CURRENT ISSUES ABOUT SECOND PRIMARY CANCERS AFTER RADIOTHERAPY

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Second Primary Cancers

Definition: second primary cancers are iatrogenic tumours that arise as *de novo* neoplasms in a field of therapeutic radiation after a latency period that can span decades, and are not recurrences of the original cancer.

Advances in radiation therapy (and chemotherapy) have increased the survival rate of many patients treated for cancer today.

Radiotherapy is a double edged sword:

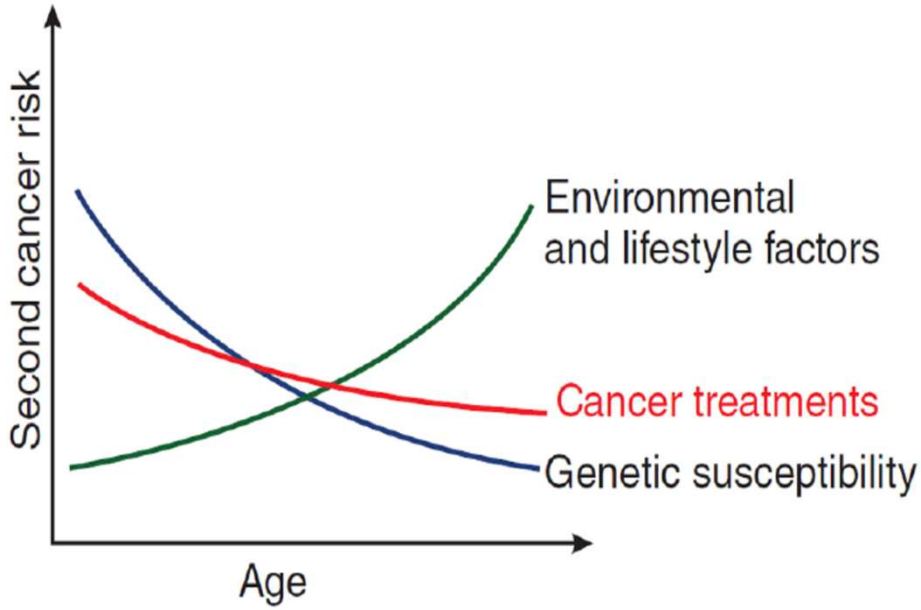
- a well-established role in the curative treatment of various solid tumors
- the potential to induce cancer decades after the treatment.

This is concerning as there is an increase in the number of long-term cancer survivors.

Epidemiology

There is an uncertainty in estimating the exact incidence of second primary cancer because of the confounding factors (patient lifestyle and genetic susceptibility).

Although there are other causes (such as common etiology with the primary cancer, and genetic or life style predisposition), many of these second primary malignancies are treatment-related, especially in pediatric and young adult cancer survivors, with a huge contribution of radiotherapy.



Epidemiology

PM Barbaro, et al. *Reduced incidence of second solid tumors in survivors of childhood Hodgkin's lymphoma treated without radiation therapy.* Ann Oncol. 2011 Dec;22(12):2569-74.

"Children with HL without RT have a substantially lower incidence of second tumors than those treated with RT."

- Age is one of the key parameters: children are 3 to 6 times more sensitive with regard to radio-induced carcinogenic effects compared to adults.
- For some types of cancers and in some pediatric cancers, SPCs cause more deaths than the primary cancers.
- As children and young adults are likely to survive for a longer duration after anti-cancer therapy, they are at the greater risk of developing radiation-induced second malignancies.
- Childhood Cancer Survivor Study:

  - the risk of developing a second cancer in the first 25 years after treatment can be as large as 12%.

  - mortality increased due to second malignancies as compared to that due to other causes at 25 years after first cancer diagnosis.

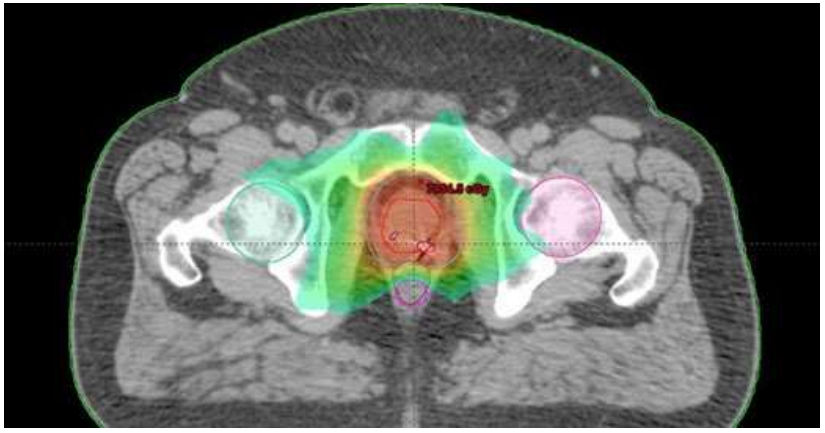
Dosimetry

Risks can be placed in perspective, and future retrospective epidemiological studies may rely on accurate organ dosimetry.

- Most frequently, radiation-induced neoplasms occur in volume exposed to high doses.

- However, the impact of "low" doses in radiation-induced carcinogenesis should be clinically considered because modern radiotherapy significantly increase the volume of tissues receiving low doses.

-The use of modern radiotherapy techniques (such as IMRT, IGRT, stereotatic,…) is of many controversial issues in the pediatric age group in spite of their proven dosimetric distribution advantages.



Dosimetry

Latest recommendations of the International Commission on Radiation Units and Measurements (ICRU) related to the **remaining volume at risk**: the search for means of **more accurately determining such doses** is of renewed clinical interest.

International Commission on Radiation Units & Measurements

Working Group 9 (Radiation Protection Dosimetry in Medicine) of the European Radiation Dosimetry Group (EURADOS): need of **a robust foundation and methodology to measure or calculate organ doses** following radiotherapy.

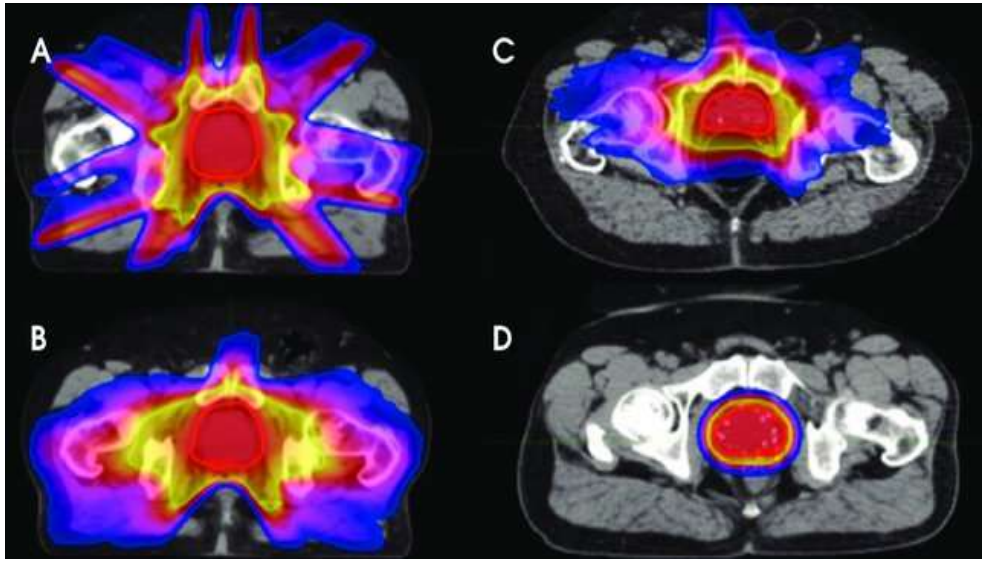
EURADOS European Radiation Dosimetry Group

Publication (2017) of a report from the Task Group 158 / AAPM (American Association of Physicists in Medicine): need of a measurement or some other means of **assessing the dose due to the dramatic inaccuracy of treatment-planning systems outside the treatment field**.

Dosimetry

Of particular interest are second cancer risk estimates for new radiation treatment modalities such as intensity modulated RT, intensity modulated arc-therapy and proton and heavy ion RT.

The long term risks from such modern RT treatment techniques are unlikely to become manifest for many years, due to the long latency time for solid tumour induction and have therefore not yet been fully quantified.



Dosimetric comparison of (A) intensity-modulated radiation **therapy (IMRT), (B) volumetric-modulated** arc therapy (VMAT), (C) stereotactic body radiation therapy (SBRT), and (D) low dose rate brachytherapy (LDR-BT). Isodose lines correspond to 25% (blue), 50% (yellow), and 100% (red) of prescription dose.

Dosimetry

The quantification of the correlation between dose and risk is affected by the uncertainties involved in relating a tumor which was induced decades after the treatment of the primary disease to the actual dose at the tumor site.

- The dose outside of the treated volume cannot be predicted by clinically used treatment planning systems with the remaining uncertainty ≈ 40%.

- Other dosimetric uncertainties: patient movement, impact of fractionation on the dose distribution, anatomical changes and simplified dose reconstructions.

Dosimetry

Prostate cancer

- Secondary long-term effects are of interest due to the large number of prostate cancer patients treated with radiation and 50% reduction in mortality after treatment.
- Clinical linear accelerators: unwanted secondary radiation (neutrons and leakage photons) can be generated and be absorbed by healthy tissues located outside the target radiation field.
- Direct dose measurements of peripheral/distant organs are needed to evaluate both photon and neutron dose contributions.
- Out-of-field dose measurements can aid in the assessment of second primary cancer risk, an aspect that is gaining more importance in today's radiotherapy treatment planning and delivery.

Dosimetry

The risk of second primary cancers due to peripheral photon and neutron doses received during prostate cancer external beam radiation therapy Physica Medica, Volume 42, 2017, pp. 253-258
Eva Bezak, Rundgham Takam, Eric Yeoh, Loredana G. Marcu

Aim:

To determine the risk of second primary cancers in the organs distal to the prostate target volume during 3D conformal radiotherapy.

- Contributions of secondary neutron doses produced by high energy photons were taken into consideration for SPC risk estimation.
- Peripheral photon and neutron dose equivalents measured using TLDs in a Rando phantom
- Quantification of the risks in developing SPC in various normal tissues/organs by the application of the competitive risk model including parameters of induction of DNA and radiation dose dependent cell.

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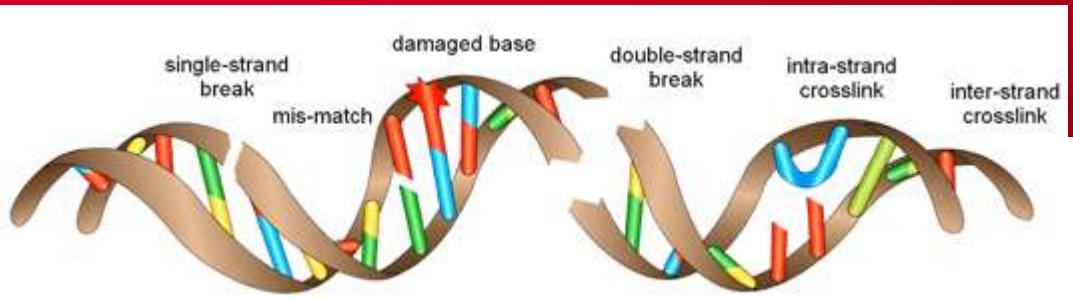
Results:
Increased risk of SPC development in normal organs distal to the target volume: the estimated risks of SPC in rectum and bladder were relatively small compared to those of thyroid and oesophagus.
The importance of actual radiation dose measurement for clinical treatment planning evaluation in terms of estimation of SPC risk is highlighted by the secondary neutron dose contribution and the higher radiobiological effect of neutrons relative to photons.

- **Radiation protection implications**: to provide radiation protective measures for the patient during high energy external beam irradiation of the prostate (use of Multileaf Shielding) or use of lower beam energy in order to minimize production of photo-neutrons.
- Depending on the disease staging: high dose rate brachytherapy treatment.

Radiobiology



- Exposure to low dose radiation is known to cause base damage, single strand DNA breaks, and double strand breaks (DSBs).

- The DSBs could lead to gene mutations, which then lead to a malignant transformation of the radiated cell . Also, impairment in the DNA repair proteins, which normally protect against DNA damage, could lead to increased susceptibility to radiation induced SPC.

- Example: mutations affecting ataxia telangiectasia mutated (ATM), a protein which senses DNA damage and initiates a repair cascade, can lead to increased radiosensitivity and cancer susceptibility.

- It has been observed that radiation doses of < 0.2 Gy fails to activate the G2/M cell cycle check point. This could result in failure to repair DNA damage and could result in carcinogenesis.

Radiobiology

- Another mechanism that has been proposed to account for SPC at sites distant from the primary treatment area is the radiation induced bystander effect and tissue inflammation.

- Bystander effect involves intercellular communication through gap junctions and systemic cytokine signaling.

- There is no consensus on a precise designation of radiation induced bystander effect which involves a number of distinct signal-mediated effects within or outside the irradiated volume.

- Several cellular mechanisms were proposed: secretion of soluble factors by irradiated cells in the extracellular matrix or the direct communication between irradiated and neighboring non-irradiated cells via gap junctions.

- This phenomenon is observed in a context of major local inflammation, linked with a global imbalance of oxidative metabolism.

Radiobiology

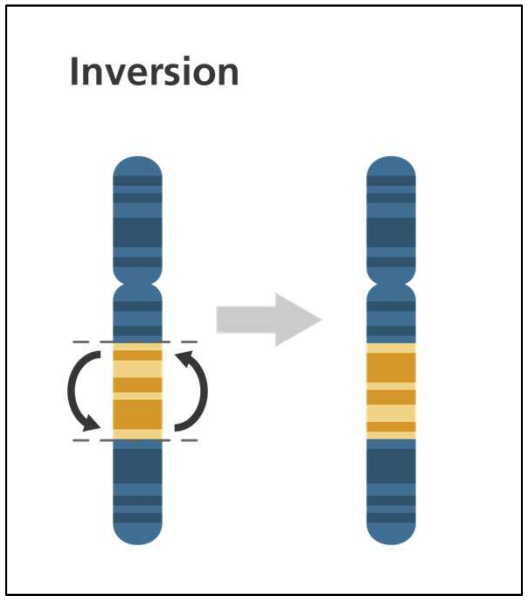
- The other major challenge in assessing radiation-induced secondary cancer risk is the limited understanding of the complex biological processes involved in radiation carcinogenesis;

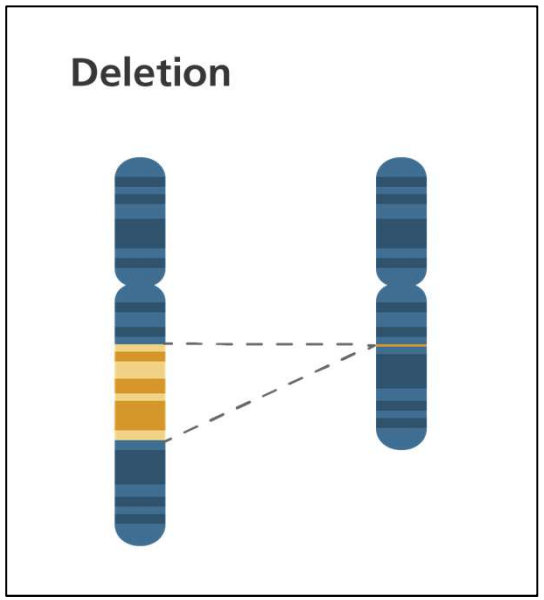
- Advances in molecular biology and genomics, bioinformatics and mathematical models can allow to understand the underlying mechanisms that may predispose or determine malignant transformation after radiotherapy, and to predict radiotherapy induced cancer risk.

Behjati S, Gundem G, Wedge, Roberts ND, Tarpey PS, Cooke SL, et al. Mutational signatures of radiation in second malignancies. Nat Commun 2016;7:12605.

The genomes of 12 radiation-associated SPCs of four different tumour types: osteosarcoma; spindle cell sarcoma; angiosarcoma; breast cancer.

Identification of two signatures: an excess of balanced inversions (change in gene order but no loss or gain of DNA) and of small deletions in radiation-associated SPCs.





Issues on second primary cancers

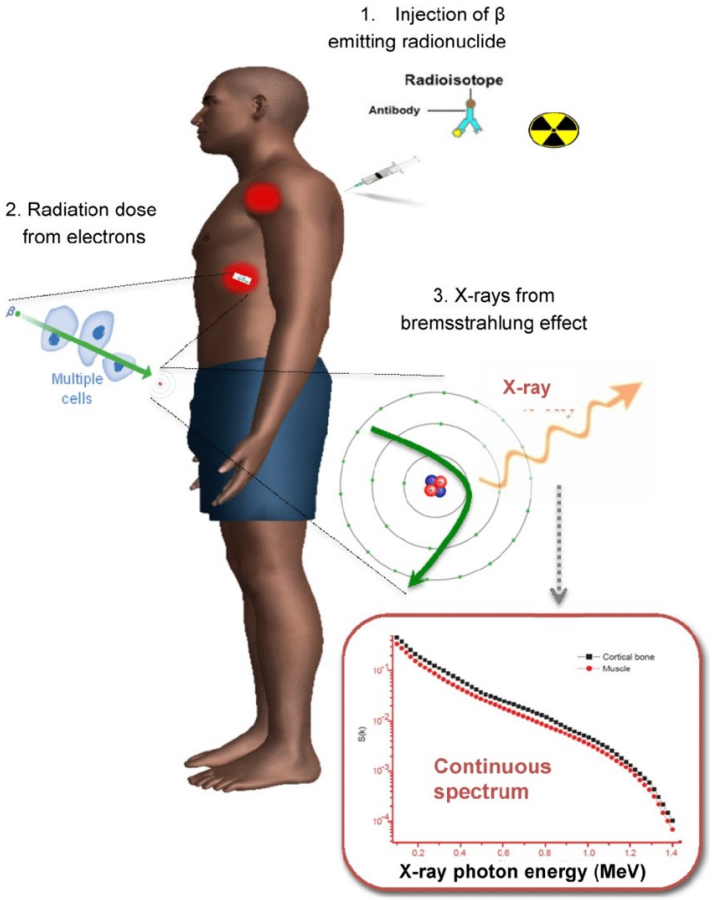
- What are the **molecular mechanisms** of radiation-induced cancer, especially of therapy-related cancers?
- The issue of **genetic susceptibility**, the possible presence of different mechanisms at low and high doses, and the problems of doses per sessions and radiation quality;
- The role of **microenvironment** in modulating **inflammatory reactions** in tumorigenesis.
- Variety of **radiation-induced non-targeted effects** (NTE) for 'out-of-field' areas: bystander and systemic effects?
- Can a **genetic mutation or polymorphism** that is associated with the primary cancer affect the risk and the mechanism of radiation-induced carcinogenesis?

Issues on radionuclide therapy

The initial results indicate that the risks of radiation-induced cancer from radionuclide therapy are on par with those predicted for external beam radiation therapy.

The risk of radiation-induced leukemia is potentially greatest given the differences in dose distributions involved.

It is imperative that more attention be afforded to investigating the cancer risks associated with radionuclide therapy.



The process for Y-90 radionuclide therapy and bremsstrahlung imaging for Y-90 dosimetry with a conventional gamma camera.

Conclusions

- What are the risks of developing SPCs after radiotherapy for different treated sites and how are they affected by the ever-changing technologies used?

- How can we optimize their risks without sacrificing the therapeutic benefits of radiotherapy?

- We have to improve radiation therapy technics and the follow-up of patients after a radiotherapy.

- We need to promote a rigorous **dosimetric framework** to test future models and to assess retrospective doses to contribute usefully to epidemiological studies.

Conclusions

- Cancer treatment has largest impact on second cancer risk among patients treated for a **first cancer at a young age** with excellent prognosis.

- **Sex and age** at time of childhood cancer diagnosis are important host-related factors.

- The impact of the **etiologic factors** of the first cancer and of cancer treatment characteristics for the first cancer on risk of second cancer has to be considered.

- **Molecular epidemiology** could improve our understanding of the pathogenesis of SPCs by identifying specific pathways, molecules and genes that influence the risk of developing SPCs.

Conclusions

- We have to address future research needs to explore how genetics and radiotherapy interact, as well as the link between radiotherapy and other cancer-causing agents.

- And to promote the development of new cancer screening strategies, sensitive and precise biomarkers of risk and early detection of second primary cancer.

The goal is to point out the carcinogenic risks, if any, of the newly introduced radiotherapy techniques, in order to help Radiation Oncologists to select the best technical approach and optimize the parameters of their protocols or clinical trials for specific patient populations to deliver the optimum dose to the tumour while minimizing the risk of a second primary cancer.

Currently the time is of personalized care.

Thank you for your attention!