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

Dott. Triggiani MD, PhD Student

Start with clinical data

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

*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; DHX, 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

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

![Therapeutic Ratio Diagram](image-url)
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

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.
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 repairable, 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 low doses of the two agents and cisplatinum before RT.

DOSE:
- 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]

TIME:
- 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 subadditve 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 (TMZ) is an oral alkylating agent used as a first-line treatment for Glioblastoma Multiforme.

**Temozolomide e Radiotherapy**

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

---

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

ANTHONY J. CHAMBERS, F.R.C.R., Ph.D.,*† ELLIOT M. RAFF, M.D.,† CHRISTINE MARESDALE, B.SC.,† NADIA LYNCHYKOPF, B.SC.,† AND SUSAN C. SHORT, F.R.C.R., Ph.D.†

From the *Brighton and Sussex Medical School and †Genomic Damage and Stability Centre, University of Sussex, Falmer, UK; ‡Royal Sussex County Hospital, Eastern Road, Brighton, UK; and ‡UCL Cancer Institute, Paul O’Gorman Building, University College London, London, UK.

A. MGMT Repair

<75%

O6-meG

TMZ

≈10%

N7-meG

B. Mismatch Repair

Futile Cycling

Degradation

Ubiquitination

DNA Strand breaks

Apoptosis

Cytotoxicity

C. Base Excision Repair

Inhibitor of BER (MX)

Blockage of DNA Replication

DNA Strand breaks

Apoptosis

Cell Survival

Cytotoxicity
Conclusions

<table>
<thead>
<tr>
<th></th>
<th>Cisplatinum</th>
<th>Temozolomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Alkylating</td>
<td>Alkylating (atypical)</td>
</tr>
<tr>
<td>Clinical data</td>
<td>Approved</td>
<td>Approved</td>
</tr>
<tr>
<td>Radiobiology</td>
<td>Synergic</td>
<td>Additive</td>
</tr>
<tr>
<td>Time</td>
<td>Short time</td>
<td>Long time</td>
</tr>
<tr>
<td>Drug concentration</td>
<td>Low dose</td>
<td>High dose</td>
</tr>
<tr>
<td>Cell Sensitive</td>
<td>-</td>
<td>MGMT</td>
</tr>
</tbody>
</table>
Targeted Therapies and Radiotherapy

Start with clinical data

From Bonner, J. et al., Lancet Oncology
11:21–28, 2010
Epidermal Grown Factor Receptor (EGFR)

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

The same receptors are reactivates 60-180 min after IR

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

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

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

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
Interaction between EGFR-I (like Cetuximab) bound to
- decrease PI3-K activity
- EGFR and DNA-PK increases
- inhibits EGFR eneclaetion

**In vitro** and **in vivo** studies

Klaus Dittmann, H. Peter Rodemann

RT and EGFR

\[ \downarrow \text{Repopulation} \]

\[ \text{Proliferation} \]

<table>
<thead>
<tr>
<th>TABLE 10.2</th>
<th>Small-Molecule Inhibitors of EGFR Tyrosine Kinase in Clinical Use That Have Shown Radiosensitizing Capability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
<td><strong>Molecule</strong></td>
</tr>
<tr>
<td>Gelatinib (Astra Zeneca)</td>
<td>Anilinoquinazoline, reversible TKI (half-life 48 h)</td>
</tr>
<tr>
<td>Erlotinib (Genentech, OSI-P, Roche)</td>
<td>Anilinoquinazoline, reversible TKI (half-life 36 h)</td>
</tr>
<tr>
<td>Lapatinib (GluoxSmithKline)</td>
<td>6-Thiazolylquinazoline, reversible TKI (half-life 24 h)</td>
</tr>
<tr>
<td>BM599626, AC480</td>
<td>4-Aminopyrrolotriazine, reversible TKI</td>
</tr>
<tr>
<td><strong>AEE788</strong> (Novartis)</td>
<td>Pyrrolopyrimidine</td>
</tr>
<tr>
<td><strong>(b) Irreversible Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Peltinib/EKB-569 (Wyeth)</td>
<td>3-Cyanoquinoline</td>
</tr>
<tr>
<td>Canertinib/ci-1033 (Pfizer)</td>
<td>Anilinoquinazoline</td>
</tr>
<tr>
<td>BBW 2669 (Roehringer Ingeheim)</td>
<td>Hert1/2</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arms</th>
<th>Median Follow-up</th>
<th>MNED 5 yr</th>
<th>MNED 10 yr</th>
<th>DMF Survival 5 yr</th>
<th>DMF Survival 10 yr</th>
<th>CSS 5 yr</th>
<th>CSS 10 yr</th>
<th>OS 5 yr</th>
<th>OS 10 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 05-01 (n = 977)</td>
<td>I: RT + goserelin (pedestal)</td>
<td>7.0 yr (11 yr living)</td>
<td>62%</td>
<td>58%</td>
<td>85%</td>
<td>76%</td>
<td>94%</td>
<td>84%</td>
<td>79%</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>II: RT alone</td>
<td></td>
<td>44%</td>
<td>35%</td>
<td>61%</td>
<td>67%</td>
<td>73%</td>
<td>71%</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>p</em> &lt;.001</td>
<td><em>p</em> &lt;.001</td>
<td><em>p</em> = .0052</td>
<td><em>p</em> = .002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC 22963 (n = 411)</td>
<td>I: RT + 3 yr GnRH</td>
<td>9.1 yr</td>
<td>74%</td>
<td>38%</td>
<td>90%</td>
<td>61%</td>
<td>94%</td>
<td>80%</td>
<td>79%</td>
<td>59%</td>
</tr>
<tr>
<td></td>
<td>II: RT alone</td>
<td></td>
<td>45%</td>
<td>19%</td>
<td>71%</td>
<td>50%</td>
<td>79%</td>
<td>62%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>p</em> &lt;.001</td>
<td><em>p</em> &lt;.001</td>
<td><em>p</em> &gt; .01</td>
<td><em>p</em> &gt; .001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 86-10 (n = 409)</td>
<td>I: 4 mo TAS + RT</td>
<td>8.7 yr (11.9 yr living)</td>
<td>34%</td>
<td>35%</td>
<td>66%</td>
<td>65%</td>
<td>85%</td>
<td>23%</td>
<td>73%</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td>II: RT alone</td>
<td></td>
<td>15%</td>
<td>20%</td>
<td>56%</td>
<td>53%</td>
<td>80%</td>
<td>30%</td>
<td>71%</td>
<td>34%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>p</em> &lt;.001</td>
<td><em>p</em> &gt; .05</td>
<td><em>p</em> &gt; .01</td>
<td><em>p</em> &gt; .12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THOG 90-01 (n = 813)</td>
<td>I: RT alone</td>
<td>5.9 yr</td>
<td>36%</td>
<td>—</td>
<td>81%</td>
<td>NS</td>
<td>91%</td>
<td>NS</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>II: 3 mo TAS + RT</td>
<td></td>
<td>52%</td>
<td>—</td>
<td>78%</td>
<td>NS</td>
<td>92%</td>
<td>NS</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>III: 6 mo TAS + RT</td>
<td></td>
<td>50%</td>
<td>—</td>
<td>87%</td>
<td>—</td>
<td>94%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

(MNED, 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

Neoadjuvant ADT: downsizing

↓rectal, bladder and bower in high dose area → normal tissue protection
Combine Hormonotherapy with Radiotherapy

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

Bentez SM 2007
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,1,4,8 Ants Tol,5
Tony Panzarella,3,7 Padraig Warde,1,5 Charles Catton,1,2 Cynthia Menard,1,3
Andrew Bayley,1,5 Mary Gospodarowicz,1,5 and Richard Hill1,4,5

Figure 1. Pretreatment versus posttreatment marginal mean prostate cancer $pO_2$ levels in 22 patients. Dark points, significant ($P < 0.001$) changes in oxygenation with androgen withdrawal; bars, SEIs. 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

---

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: 1Department of Radiology, University hospital, Robert Koch str. 40, 37075 Göttingen, Germany; 2Department of Gynecology, University hospital Göttingen, Robert Koch str. 40, 37075 Göttingen, Germany; 3Department of Urology, University hospital Göttingen, Robert Koch str. 40, 37075 Göttingen, Germany and 4Department of Radiotherapy, University hospital, Langenbeckstr. 1, 35394 Mainz, Germany

Email: Robert M Hermann - r.m.hermann@med.uni-goettingen.de; Dag Schwarten - d.schwarten@med.uni-goettingen.de; Stefanie Fister - stefanie.fister@med.uni-goettingen.de; Carsten Grundker - carsten.grundker@med.uni-goettingen.de; Margret Rave-Frank - margret.rave-frank@med.uni-goettingen.de; Mirko Nitsche - mirko.nitsche@med.uni-goettingen.de; Andrea Hille - andrea.hille@med.uni-goettingen.de; Paul Thelen - p.thelen@med.uni-goettingen.de; Heinz Schmidberger - h.schmidberger@med.uni-mainz.de; Hans Christiansen - hans.christiansen@med.uni-goettingen.de

* Corresponding author

---

Research

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: 1Department of Radiology, University hospital, Robert Koch str. 40, 37075 Göttingen, Germany; 2Department of Gynecology, University hospital Göttingen, Robert Koch str. 40, 37075 Göttingen, Germany; 3Department of Urology, University hospital Göttingen, Robert Koch str. 40, 37075 Göttingen, Germany and 4Department of Radiotherapy, University hospital, Langenbeckstr. 1, 35394 Mainz, Germany

Email: Robert M Hermann - r.m.hermann@med.uni-goettingen.de; Dag Schwarten - d.schwarten@med.uni-goettingen.de; Stefanie Fister - stefanie.fister@med.uni-goettingen.de; Carsten Grundker - carsten.grundker@med.uni-goettingen.de; Margret Rave-Frank - margret.rave-frank@med.uni-goettingen.de; Mirko Nitsche - mirko.nitsche@med.uni-goettingen.de; Andrea Hille - andrea.hille@med.uni-goettingen.de; Paul Thelen - p.thelen@med.uni-goettingen.de; Heinz Schmidberger - h.schmidberger@med.uni-mainz.de; Hans Christiansen - hans.christiansen@med.uni-goettingen.de

* Corresponding author
Antagonistic Interaction Between Bicalutamide\textsuperscript{TM} (Casodex\textsuperscript{TM}) and Radiation in Androgen-Positive Prostate Cancer LNCaP Cells

Laurent Quéro,\textsuperscript{1,2,3} Nicole Giocanti,\textsuperscript{1,2} Christophe Hemequin,\textsuperscript{1,2,3} and Vincent Favaudon\textsuperscript{1,2,4}

\textsuperscript{1}Institut Curie, Bât. 110-112, Centre Universitaire, Orsay, France
\textsuperscript{2}INSERM, U902, Bât. 110-112, Centre Universitaire, Orsay, France
\textsuperscript{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.,* FAREEZA ASHBORE, M.D.,* CHARLES SIKES, B.S.,* DARYL LIM YOON, M.D.,* ANDREW C. VAN ESCHENBACH, M.D.,* GUNAR K. ZAGARI, M.D.,* AND MARVIN L. MEISTER, PH.D.*
Combine Hormonotherapy with Radiotherapy

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

Certainly Addictive...maybe  
Superadditive...but...new molecules...

Prostate Cancer 2015

- RT+ADT
- Oligorecurrent and SBRT
- Radium-223
- RT Bone (immunotherapy)

...still Medical Oncology...
Androgen Receptor Signaling Regulates DNA Repair in Prostate Cancers


A

- **AR**
- MRE11A
- NBN
- ATR
- DNA damage sensors
  - XRCC4
  - XRCC5
- PARP1
- LIG3
- BER
- NHEJ
- HR
- MMR
- FANCD1
- FANCC
- USP1

B

- **AR-associated DNA repair genes (144)**
- **Primary prostate tumors**
- Genes induced by androgen (74)
  - In vitro LNCaP RNA-seq
- Direct AR target genes (32)
  - In vitro LNCaP AR ChIP-seq

C

- **γ-H2AX**
  - DMSO
  - ARN 509

D

- **Surviving fraction**
  - IR (Gy)
  - **DMSO**
  - **ARN**

- **Tunnel Assay**
  - DMSO
  - ARN 509

- **Graph**
  - Surviving fraction vs. IR (Gy)
  - 0, 2, 6 h
Radiotherapy and Immunotherapy: new radiobiology

Immunoediting theory
Mechanism of Action of Immunotherapies

Old-Idea...

...commonly it was thought that radiation therapy exerted **immunosuppressive** effects....

↓

...the true relationship between radiation and the immune system is certainly more complex, and it appears that irradiation would be more **immunomodulatory** 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.

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).
Ongoing trials studying combination RT and immunotherapy

<table>
<thead>
<tr>
<th>Clinical/Trials.gov Identifier</th>
<th>Disease site</th>
<th>Design</th>
<th>Phase</th>
<th>Primary outcome</th>
<th>ImmunoTherapy</th>
<th>RT</th>
<th>Treatment timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01449279</td>
<td>Melanoma (advanced)</td>
<td>1 arm: ipilimumab prior to RT</td>
<td>1</td>
<td>Tumor response</td>
<td>Ipilimumab</td>
<td>30 Gy in 5 fractions</td>
<td>RT &lt;2 days after ipilimumab, RT starts 4 days prior to ipilimumab</td>
</tr>
<tr>
<td>NCT01689974</td>
<td>Melanoma (advanced)</td>
<td>2 arms, randomized: ipilimumab prior to RT or ipilimumab alone</td>
<td>2</td>
<td>Tumor response</td>
<td>Ipilimumab</td>
<td>30 Gy in 5 fractions</td>
<td>RT starts 4 days prior to ipilimumab</td>
</tr>
<tr>
<td>NCT01557714</td>
<td>Melanoma (advanced)</td>
<td>1 arm: ipilimumab prior to RT</td>
<td>2</td>
<td>Safety, tolerability</td>
<td>Ipilimumab</td>
<td>30 Gy in 5 fractions</td>
<td>RT &lt;2 days after ipilimumab, RT starts 4 days prior to ipilimumab</td>
</tr>
<tr>
<td>NCT01566837</td>
<td>Melanoma (advanced)</td>
<td>1 arm: SRT</td>
<td>1</td>
<td>Tumor response</td>
<td>Ipilimumab</td>
<td>30 Gy in 5 fractions</td>
<td>RT &lt;2 days after ipilimumab, RT starts 4 days prior to ipilimumab</td>
</tr>
<tr>
<td>NCT01497808</td>
<td>Melanoma (advanced)</td>
<td>1 arm: SRT</td>
<td>1</td>
<td>Tumor response</td>
<td>Ipilimumab</td>
<td>30 Gy in 5 fractions</td>
<td>RT &lt;2 days after ipilimumab, RT starts 4 days prior to ipilimumab</td>
</tr>
<tr>
<td>NCT01616114</td>
<td>Prostate (castrate resistant)</td>
<td>3 arms, randomized: RT prior to ipilimumab vs. RT alone</td>
<td>3</td>
<td>Overall survival</td>
<td>Ipilimumab</td>
<td>Not specified</td>
<td>RT prior to ipilimumab</td>
</tr>
<tr>
<td>NCT01570334</td>
<td>Soft tissue sarcoma</td>
<td>2 arms, nonrandomized: RT alone vs. RT plus dendritic cell therapy, then surgery</td>
<td>2</td>
<td>Immune response</td>
<td>Autologous dendritic cell transfusional injection</td>
<td>Conventional RT with bevacizumab</td>
<td>RT &lt;2 days after ipilimumab, RT starts 4 days prior to ipilimumab</td>
</tr>
<tr>
<td>NCT01421017</td>
<td>Breast cancer with skin metastases</td>
<td>1 arm: imiglimumab to all skin metastases plus RT to all skin metastases</td>
<td>1/2</td>
<td>Tumor response</td>
<td>Ipilimumab</td>
<td>600 cGy in 5 fractions</td>
<td>Imiglimumab starts evening of first RT</td>
</tr>
<tr>
<td>NCT009751270</td>
<td>Supratentorial malignant glioma</td>
<td>1 arm: surgical resection with Adv-ex injection followed by pre-RT (raspberries) and RT</td>
<td>1</td>
<td>Safety, immune response</td>
<td>Adv-ex injection into tumor bed</td>
<td>Standard of care</td>
<td>Start RT 3 days after Adv-ex injection, during preoperative therapy</td>
</tr>
<tr>
<td>NCT01535921</td>
<td>Pancreatic cancer following resection (edge RT)</td>
<td>1 arm: cyclophosphamide, vaccine, ERRT, and FOLFIRINOX</td>
<td>1</td>
<td>Toxicity</td>
<td>Low-dose cyclophosphamide and vaccine</td>
<td>6.6 Gy in 5 fractions</td>
<td>Start RT &lt;12 weeks following operation and 7–14 days after first vaccine dose</td>
</tr>
<tr>
<td>NCT01439698</td>
<td>Prostate cancer, localized, intermediate or high risk</td>
<td>2 arms, double-blind, randomized: Adv-ex vs. placebo followed by EBRT with or without androgen deprivation therapy</td>
<td>3</td>
<td>Disease-free survival</td>
<td>Adv-ex intraprostate injection</td>
<td>Standard EBRT</td>
<td>Adv-ex prior to, immediately prior to, and during EBRT</td>
</tr>
</tbody>
</table>

Adv-ex: 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....
• 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.