Early/late developing normal tissue reactions following radiotherapy

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Tissue reactions - introduction

- There is a diverse range of tissues that may be damaged by radiation exposure and the threshold doses above which tissue injury is observed vary.
- The System of protection aims to avoid tissue injury, and indeed in most situations exposures are low and below threshold levels. A notable exception is where radiation is used for cancer therapy.

Early/late tissue reactions following radiotherapy in humans – some stats:

REQUITE study (2018) CTCAE v4.0 toxicity data:
For breast (1700 patients): 5 – 13% of CTCAE grade ≥2 toxicities at 2 years
For prostate (1430 patients): < 5% gastro-intestinal, 3-8% genitourinary, 20-31% sexual at 2 years
For lung (330 patients): 4-7% common toxicities, 27% dyspnoea at 1 year

CHHiP trial (2016) 3216 prostate cancer patients, 5 year follow up:
74 Gy: ≥2 toxicities: bowel13.7%, bladder: 9.1 %
60 Gy: ≥2 toxicities: bowel11.9%, bladder: 11.7 %
57 Gy: ≥2 toxicities: bowel13.3%, bladder: 6.6 %

Modification by lifestyle and environmental factors I

Cigarette smoking

There is clear evidence that smoking increases clinical radiosensitivity in most cancers. The mechanisms of the potentiating effect of smoking on radiotherapy toxicities are not clear. It cannot be excluded that the effect is related to the lower socioeconomic status and fitness of smokers compared to non-smokers.

Smoking lowers the inflammatory radiation response resulting in reduced level of pneumonitis following lung RT. This suggests an important role of the immune system in developing toxicities.

Alcohol consumption

Assessment difficult because of different beverages and association with cigarette smoking. Associated with a significantly enhanced likelihood of osteoradionecrosis in oral and oropharyngeal cancer patients. Red wine consumption was found to protect against skin toxicities in breast cancer patients. Findings must be validated.

Modification by lifestyle and environmental factors II

Chemotherapy

Despite variability with respect to tumour location and the applied chemotherapy drugs, the results of published studies clearly show that chemotherapy potentiates the incidence and severity of both early and late side effects.

Mechanistically, the effect is rather the outcome of biological cooperation (targeting distinct cell populations) than of cytotoxic enhancement. This conclusion fits well with the findings that the immune system plays an important role in modulating the likelihood of side effects to RT.

Body mass index (BMI) and diet

A low BMI is sometimes associated with increased toxicities. This may be related to the fact that wound healing is impaired in underweight (malnourished) patients.

Modification by the immune system

Impact of immune therapy

Results of limited studies on combining radiotherapy and checkpoint inhibitors to mainly treat melanomas do not demonstrate an increased level of toxicity.

No studies exist on the impact of TLR agonists on normal tissue toxicity in patients receiving radiotherapy.

No studies exist on the impact of MHC/HLA genotype or blood group on normal tissue toxicity in patients receiving radiotherapy.

Impact of the microbiome

Results from few, small scale studies suggest that the microbiome may modulate the development of toxicities.

Modification by age and sex

Impact of age

For early tissue reactions children are more sensitive than people of advanced age, but less sensitive than middle-aged adults. The reason for this is complex and involves an interplay of various sensitising and protecting factors, the balance of which changes with age at exposure. For late tissue reactions children are more sensitive than adults, but not for all organs and tissues.

Impact of sex

The findings on the impact of sex on radiotherapy toxicity are mixed, with a tendency towards females showing a higher sensitivity. This likely results from differences in pharmacokinetics of chemotherapy drugs, hormone status and differences in radiation energy deposition rather than differences in intrinsic radiosensitivity.

Modification by comorbidities

Systemic diseases leading to impaired wound healing such as uncontrolled diabetes or autoimmune diseases are associated with an increased risk of toxicities.

Patients with cardiovascular disease, inflammatory bowel disease and hypertension are at a somewhat increased risk of toxicity after radiotherapy.

Possibilities of prediction

Promising results that need validating were achieved with functional tests looking at:

- ATM nucleo-shuttling
- Surviving fraction at 2 Gy
- Radiation-induced lymphocyte apoptosis

Positive but inconsistent results were achieved with genetic tests for identifying single nucleotide polymorphisms in few high penetrance genes (SNP genotyping) or in many low penetrance genes (genome-wide association studies).

In phenotypically normal people, the genetic component responsible for radiation toxicities may be low, as opposed to strongly increased radiosensitivity in patients with rare monogenic diseases such as Ataxia Telangiectasia (AT), Nijmegen Breakage Syndrome (NBS) or the Bloom Syndrome (BM).

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