

NEW TRENDS IN BIOMATHEMATICS

Applications in Oncology and Immunology

ONE-DAY WORKSHOP
June 21, 2024, 8:30 a.m.

Aula Magna INGEGNERIA "Italo Falcomatà"
Università degli Studi Mediterranea
Via R. Zehender, 1 • Reggio Calabria

SPEAKERS

Filippo Castiglione
Consiglio Nazionale delle Ricerche (CNR) Roma

Pasquale Ciarletta
Politecnico di Milano

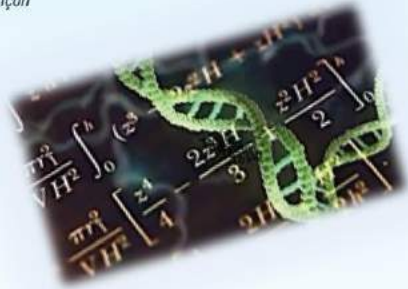
Raluca Eftimie
Université de Franche-Comté, Besançon

Francesco Pappalardo
Università di Catania

Luigi Preziosi
Politecnico di Torino

Carmelo Tuscano
G.O.M. Reggio Calabria

Program & Abstracts at:
<https://biomath-rc.unirc.it>



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LUIGI PREZIOSI
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INFORMATION AND REGISTRATION

For information, please contact **A. Amoddeo** or **V. Bonanzinga** at:

✉ biomath-rc@unirc.it

Participation is free but registration is mandatory. Therefore, people who are interested are kindly asked to

fill in the registration form, by May 31, 2024, at:

🌐 biomath-rc.unirc.it

The workshop topic is related to the project CALABRIA HUB per Ricerca Innovativa ed Avanzata (CAL.HUB.RIA) funded by Piano Operativo Salute - traiettoria 4 "Biotecnologie, Bioinformatica e Sviluppo Farmaceutico"

TECHNICAL STAFF: Maurizio Campolo - Giandomenico Posillipo

Mechanisms of integration between **radiotherapy** and **immunotherapy**: from the radiobiological perspective to the patient's bedside

Dipartimento Onco-Ematologico-Radioterapico

U.O.C. Radioterapia Oncologica

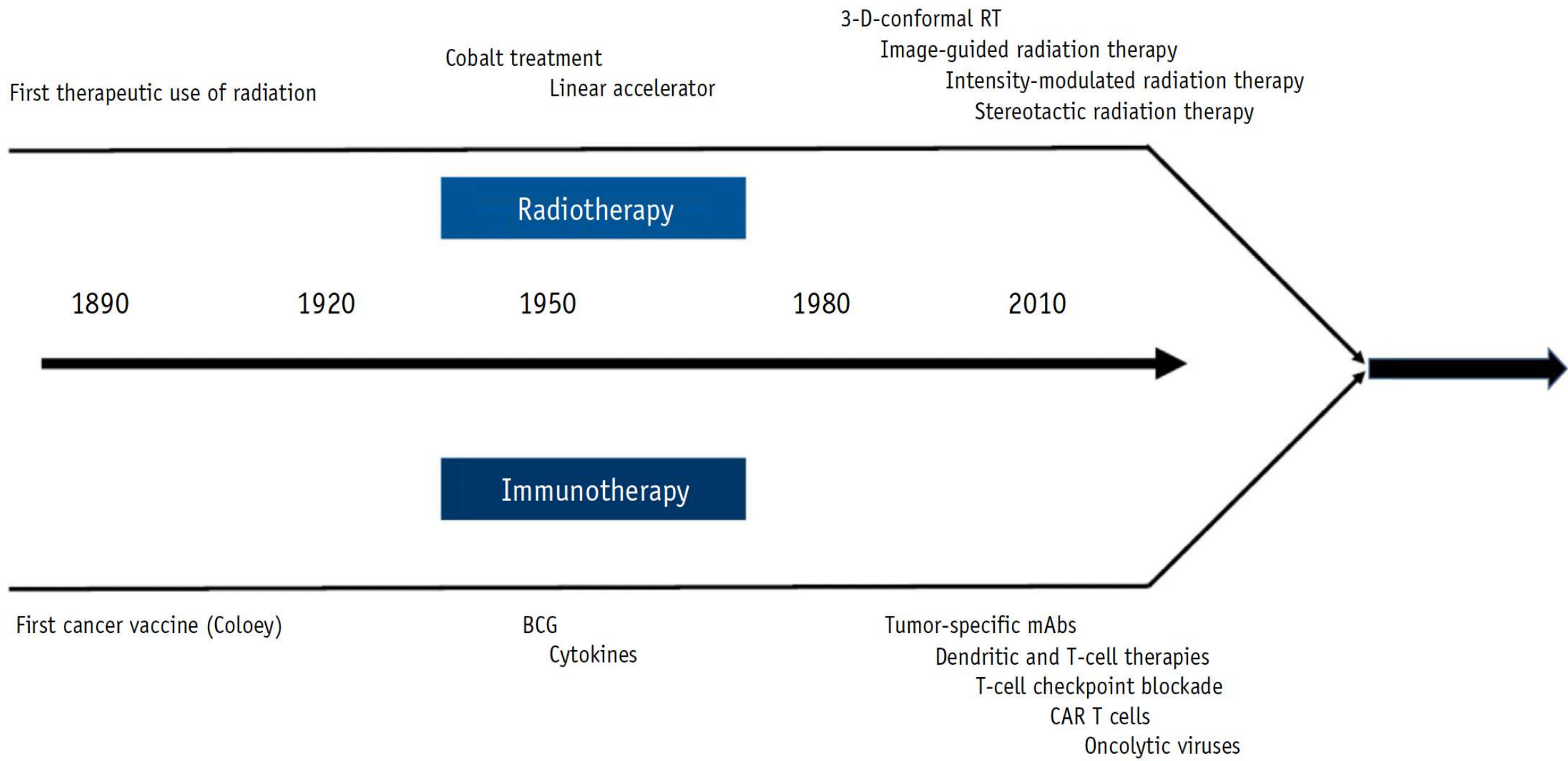
Grande Ospedale Metropolitano-Reggio Calabria



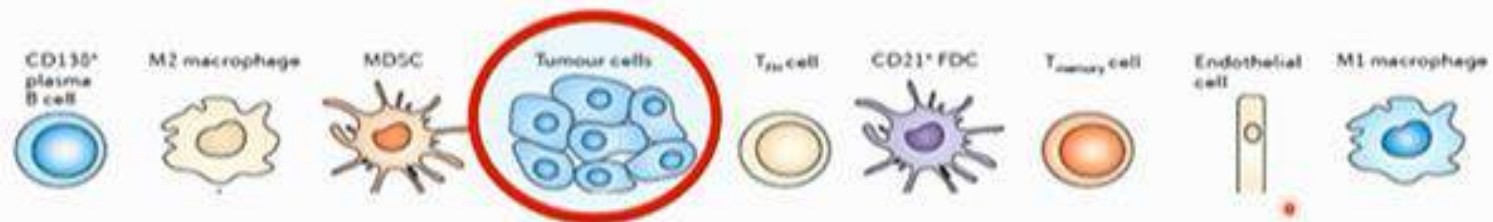
Associazione Italiana
Radioterapia e Oncologia clinica



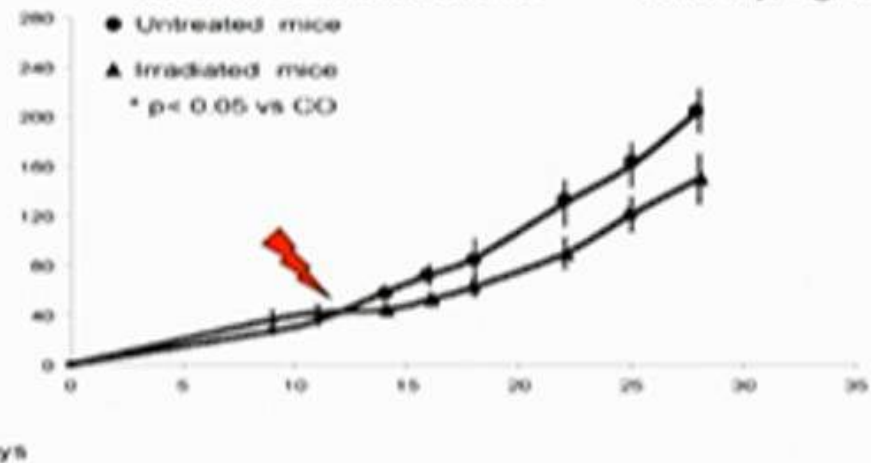
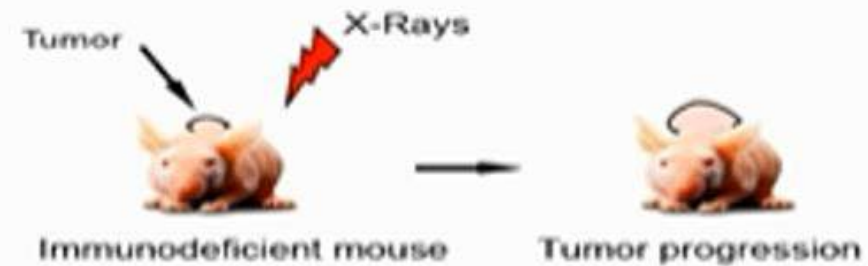
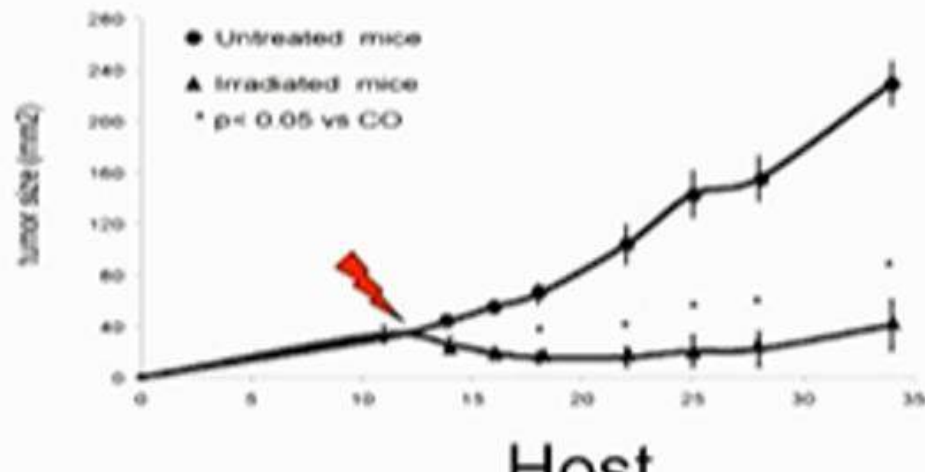
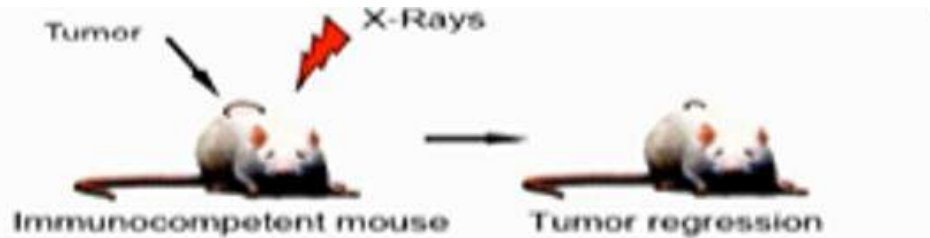
ESTRO
European Society for
RADIO THERAPY
& ONCOLOGY



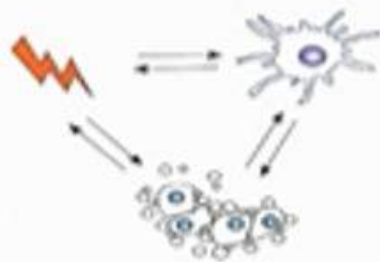
Tumor cells



RADIOTHERAPY AND MICROENVIRONMENT : MORE THAN HYPOXIA



Radiation
-ER Stress
-Apoptosis
-HMGB1 release



Tumor

Host
-TLR4 / MyD88
-P2RX7 / NLRP3
-Immunocompetent

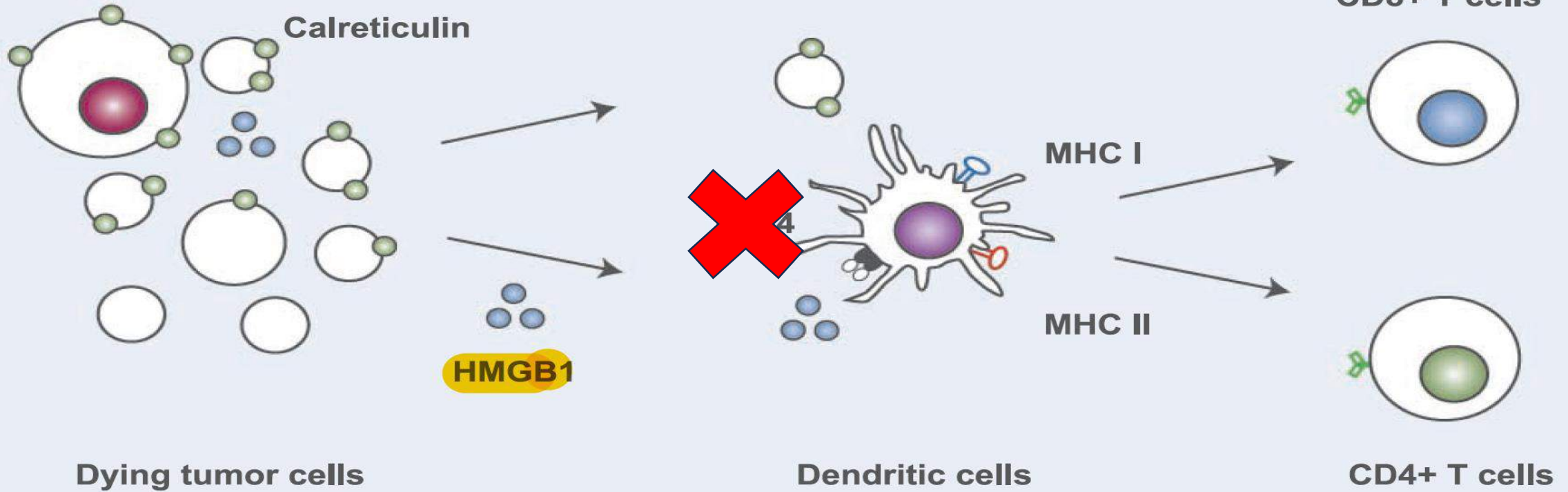
Courtesy A. Tesniere

Apetoh, Tesniere*, Ghiringhelli* et al. Cancer Research 2008*

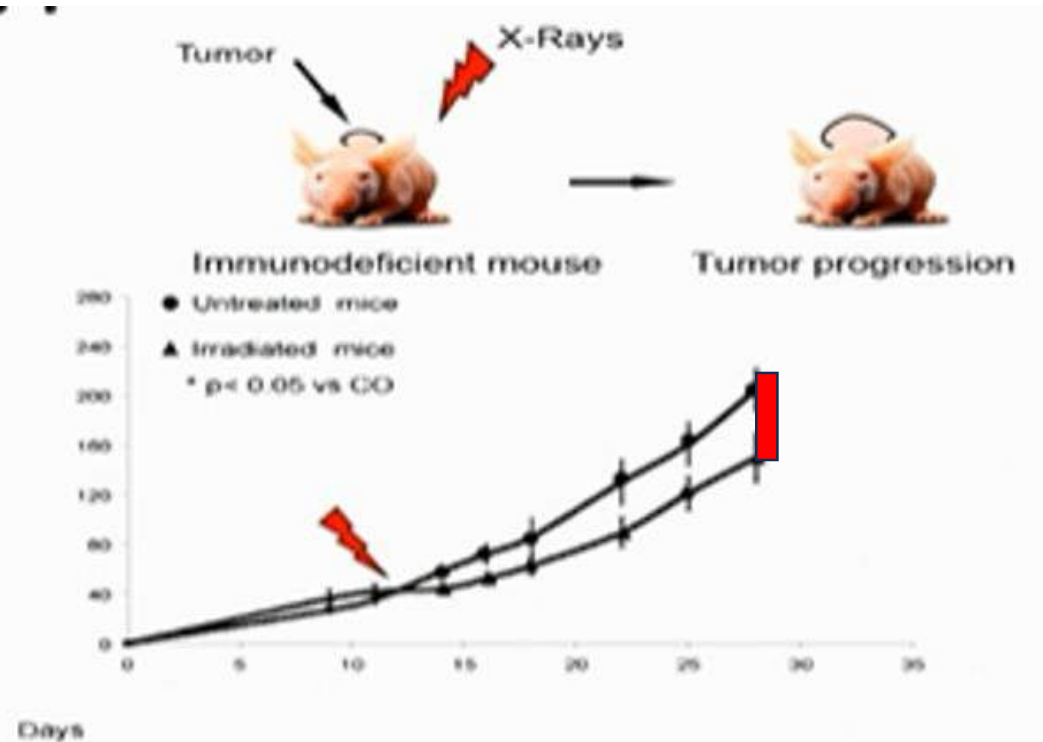
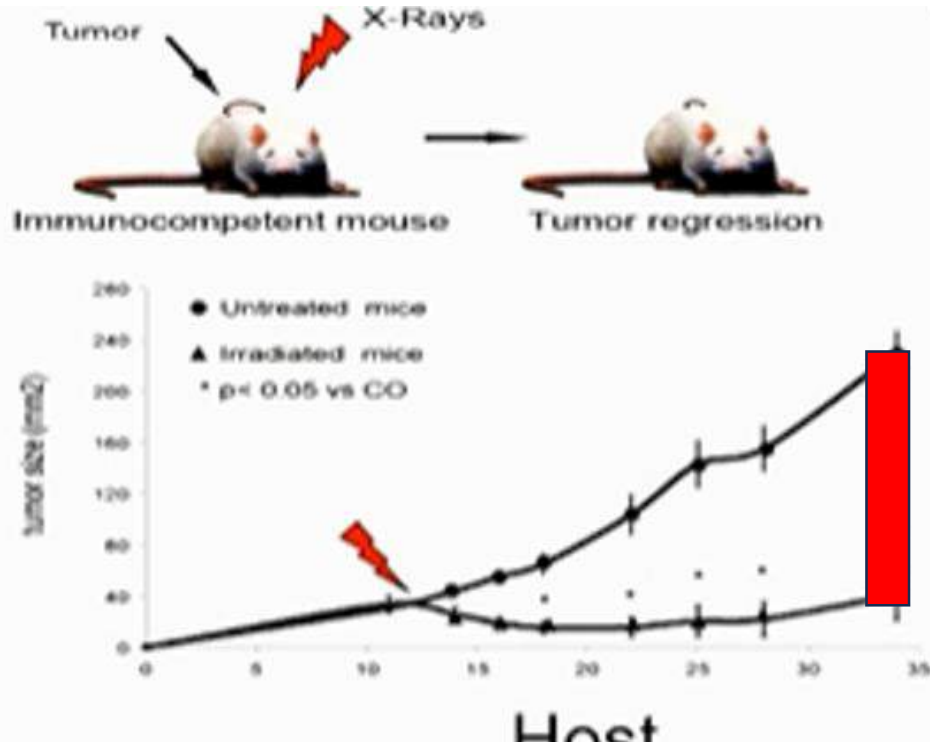
Crosspresentation of tumor derived antigens

Cell death induced by immunogenic radio/chemotherapy

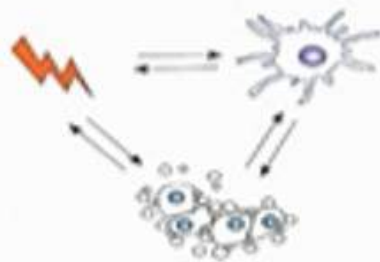
Antitumor immune response



RADIOTHERAPY AND MICROENVIRONMENT : MORE THAN HYPOXIA



Radiation
-ER Stress
-Apoptosis
-HMGB1 release



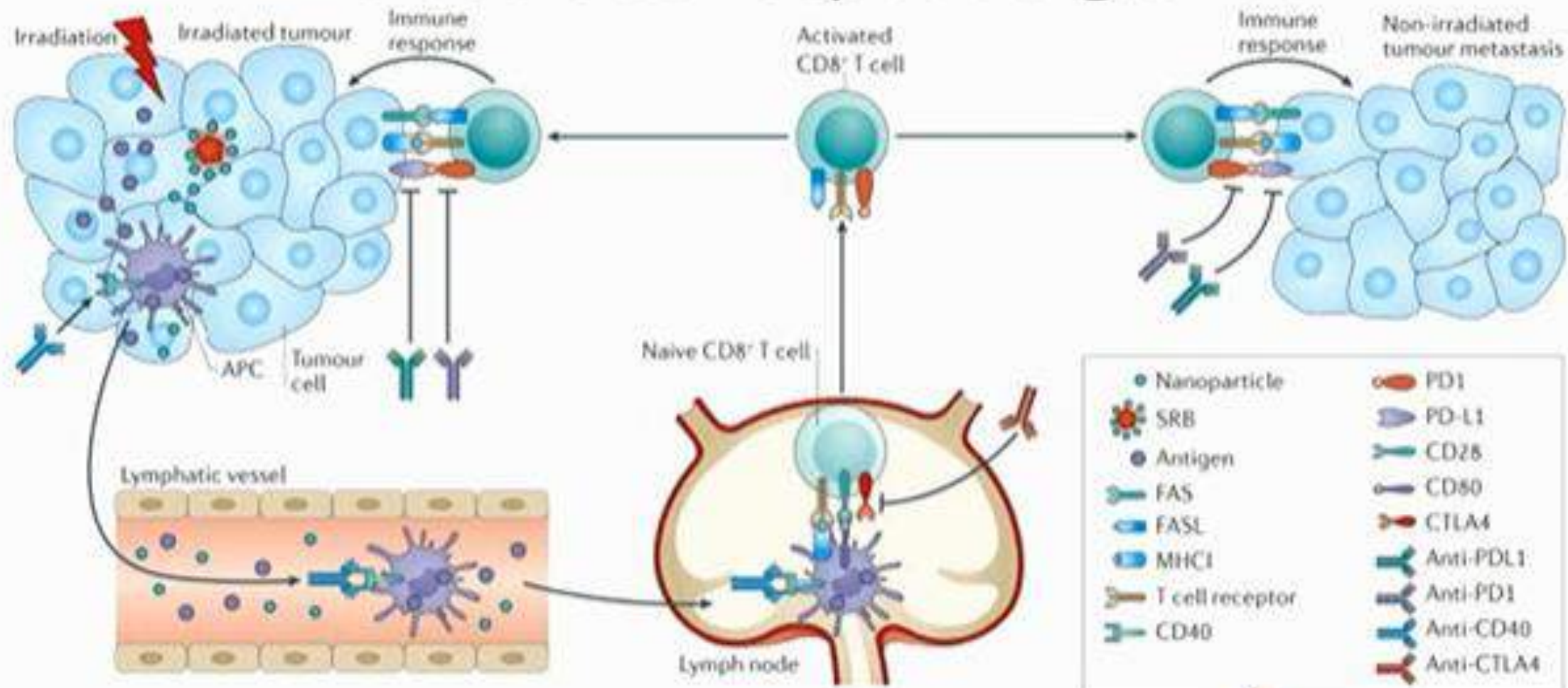
Tumor

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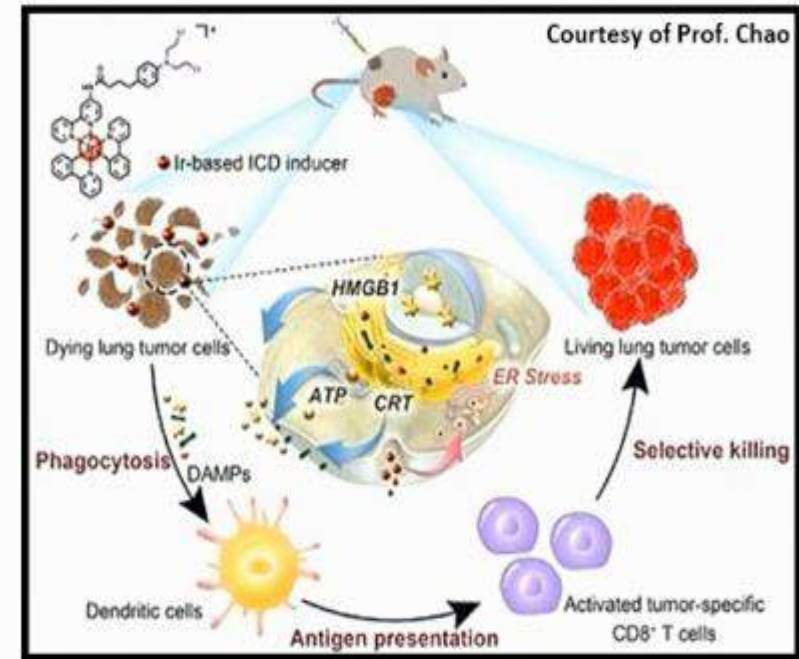
The basic concept at a glance..



Immunogenic effects of conventional RT:

Immunogenic cell death (ICD)

- Tumor cell death resulting in an immune response.
- ICD comprises the release of **DAMPs: ATP, HMGB1, calreticulin and heat shock proteins** resulting in the activation of tumor-specific immune responses.
- Radiation-induced DNA damage (nuclear fragmentation, micronuclei) activates the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway, resulting in **INTERFERON-1** production leading to upregulation of DAMPs, recruitment of APCs and subsequent adaptive immune response.
- **STING pathway plays a central role in anti-tumor immunity** and its expression is lost in several cancer types.



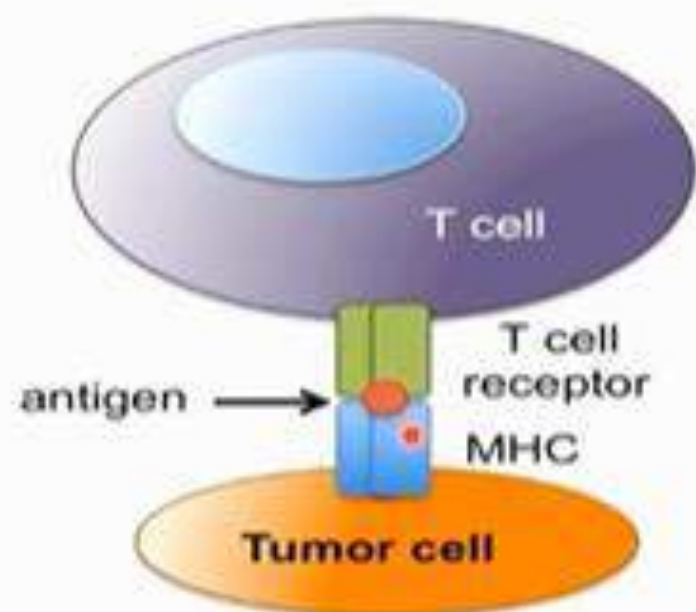
Impact of irradiation on tumor cells



→ IR \nearrow surface molecules involved in T-cell-mediated immune attack (ICAM-1, mucin-1, CEA, MHC class I)¹

→ Expression of MHC class I molecules increased in a radiation dose-dependent manner²

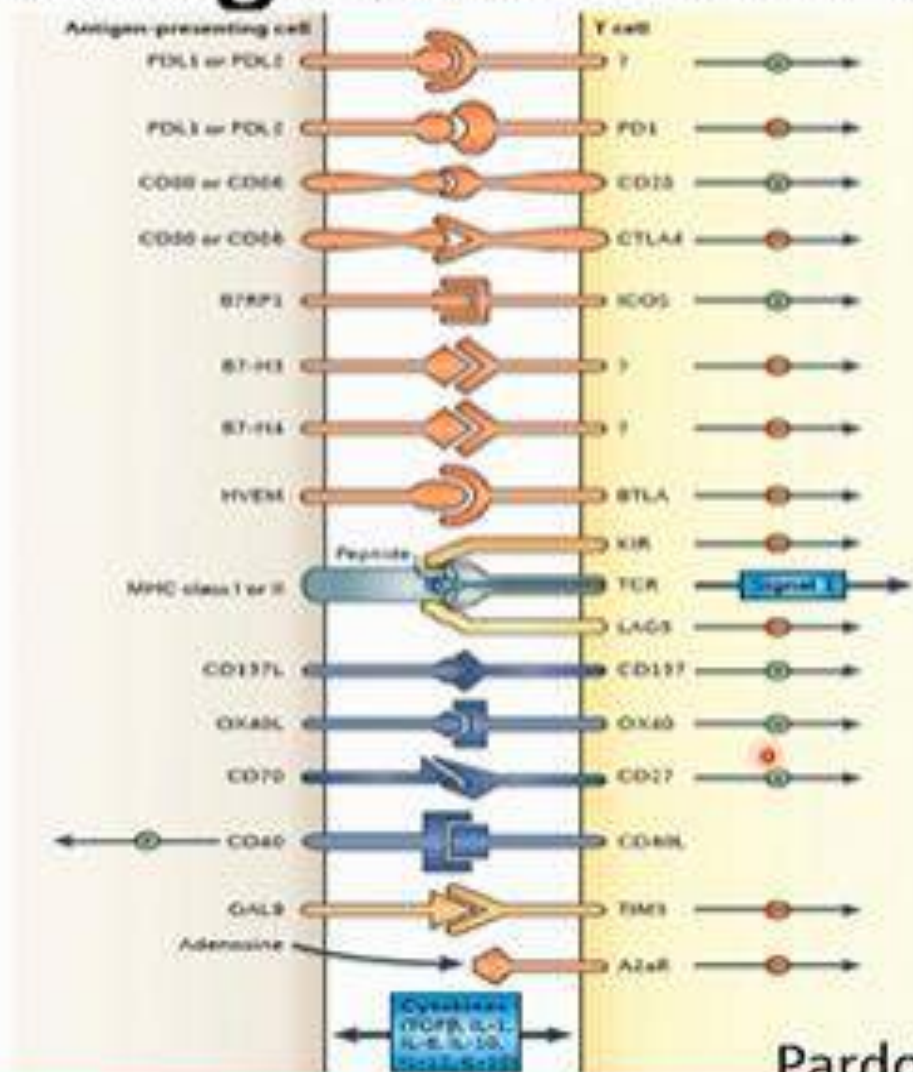
→ IR induces new peptides presented by MHC class I molecules, which are recognized by cytotoxic T cells²



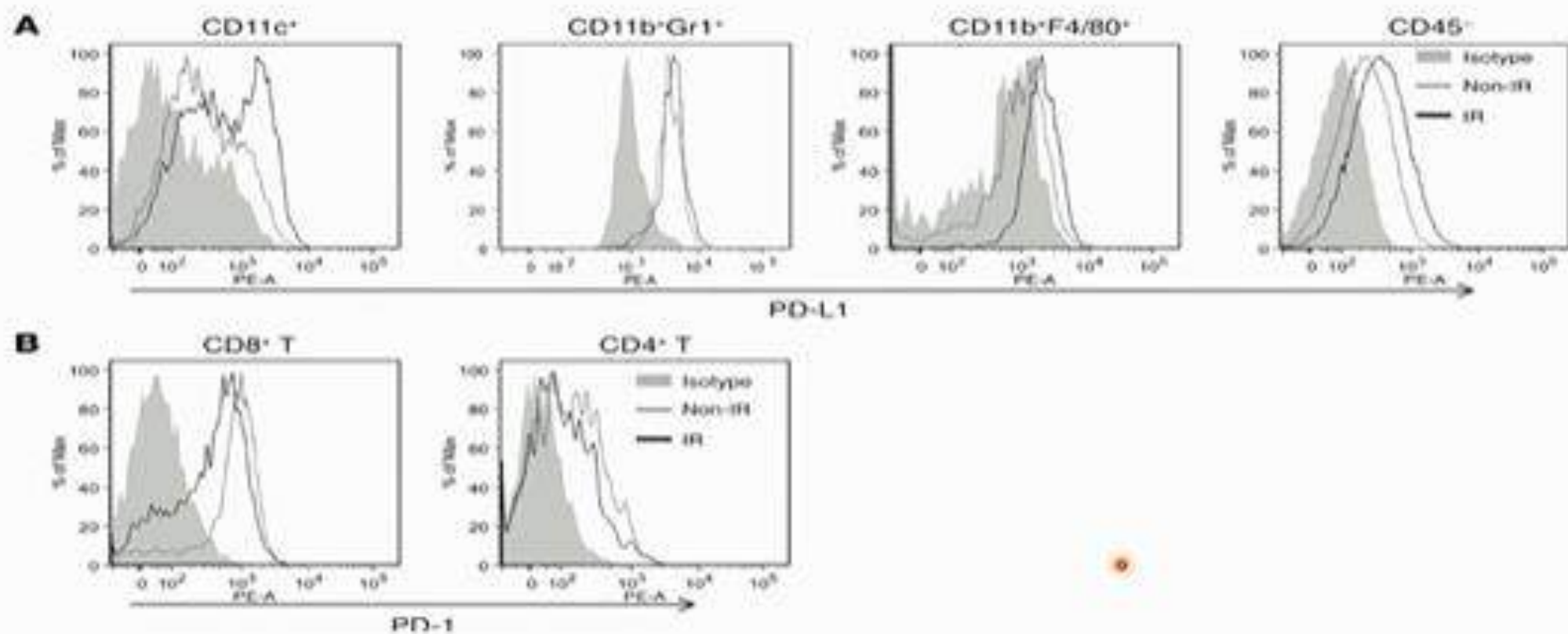
1-Garnet et al Cancer Research 2004

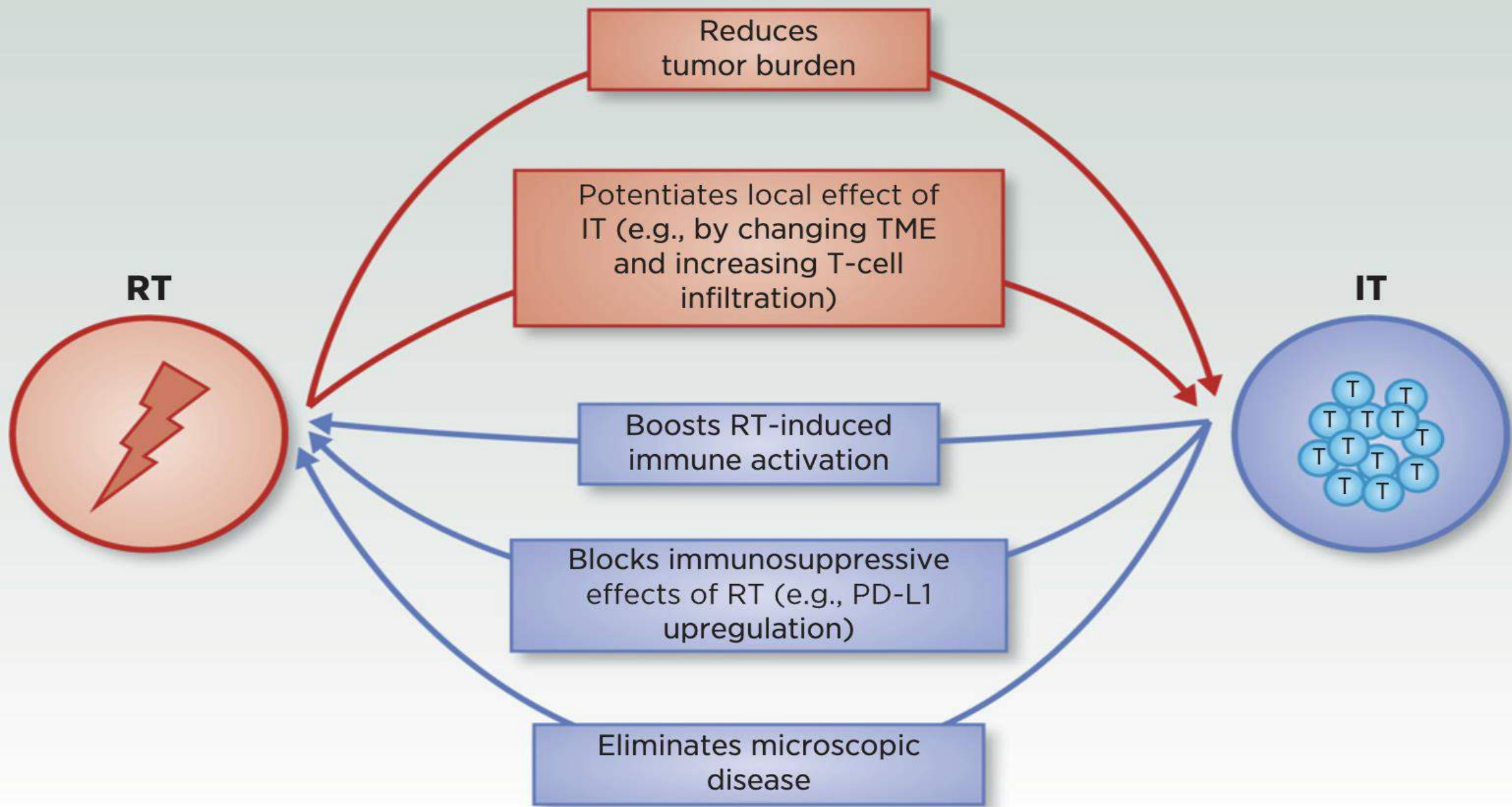
2-Reits et al J Exp Med 2006

Multiple co-stimulatory and inhibitory interactions regulate T cell responses.

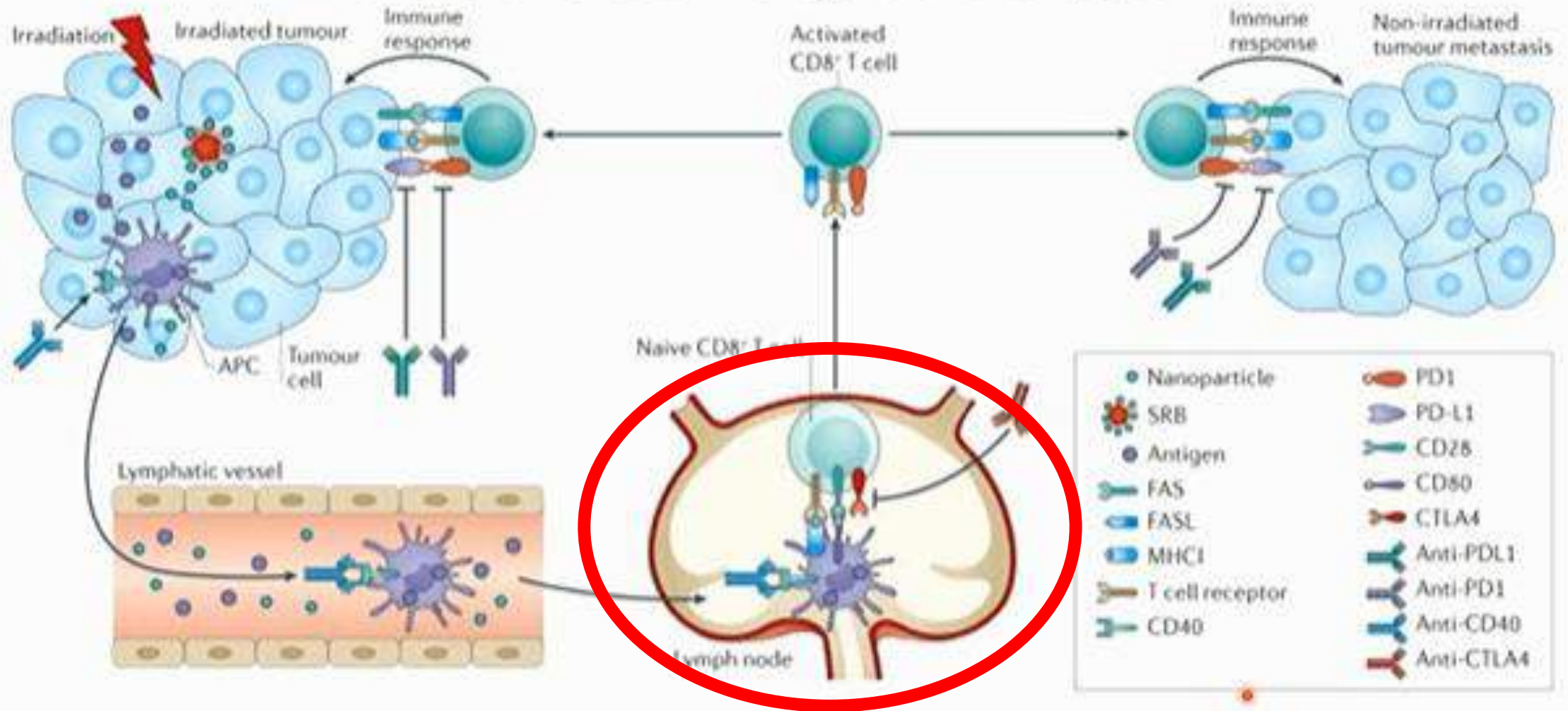


IR upregulates PD-L1

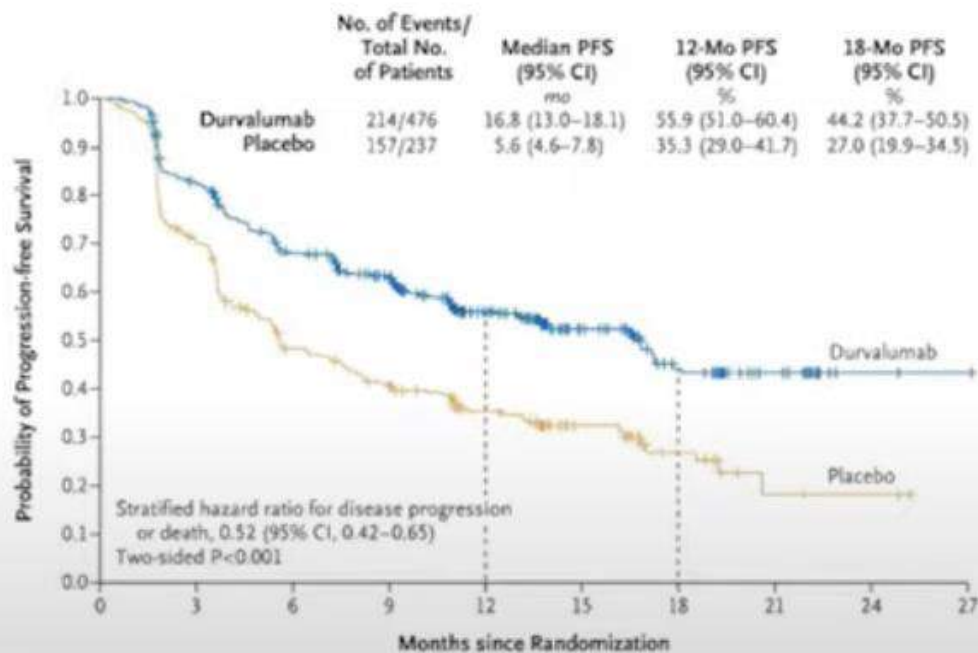
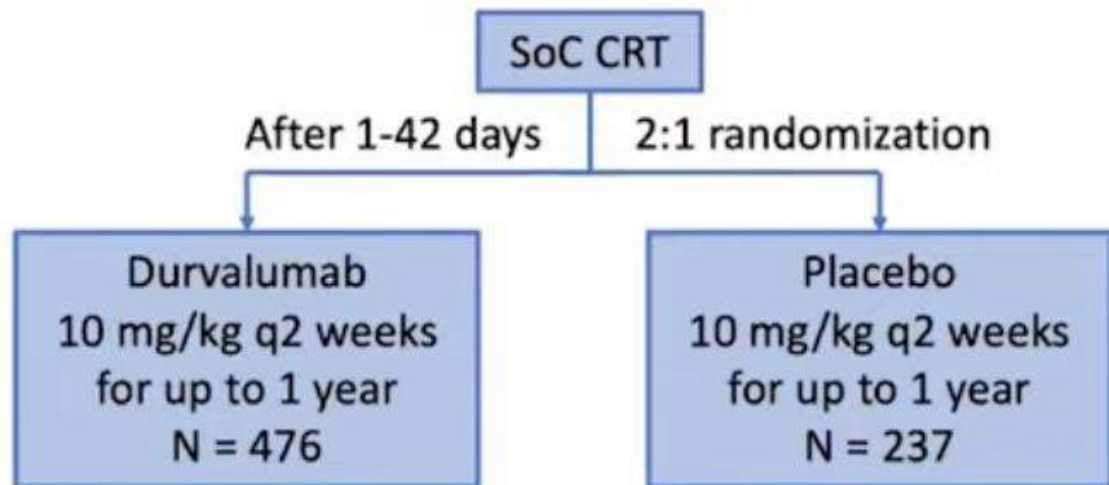




The basic concept at a glance..



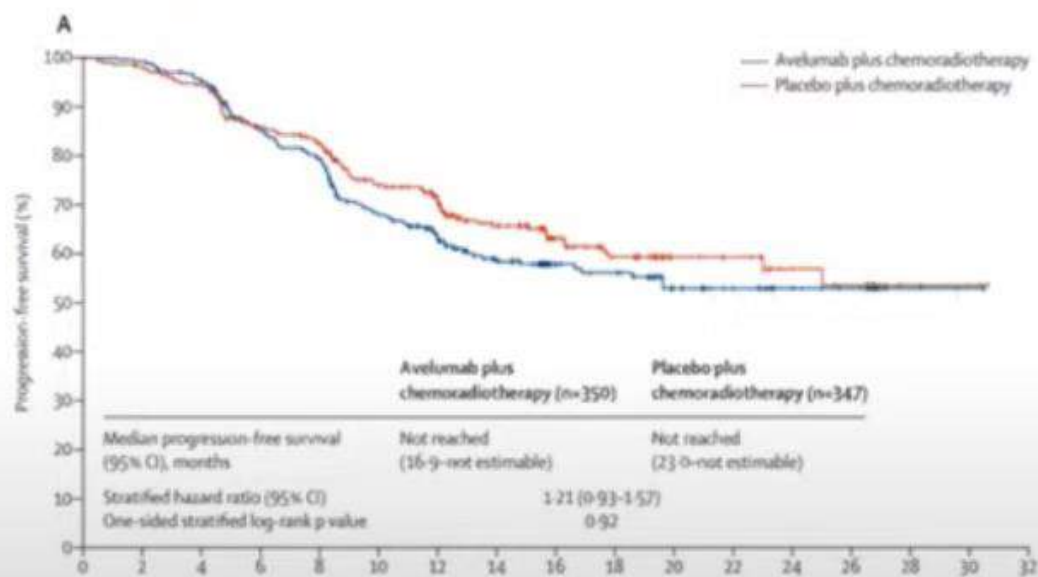
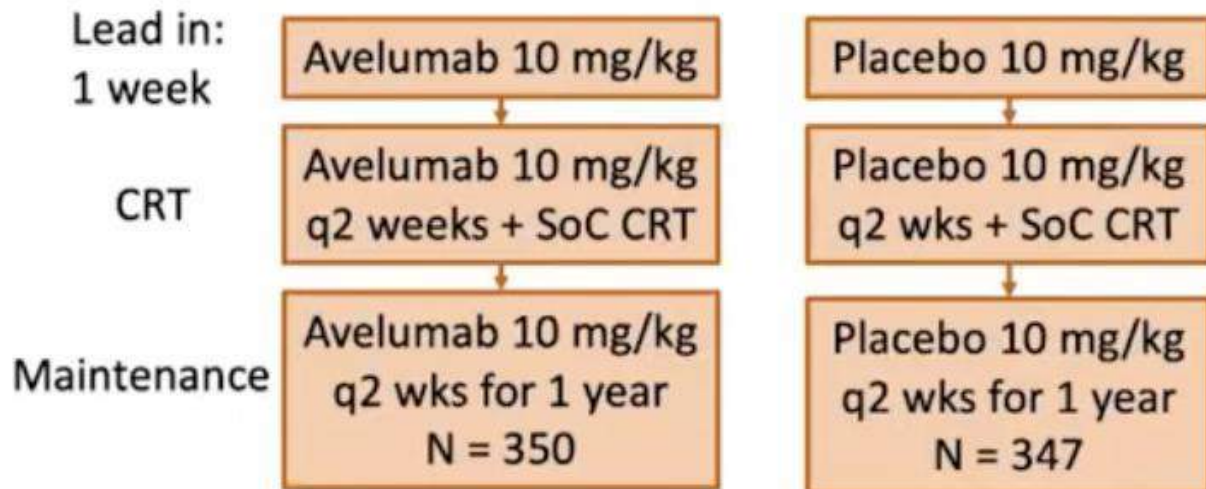
Pacific Trial



No. at Risk	0	3	6	9	12	15	18	21	24	27
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

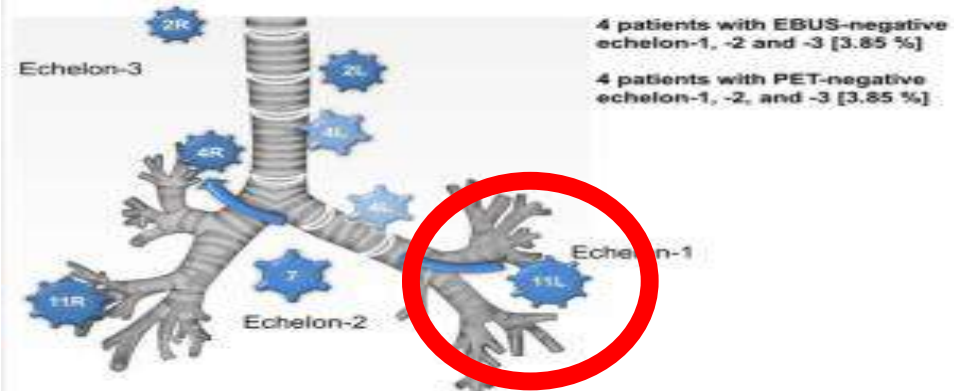
Javelin H&N 100 Trial

1:1 randomization

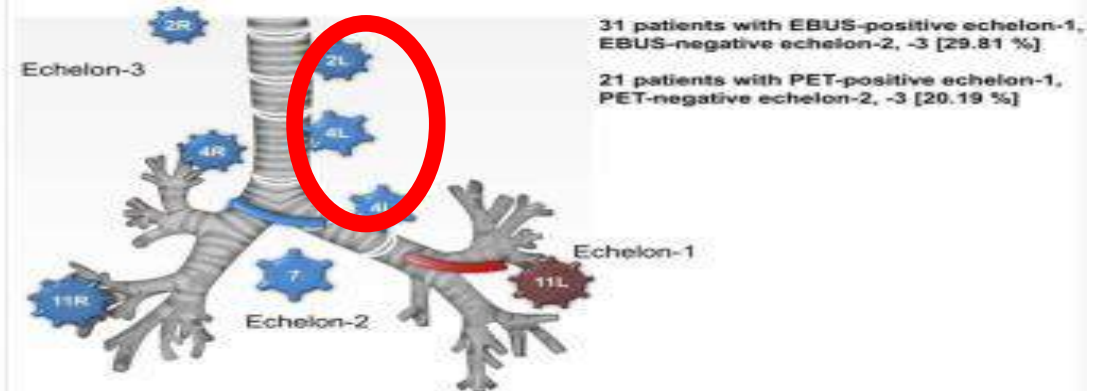


	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
Avelumab plus chemoradiotherapy	350	303	289	239	222	176	143	107	69	63	41	33	22	18	4	2	0
Placebo plus chemoradiotherapy	347	303	291	257	241	200	172	121	75	56	31	28	18	15	3	2	0

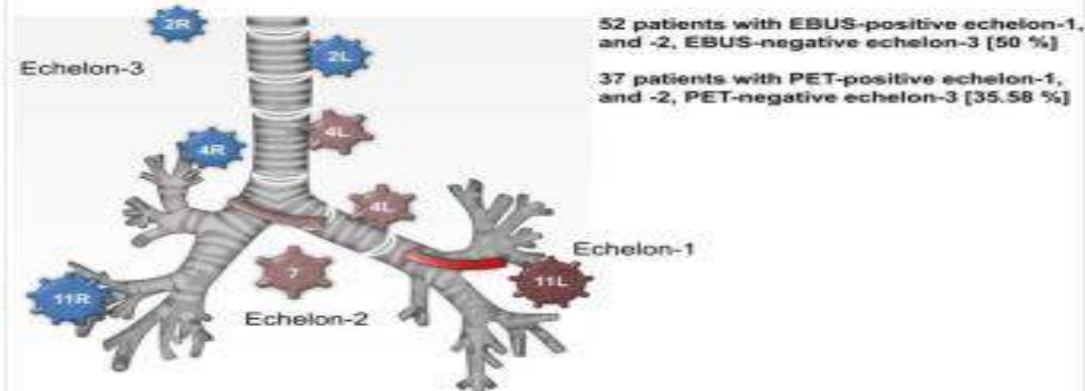
1a Pattern 1.1: Echelon-1, -2 and -3 negative by EBUS / PET



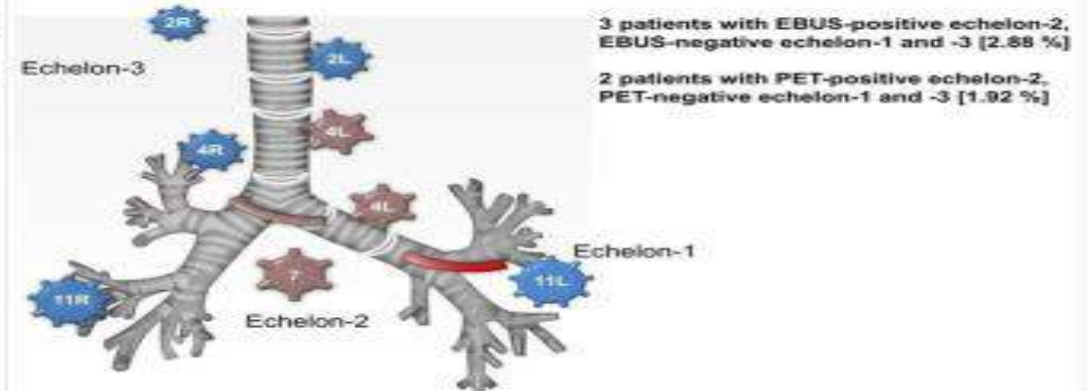
1b Pattern 1.2: Echelon-1 positive, Echelon-2 and -3 negative by EBUS / PET



1c Pattern 1.3: Echelon-1 and -2 positive, Echelon-3 negative by EBUS / PET



1d Pattern 1.4: Echelon-2 positive, Echelon-1 and -3 negative by EBUS / PET



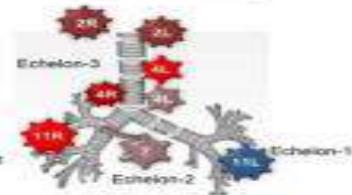
1e Pattern 1.5.1



Pattern 1.5.2



Pattern 1.5.3



Pattern 1.5.1: Echelon-1 and -2 negative, Echelon-3 positive by EBUS / PET

0 patients with echelon-1 and -2 negative, echelon-3 positive by EBUS [0.0%]
1 patient with echelon-1 and -2 negative, echelon-3 positive by PET [0.96%]

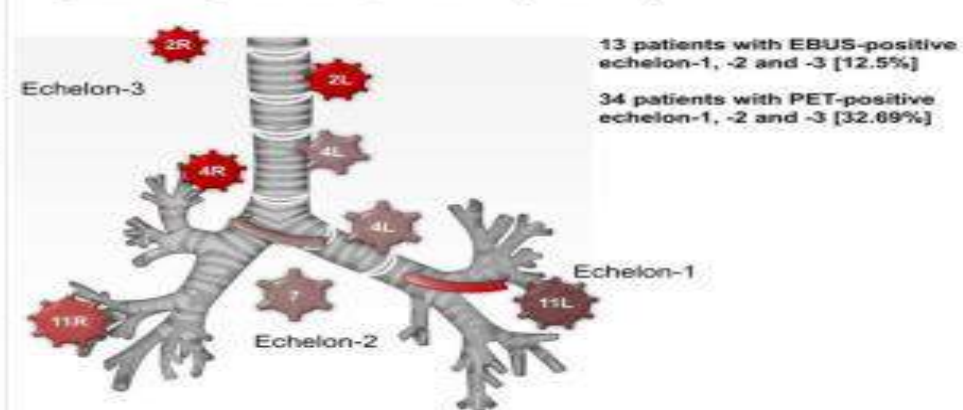
Pattern 1.5.2: Echelon-1 and -3 positive, Echelon-2 negative by EBUS / PET

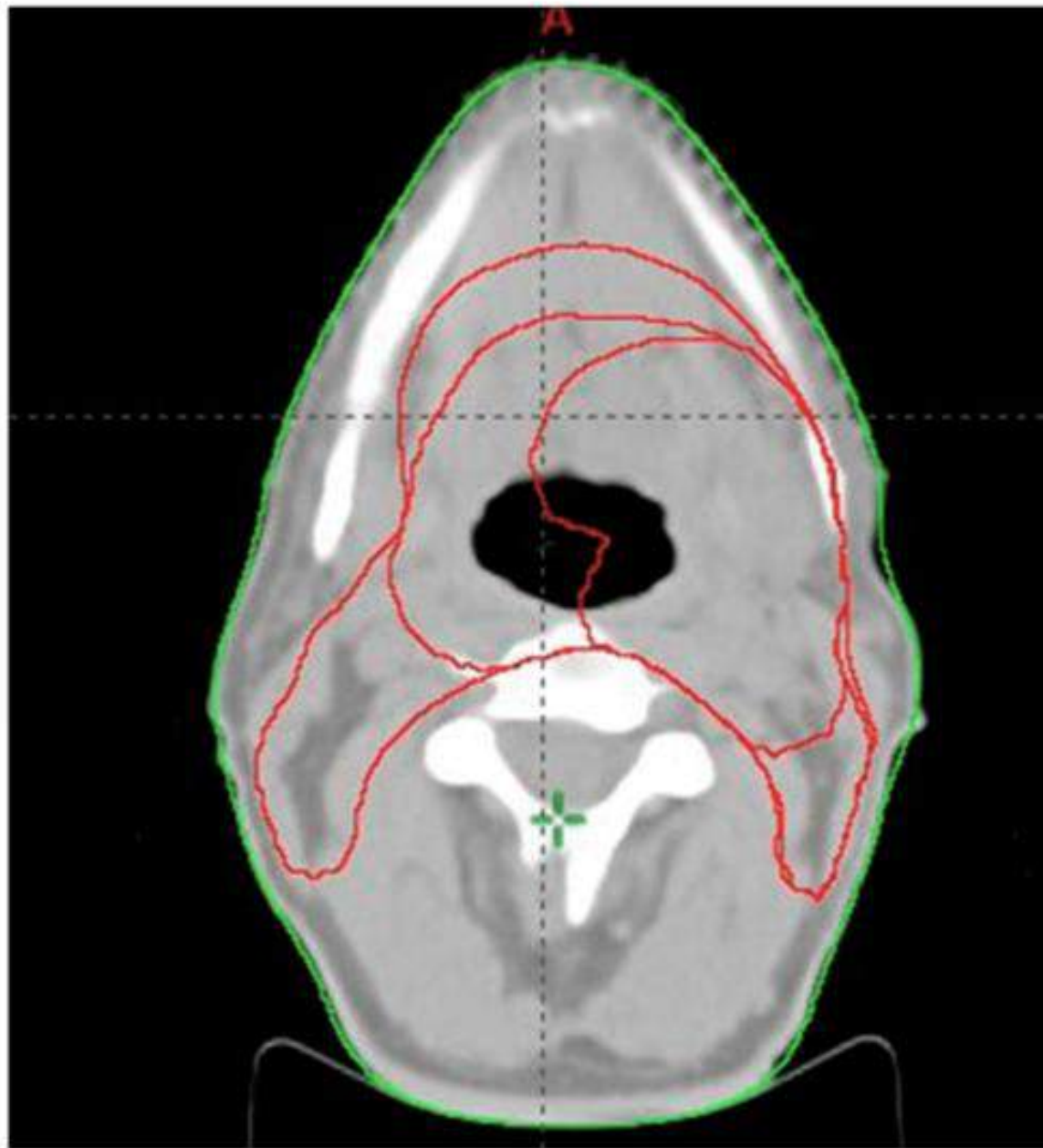
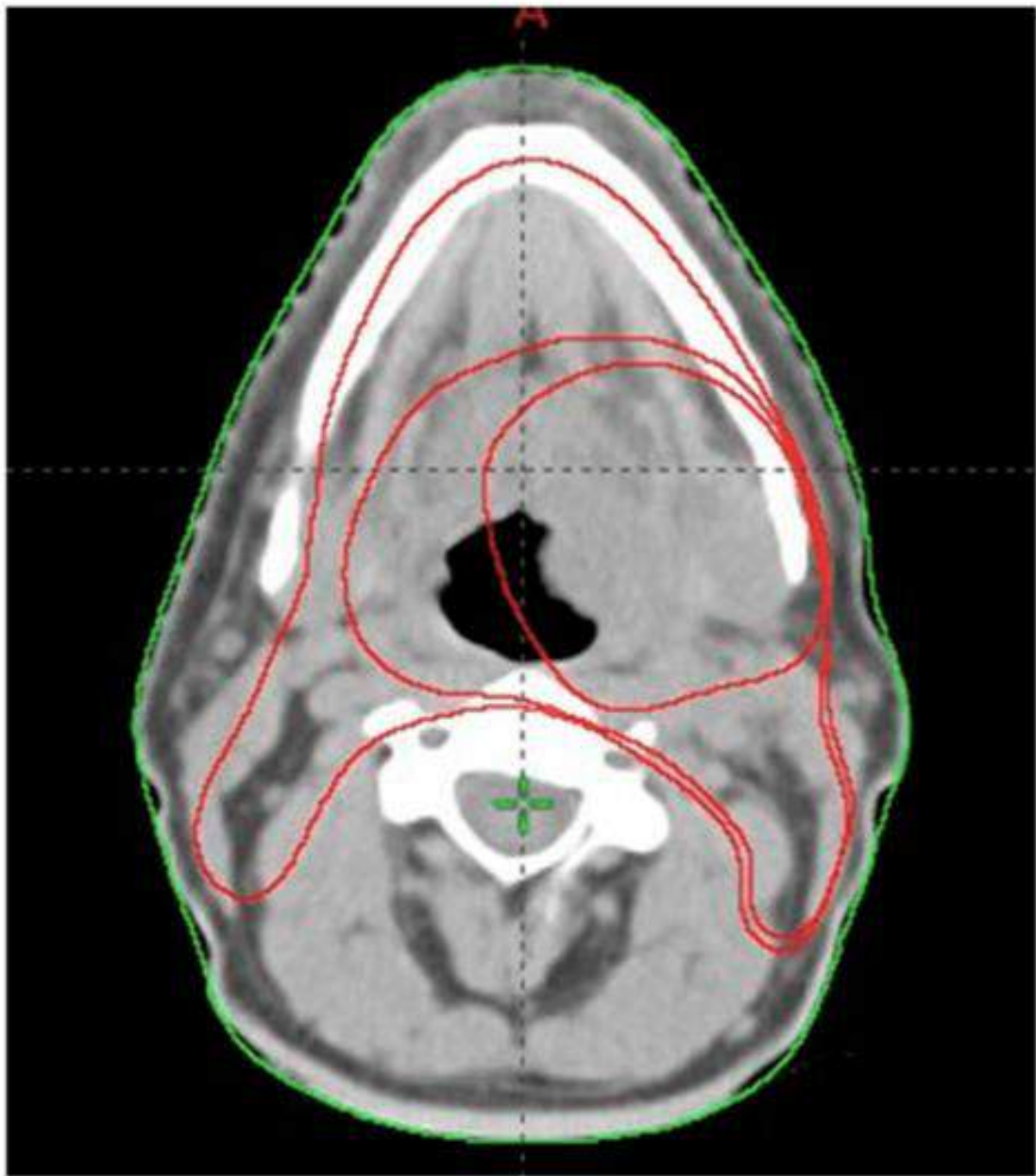
1 patient with echelon-1 and -3 positive, echelon-2 negative by EBUS [0.96%]
4 patients with echelon-1 and -3 positive, echelon-2 negative by PET [3.85%]

Pattern 1.5.3: Echelon-1 negative, Echelon-2 and -3 positive by EBUS / PET

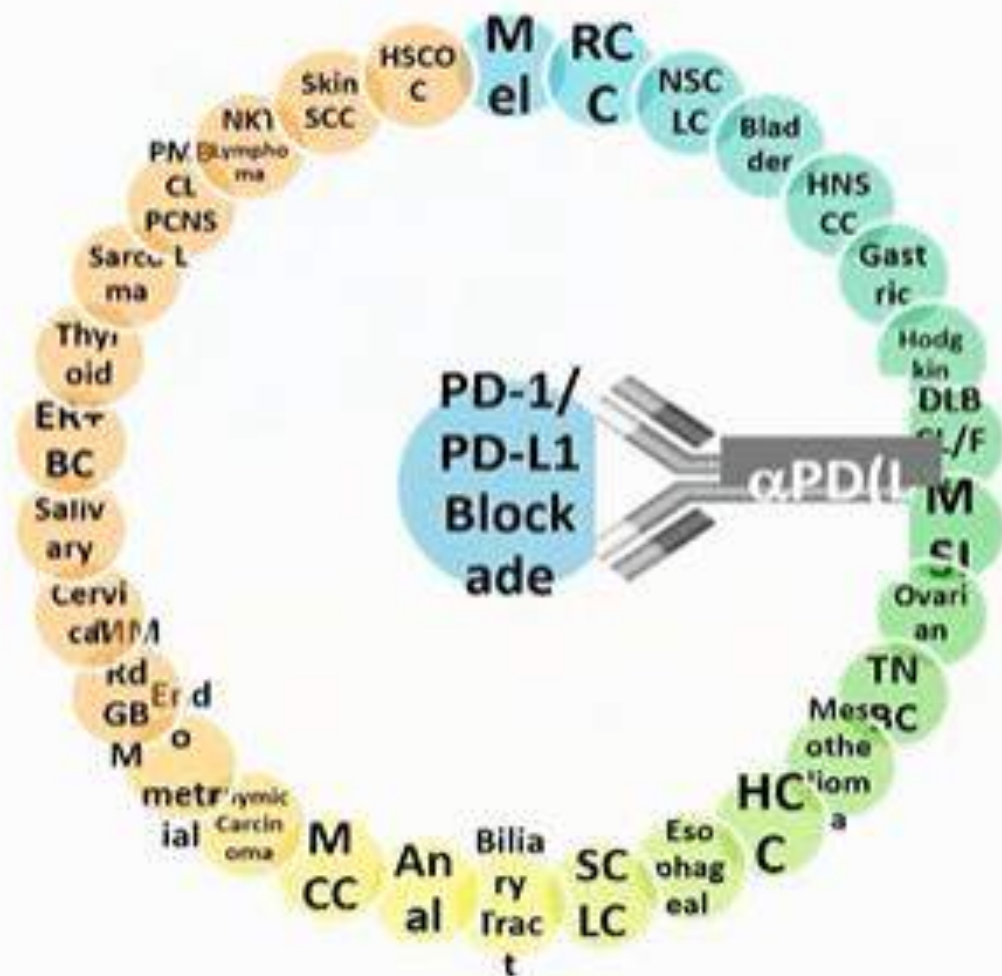
0 patients with echelon-1 negative, echelon-2 and -3 positive by EBUS [0.0%]
1 patient with echelon-1 negative, echelon-2 and -3 positive by PET [0.96%]

1f Pattern 1.6: Echelon-1, -2 and -3 positive by EBUS / PET

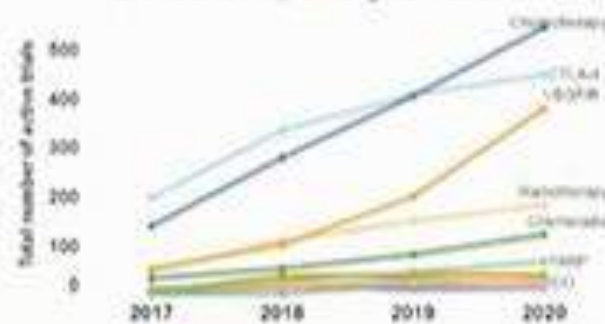




PD-Lomas



Evolution of Top 20 Targets in 2020



2000 combination trials using 253 targets (only targets with ≥ 10 trials shown below)



PD-1/L1 mAb Clinical Trial Landscape

Published by Alisha Yu and Sarah Oppenheim on Nov 21, 2020
Source: CA, CR, Analysis, and ClinicalTrials.gov



A phase I/Ib trial and biological correlate analysis of neoadjuvant SBRT with single-dose durvalumab in HPV-unrelated locally advanced HNSCC

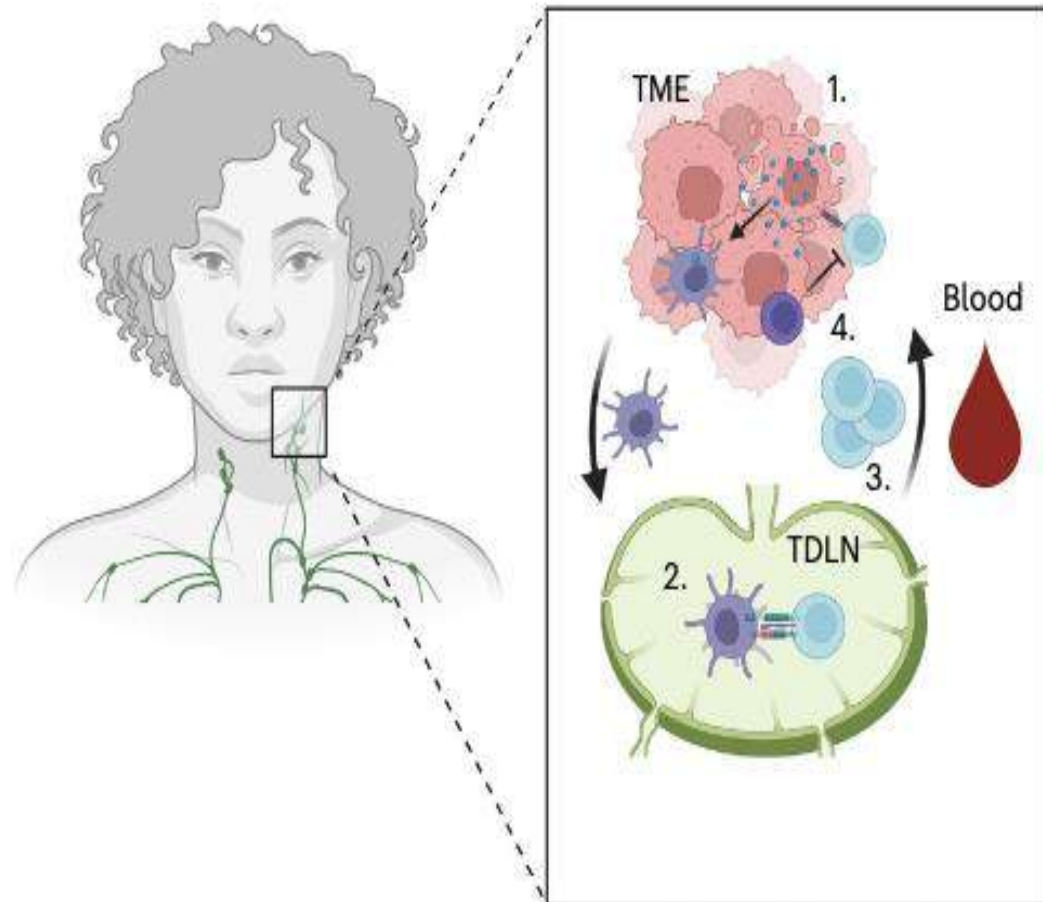
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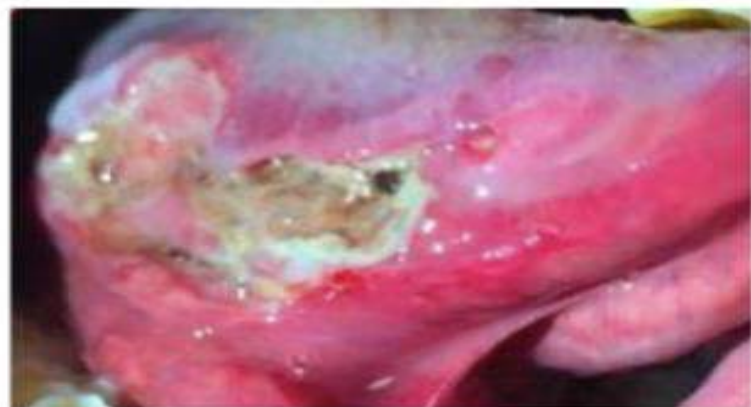
Accepted: 21 September 2022

Published online: 25 November 2022

Check for updates

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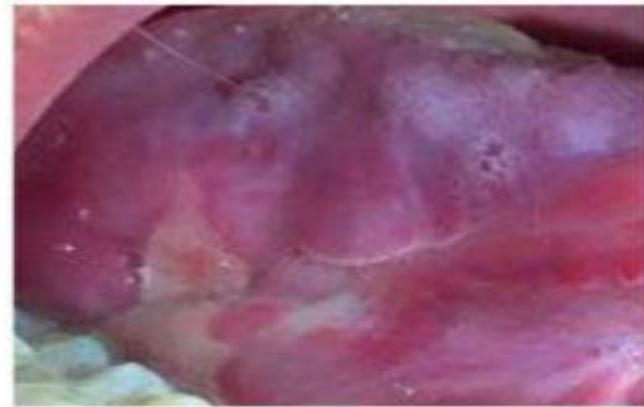
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Presentation

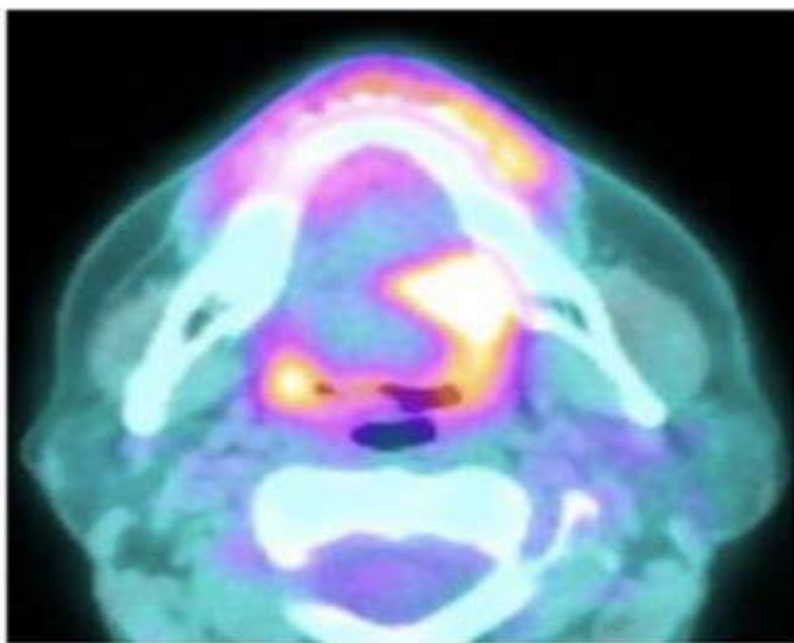


21 d later

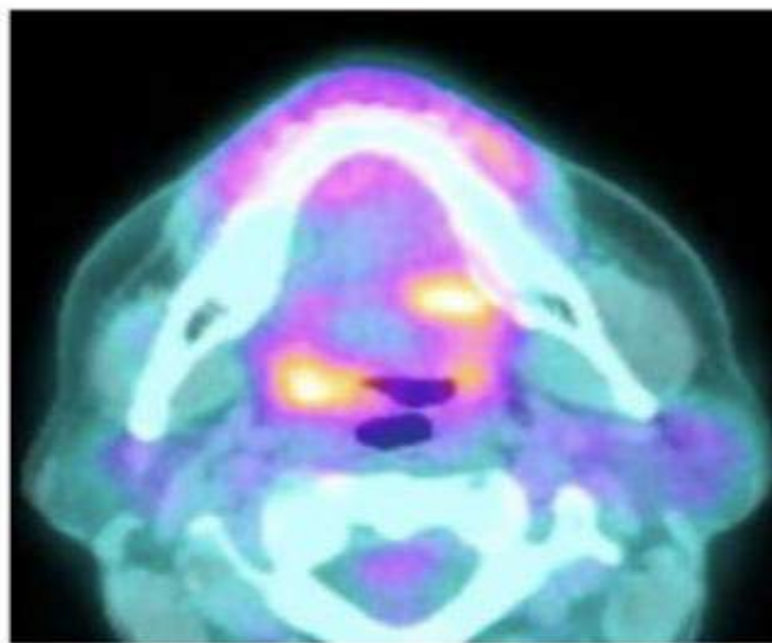


42 d later

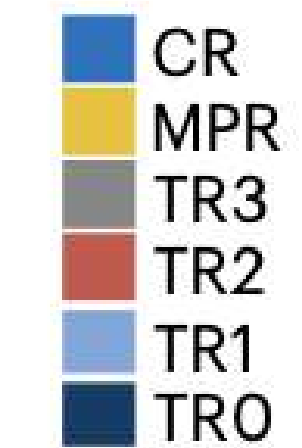
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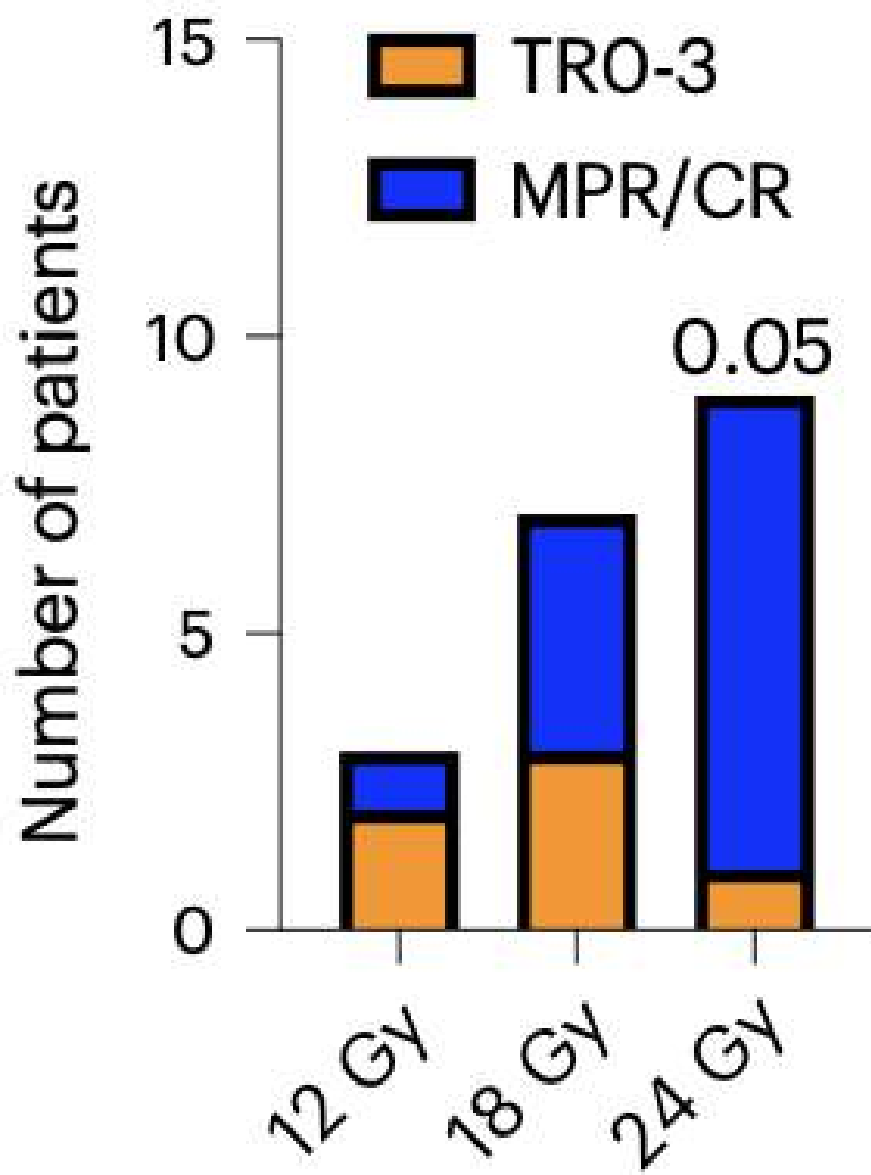
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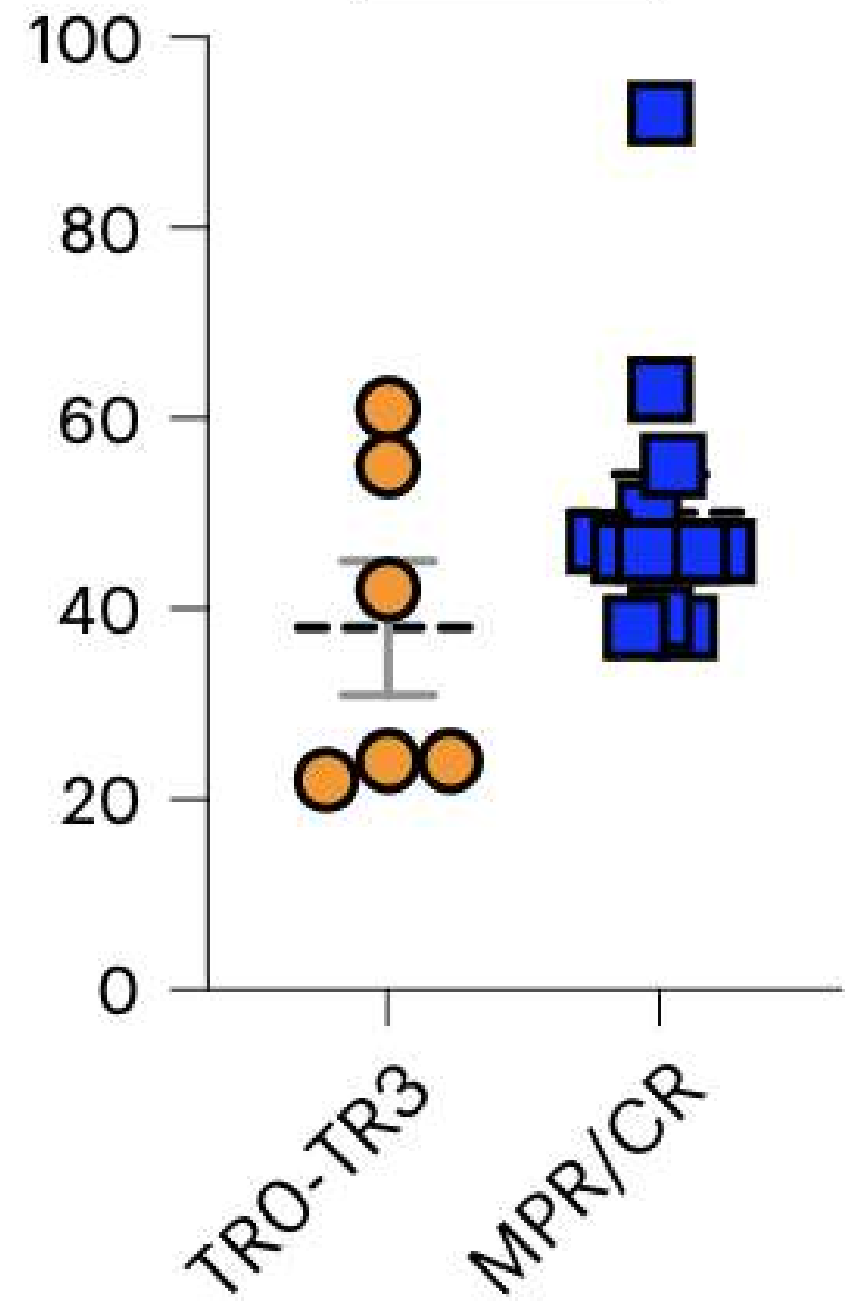
Post



Patients

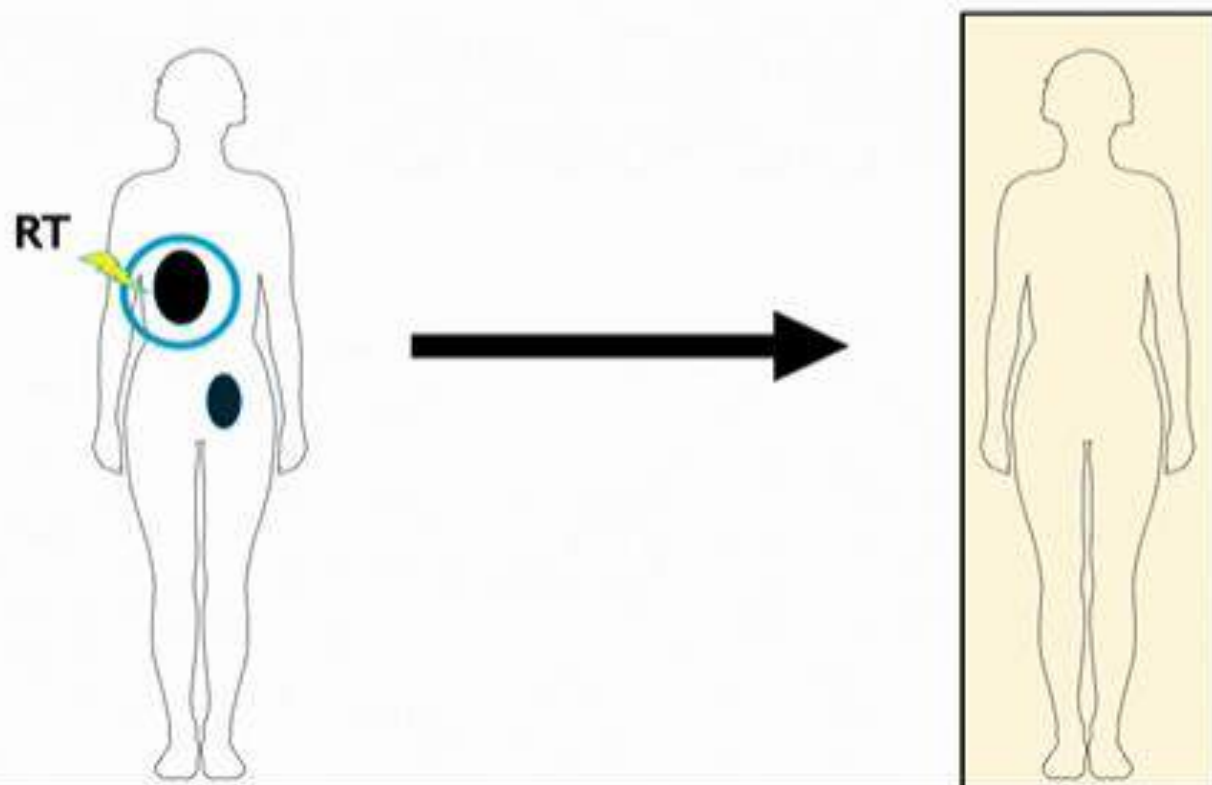


Time to surgery (d)



...Out of the field, distant sites

Abscopal (Away from the Target) effects of Radiotherapy
as evidence of *in situ*, individualized vaccination



Abscopal effects are rare

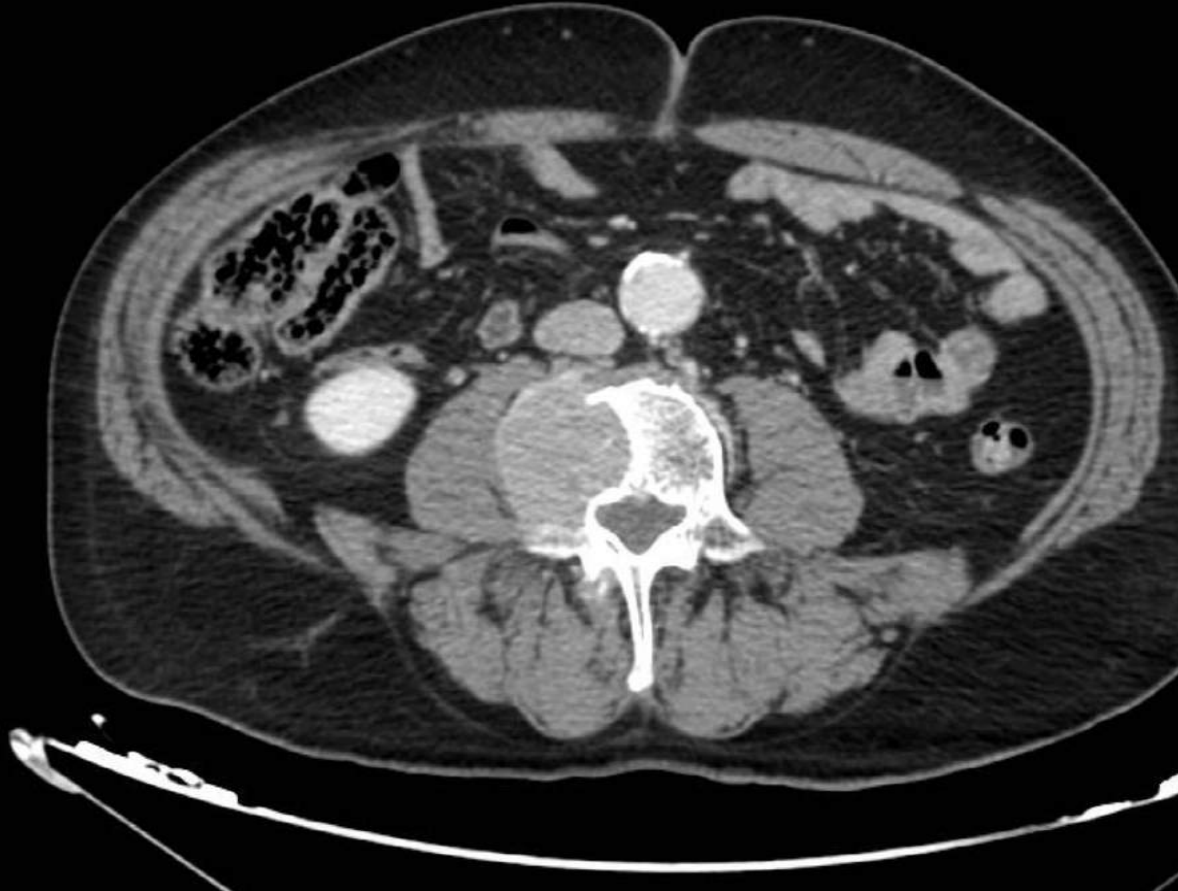
1969-2014: 46 abscopal cases (Abuodeh Y et al, *Curr Probl Cancer* 40,25-37, 2016)

R.H. Mole 1953

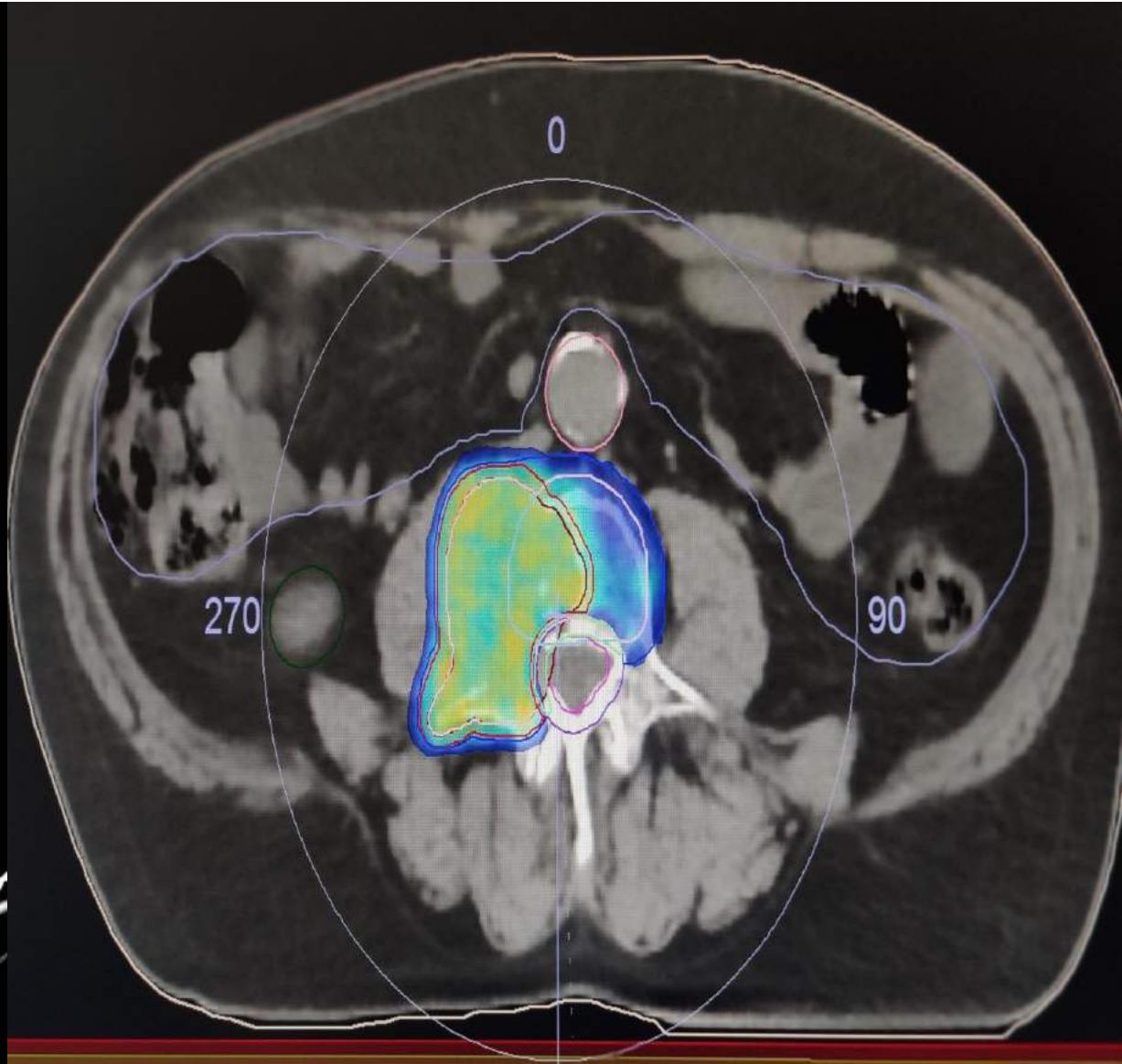
A particular case scenario: Abscopal Effect

- 71 y.o. male patient with clear cell renal carcinoma with ab onset vertebral metastatic condition with complex vertebral lesions at D3 and L4
- Because of the complex vertebral localizations, the patient began the treatment course with dual stereotactic therapy delivered every other day followed by administration of Nivolumab

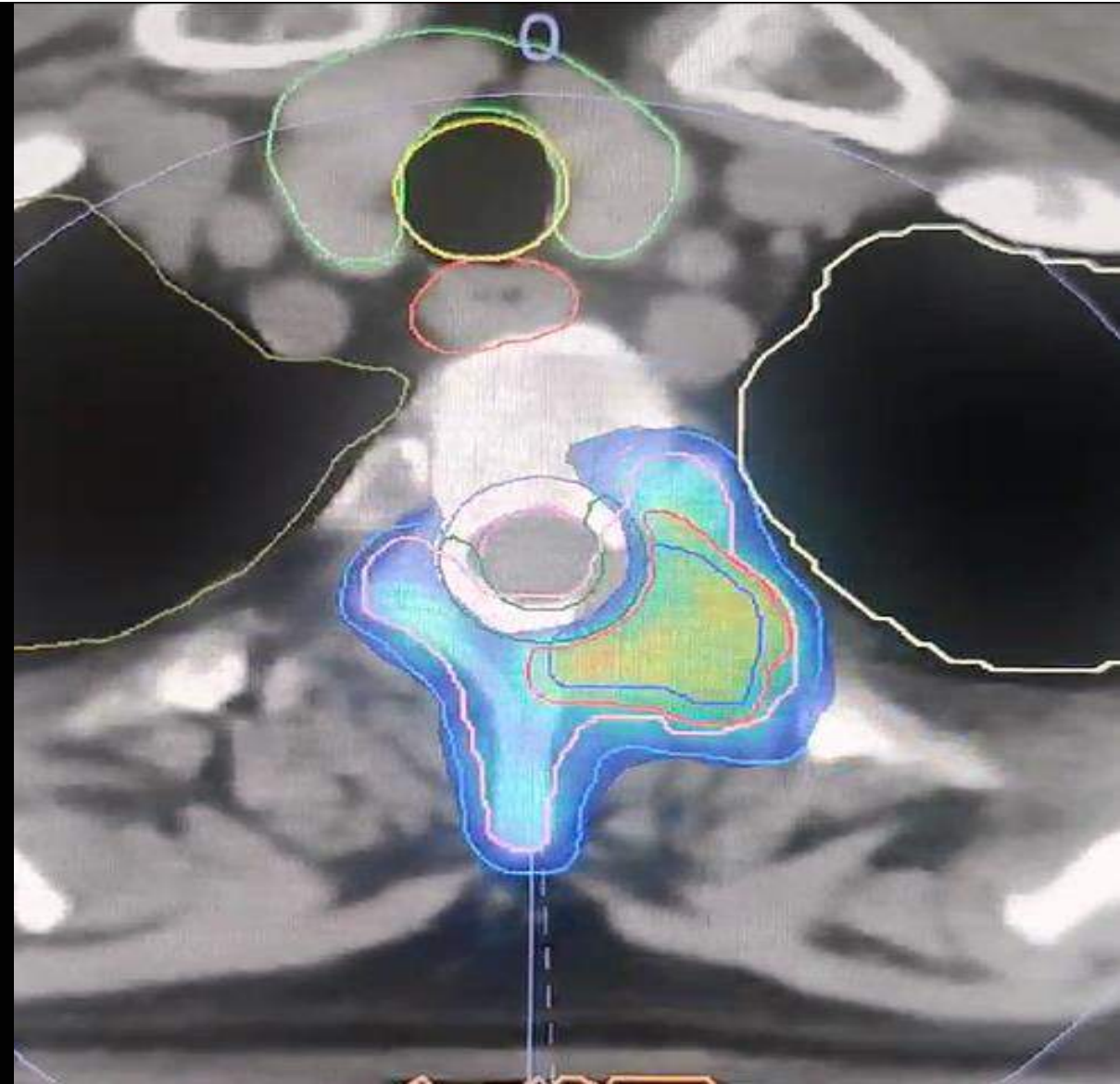
A particular case scenario: Abscopal Effect



A particular case scenario: Abscopal Effect

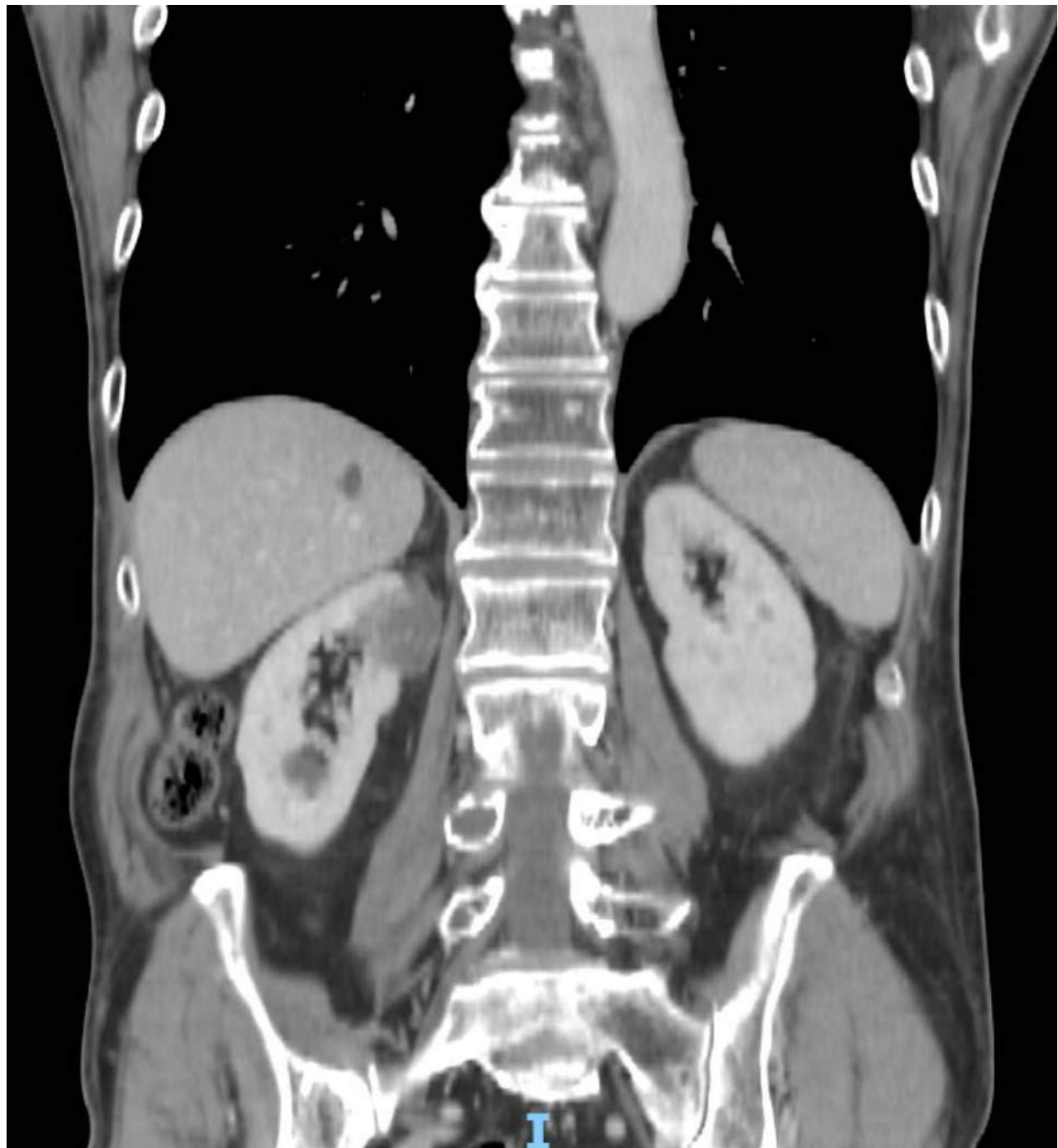
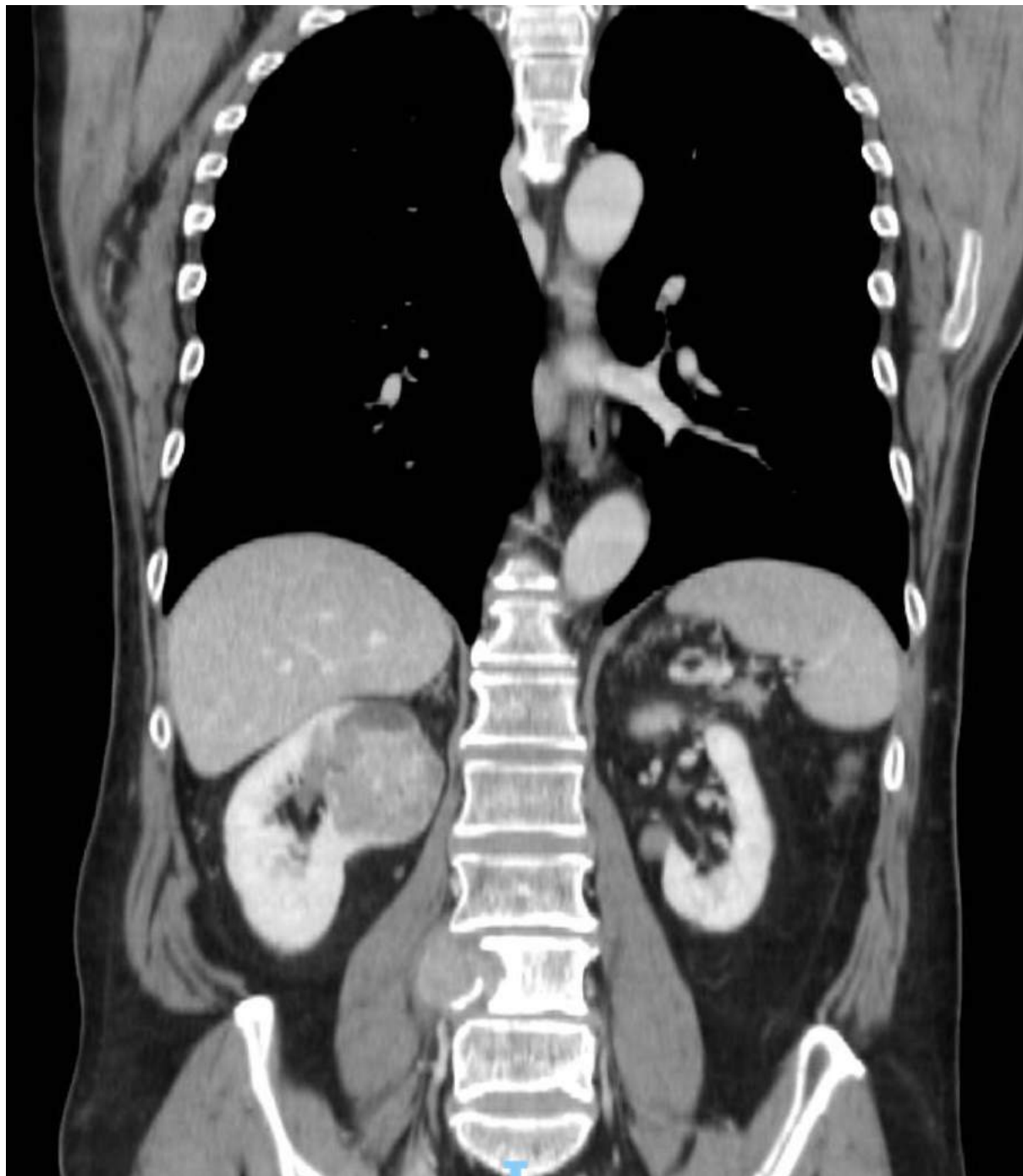


A particular case scenario: Abscopal Effect









PERSPECTIVES

OPINION

Time to abandon single-site irradiation for inducing abscopal effects

Eric D. Brooks and Joe Y. Chang

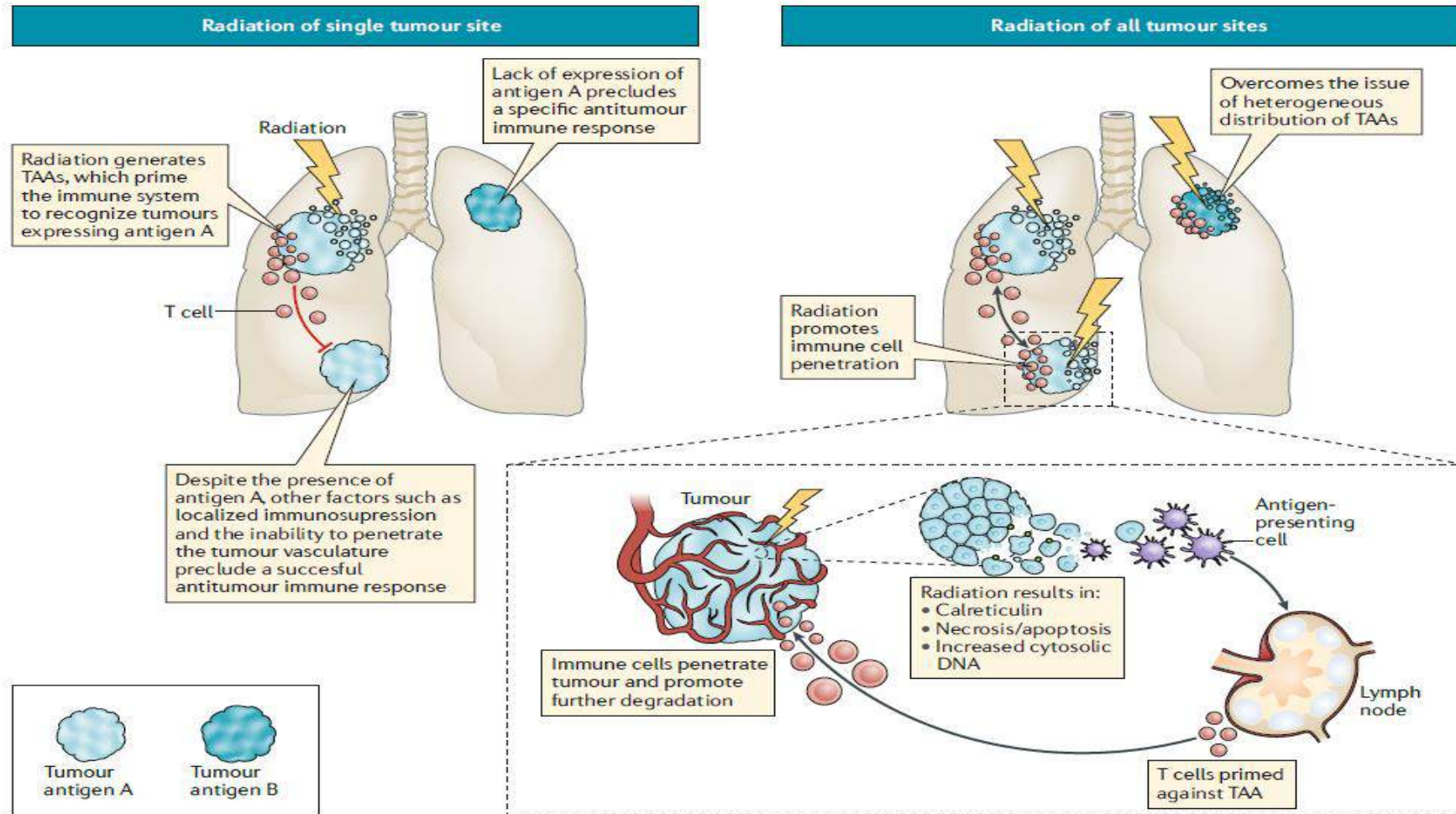
Abstract | Considerable interest is being directed toward combining immune-checkpoint inhibition (ICI) with radiotherapy to improve response rates to ICI, which have been disappointingly low at around 15–30% among patients with advanced-stage cancers other than melanoma. Since a case report published in 2012, in which authors described the resolution of metastatic disease after irradiation of a single lesion in a patient who had been receiving ICI, hundreds of clinical trials have been launched with the aim of testing the safety and/or efficacy of radiotherapy in combination with immunotherapy, nearly all of which use this single-site irradiation, or ‘abscopal’, approach. However, emerging preclinical and clinical evidence suggests that this approach likely produces suboptimal results. In this Perspective, we describe this evidence and provide a biological rationale supporting the abandonment of the single-site abscopal approach. We instead advocate exploring comprehensive irradiation of multiple/all lesions in order to enhance the likelihood of obtaining meaningful clinical outcomes — if such a clinical synergy between radiation and ICI does exist — before the failure of the current, single-site approach leads to the potential premature and inappropriate abandonment of radiotherapy in combination with ICI altogether.

PERSPECTIVES

OPINION

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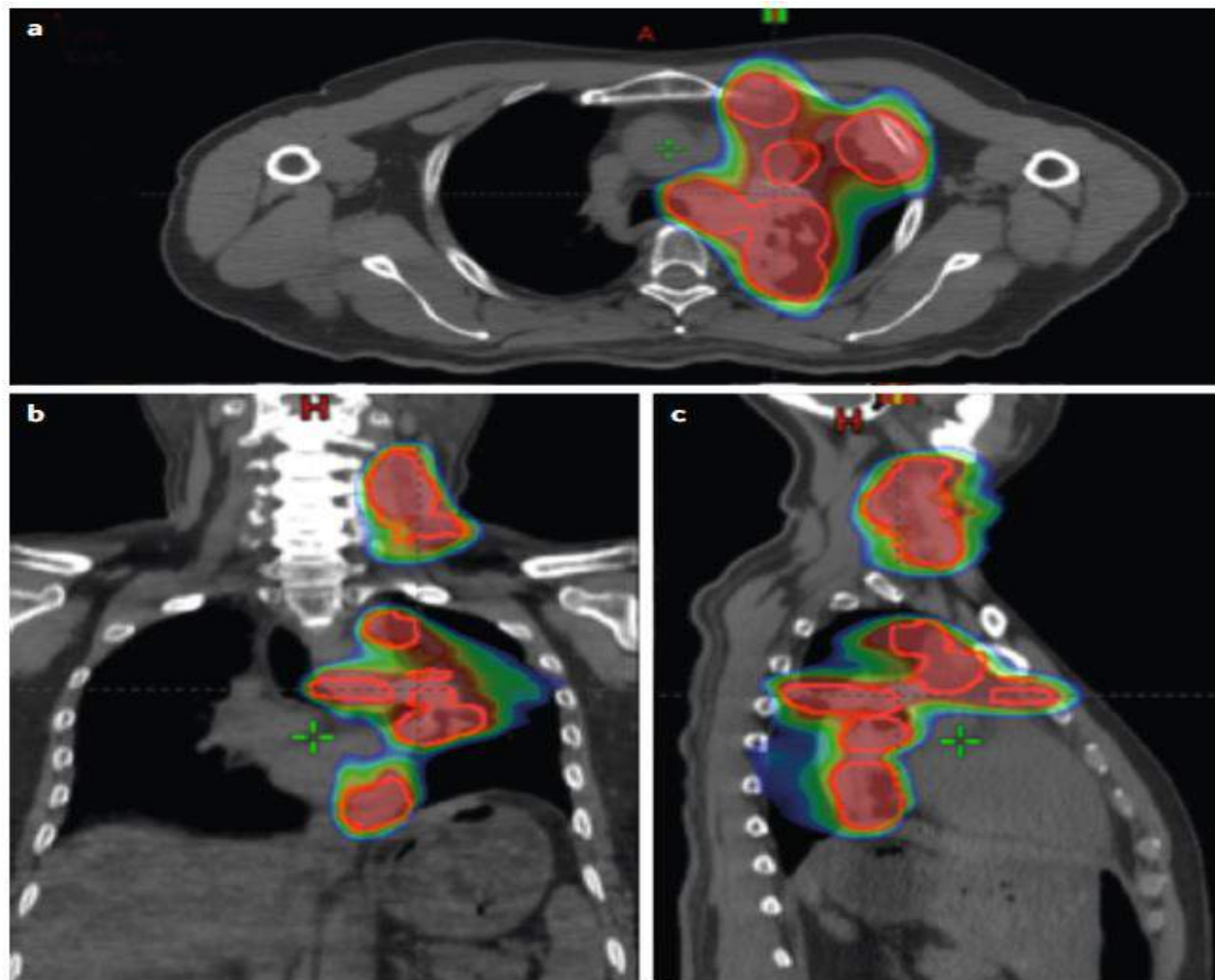


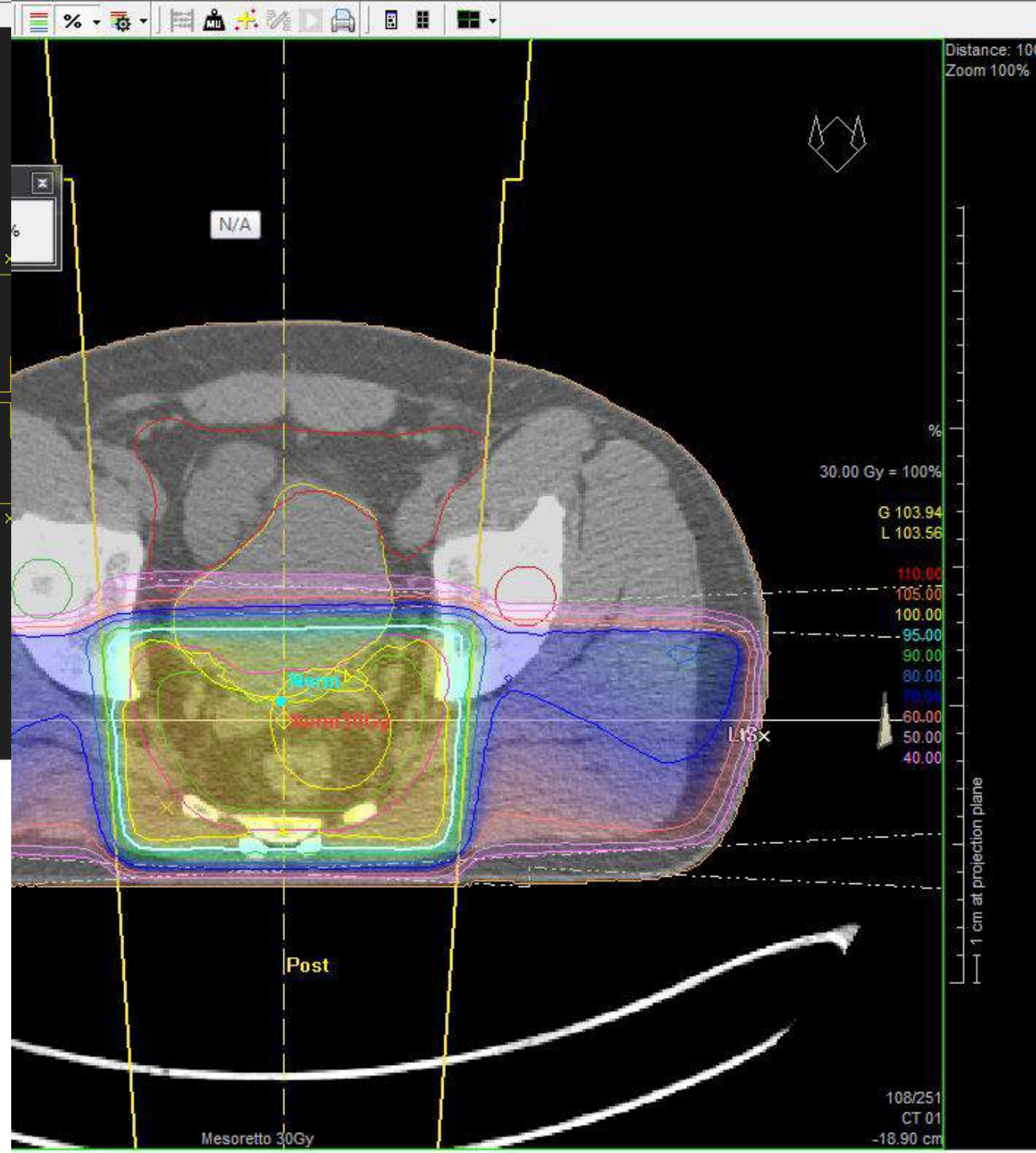
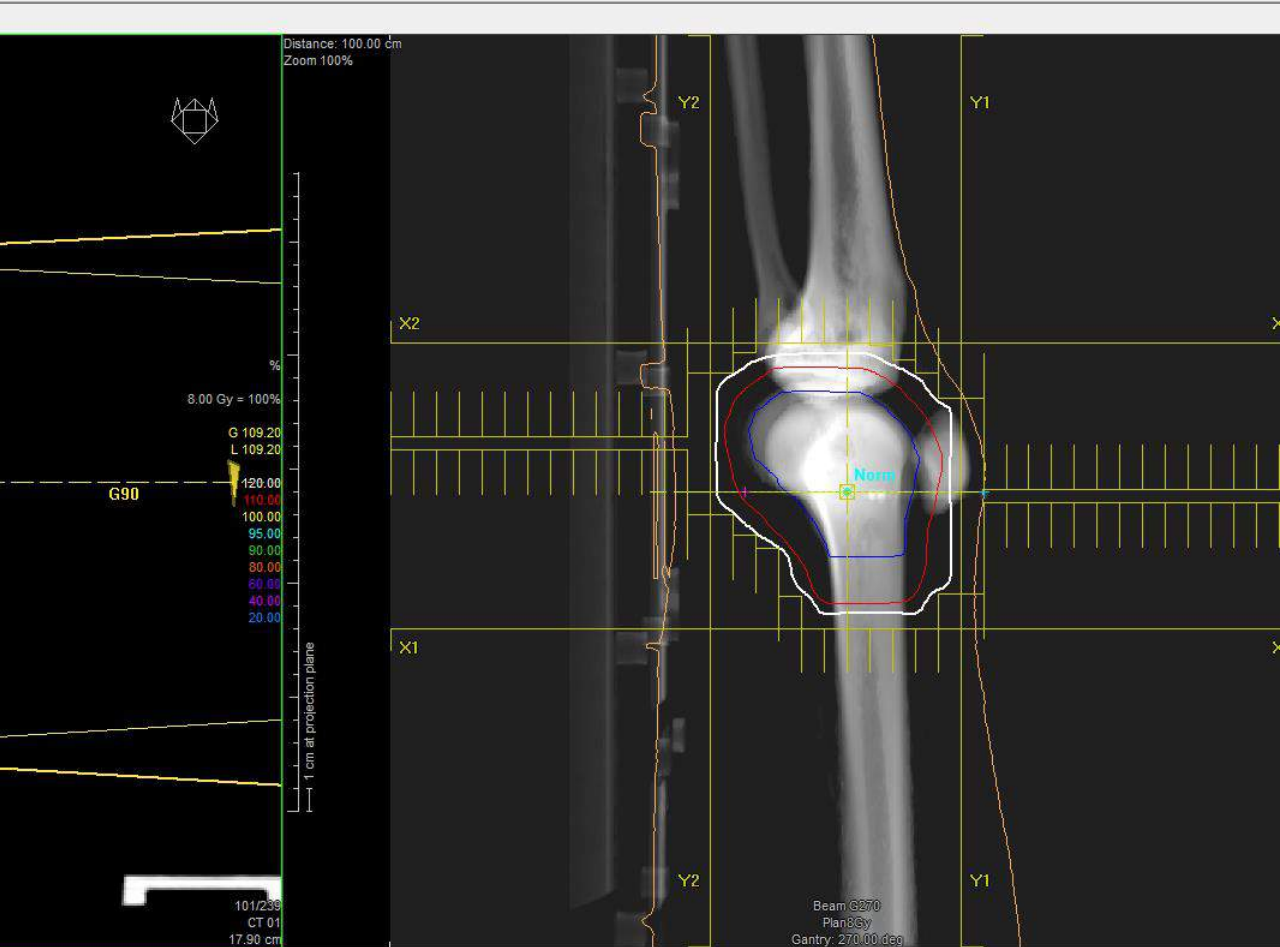
PERSPECTIVES

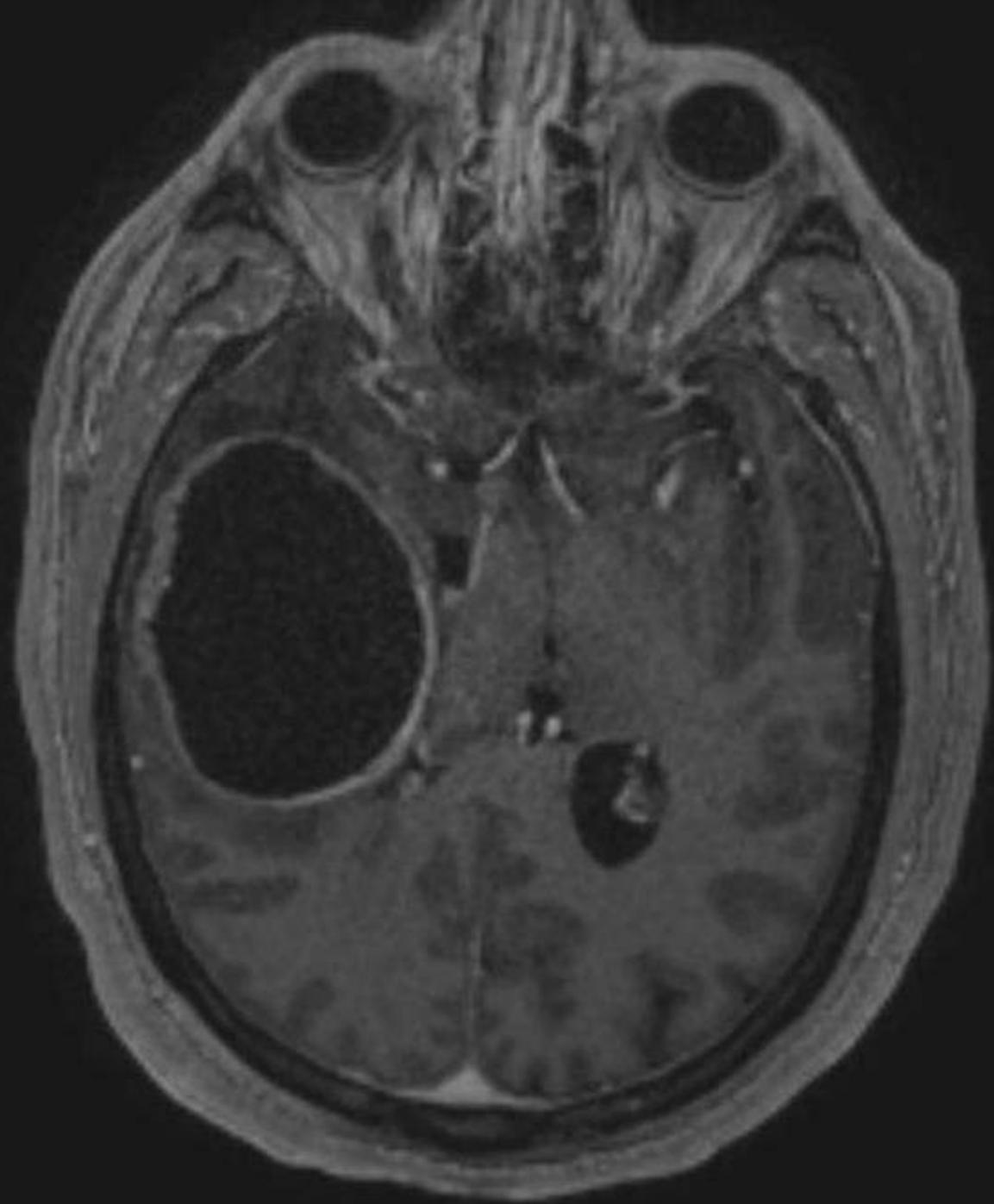
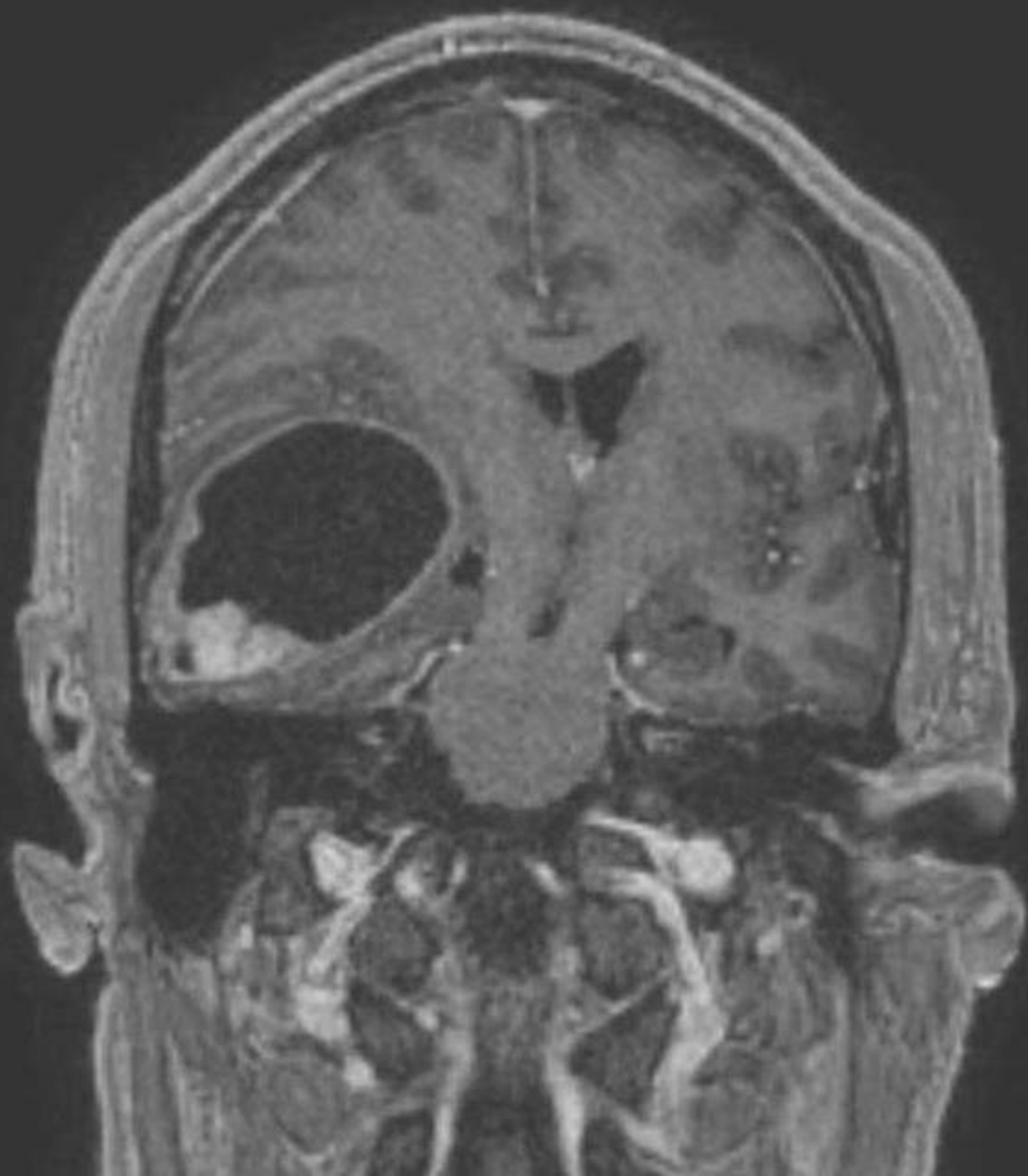
OPINION

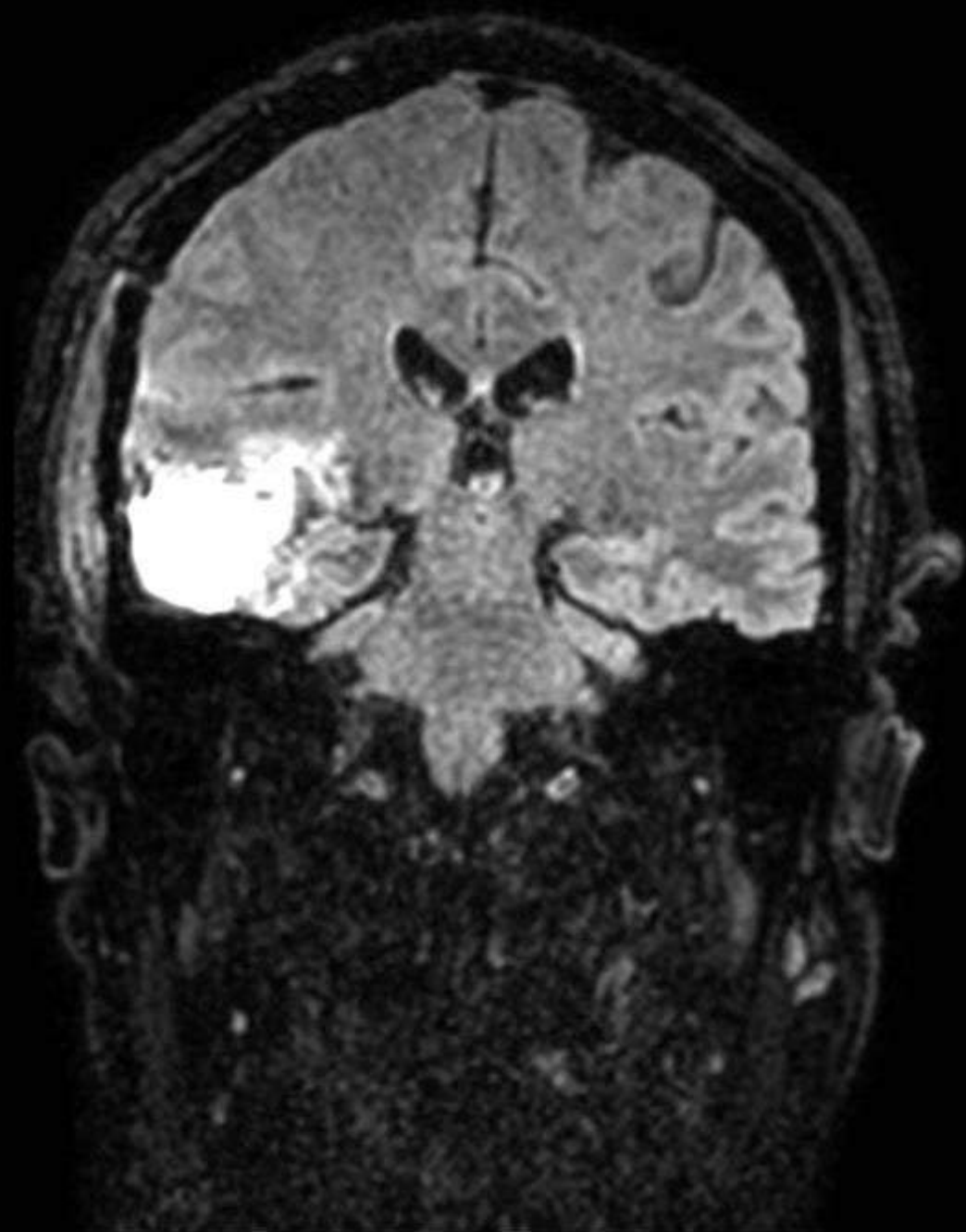
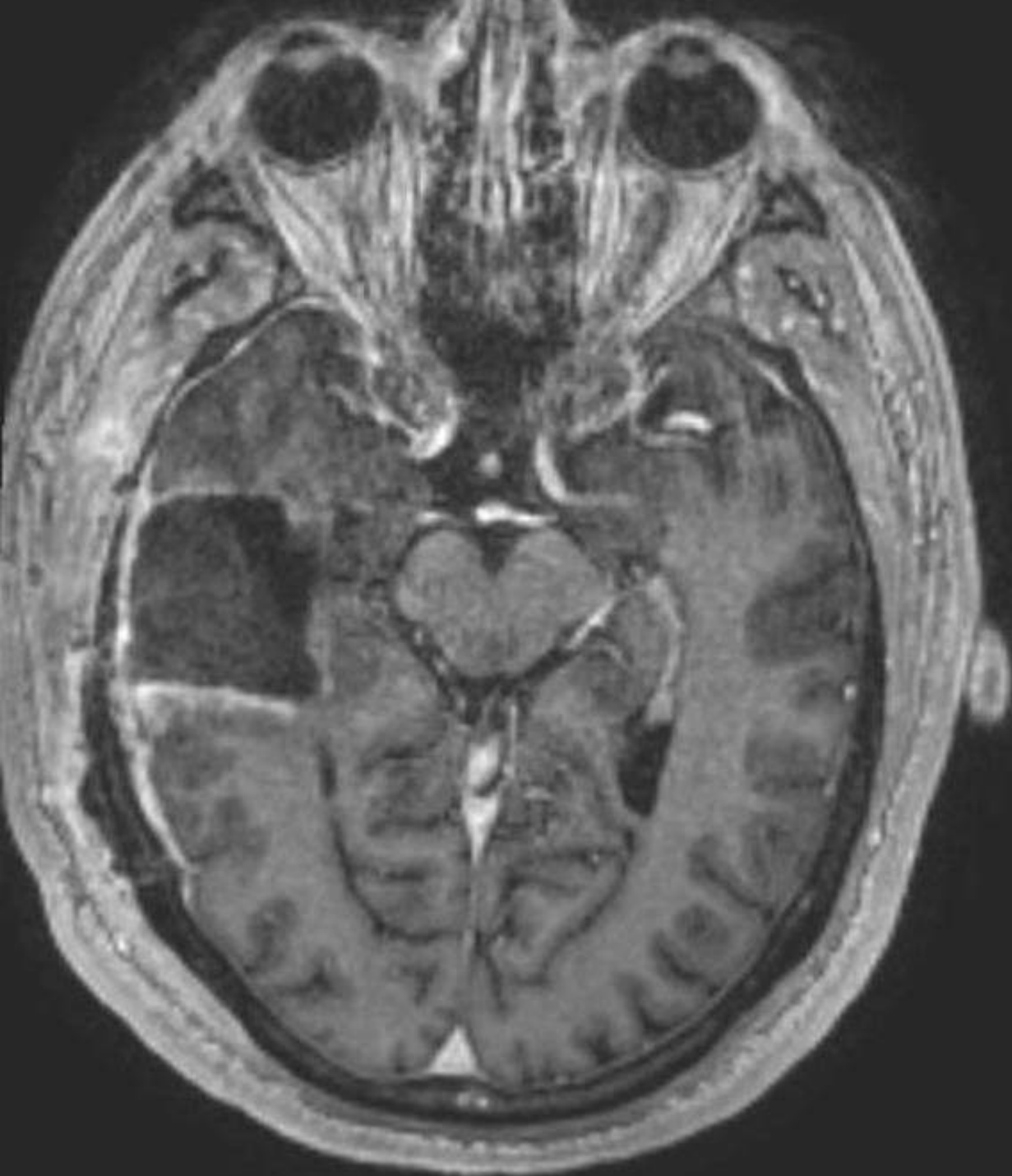
Time to abandon single-site irradiation for inducing abscopal effects

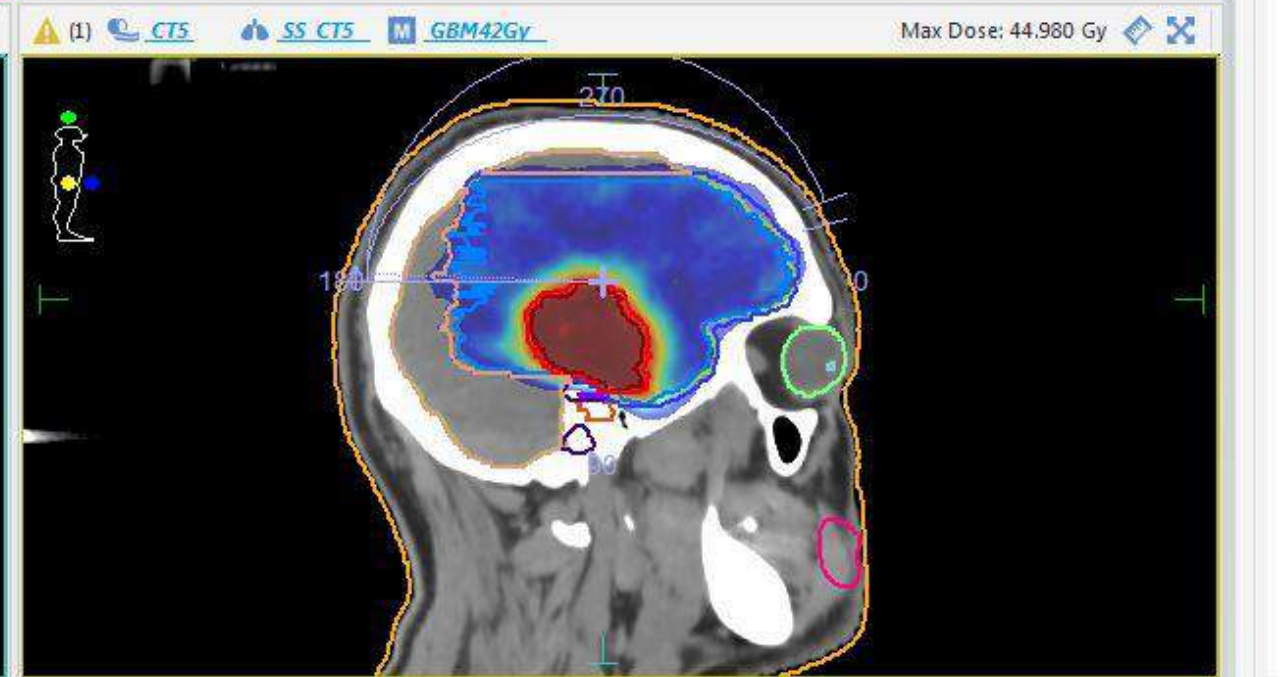
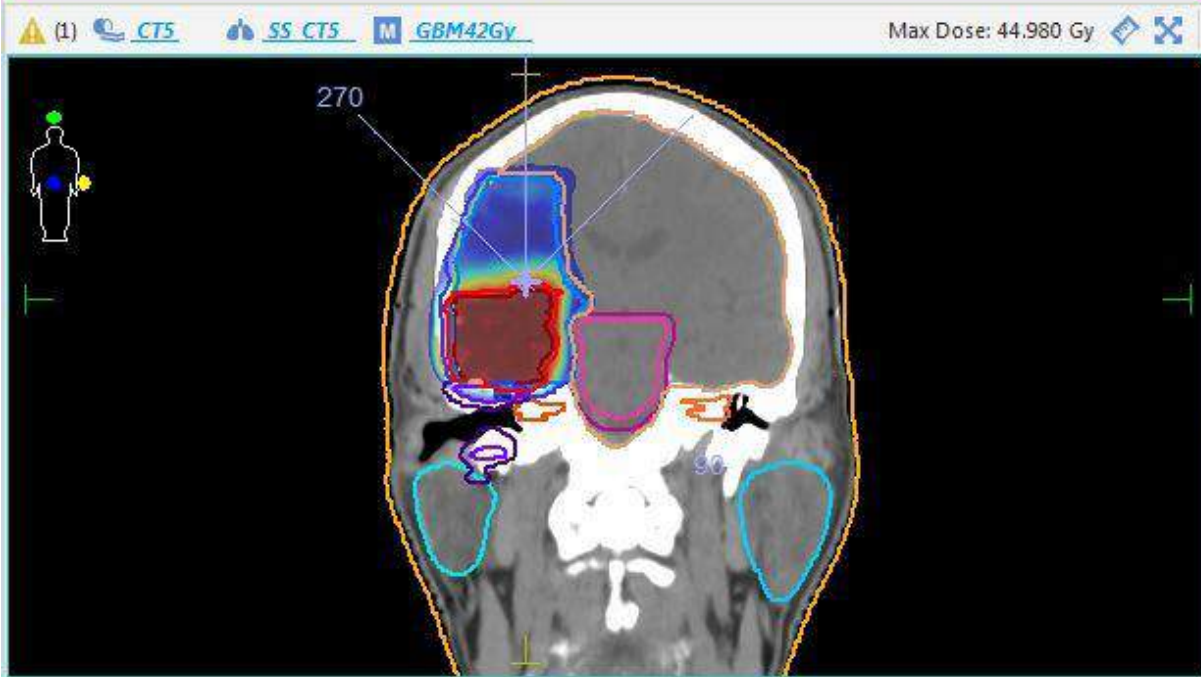
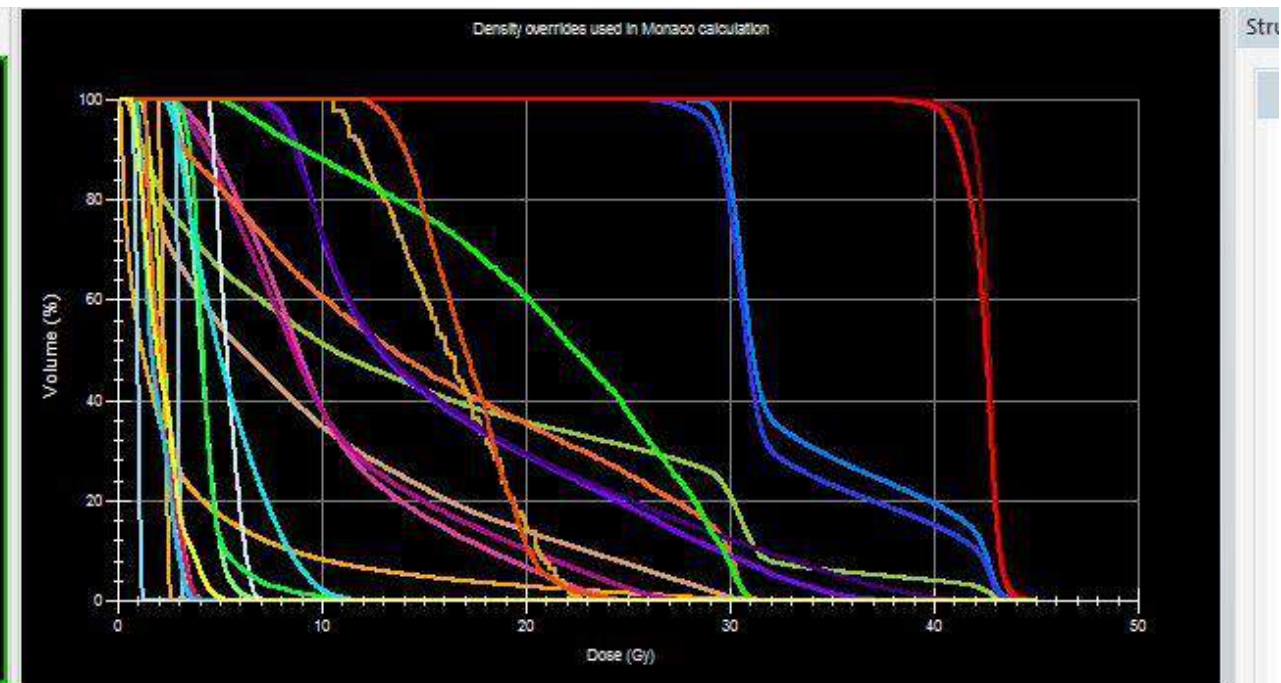
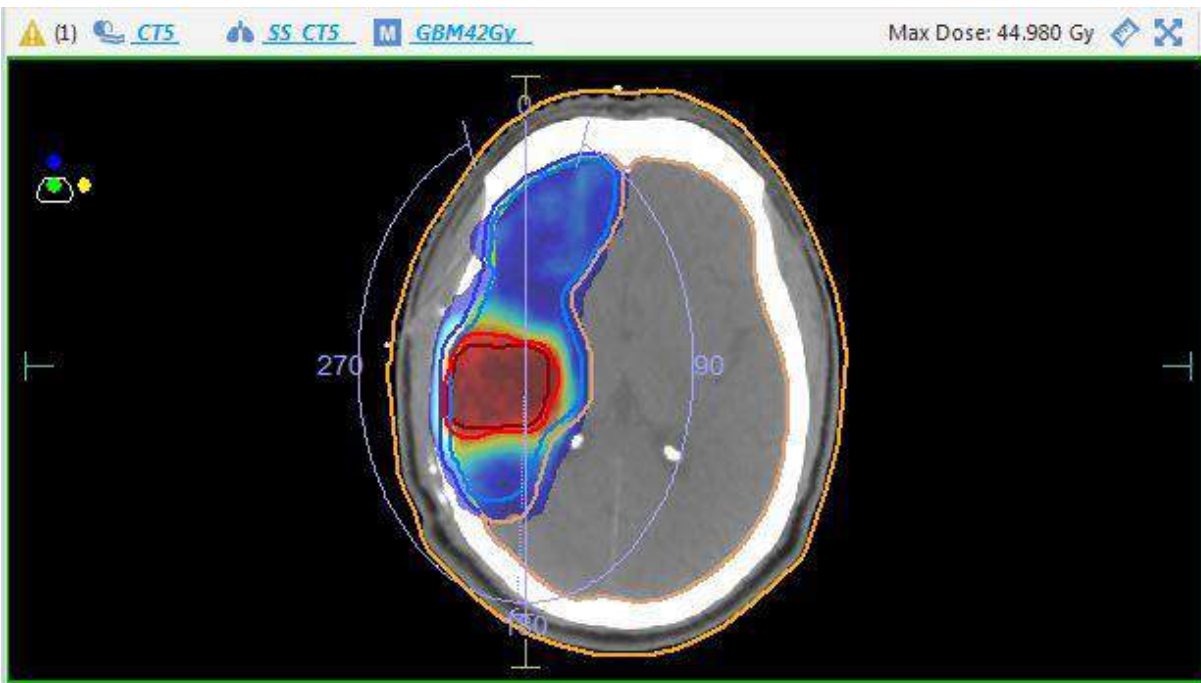
Eric D. Brooks and Joe Y. Chang

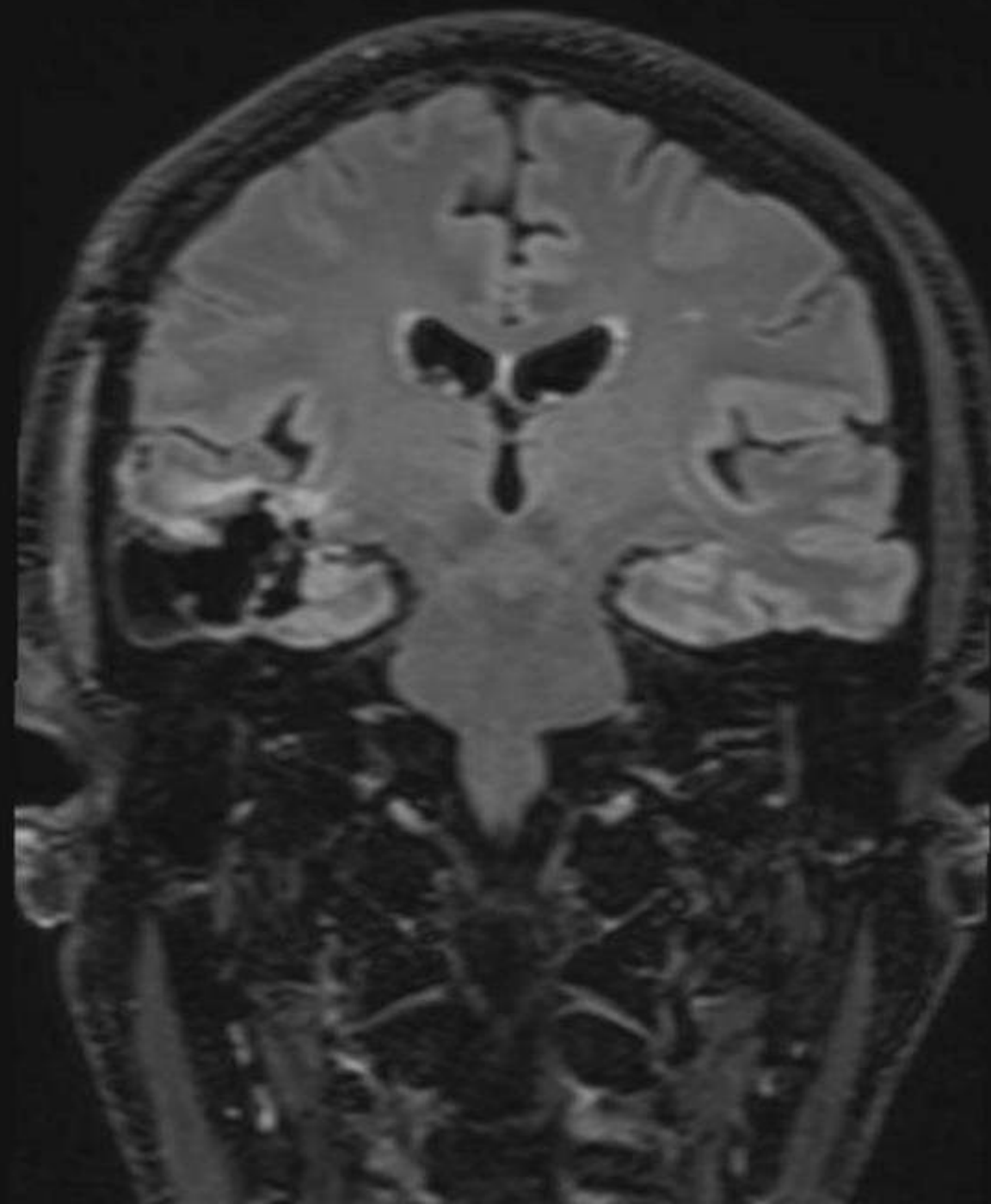
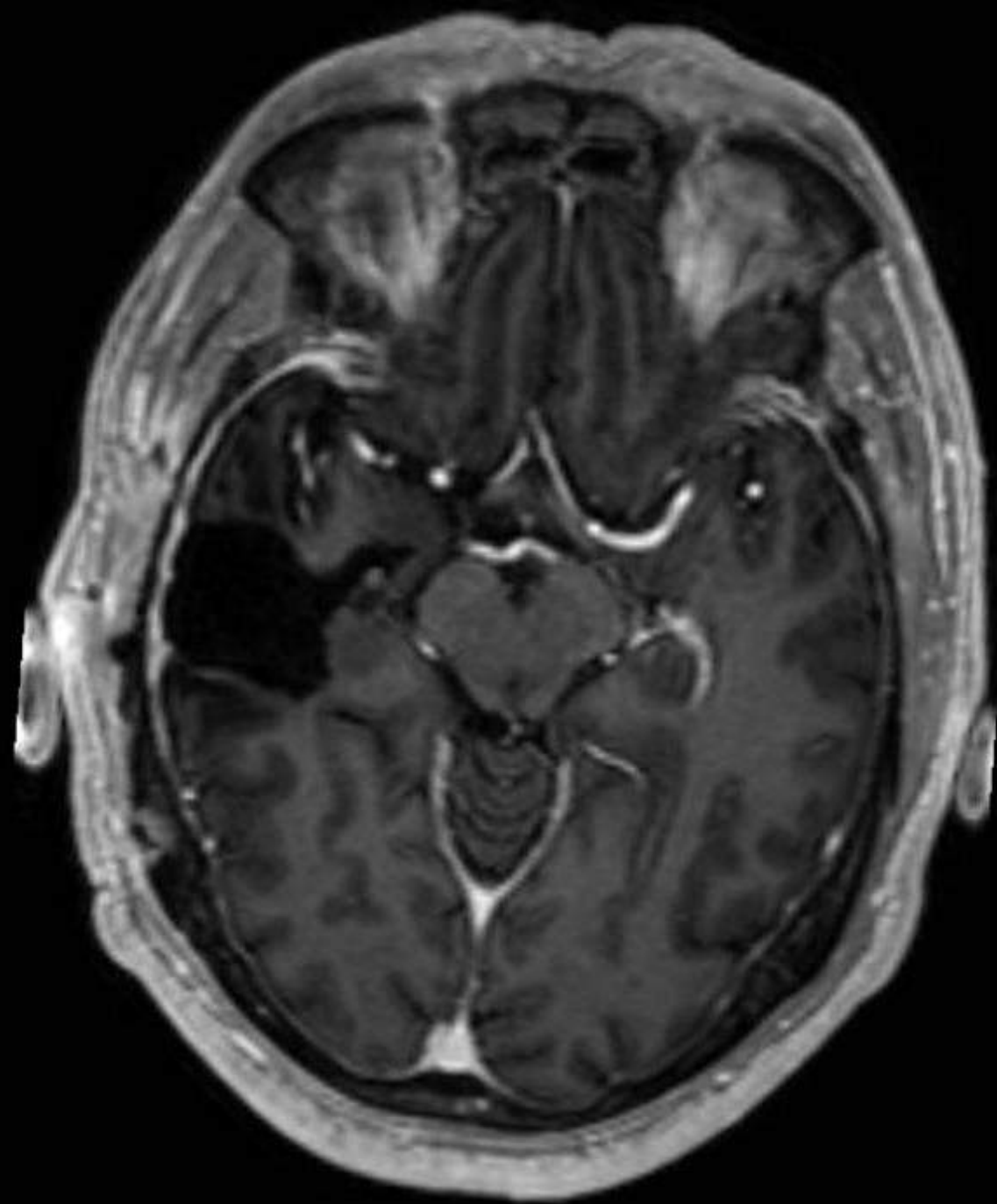


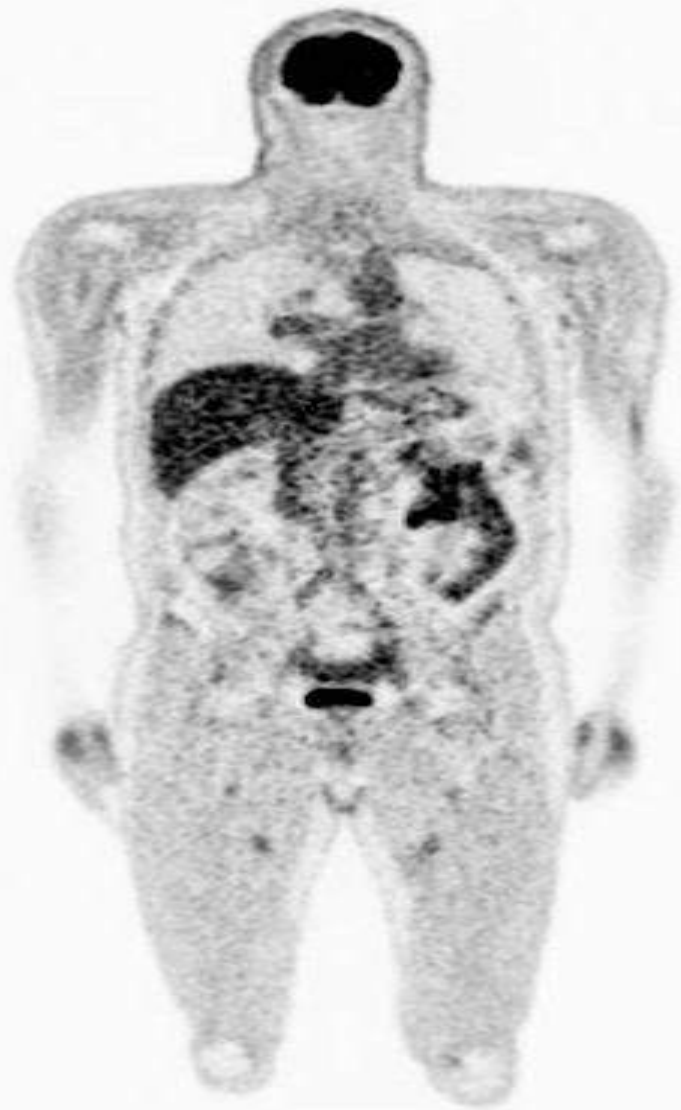








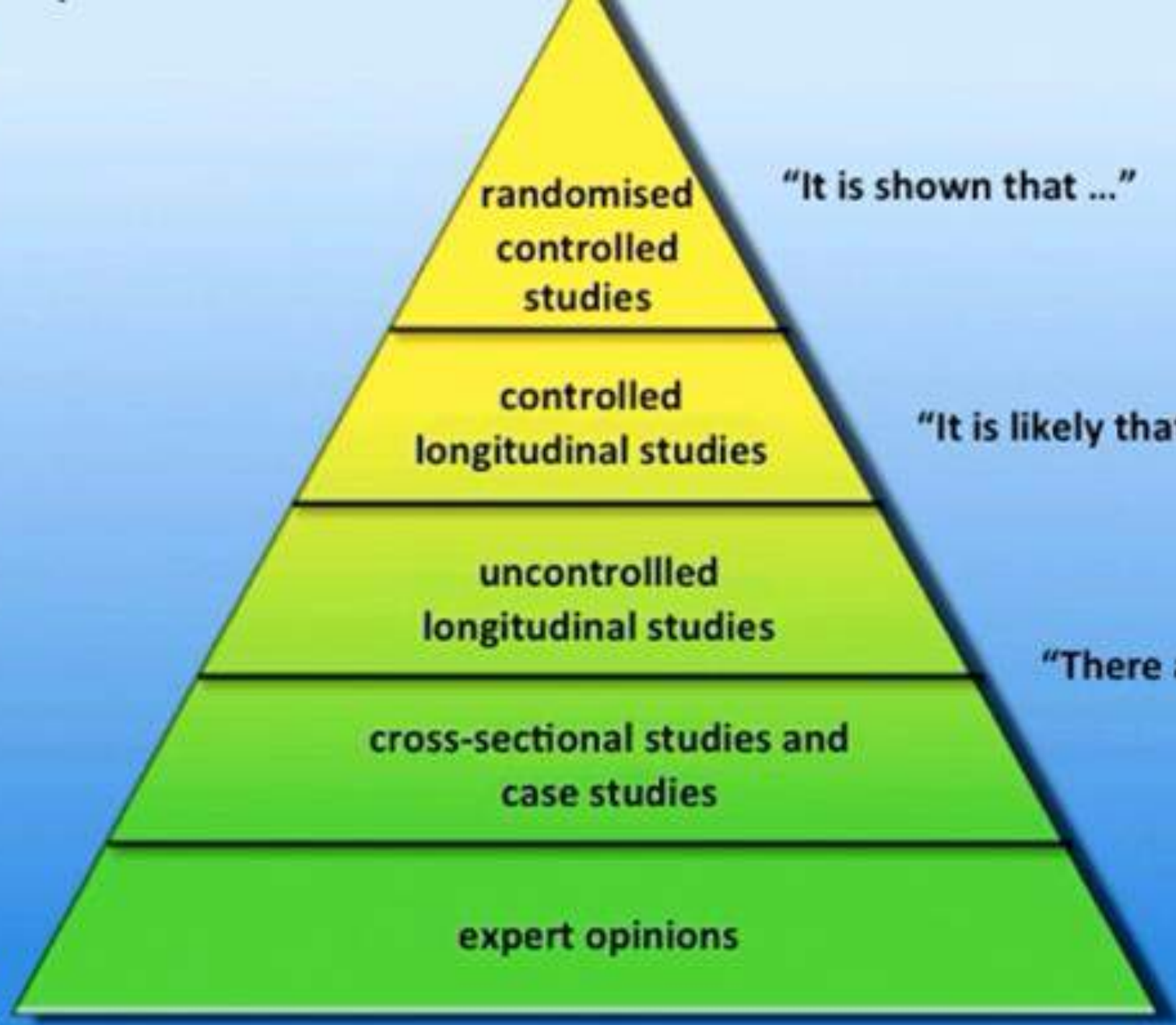




(bias --)



generate hypotheses
(bias ++)



randomised controlled studies

"It is shown that ..."

controlled longitudinal studies

"It is likely that ..."

uncontrolled longitudinal studies

"There are signs that ..."

cross-sectional studies and case studies

expert opinions

"Experts are of the opinion that ..."

Models



DOPED EVIDENCE = BAD MEDICINE