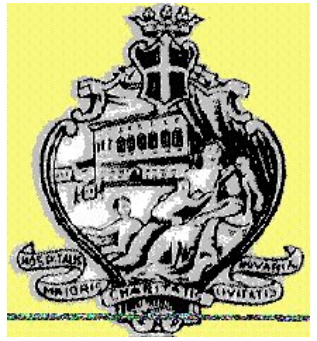
Out of field doses and associated risks of cancer in Radiotherapy



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Joint ICTP-IAEA Workshop on Radiation Protection in Image-Guided Radiotherapy (IGRT)

Summary

- Setting the scene
- Out-of-field organs and dose components
- Out-of-field organ dose measurements
- Out-of-field organ dose calculations
- Out-of-field cancer risk
  - *Estimation*
  - magnitude
- Factors affecting out-of-field cancer risk
- Conclusions

Setting the scene

- The 5-year survival for all cancer types has reached 71 % whereas 40% of these patients survive 10 years or more after primary diagnosis
- Radiation therapy either alone or combined with surgery and/or systemic treatments is applied in 50 to 60 % of patients with malignant disorders
- One of the late complications associated with the administration of radiation therapy is the development of subsequent malignancies. These second malignancies are presented not only inside and in the near periphery of the treatment volume but also at distant sites receiving low doses.
- The probability of developing second malignancies to critical sites excluded from the treatment volume may be estimated:
  - by theoretical methods based on the appropriate predictive models
  - by using data directly derived from epidemiological studies
- The measurements or calculations of the absorbed doses to out-of-field organs should always be considered as a prerequisite for the theoretical second cancer risk assessment

Out-of-field organs

Def. Out-of-field organs are those excluded from the treatment volume.

- They may be located along the beam path but outside the planning target volume (PTV) and, therefore, they are unavoidably exposed to both primary and secondary radiation (OARs).

- They may be completely excluded from the beam path. Their exposure is due only to secondary radiation (peripheral organs).

Secondary cancer

Def. (Cahan et al 1948)

- The secondary cancer is located in a region exposed to a therapeutic beam
- The tumor has a different histology than the original tumor, which means it is not a metastasis.
- Several years of time pass between treatment and occurrence of the new tumor
- The tumor was not present during the treatment
- No cancer-prone syndrome is known in the patient

Out-of-field doses

Different categorization coexists

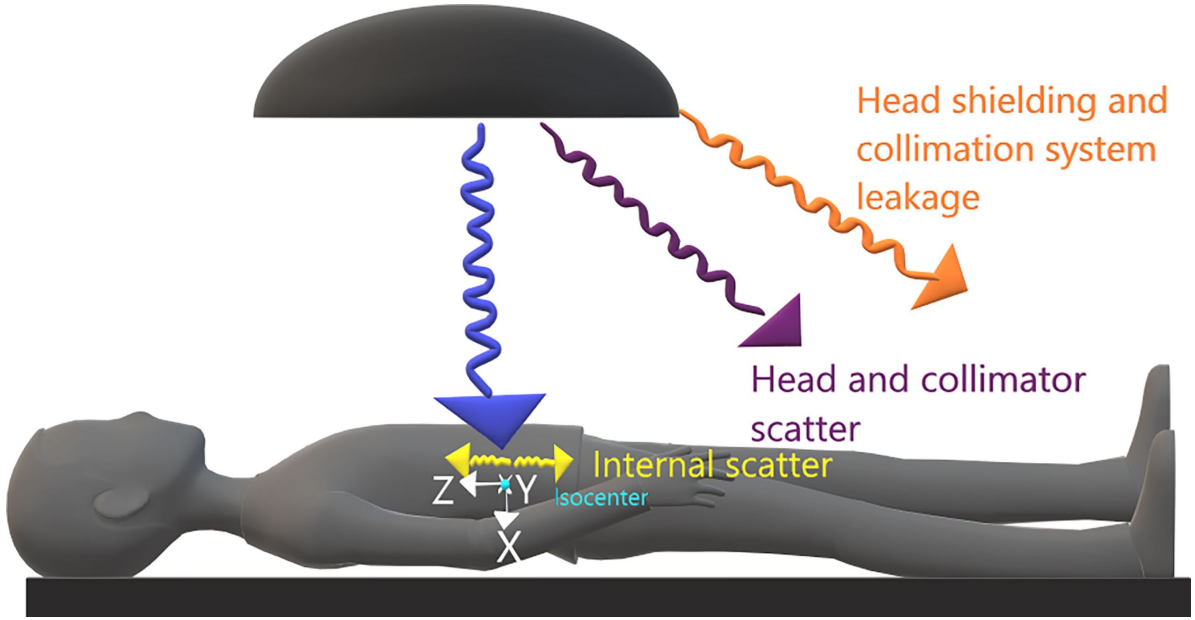
- Xu et al (2008)
  - High dose > 50 Gy
  - Intermediate doses 5 – 50 Gy
  - Low doses < 5 Gy

- AAPM
  - 30 Gy or 50% of the prescribed target dose
  - 3-30 Gy or 5-50% of the dose delivered to the tumor
  - <3 Gy or 5% of the dose delivered to the tumor

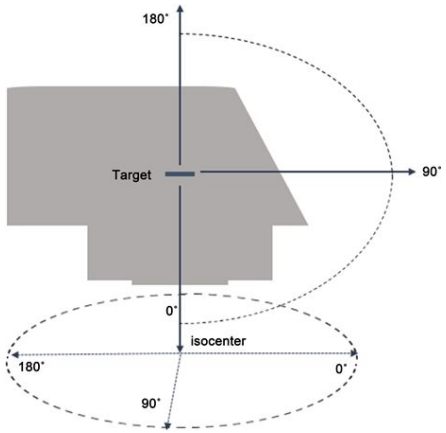
Component of peripheral organ dose

1. **Internal scattering of X rays**

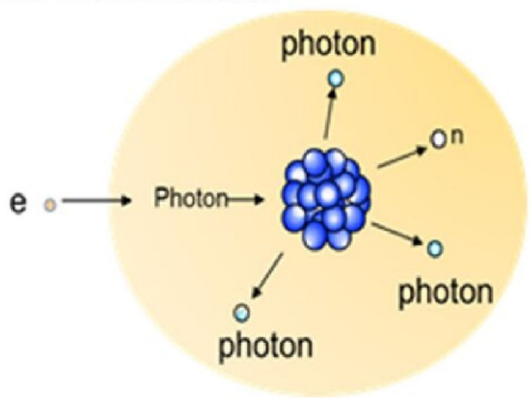
2. **Scattering produced by collimators, beam flatteners**



Leakage radiation for the Linac head



Neutrons for LINAC > 10 MV



Component of peripheral organ dose

- Internal scatter is the major contributor to the peripheral dose in the near periphery
- Head leakage prevails in the far periphery
- Internal scatter peripheral dose increases approximately in proportion with field size.
- The ratio between normalized internal scatter doses at 6 and 15 MV is approximately 2:1.
- The energy fluence spectra of the internal scatter component at all points of interest outside the field have peaks near 500 keV.

Chofor N, et al Phys Med Biol 2012

Out-of-field organ dose measurements

For a 6 MV nominal photon beam, the mean photon energy outside the primarily irradiated area varies from 0.2 to 0.5 MeV by the applied field size and off-axis distance

Scarboro SB, et al Med Phys 2011

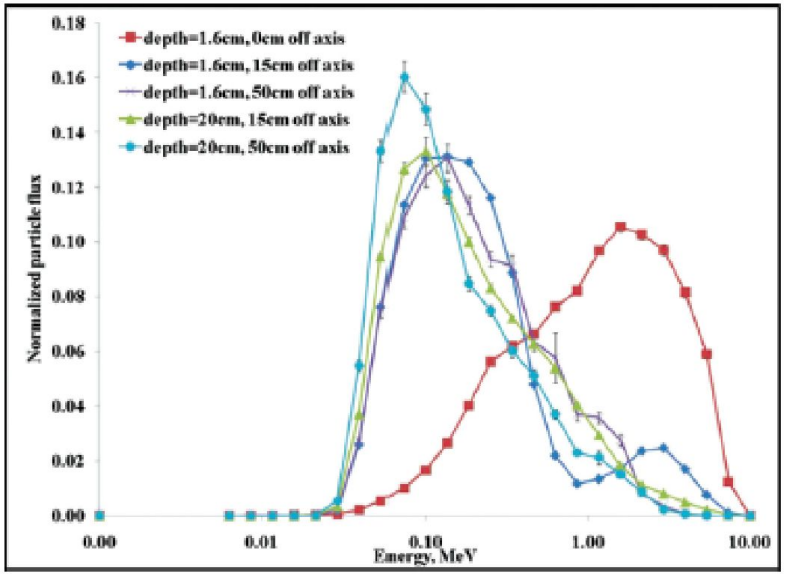


FIG. 4. Variations in out-of-field photon energy spectra as a function of distance from the central axis for 10 cm × 10 cm field.

- The calibration of the TLDs and OSLDs within the primary radiation field may result in peripheral organ dose overestimation.
- The use of individual sensitivity correction factors has been recommended

Knezevic Z, et al Radiat Meas 2013.

Out-of-field organ dose measurements

Dosimetric measurements can be performed using

Water tanks – Slab phantoms

This approach based either on water tanks or slab phantoms can not simulate the full-scatter geometry of a real patient. Considerable discrepancies between water phantom measurements and point doses determined on humanoid phantoms have been reported up to 40 % for pediatric patients. Farmer' chambers can be used in this configuration. FC within 5% mostly all depths and distances. Good choice for out of field

Gersh et al JACMP 2014

Anthropomorphic phantoms

They can simulate tissue heterogeneities such as bone and air. The anthropomorphic phantoms are usually sectional in design. Each section has a matrix of holes enabling the easy placement of TLDs or OLDs. The mean value of the TLD/OLD readings corresponds to the average organ dose.

Out-of-field organ dose calculations

Data from treatment planning systems (TPS)

Data from (TPS) have been used for estimating normal tissue complication probability and second cancer risk to organs depicted on CT scans. These organs are usually located close to the tumor site and receive intermediate to high radiation doses (OARs).

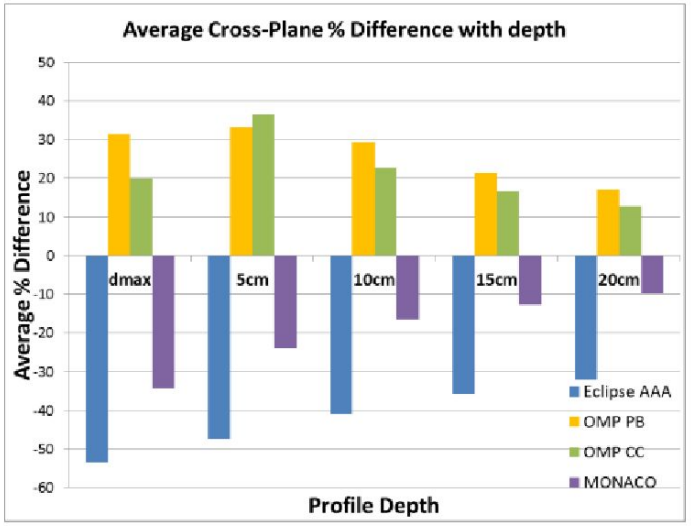
Raptis A, et al Phys Med 2020.

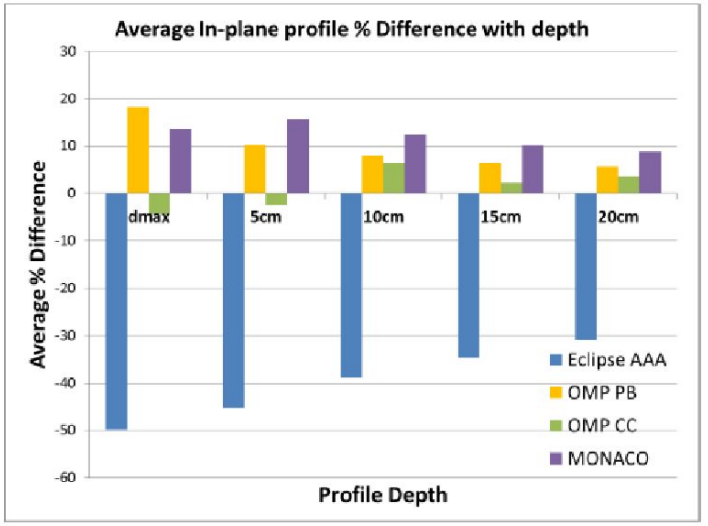
The TPS **underestimates the peripheral doses**

- from conformal fields by an average value of 40 %
- for IMRT plans by an average value of 50%
- Similar differences of 30–50 % between TPS and Monte Carlo calculations have been observed dealing with peripheral doses from flattened and unflattened 6, 10 and 15 MV photon beams

Howell RM, et al Phys Med Biol **2010**;

Not all **TPS underestimates the peripheral doses**





Out-of-field organ dose calculations

Conclusions for treatment planning systems (TPS)

Considerable variation in out-of-field dose calculation by different TPSs

- Differences between MC and TPS increased with increasing distance from the field edge but improved with increasing depth
- Not all TPS underestimated the dose
- Accuracy of TPS could be improved by refining the acceptance criteria/ improving the commissioning

Analytical models

- Analytical models have been applied for out-of-field dose estimations from D-CRT, IMRT and VMAT with 6 MV photons
- Mean differences of 11–44 % between model calculations and dosimetric measurements have been reported
- These analytical models may provide quick and useful data about the peripheral dose distribution but not directly organ doses

Hauri P, et al Med Phys 2016;

Out-of-field organ dose calculations

Monte Carlo simulations

Linear accelerator modeling

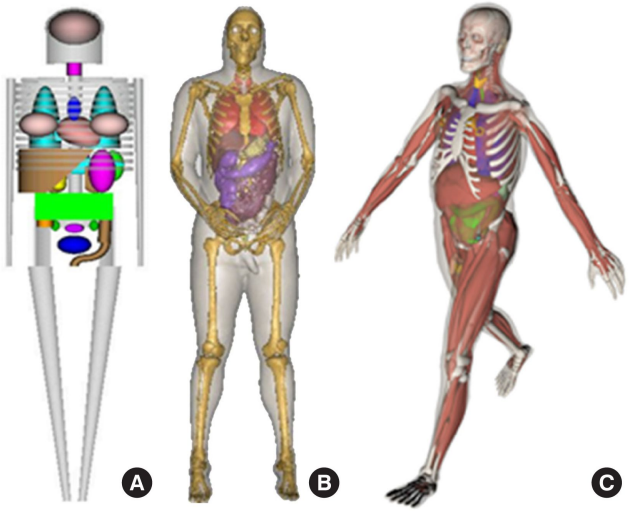
- The model usually includes the main beam modifying parts such as the target, primary collimators, monitor chamber, flattening filter, secondary collimators consisting of jaws and/or MLCs. More sophisticated models simulating the shielding parts of the linear accelerator head and structural components have also been reported in the literature
- These more complex models may lead to acceptable out-of-field dose calculations even at distances in excess of 50 cm from the central beam axis . An average difference of 16 % between Monte Carlo results and peripheral dose measurements has been reported (Kry Med Phys 2006)

Out-of-field organ dose calculations

Computational phantoms

A. Stylized(from the 1960s to the 1980s)

- mathematical representations of the exterior and interior characteristics of the human body of adults and children of both genders
- the weakness of these simple phantoms to simulate all anatomical details of the human body might lead to inaccurate results



B. Voxel (from the 1980s to present)

- Created through a series of CT or magnetic resonance (MR) images. The voxels within such a phantom simulate the density and chemical composition of each organ or tissue of interest and they may describe the human body more realistically than the stylized models.
- the weakness of these simple phantoms are the lack of deformability, the presence of stair-stepped artifacts and the difficulties to represent very thin and complicated structures

C. Hybrid (from the 2000s to present)

- They are fully deformable enabling alterations in the exterior and interior features of the phantom. They provide realistic anatomic representations including complicated or very thin structures and they allow the modeling of cardiac and respiratory motion

Cancer risk estimation

Out-of-field cancer risk assessments are made on the basis of the equivalent dose HR of any specific organ exposed to radiation R.

$$H_R = D \times w_R$$

where D is the average dose to the organ-at-risk and wR is the dimensionless weighting factor of a radiation R. The w_R for photon beams is equal to 1. The w_R value for neutrons depends upon the neutron energy and it takes values up to 20. For radiotherapy with X-rays of>10 MV, the total equivalent dose accounting for the contribution of both photons and neutrons should be used.

Cancer risk estimation (LNT)

A linear relationship between radiation exposure and carcinogenic effects may exist up to doses of 2 Gy based on the follow-up of atomic bomb survivors. The linear dose response may be valid up to 4 Gy in fractionated radiation therapy. This linearity

may extend down to a radiation dose of 0.1 Sv. The shape of the dose–response curve for radiation doses smaller than 0.1 Sv is under question.

The BEIR-VII committee [95] and the International Commission of Radiological Protection (ICRP) publication103 have suggested the extrapolation of the linear-no-threshold (LNT) hypothesis to doses below the aforementioned dose value. However, the well-known bystander effect and the presence of small populations with high radiosensitivity might constitute causes for a deviation from the linearity

Cancer risk estimation

BEIR VII model

$$ERR(e, a) \text{ or } EAR(e, a) = D\ \beta_{sex} \exp(\gamma e^*)\ (a/60)^{\eta}.$$

Where:
D is effective dose or organ dose (for site specific cancer incidence) in Sv
For ERR, the dose-parameter, βsex, is given in units of Sv^{-1}. For EAR, βsex is given in units of $(10{,}000 \text{ patient-years-Sv})^{-1}$
γ is the per-decade-exposure-age factor
e is age at exposure in years,
*e** is equal to (*e* – 30)/10 when *e* < 30, and equal to zero when *e* ≥30,
a is attained age in years.
η is the attained age exponent

Cancer risk estimation

Lifetime Attributable Risk (LAR) of cancer

The LAR for a person exposed to dose *D* at age *e* is calculated as follows:

$$LAR(D, e) = \Sigma\, aEAR\,(D, e, a) \times S(a) / S(e),$$

where the summation is from $a = e + L$ to l00, where *a* denotes attained age (years) and *L* is a risk-free latent period (*L*= 5 for solid cancers; *L* = 2 for leukemia).
S(*a*) is the probability of surviving until age *a*,
S(*a*) / *S*(*e*) is the probability of surviving to age *a* conditional on survival to age *e*.
All calculations are sex-specific; thus, the dependence of all quantities on sex is suppressed.

LAR is given in units of $(100{,}000 \text{ patient} \times 0.1 \text{ Sv})^{-1}$

Cancer risk estimation

How to interpret LAR) of cancer

The LR denotes the probability of an individual to develop a secondary malignancy at any time subsequent to the age at radiotherapy. To realize the LR magnitude, this quantity needs to be compared with the baseline risk (BR) of unexposed population. The BR may be found by data from cancer registries The combination of the LR and BR allows the calculation of the relative risk (RR) of developing secondary malignancies with the formula:

$$RR=(BR+LR)/BR$$

For example, the LR for bladder cancer induction of a 30-year-old patient undergoing paraaortic irradiation for testicular seminoma with typical field dimensions is 0.127 % [73]. The respective BR provided by SEER database equals to 3.95 % [3]. The use of the Eq. (2) results in a RR of 1.032. This implies that radiation therapy results in a bladder cancerrisk increase by 3.2 % in respect to the BR of unexposed US males.

Mazonakis et al, Phys Med 2021

Cancer risk magnitude

- The previously published out-of-field organ doses due to cancer treatment of adult patients were 5 to 2190 mSv.
- The dose range to critical organs for children was 3.6–283.0 mSv.
- The whole-body LR for adults subjected to radiation therapy varied from 0.3 % to 9.4 % by the treatment technique, the patient's age and gender.
- The organ-specific cancer risks were found to be up to 1.7 %.
- The respective probabilities for organ-dependent radiation-induced malignancies in pediatric patients were 0.01–1.4 %.

Factors affecting the risk

Radiation therapy technique

- The use of IMRT and VMAT for primary carcinomas results in an increased probability of carcinogenesis compared to that from 3D-CRT.
  - The whole-body LR for IMRT may range from 2.1 to 5.1 % by the photon energy used whereas that from 3DCRT is only 1.7%.
  - This may be attributed to the extended treatment delivery times and to large volume of irradiated healthy tissues.

- The removal of the flattening filter and the elimination of the scattered radiation produced by this machine's component reduce the out-of-field organ doses and cancer risks. Statistically significant reductions have been documented using IMRT and VMAT with the flattening filter free (FFF) mode compared to treatments with flattened beams

- Photon therapy is characterized in general by a higher overall out-of-field dose than ion therapy.

Factors affecting the risk

Radiation therapy parameters

- Therapeutic irradiation with the low beam energy of 6 MV always requires the use of increased MUs leading to elevated out-of-field organ doses and risks.

- For treatment with photon energies > 10 MV, the probabilities of carcinogenesis are enhanced with the energy increase. This is due to the unavoidable neutron generation elevating the radiation dose to sites excluded from the treatment volume.

- The out-of-field cancer risk magnitude may be also dependent upon the applied field dimensions, with an increase depending on the dimensions of the filed size

Shielding of the out-of-field organs

The use of lead shields

- May block the out-of-field organs from head leakage and scatter generated by the machine.
- Has no effect on the scattered radiation produced within the patient

- Shielding devices have been widely employed in the past for fetal dose reduction during external-beam radiation therapy.

Mazonakis M, et al Phys Med 2017

- The protection of critical out-of-field organs through shielding for the restriction of the radiogenic risks is nowadays rarely applied in clinical practice.

- Most of the relevant publications in the past refer to pediatric patients subjected to radiotherapy with lead shield thickness comprised between 1 and 10 mm Pb and a reduction ranging from 25% to 50% depending on the site of irradiation and the organ shielded.

Out-of-field organ dose

a New component

Imaging dose from cone beam computed tomography in radiation therapy

- Imaging dose in radiation therapy has traditionally been ignored due to its low magnitude and frequency in comparison to therapeutic dose used to treat patients.
- The advent of modern, volumetric, imaging modalities, often as an integral part of linear accelerators, has facilitated the implementation of image guided radiation therapy (IGRT), which is often accomplished by daily imaging of patients.
- Daily imaging results in additional dose delivered to patient that warrants new attention be given to
  - Imaging dose.
  - Peripheral dose

Alaei P, Spezi E. Phys Med. 2015;

Imaging dose

Imaging dose from cone beam computed tomography in radiation Therapy

- The doses measured in phantoms range from 0.01 to 13 cGy per acquisition due to variations of imaging devices, type and size of phantom, location of measurement within phantom, and imaging techniques used.
- The Kilovoltage dose is heterogeneously distributed and typically exhibits its maximum dose on the skin, and with the increased absorption in bone due to prominence of photoelectric effect.
- Megavoltage CBCT imaging using the 6 MV beam results in higher dose than kilovoltage one with a direct correlation to the imaging protocol.
- The patient studies generally employed TLDs or other dosimeters to measure skin dose although there have been two studies measuring the dose inside the rectum.
- The rectal dose measurements indicate 2 e 3 cGy average dose to rectum per CBCT acquisition for the protocol used in clinical practice for pelvic imaging on the Elekta system.

Alaei P, Spezi E. Phys Med. 2015;

Effective dose from CBCT

- The AAPM Task Group 75 reported effective dose values within a wide range of 1.1- 24 mSv for trunk and **0.04- 9.4 mSv for head and neck imaging, per fraction.**
- In general, low dose imaging protocols employed in head and neck imaging result in effective doses less than 2 mSv/fraction.
- Effective doses of up to **24 mSv/fraction** have been reported for standard imaging protocols.

Peripheral dose from CBCT

Perks et al. measured the peripheral dose from kV CBCT. They concluded that peripheral doses from imaging, at measurement points of equal distance from the central axis, are of the same order of magnitude as those of an IMRT treatment.

Perks JR, et al Radiother Oncol 2008;

Conclusions 1- Measure and estimation

- The out-of-field organ dose calculations derived from:
  - Water tanks and slab phantoms
  - Treatment planning systems

Suffer from some inaccuracies which must be known and taken into account when doing risk estimations. However they are easy to be implemented and used in the clinical practice.

- The most accurate way to directly determine the radiation dose to organs located outside the treatment volume relies on the use of physical humanoid phantoms representing the full-scatter geometry of an adult or pediatric patient. TLDs are usually introduced in the anthropomorphic phantoms at sites corresponding to the location of the organ of interest.

- Monte Carlo simulations combined with realistic computational phantoms have been extensively carried out for out-of-field organ dose calculations in external-beam radiation therapy. Special consideration should be given in the modeling of the linear accelerator parts influencing the non-target doses and in the model validation. The validation should always include comparisons of Monte Carlo calculations with direct peripheral dose measurements.

Conclusions 2- Risk assessment

- Epidemiological data may lead to useful information concerning the quantification of the second cancer risk attributable to radiation therapy. However, the collection of this type of data is a difficult and time-consuming task.

- Theoretical out-of-field cancer risk estimates, based on the combination of the results of organ-specific dosimetry and well-established linear models, may contain a lot of uncertainty. However, theoretical cancer risk estimates may be directly obtained without the need for a prolonged follow-up of a large number of irradiated cancer survivors.

- The theoretical methods give information of the out-of-field cancer risk due to modern irradiation techniques applied for a limited time period in clinical practice.

- The comparison of the second cancer risks associated with modern and conventional treatments may be of value in the selection of optimal irradiation technique especially for young patients with good prognosis.

Conclusions 3- Summary and perspectives

- Out of field doses in radiotherapy can be relatively high
- Modern treatment techniques can deliver low doses to larger volumes
- Need improved methods to track dose delivered out of field
  - Deformable models
- Need improved dose models and measurements to assess:
  - radiobiological impact – effects on cell types
  - clinical impact – improved optimisation and clinical DVC's
  - Cancer induction risks
- Further work on suitability of detectors for out of field measurements
- Guidelines for commissioning TPS for out of field doses?

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