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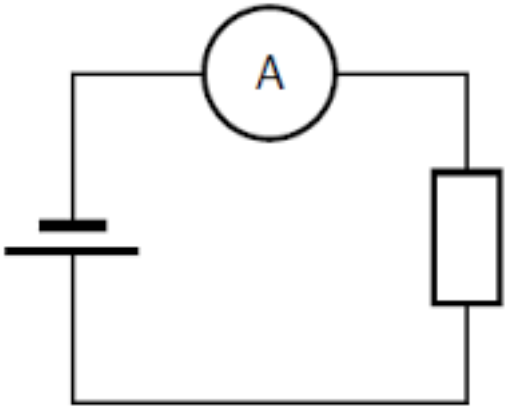
"It is axiomatic for the therapy of any malady that whether or not it can do good, it should at least do no harm."

MINIMUM INTERFERENCE

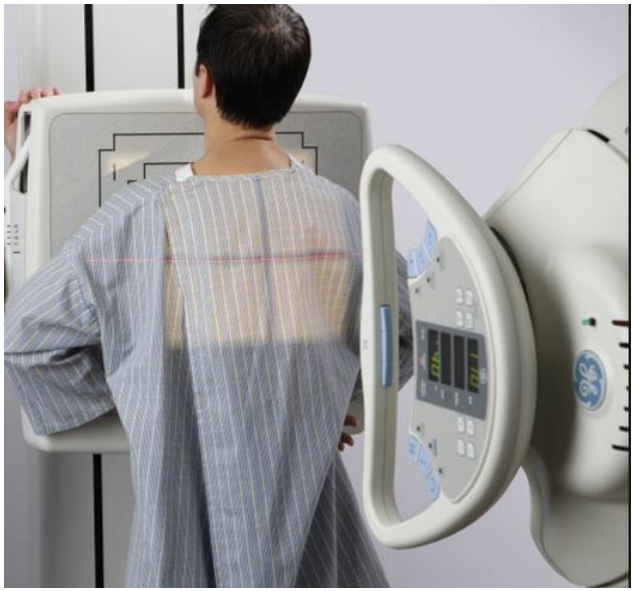
Ammeter for current measurement



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.

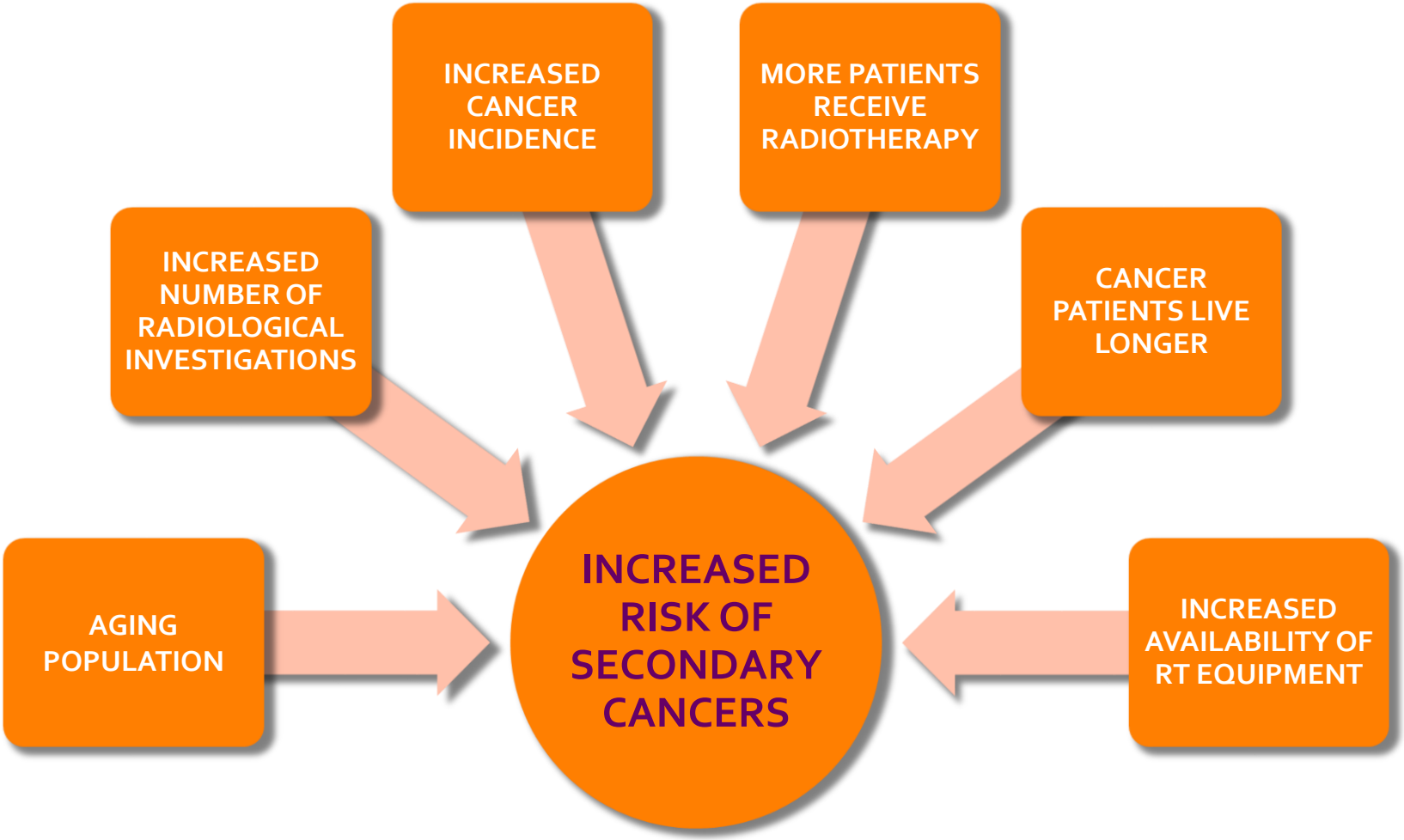
RADIATION THERAPY - A COMPROMISE

TR = TCP / NTCP

Ideally:

TR ↑ = TCP ↑/ NTCP ↓

RISK VERSUS BENEFIT



THE RADIOBIOLOGY OF PHOTON TREATMENT

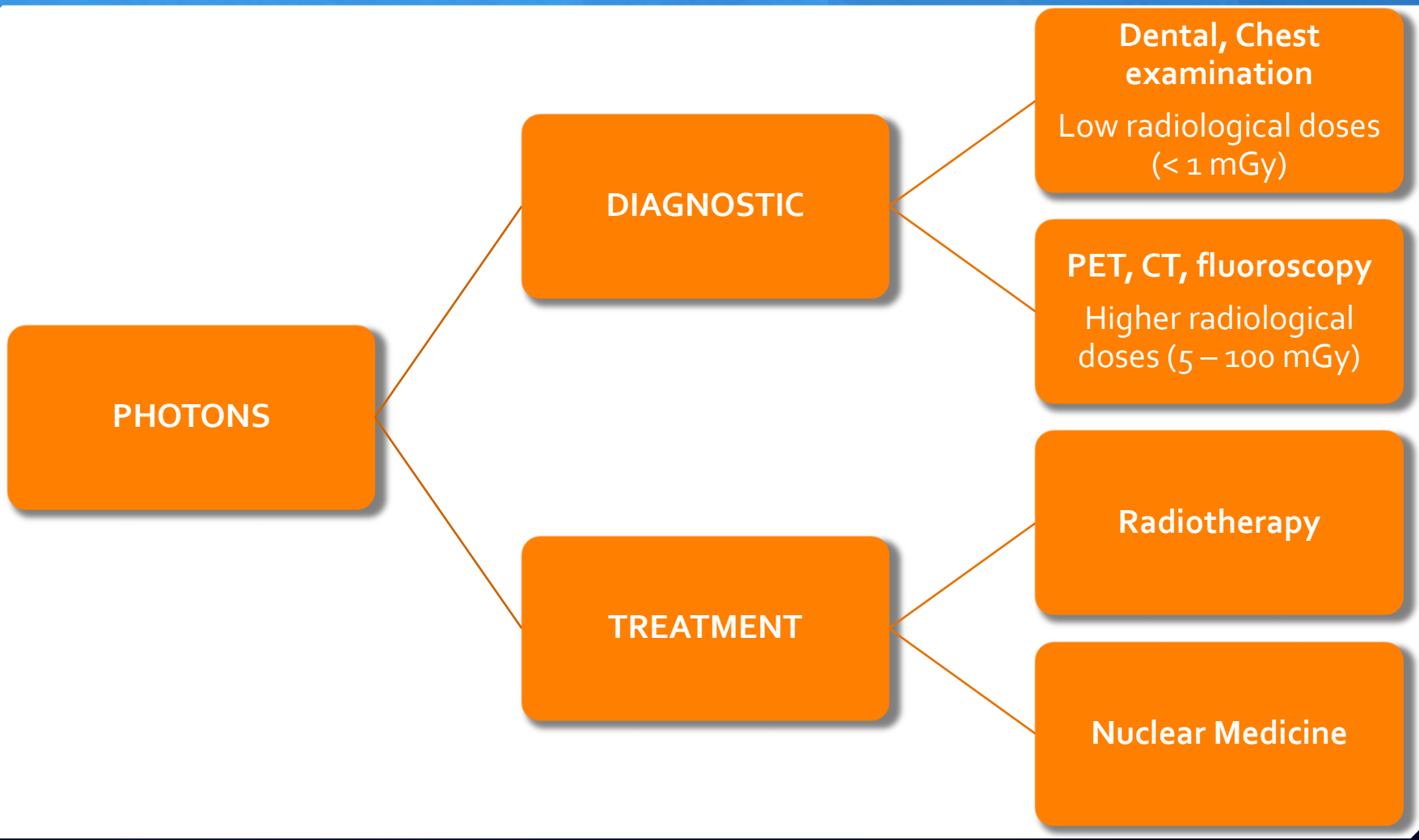
It all started with the Rs… **(R. Withers, 1975)**

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 – 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 Epidem 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)

PHOTONS – RADIOLOGICAL DOSES (II)

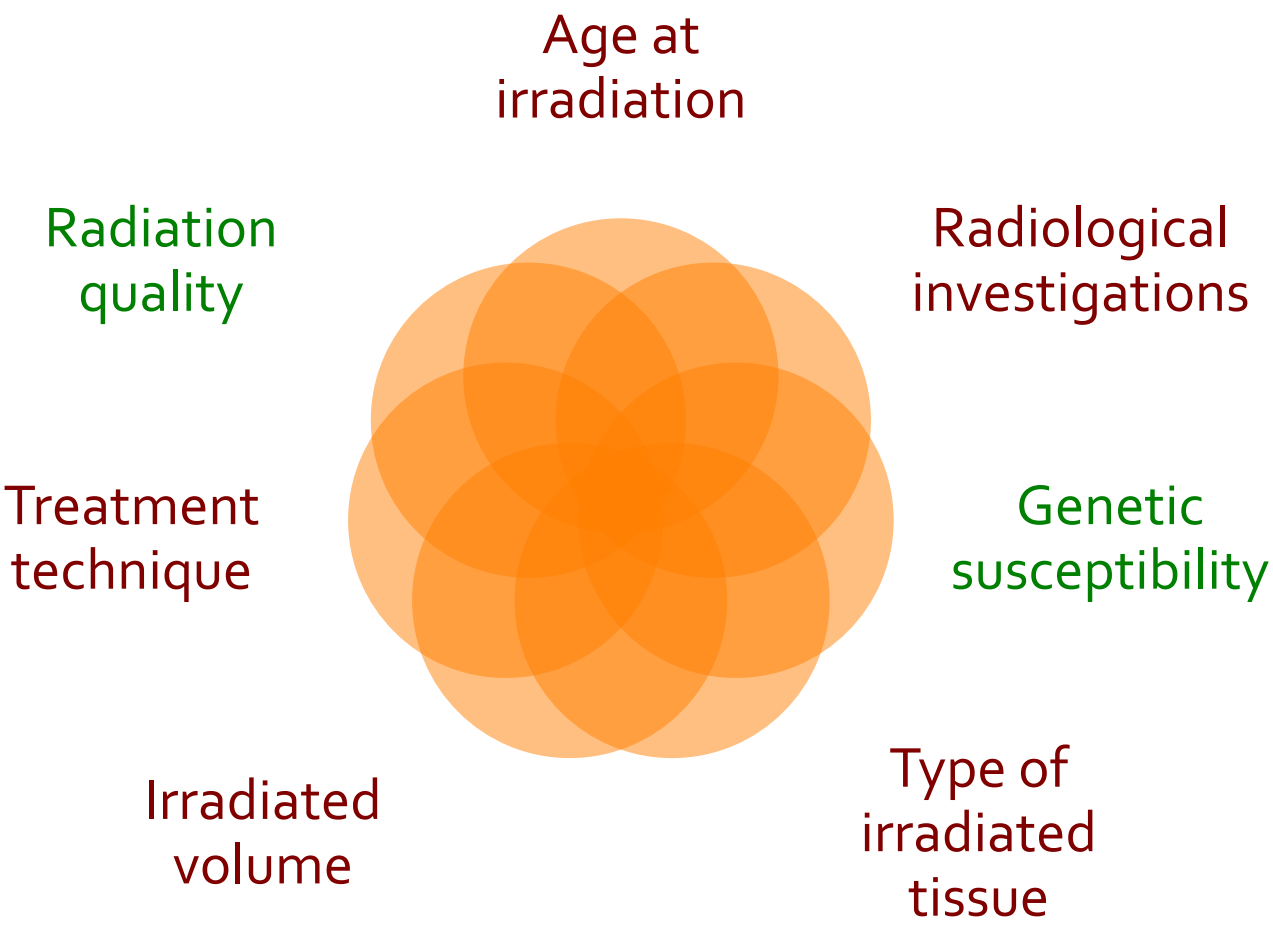
In the **higher dose range of conventional radiology** the evidence that there is a slight increase in cancer risk is fairly strong.

PLENITUDE OF EPIDEMIOLOGICAL STUDIES

The future must surely lie in
augmenting epidemiology with radiobiological concepts.

Preston R, et al *J Radiol Prot* 33:573 (2013)

FACTORS THAT IMPACT SECOND CANCER RISK



AGE-DEPENDENCE RADIOBIOLOGICAL ISSUES

Age-dependence of SPC risk is greatly supported by epidemiological studies.

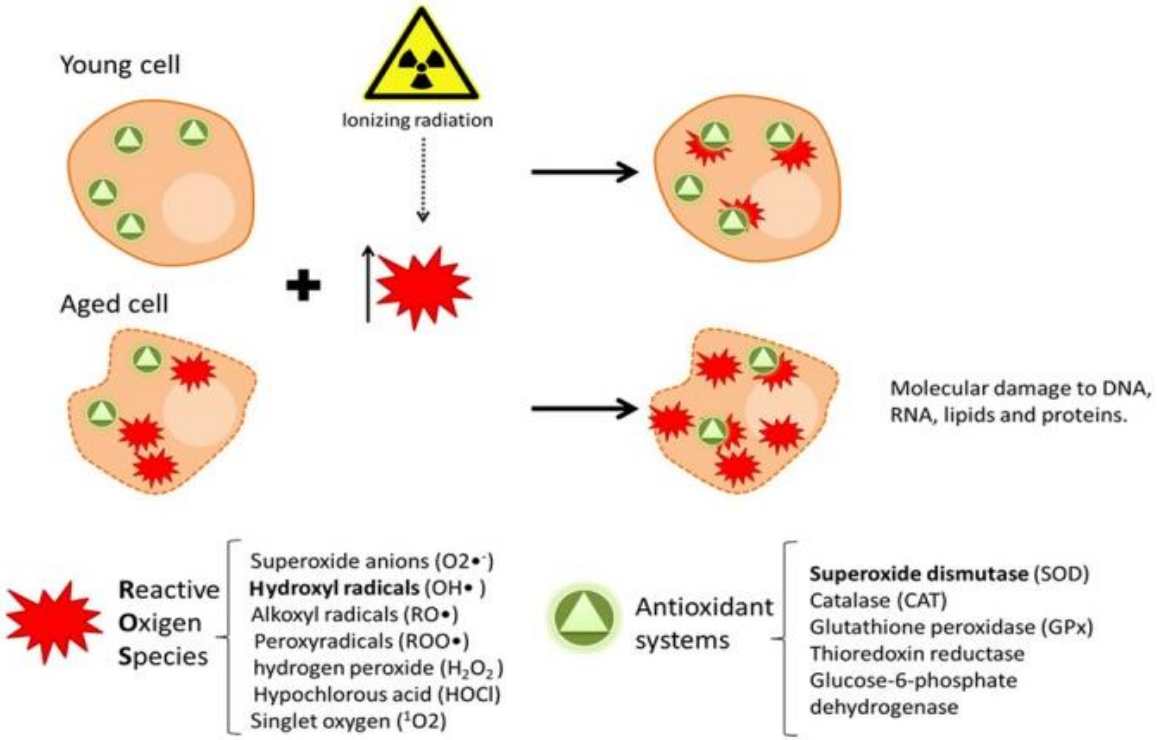
Late Effects Study Group (1380 children with Hodgkin's lymphoma) outcome: 7% incidence of SPC at 15 years post-RT; SPCs (*mainly breast*) were the next most common cause of mortality after primary disease relapse (Bhatia et al. N Engl J Med 334:745, 1996).

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):

Relative radiosensitivity of children as compared to adults	Percentage tumours	Tumour type
More radiosensitive	25%	leukemia, breast, thyroid, skin, brain
Same radiosensitivity	15%	bladder
Less sensitive	10%	lung
Not known due to weak data	20%	esophagus
Weak/no relationship between exposure and risk at any age of exposure	30%	Hodgkin's lymphoma, prostate, rectum, uterus

AGE-DEPENDENCE RADIOBIOLOGICAL ISSUES (cont)

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.

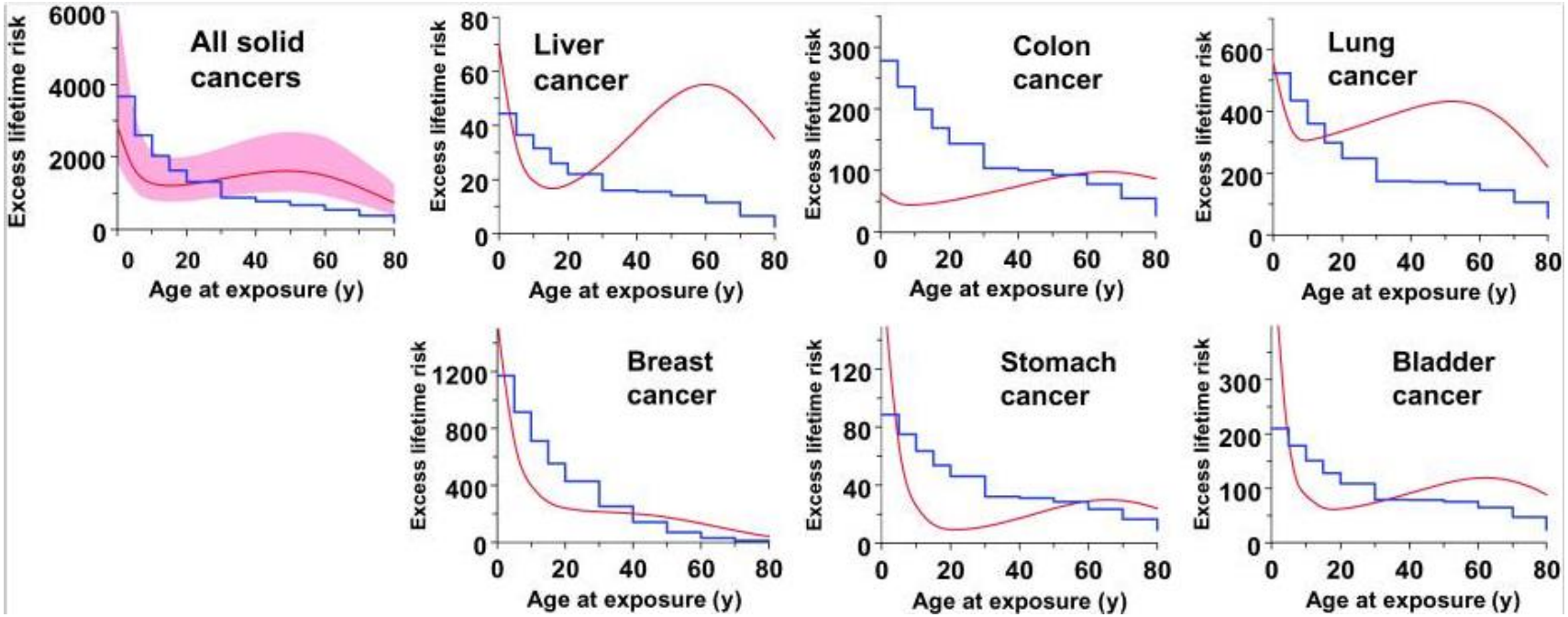


Hernandez et al. Aging cell 14:153, 2015.

AGE-DEPENDENCE & TISSUE TYPE RADIOBIOLOGICAL ISSUES

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

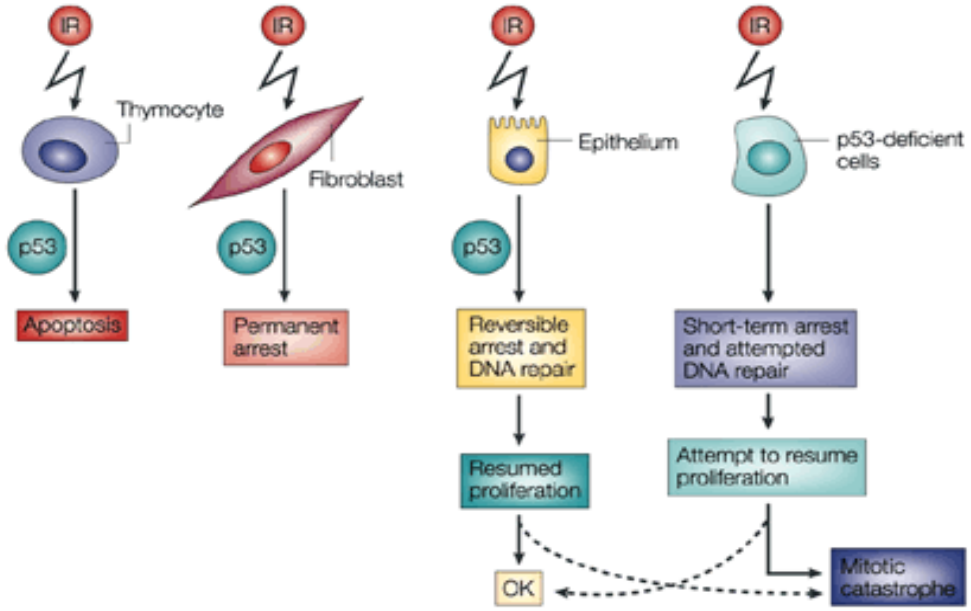


Estimates of absolute lifetime radiation-induced cancer risks (per 0.1 Gy per 100 000 persons) (stepwise line = BEIR VII data) (Shuryak et al. J Natl Cancer Inst 102:1628, 2010)

TYPE OF IRRADIATED TISSUE/ORGAN RADIOBIOLOGICAL ISSUES

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).

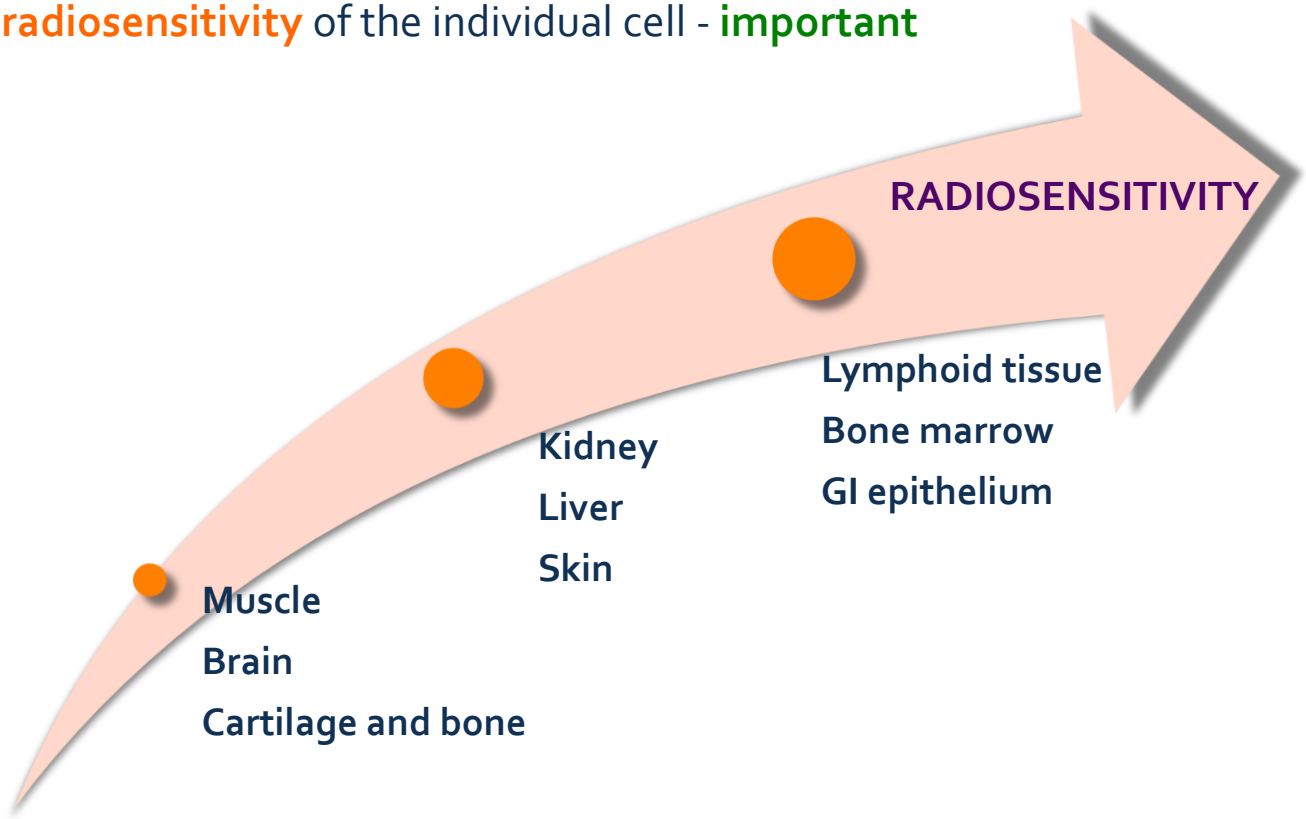


Gudkov & Komarova, Nat Rev Cancer 3, 2003 Nature Reviews | Cancer

TYPE OF IRRADIATED TISSUE/ORGAN RADIOBIOLOGICAL ISSUES (cont)

In the context of second cancer risk:

1. The **radiosensitivity** of the individual cell - **important**

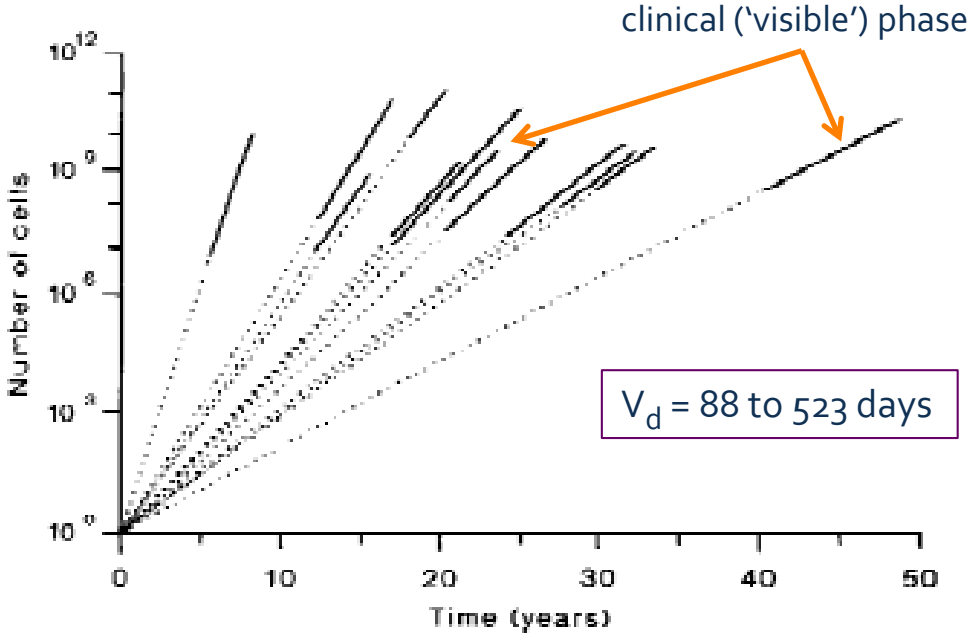


TYPE OF IRRADIATED TISSUE/ORGAN RADIOBIOLOGICAL ISSUES (cont)

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.



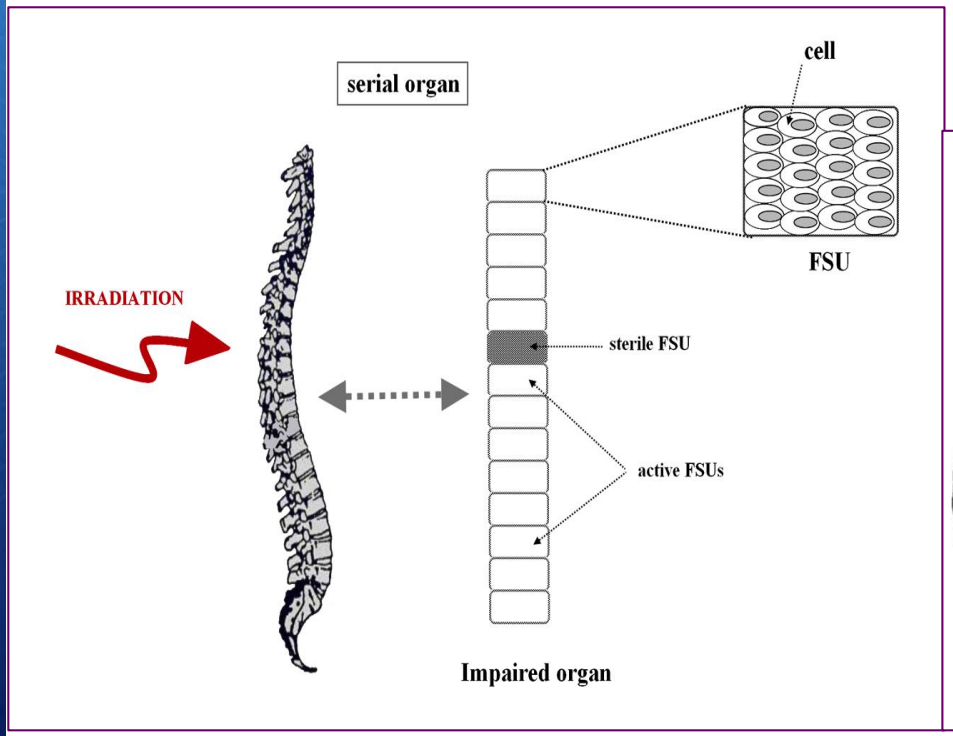
Growth rates for 12 primary breast tumours

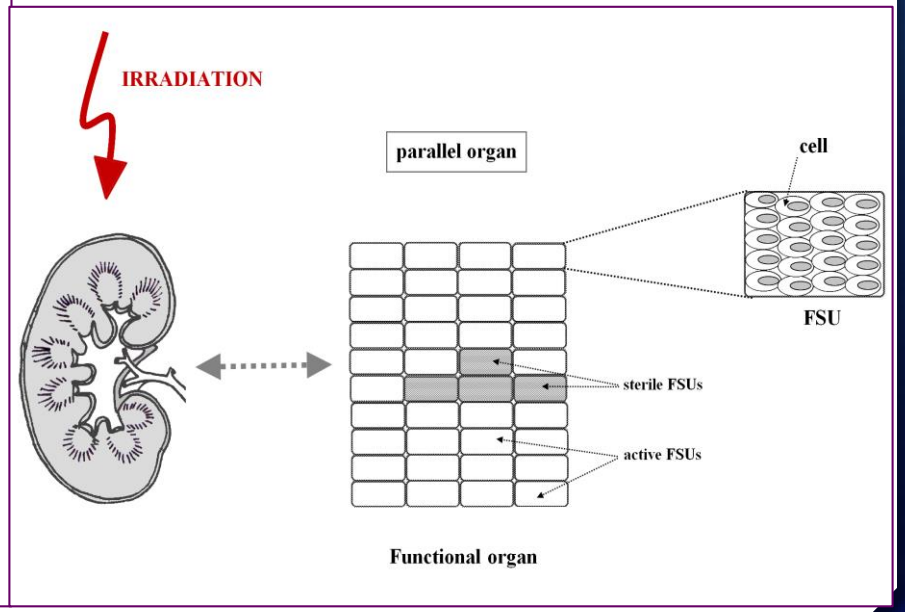
Friberg & Mattson. J Surg Oncol 65, 1997

TYPE OF IRRADIATED TISSUE/ORGAN RADIOBIOLOGICAL ISSUES (cont)

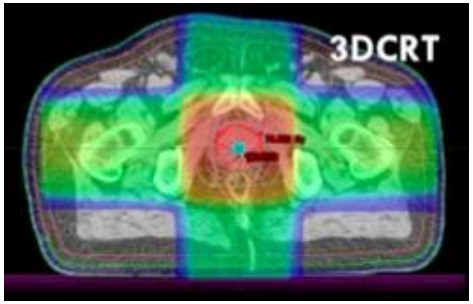
In the context of second cancer risk:

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.



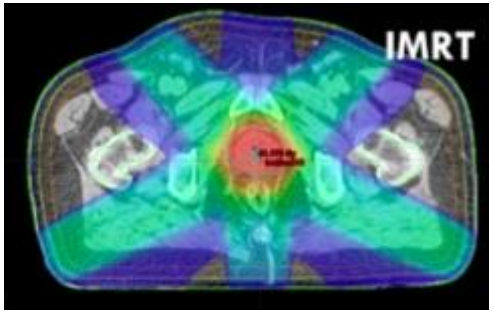


IRRADIATED VOLUME RADIOBIOLOGICAL ISSUES



INCREASED TERAPEUTIC RATIO

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

EPIRADBIO

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)

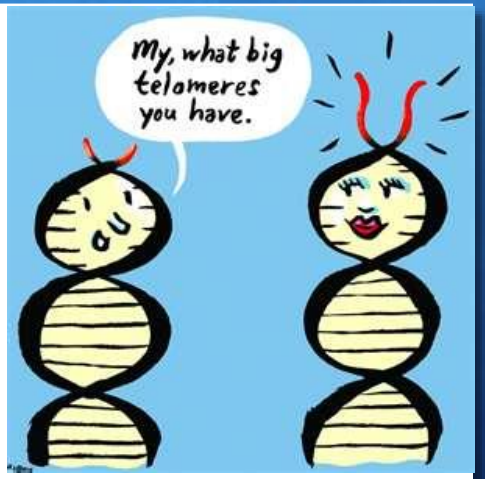
Radiobiological aims:

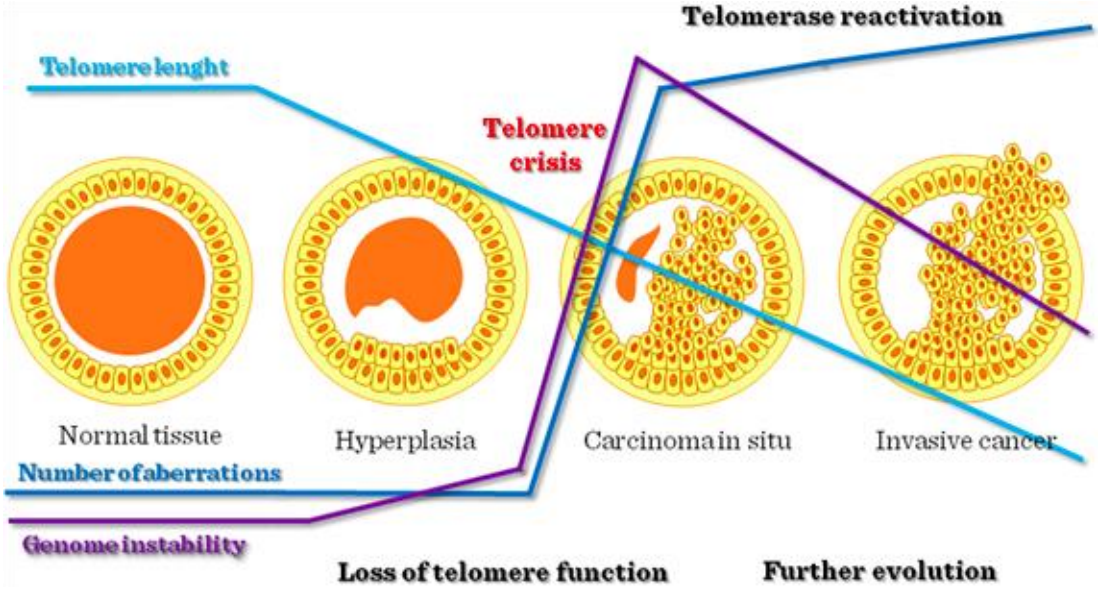
- Perform telomere length measurements (from tissue and blood samples)
- Analyse radiation response of stem cells
- Analyse low dose perturbation of intercellular communication
- Evaluate individual tissue sensitivity through genomic instability in peripheral lymphocytes (individuals with and without cancer)

TELOMERE ATTRITION AND RADIOSENSITIVITY

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.

TELOMERE ATTRITION AND RADIOSENSITIVITY (cont)

Telomeric dysfunction also relates to radiosensitivity.

Chromosomes with unprotected ends can fuse to radiation-induced DNA DSBs. (Latre et al. Exp Cell Res 287:282, 2003)

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

Radiation exacerbates the effect of telomere attrition by further compromising genomic instability.

STEM CELLS AND TELOMERE LENGTH

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:

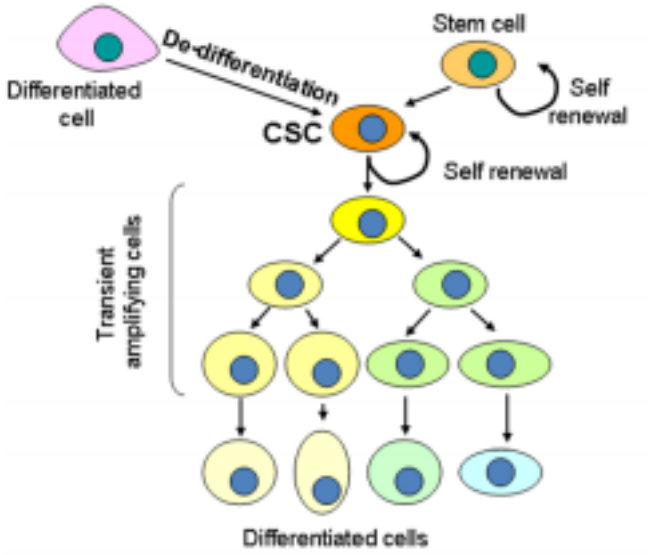
1. The use of telomerase, which can synthesize telomeres *de novo* (activated by most tumours).

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

Hu J et al. Cell 148, 2012

CANCER STEM CELLS – NEW ORIGINS?

Old model: unidirectional hierarchical CSC model.

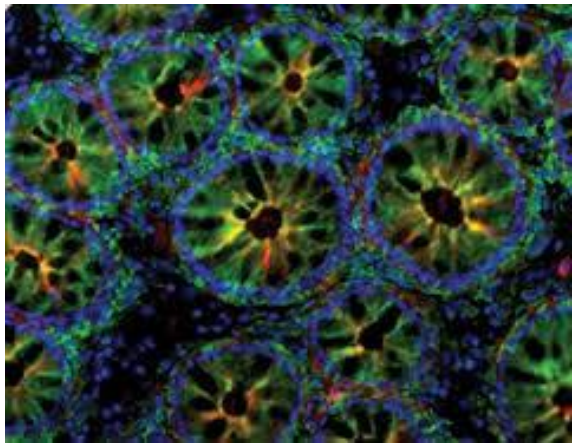


New model: tumour cell plasticity (non-CSC can dedifferentiate and acquire stem-like properties)

CANCER STEM CELLS

Cancer stem cells (CSC) are a subpopulation of cells originating from stem cells and have the following properties[1]:

- are long lived,
- have the ability to proliferate indefinitely
- can generate al heterogeneous lineages of the original tumour
- can recreate themselves by symmetric division[2]
- are more radioresistant than non-stem cancer cells[3]
- they preferentially reside in special microenvironmental niches within the tumour[4]



Nature Med 14, 814 (2008) doi:10.1038/nm0808-814

[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
[4] C. Peitzsch et al **2014** Int J Radiat Biol 90, 636

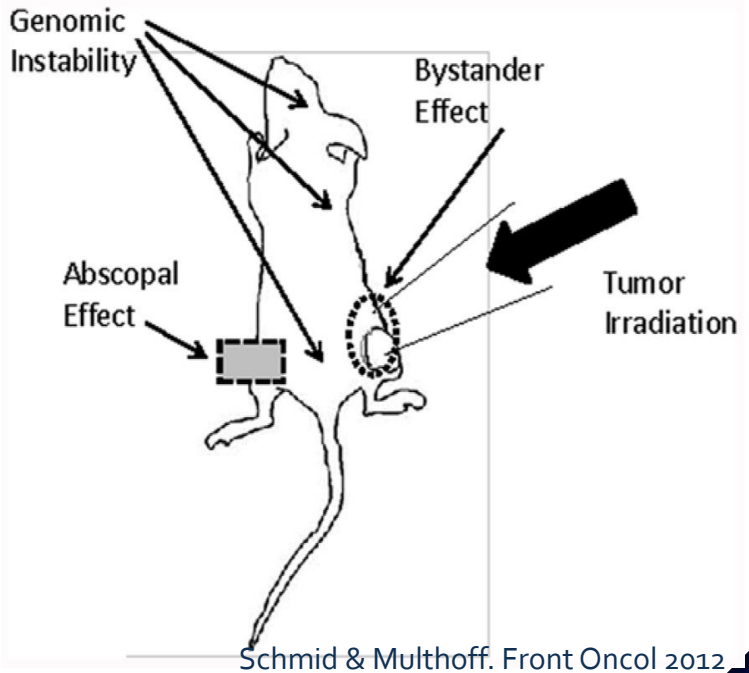
(INTER)CELLULAR COMMUNICATION / NON-TARGETED EFFECTS

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.

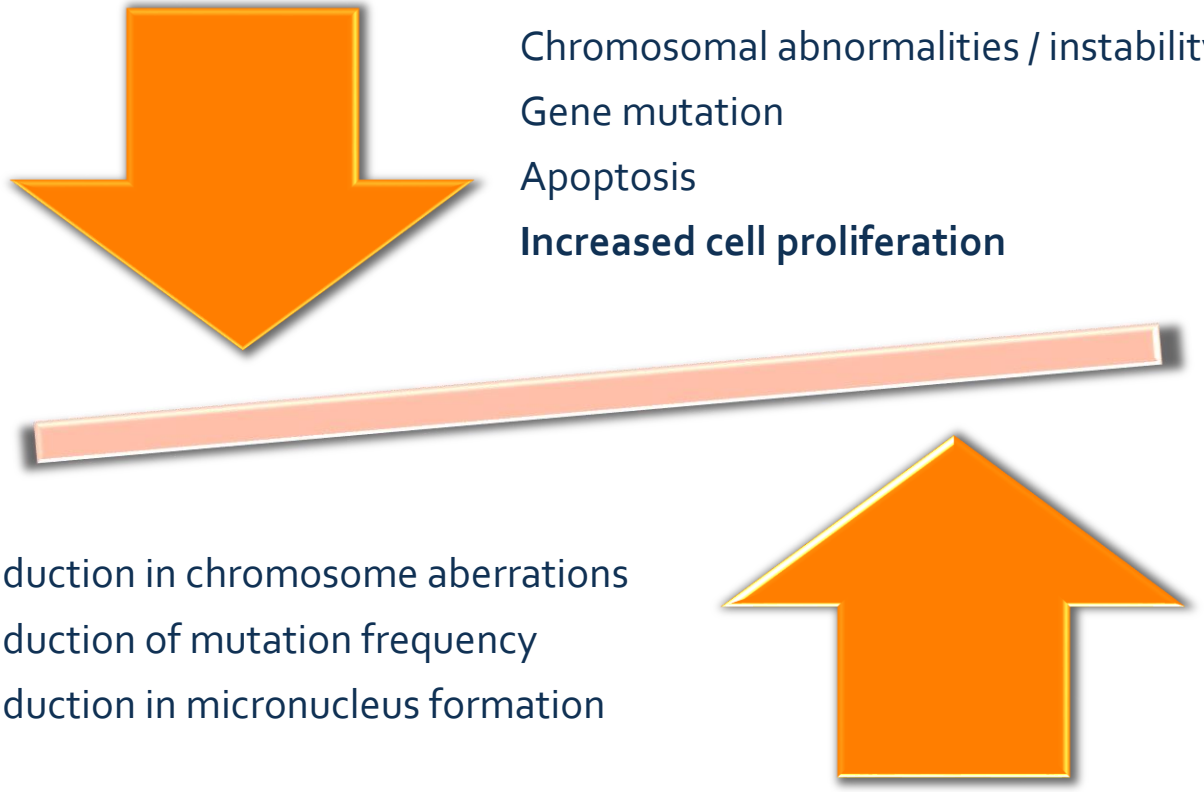
Abscopal effects = effects shown in unrelated, unirradiated organs/tissues.



Schmid & Multhoff. Front Oncol 2012

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

NON-TARGETED EFFECTS (cont)

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**

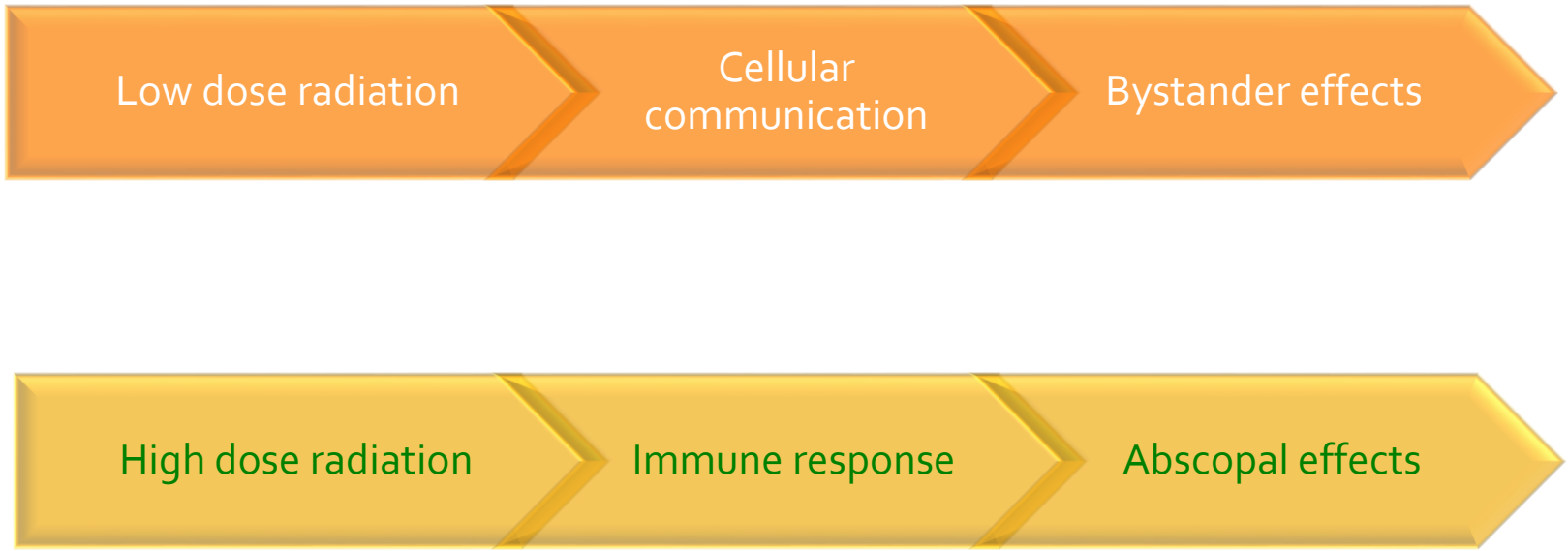
1. Murine model: surgical removal of primary tumour **accelerated the growth** of metastatic foci (determined by labeling index) (Fisher et al. Cancer Res 49, 1989)

Tumour-enhancing **abscopal effects** can be caused by:

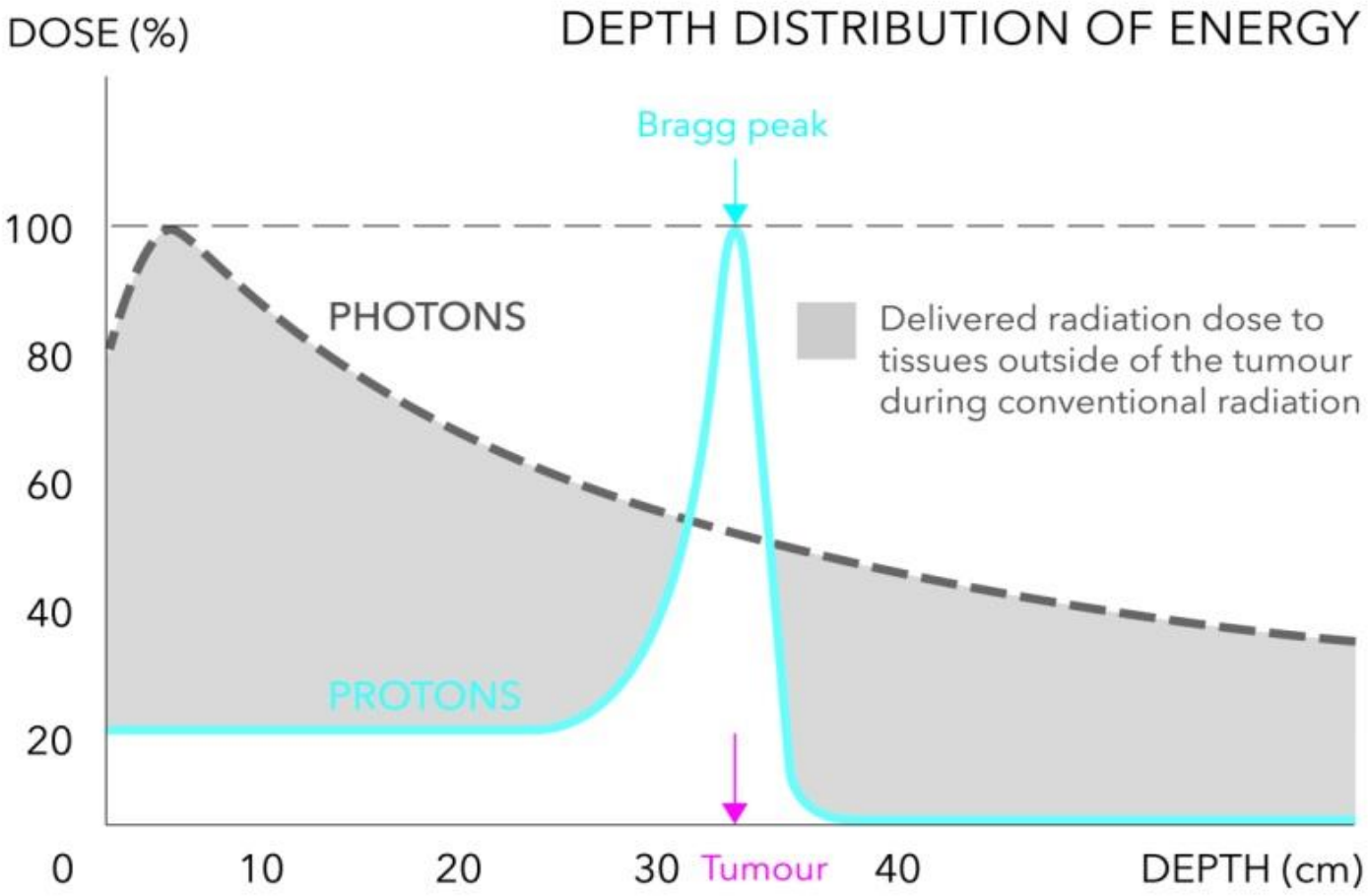
- Reactive oxygen species that 'spread' the damage to distal sites
- **Induction of inflammatory cytokines** (eg. interleukin 1)

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

NON-TARGETED EFFECTS - CONCLUSIONS

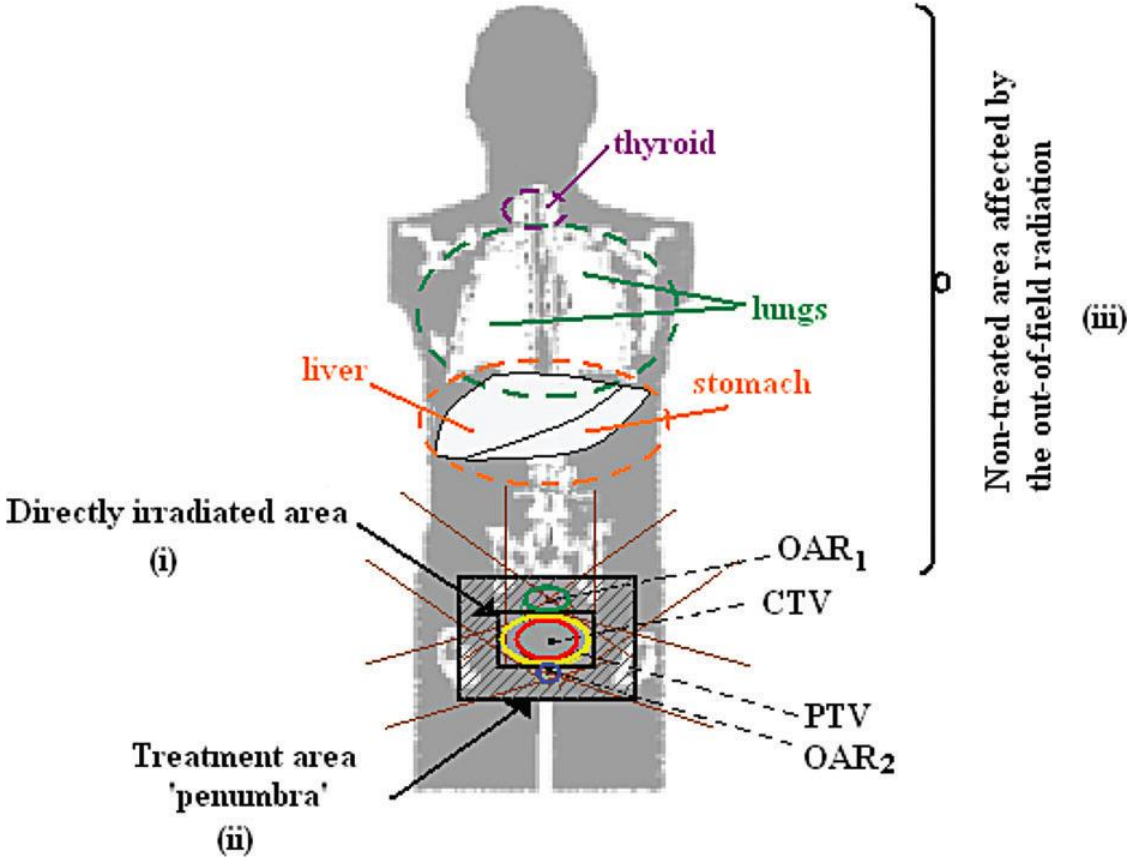


THE INEVITABLE PHYSICS OF PHOTONS



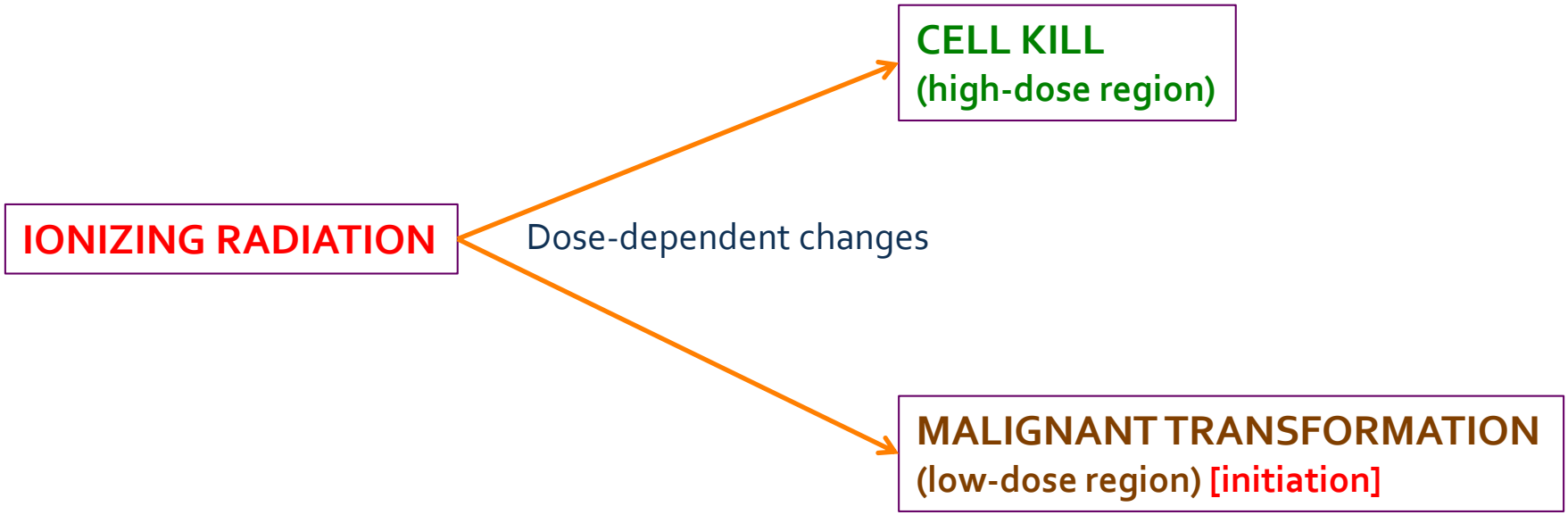
http://www.proton-cancer-treatment.com/

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



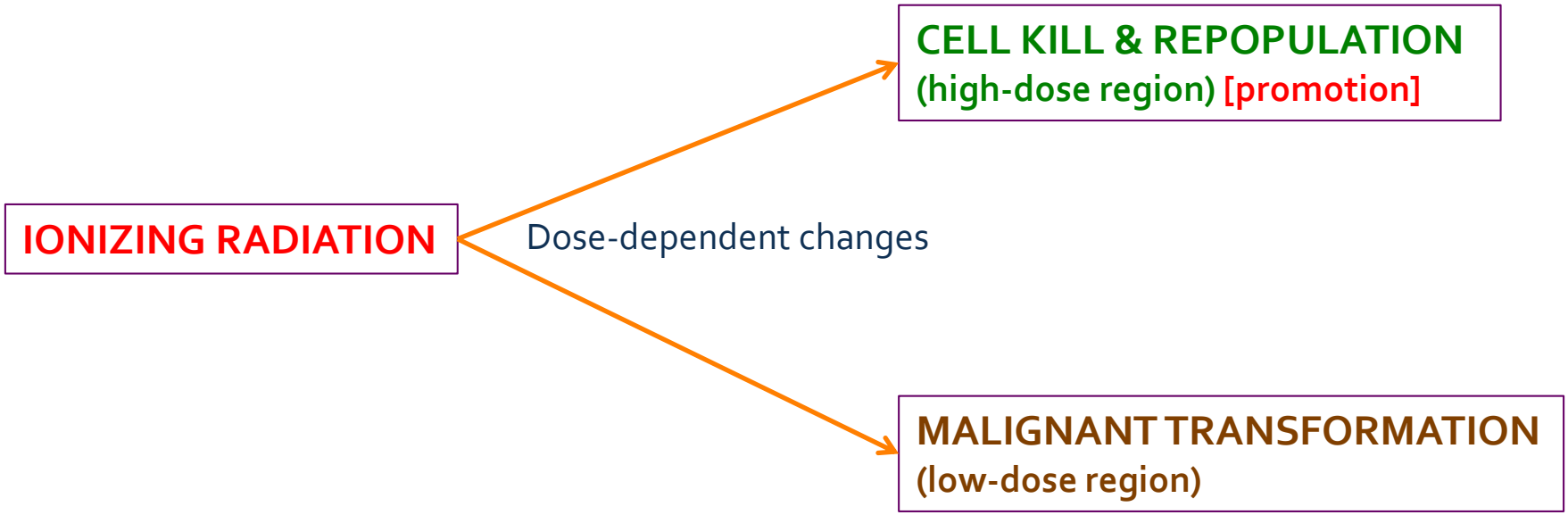
E. Bezak, R. Takam, L. Marcu *Rad Prot Dosim* 167(4):591 (2015)

DOSE-DEPENDENCE OF CELLULAR EFFECTS



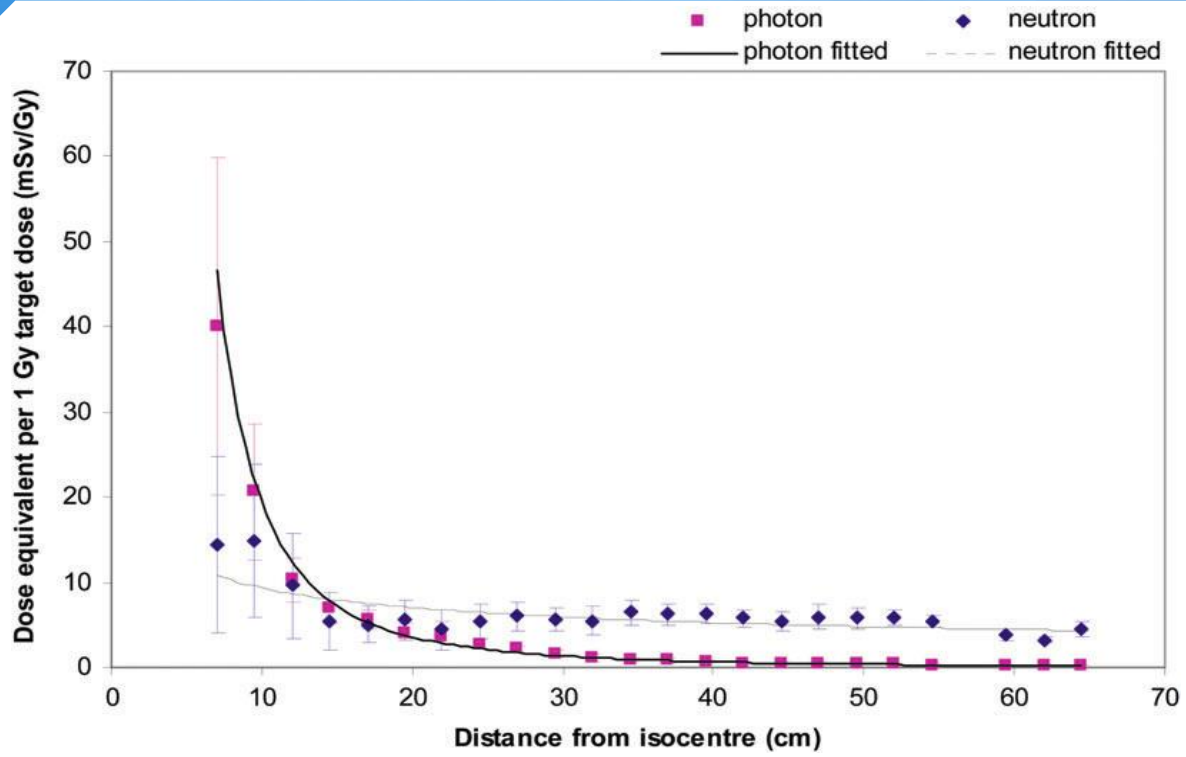
Based on this scenario, **second tumours** would mainly develop in the **out-of-field** (low-dose) region or at the **margins of the irradiated volume** rather than within the high-dose volume (where cell kill is more probable).

DOSE-DEPENDENCE OF CELLULAR EFFECTS (cont)



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).

AVERAGE PERIPHERAL PHOTON/NEUTRON DOSE EQUIVALENT (mSv) PER 1 Gy OF ISOCENTRE DOSE



- 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.

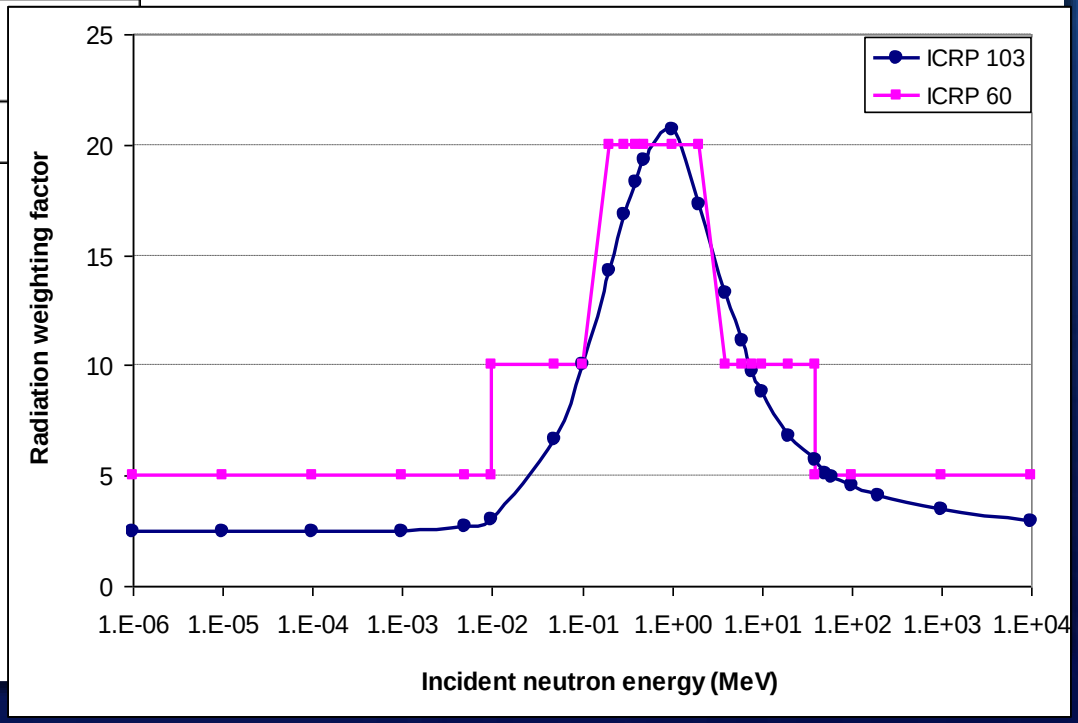
E. Bezak, R. Takam, L. Marcu *Rad Prot Dosim* 167(4):591 (2015)

- 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

Type of radiation	Radiation weighting factor (w_R)
Photons	1
Electrons	1
Muons	1
Neutrons	A continuous function of the incident neutron energy
Protons and charged pions	2
α-particles, heavy nuclei	20

$$w_R(E_n) = \begin{cases} 2.5 + 18.2\exp\left[-\dfrac{(\ln E_n)^2}{6}\right], & E_n < 1\,MeV \\ 5.0 + 17.0\exp\left\{-\dfrac{[\ln(2E_n)]^2}{6}\right\}, & 1\,MeV \le E_n \le 50\,MeV \\ 2.5 + 3.25\exp\left\{-\dfrac{[\ln(0.04E_n)]^2}{6}\right\}, & E_n > 50\,MeV \end{cases}$$



LONG-TERM THERAPEUTIC CONSEQUENCES

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)

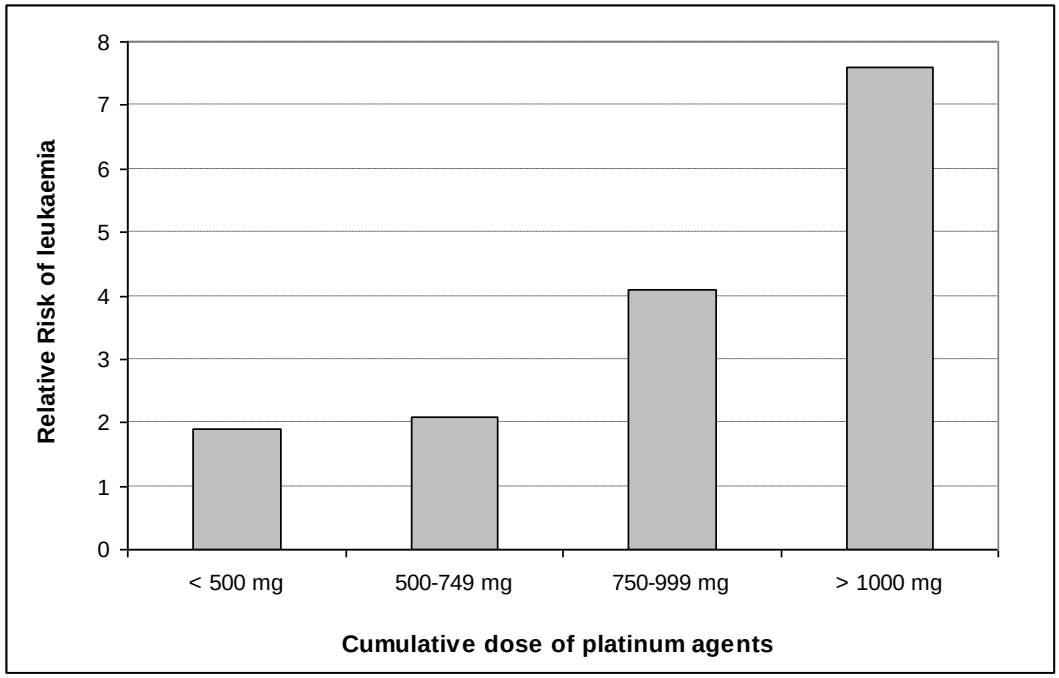
The impairment of the ability of rectal tissue to heal could imply that other organs exposed to the same high radiation doses may be at increased risk of malignant transformation (Nieder et al. J Urol 180, 2008)

It is imperative to reduce the risk of late effects by more conformal treatments.

COMBINED THERAPIES

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)

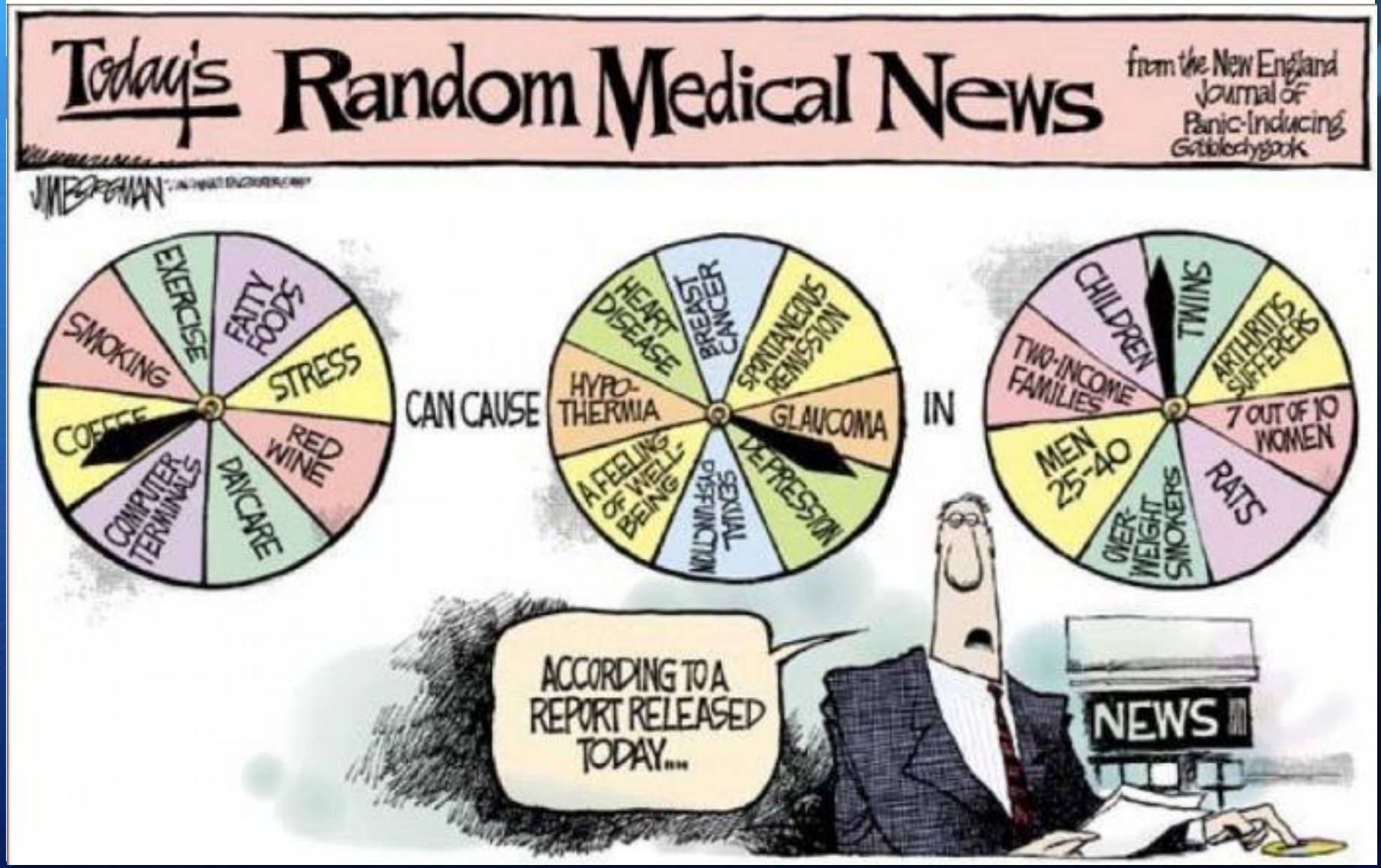
… AND THE Rs

RADIOSENSITIVITY	Intrinsic radiosensitivity and tissue tolerance given by the amount and radiosensitivity of tissue-specific target cells (stem cells).
REPAIR	Misrepair after RT damage in the out-of-field region.
REPOPULATION	Uncontrolled repopulation by misrepaired cells in areas affected by cell loss.
RECRUITMENT	Cell recruitment from the quiescent phase to assist tissue repopulation.
REMOTE EFFECTS	Remote cellular effects include abscopal and bystander effects that can promote carcinogenesis at the non-irradiated sites .

TO BE ADDRESSED BY FUTURE STUDIES

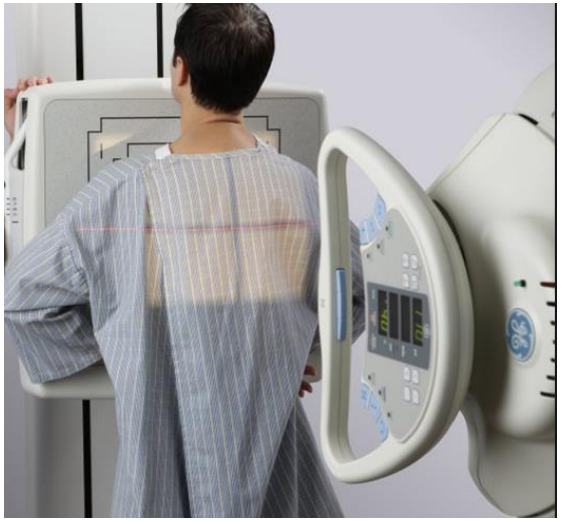
- To identify the genetic predisposition for radiation-induced cancer (biomarkers, DNA chips)
- To choose treatment strategy as a function of the above predisposition
- To determine the extent of interaction in combined treatments (additive / synergistic?)
- To determine the correlation between non-targeted effects and treatment as well as tissue type

THE KEY TO SUCCESS: PERSONALISED MEDICINE?



USE IONISING RADIATION WISELY!

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!