LA MODULAZIONE DEGLI EFFETTI: Radioprotettori, radiosensibilizzanti, effetto abscopal. Radiazioni, terapia ormonale, Target Therapy e chemioterapici antiblastici.

Dott. Triggiani MD, PhD Student

UNIVERSITÀ DEGLI STUDI DI BRESCIA

Start with clinical data

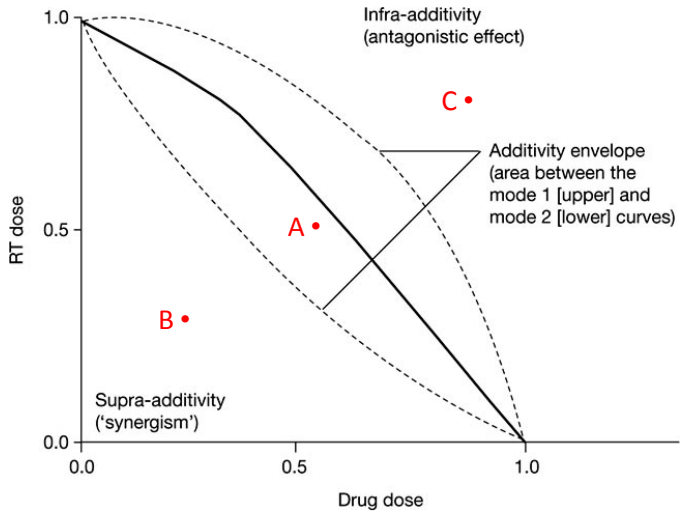
Table 1 Overview of disease entities and indications in which concurrent chemoradiotherapy is used.[a]

Disease entity	Indication and treatment	Commonly used agents	Benefit
Upper aerodigestive tract cancers			
Head and neck cancer	Locally advanced HNC—primary or adjuvant treatment	Cisplatin, 5-FU, FHX, cetuximab	Improved organ preservation and survival compared with radiation alone
Non-small-cell lung cancer	Stage IIIB, nonoperable nonmetastatic disease	Cisplatin, carboplatin/paclitaxel, cisplatin/etoposide	Curative approach in poor surgical candidates or IIIB disease
Small-cell lung cancer	Limited stage disease	Cisplatin/etoposide	Curative in ~20% of patients
Esophageal cancer	Locally advanced disease	Cisplatin/5-FU	Survival benefit, increased cure rates, organ preservation
Gastrointestinal malignancies			
Rectal cancer	Neoadjuvant	5-FU	Improved sphincter preservation, decrease in local and distal failures
Anal cancer	Mainstay of curative treatment	5-FU, MMC	Improved organ preservation
Gastric cancer	Adjuvant	Cisplatin, 5-FU	Some data indicate a survival benefit
Pancreatic cancer	Adjuvant, unresectable locoregionally advanced tumors	5-FU	Improved locoregional control, possibly a survival benefit
Cholangiocarcinoma	Adjuvant, unresectable locoregionally advanced tumors	5-FU	Some data indicate a survival benefit
Gynecological and genitourinary cancers			
Cervical cancer	Primary modality	Cisplatin, 5-FU, hydroxyurea	Improved local and distal control, organ preservation
Bladder cancer	Primary modality	Cisplatin	Improved local control
Other cancers			
Glioblastoma	Adjuvant	Temozolomide	Survival benefit
Sarcoma	Neoadjuvant	Doxorubicin	Downstaging, improved organ preservation

[a]This is a limited overview, and concurrent chemoradiotherapy is used in most solid tumors either as a standard treatment or investigationally. For further details please refer to the organ-specific literature. Abbreviations: 5-FU, 5-fluorouracil; FHX, 5-FU, hydroxyurea and radiation; HNC, head and neck cancer; MMC, mitomycin C.

Additive and Synergic

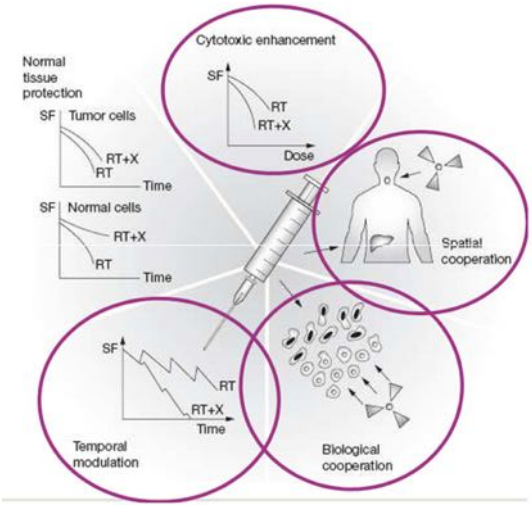
Isobologram



The concurrent chemoradiation paradigm—general principles
Tanguy Y Seiwert, Joseph K Salama and Everett E Vokes
Nature Clinical Practice Oncology (2007) **4**, 86-100

Combine Chemotherapy with Radiotherapy

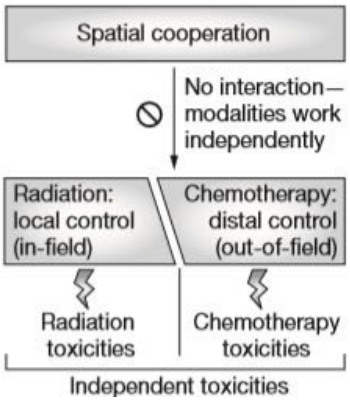
- Spatial cooperation
- Normal tissue protection
- Cytotoxic enhancement
- Biological cooperation
- Temporal modulation



Steel, Peckham 1997
Bentez SM 2007

Spatial Cooperation

- Definition: describe the scenario whereby RT acts loco regionally, and CHT acts against distant micro metastases, without interaction between the agents.



Temporal Modulation

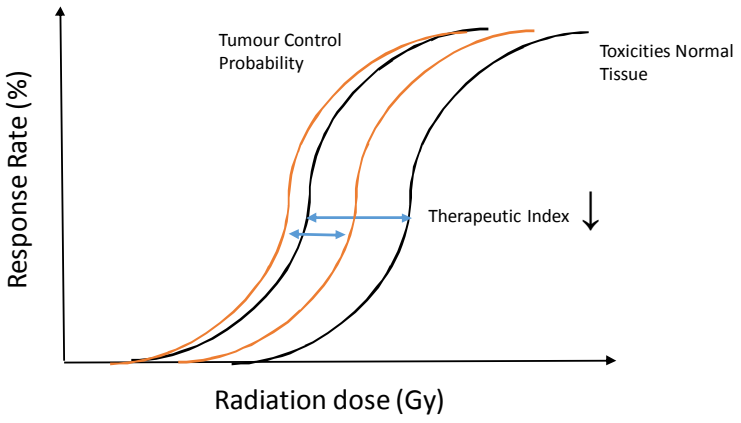
- The aim of this approach is to enhance the tumor response to fractionated radiotherapy.
- The four R's of radiotherapy:

1. Repair → DNA damage repair
2. Repopulation → cellular repopulation or proliferation
3. Reoxygenation → reoxygenation of hypoxic tumor cells
4. Redistribution → redistribution to more sensitive phases of the cell cycle

For example: radioenhancing drugs in this context could function by inhibiting repair taking place between dose fractions.

Normal tissue protection

The therapeutic Ratio



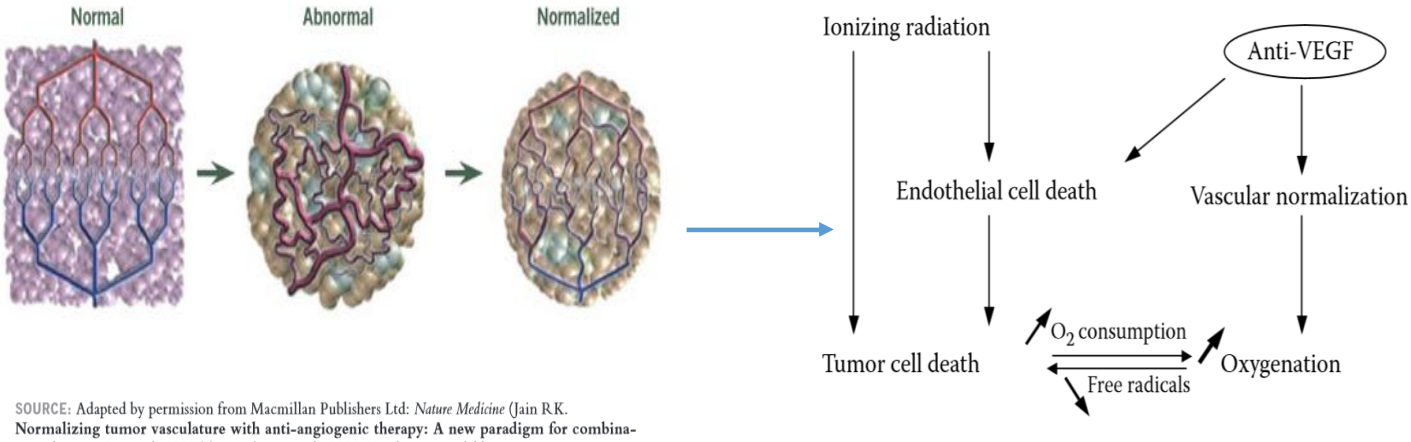
Biological Cooperation

Definition: this is the second of the mechanisms of radiosensitization and refers to strategies that:

- ❑Target distinct cell populations
- ❑Employ different mechanisms for cell killing
- ❑Delaying tumor regrowth

N.B: the cells targeted are not necessarily the malignant cells only

Biological Cooperation: Anti-VEGF/VEGFR Targeting non-Tumour Cells



SOURCE: Adapted by permission from Macmillan Publishers Ltd: *Nature Medicine* (Jain R.K. **Normalizing tumor vasculature with anti-angiogenic therapy: A new paradigm for combination therapy.** *Nat Med* 2001;7(9):987-9), copyright 2001. No abstract available

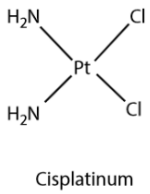
Cytotoxic Enhancement

Definition: combined-modality treatment seek to determine the combination of therapies that leads to an interaction on some level that generates an improved antitumor effect relative to each treatment alone

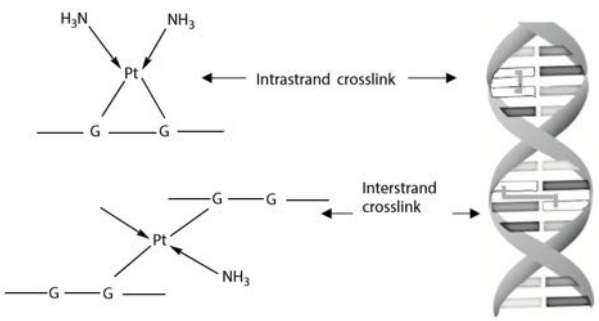
- Exacerbation of DNA Damage
- Inhibition of DNA Repair
- Cell Cycle Effects
- Enhanced Apoptosis
- Targeted Radiosensitizers

Platinum Drugs and Radiotherapy

Cytotoxicity of Cisplatin: reacts with cellular DNA to form interstrand and intrastrand cross-links.



Cisplatinum

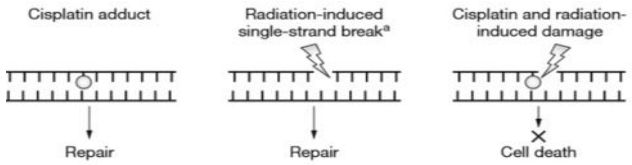


Cisplatin–DNA lesions trigger apoptosis

Platinum Drugs and Radiotherapy

Mechanism of Radiosensitization by Cisplatinum

- RT induces free radicals and the subsequent formation of toxic platinum intermediates, which increase cell killing
- Ionizing radiation can increase cellular uptake of platinum
- Damage to DNA by ionizing radiation, which would normally be reparable, can become fixed and lethal through cisplatin's free electron– scavenging capacity. The integration of cisplatin into DNA or RNA in close proximity to a radiation-induced single-strand break can act synergistically to make the defect significantly more difficult to repair.



Platinum Drugs and Radiotherapy

Schedules are important: the best results are achieved by using <u>low doses of the two agents</u> and <u>cisplatinum before RT</u>.

<u>DOSE</u>:

- Radiosensitization of murine embryonic fibroblasts (MEF) cells was shown at 1 µg/mL of cisplatin, but an increase in concentration did not increase in radiosensitization but instead increased radioresistance [*Myint, W.Examining the non-homologous repair process following cisplatin and radiation treatments. Int J Radiat Biol 2002.*]

- When OV-1063 and EMT-6 cell lines were preirradiated with 2 Gy, addition of the drug produced a clear additional effect but this was almost totally eliminated when cells were irradiated with a higher dose (6 Gy). *[Gorodetsky, R. Combination of cisplatin and radiation in cell culture: Effect of duration of exposure to drug and timing of irradiation. Int J Cancer 2006]*

<u>TIME:</u>

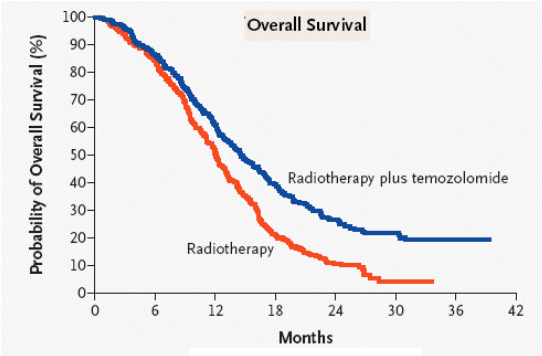
-In two cell lines (EMT-6 and OV-1063) cells, a 2-h preirradiation drug exposure resulted in a supra-additive combined effect, whereas a 24-h preirradiation exposure or protracted postirradiation exposure yielded an additive or slightly subadditive response*[Gorodetsky, R. Combination of cisplatin and radiation in cell culture: Effect of duration of exposure to drug and timing of irradiation. Int J Cancer 1998]*

-In experimental tumors, the greatest dose-enhancement factors were observed when cisplatin was administered immediately before a daily fraction of radiation [*Myint, W.Examining the non-homologous repair process following cisplatin and radiation treatments. Int J Radiat Biol 2002*]

Temozolomide e Radiotherapy

Temozolomide (TMZ) is an oral alkylating agent used as a first-line treatment for Glioblastoma Multiforme

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma



N Engl J Med 2005;352:987-96.

Temozolomide: radiosensitizer or additive effect?

- High doses of TMZ seem to have greater radiosensitizing potential and to interact with radiation at earlier time points. [Caporali, S.] and increased apoptosis when high-dose TMZ was given 2 h pre-radiation was also observed [Chakravarti, A] → independent of Mismatch Repairing futile cycling.

- At clinically TMZ concentrations (10 µM) it seems unlikely that TMZ directly induces DSB: the interaction with radiation is frequently additive rather than synergistic, and cellular sensitivity to TMZ is predictive of the effect of combination treatment

BIOLOGY CONTRIBUTION

CYTOTOXIC EFFECTS OF TEMOZOLOMIDE AND RADIATION ARE ADDITIVE- AND SCHEDULE-DEPENDENT

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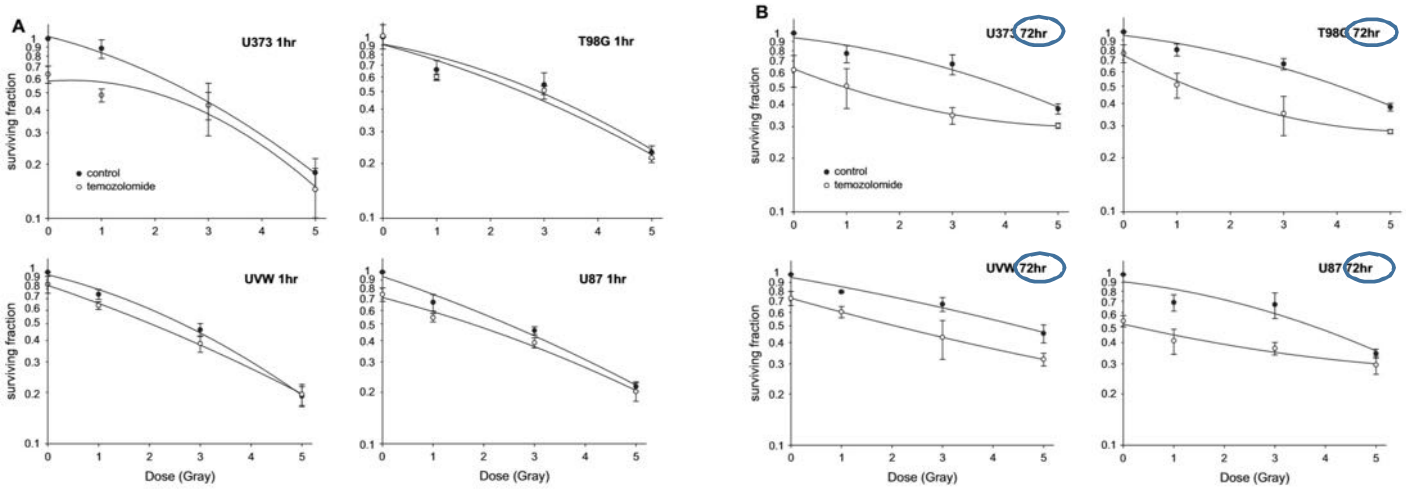
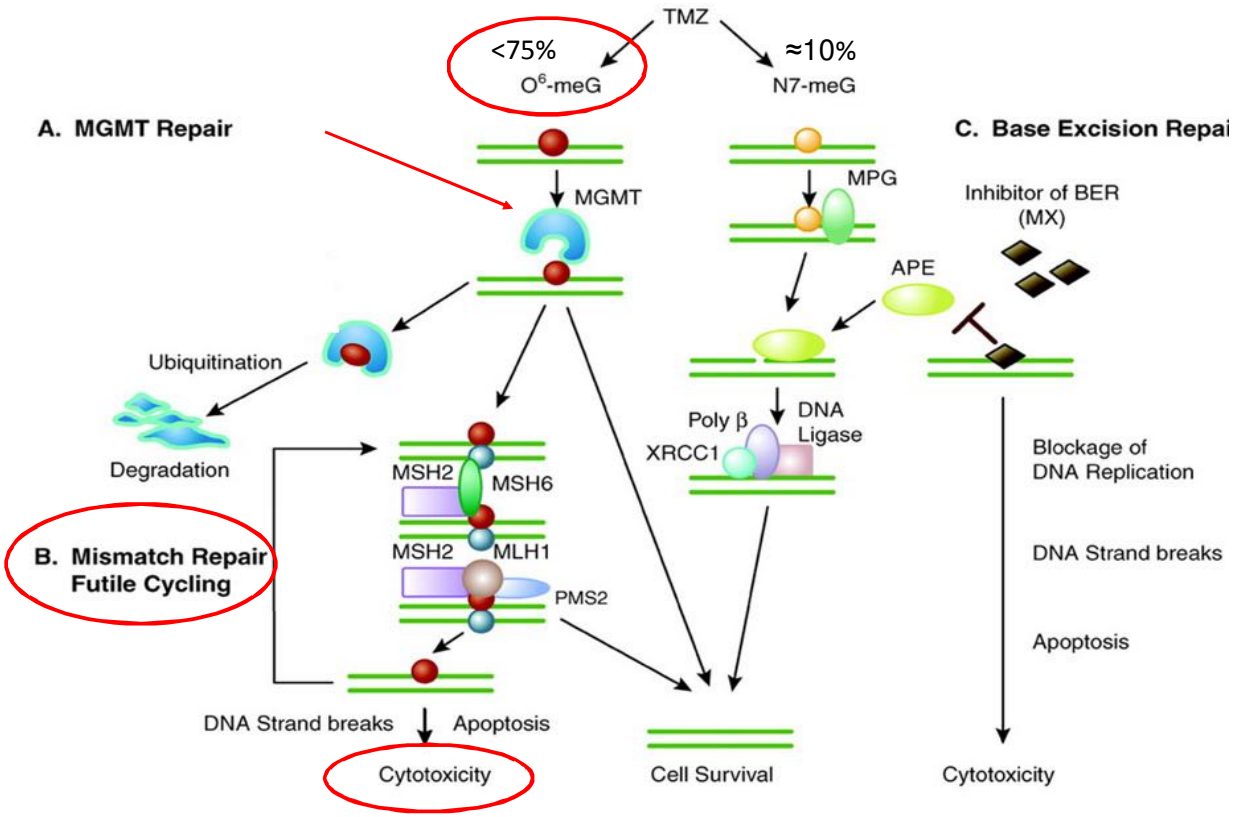
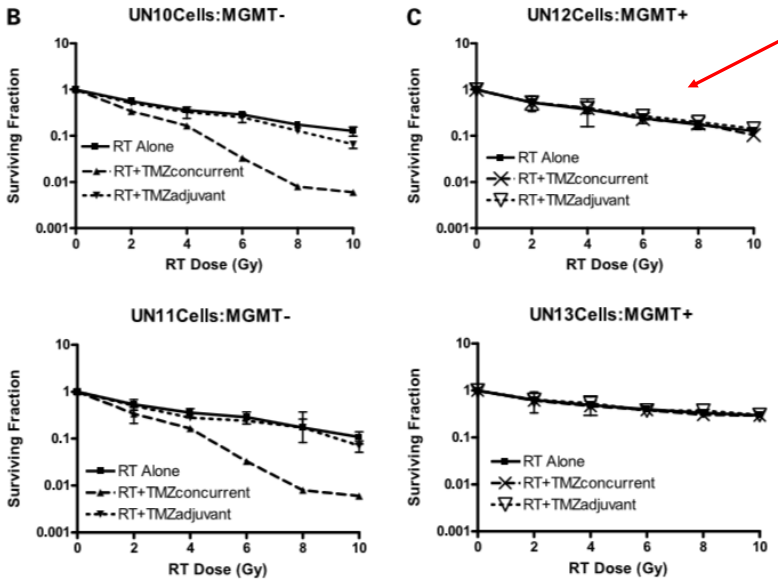




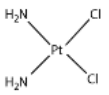
Temozolomide-Mediated Radiation Enhancement in Glioblastoma: A Report on Underlying Mechanisms

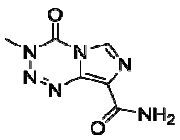
Arnab Chakravarti,[1] Michael G. Erkkinen,[1] Ulf Nestler,[1] Roger Stupp,[3] Minesh Mehta,[4] Ken Aldape,[5] Mark R. Gilbert,[6] Peter McL. Black,[2] and Jay S. Loeffler[1]



MGMT+
(non-metilation
promotere gene MGMT)

Conclusions

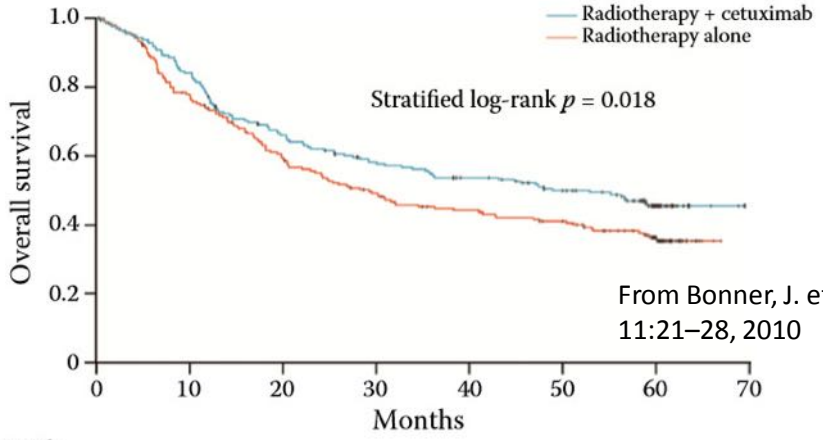




	Cisplatinum	Temozolomide
Mechanism of action	Alkylating	Alkylating (atypical)
Clinical data	Approved	Approved
Radiobiology	Synergic	Additive
Time	Short time	Long time
Drug concentration	Low dose	Higt dose
Cell Sensitive	-	MGMT

Targeted Therapies and Radiotherapy

Start with clinical data



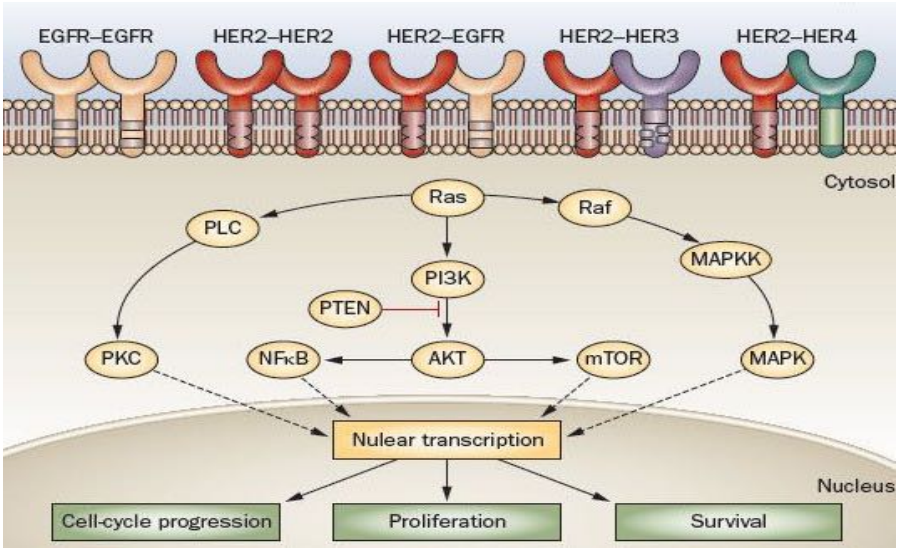
From Bonner, J. et al., Lancet Oncology 11:21–28, 2010

Number at risk								
Radiotherapy + cetuximab	211	177	136	117	105	90	49	..
Radiotherapy alone	213	162	122	98	85	77	49	..

Other cancers			
Glioblastoma	Adjuvant	Temozolomide	Survival benefit
Sarcoma	Neoadjuvant	Doxorubicin	Downstaging, improved organ preservation

[a]This is a limited overview, and concurrent chemoradiotherapy is used in most solid tumors either as a standard treatment or investigationally. For further details please refer to the organ-specific literature. Abbreviations: 5-FU, 5-fluorouracil; FHX, 5-FU, hydroxyurea and radiation; HNC, head and neck cancer; MMC, mitomycin C.

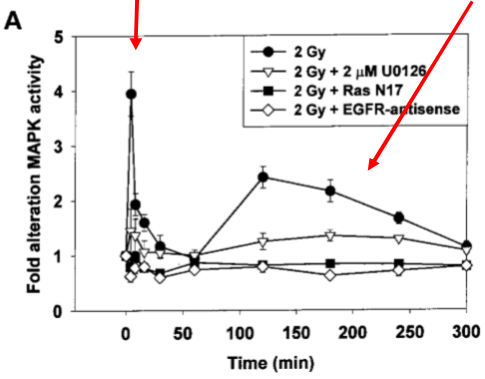
Epidermal Grown Factor Receptor (EGFR)



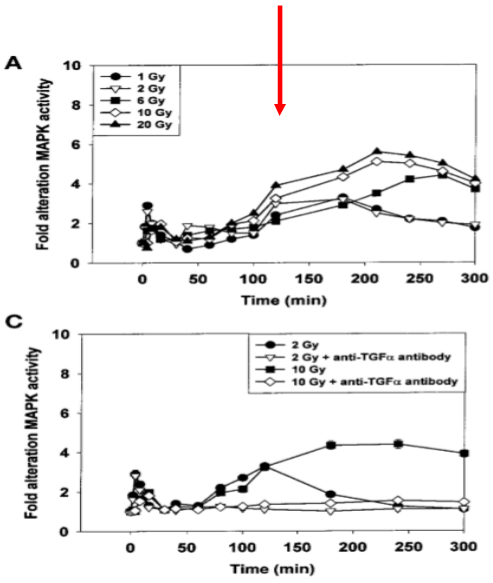
Chong CR1, Jänne PA. The quest to overcome resistance to EGFR-targeted therapies in cancer. Nat Med. 2013 Nov;19(11):1389-400.

IR induce activation ErbB receptor (0-10 min) independent of ligand blind

The same receptors are reactivates 60-180 min after IR



From 2 Gy to 10 Gy: ↑amplitude and duration secondary activation



Ionizing radiation actives survival and proliferation mechanism through simulated signalling via PI3K-AKT and Ras-MAPK (EGFR mediated)

Paul Dent,*†‡ Dean B. Reardon,*

Radiation-induced Epidermal Growth Factor Receptor Nuclear Import Is Linked to Activation of DNA-dependent Protein Kinase*

Received for publication, June 17, 2005
Published, JBC Papers in Press, July 5, 2005, DOI 10.1074/jbc.M506591200

Klaus Dittmann‡§, Claus Mayer‡, Birgit Fehrenbacher¶, Martin Schaller¶, Uma Raju‖, Luka Milas‖, David J. Chen**, Rainer Kehlbach‡‡, and H. Peter Rodemann‡

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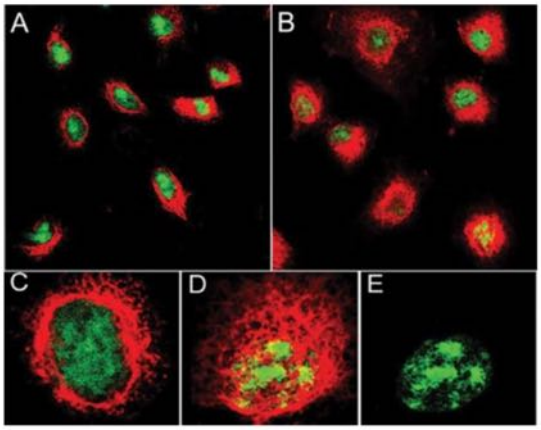

DNA
EGFR

Radiation stimulates the pathways activated by epidermal growth factor (EGFR) and in addition can the translocation of phosphorylated EGFR (pEGFR) into the nucleus.

Result in increased repair of DNA strand breaks → DNApK, Ku 70 e Ku 80

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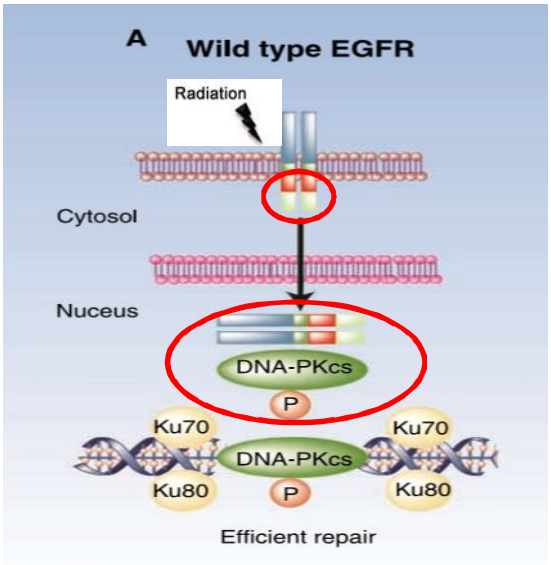
RT- induce cell damage activate repair:

-Increased PI3-K and DNA-PK
-EGFR enter nucleus bound Ku70/80 and increase DNA –DNA – PK complex repair



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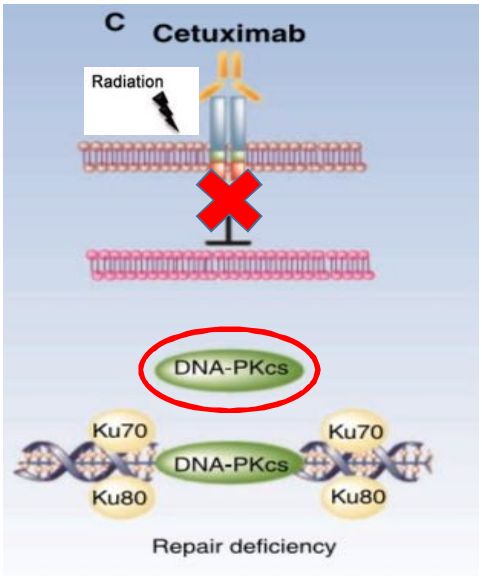
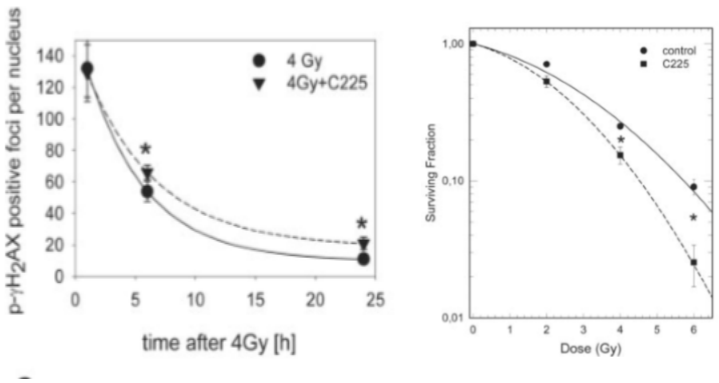


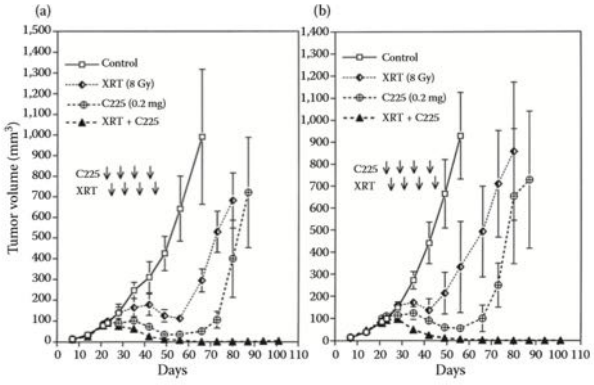
Interaction between EGFR-I (like Cetuximab) bound to

- decreasePI3-K activity
- EGFR and DNA-PK increases
- inhibits EGFR eneclaetion

In *vitro* and in *vivo* studies

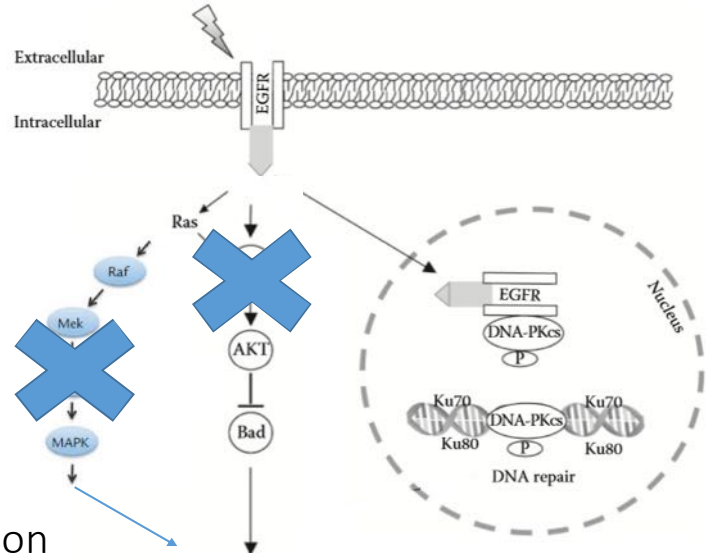


Klaus Dittmann, H. Peter Rodemann



Huang, S., and Harari, P., Clinical Cancer Research 6:2166–2174, 2000

RT and EGFR



↓ Repopulation

Proliferation

TABLE 10.2 Small-Molecule Inhibitors of EGFR Tyrosine Kinase in Clinical Use That Have Shown Radiosensitizing Capability

Agent	Molecule	Specificity	Status	Radiosensitization
		(a) Reversible Inhibitors		
Gelfitinib (Astra Zeneca)	Anilinoquinazoline, reversible TKI (half-life 48 h)	HER1	FDA approved NSCLC	GBM line U251 expresses high levels of EGFR, and is hypersensitive to inhibition of the EGFR signaling pathway. Gelfitinib enhanced radiosensitivity, maximal effectiveness of combined treatments was dose-dependent and time-dependent [44]
Erlotinib (Genentech, OSIP, Roche)	Anilinoquinazoline, reversible TKI (half-life 36 h)	HER1	FDA approved NSCLC, pancreatic cancer	Radiosensitizing effect of erlotinib, was evaluated in three human cancer cell lines with different levels of HER1/EGFR expression. Extent of radiosensitization was proportional to HER1/EGFR expression, and to autophosphorylation of EGFR (HER1) [45]
Lapatinib (GlaxoSmithKline)	6-Thiazolyl-quinazoline, reversible TKI (half-life 24 h)	HER1/2	Approved (breast cancer)	Lapatinib combined with fractionated radiotherapy caused tumor growth inhibition in xenografted EGFR$^+$ and HER2$^+$ breast cancers. Inhibition of downstream signaling to ERK1/2 and AKT correlates with sensitization in EGFR$^+$ and HER2$^+$ cells, respectively [46]
BMS599626, AC480 Bristol Myers Squibb	4-Amino-pyrrolotriazine, reversible TKI	HER1/2/4	Phase I clinical trials	AC480 significantly enhanced the radiosensitivity of HN-5 cells, expressing both EGFR and Her2. Mechanisms included cell cycle redistribution and inhibition of DNA repair [51]
AEE788 (Novartis)	Pyrrolopyramidine	HER1/2 VEGFR2	Phase II clinical trials	Combined treatment effective *in vitro*/*in vivo* with DU145 prostate cancer model whereas PC-3 adequately treated with XRT alone. Correlated with differences in EGFR expression and showed effects on cell proliferation and vascular destruction [47]
		(b) Irreversible Inhibitors		
Pelitinib/EKB-569 (Wyeth)	3-Cyanoquinoline	HER1/2	1/II	EKB-569 radiosensitizes squamous cell carcinoma *in vitro*. Mechanism involves selective targeting of IR-induced NFκB-dependent survival signaling [48]
Canertinib/ci-1033 (Pfizer)	Aniloquinazoline	HER1/2/4	II	Caco-2 and LoVo cells, with high levels of EGFR and ErbB2 TK activity, were affected by CI-1033, SW620 cells, with low levels were not. Whereas CI-1033 produced only minimal radiosensitization in LoVo and Caco-2 cells *in vitro*, the combination caused prolonged suppression of tumor growth in both tumor types compared with either treatment alone [49]
BIBW 2992 (Boehringer Ingeheim)		Her1/2	II	BIBW 2669 and BIBW 2992 had clear antiproliferative effects *in vitro* and *in vivo*, but cellular radiosensitization was minimal. There was an effect of combined treatment on tumor growth delay *in vivo* cancer treatment [50]

Radiotherapy and hormonotherapy

Start to clinical data

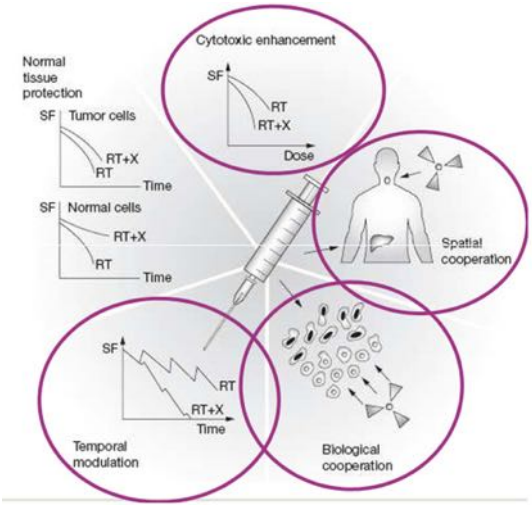
TABLE 51-15 Phase III Trials of External Beam Irradiation with or without Adjuvant Hormone Therapy for Locally Advanced Prostate Cancer

			bNED		DMF Survival		CSS		OS	
Trial	**Arms**	**Median Follow-up**	**5 yr**	**10 yr**	**5 yr**	**10 yr**	**5 yr**	**10 yr**	**5 yr**	**10 yr**
RTOG 85-31 ($n = 977$)	I: RT + goserelin (indefinitely)	7.6 yr (11 yr living)	62%	31%	85%	76%	91%	84%	76%	49%
	II: RT alone		44%	23%	71%	61%	87%	78%	71%	39%
			$p < .0001$		$p < .0001$		$p = .0052$		$p = .002$	
EORTC 22863 ($n = 415$)	I: RT + 3 yr GnRH	9.1 yr	76%	38%	90%	51%	94%	89%	78%	58%
	II: RT alone		45%	18%	71%	30%	79%	69%	62%	40%
			$p < .0001$		$p < .0001$		$p = .001$		$p = .0004$	
RTOG 86-10 ($n = 456$)	I: 4 mo TAS + RT	8.7 yr (11.9 yr living) 7.3 yr	36%	35%	66%	65%	85%	23%	73%	43%
	II: RT alone		15%	20%	59%	53%	80%	36%	71%	34%
			$p < .0001$		$p = .006$		$p = .01$		$p = .12$	
TROG 96.01 ($n = 818$)	I: RT alone	5.9 yr	38%	—	81%	NS	91%	NS	—	—
	II: 3 mo TAS + RT		52%	—	78%	NS	92%	NS	—	—
	III: 6 mo TAS + RT		56%	—	87%	—	94%	—	—	—
			$p = .002$ (3 mo) $p < .001$ (6 mo)		$p = .046$ (6 mo)		$p = .040$ (6 mo)			

bNED, biochemical no evidence of disease; DMF, disease/metastasis free; CSS, cause-specific survival; NS, not specified; OS, overall survival.

Combine Hormonotherapy with Radiotherapy

- Spatial cooperation
- Normal tissue protection
- Cytotoxic enhancement
- Biological cooperation
- Temporal modulation



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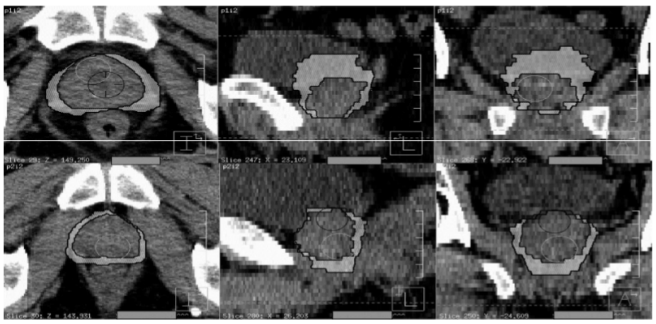
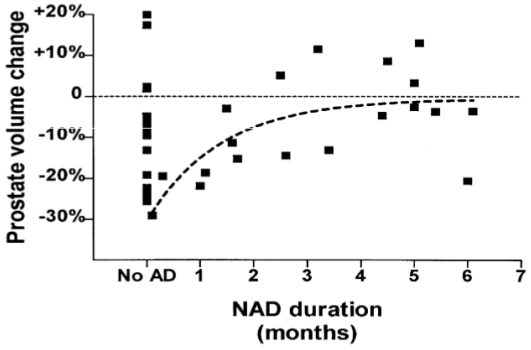
Neoadjuvant ADT: downsizing



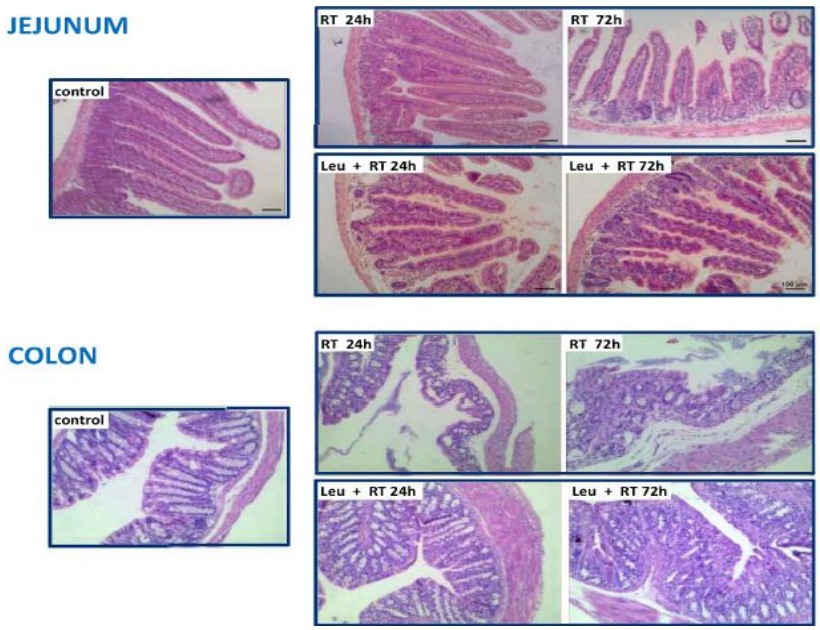


↓rectal, bladder and bower in high dose area→ normal tissue protection

Anticancer Res. 2015 Jul;35(7):3875-84.

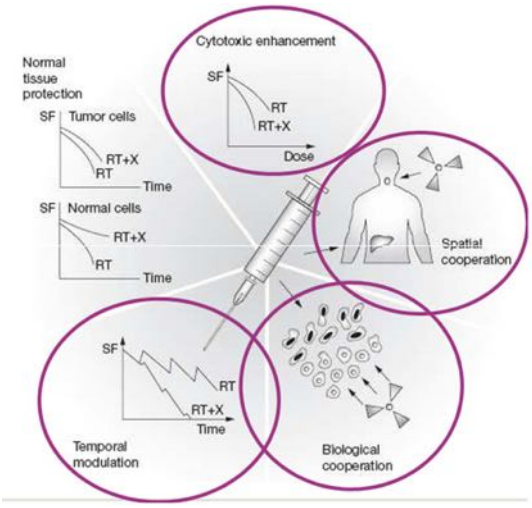
Protective Effect of Leuprorelin on Radiation-induced Intestinal Toxicity.

Mangoni M[1], Sottili M[2], Gerini C[2], Fucci R[2], Pini A[3], Calosi L[3], Bonomo P[2], Detti B[2], Greto D[2], Meattini I[2], Simontacchi G[2], Loi M[2], Scartoni D[2], Furfaro I[2], Pallotta S[4], Livi L[2].



Combine Hormonotherapy with Radiotherapy

- Spatial cooperation ✓
- Normal tissue protection ✓
- Biological cooperation
- Cytotoxic enhancement
- Temporal modulation



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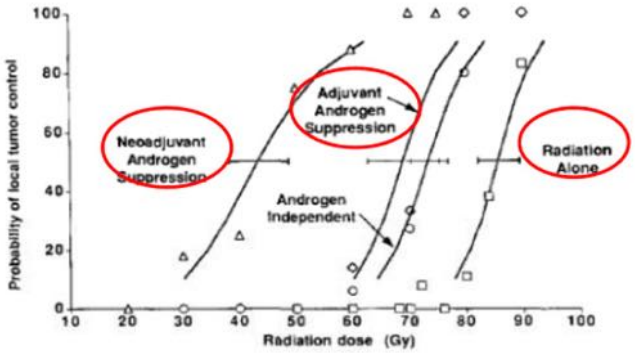
Biological effects of ADT and Radiotherapy

- The majority of cells are dependent on Androgen Receptor activation
- ADT decreases hypoxia
- ADT promotes apoptosis



Androgen Withdrawal in Patients Reduces Prostate Cancer Hypoxia: Implications for Disease Progression and Radiation Response

Michael Milosevic,[1,5] Peter Chung,[1,5] Chris Parker,[9] Robert Bristow,[1,4,5,8] Ants Toi,[2,6] Tony Panzarella,[3,7] Padraig Warde,[1,5] Charles Catton,[1,5] Cynthia Menard,[1,5] Andrew Bayley,[1,5] Mary Gospodarowicz,[1,5] and Richard Hill[4,8]

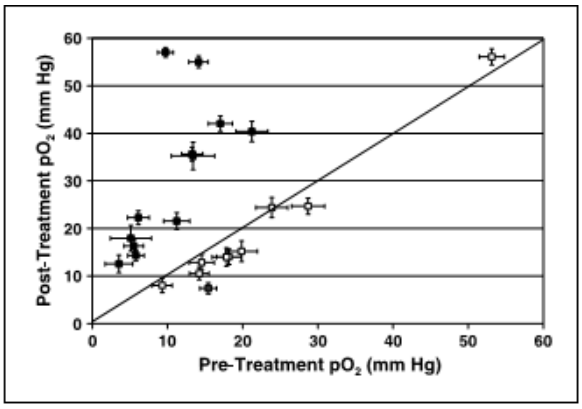
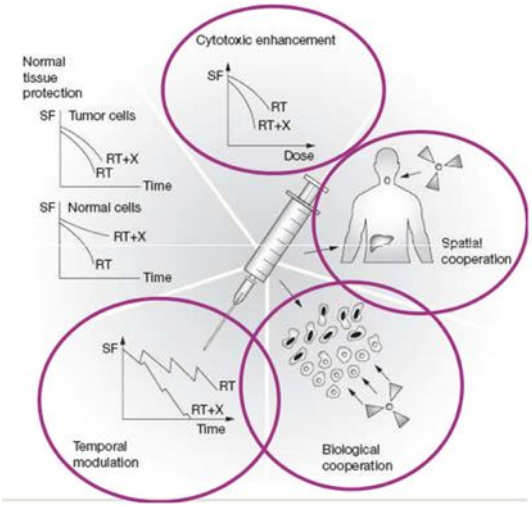


Figure 1. Posttreatment versus pretreatment marginal mean prostate cancer pO_2 levels in 22 patients. *Dark points,* significant ($P \leq 0.001$) changes in oxygenation with androgen withdrawal; *bars,* SEs. The line of unity is also shown.

Combine Hormonotherapy with Radiotherapy

- Spatial cooperation ✓
- Normal tissue protection ✓
- Biological cooperation ✓
- Cytotoxic enhancement
- Temporal modulation



Bentez SM 2007

Research

Open Access

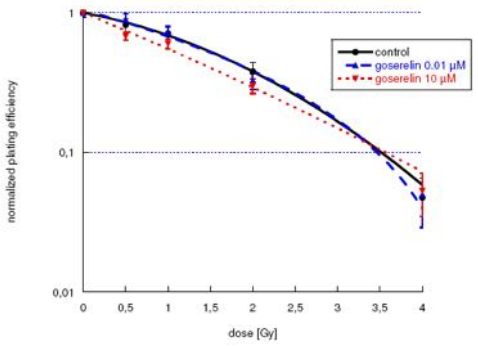
No supra-additive effects of goserelin and radiotherapy on clonogenic survival of prostate carcinoma cells *in vitro*

Robert M Hermann*[1], Dag Schwarten[1], Stefanie Fister[2], Carsten Grundker[2], Margret Rave-Frank[1], Mirko Nitsche[1], Andrea Hille[1], Paul Thelen[3], Heinz Schmidberger[4] and Hans Christiansen[1]

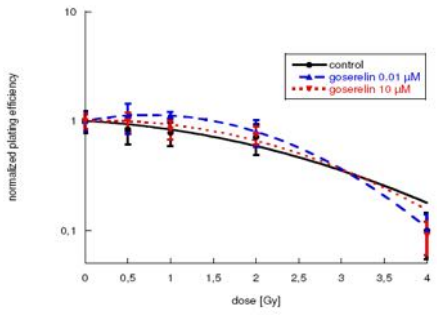
Address: [1]Department of Radiotherapy, University hospital, Robert-Koch-Str. 40, 37075 Göttingen, Germany, [2]Department of Gynecology, University hospital Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany, [3]Department of Urology, University hospital Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany and [4]Department of Radiotherapy, University hospital, Langenbeckstr. 1, 55131 Mainz, Germany

Email: Robert M Hermann* - ro.hermann@t-online.de; Dag Schwarten - djschwarten@web.de; Stefanie Fister - sfister@gwdg.de; Carsten Grundker - grundker@med.uni-goettingen.de; Margret Rave-Frank - mfraenk@med.uni-goettingen.de; Mirko Nitsche - mnitsche@med.uni-goettingen.de; Andrea Hille - a.hille@med.uni-goettingen.de; Paul Thelen - pthelen@gwdg.de; Heinz Schmidberger - H.Schmidberger@klinik.uni-mainz.de; Hans Christiansen - hans.christiansen@medizin.uni-goettingen.de

* Corresponding author



LNCaP

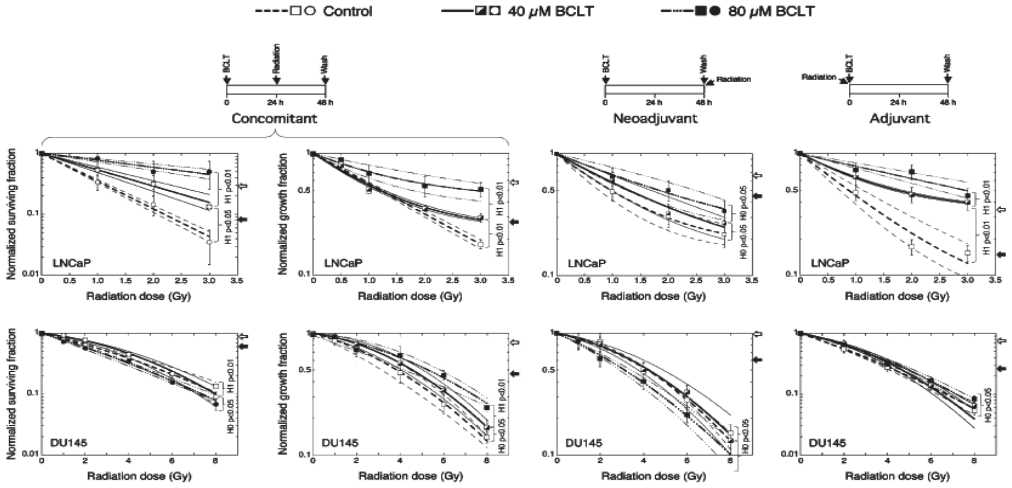


PC-3

Antagonistic Interaction Between Bicalutamide™ (Casodex®) and Radiation in Androgen-Positive Prostate Cancer LNCaP Cells

Laurent Quéro,[1,2,3] Nicole Giocanti,[1,2] Christophe Hennequin,[1,2,3] and Vincent Favaudon[1,2*]

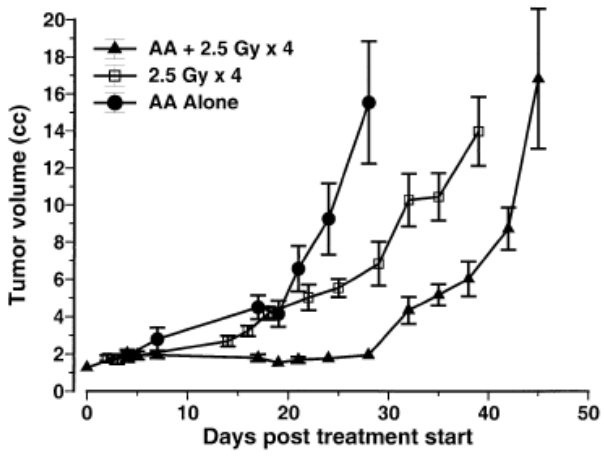
[1]Institut Curie, Bât. 110-112, Centre Universitaire, Orsay, France
[2]INSERM, U612, Bât. 110-112, Centre Universitaire, Orsay, France
[3]Hôpital Saint Louis, Assistance Publique-Hôpitaux de Paris, Paris, France

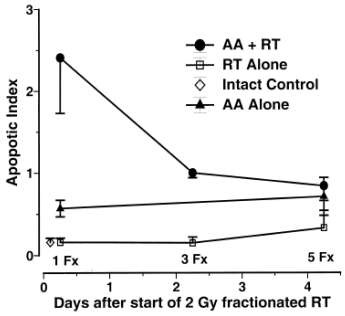


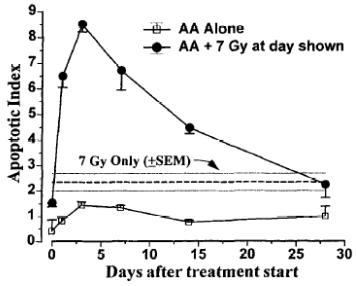
BIOLOGY CONTRIBUTION

THE EARLY SUPRA-ADDITIVE APOPTOTIC RESPONSE OF R3327-G PROSTATE TUMORS TO ANDROGEN ABLATION AND RADIATION IS NOT SUSTAINED WITH MULTIPLE FRACTIONS

Alan Pollack, M.D., Ph.D.,* Faramarz Ashoori, M.D.,† Charles Sikes, B.S.,† Daryl Lim Joon, M.D.,† Andrew C. von Eschenbach, M.D.,‡ Gunar K. Zagars, M.D.,* and Marvin L. Meistrich, Ph.D.†

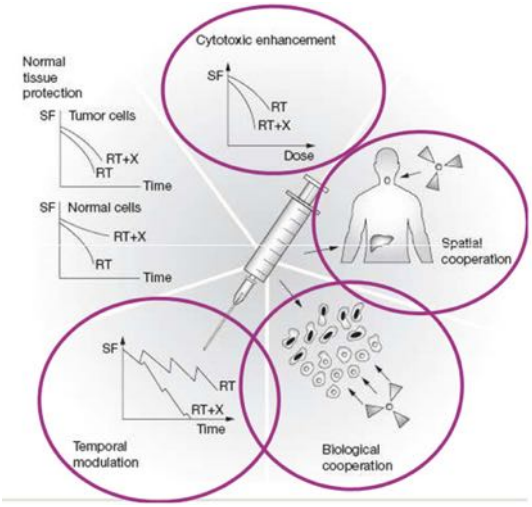






Combine Hormonotherapy with Radiotherapy

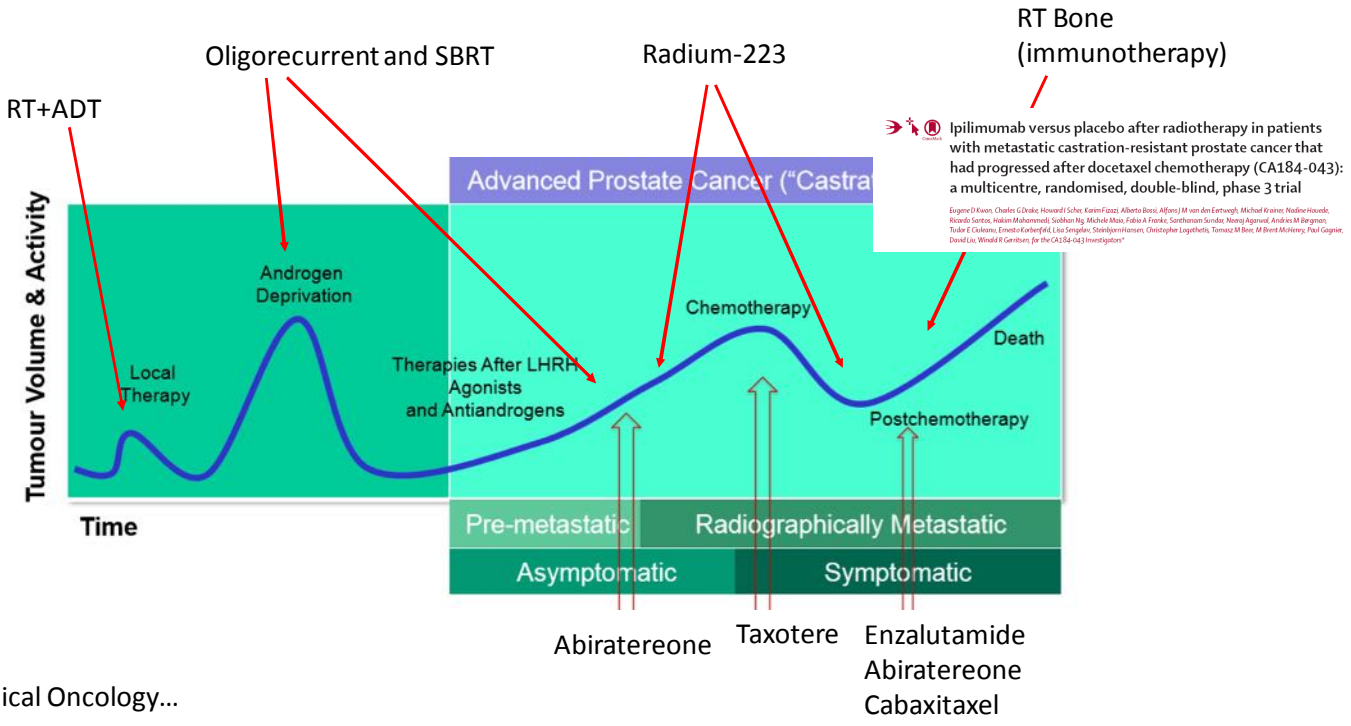
- Spatial cooperation ✓
- Normal tissue protection ✓
- Biological cooperation ✓
- Cytotoxic enhancement ≈
- Temporal modulation ≈



Certainly Addictive…maybe
Superadditive…but…new molecules…

Bentez SM 2007

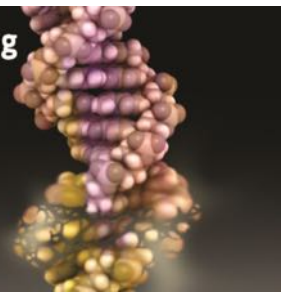
Prostate Cancer 2015

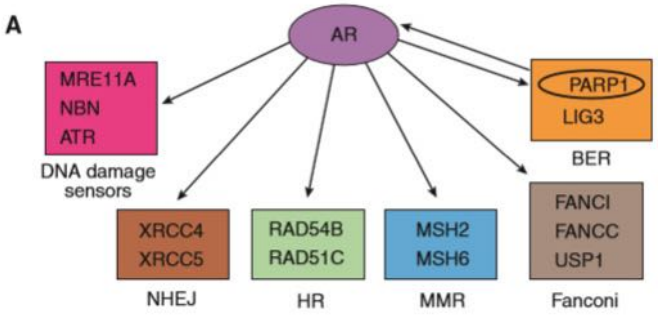


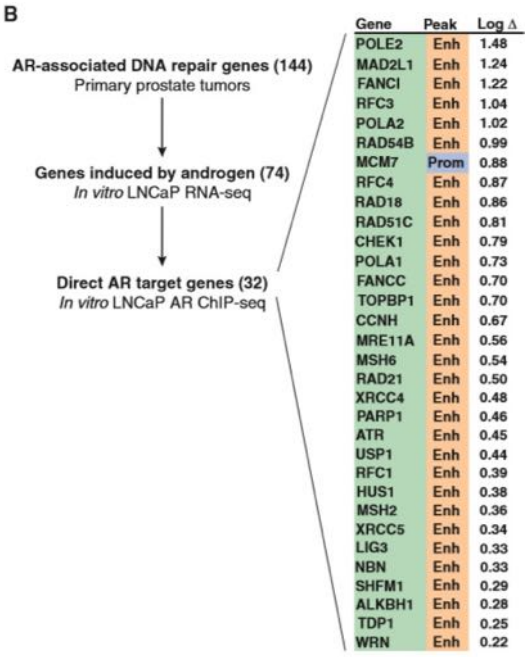
…still Medical Oncology…

Androgen Receptor Signaling Regulates DNA Repair in Prostate Cancers

William R. Polkinghorn[1,4], Joel S. Parker[10,11], Man X. Lee[1], Elizabeth M. Kass[2], Daniel E. Spratt[1], Phillip J. Iaquinta[1], Vivek K. Arora[1,5], Wei-Feng Yen[3], Ling Cai[1], Deyou Zheng[9], Brett S. Carver[1,6], Yu Chen[1,5], Philip A. Watson[1], Neel P. Shah[1], Sho Fujisawa[8], Alexander G. Goglia[4], Anuradha Gopalan[7], Haley Hieronymus[1], John Wongvipat[1], Peter T. Scardino[6], Michael J. Zelefsky[1], Maria Jasin[2], Jayanta Chaudhuri[3], Simon N. Powell[4], and Charles L. Sawyers[1]



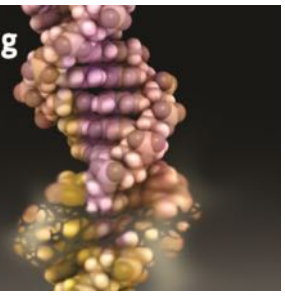


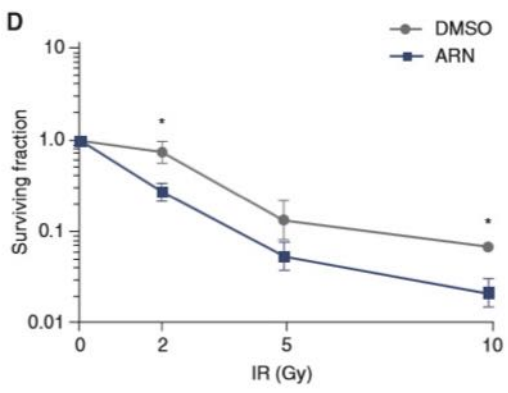


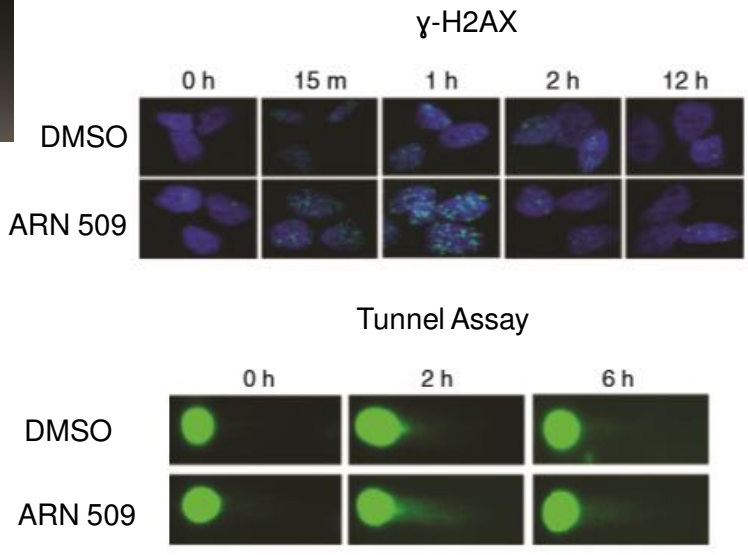
Gene	Peak	Log Δ
POLE2	Enh	1.48
MAD2L1	Enh	1.24
FANCI	Enh	1.22
RFC3	Enh	1.04
POLA2	Enh	1.02
RAD54B	Enh	0.99
MCM7	Prom	0.88
RFC4	Enh	0.87
RAD18	Enh	0.86
RAD51C	Enh	0.81
CHEK1	Enh	0.79
POLA1	Enh	0.73
FANCC	Enh	0.70
TOPBP1	Enh	0.70
CCNH	Enh	0.67
MRE11A	Enh	0.56
MSH6	Enh	0.54
RAD21	Enh	0.50
XRCC4	Enh	0.48
PARP1	Enh	0.46
ATR	Enh	0.45
USP1	Enh	0.44
RFC1	Enh	0.39
HUS1	Enh	0.38
MSH2	Enh	0.36
XRCC5	Enh	0.34
LIG3	Enh	0.33
NBN	Enh	0.33
SHFM1	Enh	0.29
ALKBH1	Enh	0.28
TDP1	Enh	0.25
WRN	Enh	0.22

Androgen Receptor Signaling Regulates DNA Repair in Prostate Cancers

William R. Polkinghorn[1,4], Joel S. Parker[10,11], Man X. Lee[1], Elizabeth M. Kass[2], Daniel E. Spratt[1], Phillip J. Iaquinta[1], Vivek K. Arora[1,5], Wei-Feng Yen[3], Ling Cai[1], Deyou Zheng[9], Brett S. Carver[1,6], Yu Chen[1,5], Philip A. Watson[1], Neel P. Shah[1], Sho Fujisawa[8], Alexander G. Goglia[4], Anuradha Gopalan[7], Haley Hieronymus[1], John Wongvipat[1], Peter T. Scardino[6], Michael J. Zelefsky[1], Maria Jasin[2], Jayanta Chaudhuri[3], Simon N. Powell[4], and Charles L. Sawyers[1]

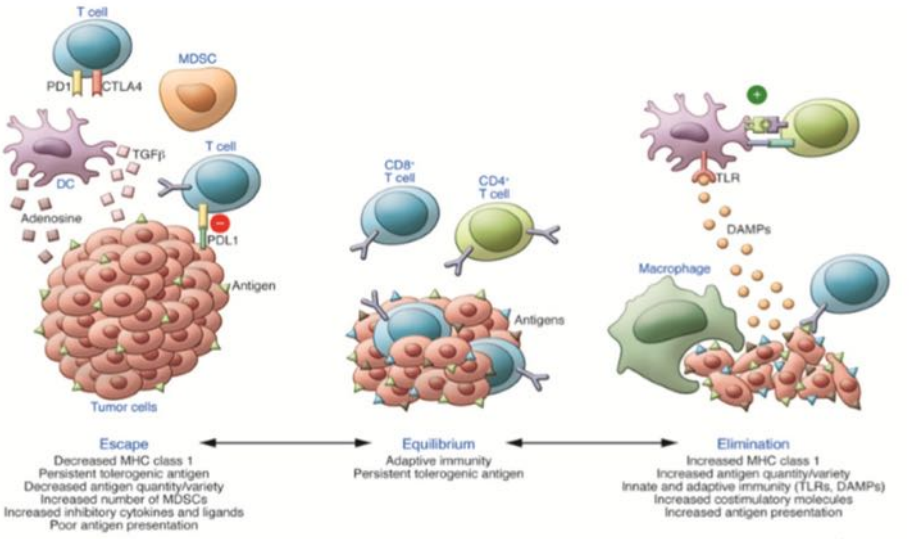






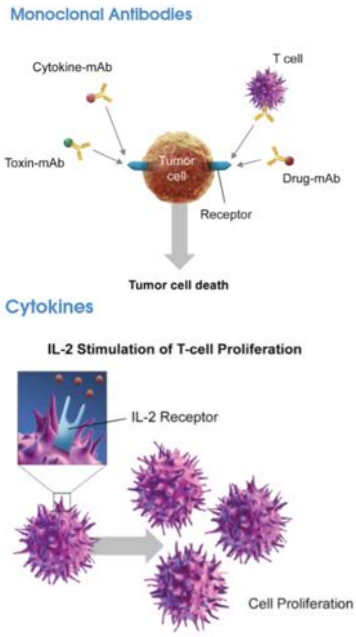
Radiotherapy and Immunotherapy: new radiobiology

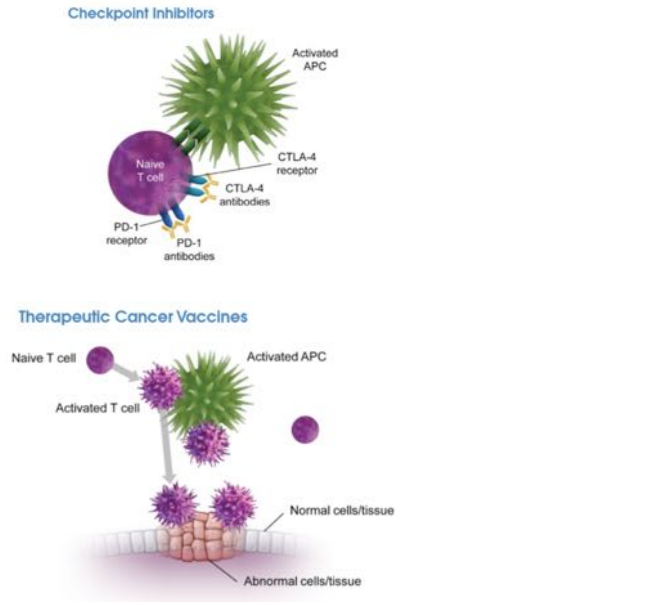
Immunoediting theory



Immunotherapy

Mechanism of Action of Immunotherapies





CANCER IMMUNOTHERAPY: FUNDAMENTAL CONCEPTS AND EMERGING ROLE

Old-Idea…

…New concept!

….commonly it was thought that radiation therapy exerted <u>immunosuppressive</u> effects….

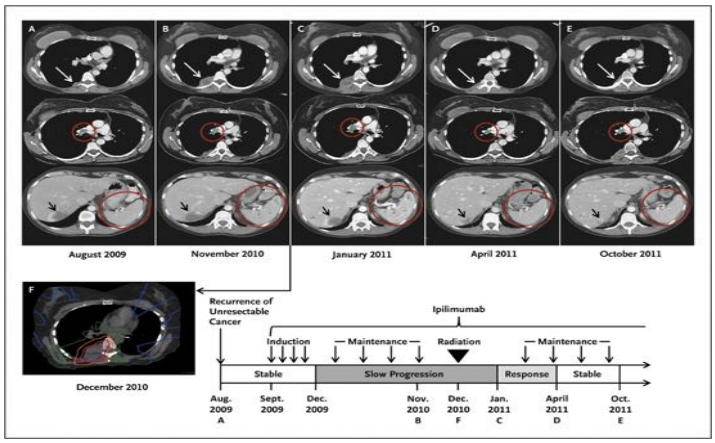
↓

…..the true relationship between radiation and the immune system is certainly more complex, and it appears that irradiation would be more <u>immunomodulatory</u> rather than only immunosuppressive.

Abscopal Effect

The term "abscopal", deriving from the latin ab (away from) and the ancient Greek skopos (target) was introduced in 1953 (*Mole RH et al.*) to describe a rare phenomenon in which the effects of RT are seen outside of the treated area (distant Bystander).

In 2012 two case reports (*Postow MA, et al. Stamell EF et al.*) highlighted the immunoadjuvant effect of RT in melanoma, which was classically thought to be an immunogenic tumor



Postow MA et al. N Engl J Med 2012;366:925-931.

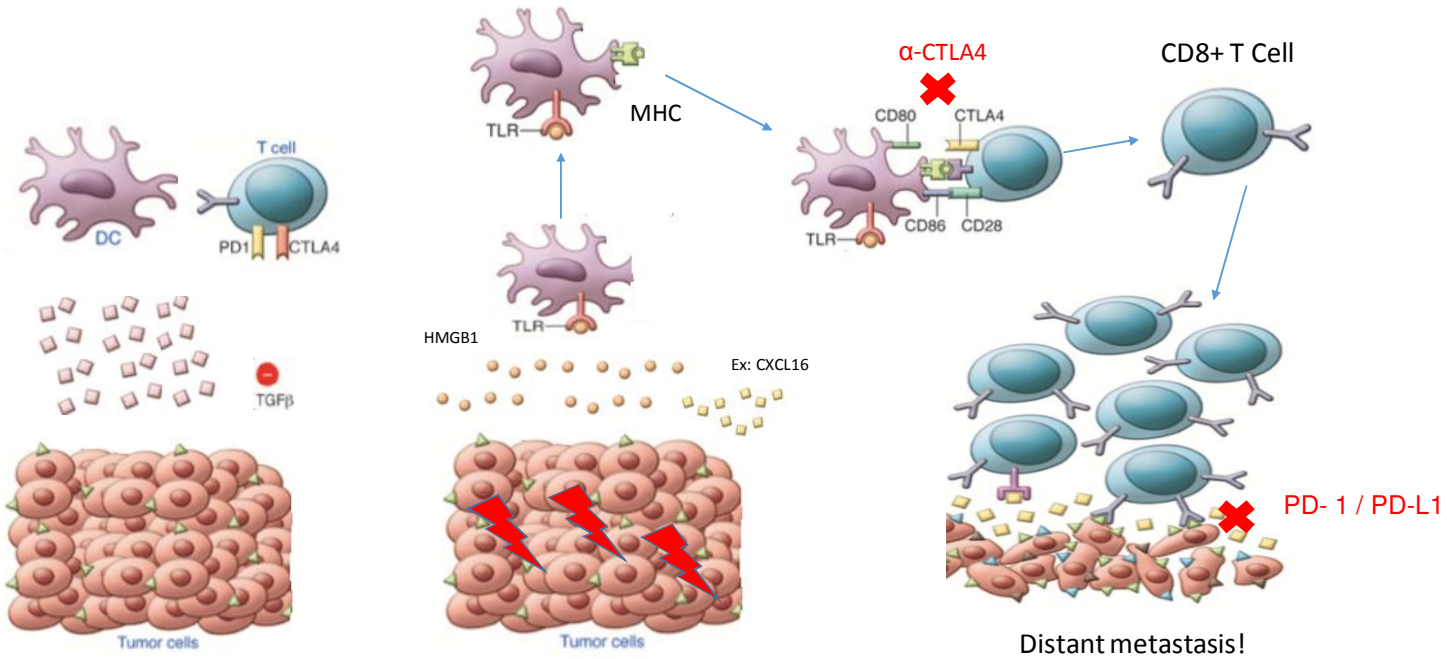
Abscopal effect: How RT counters Immune evasion

- Antigen quantity, variety and presentation: in *vitro* and in *vivo* mouse studies indicate that tumor irradiation exposes this complex antigenic environment by generating new peptides and increasing the pool of intracellular peptides for cross-presentation (Reits EA, et al. Sharma A, et al). RT augments MHC-I expression (Zeng J et al).

- Bridging innate and adaptive immunity: RT causes dying tumor cells to release high mobility group box 1 (HMGB-1), a well-described "danger signal" that binds TLR4 . Tumor antigen processing and presentation on MHC-I molecules is dependent on the HMGB-1/TLR4 interaction. This suggests a link between innate and adaptive responses (Apetoh et al)

- Inducing a T cell response: The most recent and promising immunotherapeutics shift the tumor microenvironment in favor of T cell activation by blocking negative inhibitory molecules (CTLA4, PD-1) (Drew M. Pardoll).

Abscopal Effect



Ongoing trials studying combination RT and immunotherapy

ClinicalTrials.gov identifier	Disease site	Design	Phase	Primary outcome measure	Immunotherapy	RT	Treatment timing
NCT01449279	Melanoma (advanced)	1 arm: ipilimumab prior to palliative RT	1	Safety	Ipilimumab	Palliative	RT <2 days after ipilimumab
NCT01689974	Melanoma (advanced)	2 arms, randomized: ipilimumab prior to RT or ipilimumab alone	2	Tumor response	Ipilimumab	30 Gy in 5 fractions	RT starts 4 days prior to ipilimumab
NCT01557114	Melanoma (advanced)	1 arm: ipilimumab prior to RT	1	Maximum tolerated dose	Ipilimumab	9, 15, 18, 24 Gy in 3 fractions	RT from week 4 to week 10 of ipilimumab
NCT01565837	Melanoma (advanced)	1 arm: ipilimumab prior to SRT	2	Safety, tolerability	Ipilimumab	SRT to 1–5 lesions	RT after first dose of ipilimumab, before week 6
NCT01497808	Melanoma (advanced)	1 arm: SRT prior to ipilimumab	1/2	Dose-limiting toxicity	Ipilimumab	SRT to 1 lesion	RT prior to ipilimumab
NCT00861614	Prostate (castrate resistant)	2 arms, randomized: RT prior to ipilimumab vs. RT alone	3	Overall survival	Ipilimumab	Not specified	RT prior to ipilimumab
NCT01347034	Soft tissue sarcomas	2 arms, nonrandomized: RT alone vs. RT plus dendritic cell therapy, then surgery	2	Immune response	Autologous dendritic cell intratumoral injection	Conventional RT with boost	Dendritic cell injection during RT
NCT01421017	Breast cancer with skin metastases	1 arm: imiquimod to all skin metastases plus RT to select skin metastases	1/2	Tumor response	Topical imiquimod	600 cGy in 5 fractions	Imiquimod starts evening of first RT
NCT00751270	Supratentorial malignant glioma	1 arm: surgical resection with Adv-tk injection, followed by pro-drug (valacyclovir) and RT	1	Safety; immune response	Adv-tk injection into tumor bed	Standard of care	Start RT 3 days after Adv-tk injection, during prodrug therapy
NCT01595321	Pancreatic cancer following resection (stage R0)	1 arm: cyclophosphamide, vaccine, SRT, and FOLFIRINOX	1	Toxicity	Low-dose cyclophosphamide and vaccine	6.6 Gy in 5 fractions	Start RT <12 weeks following operation and 7–14 days after first vaccine dose
NCT01436968	Prostate cancer, localized, intermediate or high risk	2 arms, double-blind, randomized: Adv-tk vs. placebo followed by valacyclovir; EBRT with or without androgen deprivation therapy	3	Disease-free survival	Adv-tk intraprostate injection	Standard EBRT	Adv-tk prior to, immediately prior to, and during EBRT

Adv-tk, adenovirus-mediated herpes simplex virus thymidine kinase; EBRT, external beam RT.

Conclusion (1)

- Oncology has increasingly become a multidisciplinary field of medicine: in the past 20 years there has been an explosion of preclinical and clinical efforts to combine therapies for improved outcomes.
- Researchers have learned a great deal about the interactions between CHT and IR from clinical trials.
- Laboratory investigations demonstrated key molecular targets and pathways that can potentially be exploited for improved outcomes.

Conclusion(2)

- The combination of chemotherapy and irradiation has changed the management approach in several neoplasms
- Radio-hormone-therapy is the standard of care for local treatment in prostate cancer
- New hormone therapy + IR in prostate cancer!

- The next future is radio-immunotherapy….

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Education Original Article

Current Status and Recommendations for the Future of Research, Teaching, and Testing in the Biological Sciences of Radiation Oncology: Report of the American Society for Radiation Oncology Cancer Biology/Radiation Biology Task Force, Executive Summary

- Although the ability to deliver higher and more accurate doses of radiation has advanced the treatment of many cancers, maximizing further improvements in the outcome of cancer patients treated with radiation therapy will likely not depend on technological improvements in dose delivery, but instead will depend on advances in understanding and using the effect of radiation as a potent modulator of genetic and cellular activity.

Grazie per l'attenzione!