

XXXII CONGRESSO NAZIONALE AIRO
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AIRO2022

Radioterapia di precisione per un'oncologia innovativa e sostenibile

BOLOGNA, 25-27 NOVEMBRE
PALAZZO DEI CONGRESSI

 Associazione Italiana
Radioterapia e Oncologia clinica

 Società Italiana di Radiobiologia

 Associazione
Italiana
Radioterapia
e Oncologia
clinica




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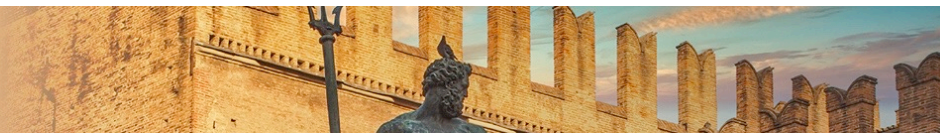
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Radiobiologia e ipofrazionamento

Dr Mauro Loi, MD MSc

AOU Careggi, Firenze



DICHIARAZIONE

Relatore: MAURO LOI

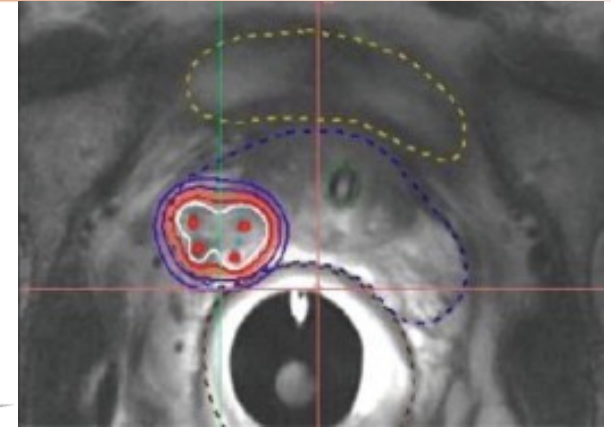
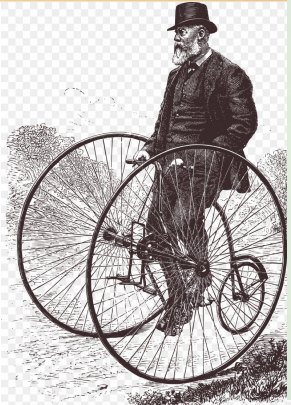
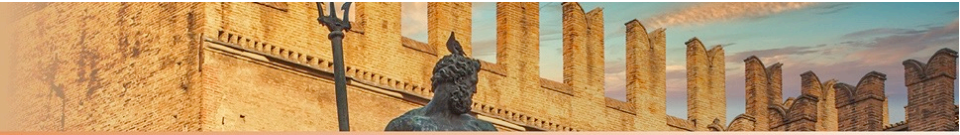
Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

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

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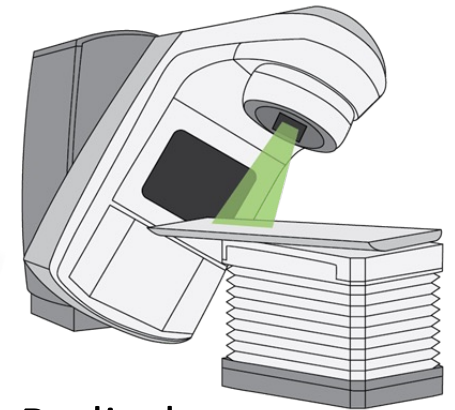
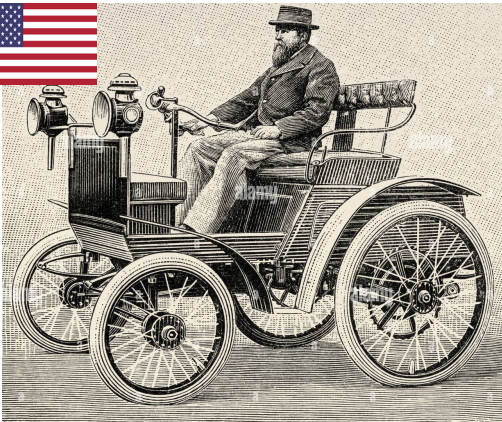
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Radium applicators

Modern Brachytherapy

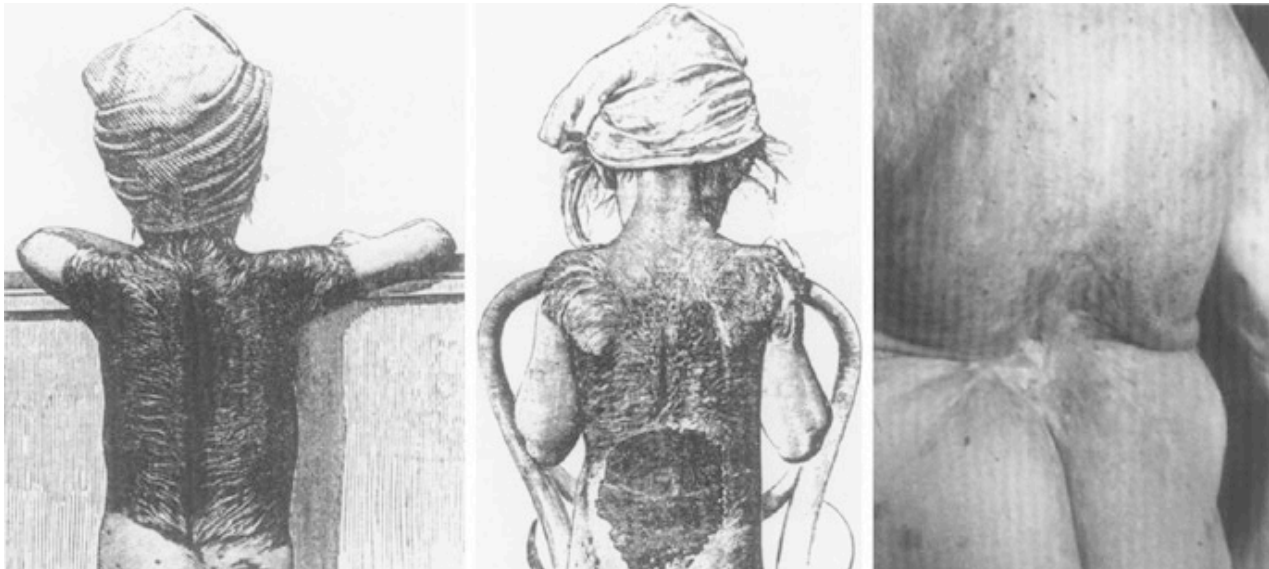


X-ray vacuum tube teletherapy

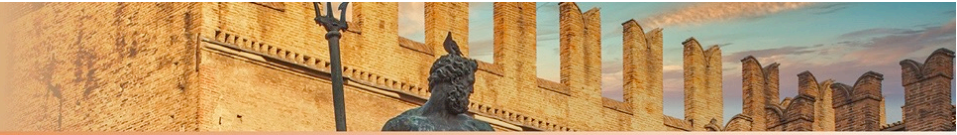
Modern External Beam Radiotherapy



- «Surgical» philosophy: eradicate the tumor in one single or few procedures with large dose
- Assumption: avoid tumor resistance and reduce «cumulative injury» on healthy tissue

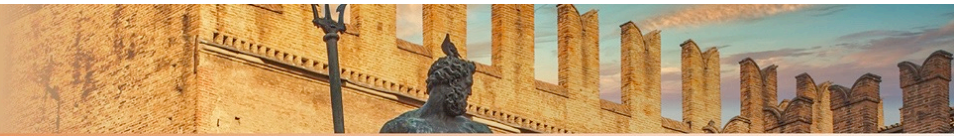


- Severe normal tissue complications
- Unacceptably high rate of local tumor recurrence



- Radium applications: longer overall treatment times vs X-Ray (low activity source)
- Less convenient in terms of patient throughput, better clinical outcomes



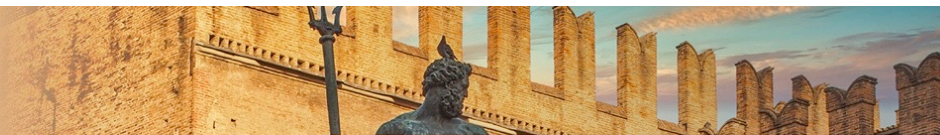


- 1906 Tribondeau/Bergonnier:** radiation selectivity for actively dividing poorly- or undifferentiated cells
- 1920s Regaud:** multiple, smaller radiation doses sterilized the testis without producing severe injury to the scrotum
- 1930s Coutard:** «protracted fraction method»: long durations of radiation (several weeks) produced tumor regression and allowed tissue to recover between sessions
- 1960s Fowler:** according to LQ model hypofractionation is discouraged because it would likewise exacerbate late effects

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Radiation Oncology



1920s

Hypofractionation



1990s



2000s

Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial

Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial

The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials

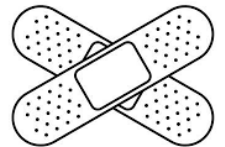
Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma

Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial

Accelerated Hypofractionated Image-Guided vs Conventional Radiotherapy for Patients With Stage II/III Non-Small Cell Lung Cancer and Poor Performance Status
A Randomized Clinical Trial

Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial

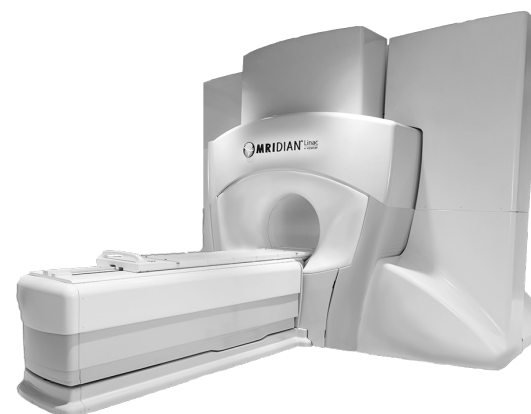
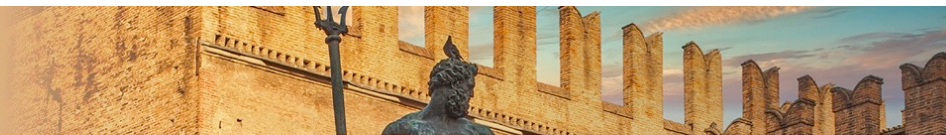
CFRT



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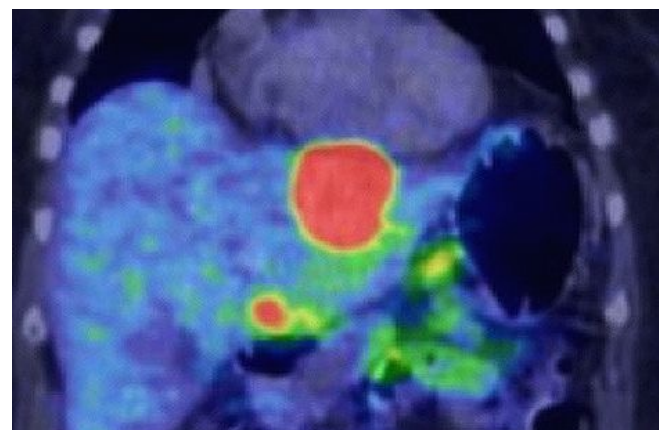
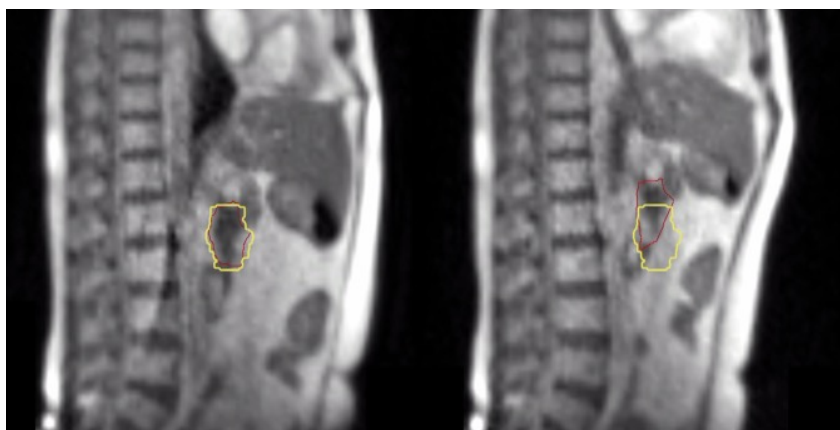
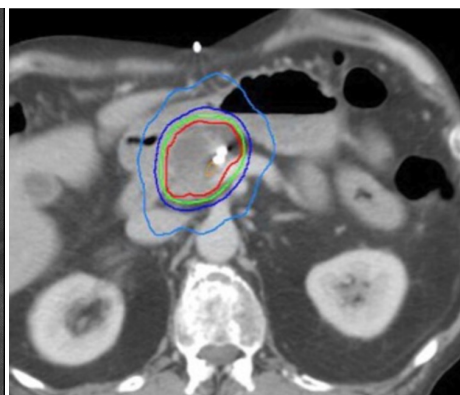
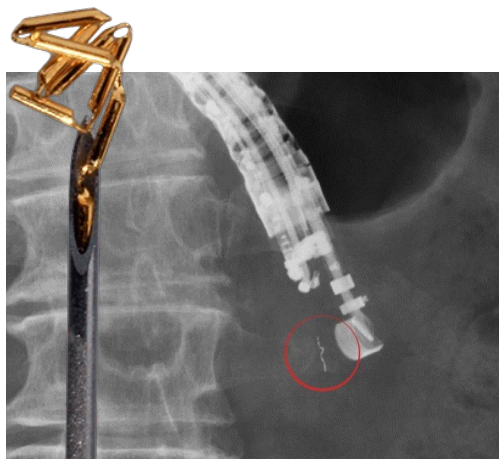
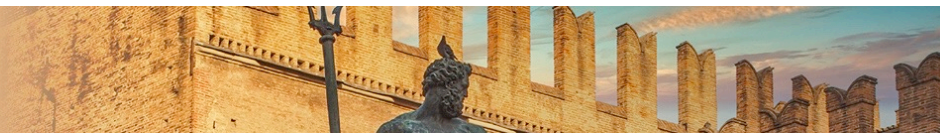
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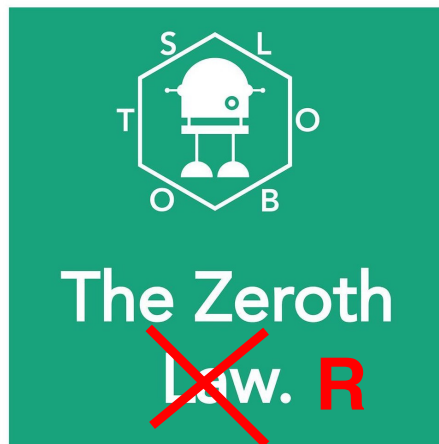
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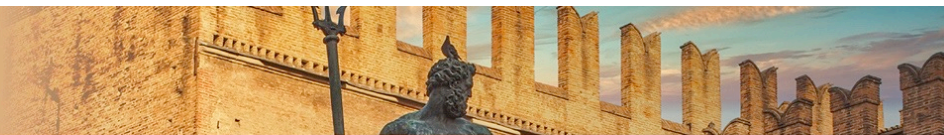
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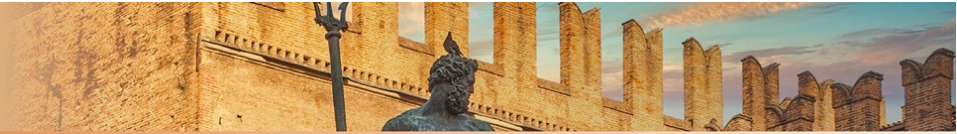


- Precise targeting, sharp dose fall-off, motion control, dose modulation
 - allows for safe moderate and extreme hypofractionations
- Is Radiobiology still relevant?? All the 4,5,6... Rs may be now irrelevant face to the “0th R”
 - Technical advancement may supplant biological distinctiveness of tissues
 - Just use tech to increase the BED to the tumor and spare normal tissues





	EQD2 $\alpha/\beta=3$	EQD2 $\alpha/\beta=10$
60 Gy/20#/3Gy	72	65
40 Gy/15#/2,67Gy	45	42
64,6Gy/19#/3,4 Gy	82,7	72,1
26 Gy/5#/5,2 Gy	42,6	32,9
55 Gy/20#/2,75 Gy	63	58,4

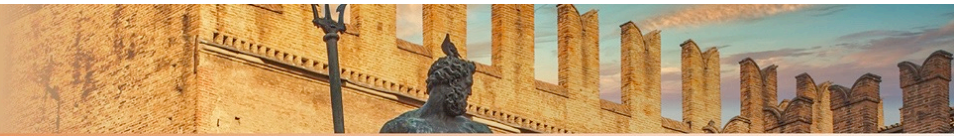


REPOPULATION

- Given that accelerated repopulation is not thought to begin until several weeks into treatment the relevance of repopulation in comparing moderately- and ultrahypofractionated regimens is diminished

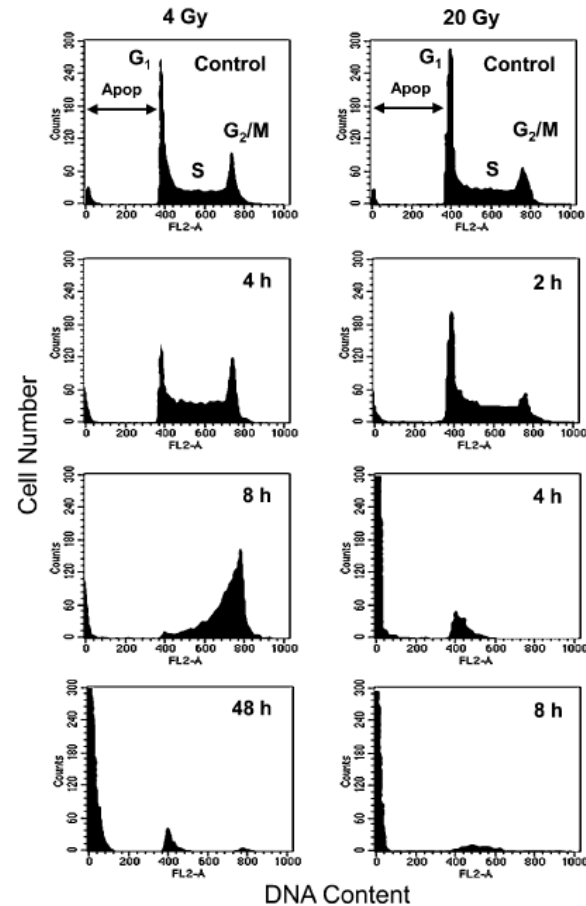
Withers, Acta Oncol 1988



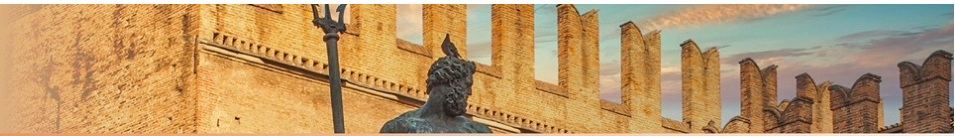


REDISTRIBUTION

- Fractionation allows multiple chances to irradiate cells in radiosensitive phases (G₂/M).
- Conventional or moderate fractionation
 - Temporary cell cycle arrest, apoptosis in late S/G₂
 - Redistribution around the cell cycle.
- Extreme hypofractionation
 - No cell cycle progression: interphase death

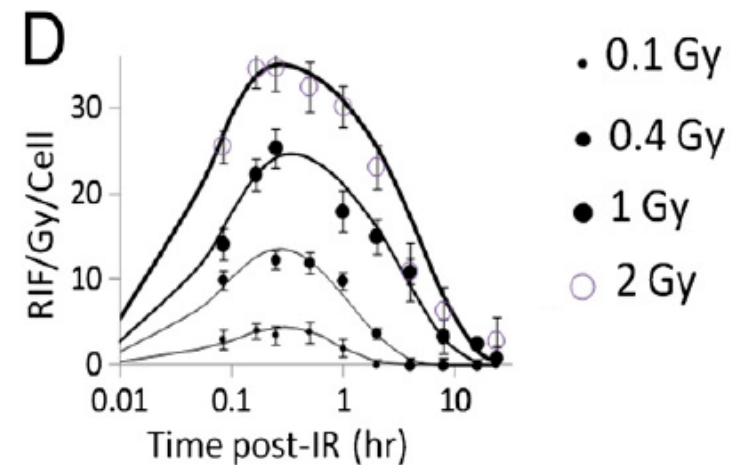


Park Radiat Res 2000



REPAIR

- High levels of DNA damage, repair evident @ 80 Gy
- No evidence of repair saturation
- High-dose radiation-induced foci (RIF)
- formed relatively faster and resolved slower than low-dose RIF1
- More intense clusters of DNA repair proteins formed (repair centers), in fewer locations



Neumaier PNAS 2012

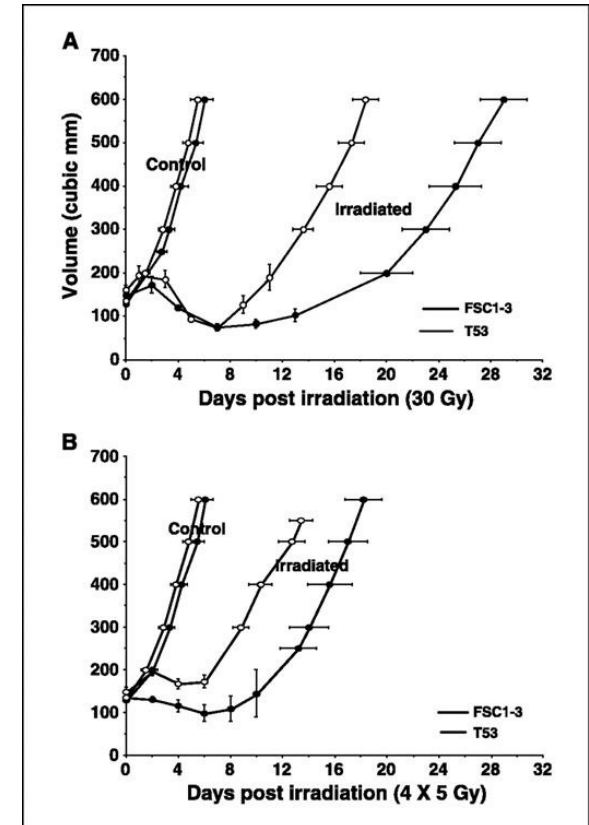


RADIOSENSITIVITY

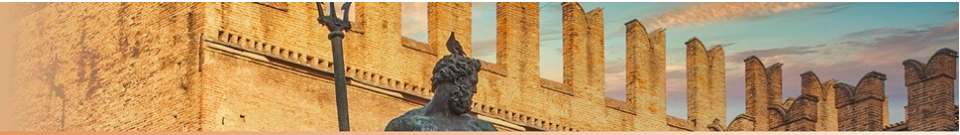
Tumor Cell Radiosensitivity Is a Major Determinant of Tumor Response to Radiation

Leo E. Gerweck,¹ Shashirekha Vijayappa,¹ Akihiro Kurimasa,² Kazuhiko Ogawa,¹ and David J. Chen³

- Established tumors from DNA-PKcs^{-/-} and DNA-PKcs^{+/+} cells
- 4 x 5 Gy and 30 Gy – measure tumor growth delay
- DNA-PKcs^{-/-} cells - significantly longer growth delay
- Tumor radiosensitivity is a major determinant of response after 15-30 Gy not cell stroma



Gerweck *Can Res* 2006



REOXYGENATION

- Chronic hypoxia due to interstitial pressure in tumors relieved over weeks by shrinkage
 - Reoxygenation +++ if multiple fractions and longer overall treatment time

- Brown et al: modeling cell killing for SABR 20 Gy x 3#
 - If hypoxia not considered : 99% TCP for a 4 cm (LQ) to 6 cm (USC) tumor
 - If hypoxia considered (20% hypoxic fraction, OER 2.8): <90% for a 1 cm tumor
 - Is a radiosensitizer needed??

Brown et al, IJROBP 2010



REOXYGENATION

- Clinical outcomes for NSCLC with SBRT are good??
- This suggests the possible contribution of other mitigating factors such as:
 1. No hypoxia in some tumors (e.g., the smallest ones)
 2. Small proportion (1/10²–10⁴) of clonogenic stem cells
 3. An active immune response is sufficient to eradicate microscopic residual tumor
 4. High single doses of radiation cause acute damage to the tumor vessel endothelial cells

Brown et al, IJROBP 2010



REOXYGENATION

- <2.5 Gy \rightarrow Blood flow decrease for 6-12 hours then returns to normal
- 5-10 Gy \rightarrow Blood flow decreases, returns in 2–3 days
- 10-15 Gy \rightarrow Blood flow initially decreases for 1–7 days
- 15-20 Gy \rightarrow Blood flow decreases rapidly

Garcia Barros, Science 2003

Bussink, Radiat Res 2000

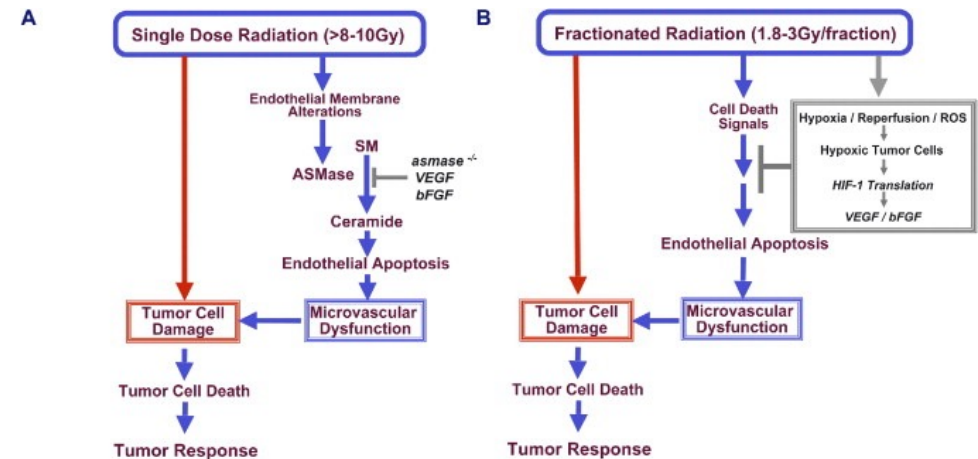
Solesvik Radiat Res 1984

Kioi Int J Can 2010



REOXYGENATION

- Fuks et al: apoptotic death of vascular endothelial cells for large doses/fraction (>10 Gy)
→ acid sphingomyelinase pathway activation and Ceramide-mediated apoptosis
- Low dose per fraction:
→ Endothelial damage counterbalanced by HIF+
- High dose per fraction
→ Enhanced endothelial cell death 2-3 days after

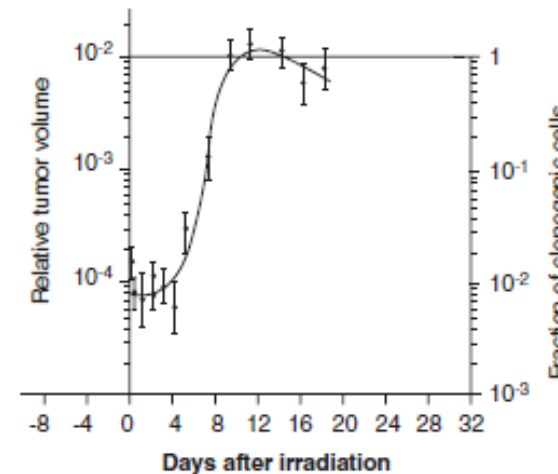
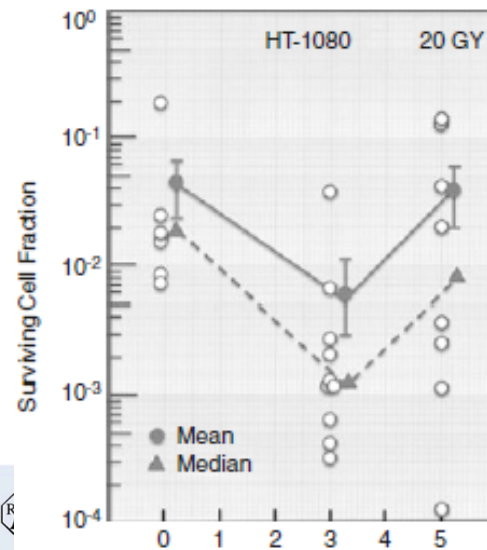
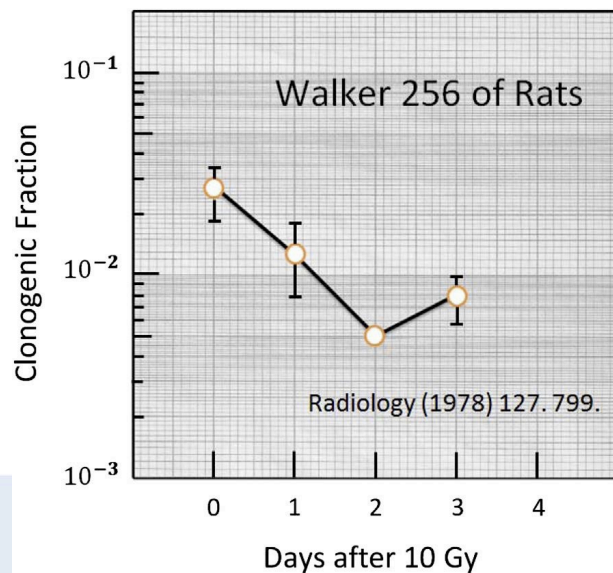


Fuks, Cancer Cell 2005

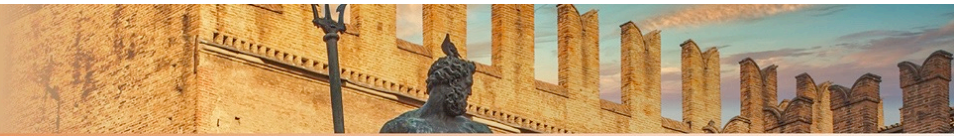


REOXYGENATION

- Unclear whether endothelial cell damage increase tumor cell death?
- Clonogenic cell survival decreased for 2–3 days after irradiation (left)
- Or not (right)

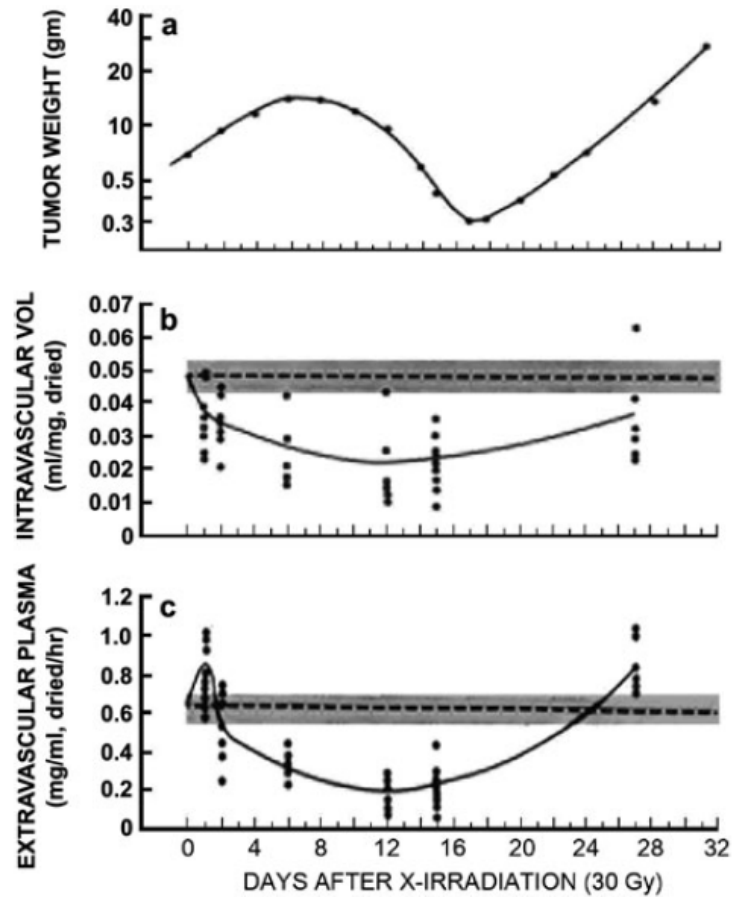


Song, IJROBP 2015
Hermens Eur J Cancer 1969
Clement Radiology 1978

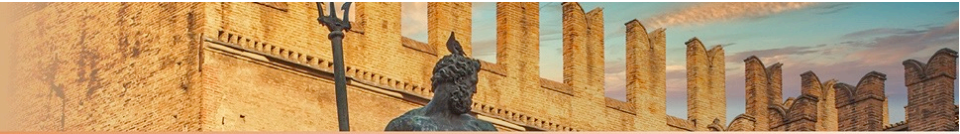


REOXYGENATION

- Loss of T volume
- Loss of vascular volume
- Reduction of exchanges



Song, IJROBP 2015



REOXYGENATION

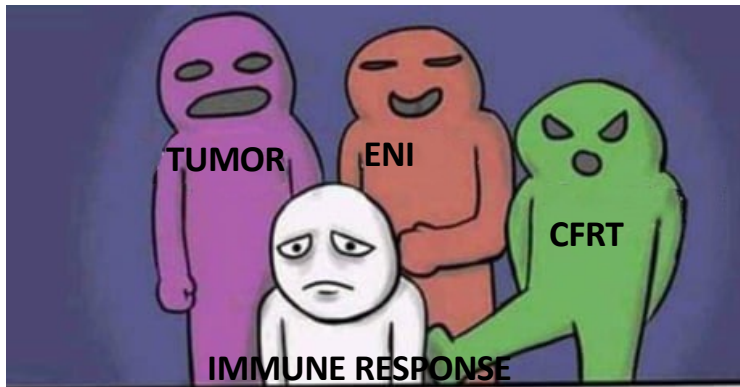
- Indirect effect ?
- Cancer Stem Cells (CSCs) consistute the radioresistant bulk of disease
- CSCs located in the perivascular niche
- Vascular collapse by SBRT entailing disruption of the perivascular niche
- Still unproven



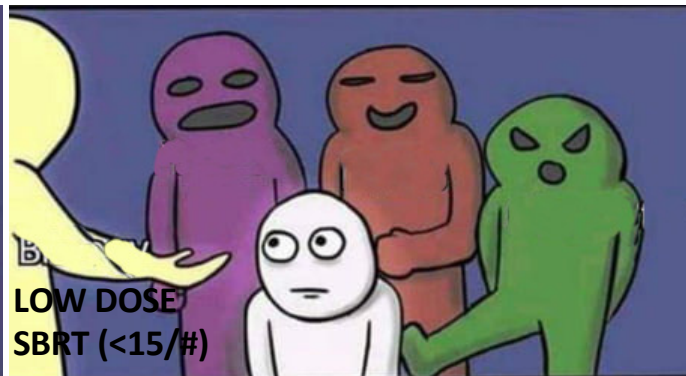
Charles, Cell Cycle 2010



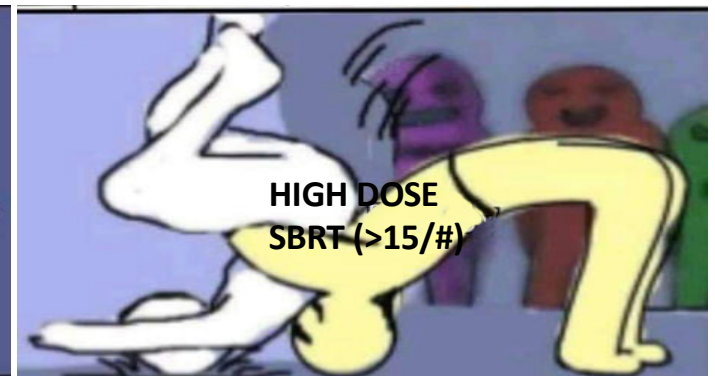
REACTIVATION OF IMMUNE RESPONSE



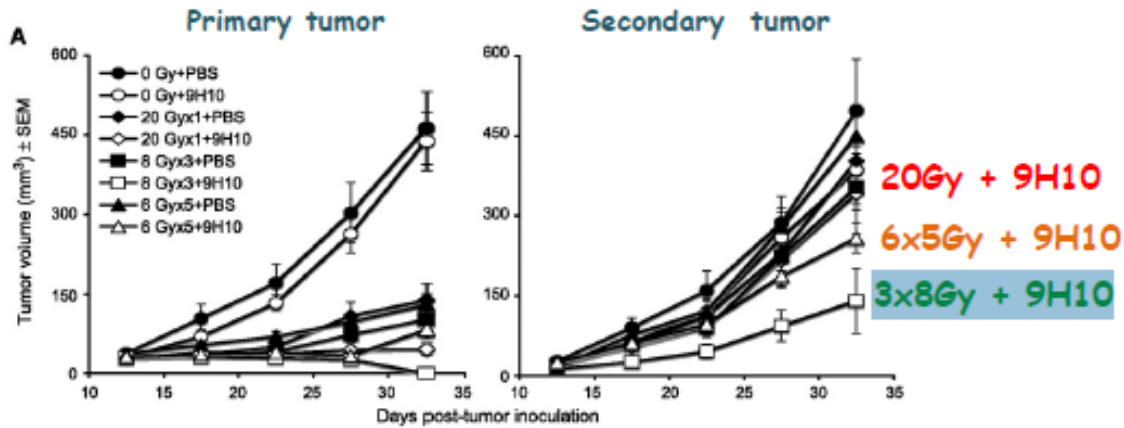
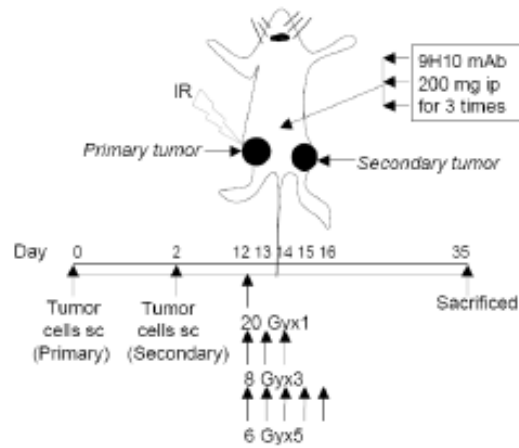
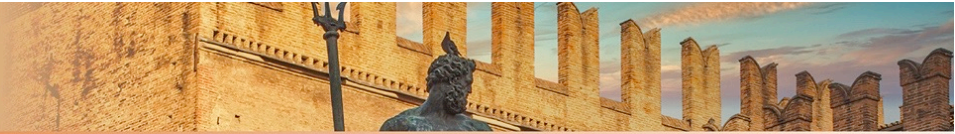
- Tumor immune evasion
- Lymphopenia/immune system impairment due to protracted RT and larger volumes

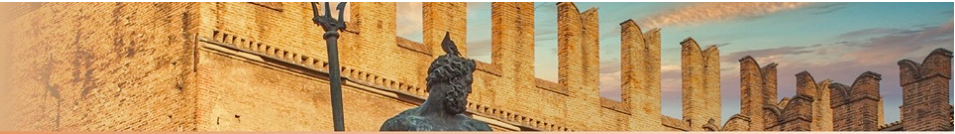


- Immunogenic Cell Death
- Eat-me signal and antigen processing trigger
- Short duration: ↓ lymphopenia



- Trex1 activation (DNA exonuclease)
- Impaired priming





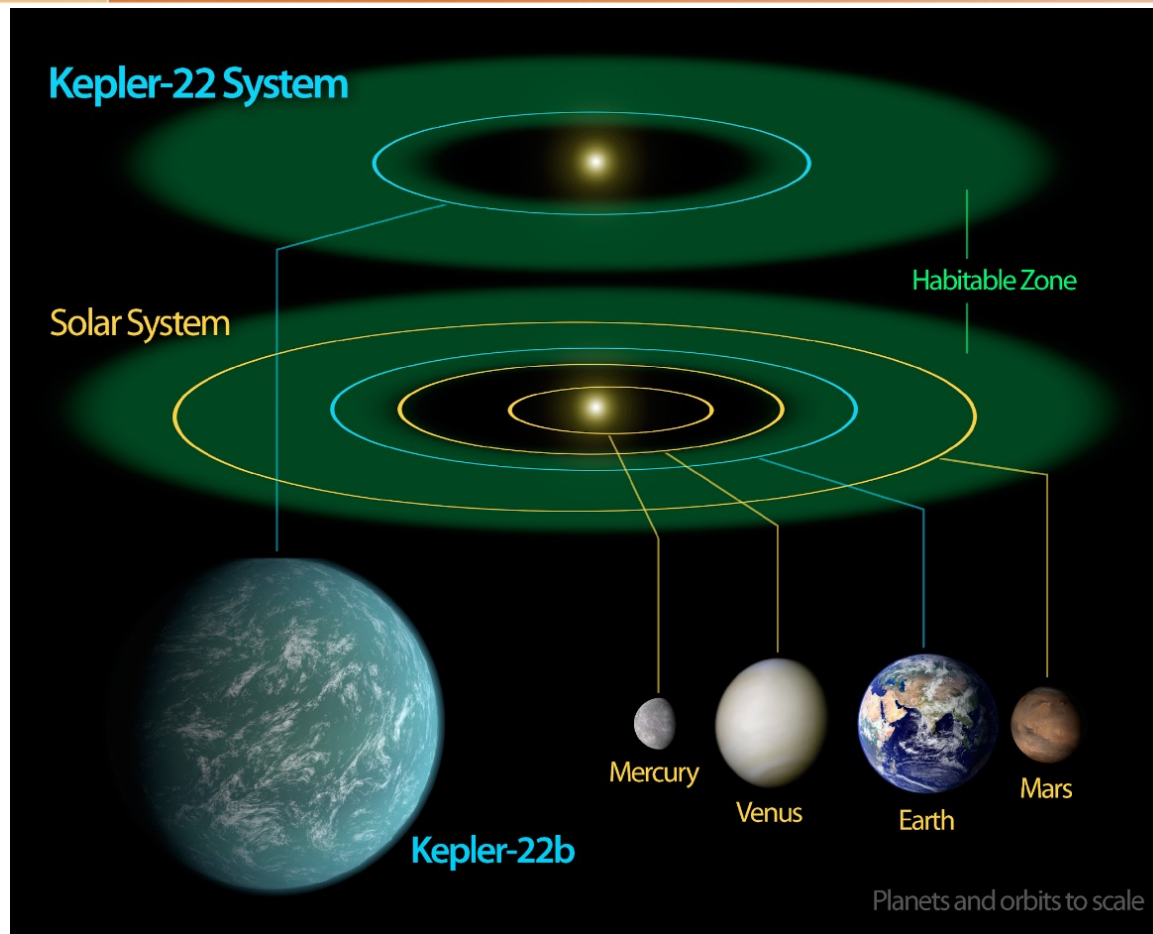
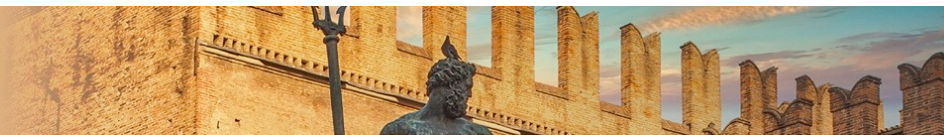
Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial

original report
Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma

JAMA Oncology | Original Investigation

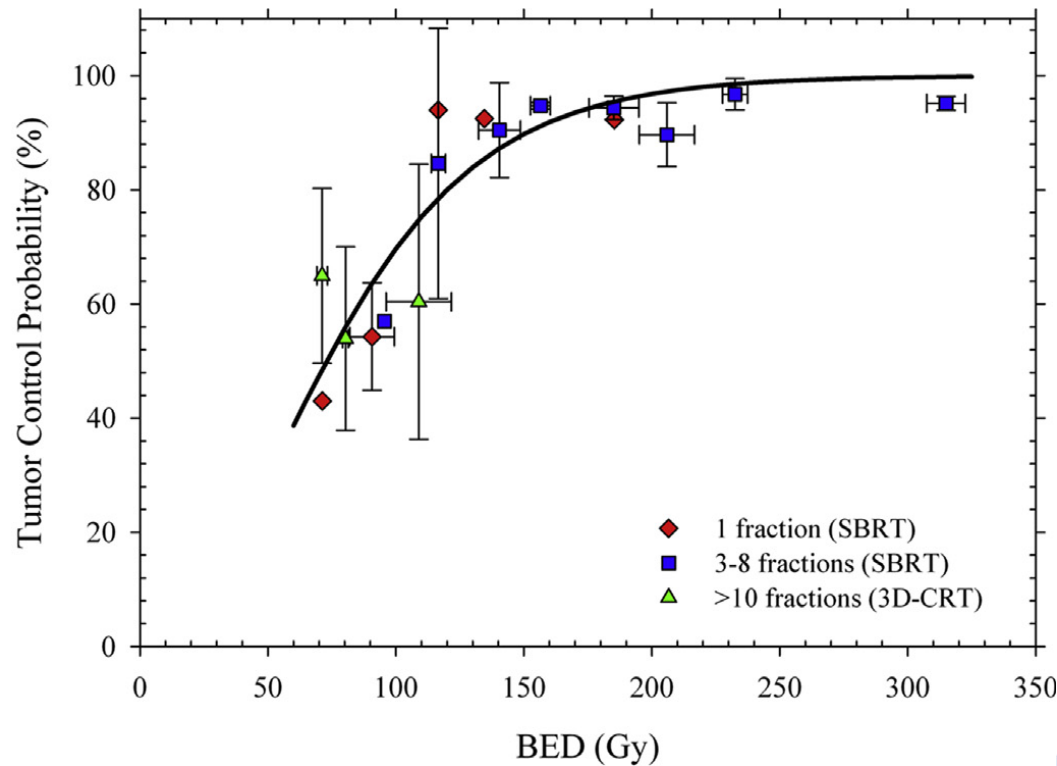
Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial







“..the efficacy of single doses, a few SBRT fractions, and conventional radiation therapy produce the same overall TCP for the same BED”



Brenner IJROBP 2014



CONCLUSIONS

- Hypofractionation: back with a vengeance and here to stay
- Moderate hypofraction schedule: lower EQD2 and better tech
- No substantial differences for moderate hypofractionation in RB mechanics



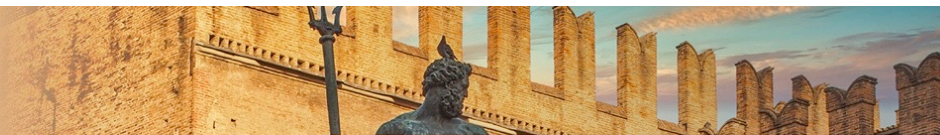
CONCLUSIONS

- Extreme hypofractionation
 - ↔ Radiosensitivity, Repair
 - ↓ Repopulation, Redistribution, Reoxygenation (?)
 - ↑ or ↓ Reactivation of the immune system
- LQ may still work at least below 20 Gy/fraction
- Indirect effects beyond classical RB uncertain

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THANK YOU FOR YOUR ATTENTION

