Pathogenesis of normal tissue side-effects

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9.10.2015

From a clinical point of view...

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Pool of Italian Cancer Registries - 1 January 2010

TUTTI I TUMORI ESCLUSI I TUMORI NON MELANOMATOSI DELLA CUTE
ALL TYPES BUT SKIN NON-MELANOMA
(ICD-10 C00-43, C45-96, D09.0, D30.3, D41.4)

COMPLETE PREVALENCE BY YEARS SINCE DIAGNOSIS

YEARS →	< 2	(2 - 5]	(5 - 10]	(10 - 15]	(15 - 20]	> 20
No. →	493 439	550 376	625 093	370 198	218 987	329 254
% →	19%	21%	24%	14%	8%	13%
PROPORTION → PER 100 000	866	969	1 102	653	385	583

MALE 44% FEMALE 56%

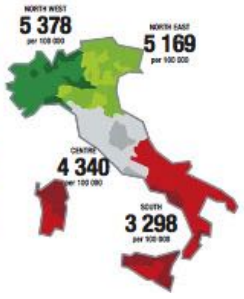
2 587 347 CANCER SURVIVORS

2 587 347
CANCER SURVIVORS

ALREADY CURED at 1 JANUARY 2010
704 648 (27%)

COMPLETE PREVALENCE BY SEX, MACRO-AREA, AND AGE
(PROPORTION PER 100 000)

AGE CLASS →	0-44	45-59	60-74	75+	ALL AGES
MALE					
NORTH WEST	603	2 856	12 024	22 395	4 988
NORTH EAST	582	2 872	11 873	22 820	4 758
CENTRE	556	2 537	9 392	19 125	4 021
SOUTH	525	2 239	8 244	15 198	3 013
POOL	566	2 643	10 683	20 222	4 197
FEMALE					
NORTH WEST	797	5 178	11 520	15 029	5 734
NORTH EAST	811	5 309	11 747	15 029	5 558
CENTRE	802	4 809	9 774	15 323	4 639
SOUTH	721	4 237	8 455	12 649	3 566
POOL	775	4 891	10 589	13 645	4 896
BOTH SEXES					
NORTH WEST	699	4 042	11 752	17 665	5 378
NORTH EAST	694	4 097	11 807	17 665	5 169
CENTRE	678	3 703	9 592	18 066	4 340
SOUTH	623	3 267	8 357	15 167	3 298
POOL	669	3 788	10 634	16 092	4 558



Dal Maso L. et al, **Epidemiol Prev 2014**

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RADIOTHERAPY

Normal tissue radiation toxicity can influence treatment outcomes, patient quality of life and survivorship.

Despite all progress, the efficacy of radiation-based treatment approaches is still limited by different
- technological,
- biological, and
- clinical constraints.

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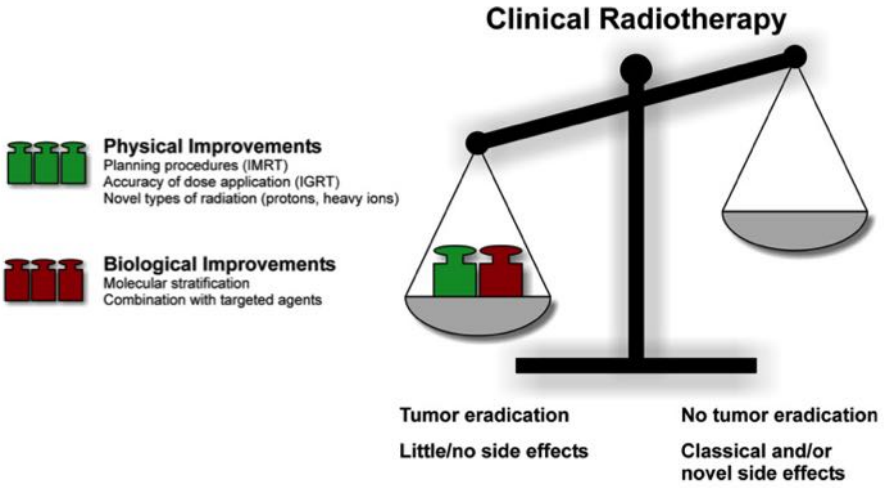
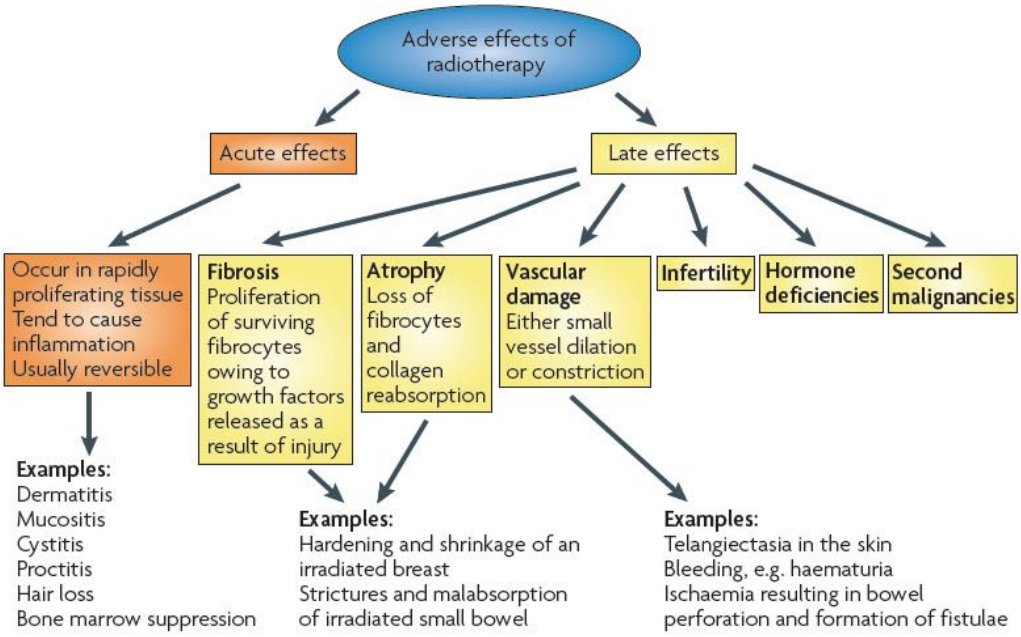
From a clinical point of view...



Major issues that can be distinguished are:
1) The intrinsic radiation resistance of several tumors is higher than that of the surrounding normal tissue,
2) The true patho-anatomical borders of tumors or areas at risk are not perfectly identifiable,
3) The treatment volume cannot be adjusted properly during a given treatment series,
4) The individual heterogeneity in terms of tumor and normal tissue responses toward irradiation is immense.

Orth M et al, **Radiat Environ Biophys 2014**

The responses of normal tissue to irradiation can be classified as early, intermediate or late depending on the time it takes for them to develop following radiation exposure.



Barnett GC. et al., **Nature Rew Cancer 2009**

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The early radiation responses, that occur in days to weeks following irradiation, are dominated by the effects on the hematopoietic, gastrointestinal and cerebrovascular systems.

Table 1. Effects of radiation on normal tissue

Temporal classification	*Tissue*	*Effects*
Early (hours to weeks)	Hematopoietic	Lymphopenia, neutropenia, thrombopenia, anemia, death (2.5–5 Gy)
	Gastrointestinal	Bloody diarrhea, denudation of epithelia, destruction of intestinal crypt cells, death (5–12 Gy)
	Cerebrovascular	Rapid cardiovascular and neurologic breakdown, death (12 Gy+)
	Skin	Erythema, desquamation
Intermediate (weeks to months)	Lung	Acute pneumonitis
Late (months to years)	Gastrointestinal	Epithelial thickening, fibrosis
	Lungs	Fibrosis
	Bladder	Fibrosis
	Heart	Fibrosis, pericarditis
	Kidneys	Nephropathy, arterial hypertension, anemia
	Liver	Hepatitis, rapid loss of function
	CNS	Transient demyelination, leukoencephalopathy, radionecrosis

Abbreviation: CNS, central nervous system.

Everett and Curiel, **Cancer Gene Therapy 2015**

The intermediate effects of radiation damage occur within a few months of radiation exposure. The main form of intermediate radiation response is acute pneumonitis of the lung, which may occur 2–6 months after irradiation.

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Temporal classification	*Tissue*	*Effects*
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Abbreviation: CNS, central nervous system.

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The late effects of radiation damage occur months to years following exposure. Thickening of epithelium and fibrosis occur throughout the gastrointestinal tract, in the lungs, bladder, liver, heart and central nervous system.

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Temporal classification	*Tissue*	*Effects*
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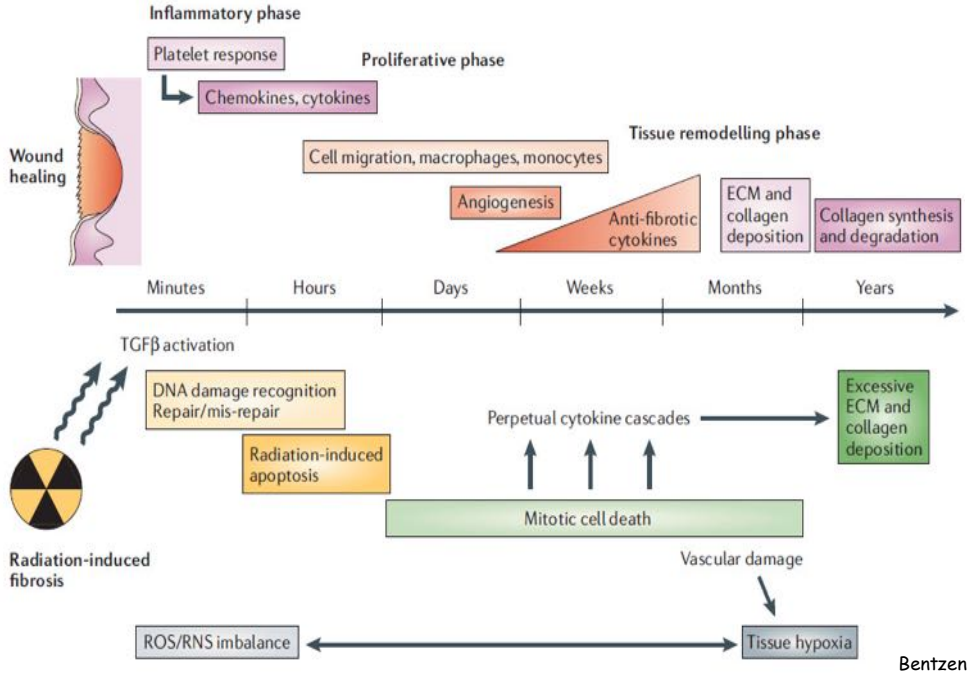
From a molecular point of view...

Ionizing radiations are used to cure cancers based on their properties to kill cells by:
- energy deposition in tissues,
- water radiolysis,
- production of free radicals damaging DNA, proteins and lipids.



Bentzen SM, **Nat Rev Cancer. 2006**

Target cell theory

The **target cell concept** sustein that tissue response to radiation exposure is governed by cell death in a target radiosensitive compartment, often the stem cell compartment, and that tissue regeneration depends on the surviving and proliferation of stem or progenitor cells.

OBSOLETE

Target cell concept **does not reflect** what really happen in the vicinity of irradiated organs

Consequential late effects theory

During the eighties improved understanding of the pathophysiology and pathogenesis of delayed normal tissue injury, serves an important purpose by helping to eradicate the old dogma of independence between early and delayed radiation effects: the **Consequential late effects theory**

INCOMPLETE

However, this terminology **fails** to recognize the complexity of radiation effects in multicellular tissues and organs.

Actual theory, proposed in 2001, sustain that...

...All cell types are sensitive to ionizing radiation, and tissue scaring process initiates immediately after radiation exposure, involving **all cell types and compartments** of the tissue.

Healthy tissue radiation responses are considered as a continuum between very acute events and late tissue fibrosis.

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

More in details...

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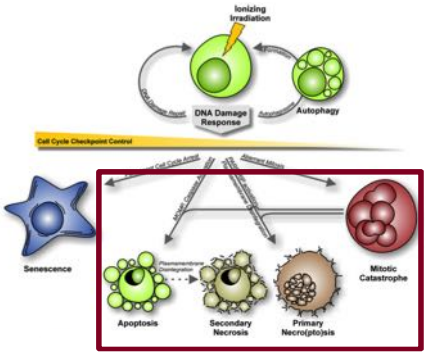
CYTOCIDAL EFFECTS

Radiation-induced molecular damage on DNA can induce cell phenotypic modifications and/or death by **apoptosis, necrosis, or mitotic catastrophe.**



Orth M. et al., **Radiat Environ Biophys 2014**

FUNCTIONAL EFFECTS

Radiation leads to changes including **transcription factor activation and protein modification** in the intracellular environment, plasma membrane and extracellular space.

SECONDARY EFFECTS

Excessive production of cytokines, chemokines and growth factors. **IL-1, IL-6, TNF-α, and TGF-β** are involved in the response of skin, lung, and brain.

Chemokines responsible for the recruitment of bone marrow-derived cells (BMDC) into the irradiated tissues include **CXCL-12** and **CXCR4**

Bone Marrow-Derived Cells (BMDC)

Three different sub-populations of BMDC are mobilized following local irradiation, i.e., **mesenchymal stem cells, endothelial progenitor cells, and myelomonocytic cells**.

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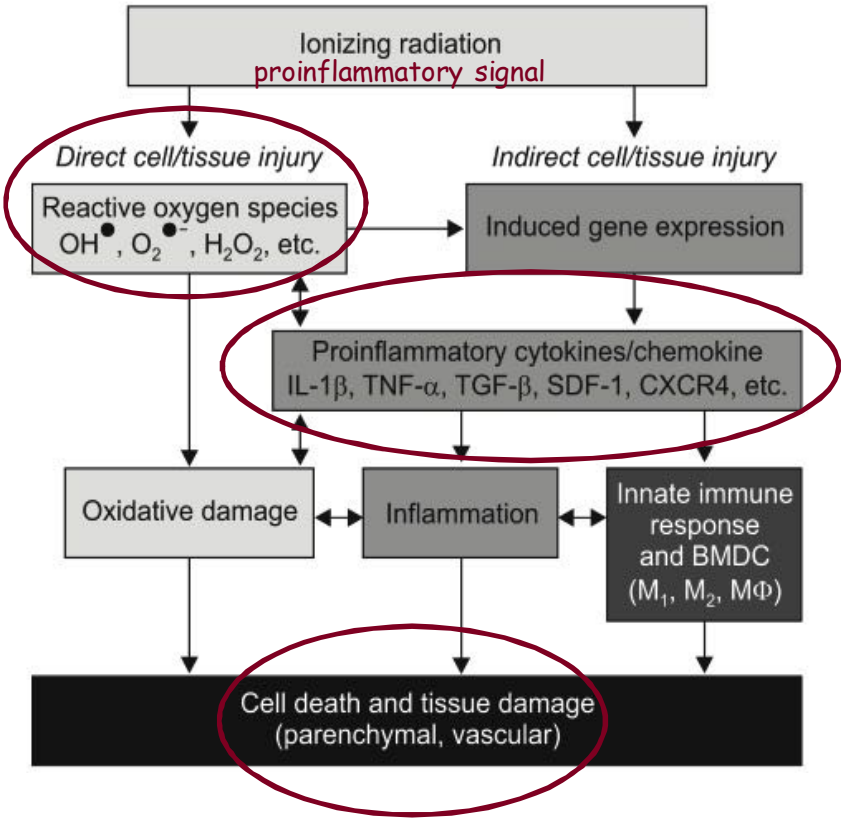
Normal tissue response to radiation exposure is immediate and endures with time.



Radiation-induced inflammatory response is initiated by:
- the production of reactive oxygen/nitrate species,
- the induction of apoptosis and clonogenic cell death,
- the activation of the transcription of several proinflammatory cytokines, chemokines, and growth factors (presumably by recruited immune cells).

Jae Ho Kim et al., **Radiat Oncol J 2014**

Role of the Vascular Endothelium

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The vascular endothelium is a critical target compartment involved in tissue response to radiation exposure and strongly participates in the initiation and development of radiation lesions.

Early endothelial effects	Late endothelial effects
▪ Apoptosis ▪ Activation: increased expression of cell adhesion molecules and cytokine secretion ▪ Recruitment of inflammatory cells ▪ Pro-coagulant and pro-thrombotic phenotype ▪ Increased permeability ▪ ROS production	▪ Microvessel collapse: rupture and dilatation of capillaries ▪ Thickening of the basal membrane Thrombosis ▪ Chronic pro-inflammatory phenotype ▪ Chronic production of ROS ▪ Senescence

Effects of irradiated endothelium on surrounding normal tissues
▪ Ischemia ▪ Necrosis ▪ Tissue fibrosis

Corre I et al., **Int. J. Mol. Sci. 2013**

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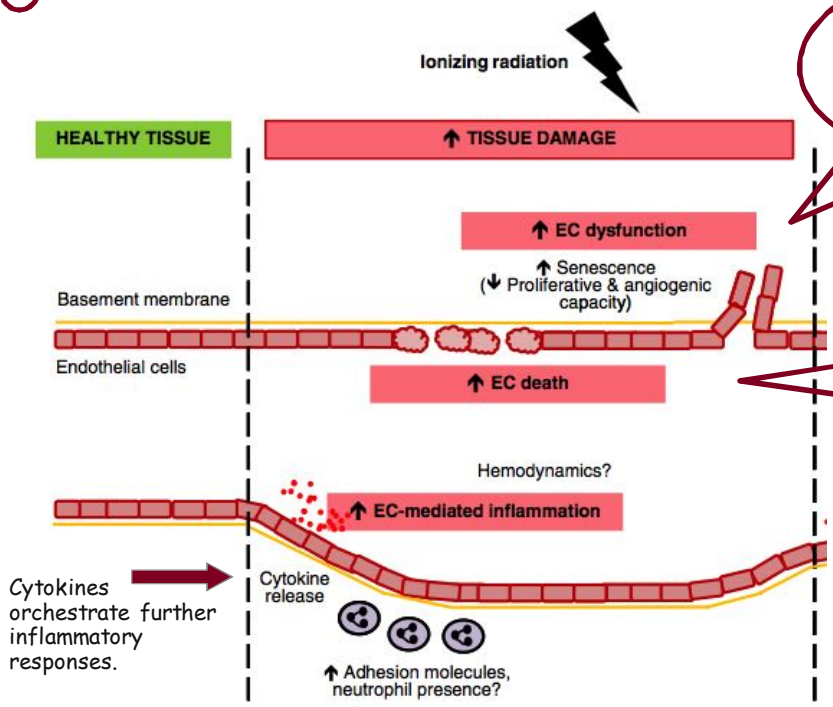

RT exposure induces senescence which reduces ECs proliferative and angiogenic capacity and causes a chronic pro-inflammatory phenotype

RT induces endothelial cells (ECs) loss through apoptosis and other mechanisms.

ECs become activated, expressing cell surface adhesion molecules and enabling neutrophil transendothelial migration.

Cytokines orchestrate further inflammatory responses.

The timing of heightened neutrophil presence may be important for their effect on tissue damage

Korpela and Liu, **Radiation Oncology 2014**

Progressing from normal tissue to a fibrotic state

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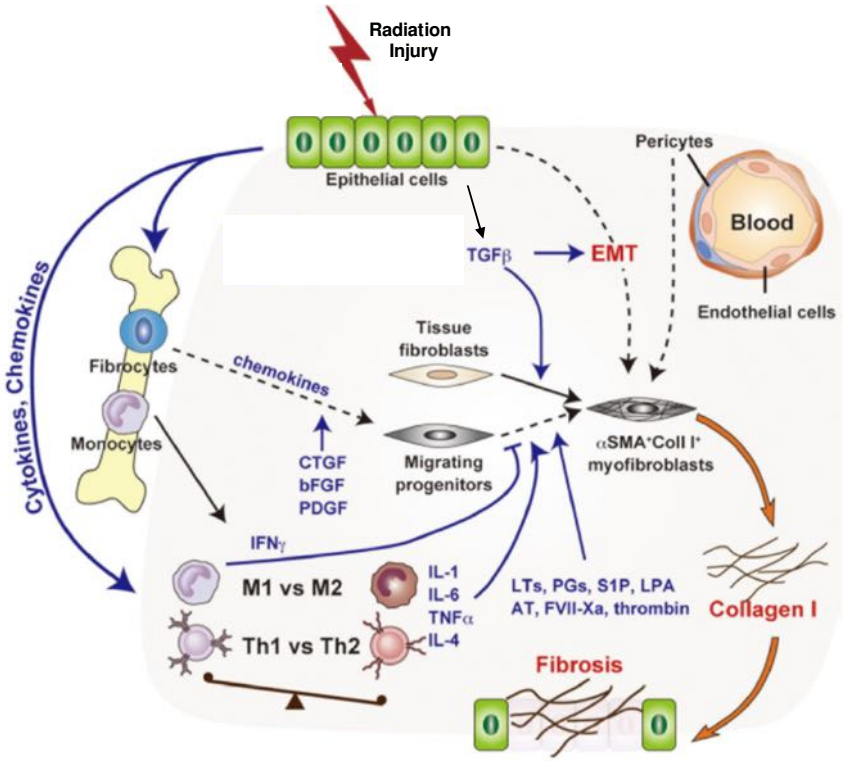

Endothelial and epithelial dysfunction "drive" the cycle in a chronic process until radiation fibrosis.

Adapted from Ueha et al. **Frontiers in Immunology, 2012**

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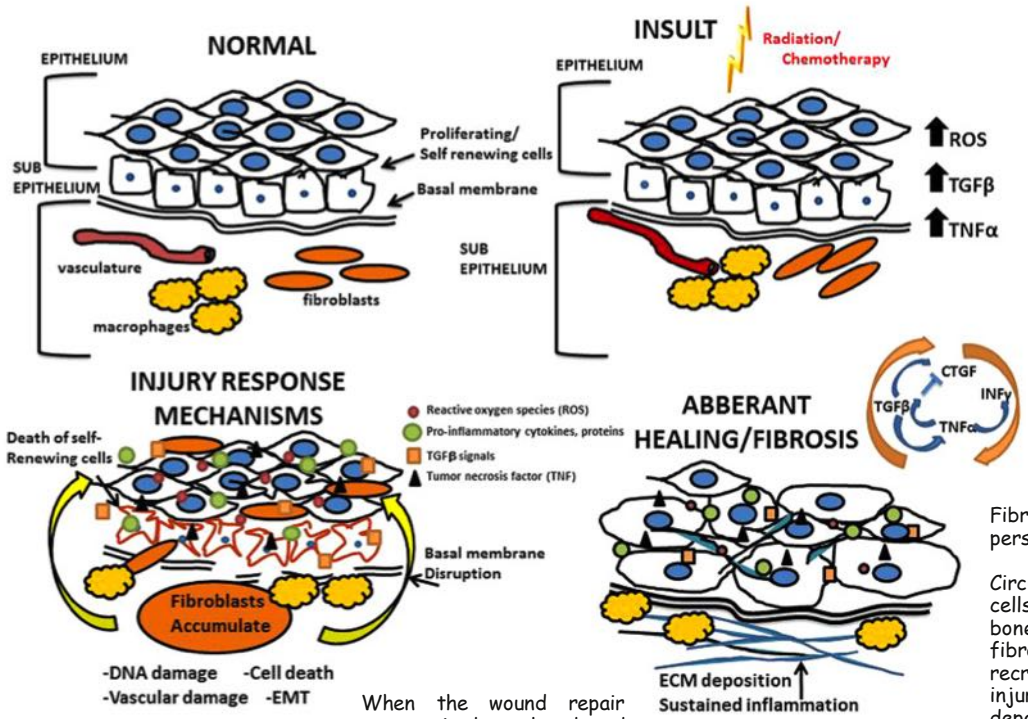
Under normal circumstances of wound repair, the expanded ECM would be provisional until the process of re-epithelialization occurs.



When the wound repair process is deregulated, and re-epithelialization is prevented, fibrosis occurs.

Fibrosis arises and persists systemically.

Circulating immune cells, chemokines, and bone marrow derived fibroblasts are recruited to sites of injury generating and depositing excess ECM proteins.

Mancini ML and Sonis ST, **Frontiers in Pharmacoloy 2014**

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IN CONCLUSION...

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

It appears necessary to increase the knowledge concerning:
i) enduring oxidative stress,
ii) vascular endothelial cell activation,
iii) immune cells recruitment and their phenotypic orientations

⇩

Strong evidence suggests that ongoing researches in these directions are an opportunitie to discover new therapeutic tools to manage normal tissue radiation damage.

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Radiotherapy represents a crucial treatment option in the cure of malignant diseases

In the recent years, the efficacy of radiotherapy has been improved by new techniques (IMRT, IGRT).

↳ Despite technological advances, **healthy tissue side effects constitut a major dose-limiting factor in RT**

In parallel, novel approaches that combine radiotherapy with molecularly designed agents specifically targeting the hallmarks of cancer have been deployed and revealed promising results both in preclinical models and in clinical trials.

↳ Improve employment of such targeted agents often coincides with new kinds of side effects demanding new biomarkers, which might allow a detailed patient stratification.

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The risk of normal tissues radiation effects limits the uncomplicated cancer cure rate and adversely affects the quality of life of cancer survivors.

As the number of cancer survivors steadily increases, side effects of radiation represent a significant challenge for future research.

Finding safe and effective methods to reduce the incidence and severity of radiation side effects is an unmet need.

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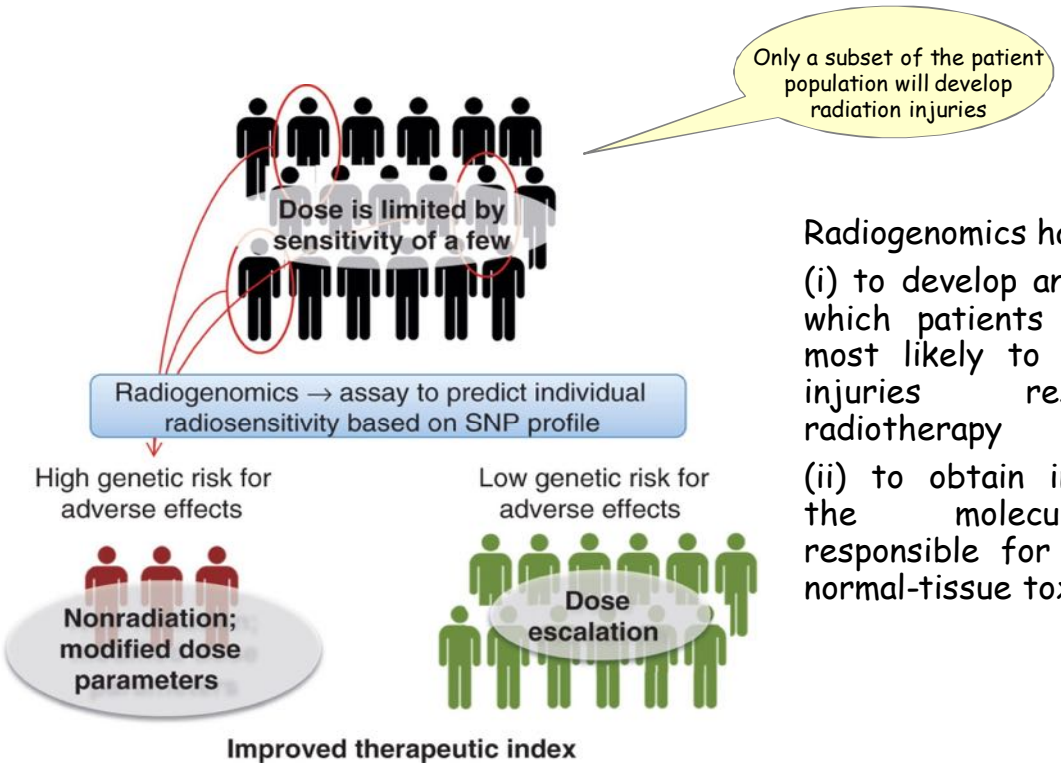
RADIOGENOMICS



Radiogenomics has two goals:

(i) to develop an assay to predict which patients with cancer are most likely to develop radiation injuries resulting from radiotherapy

(ii) to obtain information about the molecular pathways responsible for radiation-induced normal-tissue toxicities.

Kerns SL et al., **Cancer Discovery 2014**

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Advances in knowledge of tissue and organ biology, mechanisms of injury, development of predictive biomarkers and mechanisms of radioprotection energize the field of normal tissue protection and mitigation.

Since **various factors vary among tissues**, successful development of radioprotectors/mitigators/treatments may require **multiple approaches**.

All these efforts to offer considerable improvement in the benefit of anticancer radiotherapy as well as in the management of normal tissues side effects.

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Thank you very much for your attention !