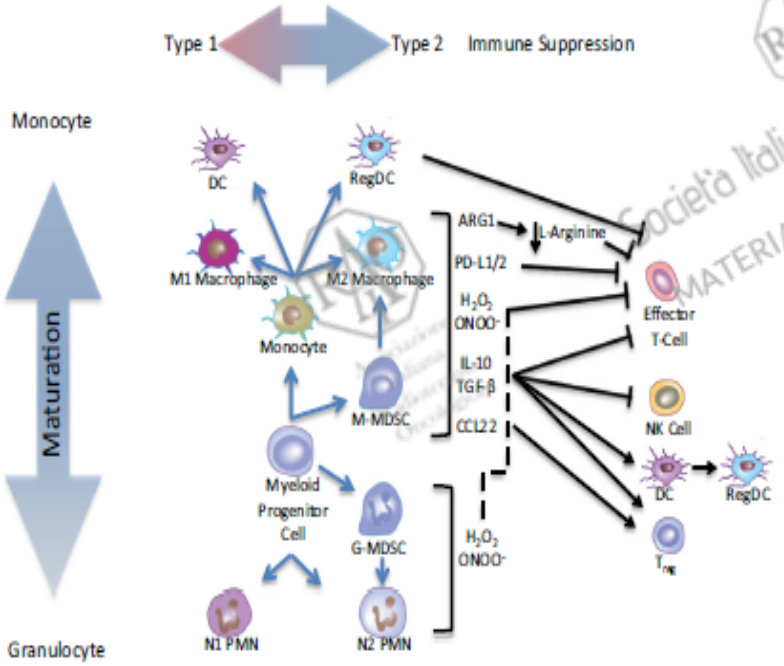
ELSEVIER

Seminars in RADIATION ONCOLOGY

Myeloid-Derived Cells in Tumors: Effects of Radiation

Ralph E. Vatner, MD, PhD and Silvia C. Formenti, MD

Semin Radiat Oncol 25:18-27 © 2015



- **Reclutamento** di cellule TAM M2 e MSDC nel microambiente tumorale attraverso iperespressione di CSF-1 (dosi 3 Gy) e di HIF-1 (Hypoxia-inducible factor) in seguito alla necrosi cellulare indotta da alte dosi di radioterapia (15-20 Gy).

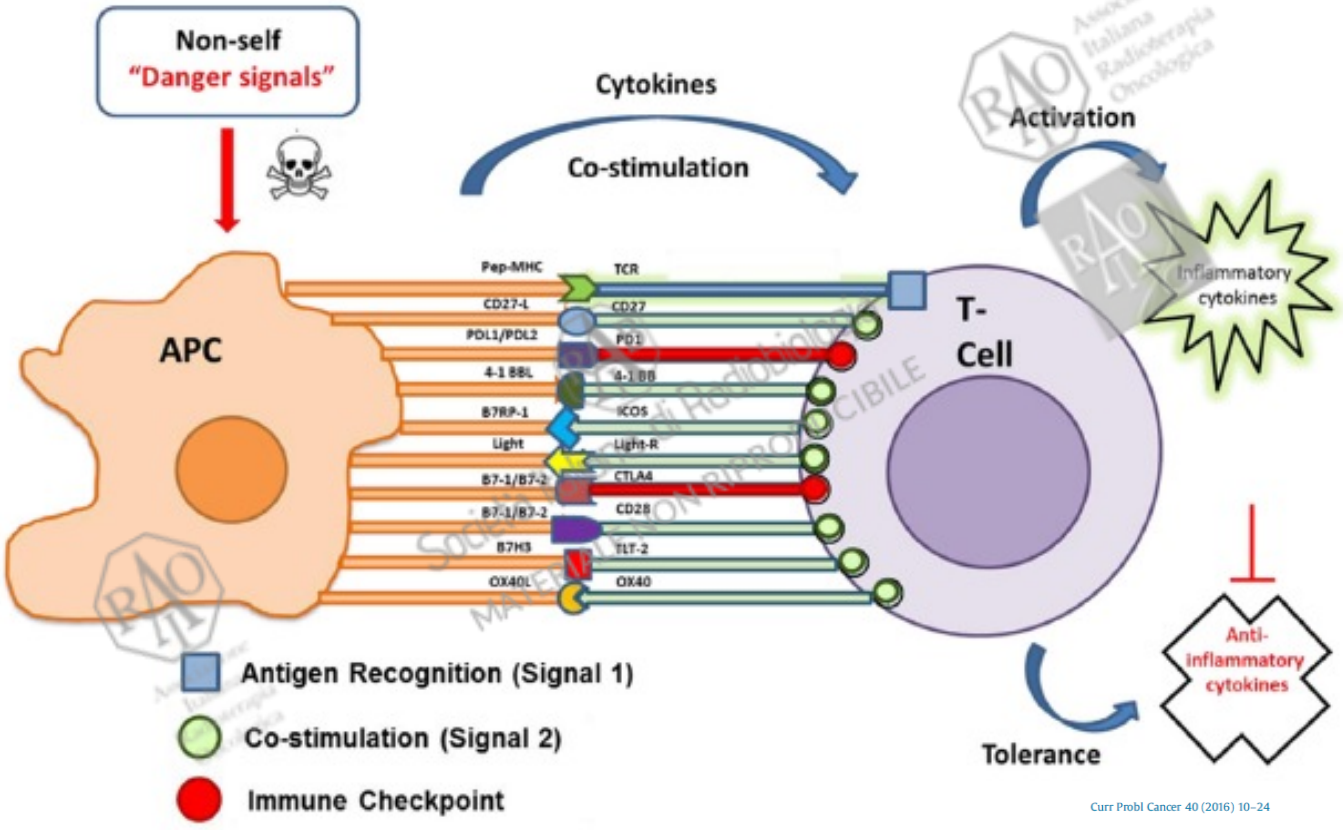
- **Rimozione** di cellule MSDC.

- **Riorganizzazione** delle cellule TAM $CD11b^{low}/CD\ 68^{+}$ e MSDC e PMNs nelle regioni ipossiche e necrotiche del tumore.

- **Ripolarizzazione** delle TAM M2 nel fenotipo M1 che promuovono l'attivita antitumorale.

- **Ripresentazione** degli antigeni tumorali da parte delle cellule APC, DC e dei macrofagi attraverso i recettori MHC di classe 1 e 2 ai linfociti T CD8+ (15-20 Gy).

SISTEMA IMMUNITARIO E RADIOTERAPIA



Curr Probl Cancer 40 (2016) 10–24

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The immune mechanisms of abscopal effect in radiation therapy

G. Daniel Grass, MD, PhD, Niveditha Krishna, MS, Sungjune Kim, MD, PhD

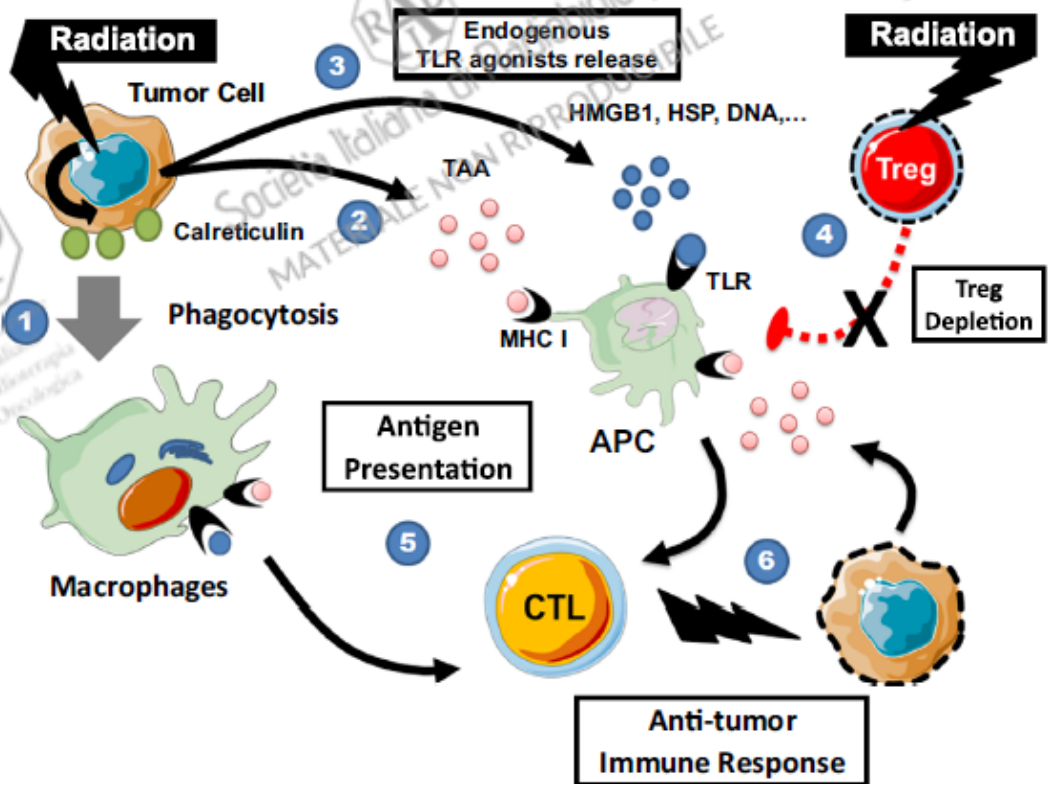
SISTEMA IMMUNITARIO E RADIOTERAPIA

ELSEVIER

Seminars in RADIATION ONCOLOGY

Radiotherapy and Toll-Like Receptor Agonists

Aurelien Marabelle, MD, PhD,* Alex Filatenkov, PhD,† Idit Sagiv-Barfi, PhD,† and Holbrook Kohrt, MD, PhD† Semin Radiat Oncol 25:34-39 © 2015



SISTEMA IMMUNITARIO E RADIOTERAPIA

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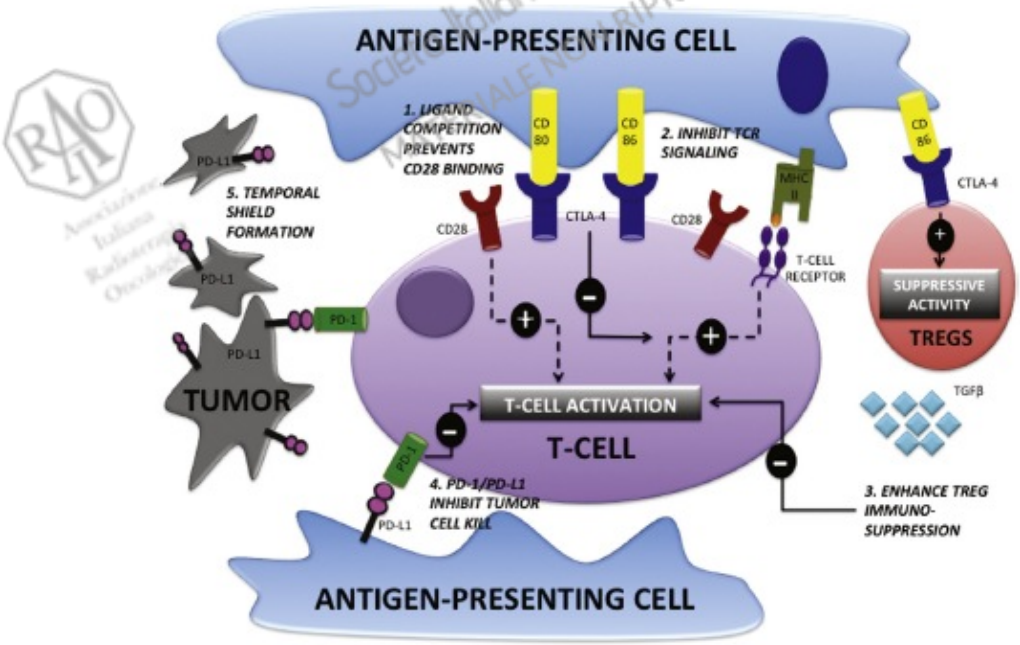
Semin Radiat Oncol 25:28-33 © 2015

Seminars in RADIATION ONCOLOGY

Combination of Radiotherapy and Immune Checkpoint Inhibitors

Karsten A. Pilones, MD, PhD,* Claire Vanpouille-Box, PhD,* and Sandra Demaria, MD*,†,‡

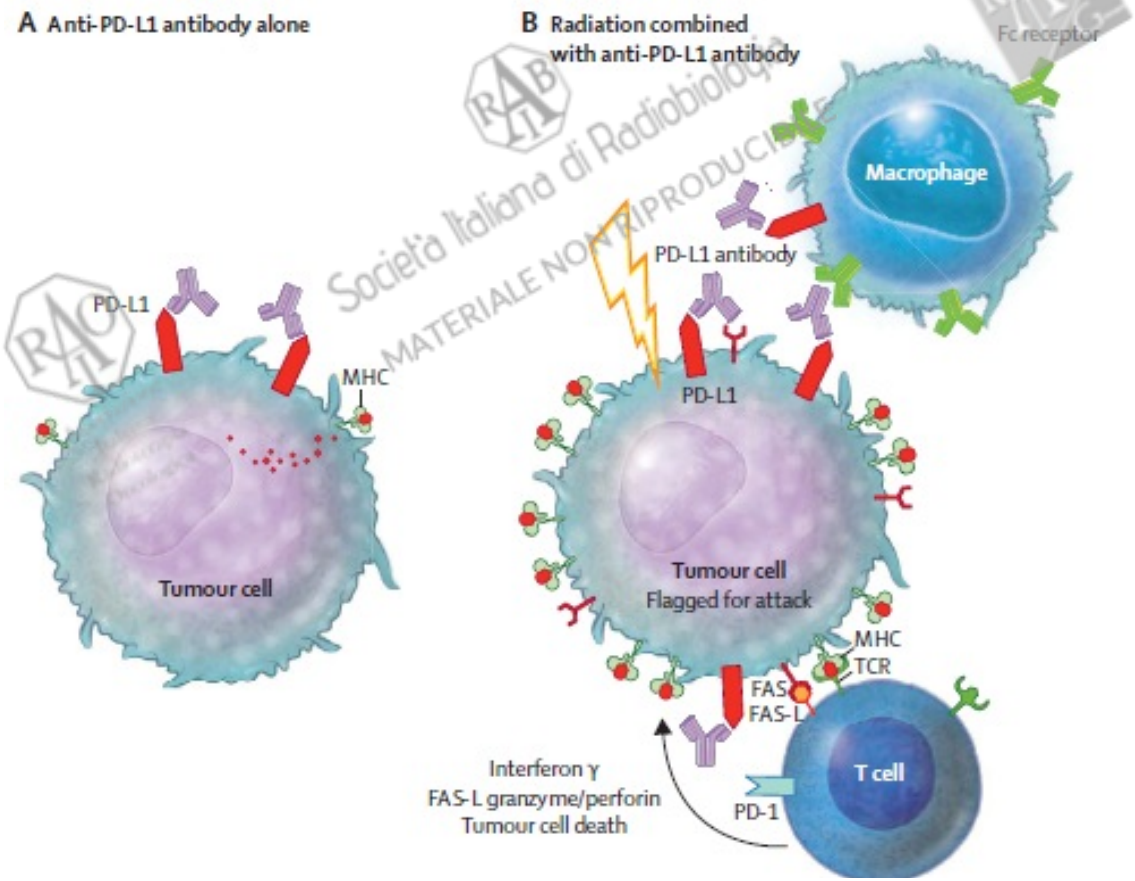


SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA – Blocco delle molecole di checkpoint "MPDL3280A"-

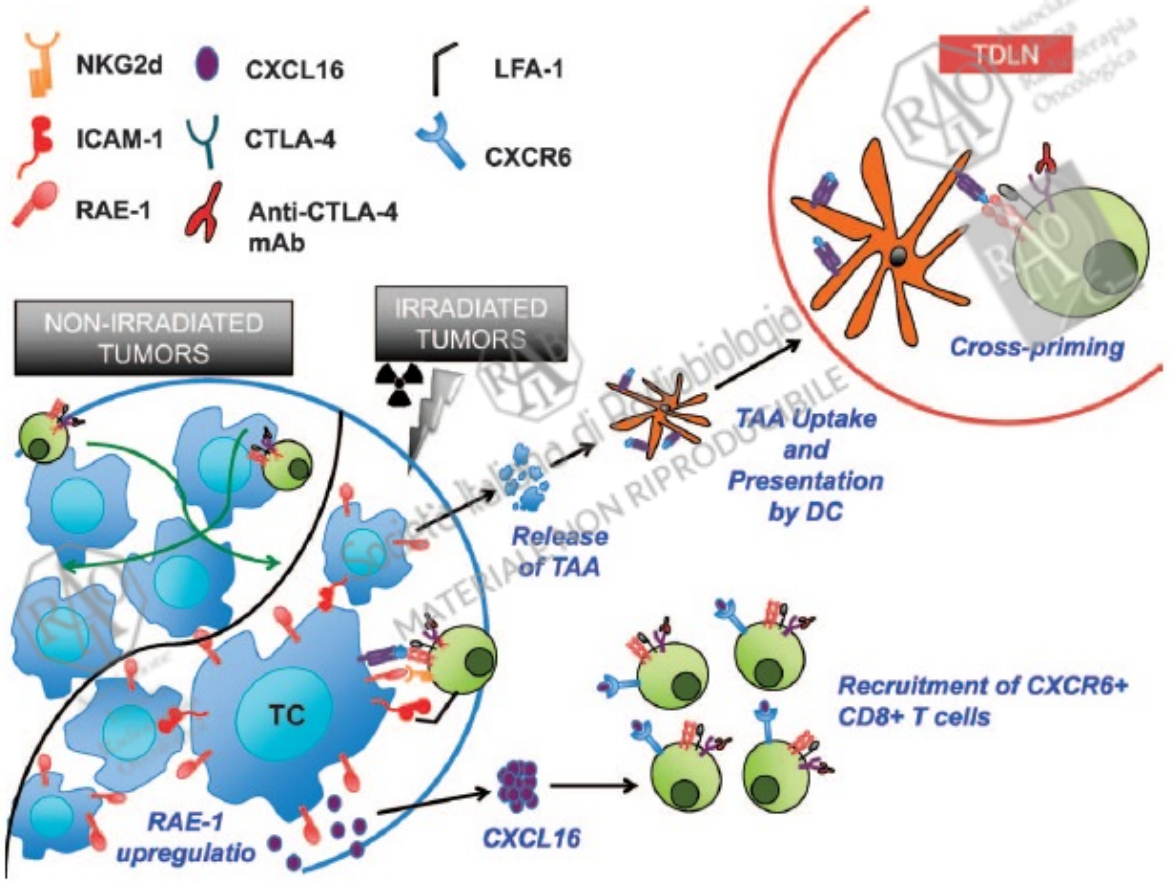
THE LANCET Oncology
2015; 16: e498–509

Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy

Andrew B Sharabi, Michael Lim, Theodore L DeWeese, Charles G Drake



SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA ED – Blocco delle molecole di checkpoint "Ipilimumab"-



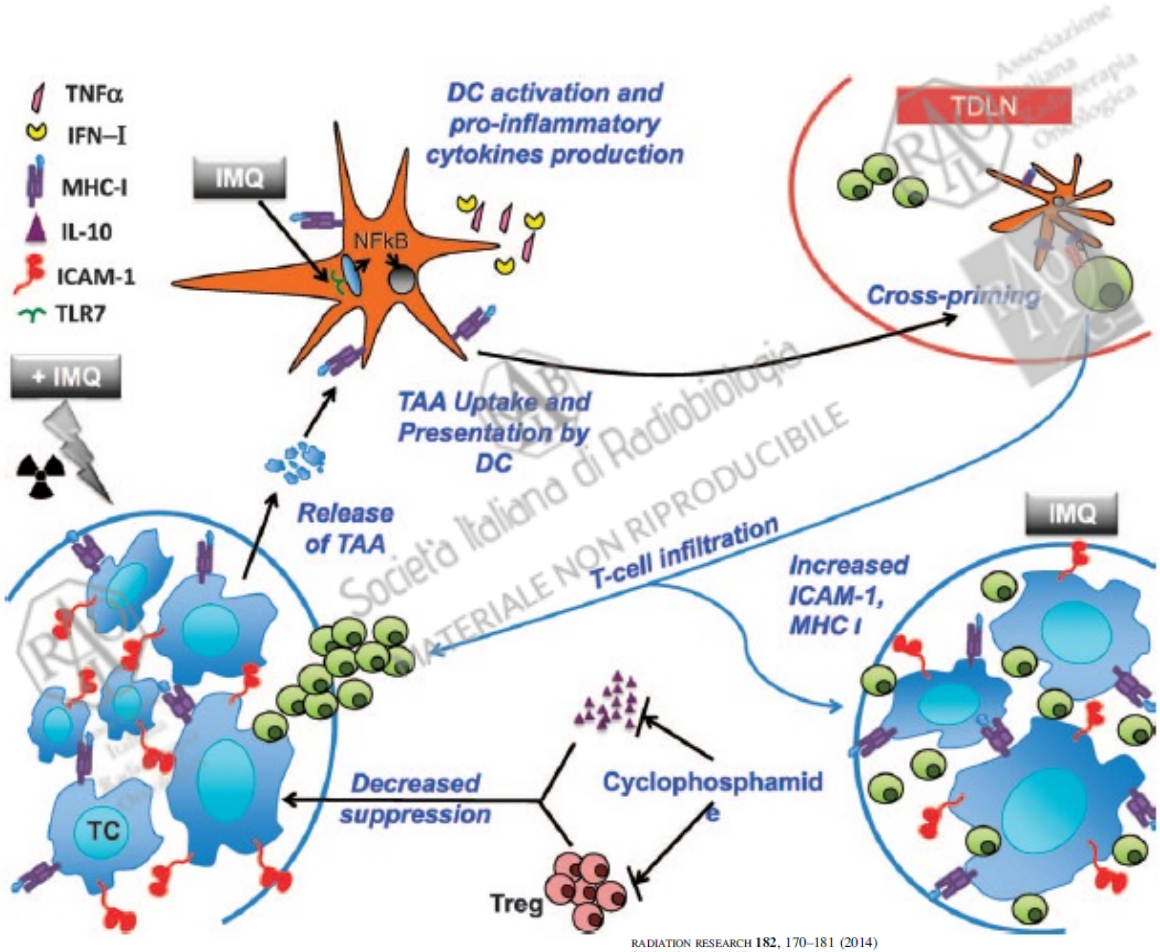
RADIATION RESEARCH 182, 170–181 (2014)
0033-7587/14 $15.00

DOI: 10.1667/RR13500.1

The Optimal Partnership of Radiation and Immunotherapy: from Preclinical Studies to Clinical Translation

Sandra Demaria,[a,b,1] Karsten A. Pilones,[a] Claire Vanpouille-Box,[a] Encouse B. Golden[b] and Silvia C. Formenti[b,1]

SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA ED – Agonisti toll like receptors "Imiquimod"-



RADIATION RESEARCH 182, 170–181 (2014)
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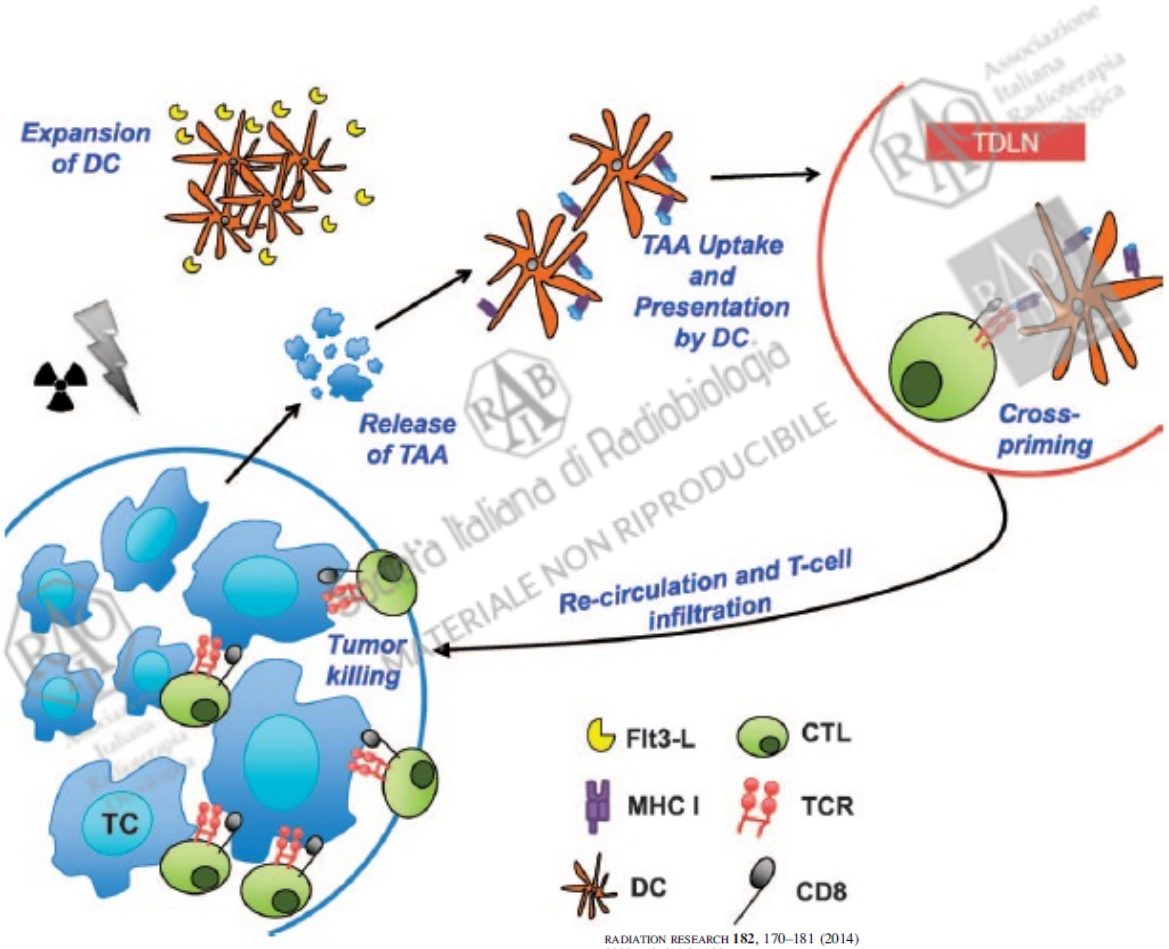
The Optimal Partnership of Radiation and Immunotherapy: from Preclinical Studies to Clinical Translation

Sandra Demaria,[a,b,1] Karsten A. Pilones,[a] Claire Vanpouille-Box,[a] Encouse B. Golden[b] and Silvia C. Formenti[b,1]

SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA ED - Fattori di crescita linfocitari "GM-CSF"-



RADIATION RESEARCH 182, 170–181 (2014)
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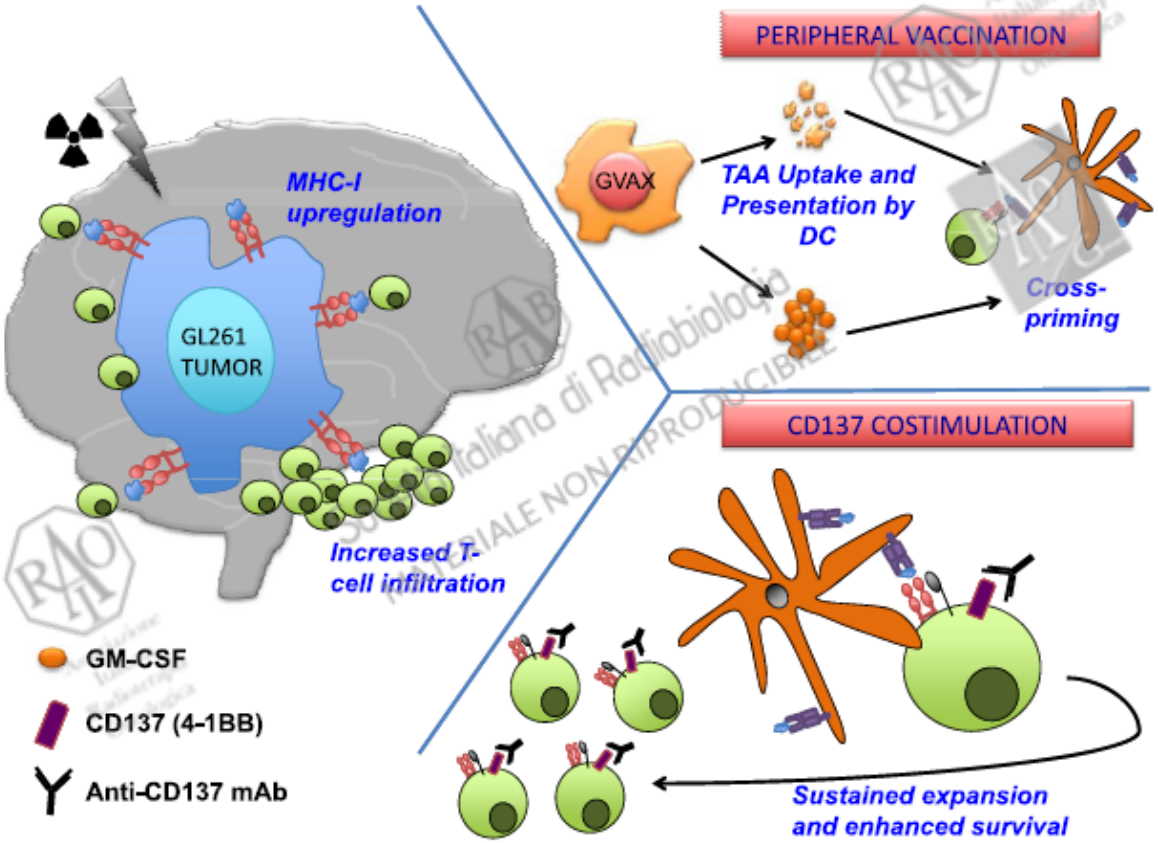
DOI: 10.1667/RR13500.1

The Optimal Partnership of Radiation and Immunotherapy: from Preclinical Studies to Clinical Translation

Sandra Demaria,[a,b,1] Karsten A. Pilones,[a] Claire Vanpouille-Box,[a] Encouse B. Golden[b] and Silvia C. Formenti[b,1]

SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA
- Vaccini -



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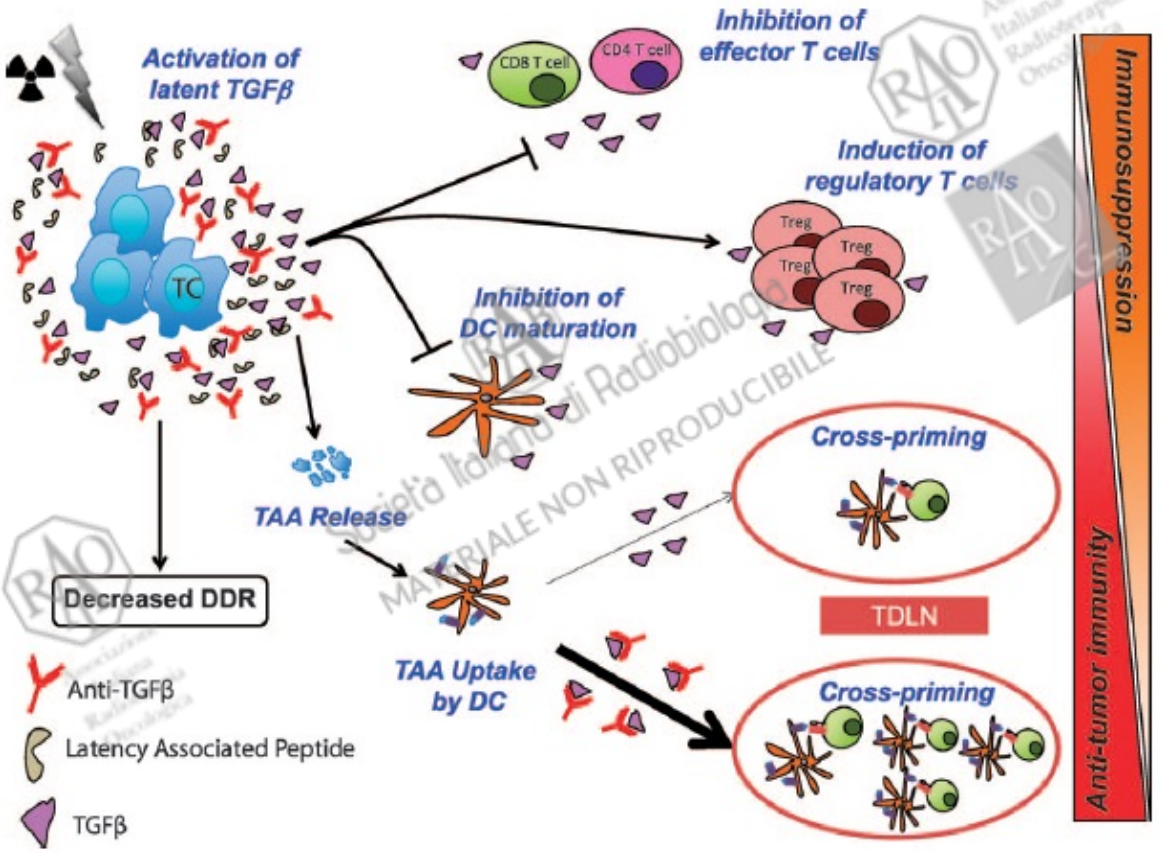
SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA ED

– Anti TGFb "Fresolimumab" -



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SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA
- Timing-

RESEARCH ARTICLE

Optimizing Timing of Immunotherapy Improves Control of Tumors by Hypofractionated Radiation Therapy

Kristina H. Young[1,2]*, Jason R. Baird[1], Talicia Savage[1], Benjamin Cottam[1], David Friedman[1], Shelly Bambina[1], David J. Messenheimer[1], Bernard Fox[1], Pippa Newell[2,3], Keith S. Bahjat[1], Michael J. Gough[1], Marka R. Crittenden[1,2]

Abstract

The anecdotal reports of promising results seen with immunotherapy and radiation in advanced malignancies have prompted several trials combining immunotherapy and radiation. However, the ideal timing of immunotherapy with radiation has not been clarified. Tumor bearing mice were treated with 20Gy radiation delivered only to the tumor combined with either anti-CTLA4 antibody or anti-OX40 agonist antibody. Immunotherapy was delivered at a single timepoint around radiation. Surprisingly, the optimal timing of these therapies varied. Anti-CTLA4 was most effective when given prior to radiation therapy, in part due to regulatory T cell depletion. Administration of anti-OX40 agonist antibody was optimal when delivered one day following radiation during the post-radiation window of increased antigen presentation. Combination treatment of anti-CTLA4, radiation, and anti-OX40 using the ideal timing in a transplanted spontaneous mammary tumor model demonstrated tumor cures. These data demonstrate that the combination of immunotherapy and radiation results in improved therapeutic efficacy, and that the ideal timing of administration with radiation is dependent on the mechanism of action of the immunotherapy utilized.

PLOS ONE | DOI:10.1371/journal.pone.0157164 June 9, 2016

SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA
- Timing-

- Il timing tra somministrazione dell'immunoterapia e la radioterapia è legato al tipo di farmaco impiegato.

- Gli anticorpi agonisti dei costimolatori OX-40 è bene che siano somministrati nelle ore immediatamente successive all'irradiazione, in quanto l'iperespressione delle antigene sulle T cells è di breve durata

- Gli anticorpi anti CLA4 è bene che vengano somministrati prima dell'irradiazione in quanto si ha una deplezione delle cellule Treg, che viene potenziato dalla successiva radioterapia.

- La combinazione di più immunoterapici sembra migliorare l'efficacia dell'irradiazione.

RESEARCH ARTICLE

Optimizing Timing of Immunotherapy Improves Control of Tumors by Hypofractionated Radiation Therapy

Kristina H. Young[1,2]*, Jason R. Baird[1], Talicia Savage[1], Benjamin Cottam[1], David Friedman[1], Shelly Bambina[1], David J. Messenheimer[1], Bernard Fox[1], Pippa Newell[2,3], Keith S. Bahjat[1], Michael J. Gough[1], Marka R. Crittenden[1,2]

1 Earle A. Chiles Research Institute, Robert W. Franz Cancer Center, Providence Portland Medical Center, 4805 NE Glisan St, Portland, OR, 97213, United States of America, 2 The Oregon Clinic, Portland, OR, 97213, United States of America, 3 Providence Hepatobiliary and Pancreatic Cancer Program, Providence Portland Medical Center, 4805, NE Glisan St, Portland, OR, 97213, United States of America

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SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA
- Dosi e frazionamenti-

		Classical fractionation	Hypofractionation	High-dose radiotherapy
positive effects	in vitro	Induction of ICD and Hsp70 release (5x2 Gy; U87MG, T98G, U251) (79) Enhanced DC stimulation and maturation (5x2 Gy; SW480 SN) (80) Induction of pro-inflammatory gene subsets (5x2 Gy; MCF7, DU145, SF539) (81)	Enhanced DC stimulation and maturation (3x 5 Gy; SW480 SN) (80)	IFNγ induction, anti-tumor effect (1x20 Gy, BMDCs) (82)
	in vivo	Enhanced tumor growth control and abscopal effect (5x6 Gy; TSA, MCA38 + CTLA-4 AB) (84) Increase in APC activity and tumor infiltrating immune cells (5x3 Gy; B16-F0) (61)	Superior tumor growth control and abscopal effect (3x8 Gy; TSA, MC38 + CTLA-4 AB) (84) Enhanced tumor growth control and induction of anti-tumor immunity; Tregs ↓ (7.5 Gy/fraction; B16-OVA) (85)	Enhanced tumor growth control (1x20 Gy; TSA, MCA38 + CTLA-4 AB) (84) Dose-dependent impact on tumor growth (7.5-15 Gy; B16-OVA) (85) Induction of CD8+ T cell-mediated immunity alongside with tumor reduction ; abscopal effect (1x15-25 Gy; 4T1, B16, B16-SIY, B16-CCR7, A549)(63) Strong increase in APC activity and tumor infiltrating immune cells (1x15 Gy; B16-F0) (61) Enhanced anti-tumor effects (1x5/10/15 Gy; EMT6+CD137 AB; 1x15 Gy; M109 + CD137 AB) (87) Enhanced apoptosis (max.70 Gy, glioma) (88)
negative effects	in vitro	Radiosensitivity of lymphocytes		Reduced stability of gene induction (1x10 Gy; MCF7, DU145, SF539) (81) No abscopal effect (1x20 Gy; TSA, MCA38 + CTLA-4 AB) (84)
	in vivo	Radiosensitivity of lymphocytes (86, 72) No impact on tumor growth in an melanoma model (5x3 Gy) (61) Abrogation of $CD8^+$-mediated immunity, tumor reduction, and abscopal effect (63)		No anti-tumor immunity (1x20 Gy; TSA MCA38) (84) Treg induction (15 Gy; B16-OVA) (85) No impact on tumor growth in the used melanoma model (1x15 Gy) (61)

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Modern Radiotherapy Concepts and the Impact of Radiation on Immune Activation

*Lisa Deloch†, Anja Derer†, Josefin Hartmann, Benjamin Frey, Rainer Fietkau and Udo S. Gaipl**

SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA
- Dosi e frazionamenti-
Studi pre clinici

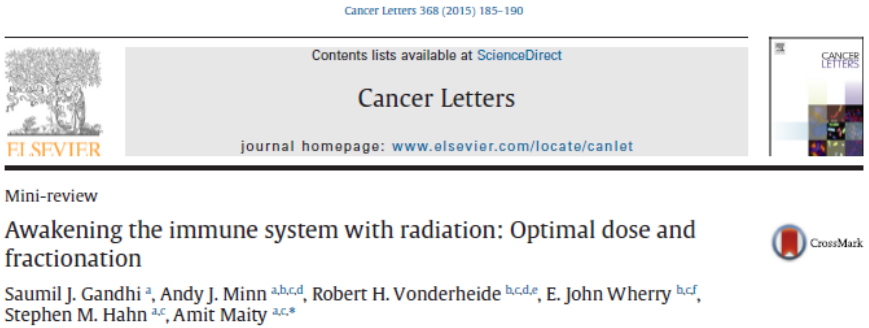
- M. Chakraborty et al (2003) hanno dimostrato che su linee cellulari di adenocarcinoma murino irradiate a 10, 20, 50 Gy l'iperespressione di antigeni di membrana FAS è proporzionale alla dose somministrata.
- Reits et al (2006) hanno evidenziato che con l'irradiazione di cellule umane di melanoma a dosi di 1,4,7,10 o 25 Gy l'iperespressione delle molecole MHC 1 di superficie raddoppia a dosi comprese tra 10 e 25 Gy.
- Schaue et al. (2012) hanno rilevato che l'irradizione di topi con melanoma con dosi di 15 Gy somministrati in 5, 3, o 2 frazioni determina una maggiore attivazione dei linfociti T sia CD8 che CD4 con lo schema di frazionamento di 7.5 Gy/2F
- Golden et al (2014) sottoponendo topi affetti da melanoma a dosi di radioterapia variabili da 20 G/F, 8 Gy x 3 F, o 6 Gy x 5 F associati o meno ad ipilimumab si osservava regressione di malattia sia sulla sede irradiata che sulle sedi secondari con regimi di 8 Gy x 3 F. Nessun controllo tumorale si osservava nei topi non irradiati.
- Verbrugge et al. (2012) hanno osservato che l'irradiazione di topi con tumore mammario triplo negativo con dosi di 12 G/1F, 4 Gy/5F o 5 Gy in 4 F associato ad anticorpi anti PD – 1 (nivolumab) determina regressione della sede tumorale primaria prevalentemente con il primo schema di radioterapia

SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA
- Dosi e frazionamenti-
Studi clinici

- Postow et al (2009) hanno evidenziato regressione tumorale in 1 paziente affetto da melanoma metastatico con l'irradiazione a dosi di 9.5 Gy x 3 F di una massa paraspinale e con la somministrazione d ipilimumab.

- Golden et al (2014)) hanno evidenziato regressione tumorale in 1 paziente affetto da adenocarcinoma polmonare metastatico con l'irradiazione di 2/7 lesioni epatiche a dosi di 17 Gy x 3 F e ipilimumab.

- Seung et al (2012) hanno evidenziato regressione tumorale in 8/12 pazienti (66%) affetti da tumore renale o melanoma metastatici con l'irradiazione di una sola sede metasatica con dosi di 20 Gy in 1, 2, o 3 frazioni e l'associazione di IL2. Tale effetto era in contrasto con un precedente studio (Lange et al del 1992) dove solo il 7% dei pazienti mostrava risposta terapeutica parziale. Le dosi di SBRT impiegate variavano da 10 a 20 Gy somministrate in due frazioni giornaliere di 5 Gy.


Cancer Letters 368 (2015) 185–190

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Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Awakening the immune system with radiation: Optimal dose and fractionation

Saumil J. Gandhi [a], Andy J. Minn [a,b,c,d], Robert H. Vonderheide [b,c,d,e], E. John Wherry [b,c,f], Stephen M. Hahn [a,c], Amit Maity [a,c,*]

SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA ED EFFETTO ABSCOPALE

	♂♀	Age	Histology	Primary site	Treatment of primary	RT treated sites	Treatment + RT Dose/ fractions	Non-irradiated abscopal regression	Time until abscopal response	PFS after response*
2014	M	74	Adenocarcinoma	Lung	Resection	Supraclavicular LN	BCG-vaccine 58 Gy/29x	Lung M+	6 m	47 m
2013	M	64	Adenocarcinoma	Lung	CT (PD)	Hepatic M+	Ipilimumab 30 Gy/5x	Liver M+/Bone M+/Lung M+	3 m	5 m
2012	M	57	Melanoma	Arm	Wide excision/axillary dissection	Hepatic M+	Ipilimumab 54Gy/3x	Cutaneous M+	6 m	6 m
2012	M	67	Melanoma	Scalp	CT (PD)	Brain M+	Ipilimumab SRT**	Nodal M+	NR	NR
2012	F	33	Melanoma	Upper back	Wide excision	Paraspinal M+	Ipilimumab 28,5 Gy/3x	Splenic M+/hilar LN	4 m	6 m

SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA
- Tossicità-

- Effetti avversi comuni degli inibitori delle molecole del check-point sono enterocolite, epatite, ipofisite, uveite, dermatite, fatigue, eventi muscoloschelitrici.

- Boyer et al (2016) su 7 pazienti affetti da NSLC e trattati con radioterapia adiuvante successivamente alla somministrazione di ipilimumab non hanno osservato tossicità di Grado 3 o superiore in nessuno di essi.

- Sibaud et al (2014) ha evidenziato un fenomeno di recall su un paziente affetto da lesioni secondarie da melanoma dopo radioterapia palliativa su gomito (esantema cutaneo) con una dose di 30 Gy in 6 frazioni eseguita con tecnica 3dCRT con due campi contropposti e contemporanea somministrazione di pembrolizumab.

- I futuri trials clinici saranno determinanti per valutare il rischio di tossicità cumulativa nei trattamenti combinati radio-immunoterapici.


Radiotherapy and Oncology 120 (2016) 185–194

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review

Immune modulation by hypofractionated stereotactic radiation therapy: Therapeutic implications

Ilinca Popp [a,b], Anca Ligia Grosu [a,b], Gabriele Niedermann [a,b], Dan G. Duda [c,*]

[a] Department of Radiation Oncology, University Medical Center Freiburg, Germany; [b] German Cancer Consortium (DKTK), Partner Site Freiburg, Germany; and [c] Steele Laboratories, Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, USA

SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA
Studi clinici aperti - Citochine

Drug class	Study ID	Title	Tumor site/stage	Design	Phase	Study aims	Immune agents	RT	Key inclusion criteria	Institution
TGF-B antagonist	NCT01401062	Fresolimumab and RT in Metastatic Breast Ca	Breast cancer (metastatic)	2 Arms: RT + Fresolimumab (A) 1 (B) 10 mg/kg dose	I/II	(1) Safety and feasibility (2) local response rate and to determine if the treatment elicits abscopal regression	TGF-B antagonist (Fresolimumab)	7.5 Gy × 3	3 Distinct measurable metastatic sites, 1 at least 1 cm in size, failed at least 1 line of therapy	New York University
IFN	ISRCTN62866759	Comparison of three different therapies (radio-, chemo-, and immunotherapy) in patients with resected pancreatic adenocarcinoma	Resected Pancreatic	3 Arms: (A) Cisplatin + 5FU +IFN +RT (B) 5FU+ IFN+ RT (C) 5FU + IFN	II	(1) Event-free survival (grade > toxicity, death, recurrence) (2) RFS, OS, QOL, Immunologic parameters	IFN-a	50.4 Gy/28 fractions over 5.5 weeks	R0/R1 resected pancreatic ductal adenocarcinoma, started <8wks after surgery	University of Heidelberg (Germany)
IL-2	NCT01416831	SBRT and high-dose IL-2 in Metastatic Melanoma	Melanoma (metastatic)	2 Arm: (A) IL-2 (B) IL-2 + SBRT	II	(1) Response rate with the addition of SBRT (2) Response of SBRT in patients who cross over owing to disease progression on IL-2 alone (3) Evaluate difference in markers (tumor lysis, inflammation, and immune activation) with the addition of SBRT	High-dose IL-2	20 Gy × 1 or 20 Gy × 2	2 Distinct measurable sites with at least 1 metastatic lesion amenable to SBRT in lung, mediastium, or liver	Earle A. Chiles Research Institute, Providence Cancer Center
	NCT02306954	Study of High Dose Interleukin-2 (IL-2) and Stereotactic Body Radiation (SBRT) in Patients With Metastatic Renal Cancer	RCC (metastatic)	2 Arm: (A) IL-2 (B) IL-2 + SBRT	II	(1) Response rate with the addition of SBRT (2) Response of SBRT in patients who cross over owing to disease progression on IL-2 alone	High-dose IL-2	20 Gy × 2	2 Distinct measurable sites with at least 1 metastatic lesion amenable to SBRT in lung, mediastium, or liver	Earle A. Chiles Research Institute, Providence Cancer Center

SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA
Studi clinici aperti – Attivatori linfocitari

Drug class	Study ID	Title	Tumor site/stage	Design	Phase	Study aims	IMMUNE AGENTS	RT	Key inclusion criteria	Institution
TLR Agonist	NCT01421017	Imiquimod, Cyclophosphamide and RT in Breast Cancer patients with Chest wall or Skin Metastasis	Breast (metastatic)	3 Arms: (A) IMQ + RT + cyclophosphamide (B) IMQ +RT (C) CTX + RT	I/II	(1) Safety and feasibility (2) If the treatment elicits abscopal tumor regression (3) Examine if treatment is associated with immunologic changes	TLR7 agonist (Imiquimod)	6 Gy × 5	2 Distinct measurable lesions, 1 of which must be either at least 1 cm or a skin metastasis	New York University
	NCT02254772	TLR9 Agonist SD-101, Ipilimumab, and Radiation Therapy in Treating Patients With Low-Grade Recurrent B-cell Lymphoma	recurrent B-cell Lymphoma (low grade)	1 Arm: ipi + RT + TLR9	I	(1) Incidence of dose-limiting toxicity and determination of dose of intratumoral ipilimumab between two doses tested (2) Clinical response rate including un-injected sites of disease and Induction of tumor-specific immune response	CTLA-4 antagonist (ipilimumab; dose escalated), TLR9 agonist (SD-101)	2G y × 2	Relapse or refractory to prior therapy, at least 1 site accessible for intratumoral injection (at least 1 cm)	Stanford
	NCT02266147	Study of SD-101 in Combination With Localized Low-dose Radiation in Patients With Untreated Low-grade B-cell Lymphoma	B-cell Lymphoma (low grade)	1 Arm: TRL9 + RT	I	Number of participants experiencing dose-limiting toxicities (DLTs), injection-site reactions (ISRs), adverse events (AEs), and serious adverse events (SAEs).I Changes in interferon (IFN)-inducible genesIResponse rate of treated tumor according to Cheson criteriaI Response rate of untreated tumor according to Cheson criteria	TLR9 agonist (SD-101; Dose escalated: 1 vs 2 vs 4 vs 8 mg/mL)	Low dose	2 Sites of measurable disease, 1 must be palpable and easily accessible for intratumoral injection, 1 site not in RT field	Dynavax technologies corporation
PDE5 Inhibitor	NCT01903083	Chemoimmunotherapy and Radiation in Pancreatic Cancer	Pancreas (LA/BR)	1 Arm: Gemcitabine + tadalafil + hypofractionated RT	I	(1) Safety and feasibility (2) Assess immune tumor infiltration (3) Influence of combined treatment on immunity	PDE5 inhibitor (tadalafil)	8-10 Gy × 3	Nonmetastatic, locally advanced unresectable or borderline resectable pancreatic adenocarcinoma	Earle A. Chiles Research Institute, Providence Cancer Center

SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA
Studi clinici aperti – Vaccini

Drug class	Study ID	Title	Tumor site/stage	Design	Phase	Study aims	Immune agents	RT	Key inclusion criteria	Institution
DC Vaccine	NCT01807065	Sipuleucel-T With or Without Radiation Therapy in Treating Patients With Hormone-Resistant Metastatic Prostate Cancer	Prostate (metastatic)	2 Arms: (1) sipuleucel-T (2) RT + sipuleucel-T	II	(1) Compliance and safety of vaccination 3 infusions (2) Toxicity and immune response	DC vaccine (sipuleucel-T)	Palliative RT dose in weeks 1-2	Measurable metastatic disease, castration resistant	City of Hope Medical Center
	NCT01818986	Sipuleucel-T and stereotactic ablative body radiation (SABR) for metastatic castrate-resistant prostate cancer (mCRPC)	Prostate (metastatic)	1 Arm: sipuleucel-T +SBRT	II	(1) Tme to progression (2) Immune response	DC vaccine (sipuleucel-T)	SBRT	Measurable metastatic disease, on androgen deprivation, up to 6 sites treated	UT Southwestern
	NCT01833208	Radiation therapy in treating patients with metastatic hormone-resistant prostate cancer receiving sipuleucel-T	Prostate (Metastatic)	1 Arm: Sipuleucel-T + SBRT	II	(1) Whether RT increases the immunogenic potential for sipuleucel-T, overall immunogenic response (2) Toxcity, PSA changes, OS, CSS	DC Vaccine (Sipuleucel-T)	SBRT (1 fraction) 2 days after 1st sipuleucel-T	Castration resistant, metastatic bone lesions	Roswell Park
	NCT01973322	Vaccination With Autologous Dendritic Cells Loaded With Autologous Tumor Lysate or Homogenate Combined With Immunomodulating Radiotherapy and/or Preleukapheresis IFN-alfa in Patients With Metastatic Melanoma: a Randomized "Proof-of-principle" Phase II Study	Melanoma (Metastatic)	4 Arms: (1) DC Vaccine + RT (2) DC Vaccine + IFN-a (3) DC Vaccine +IFN-a + RT (4) DC vaccine	II	(1) Safety, tolerability, immune efficacy, immune-related disease control (2) OS, immune-related TTP, biological effects	DC vaccine, IFN-a	8-12 Gy × 3	2 Lesions, with 1 measurable and at least 1 cm	Istituto Scientifico Romagnolo per lo Studio e la cura dei Tumori
	NCT01347034	Radiation therapy and intratumoral autologous dendritic	STS (intermediate/ high-grade)	2 Arms: (1) RT then surgery	II	(1) Enhanced T lymphoyte Immune response with addition of DC	DC Injection	RT (50 Gy/25 fractions with 1 10 Gy boost)	Intermediate- or high-grade STS of extremities, trunk, or chest	Moffitt Cancer center

SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA
Studi clinici aperti – Costimolatori e Blocco dei recettori check point

Drug class	Study ID	Title	Tumor site/stage	Design	Phase	Study aims	Immune agents	RT	Key inclusion criteria	Institution
CTLA-Antogonist	NCT01769222	Ipilimumab and Local Radiation Therapy in Treating Patients With Recurrent Melanoma, Non-Hodgkin Lymphoma, Colon, or Rectal Cancer	Recurrent melanoma, NHL, colorectal cancer	1 Arm: ipi + RT	I-II	(1) Safety (2) immune response (biomarker analysis), response rate, OS, duration of response	CTLA-4 antagonist (ipilimumab, intratumorally × 1 on day 1; dose escalated)	RT started within 2 days of ipi, minimum 3 fractions	2 Measurable lesions, 1 > 1 cm and amenable to biopsy, recurrent disease, failed or intolerant to 1 prior systemic treatment	Stanford
	NCT01449279	Pilot ipilimumab in Stage IV Melanoma Receiving Palliative Radiation Therapy	Melanoma (stage IV)	1 Arm: ipi + RT	I-II	(1) Safety (2) response rate, OS, duration of response	CTLA-4 antagonist (ipilimumab, 3 mg/kg q3wks × 4)	Palliative RT within 2 days of first ipi dose	Unresectable metastatic melanoma, failed 1 prior systemic therapy	Stanford
	NCT01565837	Concurrent Ipilimumab and Stereotactic Ablative Radiation Therapy (SART) for Oligometastatic But Unresectable Melanoma	Melanoma (oligometastatic but unresectable)	1 Arm: ipi + SRT	II	(1) Safety and tolerability (2) 1 and 2-Year disease control and OS	CTLA-4 antagonist (ipilimumab, 10 mg/kg IV q3wks × 4 then q12wks)	SRT 1-5 lesions between 1st and 3rd ipi cycle	Stage III-IV melanoma with 5 or less metastatic sites not resectable	Comprehensive cancer centers of Nevada
	NCT01497808	RADVAX: A Stratified Phase I/II Dose Escalation Trial of Stereotactic Body Radiotherapy Followed by Ipilimumab in Metastatic Melanoma	Melanoma (metastatic)	1 Arm: SRT + ipi	II	(1) Dose limit toxicity	CTLA-4 antagonist (ipilimumab)	SRT (dose escalated) to 1 lesion, before ipi	Metastatic melanoma with an index lesion between 1 and 5 cm in size	University of Pennsylvania
	NCT02107755	Stereotactic Radiation Therapy and Ipilimumab in Treating Patients	Melanoma (metastatic)	1 Arm: ipi +SRT	II	(1) PFS (2) Toxicity, response rate, local failure, OS	CTLA-4 antagonist (ipilimumab, IV q3wks × 4)	SRT2-3 fractions on week 5-6	1-3 Metastatic sites amenable to SBRT	Ohio State Comprehen-sive Cancer Center

SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA
Studi clinici aperti – Costimolatori e Blocco dei recettori check point

Drug class	Study ID	Title	Tumor site/stage	Design	Phase	Study aims	Immune agents	RT	Key inclusion criteria	Institution
		Untreated Stage III-IVB Head and Neck Cancer							hypopharynx, > 10 pack-yrs, > N1, T4)	
	NCT01860430	A Phase Ib Trial of Concurrent Cetuximab (ERBITUX) and intensity-modulated radiotherapy (IMRT) With ipilimumab (YERVOY) in locally advanced head and neck cancer	Head and neck (stage III-IV)	1 Arm: IMRT with cetuximab and dose escalating ipi	II	(1) MTD of ipi (2) Clinical response, PFS, biomarkers, dose response modeling	CTLA-4 antagonist (ipilimumab, Dose escalated: 1, 3, 6, or 10 mg/kg, starts wk 5, q3wks × 4) + EGFR antagonist (cetuximab, 250 mg/m^2/wk during weeks 1-8)	IMRT weeks 2–8 (70–74 Gy)	Measurable disease (> 2 cm), newly diagnosed stage III-IVB squamous cell of HN, and intermediate- or high-risk disease (HPV-, larynx, or hypopharynx, > 10 pack-yrs, > N1, T4)	University of Pittsburgh-NCI
OX40-agonist	NCT01862900	SBRT and Monocolonal Antibody to OX40 in Breast Cancer Patients with Metastatic Lesions	Breast cancer (metastatic)	1 Arm: SBRT + OX40	I/II	(1) Determine MTD and safety of SBRT (2) Estimate response rate to combined treatment (3) Determine the influence on immuno-genicity	OX40-agonist	MTD: 15 Gy × 1, 20 Gy × 1, 20 Gy × 2	2 Distinct lesions: 1 site in lung or liver amenable to SBRT and 1 evaluable disease not receiving RT	Earle A. Chiles Research Institute, Providence Cancer Center
	NCT01303705	OX40, Cyclophospha-mide, and RT in patients with Progressive Metastatic Prostate Cancer	Prostate (metastatic)	1 Arm: CTX (dose escalated) + OX40 + RT	Ib	(1) Determine MTD of CTX (2) Effect of therapy on T cells numbers (3) Measure activity of effector and memory T cells (4) Estimate response rate of combined treatment	OX40-agonist	8 Gy × 1	1 Bone metastasis or measurable distant metastasis in patients with progression after 1 androgen ablation and docetaxel treatment	Earle A. Chiles Research Institute, Providence Cancer Center

SINERGISMO RADIOTERAPIA – IMMUNOTERAPIA
Studi clinici aperti – Costimolatori e Blocco dei recettori check point

Drug class	Study ID	Title	Tumor site/stage	Design	Phase	Study aims	Immune agents	RT	Key inclusion criteria	Institution
PD-1 inhibitors	NCT02298946	AMP-224, a PD-1 Inhibitor, in Combination With Stereotactic Body Radiation Therapy in People With Metastatic Colorectal Cancer	Colorectal (metastatic)	2 Arms: (A) CTX + SBRT + AMP-224 (B) SBRT (3 days) +CTX + AMP-224	I	(1) Safety and tolerability (2) Response rate, PFS, OS, and pharmaco-kinetics	PD-1 inhibitor (AMP-224, 10 mg/kg q2wks × 6)	(A) 8 Gy × 1 on day 0 with CTX, before AMP (B) 3 Gy × 3 starting on day-2, before CTX and AMP	Progressive or intolerant to oxaliplatin and irinotecan regimen, no curative resection, 2 metastatic foci with 1 in liver amenable to SBRT and 1 outside RT field	National Cancer Institute (NCI)‖ National Institutes of Health Clinical Center (CC)
	NCT02303990	RADVAX: A Stratified Phase I Trial of Pembrolizumab With Hypofractiona-ted Radiotherapy in Patients With Advanced and Metastatic Cancers	Metastatic cancers	1 Arm: PD-1 inhibitor + RT	I	(1) Safety and feasibility	PD-1 inhibitor (Pembro-lizumab)	Hypofractionated RT	Stage IV cancer, an index lesion >1-cm amenable to hypofractionated RT and failed 1 systemic treatment of metastases	Abramson Cancer Center of the University of Pennsylvania

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Clinical trials exploring the benefit of immunotherapy and radiation in cancer treatment: A review of the past and a look into the future

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CONCLUSIONI

- I pazienti oligometastatici sono da considerare soggetti potenzialmente curabili e meritano un approccio terapeutico più aggressivo.
- La radioterapia con schemi ipofrazionati è una modalità terapeutica particolarmente efficace in questo set di pazienti.
- Oltre ad avere un effetto tumoricida diretto è in grado di determinare un attivazione del sistema immunitario contro le cellule neoplastiche sia sulla sede irradiata che sui siti secondari di metastasi.
- Tale effetto abscopale può essere potenziato dalla combinazione di vaccini o farmaci immunoterapici che a loro volta modulano il sistema immunitario dell'ospite contro le cellule tumorali.
- La sinergia tra radioterapia e immunoterapia sembra essere maggiore utilizzando schemi di irradiazione con alte dosi e ipofrazionati.
- Studi futuri, in corso, permetteranno di dimostrare l'efficacia di tali trattamenti combinati ed eventualmente di individuare i pazienti più suscettibili a tali terapie più aggressive.