PHOTONS – RADIOBIOLOGICAL ISSUES RELATED TO THE RISK OF SECOND MALIGNANCIES

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“DO NO HARM”

Do No Harm

Normal Tissue Effects

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“It is axiomatic for the therapy of any malady that whether or not it can do good, it should at least do no harm.”
MINIMUM INTERFERENCE

Ammeter for current measurement

Ammeter – low resistance to avoid significant alterations of the current.

Ideal ammeter – zero resistance.

Ionizing radiation for imaging

Dose should be reduced as much as possible to keep the interference with the system (body) to a minimum, without compromising on quality.
RADIATION THERAPY - A COMPROMISE

Ideally:

\[ \text{TR} = \frac{\text{TCP}}{\text{NTCP}} \]

\[ \text{TR} \uparrow = \frac{\text{TCP} \uparrow}{\text{NTCP} \downarrow} \]
Increased risk of secondary cancers

- Increased number of radiological investigations
- Increased cancer incidence
- More patients receive radiotherapy
- Cancer patients live longer
- Aging population
- Increased availability of RT equipment

Risk versus benefit

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THE RADIOBIOLOGY OF PHOTON TREATMENT

It all started with the Rs...  (R. Withers, 1975)

Then things got uncertain: eRRoR baRs  (S. Bentzen, early 2000)

What we would like to avoid:

soRRy, iRReveRsible Result!
PHOTONS IN IMAGING AND TREATMENT

PHOTONS

DIAGNOSTIC
- Dental, Chest examination
  - Low radiological doses (< 1 mGy)
- PET, CT, fluoroscopy
  - Higher radiological doses (5 – 100 mGy)

TREATMENT
- Radiotherapy
- Nuclear Medicine

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**PHOTONS – RADIOLOGICAL DOSES (I)**

**CHALLENGE:** little or no reliable data in the low dose range of conventional radiology.

*In vitro* models for radiation-induced cancer:
- DNA strand breaks
- Changes in gene expression
- Mutations
- Chromosome aberrations

There is no convincing quantitative association between the above endpoints and radiation-induced cancer.

Lack of data leads to controversies – ex.: mortality risks among radiologists:

**Study 1:** statistically significant increase in risk *(Matanoski et al, Am J Epidemiol 101, 1975)*
**Study 2:** statistically significant decrease in risk *(Berrington et al, Br J Radiol 74, 2001)*
**Study 3:** no significant difference compared to other physicians *(Carpenter et al, Occup Environ Med 54, 1997)*
In the higher dose range of conventional radiology the evidence that there is a slight increase in cancer risk is fairly strong.

PLENITUDE OF EPIDEMIOLOGICAL STUDIES
The future must surely lie in augmenting epidemiology with radiobiological concepts.

FACTORS THAT IMPACT SECOND CANCER RISK

- Age at irradiation
- Radiological investigations
- Genetic susceptibility
- Type of irradiated tissue
- Irradiated volume
- Treatment technique
- Radiation quality
Age-dependence of SPC risk is greatly supported by epidemiological studies.

**Late Effects Study Group** (1380 children with Hodgkin’s lymphoma) outcome: 7% incidence of SPC at 15 years post-RT; SPCs (*mainly breast*) were the next most common cause of mortality after primary disease relapse (Bhatia et al. N Engl J Med 334:745, 1996).

Age-dependence has radiobiological foundation given by the higher radiosensitivity of young as compared to adult cells. **However,** UNSCEAR advises **against generalisation** of the effects of childhood radiation exposure (UNSCEAR 2013, Effects of Radiation Exposure on Children):

<table>
<thead>
<tr>
<th>Relative radiosensitivity of children as compared to adults</th>
<th>Percentage tumours</th>
<th>Tumour type</th>
</tr>
</thead>
<tbody>
<tr>
<td>More radiosensitive</td>
<td>25%</td>
<td>leukemia, breast, thyroid, skin, brain</td>
</tr>
<tr>
<td>Same radiosensitivity</td>
<td>15%</td>
<td>bladder</td>
</tr>
<tr>
<td>Less sensitive</td>
<td>10%</td>
<td>lung</td>
</tr>
<tr>
<td>Not known due to weak data</td>
<td>20%</td>
<td>esophagus</td>
</tr>
<tr>
<td>Weak/no relationship between exposure and risk at any age of exposure</td>
<td>30%</td>
<td>Hodgkin’s lymphoma, prostate, rectum, uterus</td>
</tr>
</tbody>
</table>
ROS production is greater in aging cells in comparison to their young counterparts while the antioxidant system is compromised (= increase in the oxidative stress). Ionizing radiation further leads to increased damage in aging cells.

Radiation sensitivity: bimodal distribution

- Radiation risks after exposure at early ages are related to **initiation** of malignant processes,
- Radiation risks after exposure at later ages are mainly associated with the **promotion** of pre-existing premalignant cells

Estimates of absolute lifetime radiation-induced cancer risks (per 0.1 Gy per 100,000 persons) (stepwise line = BEIR VII data) ([Shuryak et al. J Natl Cancer Inst 102:1628, 2010](http://example.com))
The response of a tissue or organ to radiation depends primarily on three factors:

1. The **radiosensitivity** of the individual cell;
2. The **kinetics** of the cell population;
3. The **structural organization** of cells in the organ / tissue (the architecture of the functional sub-units).

Gudkov & Komarova, Nat Rev Cancer 3, 2003
In the context of second cancer risk:

1. The **radiosensitivity** of the individual cell - **important**
In the context of second cancer risk:

2. The **kinetics** of the cell population - **important**

**Tumour volume doubling time** – strong variation among patients with the same tumour type and also among different organs.

Growth rates for 12 primary breast tumours

In the context of second cancer risk:

3. The **structural organization** of cells in the organ - **not an important factor** as no significant damage is expected to FSUs that could impact on the whole organ.
IRRADIATED VOLUME
RADIOBIOLOGICAL ISSUES

INCREASED RISK OF SPC

Larger normal tissue volume exposed to radiation (due to larger number of fields in IMRT)

Increased out-of-field tissue irradiation (due to leakage X-rays caused by larger MUs)

Overall: larger total body dose

INCREASED TERAPEUTIC RATIO
EPIRADBIO = combining epidemiology and radiobiology to assess cancer risks in the breast, lung, thyroid and digestive tract after exposure to ionizing radiation.

(cumulated equivalent doses of 100 mSv or below)

Radiobiological aims:

- Perform telomere length measurements (from tissue and blood samples)
- Analyse radiation response of stem cells
- Analyse low dose perturbation of intercellular communication
- Evaluate individual tissue sensitivity through genomic instability in peripheral lymphocytes (individuals with and without cancer)
**Telomeres** are DNA-protein structures at the end of the chromosomes which protect from various chromosomal aberrations (homologous recombinations, end joining, etc).

Once a critical telomere length is reached, replicative senescence is triggered (permanent growth arrest).

However, cells can escape replicative senescence leading to unstable chromosome configurations.

Thus excessive telomere shortening can lead to genomic instability and tumorigenesis.
Telomeric dysfunction also relates to radiosensitivity.


This additional rejoining opportunity increases inaccurate repair of radiation-induced breaks.

Radiation exacerbates the effect of telomere attrition by further compromising genomic instability.
A major difference between normal tissue stem cells and cancer cells is that normal tissue stem cells do not maintain stable telomere lengths while cancer cells do.

Two mechanisms of telomere maintenance were identified in human tumors:

1. The use of telomerase, which can synthesize telomeres de novo (activated by most tumours).

2. Alternative mechanisms of telomere lengthening (incompletely understood) (activated by 10-20% tumours).

CANCER STEM CELLS – NEW ORIGINS?

**Old model:** unidirectional hierarchical CSC model.

**New model:** tumour cell plasticity (non-CSC can dedifferentiate and acquire stem-like properties)
Cancer stem cells (CSC) are a subpopulation of cells originating from stem cells and have the following properties:

- are long lived,
- have the ability to proliferate indefinitely
- can generate all heterogeneous lineages of the original tumour
- can recreate themselves by symmetric division
- are more radioresistant than non-stem cancer cells
- they preferentially reside in special microenvironmental niches within the tumour

References:

1. N. Moore et al 2011 J Oncology 396076
2. S. Morrison et al 2006 Nature 441, 1068
3. D. Ramirez-Guerrero 2015 AAAS abstract
**(INTER)CELLULAR COMMUNICATION / NON-TARGETED EFFECTS**

**RIGI** (radiation-induced genomic instability) = delayed non-clonal effects in the clonal progeny of irradiated cells (delayed chromosomal aberrations, gene mutations, cell death).

**RIBE** (radiation-induced bystander effect) = effects that appear in non-irradiated cells that are in close proximity to irradiated cells or have received damaging signals from more distant irradiated cells.

**Adaptive response** = the ability of irradiated cell to become resistant to subsequent radiation exposures.

**Abscopal effects** = effects shown in unrelated, unirradiated organs/tissues.

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NON-TARGETED EFFECTS (cont)

Conflicting phenomena at low doses?

- Chromosomal abnormalities / instability
- Gene mutation
- Apoptosis
- Increased cell proliferation
- Reduction in chromosome aberrations
- Reduction of mutation frequency
- Reduction in micronucleus formation

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There is evidence for clastogenic factors in the plasma of radiotherapy patients, capable of causing chromosome breaks in unirradiated lymphocytes, with great variations among patients (Mothersill & Seymour. Rad Res 155 2001; Morgan Rad Res 159 2003).

Clastogenic factors have been found in plasma taken from A-bomb survivors and Chernobyl liquidators.

In vivo data show significantly less damage / chromosomal instability than in vitro data.

*In vivo* evidence for bystander effect is limited.
NON-TARGETED EFFECTS (cont)

Abscopal effects = systemic effects = distant bystander effects

Evidence for abscopal effect: Crosstalk between primary tumour & metastases

- Tumour-enhancing effect
- Tumour-inhibitory effect


   Tumour-enhancing abscopal effects can be caused by:
   - Reactive oxygen species that ‘spread’ the damage to distal sites
   - Induction of inflammatory cytokines (e.g. interleukin 1)

2. Case reports: abscopal regression of metastases following radiotherapy for primary adenocarcinoma (Rees et al, BJR 56, 1983)
NON-TARGETED EFFECTS - CONCLUSIONS

- Low dose radiation
  - Cellular communication
  - Bystander effects

- High dose radiation
  - Immune response
  - Abscopal effects
THE INEVITABLE PHYSICS OF PHOTONS

DEPTH DISTRIBUTION OF ENERGY

Delivered radiation dose to tissues outside of the tumour during conventional radiation

PHOTONS

PROTONS

Bragg peak

Tumour

DOSE (%) DEPTH (cm)

http://www.proton-cancer-treatment.com/

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DIVISION OF PATIENT’S ANATOMY FOR SECOND CANCER RISK ASSESSMENT AFTER PROSTATE EBRT

DOSE-DEPENDENCE OF CELLULAR EFFECTS

Based on this scenario, second tumours would mainly develop in the out-of-field (low-dose) region or at the margins of the irradiated volume rather than within the high-dose volume (where cell kill is more probable).
However, cell kill can be **counteracted by repopulation** of stem cells, which are also the primary cells at risk for radiation-induced events. If radiation increases the number of premalignant stem cells, through further mutations and accelerated repopulation high-dose regions become an important site for SPC risk (*Sachs & Brenner, PNAS 102, 2005*).
The variation of neutrons is much less compared with that of photon dose equivalent.

Similar with photons, the neutron dose equivalents near the edge of the target volume are higher than those measured at more distal positions.

However, at 30 cm distance and further, the average neutron dose equivalents per 1 Gy of isocentre dose is relatively constant and larger than that derived from photons.

HIGH ENERGY PHOTON BEAMS AND NEUTRONS

<table>
<thead>
<tr>
<th>Type of radiation</th>
<th>Radiation weighting factor ($w_R$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photons</td>
<td>1</td>
</tr>
<tr>
<td>Electrons</td>
<td>1</td>
</tr>
<tr>
<td>Muons</td>
<td>1</td>
</tr>
<tr>
<td>Neutrons</td>
<td>A continuous function of the</td>
</tr>
<tr>
<td></td>
<td>incident neutron energy</td>
</tr>
<tr>
<td>Protons and charged</td>
<td>2</td>
</tr>
<tr>
<td>pions</td>
<td></td>
</tr>
<tr>
<td>$\alpha$-particles,</td>
<td>20</td>
</tr>
<tr>
<td>heavy nuclei</td>
<td></td>
</tr>
</tbody>
</table>

$$w_R(E_n) = \begin{cases} 
2.5 + 18.2 \exp \left( -\frac{\ln(E_n)^2}{6} \right), & E_n < 1\text{MeV} \\
5.0 + 17.0 \exp \left( -\frac{\ln(2E_n)^2}{6} \right), & 1\text{MeV} \leq E_n \leq 50\text{MeV} \\
2.5 + 3.25 \exp \left( -\frac{\ln(0.04E_n)^2}{6} \right), & E_n > 50\text{MeV} 
\end{cases}$$
Chronic proliferative processes can be induced after radiotherapy of primary tumours in various organs (Dörr & Hermann Strahlenther Onkol 184, 2008).

Example: radiation proctitis as the most common side effect after RT of pelvic malignancies

- After prostate cancer RT the risk for rectal tumours increases by a factor of 2 linked to chronic proliferative proctitis (Brenner et al. Cancer 88, 2000)

- After RT for cervical cancer there is an increased risk for rectal and bladder tumour (Kleinerman et al. Cancer 76, 1995)

The impairment of the ability of rectal tissue to heal could imply that other organs exposed to the same high radiation doses may be at increased risk of malignant transformation (Nieder et al. J Urol 180, 2008)

It is imperative to reduce the risk of late effects by more conformal treatments.
While the main focus is on radiation-induce SPC, we should keep in mind that several solid tumours are treated with combined chemo-radiotherapy.

Chemotherapy is a known carcinogenic agent and several studies support the induction of hematological cancers by chemo agents.

Marcu L, Biomed Res Intern 2013 (based on Travis 1999 data)
### ...AND THE Rs

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiosensitivity</strong></td>
<td>Intrinsic radiosensitivity and tissue tolerance given by the amount and radiosensitivity of tissue-specific target cells (stem cells).</td>
</tr>
<tr>
<td><strong>Repair</strong></td>
<td>Misrepair after RT damage in the out-of-field region.</td>
</tr>
<tr>
<td><strong>Repopulation</strong></td>
<td>Uncontrolled repopulation by misrepaired cells in areas affected by cell loss.</td>
</tr>
<tr>
<td><strong>Recruitment</strong></td>
<td>Cell recruitment from the quiescent phase to assist tissue repopulation.</td>
</tr>
<tr>
<td><strong>Remote Effects</strong></td>
<td>Remote cellular effects include abscopal and bystander effects that can promote carcinogenesis at the non-irradiated sites.</td>
</tr>
</tbody>
</table>
To be addressed by future studies:

- To identify the genetic predisposition for radiation-induced cancer (biomarkers, DNA chips)
- To choose treatment strategy as a function of the above predisposition
- To determine the extent of interaction in combined treatments (additive / synergistic?)
- To determine the correlation between non-targeted effects and treatment as well as tissue type
THE KEY TO SUCCESS: PERSONALISED MEDICINE?
If the ammeter is removed from the circuit the current will regain its initial value (the system is unchanged).

When the imaging source is removed, the effects of IR will remain (the system is changed).

soRRy, iRReveRsible Result!