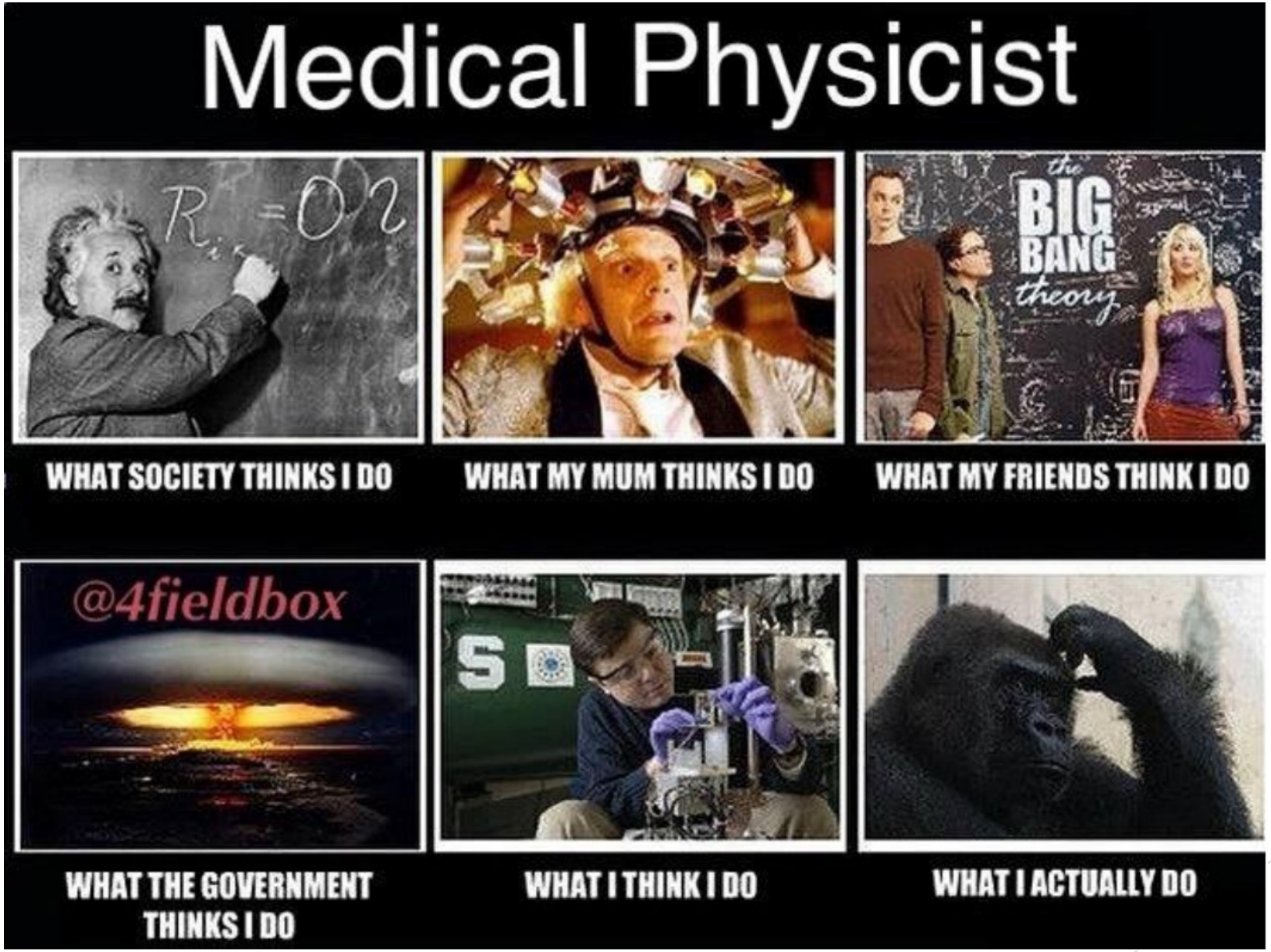
Radiation Therapy and Immunotherapy: an investigation into their synergistic effects.

Overview

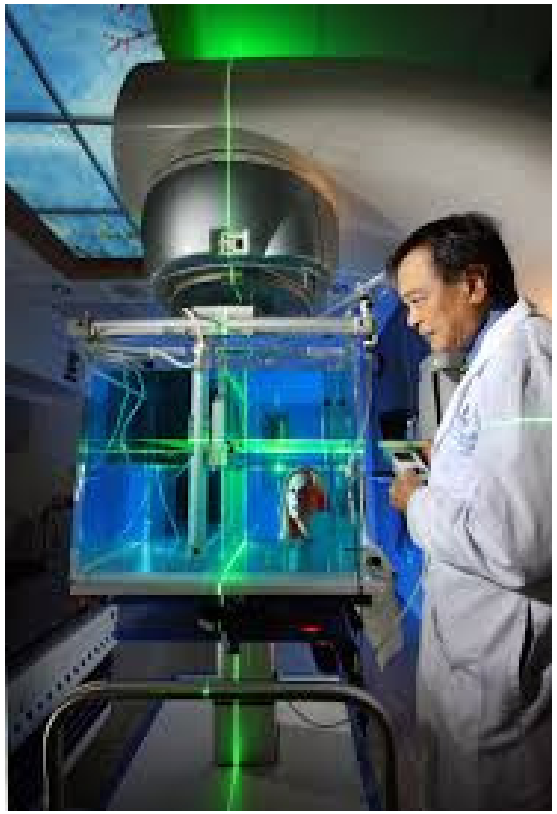
- Medical Physics
- Radiation Oncology
- Radiobiology
- Immune System
- Radiation Therapy and the Immune System
- Project



file:///V:/RadImmuno/Focus%20Newsletter-Winter%202018.pdf

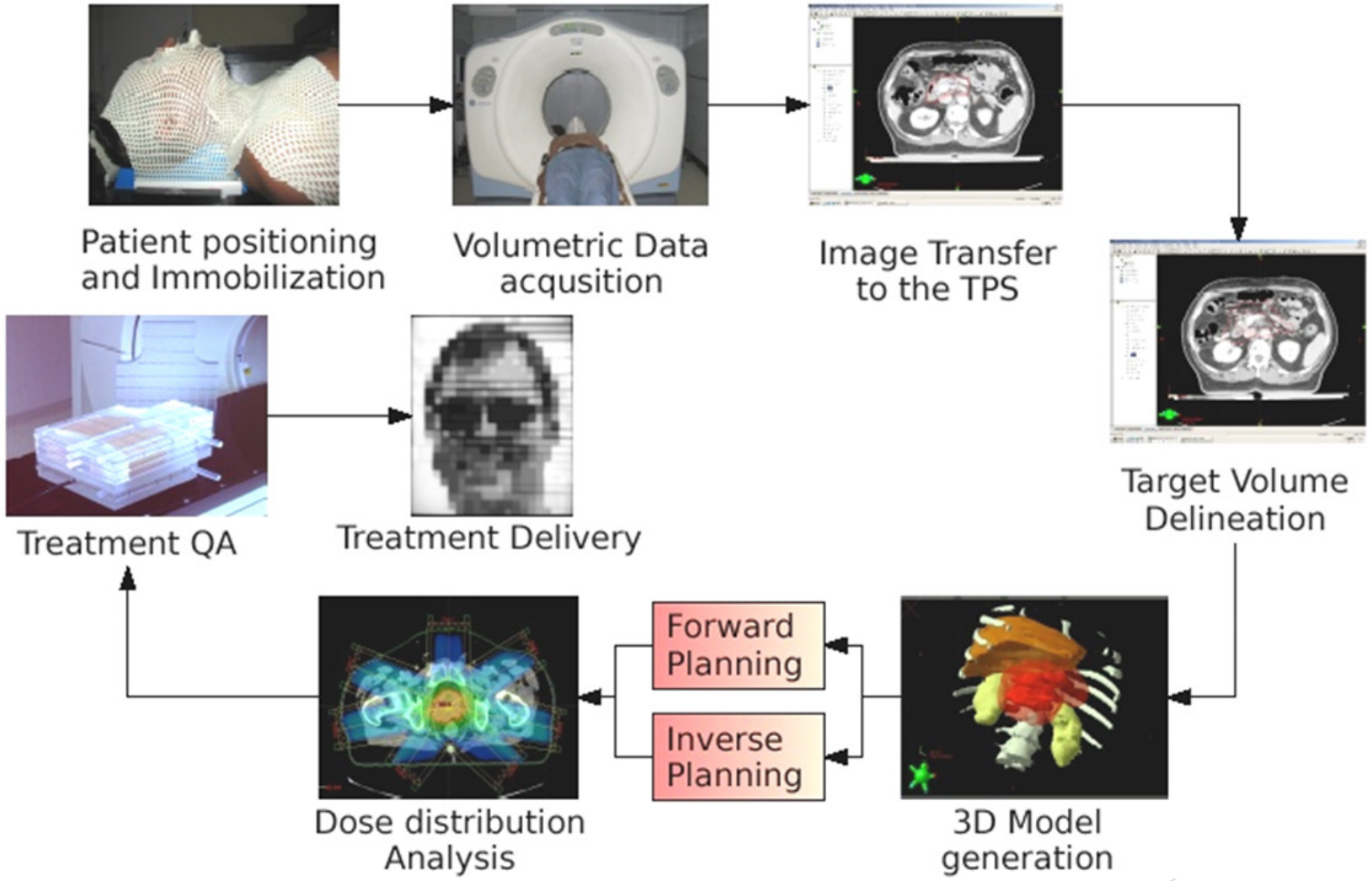
What Does a Medical Physicist Do?

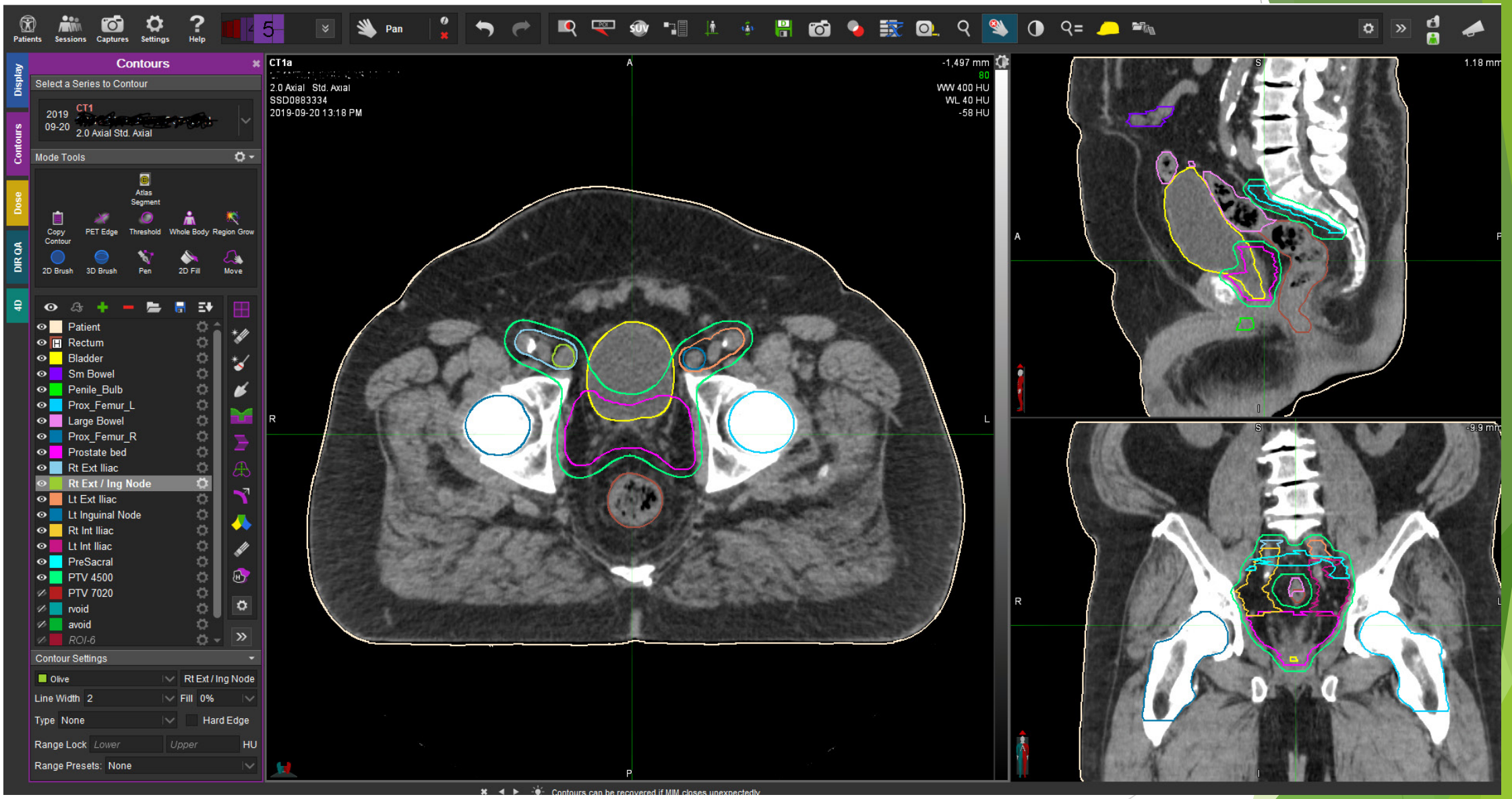
- Clinical
  - Measurement of radiation dose
  - Radiation treatment planning
    - SRS and HDR
  - Radiation audits
- Quality Assurance
  - Installation and commissioning of radiation equipment
  - Oversee radioactive materials
  - Quality management program
- Research and Teaching



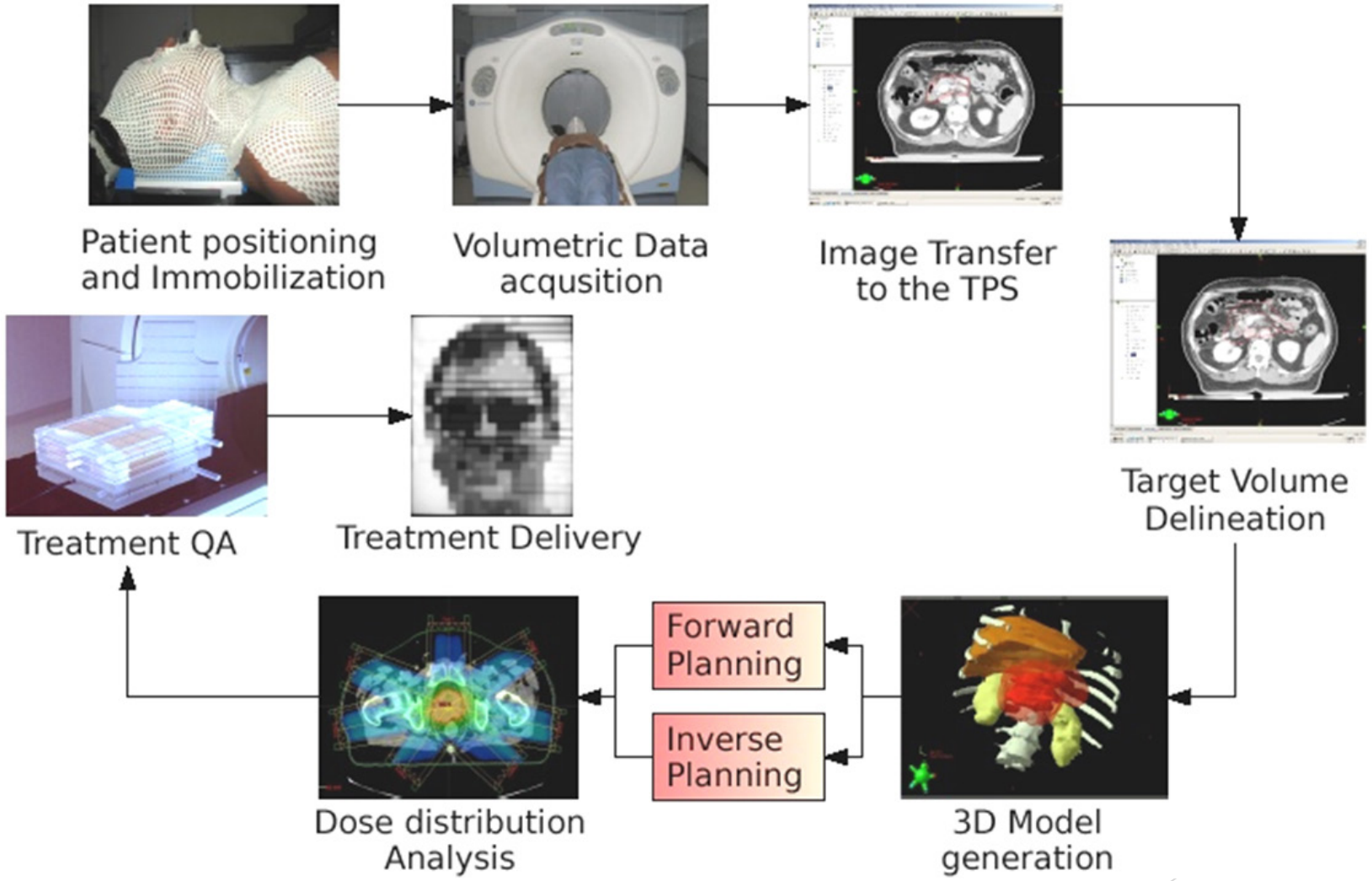
https://www.hopkinsmedicine.org/radiation_oncology/education_training/medical_physics_residency/index.html

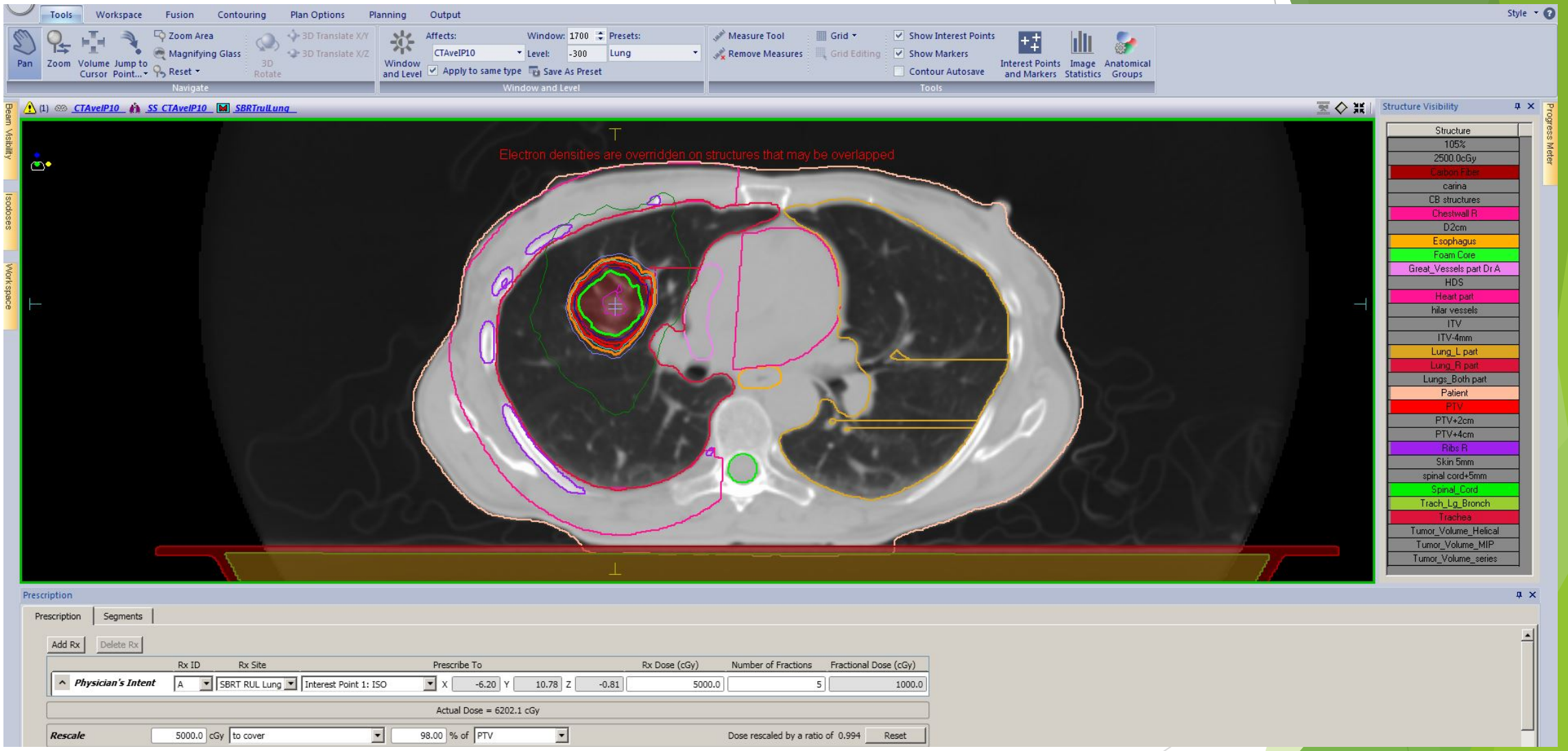
Radiation Oncology Workflow



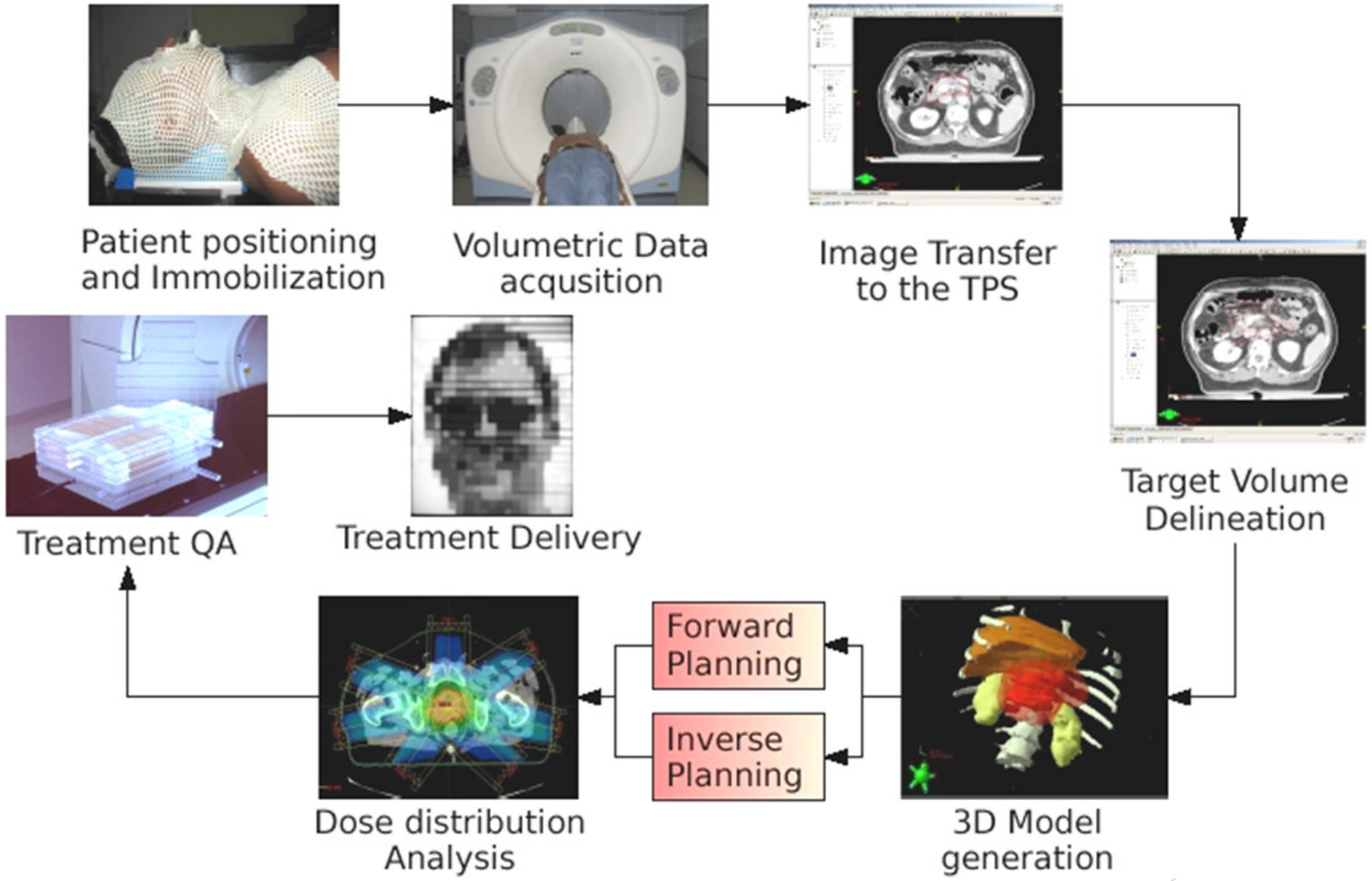

Patients
Sessions
Captures
Settings
Help
Pan
Contours
Select a Series to Contour
2019 09-20 CT1
2.0 Axial Std. Axial
Mode Tools
Atlas Segment
Copy Contour
PET Edge
Threshold
Whole Body
Region Grow
2D Brush
3D Brush
Pen
2D Fill
Move
Patient
Rectum
Bladder
Sm Bowel
Penile_Bulb
Prox_Femur_L
Large Bowel
Prox_Femur_R
Prostate bed
Rt Ext Iliac
Rt Ext / Ing Node
Lt Ext Iliac
Lt Inguinal Node
Rt Int Iliac
Lt Int Iliac
PreSacral
PTV 4500
PTV 7020
rvoid
avoid
ROI-6
Contour Settings
Olive
Rt Ext / Ing Node
Line Width 2
Fill 0%
Type None
Hard Edge
Range Lock Lower Upper HU
Range Presets: None
CT1a
2.0 Axial Std. Axial
SSD0883334
2019-09-20 13:18 PM
-1,497 mm
80
WW 400 HU
WL 40 HU
-58 HU
1.18 mm
-9.9 mm
Display
Contours
Dose
DIR QA
4D

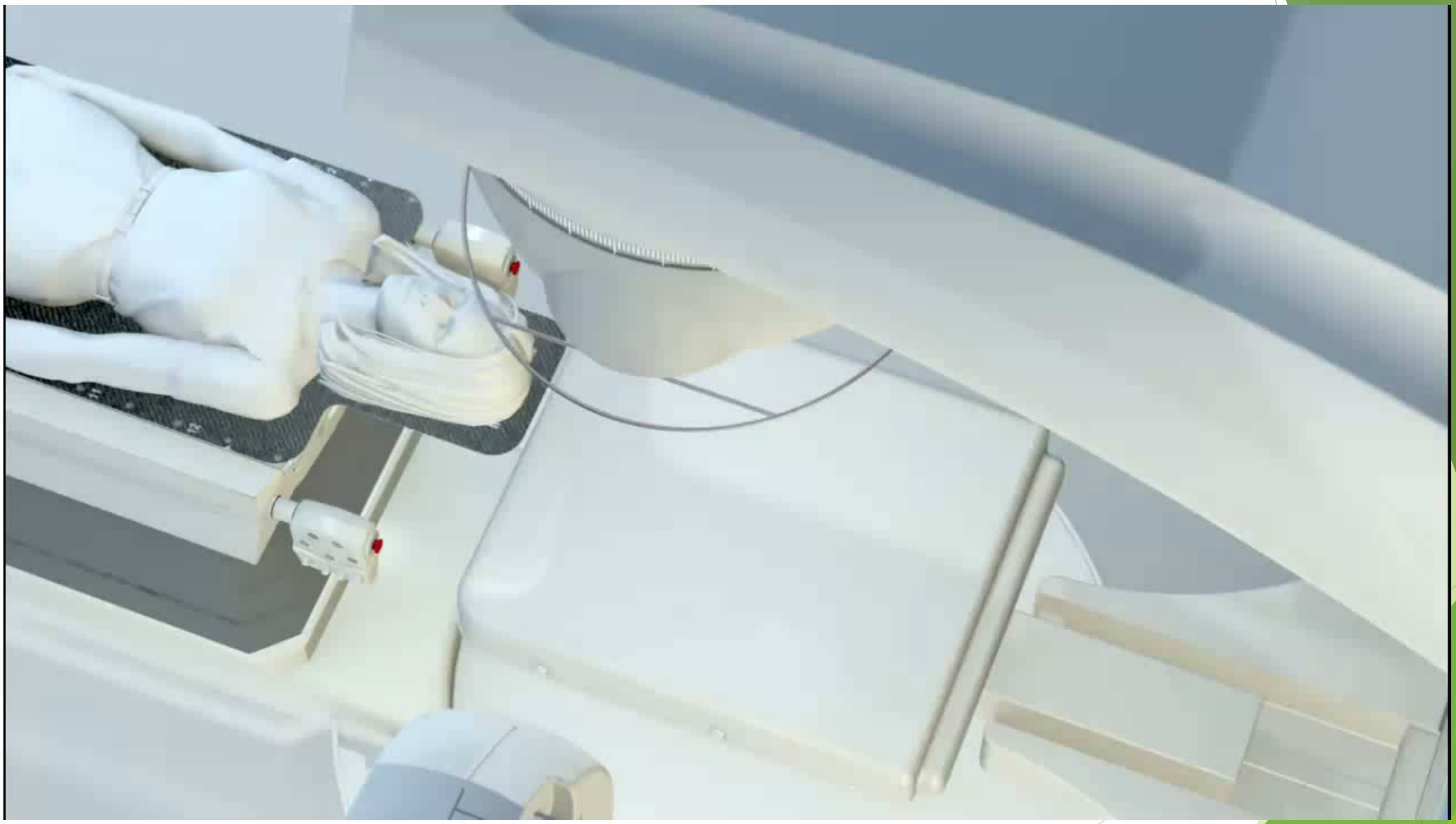
Radiation Oncology Workflow




Tools
Workspace
Fusion
Contouring
Plan Options
Planning
Output
Style
Pan
Zoom
Volume Cursor
Jump to Point...
Zoom Area
Magnifying Glass
Reset
3D Rotate
3D Translate X/Y
3D Translate X/Z
Navigate
Window and Level
Affects:
CTAvelP10
Window: 1700
Level: -300
Presets:
Lung
Apply to same type
Save As Preset
Window and Level
Measure Tool
Remove Measures
Grid
Grid Editing
Show Interest Points
Show Markers
Contour Autosave
Interest Points and Markers
Image Statistics
Anatomical Groups
Tools
CTAvelP10
SS CTAvelP10
SBRTrulLung
Electron densities are overridden on structures that may be overlapped
Structure Visibility
Structure
105%
2500.0cGy
Carbon Fiber
carina
CB structures
Chestwall R
D2cm
Esophagus
Foam Core
Great_Vessels part Dr A
HDS
Heart part
hilar vessels
ITV
ITV-4mm
Lung_L part
Lung_R part
Lungs_Both part
Patient
PTV
PTV+2cm
PTV+4cm
Ribs R
Skin 5mm
spinal cord+5mm
Spinal_Cord
Trach_Lg_Bronch
Trachea
Tumor_Volume_Helical
Tumor_Volume_MIP
Tumor_Volume_series
Beam Visibility
Isodoses
Workspace
Progress Meter
Prescription
Prescription
Segments
Add Rx
Delete Rx
Rx ID
Rx Site
Prescribe To
Rx Dose (cGy)
Number of Fractions
Fractional Dose (cGy)
Physician's Intent
A
SBRT RUL Lung
Interest Point 1: ISO
X -6.20 Y 10.78 Z -0.81
5000.0
5
1000.0
Actual Dose = 6202.1 cGy
Rescale
5000.0 cGy
to cover
98.00 % of
PTV
Dose rescaled by a ratio of 0.994
Reset

Radiation Oncology Workflow





Quality Assurance

The report of Task Group 100 of the AAPM: Application of risk analysis methods to radiation therapy quality management

M. Saiful Huq[a)]
Department of Radiation Oncology, University of Pittsburgh Cancer Institute and UPMC CancerCenter, Pittsburgh, Pennsylvania 15232

Benedick A. Fraass
Department of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles, California 90048

Peter B. Dunscombe
Department of Oncology, University of Calgary, Calgary T2N 1N4, Canada

John P. Gibbons, Jr.

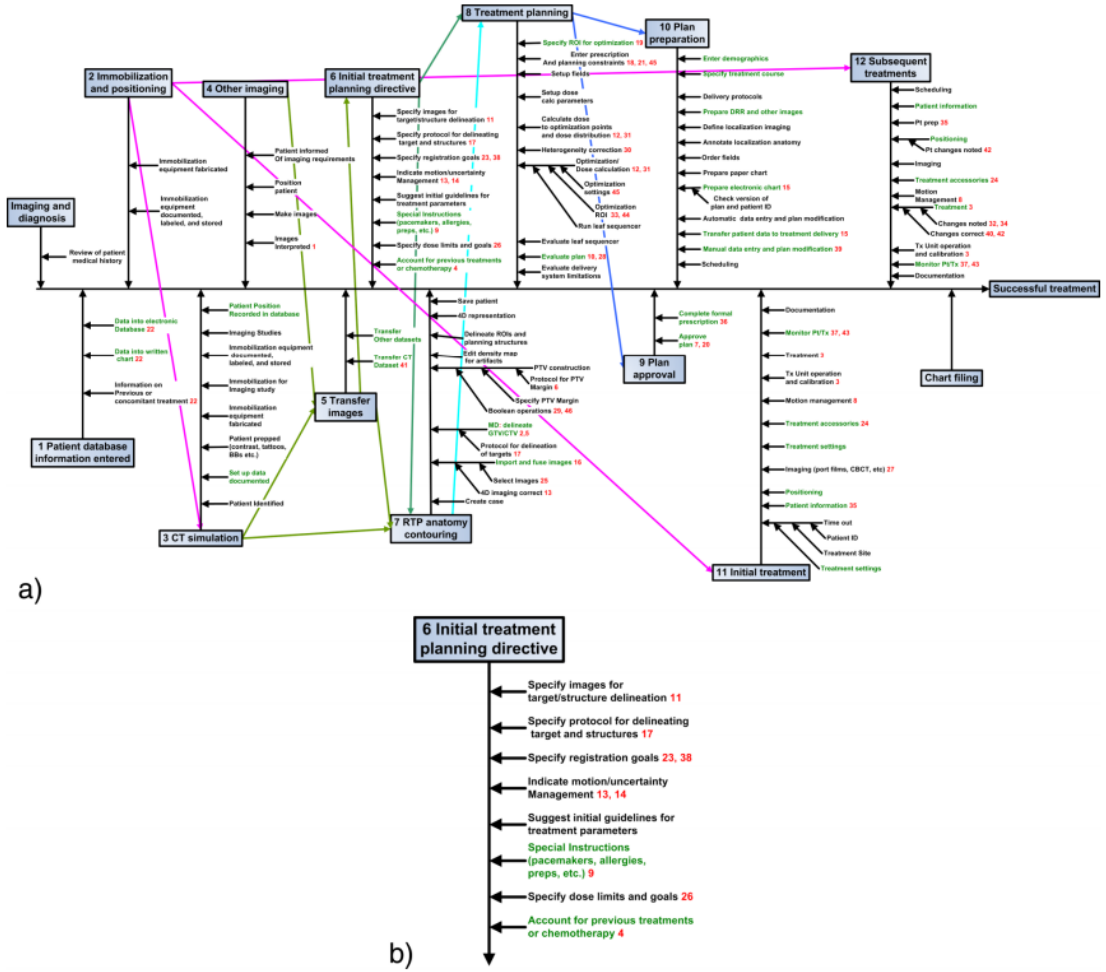
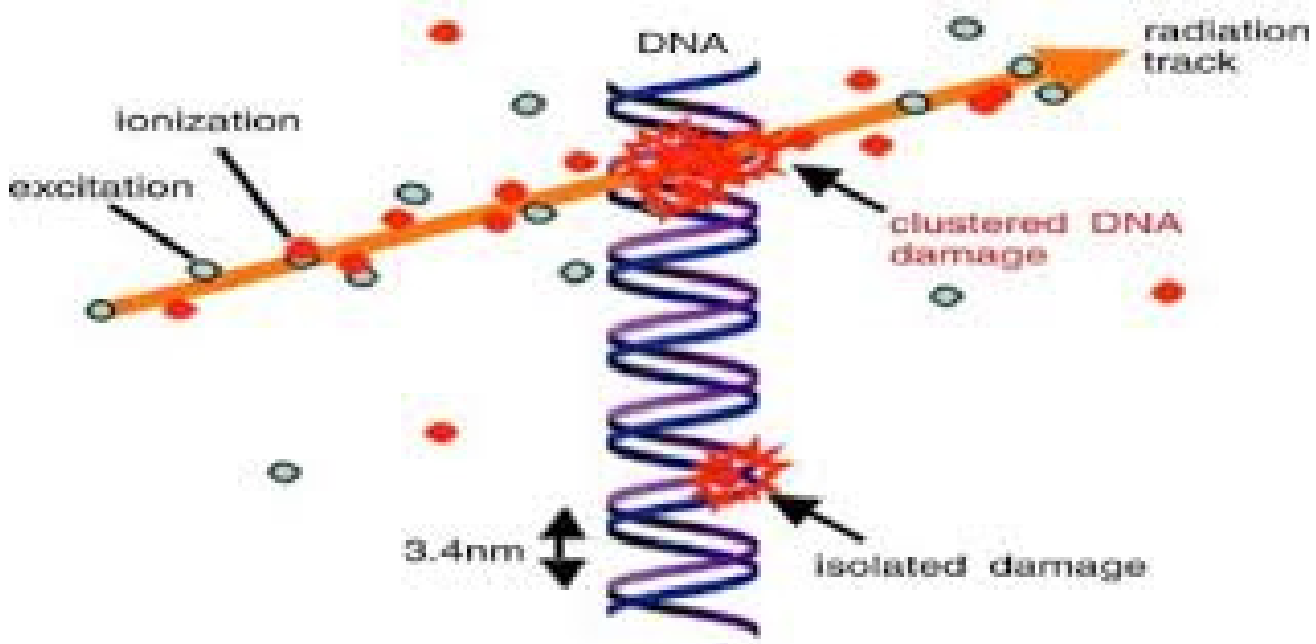


FIG. 2. (a) An IMRT process tree, (b) magnified view of the initial treatment planning directive branch. The red numbers indicate (hazard ranking) the most hazardous 20%–25% of the steps as indicated by high risk priority number values. Steps with high severity hazards are shown in green. [See text and Sec. VIII (Ref. 64) for details.] A hazard is something that can cause harm. A risk is the chance, high or low, that any hazard will actually cause somebody harm.

Radiobiology Defined

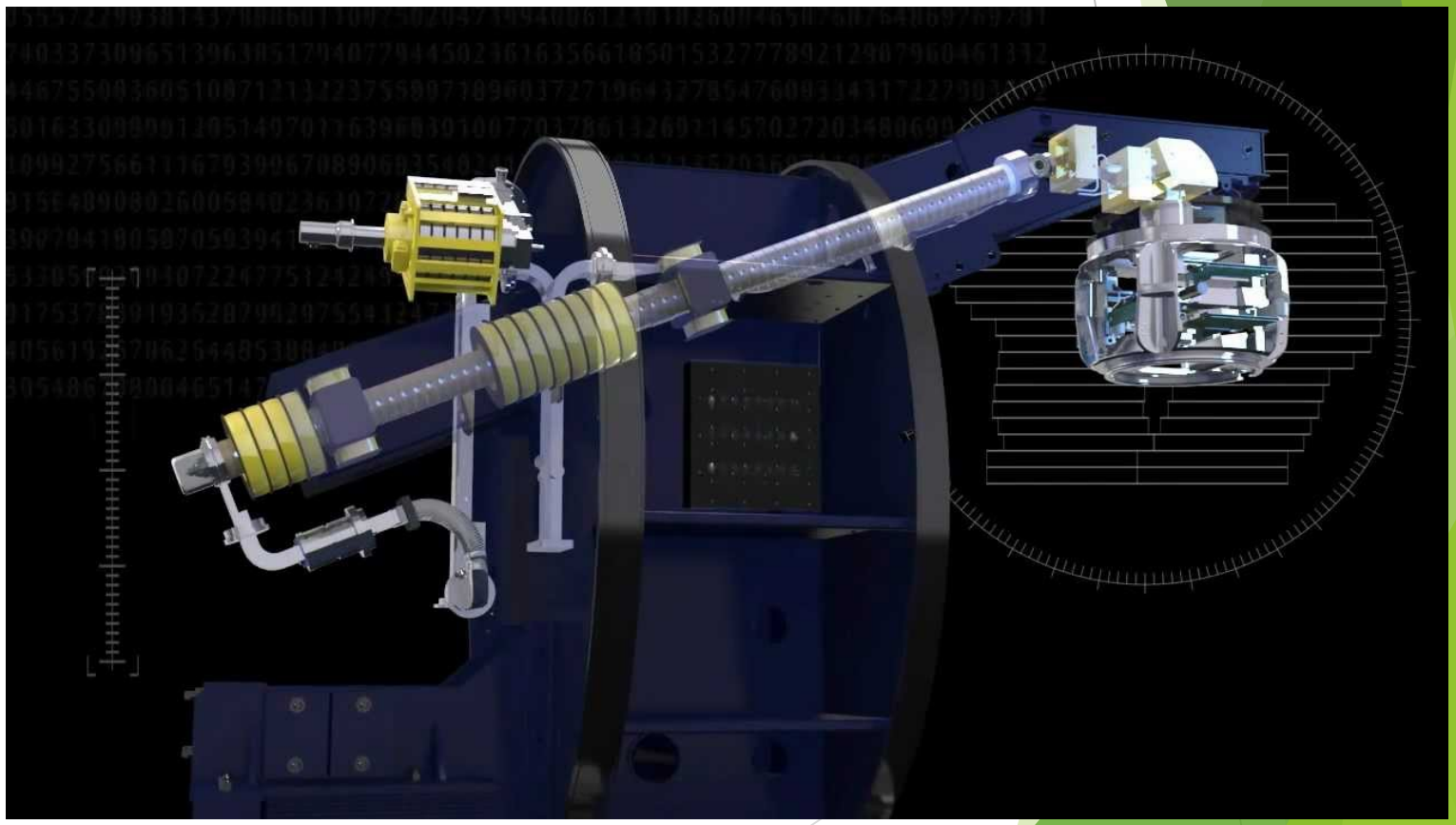
- Branch of science which combines physics and biology and considers the action of ionizing radiation on biological tissues and living organisms



https://www.assignmentpoint.com/science/biology/radiobiology.html

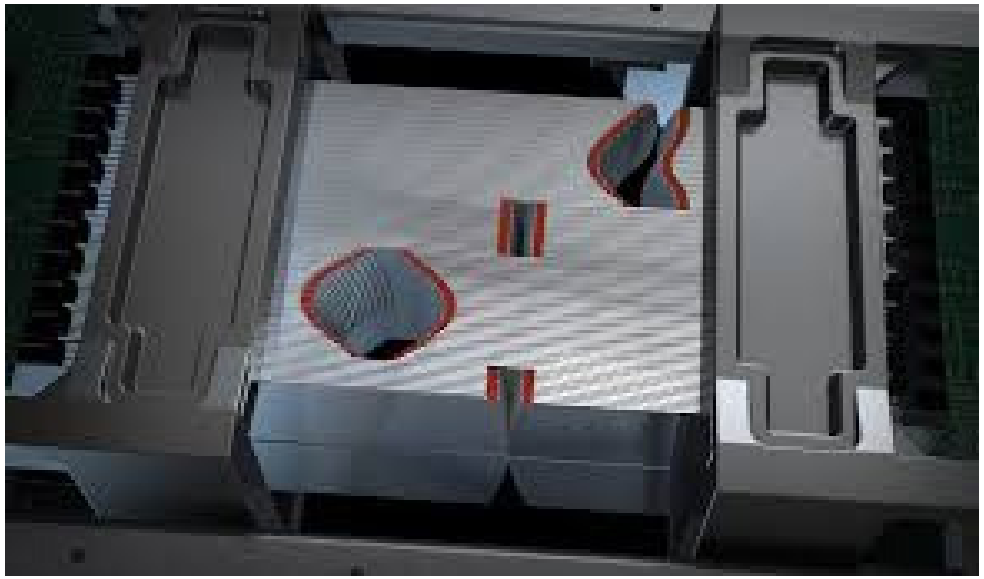
Ionizing Radiation-where does it come from?

- LINAC – Linear accelerator
  - Accelerates electrons through a waveguide to create photon and electron radiation



Multileaf Collimator

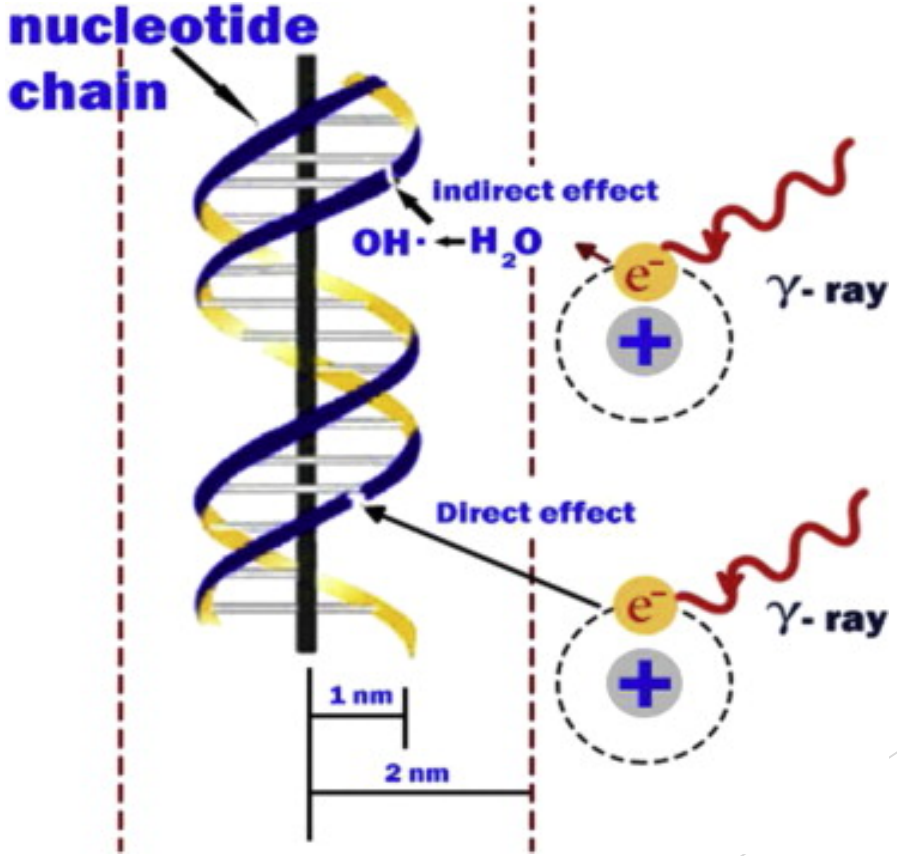
Shapes or modulates the ionizing radiation to deliver dose to the tumor while sparing any normal tissue including closely associated organs



What does ionizing radiation do?

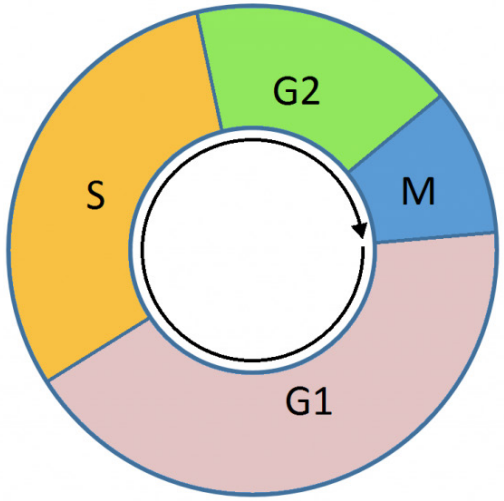
- Ionizing radiation is divided into two categories:
  - Directly ionizing – basically any particle with a charge
    - Protons, electrons, carbon ions
  - Indirectly ionizing – particle without a charge
    - Photons, neutrons

The quality or “power” of the beam is defined by the linear energy transfer (LET) – this is the energy absorbed by the patient



Ionizing Radiation Targets the Cell Cycle

- Cell proliferation Cycle
  - M phase – Mitosis
  - S phase – DNA synthesis
  - Gap 1 – DNA synthesis has not occurred
  - Gap 2 – DNA synthesis has occurred but the cell is working on other things



G1 - Growth

S - DNA synthesis

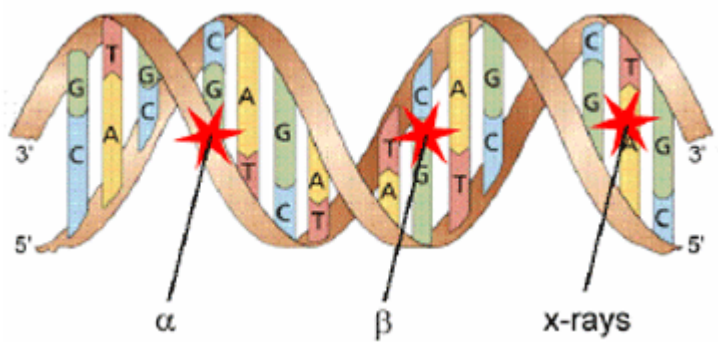
G2 - Growth and preparation for mitosis

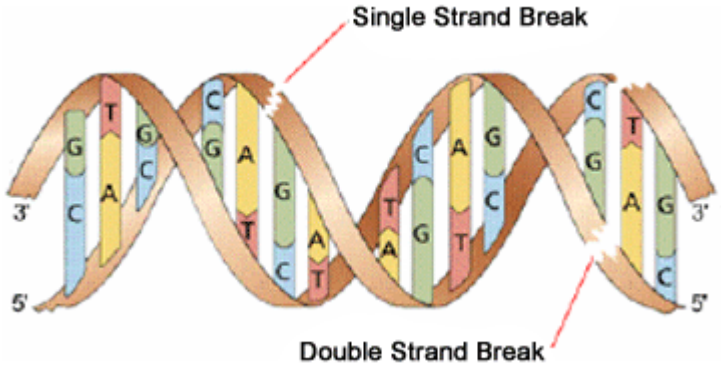
M - Mitosis (cell division)

Cell Cycle Phase	Sensitivity	Reason
Late S	Radio-resistant	Homologous recombination repair between sister chromatids
G1	Intermediate	Chromatin is accessible
G2 and M	Very radiosensitive	Chromatin is compact

Direct Action of Ionizing Radiation

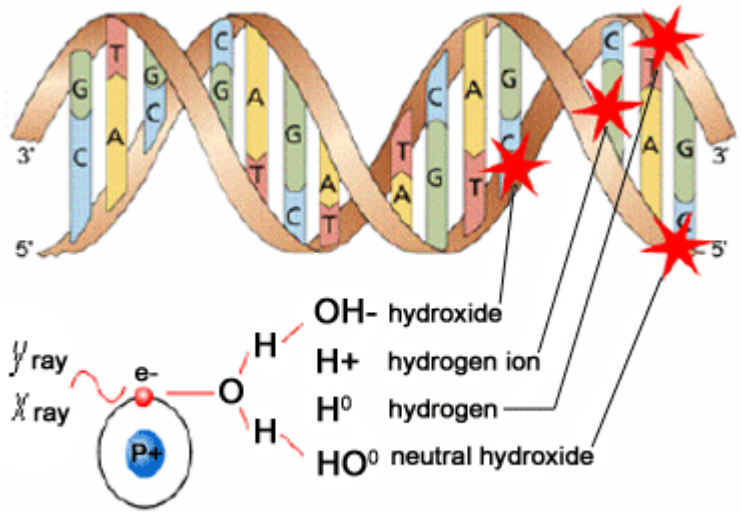
- Radiation interacts directly with cell DNA
  - High LET particles like alpha particles break the DNA molecule
  - Photons produce a charged particle like an electron or positron which damages the DNA
- Damage
  - Single strand break
  - Double strand break



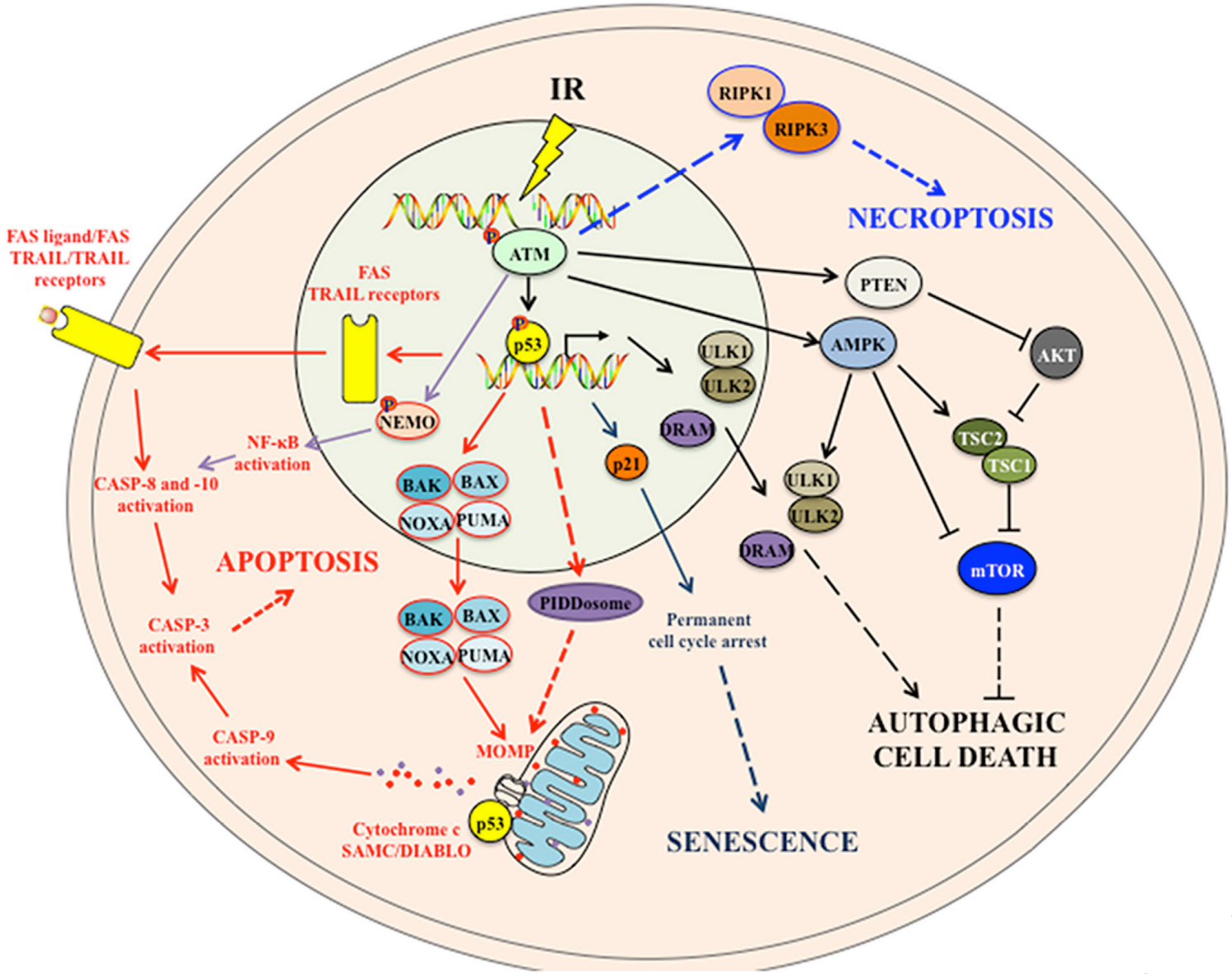


Indirect Action of Ionizing Radiation

- Photon interacts to create free radicals
  - Molecules that are highly reactive because they have an unpaired electron
  - Form compounds that cause DNA damage



Ionizing Radiation Induces Cell Death

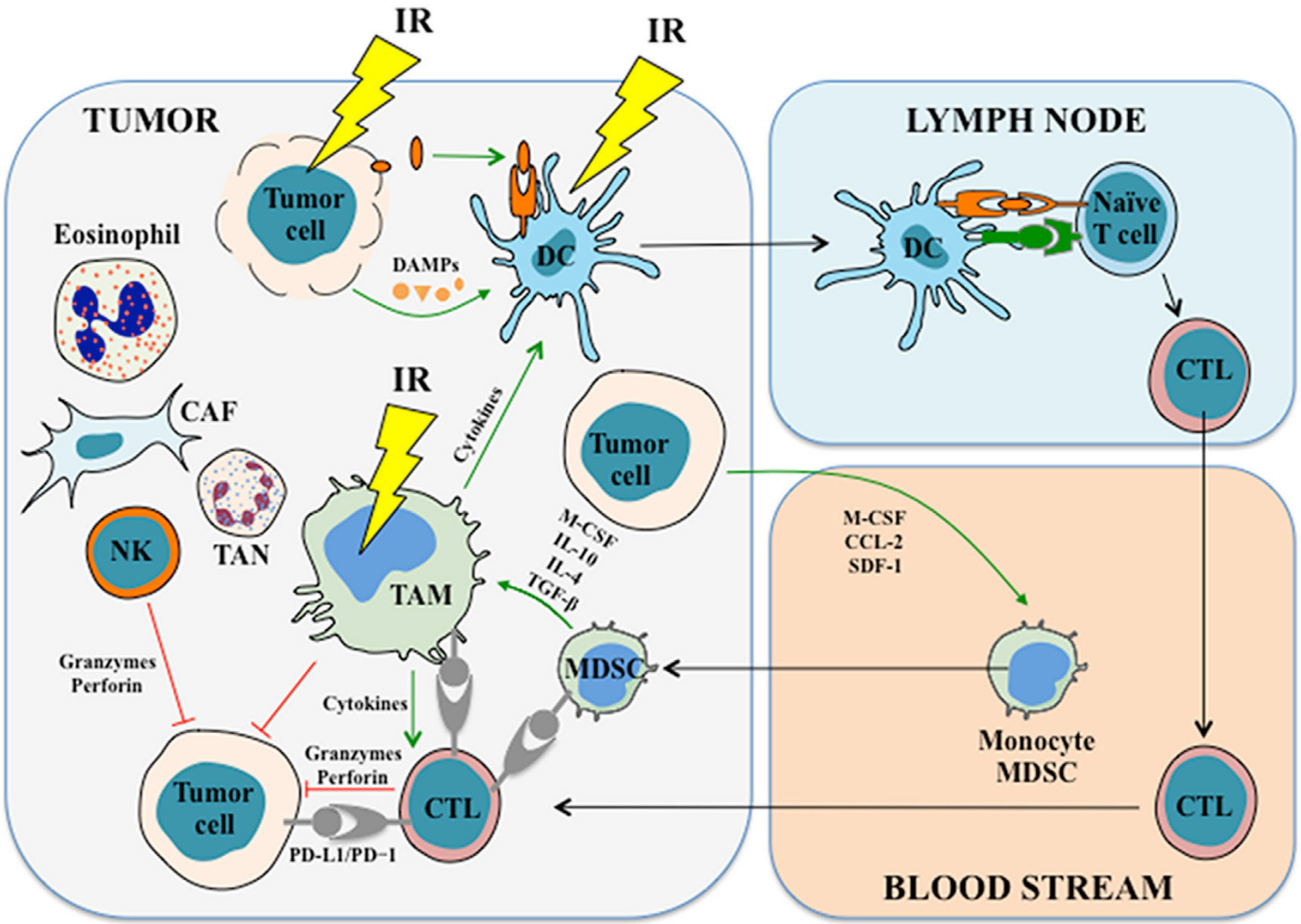


Wu et al. Modulating Both Tumor Cell Death and Innate Immunity Is Essential for Improving Radiation Therapy Effectiveness, 2017 doi: 10.3389/fimmu.2017.00613

Outcomes of cell irradiation

- No effect
- Division delay: Cell cycle interrupted
- Apoptosis: Cell death
- Reproductive failure: Cell dies when attempting to divide
- Genomic instability: Delay in reproductive failure
- Mutation: Cell contains a mutation
- Transformation: Mutation leads to a transformed phenotype and possibly carcinogenesis
- Bystander effects: Irradiated cell may send signals to neighboring cells and induce genetic changes in them
- Adaptive responses: Cell becomes radio-resistant

Effects of Ionizing Radiation on Immune Cells



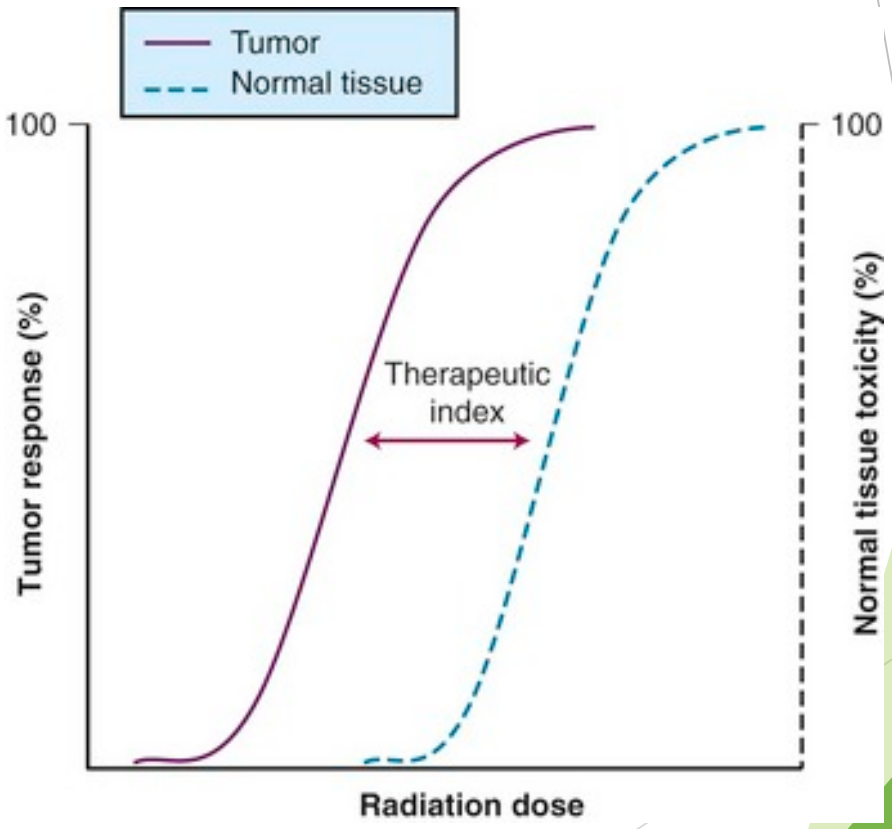
Wu et al. Modulating Both Tumor Cell Death and Innate Immunity Is Essential for Improving Radiation Therapy Effectiveness, 2017 doi: 10.3389/fimmu.2017.00613

Types of Radiation Damage

- Lethal damage – irreversible, irreparable and leads to cell death
- Sublethal damage – repaired in hours unless additional damage is incurred that leads to lethal damage
- Potentially lethal damage – damage that can be repaired when cells are allowed to remain in a non-dividing state

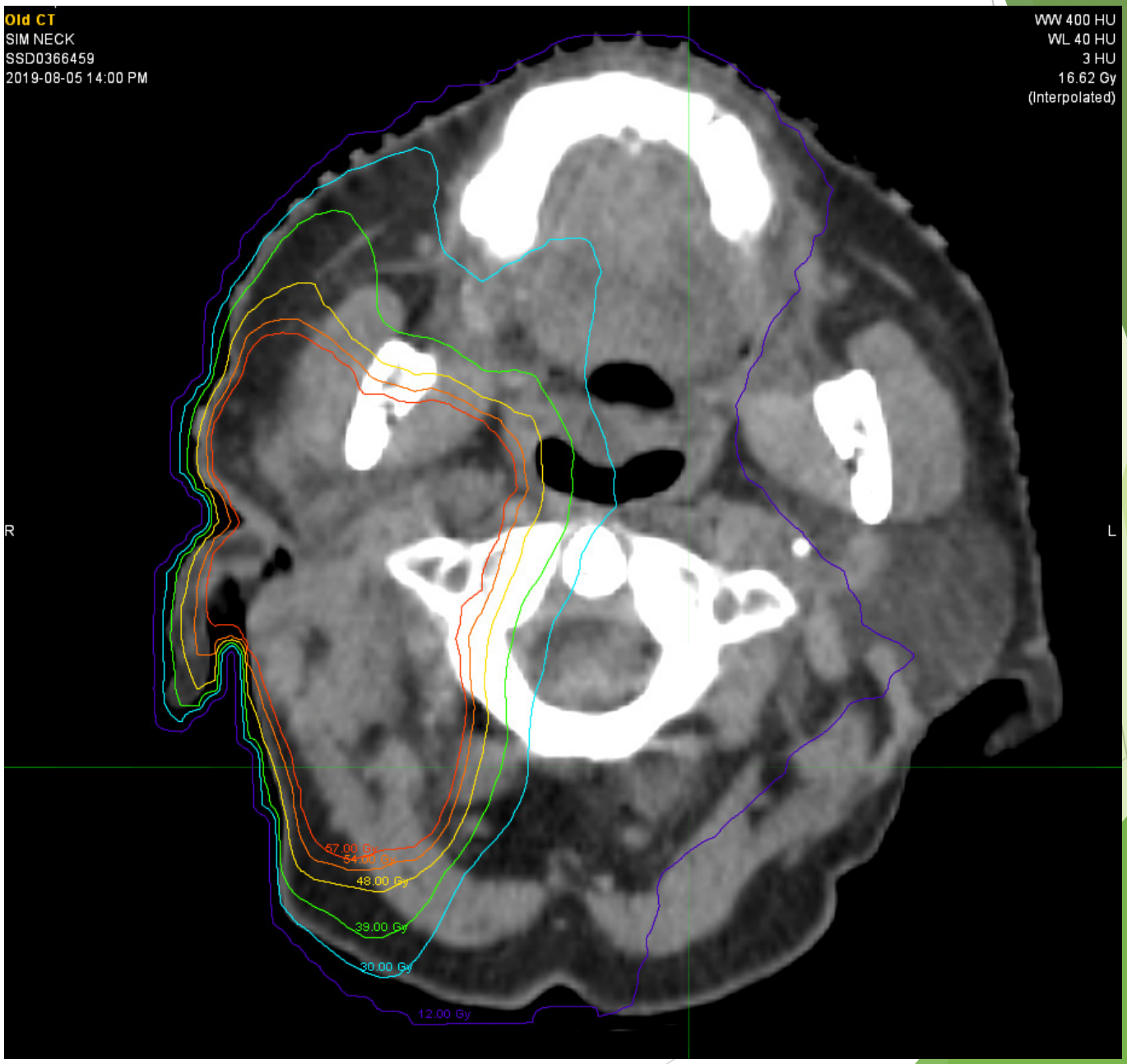
Back to Radiation Therapy: The Therapeutic Ratio

- Tumor control probablity (TCP)
  - Illustrated by the burgundy line
- Normal tissue complication probability (NTCP)
  - Illustrated by the blue line
- The farther the NTCP curve is to the right of the TCP curve:
  - The easier to achieve the radiotherapeutic goal
  - Larger the therapeutic index
  - Less like to be complications from treatment



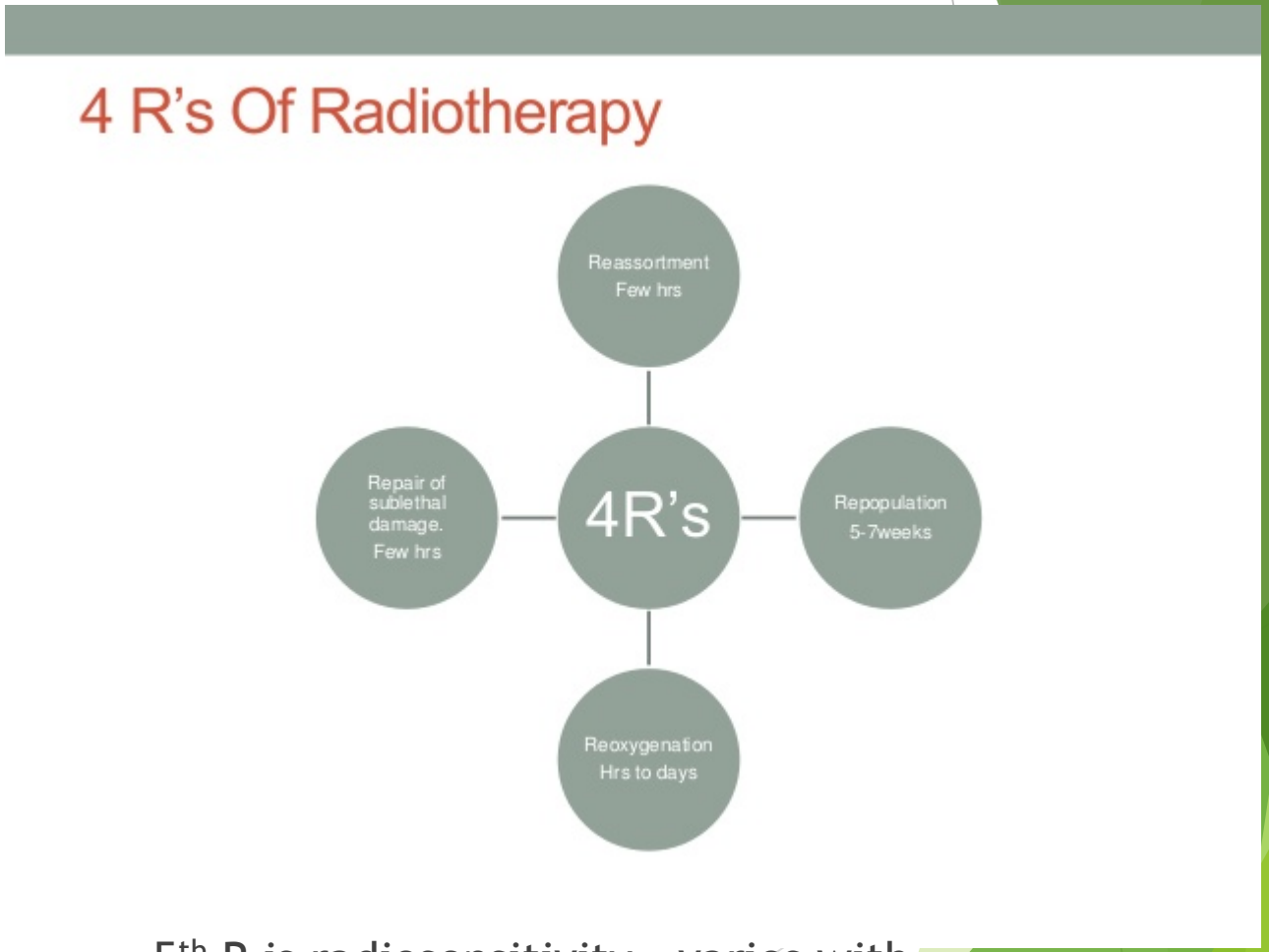
Radiation Absorbed Dose

- Abosorbed dose is measured in Gray (Gy)
  - Energy deposited per unit of mass
    - $Dm = \frac{dE}{dm}$
- 1 Gy = 1 J/kg



Radiation Dose and Fractionation

- In order to spare normal tissue radiation therapy doses are often fractionated
  - The dose is given in smaller amounts of over a period of days or weeks
    - Standard fractionation
      - 1.8 Gy – 3.0 cGy per day
      - 10 to 35 treatments
    - Hypofractionated
      - 10 Gy – 18 Gy per day
      - 3 to 5 treatments
  - Basis lies in the five Rs of radiotherapy
- However, total dose needs to be higher as must overcame sublethal damage



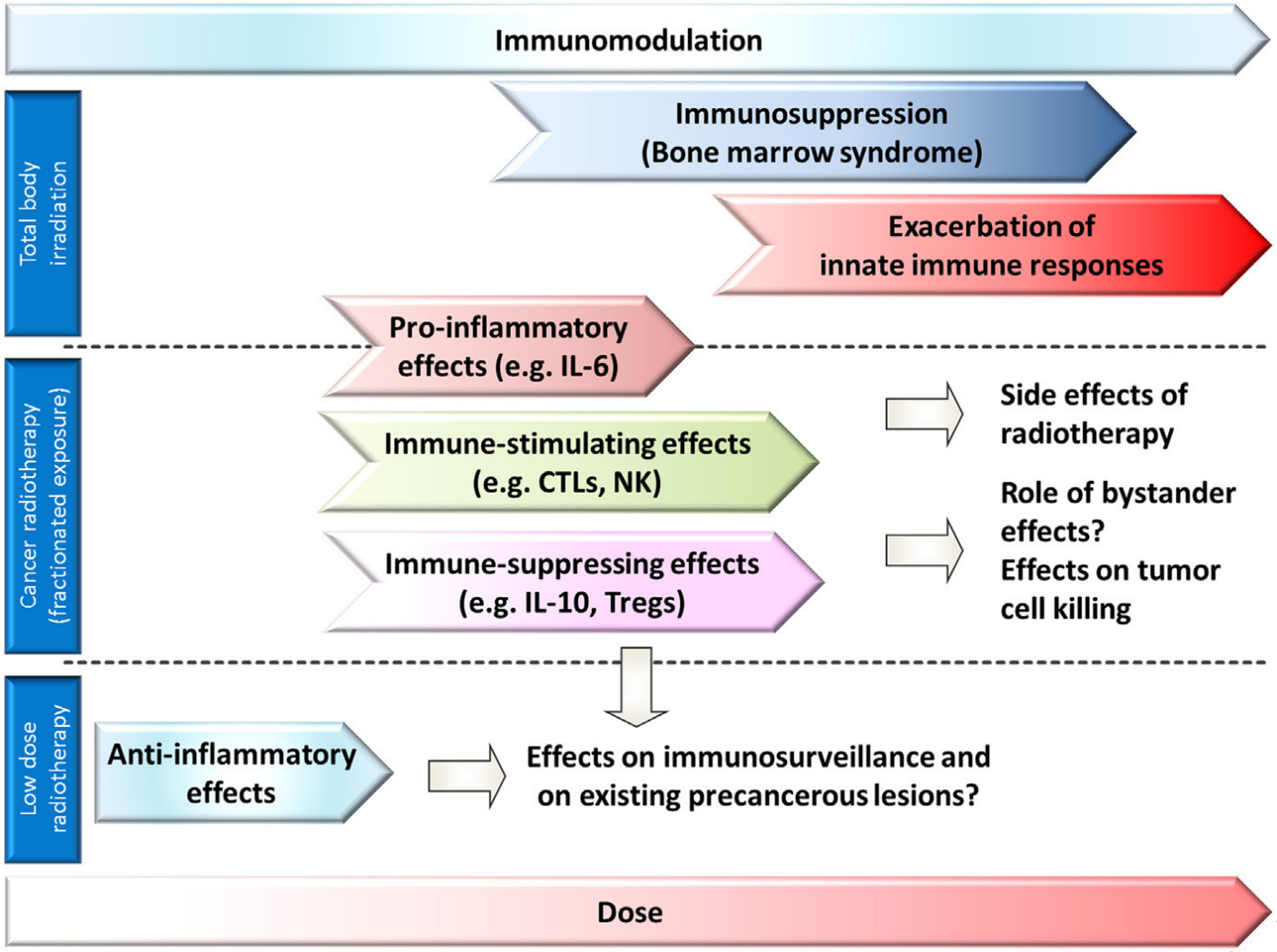
5th R is radiosensitivity – varies with maturation and metabolism

https://www.slideshare.net/swarnitasahu/4-rs-of-radiobiology-84454905

Stereotactic Body Radiation Therapy (SBRT)

- This allows larger doses per fraction (fewer fractions) to be delivered in a pinpoint manner
  - Greatly aided by the advent of image guided radio therapy (IGRT)
- Integration of SBRT vs conventional radiation therapy into immunotherapy
  - How do these affect the immune system

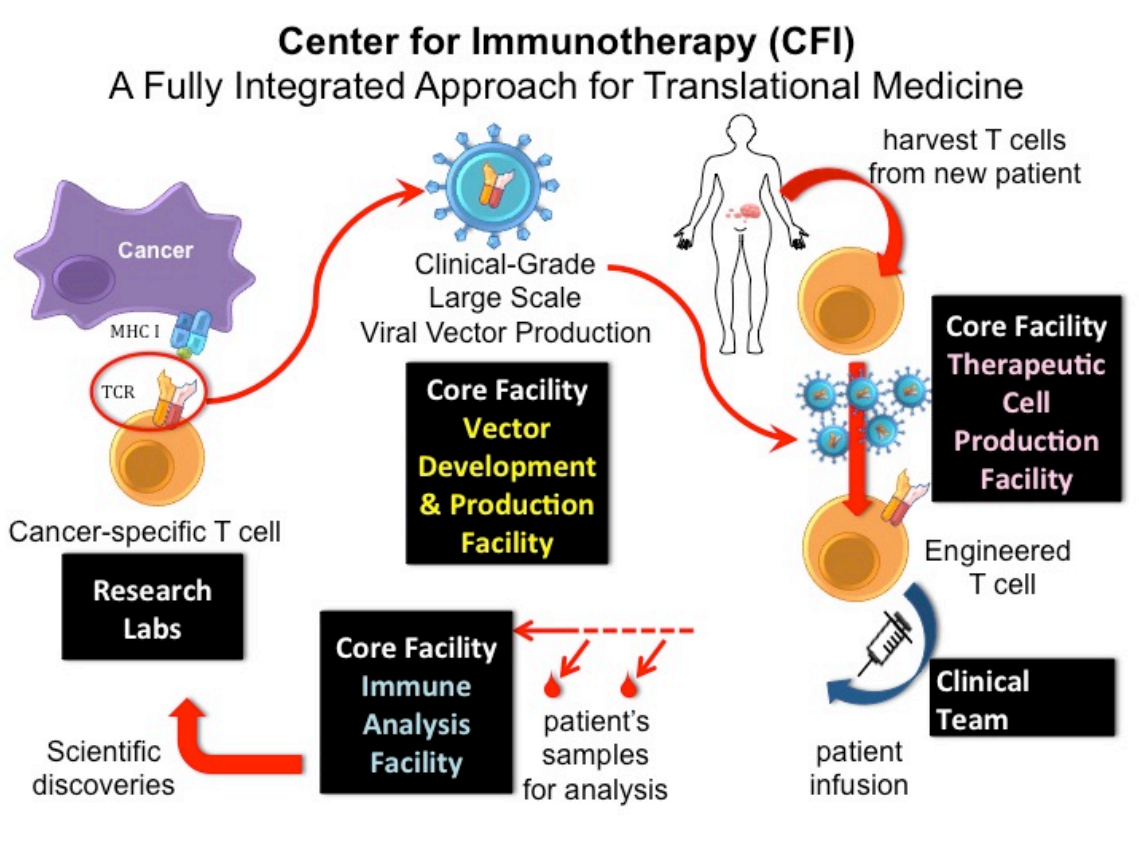
Radiation historically considered net immunosuppressive – radiosensitivity of the lymphoid system



Diegeler and Hellweg. Intercellular Communication of Tumor Cells and Immune Cells after Exposure to Different Ionizing Radiation Qualities. 2017. doi: 10.3389/fimmu.2017.00664

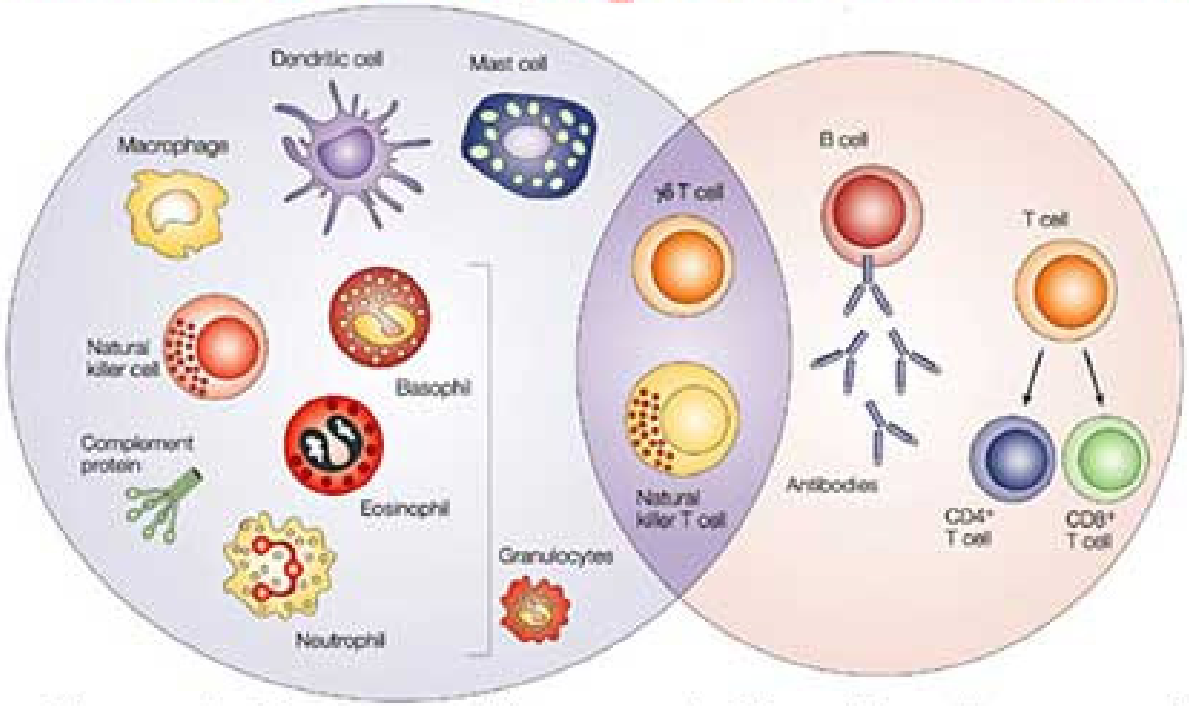
Immunotherapy

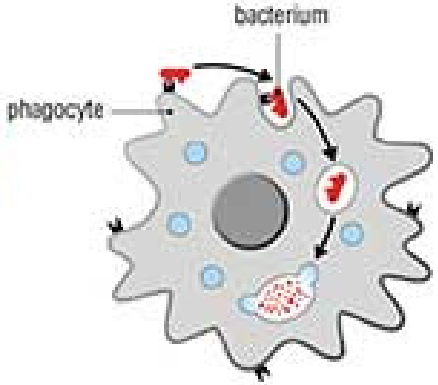
- Definition: a type of cancer treatment that helps your immune system fight cancer
- Types of immunotherapy
  - Monoclonal antibodies – flag cancer cells, block immune system inhibitors (Pembrolizumab)
  - Oncolytic virus therapy – genetically modified virus to kill cancer cells
  - T-cell therapy – genetically modify T-cells to kill cancer
  - Cancer vaccines – triggers immune system by exposing it to an antigen



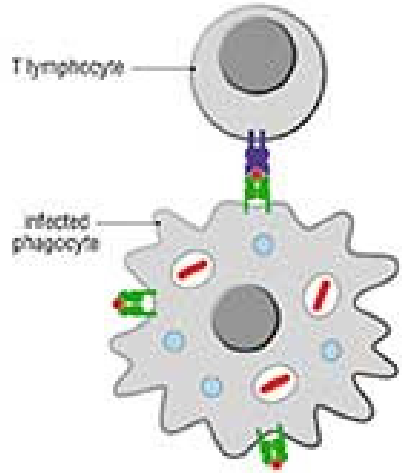
https://www.roswellpark.org/immunotherapy/about-immunotherapy/how-does-immunotherapy-work

Difference between
Innate and Adaptive Immunity



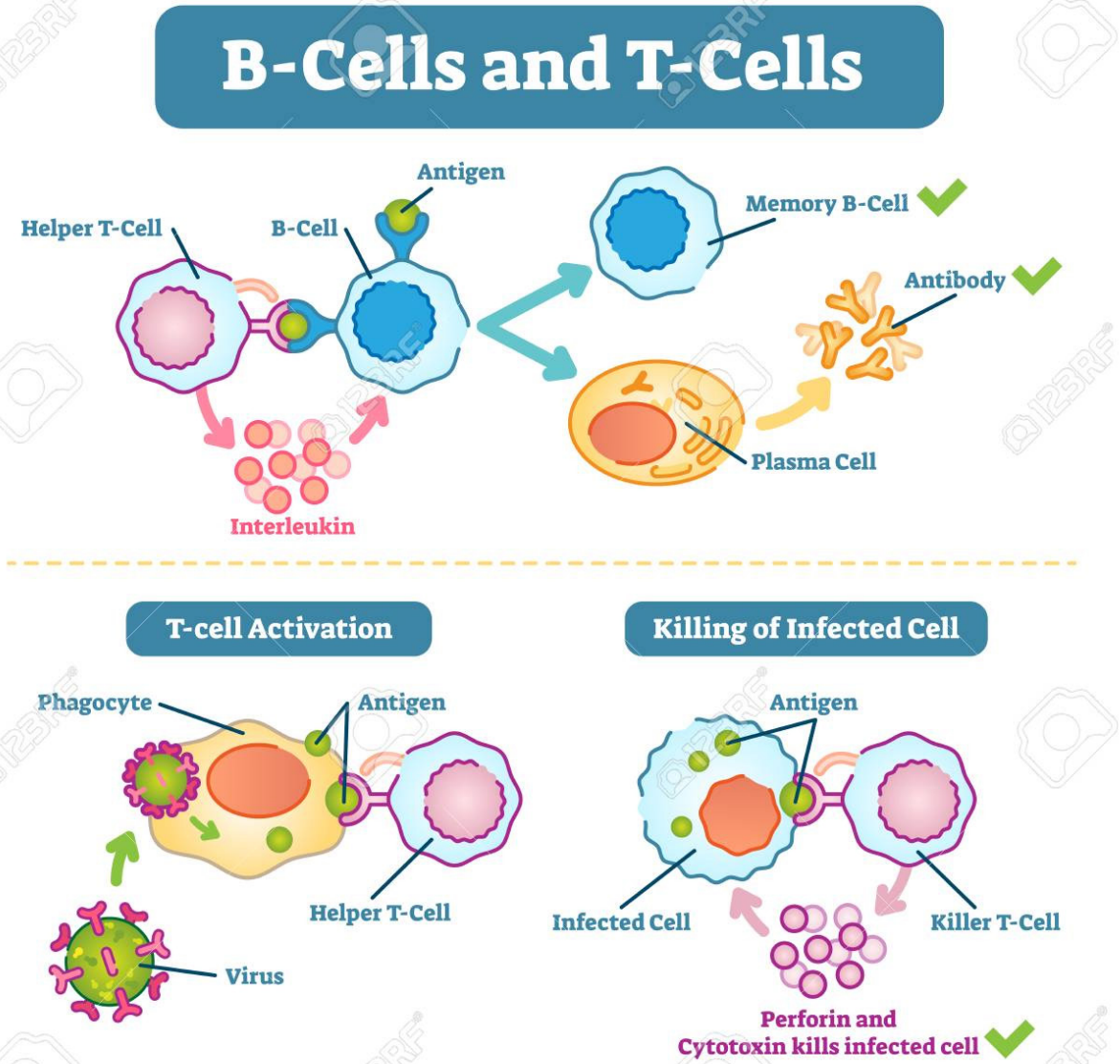


VS



Already present	Created in response to foreign substance
Non-specific	Specific
Limited/lower potency	High potency
No memory	Immunologic memory

https://microbiologyinfo.com/difference-between-innate-and-adaptive-immunity/



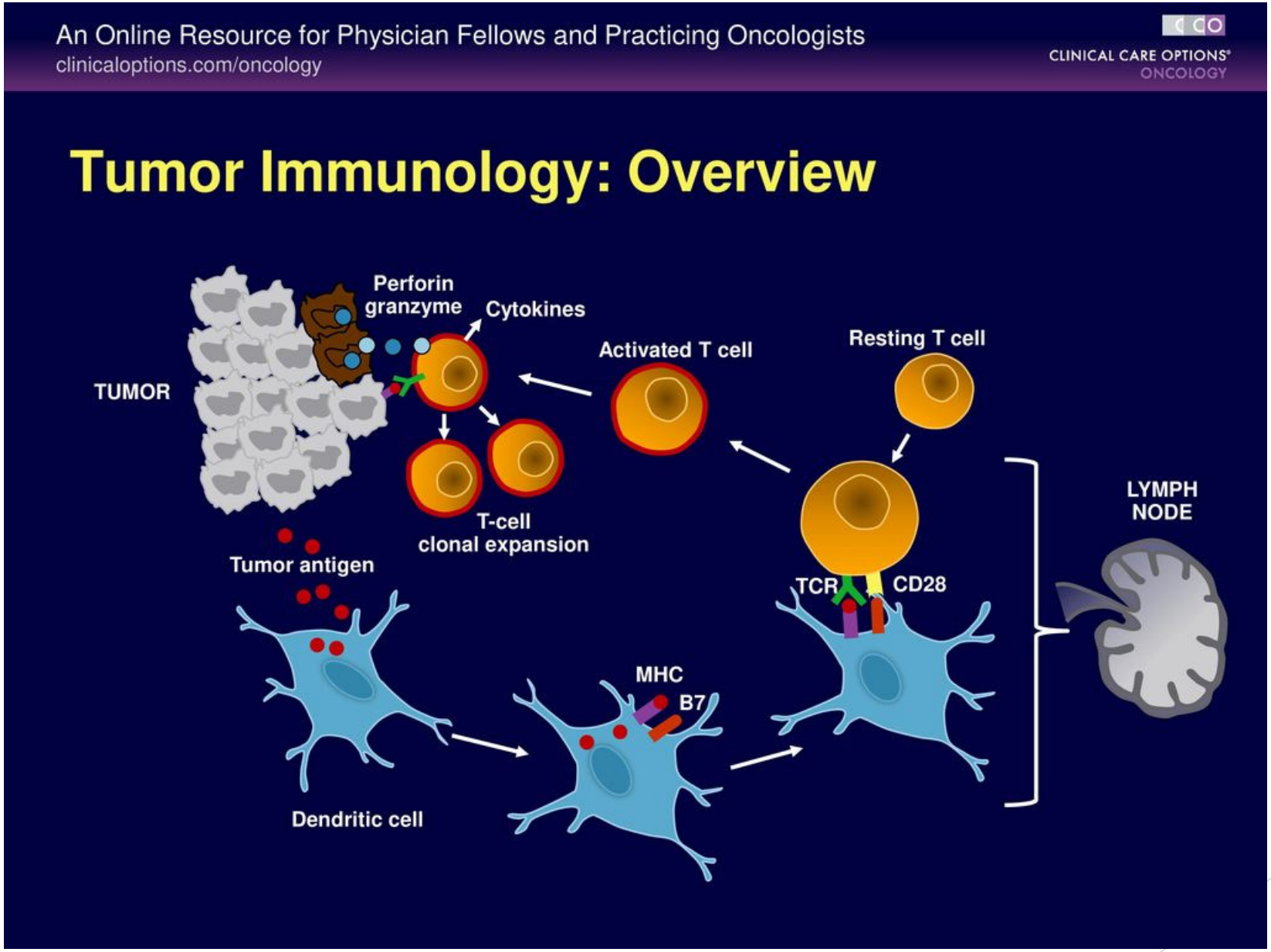
B cells

- Detect circulating antigens
- Make Antibodies

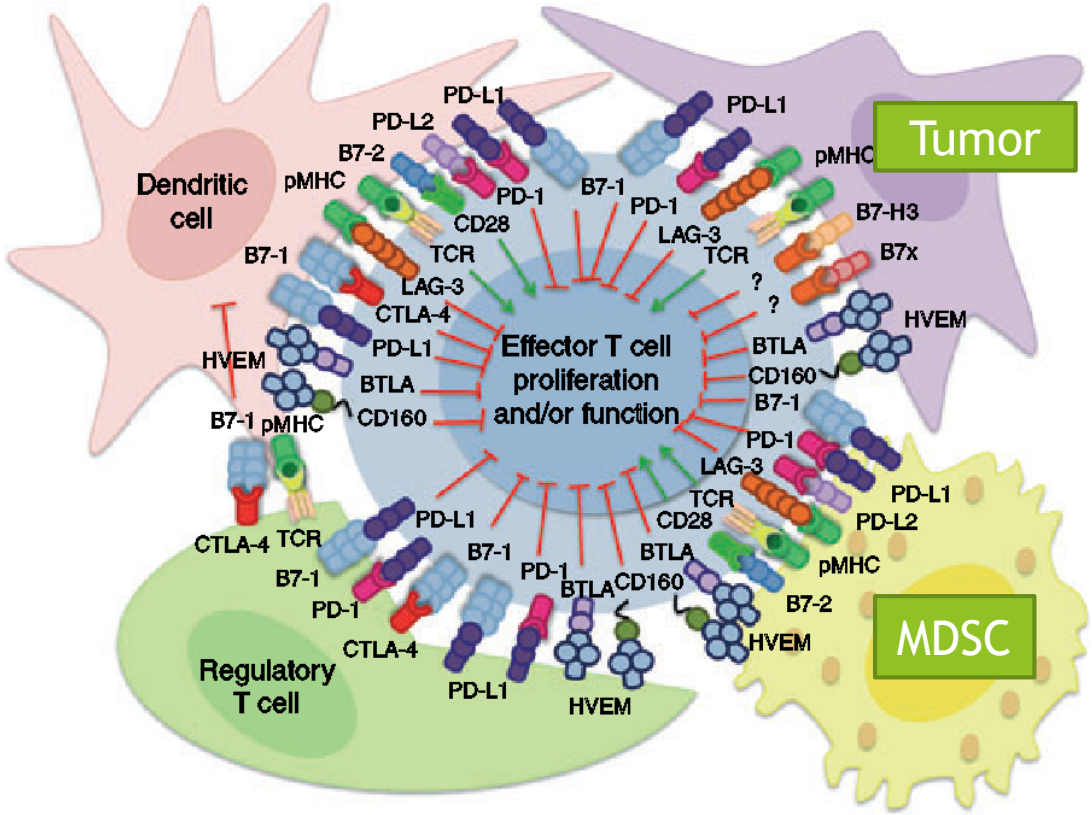
T cells

- Recognize antigens
- CD4+ T cells: synthesize cytokines
- CD8 T cells: Attack abnormal cells

https://www.123rf.com/photo_93720951_stock-vector-b-cells-and-t-cells-schematic-diagram-vector-illustration-immune-system-cell-functions-.html


An Online Resource for Physician Fellows and Practicing Oncologists
clinicaloptions.com/oncology
CLINICAL CARE OPTIONS ONCOLOGY
Tumor Immunology: Overview
Perforin
granzyme
Cytokines
Activated T cell
Resting T cell
TUMOR
T-cell
clonal expansion
LYMPH
NODE
Tumor antigen
TCR
CD28
MHC
B7
Dendritic cell

Tumor Microenvironment – What can we target?

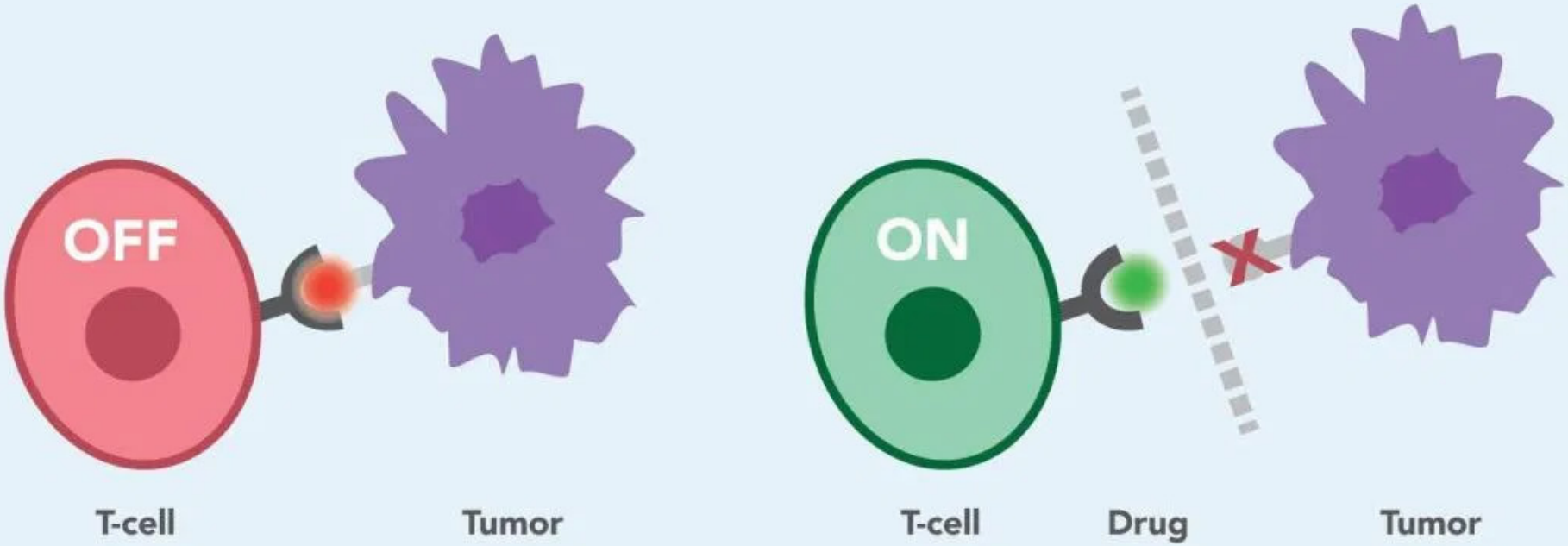


Pentcheva-Hoang et al, 2009.

How Does Immunotherapy Work?

Tumor cells bind to T-cells to deactivate them

Immunotherapy drugs can block tumor cells from deactivating T-cells

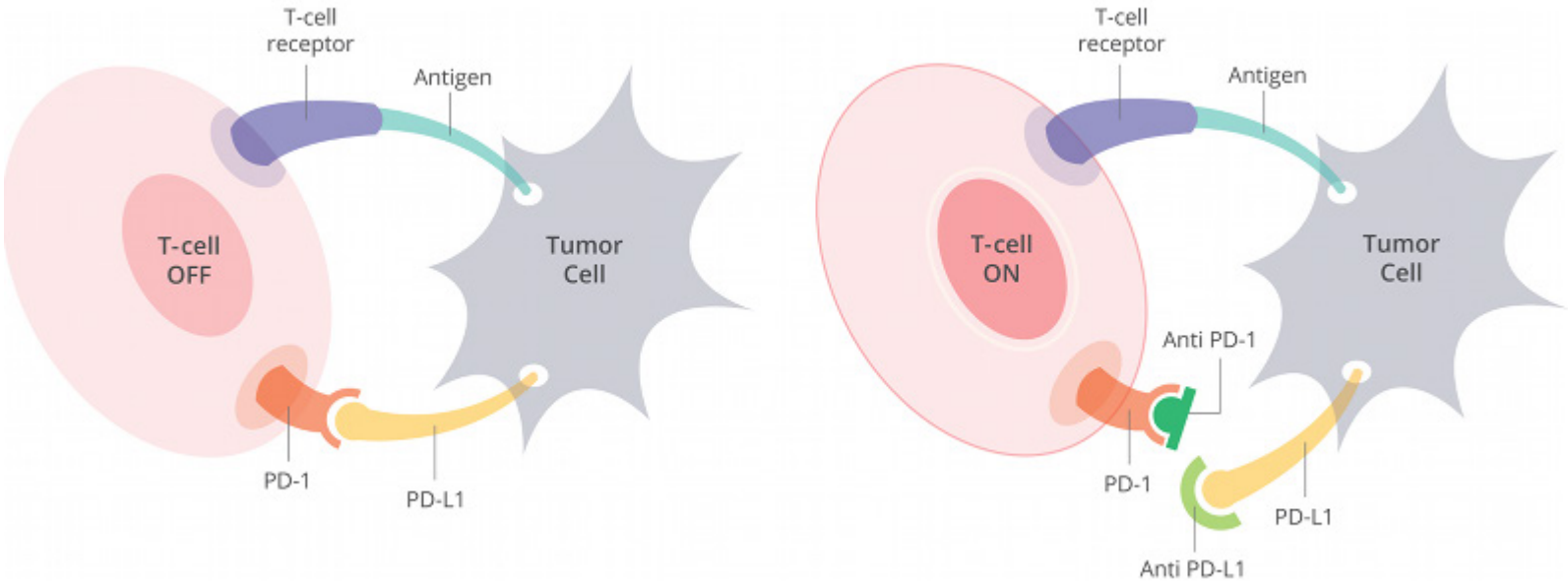


Columbia University Medical Center

https://www.google.com/url?sa=i&source=images&cd=&cad=rja&uact=8&ved=2ahUKEwimoPqDwoDlAhVDFTQIHdfmD80QjRx6BAgBEAQ&url=https%3A%2F%2Fangelflighteast.org%2Fwhat-is-immunotherapy-the-basics-on-these-cancer-treatments%2F&psig=AOvVaw0D9ihiJPfB6zZ-CO1kRqOQ&ust=1570206653688572

Promising Target

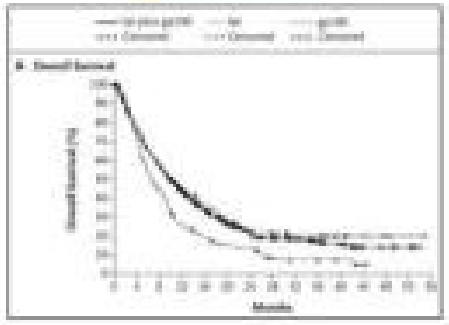
PD-1 inhibitors
- Pembrolizumab (Keytruda)
- Nivolumab (Opdivo)
- Cemiplimab (Libtayo)



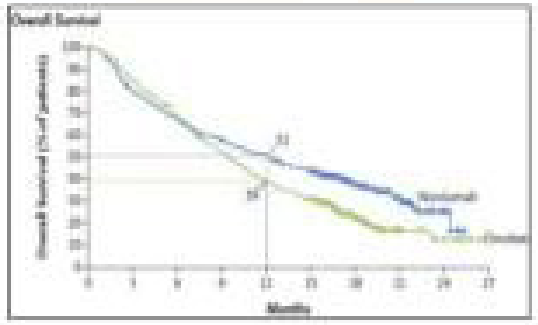
PD-L1 inhibitors
- Atezolizumab (Tecentriq)
- Avelumab (Bavencio)
- Durvalumab (Imfinzi)

cancer.org and bocsci.com

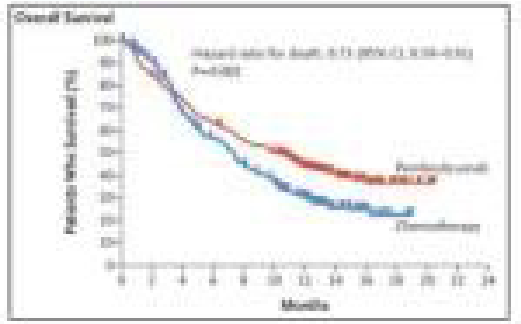
Immunotherapy (PD-L1) works



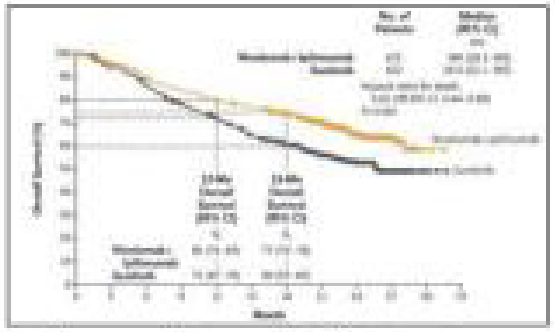
Metastatic Melanoma
Hodi NEJM 2010



Advanced NSCLC
Borghaei NEJM 2015

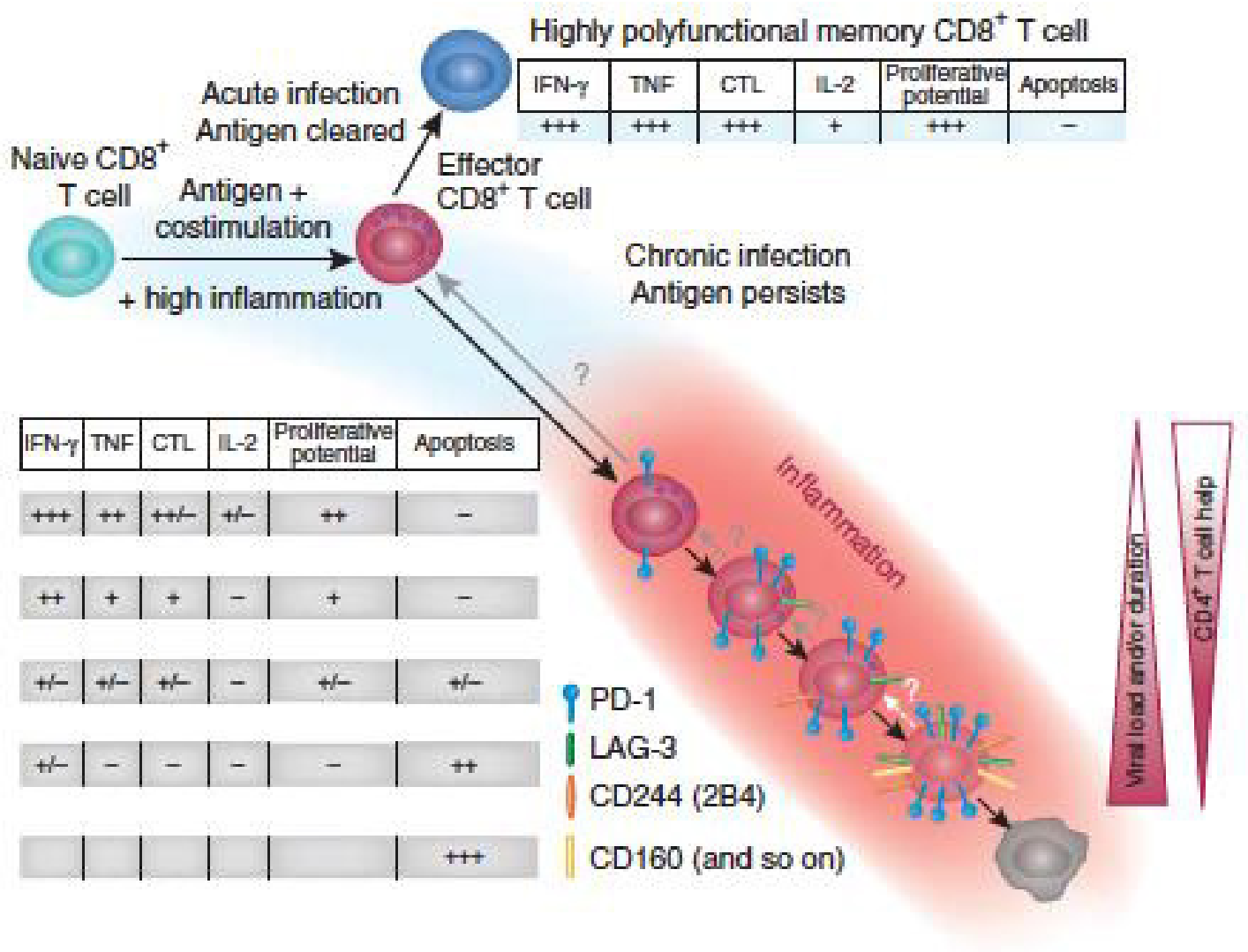


Advanced Urothelial Carcinoma
Bellmunt NEJM 2017



Advanced Renal Cell Carcinoma
Motzer NEJM 2018

15%-20% responders



Wherry. T cell exhaustion. Nat Immunol. 2011 Jun;12(6):492-9

Summary

- Immune system has innate (nonspecific) and adaptive (specific) elements
- Cancer can induce immune system dysfunction
  - T cell exhaustion
- Targets for drug development are immune checkpoints and features of the tumor microenvironment

So.. Now we know the basics of radiation therapy and immunotherapy.

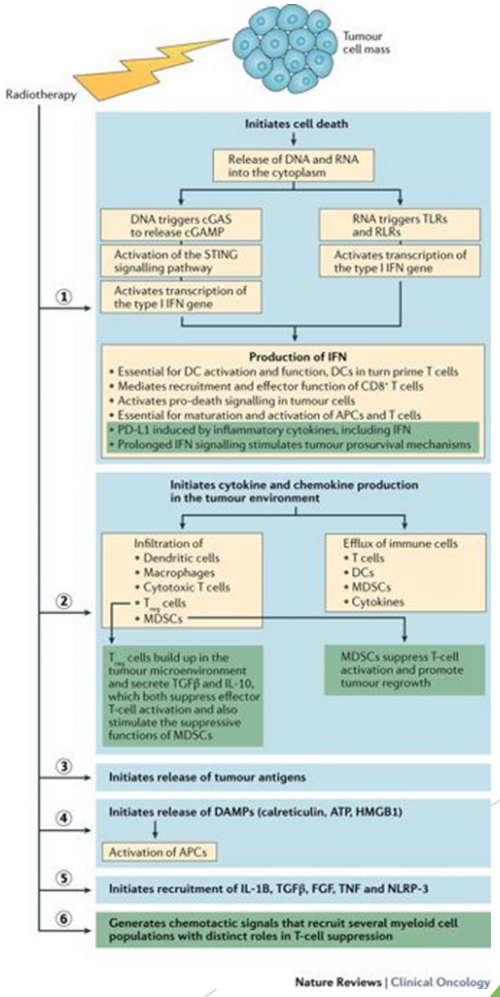
What Next?

“At present, the opinions about the interaction between ionizing radiation and the immune system are largely controversial”

Editorial: Radiation and the Immune System: Current Knowledge and Future Perspectives

Katalin Lumniczky[1], Serge M. Candéias[2], Udo S. Gaipl[3] and Benjamin Frey[3]*

- Radiation can induce an immune response
  - Promote the release of danger signals and chemokines and activate cytotoxic T cells
  - Abscopal effect



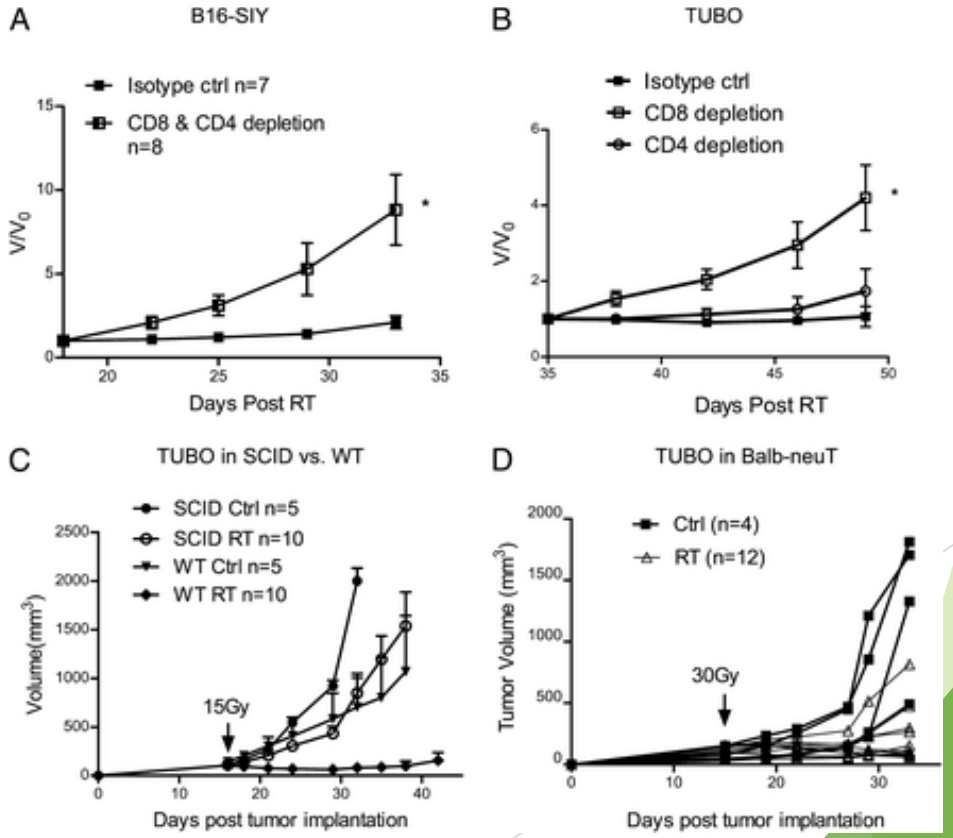
What do we know about radiation and immunotherapy interactions?

Radiation-Induced Equilibrium Is a Balance between Tumor Cell Proliferation and T Cell–Mediated Killing

Hua Liang, Liufu Deng, Steven Chmura, Byron Burnette, Nicole Liadis, Thomas Darga, Michael A. Beckett, Mark W. Lingen, MaryEllyn Witt, Ralph R. Weichselbaum and Yang-Xin Fu

J Immunol June 1, 2013, 190 (11) 5874-5881; DOI: https://doi.org/10.4049/jimmunol.1202612

- Animal model
  - Post radiation
    - Depleted CD4 and CD8
    - Increased Growth
  - Concluded radiation induced tumor equilibrium is a balance between cell birth and cell death mediated principally by $CD8^+$ T cells



Blood. 2009 Jul 16; 114(3): 589–595.
Prepublished online 2009 Apr 6. doi: 10.1182/blood-2009-02-206870
Immunobiology

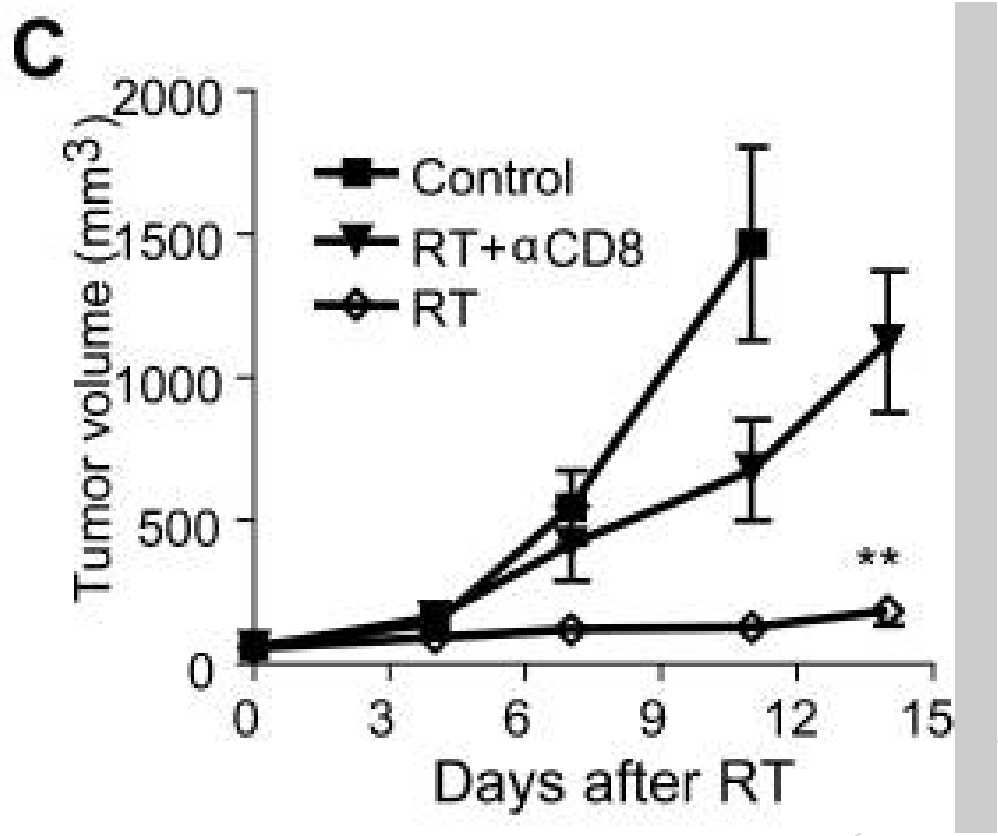
PMCID: PMC2713472
PMID: 19349616

Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment

Youjin Lee,[1,*] Sogyong L. Auh,[1,*] Yugang Wang,[1] Byron Burnette,[1] Yang Wang,[1] Yuru Meng,[2] Michael Beckett,[2] Rohit Sharma,[3] Robert Chin,[1] Tony Tu,[1] Ralph R. Weichselbaum,[✉2] and Yang-Xin Fu[✉1]

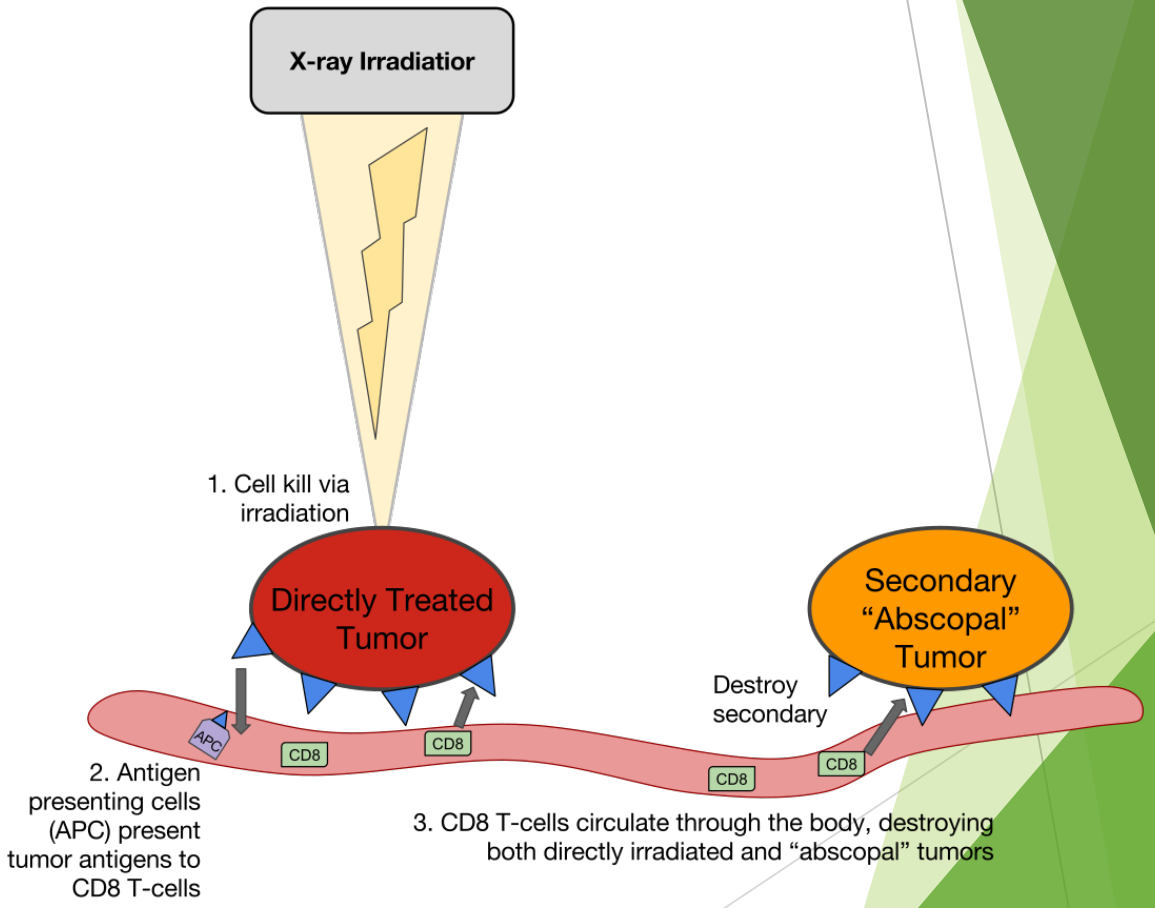
Animal Model

- SBRT dose 1 x 20Gy
- Substantial increase in tumor size with the removal of CD8



Abscopal Effect

- Hypothesis in the treatment of metastatic cancer whereby the tumors that have not been directly radiated are destroyed by the immune system
- But! Appears to happen rarely.



Abscopal Response

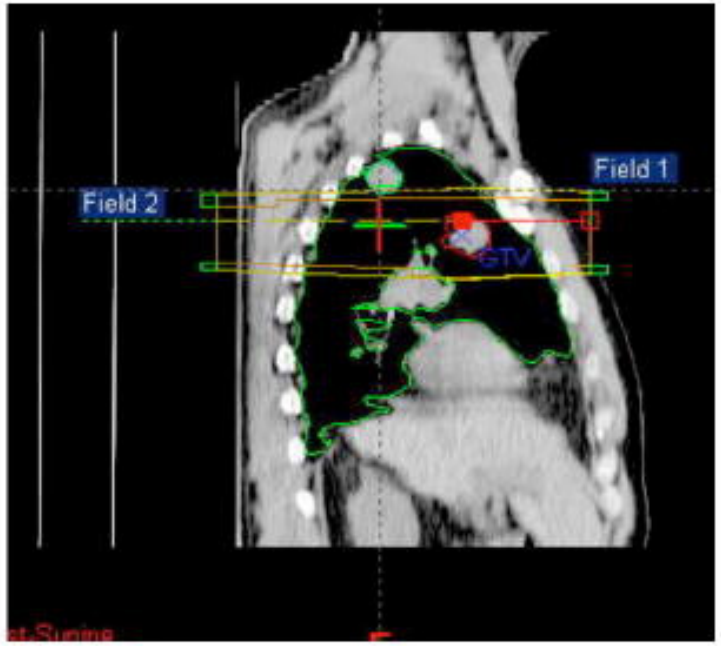
Lancet Oncol. Author manuscript; available in PMC 2010 Jul 1.
Published in final edited form as:
Lancet Oncol. 2009 Jul; 10(7): 718–726.
doi: 10.1016/S1470-2045(09)70082-8

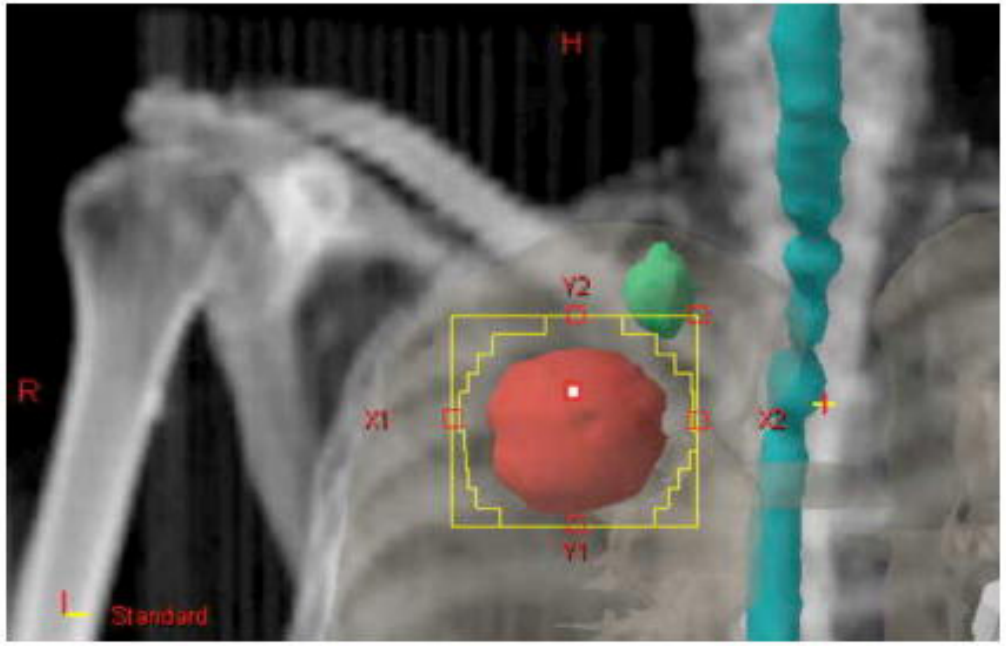
PMCID: PMC2782943
NIHMSID: NIHMS146690
PMID: 19573801

Systemic effects of local radiotherapy

Silvia C. Formenti, M.D.[1,3] and Sandra Demaria, M.D.[2]

- Patients
  - Three measurable lesions
  - Stable disease or progression during systematic chemotherapy
  - Radiated a single lesion
    - 3.5 Gy for 10 fractions
  - On day 7 of radiation GM-CSF (granulocyte-macrophage colony-stimulating factor) – a cytokine
    - Given for 14 days



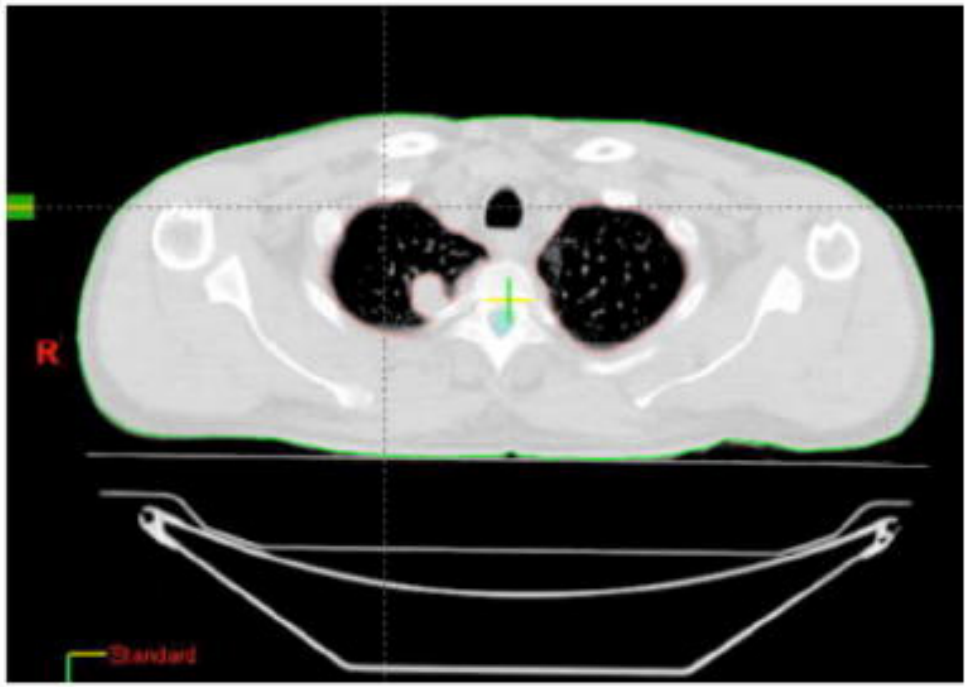


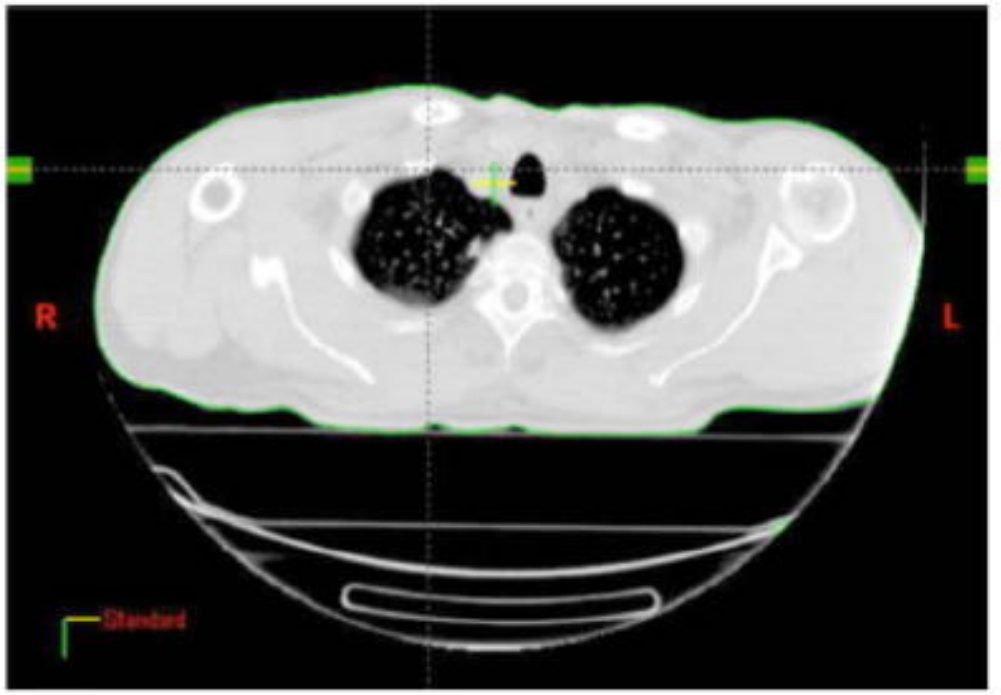
- 14 patients
  - Lung, thymus, breast, bladder, eccrine
- Results
  - Four patients achieved an abscopal response
  - Five patients decreased SUV of non-irradiated lesions on PET

Lancet Oncol. Author manuscript; available in PMC 2010 Jul 1.
Published in final edited form as:
Lancet Oncol. 2009 Jul; 10(7): 718–726.
doi: 10.1016/S1470-2045(09)70082-8
PMCID: PMC2782943
NIHMSID: NIHMS146690
PMID: 19573801

Systemic effects of local radiotherapy

Silvia C. Formenti, M.D.[1,3] and Sandra Demaria, M.D.[2]





Effective Combination of Radiation Therapy and Immunotherapy

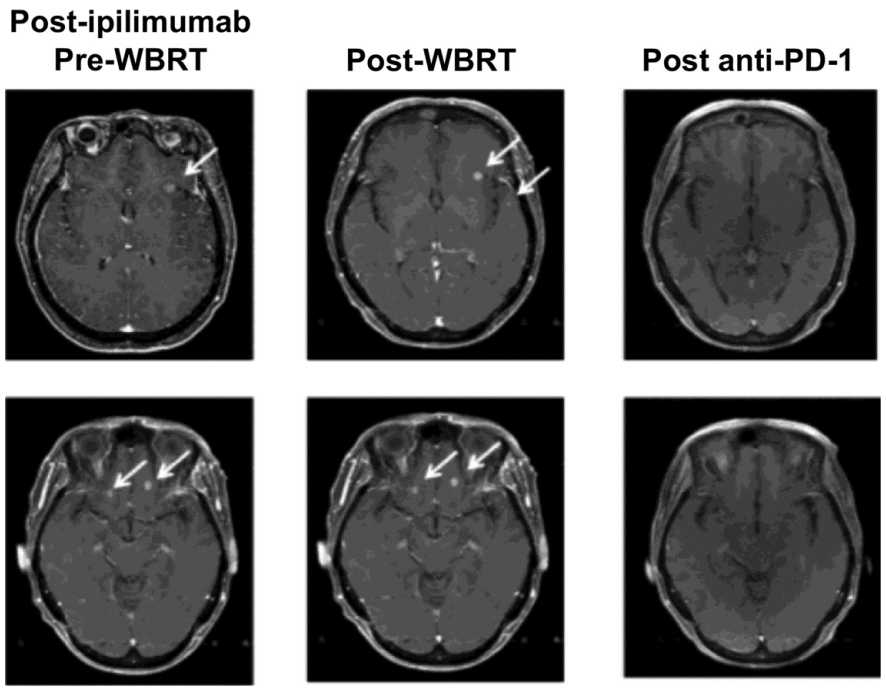
- 60-year-old female
- After ipilimumab, 17 new brain lesions
- Received WBRT (30 Gy in 10 fractions)
  - No new lesions, but existing lesions had not responded
- Initiated pembrolizumab
- All lesions resolved after 10 doses of pembrolizumab
- Disease free for 29 months (counting from first dose of pembrolizumab)

Cancer Immunology Miniatures

Metastatic Melanoma Patient Had a Complete Response with Clonal Expansion after Whole Brain Radiation and PD-1 Blockade

Cara L. Haymaker, DaeWon Kim, Marc Uemura, Luis M. Vence, Ann Phillip, Natalie McQuail, Paul D. Brown, Irina Fernandez, Courtney W. Hudgens, Caitlin Creasy, Wen-Jen Hwu, Padmanee Sharma, Michael T. Tetzlaff, James P. Allison, Patrick Hwu, Chantale Bernatchez, and Adi Diab

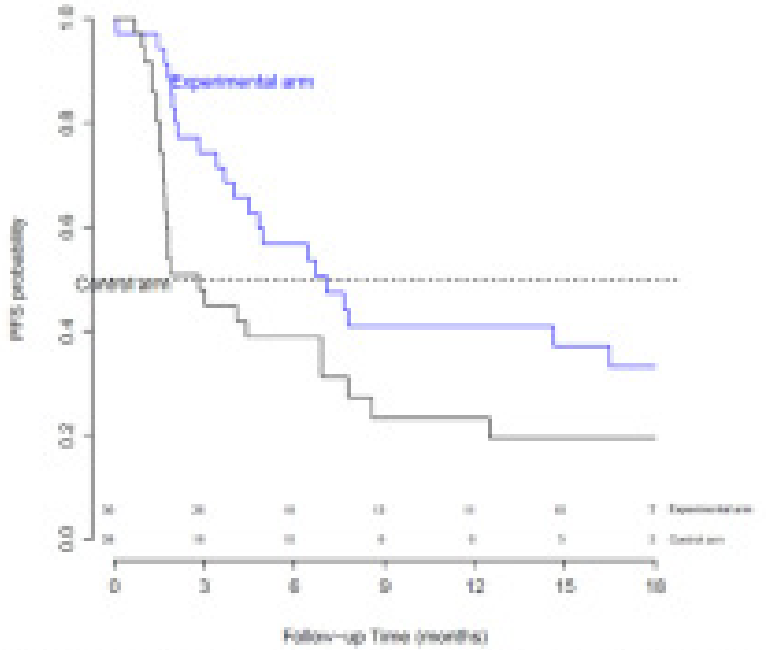
DOI: 10.1158/2326-6066.CIR-16-0223 Published February 2017



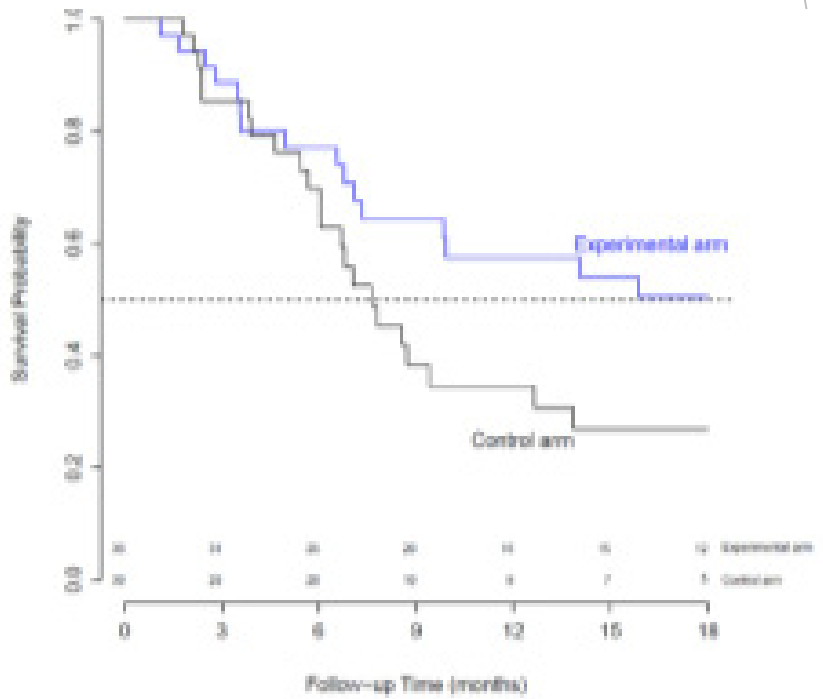
Theorize response due to activated $CD8^+$ T cells in the blood

Radomized phase II study of anti-PD-1 alone vs. anti-PD-1+SBRT in patients with advanced NSCLC (n=64)

Figure 1. Progression-free Survival



Median PFS is 7.1m (95% CI 4.5 – NA) in the experimental arm and 2.8m (95% CI 1.7 – 7.8) in the control arm. HR 0.61 (95% CI 0.35-1.06, p = 0.08).



Median OS is 19.2m (95% CI 7.3-NA) in the experimental arm and 7.6m (95% CI 6-13.9) in the control arm. HR 0.58 (95% CI 0.31-1.1, p = 0.1)

Median PFS was 1.8 months in PD-1 alone arm and 6.4 months in the PD-1+SBRT arem

ASCO 2018 abstract: Theelan W et al. and Chmura AAPM 2019

Questions That Need To Be Answered

- Is there a dose threshold?
- Is there a tumor volume threshold?
- Can this immune response treat tumor cells that are not directly irradiated (abscopal effect)?
- What clinical evidence exists that radiation is an immune modulator before the introduction of immunotherapy?
- How will the optimal timing and dose of radiation be determined?

Current Challenges

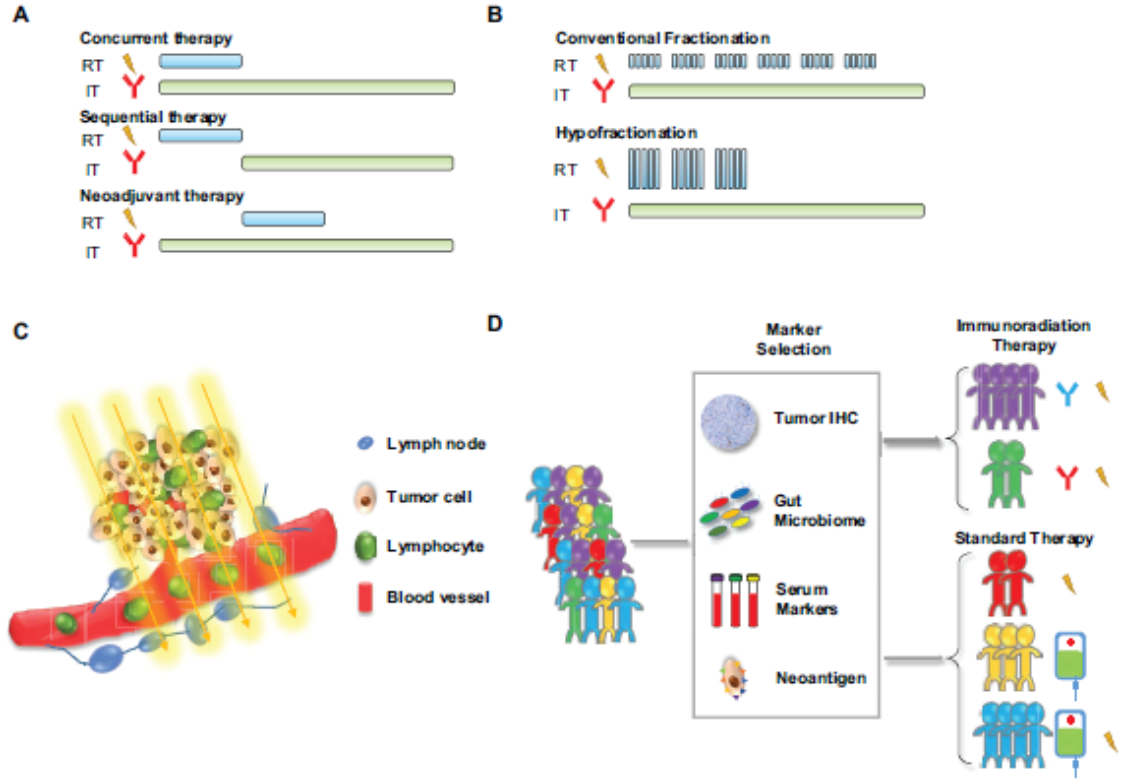


FIGURE 1 | Current challenges in combining radiotherapy with immunotherapy. **(A)** Optimization of treatment timing: using immunotherapy concurrently, sequentially, or as neoadjuvant therapy with radiotherapy. **(B)** Optimization of radiation dosing: conventional fractionation or hypofractionation. **(C)** Reduction of the radiation-induced toxicity of circulating and tumor-infiltrated lymphocytes. **(D)** Selection of immunoradiation therapy or standard therapy for patients based on predictive biomarkers.

Wang Y, et al.(2018) Combining Immunotherapy and Radiotherapy for Cancer Treatment: Current Challenges and Future Directions. Front. Pharmacol. 9:185.doi: 10.3389/fphar.2018.00185

Current Project

- Utilize the current Avera database
- Analyze patients that have undergone both radiation therapy and immunotherapy at Avera
  - Administrations being within 30 days of each other
    - Approximately 35 patients
  - Longer breaks between fractions schemes
  - Recorded fractionation schemes
- Evaluate response radiographically, if possible
- Goal:
  - Say something intelligent about dose fractionation schemes and/or timing?
  - Do we see anything comparable to published literature?
  - Can we combine schools of thought with bioinformatics?

Thank you for your attention!

Special thanks to:

- Radiation Oncology Staff
- Bioinformatics Group