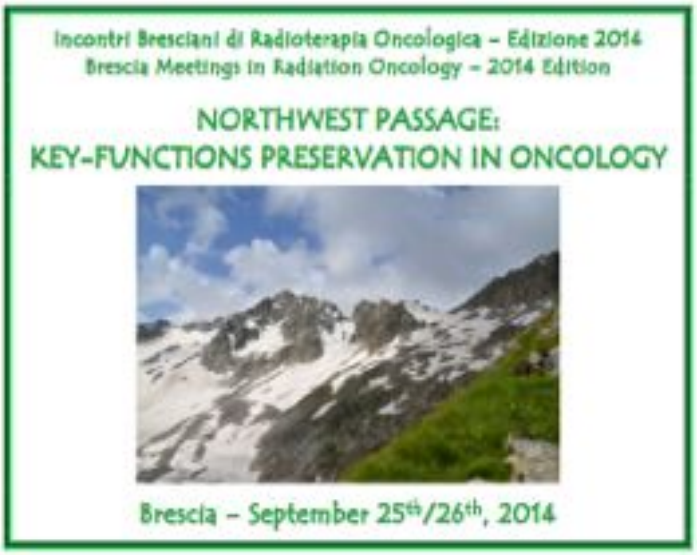
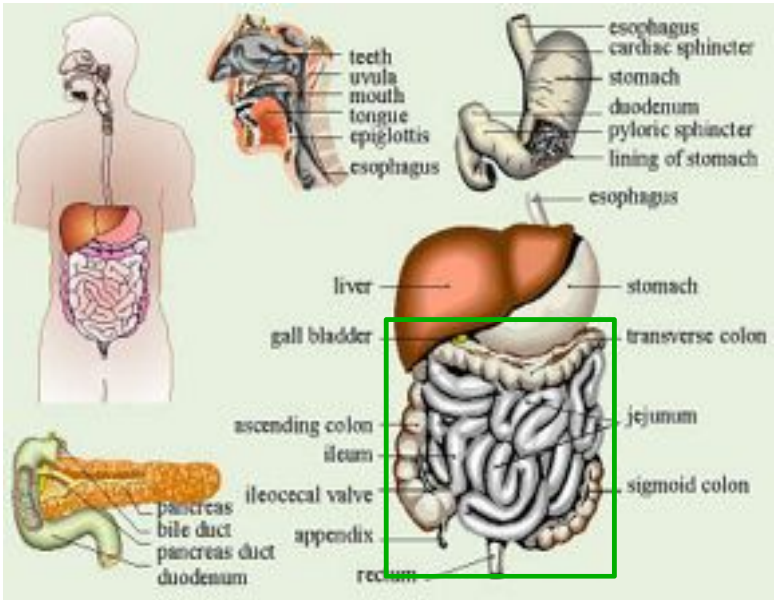
NADIA PASINETTI MD PhD

Biological basis of radiation damage to the digestive system



Introduction

The human digestive system



The largest component of the GI tract is the lower gastrointestinal tract, that include small and large intestine (also called bowel or gut)

Radiation therapy is used in at least 50% of patients with cancer and has a crucial role in 25% of cancer cures.

Despite advances in treatment delivery techniques, radiation toxicity to healthy tissue remains the most important barrier to cancer cure in patients with localized disease.

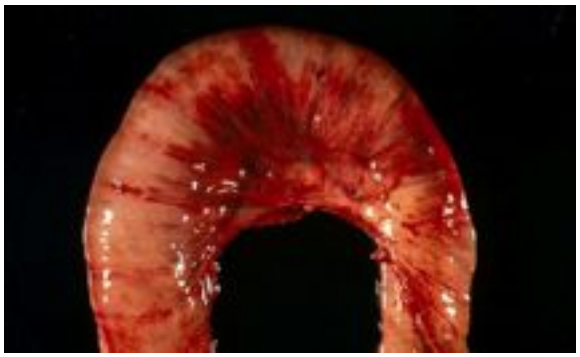
During radiation therapy of tumors in the abdomen or pelvis
the bowel is at risk of damage

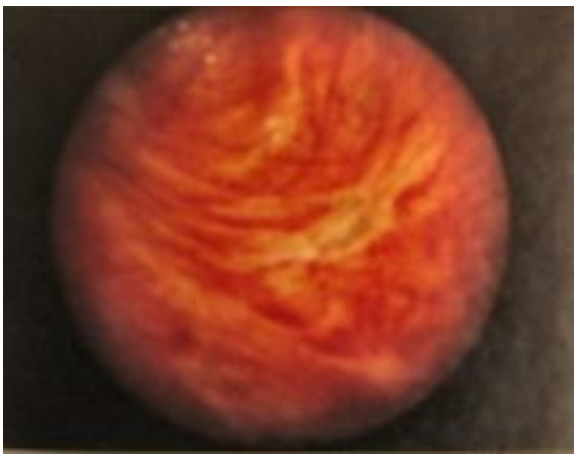
DeVita, V. T. et al..**Principles & Practice of Oncology (Wolters Kluwer Health/Lippincott Williams & Wilkins, 2011)**

Symptoms of intestinal radiation injury may occur during and/or after treatment

Depending on the time of onset intestinal radiation injury is divided into: acute/early and chronic/delayed radiation injury.

DeVita, V. T. et al..**Principles & Practice of Oncology (Wolters Kluwer Health/Lippincott Williams & Wilkins, 2011)**



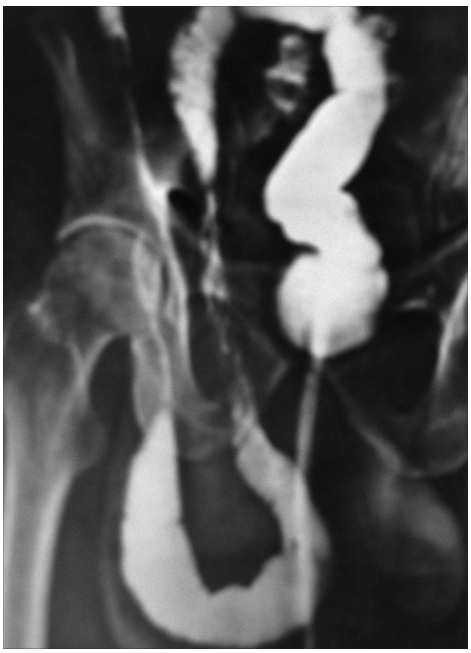


Early/acute radiation enteropathy

Occurs within 3 months of radiation therapy and affects the quality of life at the time of treatment.

Delayed/chronic radiation enteropathy

Is a major issue for long-term cancer survivors; this progressive condition has few therapeutic options available and can lead to substantial long-term morbidity and mortality.



Understanding the toxicity

'Target cell' theory (1920s – 1940s)

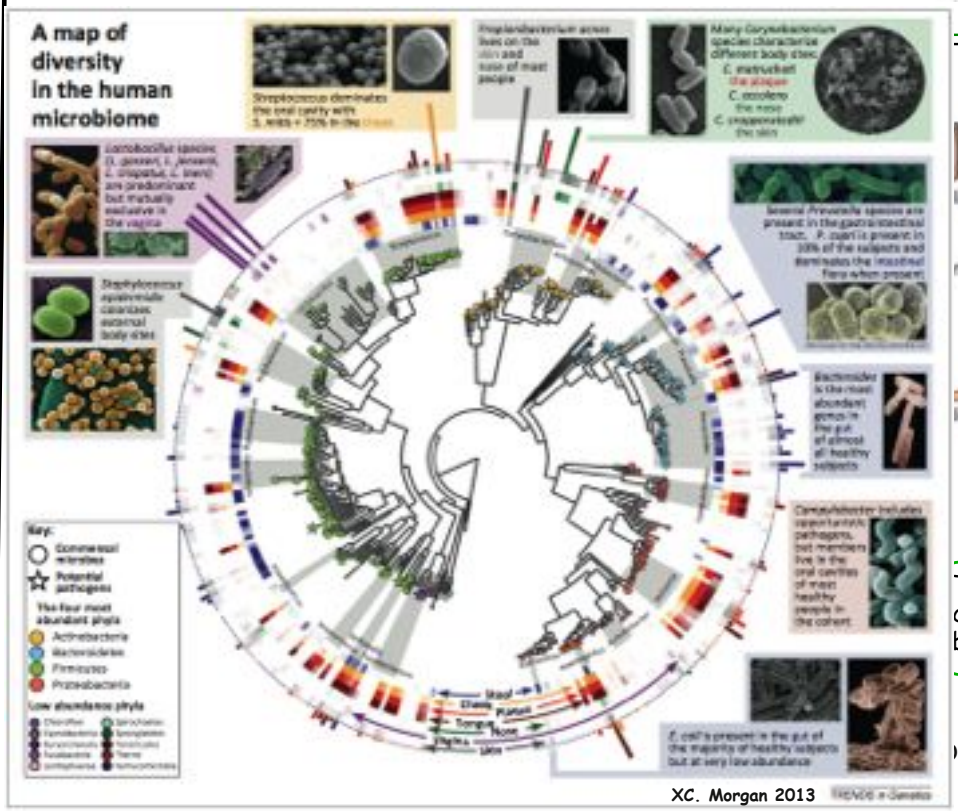
The intestine was considered a more or less inert tube, covered internally by a rapidly proliferating epithelium, with the rest of the bowel tissues more or less irrelevant.
The severity of epithelial injury was the only determinant of early pathology, whereas a different, more slowly proliferating, target cell (fibroblast, endothelial cell) was used to explain delayed effects.

'Contemporary' theory

The sequence of structural and functional manifestations of radiation enteropathy has not changed, but our understanding of the underlying pathobiology has improved over the years.

The contemporary view is that:
many tissues and cell types in the gut participate and contribute to injury

Martin Hauer-Jensen et al.
Nat Rev Gastroenterol Hepatol. 2014



The total microbial community, including biomolecules

Martin Hauer-Jensen et al.
Nat Rev Gastroenterol Hepatol. 2014

Bourne, Peters and colleagues clinically recognized that delayed radiation injury might develop in the wake of severe acute injury.

Consequential late effects theory
(1980)

~~Independence between early and delayed radiation effects~~

OLD DOGMA

improving our understanding of the pathophysiology and pathogenesis of delayed normal tissue injury

interpreting and **modelling** radiation responses *in vivo*

Bourne, R. G., **Int. J. Radiat. Oncol. Biol. Phys.1983**

Peters, L. J., **Acta Oncol. 1988.**

However, it has become increasingly clear that the terminology **"consequential late tissue injury"** **fails** to recognize the complexity of radiation effects in multicellular tissues and organs.

A new terminology for classifying healthy tissue radiation responses was proposed in **2001**

According to this classification, there are **three types of effect**:

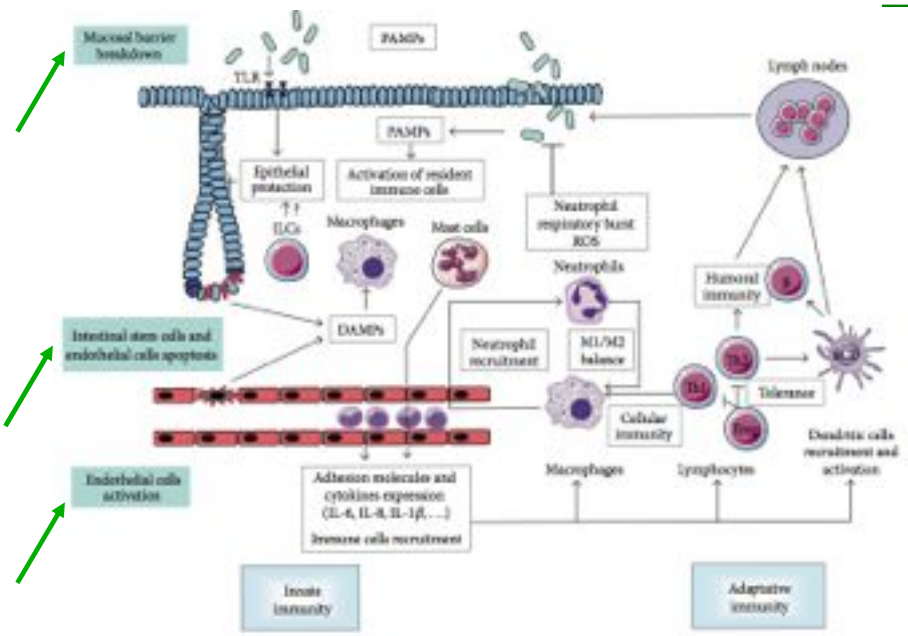
First, **cytocidal effects**, in which radiation causes cell death including clonogenic cell death, mitotic catastrophe and apoptosis.

Second, **functional effects**, in which radiation leads to changes including transcription factor activation and protein modification in the intracellular environment, plasma membrane and extracellular space.

Third, **secondary effects** that occur in response to the initial radiation insult, such as cellular inflammation and release of cytokines and other mediators.

All three types of effect interact and contribute to organ dysfunction

Denham, J. W. **Int. J. Radiat. Oncol. Biol. Phys. 2001**



1. production of reactive oxygen/nitrate species;

2. induction of apoptosis and clonogenic cell death;

3. mucosal breakdown;

4. activation of the transcription of several proinflammatory cytokines, chemokines, and growth factors in the microvascular and mucosal compartments.

François A, et al., **BioMed Research International Volume 2013**

Critical target compartment involved in tissue response to radiation exposure is the **vascular endothelium**

Irradiation of the vascular endothelium leads to endothelial cell apoptosis and the acquisition of a

proinflammatory phenotype

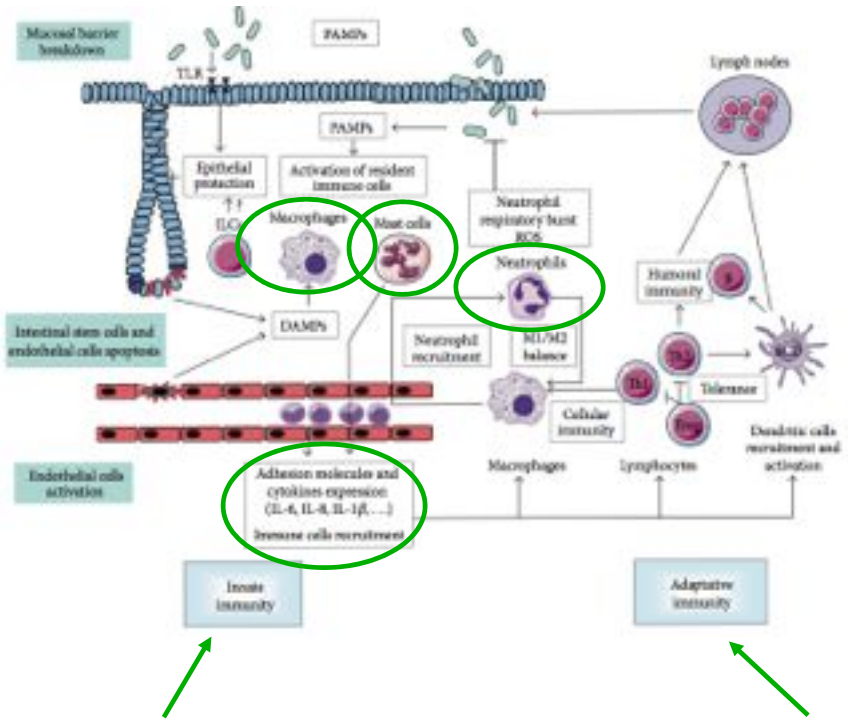
prothrombotic phenotype

antifibrinolytic phenotype

with increased secretion of soluble mediators such as cytokines, chemokines, and growth factors

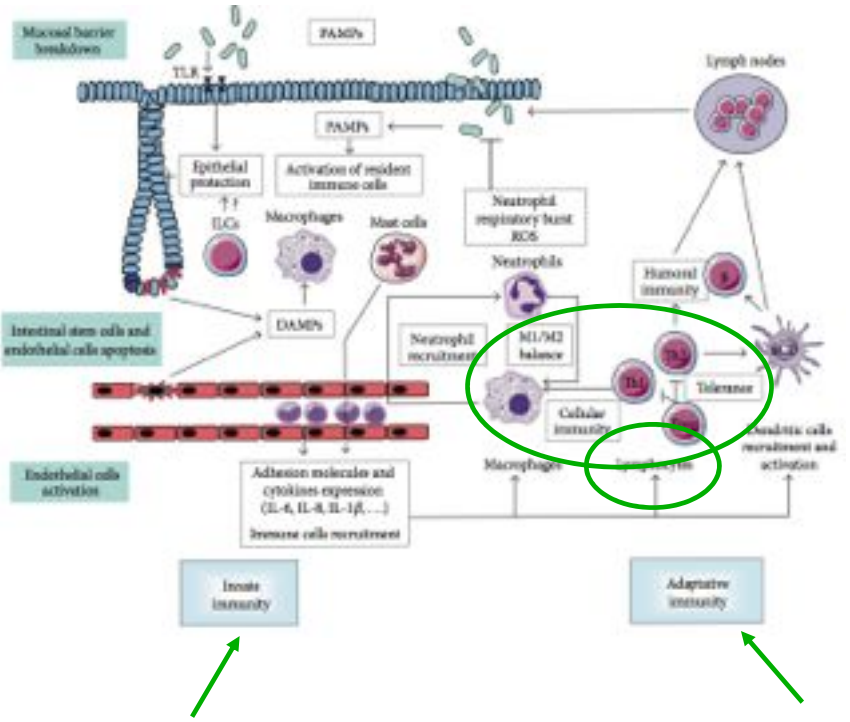
J.Wang et al., **World Journal of Gastroenterology 2007**

Proinflammatory soluble mediators by irradiated endothelial cells activate resident macrophages and favour the early recruitment of polymorphonuclear neutrophils from the bloodstream.



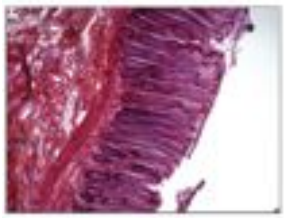
Inflammatory process is amplified by the recruitment and transmigration of monocytes and the activation of resident mast cells, both producing proinflammatory and profibrosing mediators such as IL-1β, IL-6, IL-8, CXCL-1, CXCL-2, TNF-α or TGF- β

Lymphocyte infiltrate is a common feature of irradiated normal tissues, especially in the subacute and chronic inflammatory phases of radiation damage.

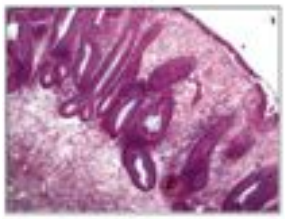


Globally, radiation exposure, by its direct effects on adaptative immune cells and by the generation of innate immune response and inflammation, triggers an imbalance in immune populations which still remains obscure

Radiation-induced damage to the rectal wall



Healthy rectal mucosa

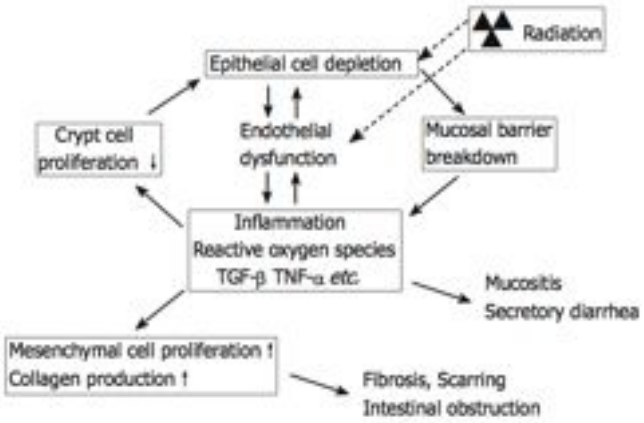


Epithelial atypia with mucosal oedema and inflammation. Crypt positioning is disorganized and some are bifid and show hyperplasia, both signing epithelial regeneration.

Severe mucosal ulceration with submucosal oedema and dense inflammatory infiltrate.
Crypt number is drastically reduced.

François A, et al., **BioMed Research International Volume 2013**

Model of interaction between epithelial and endothelial radiation injury in the intestine



Endothelial dysfunction may exacerbate the early intestinal radiation response and "drive" the cycle of chronicity of intestinal radiation fibrosis

The combination of **loss of epithelial barrier function** and **endothelial dysfunction:**
- enhances the post-radiation inflammatory response,
- inhibits restitution of the epithelium,
- promotes extracellular matrix deposition.

Wang J. et al., **World J Gastroenterol. 2007 Review.**

In conclusion...

Normal gut tissue response to radiation exposure is the result of cell death and activation in all tissue compartments, with a strong oxidative and immunoinflammatory component.

Given the relatively poor therapeutic efficiency of "classic" anti-inflammatory strategies, it appears necessary to **increase** the **knowledge** concerning:

- enduring oxidative stress,

- vascular endothelial cell activation,

- immune cells recruitment and their phenotypic orientations such as M1/M2 macrophages and lymphocytes Th1/Th2/Th17/Treg balances

- conditions necessary to the resolution of radiation-induced inflammation.

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Table 1 Potential pharmacological strategies for modulating post-radiation endothelial dysfunction to ameliorate development of radiation enteropathy and some of their respective limitations

Intervention	Major limitation
Platelet aggregation inhibitors	Narrow therapeutic window (bleeding)
Direct thrombin inhibitors	Narrow therapeutic window (bleeding)
Thrombin receptor blockers	Blocks only cellular thrombin effects
Recombinant thrombomodulin	Does not restore endothelial thrombomodulin
Activated protein C	Only partly blocks the effects of preformed thrombin
Statins	Non-specificity
Pentoxifylline	Non-specificity
Vitamin E	Non-specificity and variable efficacy

Wang J. et al., **World J Gastroenterol. 2007 Review.**

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- conditions necessary to the resolution of radiation-induced inflammation.

The precise roles of the different resident and recruited immune cells described in irradiated normal tissues are still obscure, as well as the part played by innate and adaptative immunities.

Strong evidence suggests that ongoing researches in this direction warrant opportunities to discover new therapeutic tools to manage normal tissue radiation damage.

Wang J. et al., **World J Gastroenterol. 2007 Review.**

Key points

- There is an urgent need for novel agents to prevent and/or reduce bowel radiation injury in patients being treated for abdominal and pelvic tumors.

- There are promising "novel" radioprophylactic and mitigating agents include statins, growth factors, agents acting on the toll-like receptor 5 pathway, endothelial protectants, and the vitamin E analogue γ- tocotrienol.

- Before these drugs can be clinically implemented, further research is needed to establish their safety and efficacy in reducing both acute and chronic toxicities in patients.

TLRs are expressed on the surface of multiple cell types such as immune cells, fibroblasts, or intestinal epithelial cells. TLRs play a putative role in tissue homeostasis and repair such as postradiation exposure.

Priorities for future research

- Obtain an improved understanding of physiological versus pathological responses of the intestine to radiation injury

- Perform clinical, epidemiological and outcomes studies in well-defined cohorts of cancer survivors to define true prevalence of late effects of radiation

- Determine the medical, quality-of-life-related, social and financial consequences of radiation-induced bowel injury

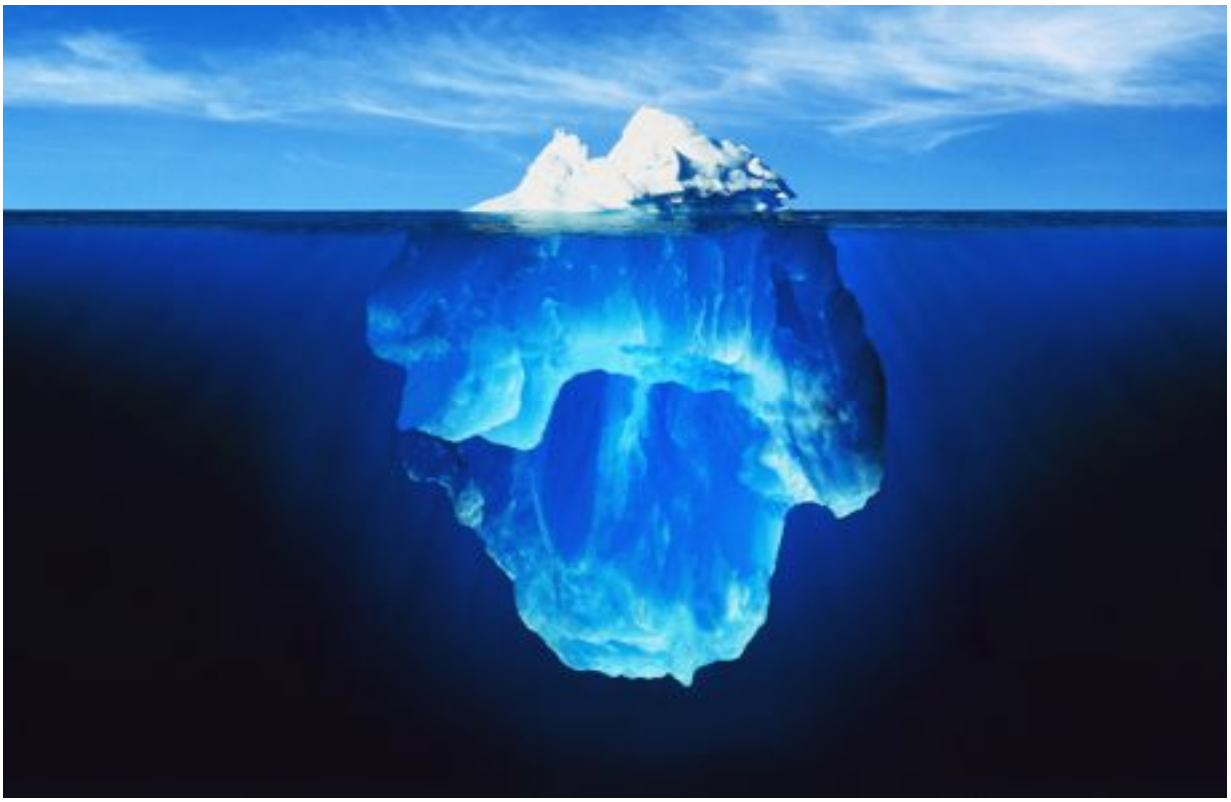
- Develop predictive assays to identify patients who are more prone than others to develop delayed healthy tissue toxicity after radiation therapy

- Strengthen molecular epidemiology research to identify genetic or epigenetic characteristics that correlate with susceptibility to delayed radiation enteropathy

- Testing radiation response modifiers in clinical trials

- Engage pharma and biotech industries to develop strategies against radiation enteropathy

The tip of the iceberg



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National (and international) collaborations to support **joint research programs**

Thank you very much for your attention!

TIMETABLE

LUNEDÌ 10 NOVEMBRE	SALA PLENARIA
[illegible]	SIMPOSIO AIRO-AIRB Microambiente e modulazione della risposta alla radioterapia
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