Society for Immunotherapy of Cancer (SITC)

Is There a Role for Radiation Therapy and Immunotherapy?

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Society for Immunotherapy of Cancer

Outline

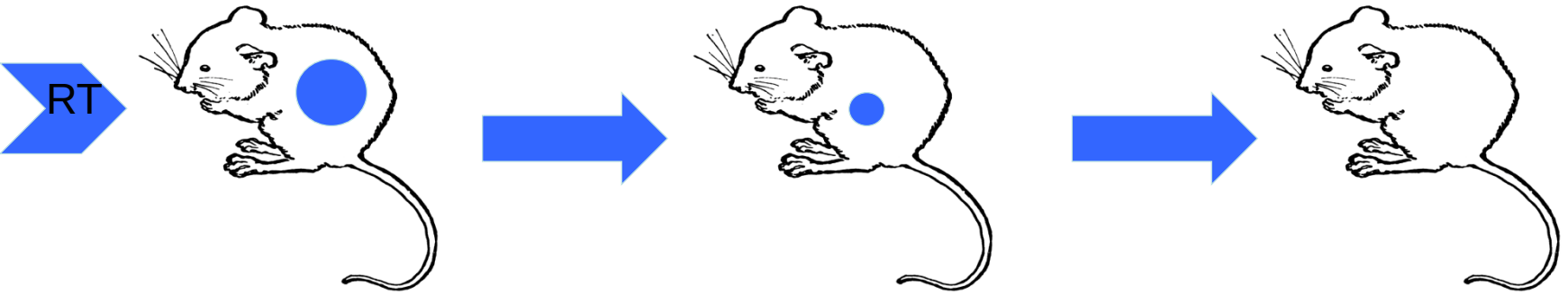
- Ionizing radiation and its interaction with the immune system
- Radiation-induced tumor cell death
- RT + immune therapy

T-cells help tumors respond to RT

Fibrosarcoma model	TCD 50	Metastases	Able to reject FSA cells
Normal mice	3040 cGy	1%	Yes
Immunosuppressed mice	5080 cGy	4%	Yes
T cell-deprived mice	6450 cGy	79%	No

Stone HB, Peters LJ JNCI 1979

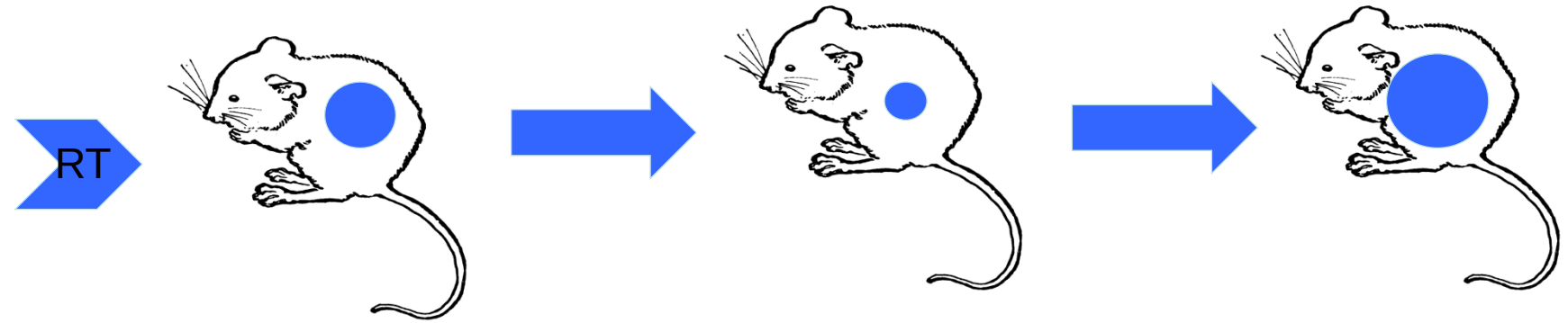
A competent immune system is required for radiation response



T cell competent

Tumor inhibition

Tumor response



T cell deficient

Tumor inhibition

Tumor growth

Does ionizing RT interact with the IS?

- Local radiation increases tumor antigen specific effector cells that traffic to tumor
  - Mice treated with 15 Gy or 5 Gy x 3 for OVA-expressing B16-F0 tumors (melanoma)
- Irradiated mice had greater capability to present tumor Ags and specific T cells and tumor-infiltrating lymphocytes than non-irradiated mice

Lugade A et al, 2005

Does ionizing RT interact with the IS?

- B16-OVA melonoma models treated with up to 15 Gy in various fx size

- Tumor control increased with size of RT dose as did tumor-reactive T cells
  - But at the highest doses, there was a high number of Tregs
  - 7.5 Gy/fx gave best tumor control and tumor immunity with lowest number of Tregs

Schaue D et al IJROBP 2012

Does ionizing RT interact with the IS?

- Pre-tx and post-tx serum samples from nonmetastastic prostate cancer pts and 50 controls evaluated

- Tumor specific antibody responses in patients:

  neoadjuvant hormone therapy 29.2%
  external beam radiation therapy 13.8%
  brachytherapy 25%
  radical prostatectomy 0%
  controls 5.6%

Nesslinger NJ CCR 2007

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How does RT induce tumor cell death?

- RT can directly kill cancer cells
  - Apoptosis, necrosis, mitotic catastrophe, autophagy, senescence, etc
  - Immunogenic cell death
    - RT modulates immune system and can help mount an immune response
    - RT always elicits activation of both innate +adaptive IS (McBride 2004)

- RT can cause immunogenic tumor cell death
  - Cross-priming of tumor-specific T-cells
  - RT acts as an in-situ tumor vaccine—RT may immunize the patient against cancer and can provide immunological memory for the lifetime of the host

Golden E, Front Oncol 2012
Formenti S, IJROBP 2012

How does RT induce tumor cell death?

- RT leads to:
  - Immunogenic cell death
    - Kills tumor-infiltrating lymphocytes→
    - Ablation of immune cells within the RT target→
    - Deplete CTLs and NK cells directed against the tumor
    - Immune system senses this change
  - Modulates antigen presentation by cancer cells
  - Changes the microenvironment within the RT field
    - Deplete Tregs which locally reduce anti-tumor immunity

RT Immunogenic tumor cell death

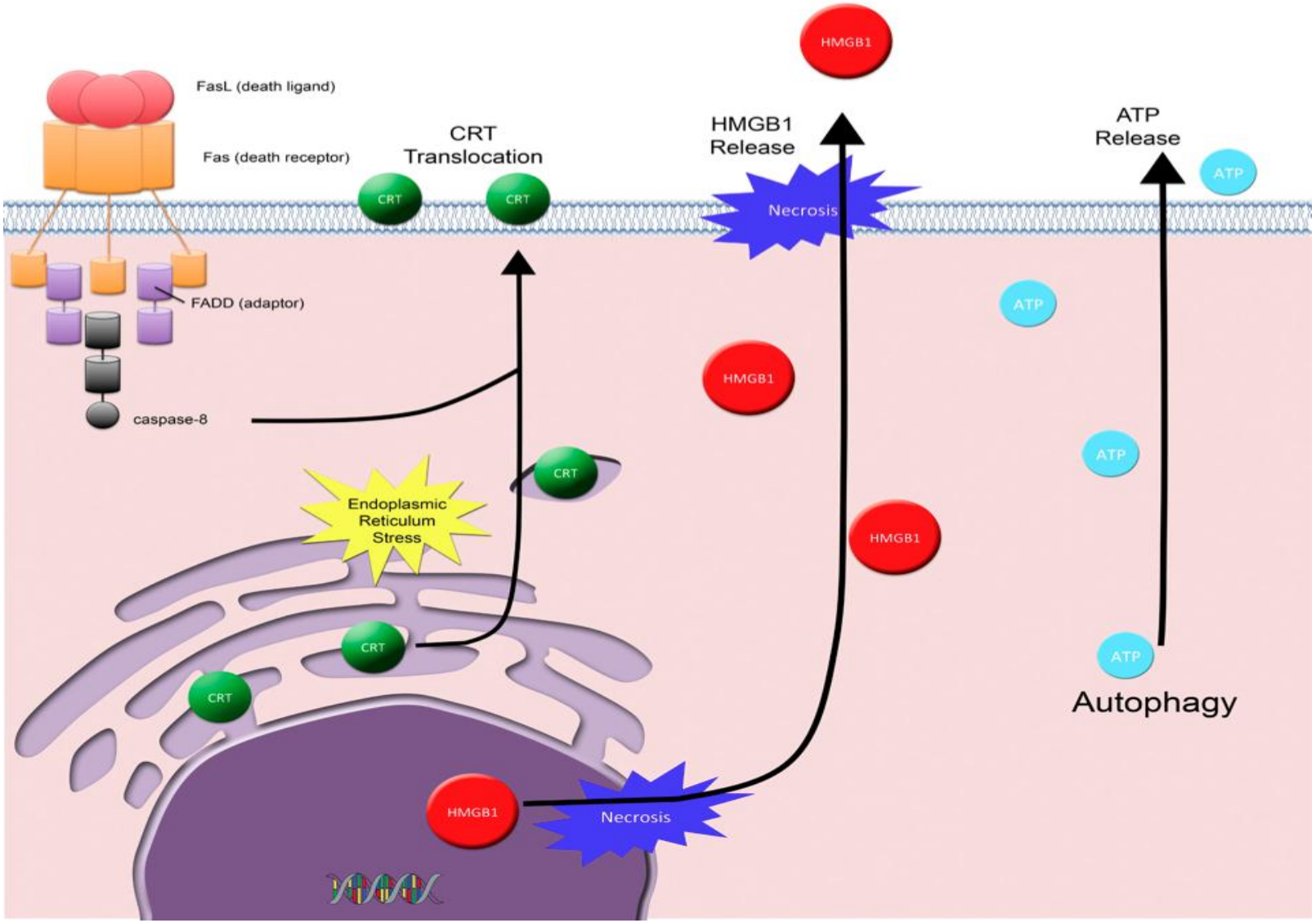
- RT releases tumor antigens→ facilitates tumor antigen uptake by DCs and cross complementation on MHC-I
  - RT enhances presentation of antigens
  - RT potentiates cross priming of tumor specific CTLs in lymph nodes
  - RT enhances MHC-I expression (Reits 2006)
    - Surface MHC-I expression is enhanced in response to increased availability of antigenic peptides to load onto MHC-I

Demaria S, Front Oncol 2012

RT Immunogenic tumor cell death

- Translocation of calreticulin to the tumor cell surface and release of
  - ATP
  - HMGB1—high mobility group protein B1
  - heat shock proteins

Immunogenic Cell Death by RT



Golden, Front Oncol 2012

How does RT induce tumor cell death?

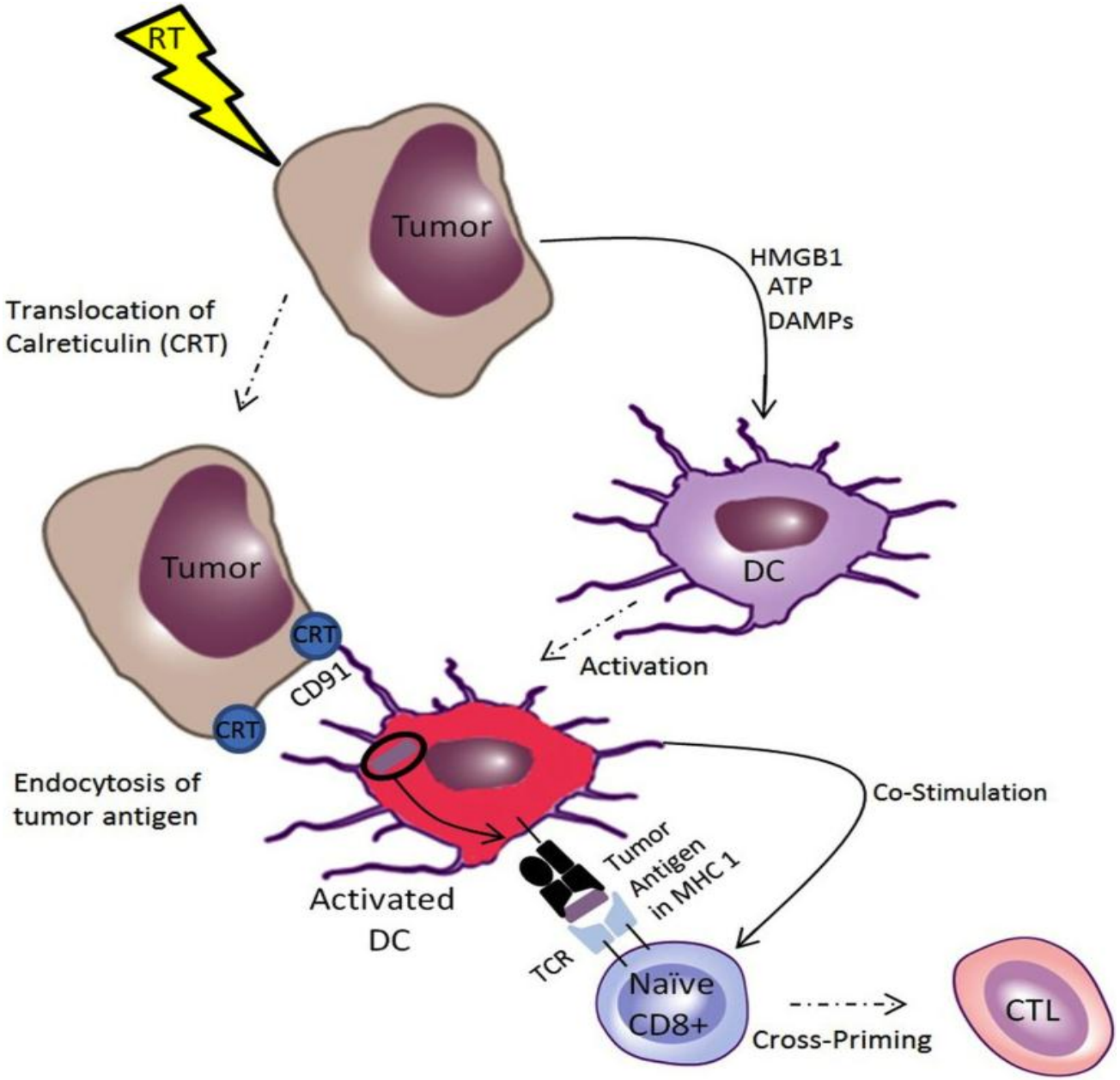
- Toll Like Receptors (TLRs)
- TLR respond to pathogen associated molecular patterns (PAMPs)
  - PAMPs: bacterial endotoxins, RNA from viruses

- TLR also respond to Danger Associated Molecular Pattern (DAMPs) (ie ATP, HMGB-1)
  - DAMPs: PAMPs+ endogenous intracellular molecules from necrosis
  - DAMPs link innate and adaptive immune system by activating APCs/DCs to provide co-stimulatory signals to naïve T cells and then cross-priming of CTLs
  - Important for immune mediated RT cell death

RT causes cross priming

- Tumor-associated antigens are cross-presented by DCs after RT →cross-priming of tumor-specific CTLs
  - Depends on TLR-4

- Release of HMGB1 by the dying cancer cells provides a danger signal that activates dendritic cells to +macrophages clear cells through the TLR-4 pathway.
  - HSP help mediate this process



Vatner R, Front Oncol

Chemokines

- RT recruits T cells to tumors by using chemokines to send signals
  - Allows lymphocytes primed against tumor antigens to home to tumors and attack them
  - CXCL16: chemokine, induced by RT, helps recruit effector CD8+ T cells to tumor
    - Shown to correlate with improved survival and increased in tumor-infiltrating lymphocytes in CRC and RCC (Hojo S 2007, Gutwein 2009)
- Chemokines recruit WBCs for anti-tumor immunity
  - Tumors produce chemokines to recruit Tregs and other suppressive elements
- May help explain systemic effects of RT

RT may also be anti-immunogenic

- Can reduce DC function with reduced cross-priming
- RT can recruit MDSCs
- Enrich tumor infiltrating Tregs
- Conflicting reports, model dependent
- ***RT most likely results in a macrophage mediated pro-immunogenic microenvironment to help vaccinate against tumors

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RT + Immunotherapy

- RT strengthens the immune response

- RT+ immunotherapy:
  - Enhanced cross-priming of tumor-specific CTLs
  - Stimulation of immune effector function of CTLs primed by RT
  - Neutralize the immunosuppressive effects of the tumor microenvironment

CTL Stimulation

- IL-2 is a cytokine necessary for growth, proliferation and differentiation of T-cells to become antigen-specific CD4+ and CD8+ T cells
  - RT+IL-2 →increases cytokines, upregulation of MHC-I, and B7.1
  - IL-2 +SBRT in metastatic RCC + melanoma showed a CR in 8/12 pts
  - Higher frequency of proliferating CD4+ T cells with and early activated memory phenotype in responders (Sueng SK Sci Transl Med 2012)

- Finkelstein (Immunotherapy 2012)
  - High risk prostate cancer pts tx with ADT +EBRT 45Gy+ DC injections into prostate
    - Autologous DCs were cultured in vitro
    - Reintroduced directly into prostate
  - Serial bx show tumor cell apoptosis and increase in tumor-infiltrating CD8+ T-cells and prostate specific CD8+ T cells in the peripheral blood

Abscopal Effect of RT

- Irradiation of a tumor causes response at distant metastatic site
- Probably mediated by the immune system
- Although RT can cause cross-priming of CTLs, the effect of RT elsewhere may be weak
- With the addition of immunotherapies, this rare effect may be more reproducible

CTL Stimulation

- Checkpoint blockade
  - CTLA-4
    - CTLA-4 inhibition allows increased proliferation and function of activated T-cells, including tumor-specific CTLs
  - PD-1
  - Both upregulated on activated T-cells and transmit inhibitory signals which suppress T-cell proliferation and function

- CTLA-4 blockade is synergistic with RT to produce an abscopal response in breast and colon cancer models
  - 8 Gy x 3 is more effective than 20 Gy x 1 or 6 Gy x 5 (Dewan MZ, CCR 2009) in mouse models with anti-CTLA-4 therapy
  - Re: dose—Gulley et al studied 70 Gy/35 fx in 17 Prostate Cancer pts +pox virus vaccine encoding PSA
    - 2 pts showed increased responses
    - 6/8 pts showed T cell responses against antigens not present in the vaccine→RT promoted T cell activation

Original Article: Brief Report

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D., Shigehisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasalan, B.S., Matthew Adamow, B.S., Erika Ritter, B.S., Christine Sedrak, B.S., Achim A. Jungbluth, M.D., Ramon Chua, B.S., Arvin S. Yang, M.D., Ph.D., Ruth-Ann Roman, R.N., Samuel Rosner, Brenna Benson, James P. Allison, Ph.D., Alexander M. Lesokhin, M.D., Sacha Gnjatic, Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

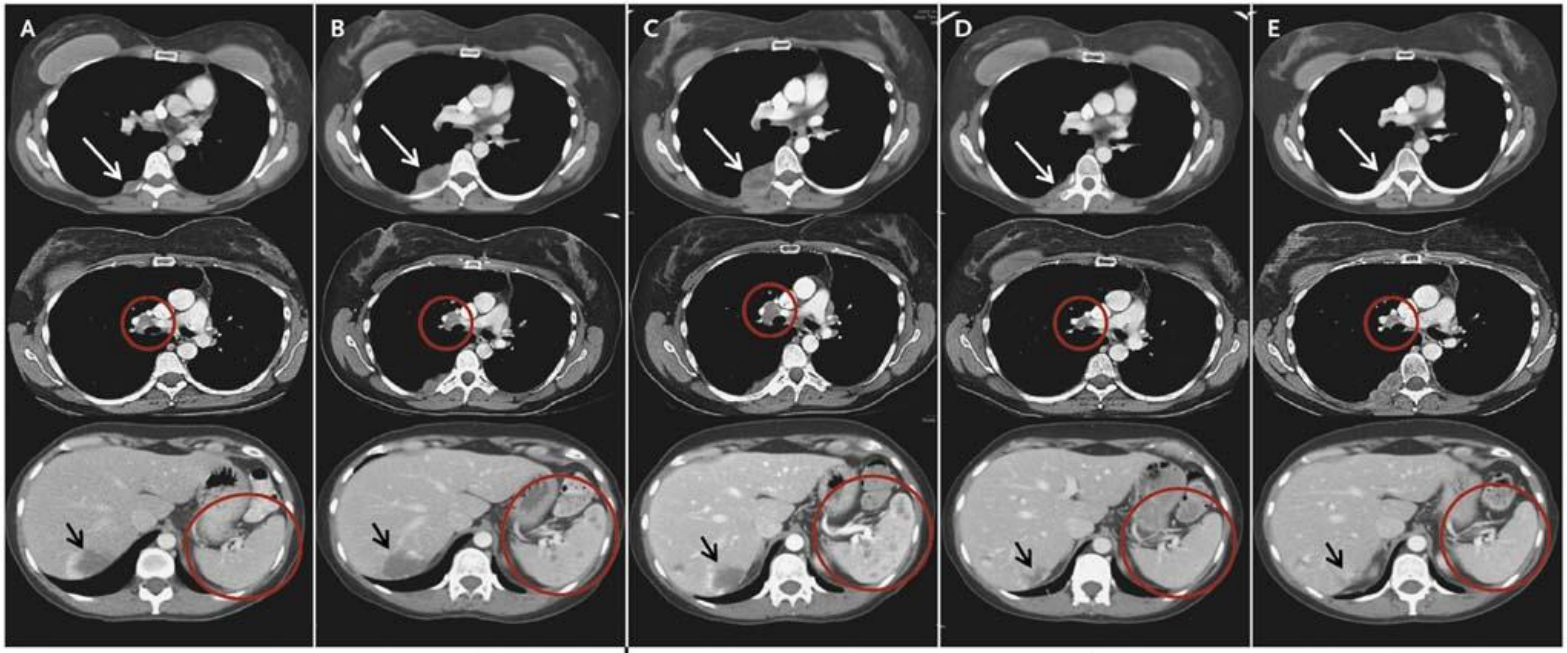
N Engl J Med
Volume 366(10):925-931
March 8, 2012

The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

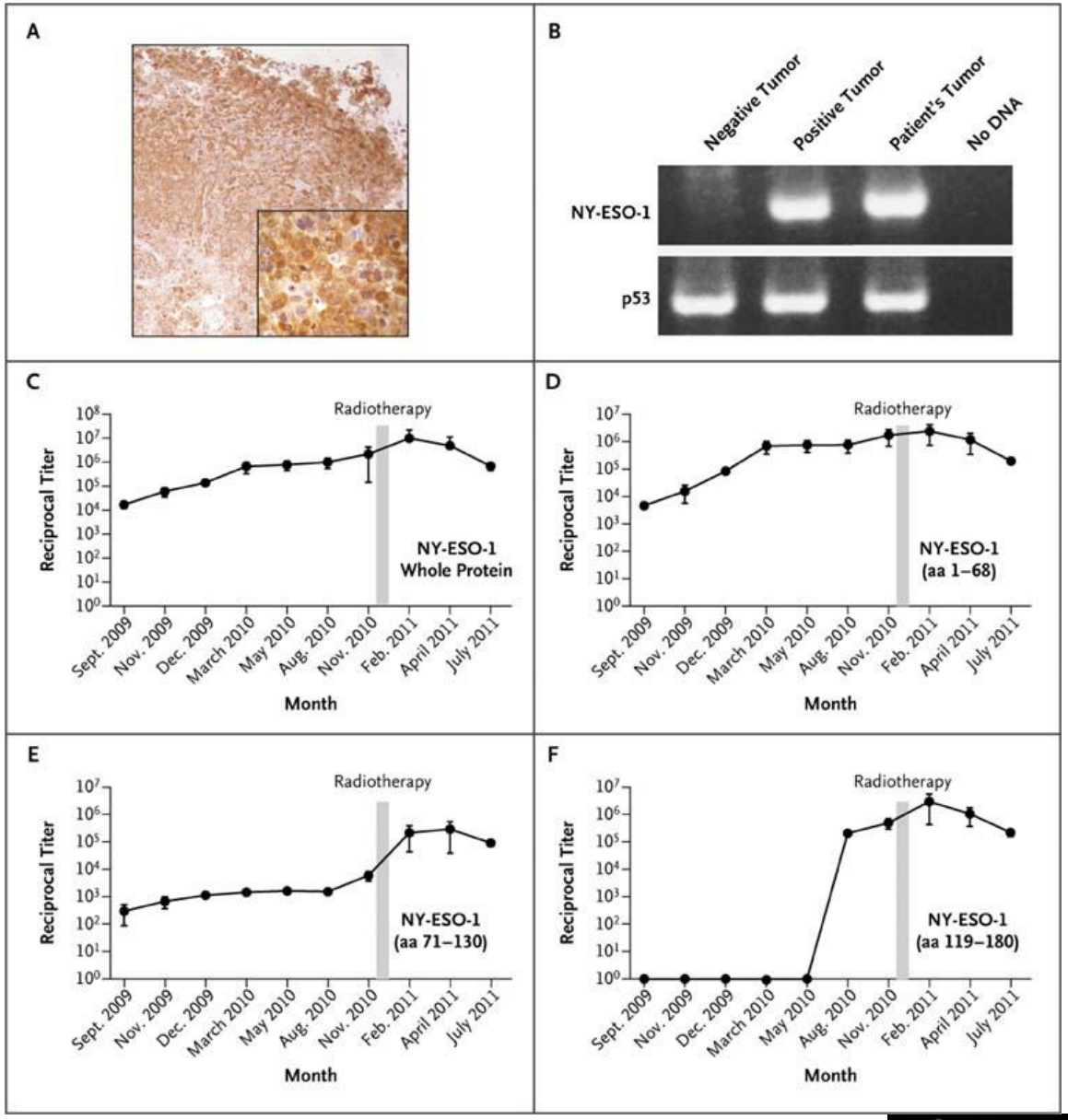
- A patient with metastatic melanoma with slowly progressive disease while receiving ipilimumab underwent radiotherapy for a pleural-based metastasis.
- Tumor lesions in nonirradiated sites began to disappear, and titers of antibody against a tumor-associated antigen increased.

Results of Diagnostic and Radiotherapy Simulation Imaging throughout the Disease Course.



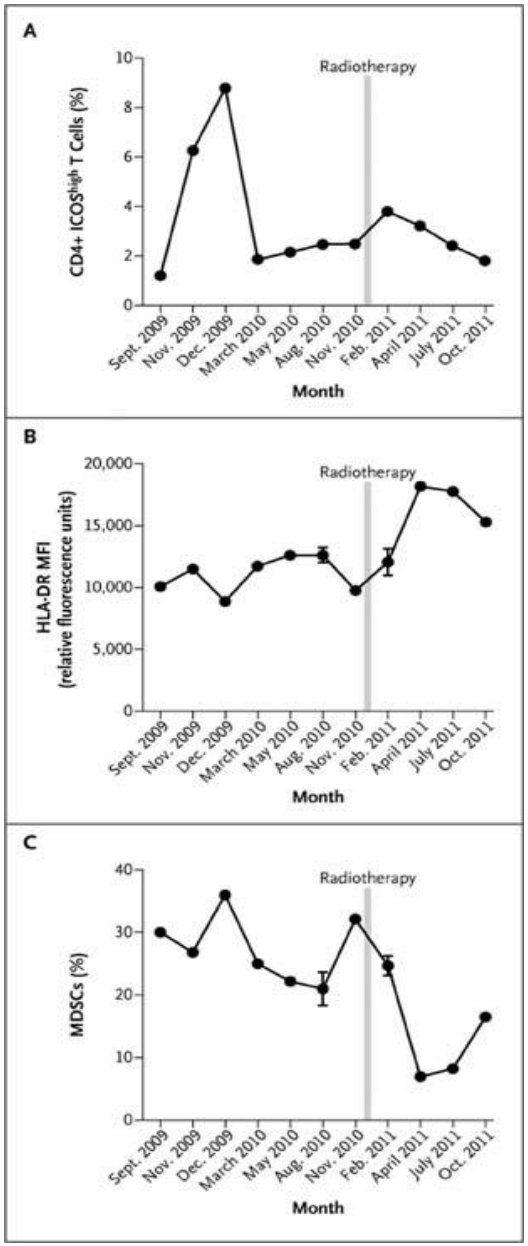
The NEW ENGLAND JOURNAL of MEDICINE

NY-ESO-1 Expression and Antibody Response to Ipilimumab and Radiotherapy.



The NEW ENGLAND JOURNAL of MEDICINE

Results of Flow Cytometry of Peripheral-Blood Mononuclear Cells.



TGF-β can predict immune response for RT

- TGF-β: an immunosuppressive cytokine
- Reduced TGF-β can correlate with a favorable immune response to RT
  - Tx with MMP14 inhibitory antibody, DX-2400, associated with decrease inTGFβ in murine br ca tissue. Macrophages were shifted towards antitumor phenotype (Ager EI, JNCI 2015)
  - TGFβ neutralizing antibodies increased radiation sensitivity, increased tumor growth delay in 4T1 murine mammary tumors in response to single and fractionated radiation exposures (Bouquet F, CCR 2011)

PD-1 blockade + RT

- Sharabi A et al, Cancer Immunol Research 2015 (melanoma)
  - RT and anti–PD-1 immunotherapy altered the ratio of CD4 to CD8 T cells and decreased percentages of CD4 Tregs and absolute increases in CD8 T-cell populations
  - Zeng J, IJROBP 2013 (glioma): RT+ antiPD-1 tx
  - increased survival and tumor infiltration by cytotoxic T cells (CD8+/interferon-γ+/tumor necrosis factor-α+) and decreased regulatory T cells (CD4+/FOXP3)

Conclusions

- RT interacts favorably with the immune system
- RT generates anti-tumor immunity
  - Creates an in-situ vaccine
  - Positively impacts all aspects of the immune response
- RT is synergistic with immunotherapies
- Clinical trials are ongoing and necessary