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Photons – Radiobiological issues related to the risk of second malignancies

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A B S T R A C T

Photons are widely used in radiotherapy and while they are low LET radiation, can still pose a risk in developing second malignant neoplasms (SMN). Due to the physics of photons that allow distribution of energy outside the target volume, out-of-field irradiation is an important component of SMN risk assessment. The epidemiological evidence supporting this risk should be augmented with radiobiological justifications for a better understanding of the underlying processes.

There are several factors that impact second cancer risk which can be analysed from a radiobiological perspective: age at irradiation, type of irradiated tissue, irradiated volume, treatment technique, previous irradiation/radiological investigations. Age-dependence has a radiobiological foundation given by the higher radiosensitivity of children as compared to adult patients. However, in its 2013 report, UNSCEAR advises against generalisation of the effects of childhood radiation exposure, given the fact that these effects are strongly organ dependent. Furthermore, the age-dependent radiation sensitivity has a bimodal distribution, since aging cells present an increase in the oxidative stress, which can promote pre-malignant cells.

Non-targeted effects such as radiation-induced genomic instability, bystander or abscopal effects could also impact on the risk of SMN. Recent studies show that beside the known cellular changes, bystander effects can be manifested through increased cell proliferation, which could be a culprit for SMN development. Furthermore, new evidence on the existence of tumour-specific cancer stem cells that are long-lived and more quiescent and radioresistant than non-stem cancer cells can raise questions about their association with SMN risk.

1. Introduction

Similar to an electrical circuit where in order to measure the current, the system will unavoidably be perturbed by the introduction of an ammeter, to diagnose or treat a disease in the human body, one is interfering with the system, potentially inducing unwanted effects. The ammeter's resistance is optimised to a value which is low enough to cause insignificant perturbance yet high enough to produce a measurable output. Similarly, when imaging or treating a patient with ionising radiation interferences are produced and therefore the benefits should outweigh the risks.

The role of medical imaging is to accurately diagnose a disease in order to treat the patient accordingly. Medical imaging plays a critical role in healthcare systems worldwide and the number of individuals exposed to radiation from imaging technologies constantly increases. The exposure of an individual for diagnostic purposes should be small enough not to interfere with the patients' wellbeing in the long term and large enough to create an image correctly interpretable by the physician.

The situation is different in radiotherapy, where the aim is to attain a high therapeutic ratio, by balancing tumour control and normal tissue toxicity. Hippocrates's advice "do no harm" should be translated here into a better protection of the normal tissue and a high target dose conformity while trying to avoid long-term effects. Unfortunately, linear accelerator-based radiation has been proven by several studies to increase the risk of second malignant neoplasms.

2. Photon-induced increase in second cancer incidence

Cancer is a multifactorial disease. While it can arise at any age, the incidence of malignancies is more common in the older individuals [1]. The increased cancer incidence is due to a reduced

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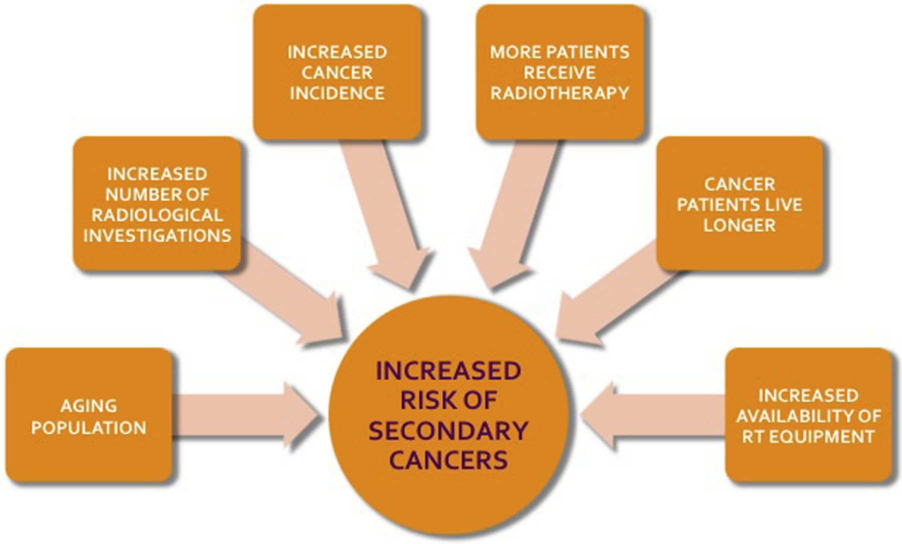

Fig. 1. Factors that contribute to the increased risk of second cancer.

ability to accurately repair the DNA damage, which is linked to the deterioration of cancer-fighting mechanisms over time. Thus, the accumulation of pre-cancerous lesions can, eventually, develop into various neoplasms.

Through interaction with the living cells, ionising radiation can disrupt atomic structures causing physical, chemical and biological changes. Being uncharged, photons interact indirectly with cells through water radiolysis, producing therefore reactive chemical species that affect cellular components. Depending on the level of the biochemical damage induced by radiation, cells can either repair the lesion or die. An accurate repair of the DNA damage will have no unwanted consequences, while misrepair can lead to permanent alterations, induction of mutations and cancer promotion.

The wide availability and use of modern imaging techniques has greatly increased the number of radiological investigations, which in turn resulted in early diagnosis of cancer in a large number of individuals. The early detection has led to treatment, most often in the form of radiotherapy. Today's technological advancements result in better patient management and high tumour control, with many patients living a longer life. The increase in life expectancy poses an increased risk in cancer development, either because of age, or because of previous irradiation (see Fig. 1). This vicious circle is responsible for the increased risk of second malignant neoplasms, where photons play an important role. While high LET therapy is becoming more common, linear accelerator-based treatment keeps overshadowing other forms of radiotherapy. Whereas the physics of photons is responsible for tumour cure, it is also responsible for its side effects.

3. Photons in diagnostic imaging and treatment guidance

Photons are involved in medical imaging, treatment guidance and radiotherapy across a wide dose range. According to the UNSCEAR 2012 report [2], low doses are referred to values below 100 mGy, however, within diagnostic imaging, the range can be further stratified into low radiological doses (<1 mGy) and higher radiological doses (5–100 mGy) (Table 1). As mentioned above, the prevalence of medical imaging and of image-guided therapy is on the rise. Also, older techniques are being replaced by newer developments, which often result in larger doses to the patient. Such an example is the cone beam computed tomography (CBCT), now widely used in dental imaging, that is slowly overtaking conventional dental radiographs. CBCT offers higher quality diagnosis through a better understanding of the extent of dental disease, however this comes with higher doses delivered to the patient. Depending on the imaging detector, field of view and the used voxel size for scanning [3], doses from CBCT can be borderline between low and high radiological doses, as shown in Table 1. Therefore, next to the ALARA principle, the radiologist should also be mindful of the three fundamental principles of radiological protection as recommended by the ICRP: justification, optimisation, and the application of dose limits [4].

Table 1
The use of photons in medical settings.

Photons	Diagnostic	Imaging involving low radiological doses (<1 mGy): dental radiograph, chest examination Imaging involving higher radiological doses (5–100 mGy): CT, PET, SPECT, fluoroscopy, Cone-beam CT Nuclear medicine
	Interventional radiology	Fluoroscopy (>100 mGy)
	Treatment	External beam radiotherapy Brachytherapy

In radiotherapy, CBCT is an important tool for patient setup verification and its use is still on the rise. Also, cancer diagnosis and management makes increasing use of PET and other image guided radiotherapy methods, all contributing to patient exposure and elevation of SMN risk.

Interventional radiology, particularly fluoroscopically guided medical procedures, are a crucial component of modern medicine. Due to the extent of these procedures, doses received by patients via interventional radiology can be significant, even of the order of a few Gy [5]. A comprehensive clinical study (RAD-IR) undertaken by Miller et al. on over 2100 instances of interventional radiology procedures has shown that the high doses received by patients justify data logging in the medical records together with indicators of the risks of stochastic and deterministic effects [5]. Fluoroscopically guided procedures are also common in brachytherapy.

The challenge regarding risk estimations in the low dose range area of radiological imaging consist of the lack or scarcity of reliable data in this dose range (<1 mGy). While *in vitro* models for the assessment of radiation-induced cancer include a series of tests